Integrating Palliative Care Into Oncology: A Way Forward

Improving the Quality of Palliative Care Through National and Regional Collaboration Efforts

Palliative Pharmacotherapy: State-of-the-Art Management of Symptoms in Patients With Cancer

Pharmacological Management of Cancer-Related Pain

Clinical Implications of Opioid Pharmacogenomics in Patients With Cancer

Palliative Sedation in Patients With Cancer

Integrating Psychosocial Care Into Routine Cancer Care

Systematic Review of Palliative Care in the Rural Setting

New Frontiers in Outpatient Palliative Care for Patients With Cancer

Palliative Care in Adolescents and Young Adults With Cancer

Palliative Care in Older Patients With Cancer

Prognostication of Survival in Patients With Advanced Cancer: Predicting the Unpredictable?
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Ten Best Readings Relating to Palliative Care for Oncology

About the art in this issue:
Lisa Scholder is a multimedia artist whose canvas is the human body. Her technique involves applying body paint to nude models, then digitally photographing the painted body. The explosion of illuminating color on the human form is Scholder's artistic trademark. All of the models shown in this issue are survivors of breast cancer of varying ages and body types, and they are part of the Bodies of Courage project.

Scholder takes several hours to hand-paint the model with a crème-based paint and often incorporates other body-painted images in the final piece, which does not include the face of her model. Her artwork focuses on the abstract portrayal of the body infused with vibrant colors. Scholder's late father-in-law, renowned Indian artist Fritz Scholder, had an unmistakable influence on her bold color combinations. Each model's unique strength is represented with abstract and, at times, expressionist art forms on her body. The artist's driving force is the self-empowerment that this process can bestow on her model, enabling her to see her body as a colorful, unique piece of art.

With no formal art training, she began body painting in 2000 and developed her distinct body painting and photography style. Her first public exhibition was in 2004, and she progressed to gallery and art museum exhibitions since then.

Bodies of Courage is an Arts in Medicine project (www.bodiesofcourage.org) in partnership with the Faces of Courage Foundation (www.facesofcourage.org), which provides day outings and overnight camps at no cost for women, children, and families diagnosed with any type of cancer. Lisa Scholder and Peggie D. Sherry, the founder of Faces of Courage, began this project 5 years ago as a way to raise awareness and as an artistic therapy for survivors of cancer. This project is an artistic testimony to the strength and determination of these survivors throughout their battles with cancer, their celebration of life, and their reconnection with the beauty of their own bodies.

For information about the traveling gallery, please contact Peggie D. Sherry at psherry@facesofcourage.org or 813-948-7478. Further information on these projects is available at www.bodiesofcourage.org and www.facesofcourage.org.

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Dear Readers,

Beginning with the January 2016 issue, Cancer Control: Journal of the Moffitt Cancer Center will be published in digital format only. With the launch of our new and improved website, readers will still be able to download and print the articles they wish to keep by visiting us at cancercontroljournal.org (formerly MOFFITT.org/ccj). The new URL links to our existing webpage under MOFFITT.org and will redirect readers to the new website as soon as it is available. Reprint requests will continue to be handled by the editorial office and will be reviewed and responded to on an individual basis.

The decision to abandon the paper edition was based on considerations of cost effectiveness paramount for all fields of health care today. As the price of paper continues to rise and more and more people utilize electronic devices to read books, newspapers, and magazines, the increasing costs of printing no longer appear justified. Limited resources may be better utilized in maintaining and improving the quality and timeliness of our publication. For those of us who grew up in the pre-electronic era, who were used to waiting with anticipation for the new issue of our favorite medical journal in the mail, this change is a little disconcerting, as is the experience of seeing a daughter, now an adult, leave home and start her new family. It is disconcerting but necessary: as much as we regretted retiring our cherished stethoscope, we conceded that an echocardiogram was a more precise way to detect valvular disease or myocardial dysfunction than the human ear.

Indeed, we plan to utilize the resources of the journal to fulfill our ongoing commitment to quality and practicality. Since its inception more than 20 years ago, Cancer Control promised to provide practicing oncologists with exhaustive and user-friendly reviews of important issues that could not be otherwise found in the literature.

John Horton, MB, ChB, the founding editor and the quintessential clinical teacher, received universal praise for the impact Cancer Control had on the practice of oncology in the country and around the world. John C. Ruckdeschel, MD, the first chief executive officer of the H. Lee Moffitt Cancer Center & Research Institute and cofounder of Cancer Control, gave unlimited support to the educational mission of Moffitt and considered the journal to be the most effective means to fulfill this mission.

The scope of oncology is rapidly enlarging and diversifying, and the practitioner is exposed to a barrage of new information that is both incomplete and contradictory. The main challenge of oncology education is to harness the energy of this scientific upsurge into a coherent discourse that highlights scientific advances together with new clinical questions. Fully committed to guide the practitioner to a safe exit from this informational maze, Cancer Control will devote the next issues to novel and timely topics. These include minimally invasive surgery, prospective radiosurgery and interventional radiology, imaging techniques based on biological markers, the use of genomic testing, the interpretation of results from clinical trials of targeted therapy, the use of mathematical models to predict tumor progression, overviews of tumor immunology and signal transduction, and the new scope of palliative care. Since establishing Cancer Control, Moffitt has grown to be the third largest comprehensive cancer center in the country. Basic, translational, and clinical investigators working at Moffitt illustrate the array of treatments and clinical trials available at our institution for the patients of Florida, the United States, and the world.

A digital publication will allow us to focus unimpeded on the exciting and continual progress of cancer care. We would like to think that the adoption of a digital format represents a new step, rather than a new era, in the life of our journal — a step congruent with technological and scientific changes that will permit us to fulfill our mission in a rapidly changing world.

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In 2010, Temel et al. demonstrated improved outcomes, including longer survival, in patients with metastatic non–small-cell lung cancer receiving palliative care along with usual oncology treatment. A provisional opinion published in 2012 by the American Society of Clinical Oncology further supported early palliative care for any cancer patient with advanced disease or high symptom burden. The Center to Advance Palliative Care, the American Cancer Society, and other national organizations have been instrumental in the advancement of the education, research, and literature base for supportive and palliative care in cancer settings. They have led the charge to support patient and family quality of life and align care with patient goals. Study results have demonstrated improved costs of care while maintaining quality, leading to significant advances in the penetration and growth of palliative care programs nationwide.

However, more than a decade after the Institute of Medicine first studied the quality of cancer care, the obstacles to provision of quality palliative care for patients with cancer remain formidable. Patients frequently do not receive adequate symptom control or management of treatment-related side effects, and decisions about care often are not patient-centered or rooted in the most recent scientific evidence. In Dying in America, the Institute of Medicine’s 2014 consensus report on care of the dying, a committee of experts found that improving the quality and availability of medical and social services for patients and their families could not only enhance quality of life through the end of life, but may also contribute to a more sustainable care system.

In this issue of Cancer Control, we present topics on palliative care that highlight the progress made to support the well-being of patients with cancer and the challenges to continued integration and advancement of the field of palliative care in oncology.

Dr. Ramchandran and colleagues review the compelling case for palliative care integration, the barriers to progress, and summarize key lessons gleaned from randomized controlled trials in palliative care integration in both the inpatient and outpatient oncology settings. Employing a case-study approach, they discuss means to integrate palliative care into oncology care and offer guidance for sustainability of integration. Among the strategies for scalable integration, the importance of quality measures and metric development is emphasized.

Dr. Kamal and associates provide insight into quality improvement for palliative care achieved through collaborations that examine how care is delivered and may be improved. Their article describes endeavors to enhance the provision of quality palliative care at regional and national levels through cooperative efforts within an expansive group of community and academic palliative care providers. The development of the innovative, evidence-based Quality Data Collection Tool and its utilization are described as means to generate quality improvement projects aligned with national quality measurement initiatives. Such projects are an impetus for identifying and addressing troubling symptoms associated with serious illness, such as those frequently encountered in patients with cancer.

The management of symptoms in cancer is updated in Dr. Prommer’s article on state-of-the-art palliative pharmacotherapy. The treatment of prevalent symptoms that compromise the well-being of patients and their caregivers throughout the course of cancer care is emphasized, with particular focus on those that engender distress as disease progression occurs. Symptom mechanisms, means of assessment, and management approaches utilizing both medication-based treatments and nonpharmacological therapies are described.

In a second article, Dr. Prommer reviews the pharmacological management of cancer pain. The World Health Organization analgesic ladder for the management of cancer pain of varying intensity is described, with detail provided on use of specific agents among the familiar “tried and true” gold-standard medications and more recently available agents. The additional value of adjuvants and interventional pain modalities is represented along with approaches to medication conversions and management of common opioid side effects. The epidemiology of malignant pain and the understanding of opioid responsiveness in the context of opioid receptor interactions are elucidated together with approaches to opioid-resistant pain.

Given the use of opioids for cancer pain, Dr. Bell and coauthors explore the basis of opioid analgesic responsiveness with a review of clinical studies that have assessed the connections between the effects of opioids and the genetic variants in the many genes.
that govern their actions. The evidence is examined for associations between specific genetic variants and modulation of opioid response with variability in treatment results. Despite the challenges identified and the need for prospective studies comparing pharmacogenetic-guided opioid treatment to standard practice, the authors’ suggestion of the potential use of genotyping to achieve more effective therapy in cancer-related pain palliation is compelling.

Dame Cicely Saunders, the founder of the modern hospice movement, emphasized the need for palliative care to manage “total pain”: The spiritual, psychological, social, and emotional elements that together with physical distress can cause intolerable suffering. Drs Maltoni and Setola review the controversial topic of palliative sedation for relief of refractory physical symptoms. Their article focuses on the application of proportionate palliative sedation at the end of life, consistent with national and international guidelines, as an ethical modality without effect on survival.

The multifaceted understanding and management of total pain in cancer goes beyond relief of physical suffering and necessitates the integration of psychosocial care. Drs Jacobsen and Lee review progress in this area, describing the application of standards, key clinical practice guidelines, and quality monitoring. They describe the effect of such monitoring on quality in psychosocial care. Models are provided to demonstrate efforts to enhance provision of psychosocial care by implementing such standards and guidelines in community settings.

Dr Bakitas and colleagues discuss the limitations to access and the dissemination of comprehensive palliative care for patients with cancer living in rural settings. They have gathered empirical evidence, largely focused on patients with cancer, and describe the present state in rural palliative care research and practice. The article reveals a dearth of research in this area and a paucity of rural palliative care services, resulting in limited care. However, the successful initiatives described demonstrate opportunities to establish palliative care practice services and standards specific to rural settings.

Dr Rabow and associates describe other areas of importance in community-based palliative care in their article about outpatient oncological palliative care. Recognizing the fundamental but minority role played by hospital palliative care in the context of the totality of palliative care required in oncology is pivotal. The article describes the current state in oncology palliative care and highlights vanguard elements in outpatient oncology palliative care, including the setting and timing of palliative care integration into outpatient oncology, quality and measurement, research, electronic and technical innovations, finances, and the relationship between primary and specialty palliative care.

Specialty palliative care distinguishes the activity of specialty-trained providers managing complex refractory symptoms, existential and psychosocial distress, medical futility, and advanced communications. However, specialty palliative care in oncology also encompasses expert palliative care that may be provided to special populations of patients with cancer who have unique needs. The particular challenges of these groups and their care are described in the articles on palliative care in adolescent and young adult patients with cancer by Dr Donovan and coauthors and palliative care of older patients with cancer by Dr Balducci and associates.

The article by Donovan and colleagues highlights the limited provision of palliative care and research studies on palliative care in adolescent and young adult patients with cancer. Gaps in care with high potential for distress and opportunities for earlier inclusion of palliative care are also identified. The article features guidelines supporting the integration of palliative care, the options for advance care planning, and challenges to implementation in this patient population.

Balducci et al focus on palliative care for older patients with cancer and provide a comprehensive overview of the effects of advancing age. They emphasize specialized palliative care concerns pertaining to this expanding population, a group also frequently affected by nononcological medical issues. The priorities elucidated include setting goals, prevention and management of treatment complications, management of cancer-related symptoms, and management of older survivors of cancer.

Survival prediction principles and recent literature on prognostication are reviewed by Dr Hui in the context of examining clinician prediction of survival in patients with advanced cancer. With emphases on prognostication as a process, the evolution of prognostic factors over time, the variability in prognostic accuracy, and the overriding principle of unpredictability of the exact time of death, Dr Hui highlights the uncertainty in survival prediction. Yet, use of existing validated prognostic models and factors still enable clinicians to provide approximated time frames. These can facilitate clinical decision making in the present, and the future holds promise for multiple opportunities in prognostication research.

We have compiled this compendium of topics in palliative care in oncology in the hopes of advancing our understanding and adoption of palliative care in cancer. Our goal is partnership to enhance patient and caregiver quality of life throughout the cancer continuum. We are gratified with the progress made and motivated by the opportunities that remain.
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The Department of Supportive Care Medicine at the H. Lee Moffitt Cancer Center & Research Institute is engaged in clinical care, training and research. The department includes the sections of Palliative, Behavioral, and Integrative Medicine. Consultative and management services are offered in both the outpatient and inpatient settings. The activities of the department address the physical, emotional, social, and spiritual challenges that occur throughout the course of cancer care.

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[www.MOFFITT.org](http://www.MOFFITT.org)
Palliative care should be initiated early in the treatment continuum of cancer.

Integrating Palliative Care Into Oncology: A Way Forward
Kavitha Ramchandran, MD, Erika Tribett, MPH, Brian Dietrich, MD, and Jamie Von Roenn, MD

Background: Patients with cancer have complex physical, psychosocial, and spiritual needs that evolve throughout their disease trajectory. As patients are living longer with a diagnosis of cancer, the need is growing to address the morbidity due to the underlying illness as well as treatment-related adverse events. Palliative care includes treating physical symptoms as well as addressing psychosocial and spiritual needs. When these needs are addressed, the quality of care improves, costs decrease, and goals are aligned between the medical care provided and the patient and family. However, how best to integrate palliative care into oncology care is still an area of investigation.

Methods: The authors conducted a literature search, including randomized clinical trials and practice reviews, to evaluate the evidence for integrating palliative care into oncology care. Barriers to integration as well as sustainable paths forward are highlighted. The authors also utilize case studies as representative examples of integration.

Results: Current studies demonstrate that integrating palliative care into oncology care improves symptom control, rates of patient and family satisfaction, and quality of end-of-life care. However, for systemwide integration to be successful, commitment must be made to quality improvement, an infrastructure must be built to support palliative care screening, assessment, and intervention, and stakeholders must be engaged in the program. In addition, value must be demonstrated using metrics that affect quality, care utilization, and patient satisfaction.

Conclusions: Even though most US cancer centers have a palliative care program, palliative care remains limited in scope. An integrated approach for palliative care with oncology care requires a systems-based approach, with agreement between all parties on shared common metrics for value.

Introduction
Significant progress has been made in the management and treatment of cancer, but morbidity rates continue to increase. An estimated 1,658,370 new cancer diagnoses and 589,430 cancer-related deaths are expected to occur in the United States in 2015. These data reflect a 22% decline in overall cancer mortality, translating to approximately 1,519,300 fewer cancer-related deaths from 1991 to 2011. This decrease in mortality may be associated with an increase in cancer morbidity, because a growing number of survivors experience the late-onset and long-lasting effects of cancer and its treatment. Patients and families experience physical, psychological, and spiritual symptoms throughout the disease trajectory, sometimes leading to poor quality of life and suboptimal treatment outcomes.
Palliative care can help relieve symptoms and improve well-being in patients and their families living with a serious illness. The World Health Organization (WHO) defines palliative care as:

An approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.

Palliative care should be initiated at the point of diagnosis and continued throughout survivorship and end of life. Many pivotal studies have demonstrated improvements in outcomes when palliative care is integrated into the continuum of care, including quality of life, mood, the utilization of health care, patient satisfaction, patient understanding of prognosis, and survival.

Evidence and Implications

Providing concurrent palliative care and standard care for the management of cancer has proven benefits. Studies of integrated care in the inpatient/hospital or home setting have shown that the addition of palliative care to standard care reduces hospital-based costs and improves the quality of end-of-life care and symptom management. Because medical oncology is increasingly provided in the ambulatory setting, more relevant data to assess the impact of integrating cancer and palliative care arise from studies performed in the outpatient setting. The results of 3 randomized controlled trials demonstrated improved outcomes for study participants randomized to the palliative care intervention. An investigation of these studies provides insights for the integration of palliative medicine into cancer care.

Temel et al randomized 151 patients with newly diagnosed metastatic lung cancer to receive either early palliative care in conjunction with standard oncology care or standard oncology care alone. Early palliative care consisted of a visit with a palliative care team at intervals of at least 30 days, from the point of diagnosis until end of life. Outcomes measured included changes in mood and quality of life, aggressiveness of end-of-life care (chemotherapy ≤ 14 days before death, lack of hospice care, or admission to hospice ≤ 3 days before death), and understanding of prognosis. Study patients assigned to the integrated palliative care arm had significant improvement in quality-of-life scores compared with those assigned to the standard oncology care (P = .03), as well as fewer depressive symptoms (P = .01) and less-aggressive, end-of-life care (P = .05). Despite less-aggressive, end-of-life care, study patients in the concurrent palliative care arm had prolonged rates of survival compared with those assigned to the standard treatment arm (8.9 vs 11.6 months; P = .02). In addition, those in the integrated care arm had a more accurate understanding

Call for the Integration of Palliative Care

Major organizations, such as the American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), Institute of Medicine (IOM), WHO, and the European Society for Medical Oncology (ESMO), endorse the integration of palliative care into comprehensive cancer care. ASCO published a vision for optimal oncology care for 2020 that identified integrated palliative care as an essential component of optimal cancer care. In a provisional clinical opinion, ASCO recommended integrated care for all patients with metastatic disease or high symptom burden. NCCN developed guidelines to facilitate the integration of palliative and oncological care with schematics for screening, assessments, interventions, reassessment, and after-death care. IOM explains that involving palliative care is a requirement for comprehensive care. WHO developed guidelines in 1990 for providing palliative care to patients with malignancy. ESMO has been a strong proponent of integrating palliative and cancer care. As a component of this effort, it created an accreditation program to identify cancer programs with well-integrated palliative care services.

Barriers

Significant barriers still prevent the effective integration of palliative care into the continuum of cancer care. Such barriers include an inadequately trained workforce, cultural stigma (eg, palliative care equates to end-of-life care), lack of payment models supporting early and regular palliative care, and a need for well-defined metrics for quality palliative care. In addition, guidance on methods for integration is lacking. At a minimum, integrating palliative care into cancer care requires 3 components: (1) routine identification of palliative care needs through screening, (2) standardized assessment of palliative care needs, and (3) management and treatment of identified needs. Clarity is lacking on how to accomplish all 3 areas.
of their prognosis, were more likely to have resuscitation preferences documented, and were less likely to receive chemotherapy at the end of life than their counterparts (9% vs 50%; \( P = .02 \)). At baseline, approximately one-third of all study participants said they thought their disease could be cured with treatment. The investigators hypothesized that this decreased utilization of chemotherapy at the end of life may account for the improved survival rates.

In Project Educate, Nurture, Advise, Before Life Ends, Bakitas et al\(^9\) led a randomized study of a telephone-based educational intervention in a rural setting. A total of 312 patients with advanced solid tumors and life-limiting prognoses (approximately 1 year) were randomized to receive usual care or usual care plus nursing intervention. The nursing intervention was based on a chronic care model that focused on patient empowerment and encouraged patient self-management and problem solving. It consisted of 4 weekly sessions focused on symptom management, communication and social support, problem solving, and advance care planning, followed by at least monthly telephone contact. Outcomes measured included symptom intensity, quality of life, mood, and resource use. Compared with those in the usual care group, those in the intervention group reported significant improvement in quality of life (\( P = .02 \)), depression (\( P = .02 \)), and a favorable trend in symptom intensity (\( P = .06 \)). No difference was seen in the use of health care resources between the study groups, as measured by the number of emergency department visits or days in the hospital or intensive care unit. Bakitas et al concluded that a nurse-led intervention had the potential to impact quality of life and mood, but it was less likely to impact symptom intensity or resource utilization. Rather, they hypothesized that a more intensive intervention (eg, in person) might be more likely to significantly impact symptoms and resource use, although they admitted that such a model is less feasible for patients living in rural areas.

A Canadian trial by Zimmerman et al\(^10\) also supports the finding that the early integration of palliative care into cancer care in the outpatient setting improves patient outcomes. This cluster-randomized controlled trial of 461 patients with advanced solid tumors from 24 clinics in Toronto, Canada, assessed the impact of early consultation and follow-up by a palliative care team in addition to standard oncology care compared with standard cancer care alone. Eligible participants had advanced cancer and a clinical prognosis of between 6 and 24 months. Those in the intervention arm had an initial consultation with a palliative care team and at least monthly follow-up visits. Outcomes measured included symptom severity, quality of life, satisfaction with care, and patient/family difficulties communicating with their health care team. At 3 and 4 months, patients in the intervention arm reported improvements in quality of life (\( P = .05 \) and \( P = .003 \), respectively) and satisfaction with care (\( P = .0003 \) and \( P < .001 \), respectively). Improvement in symptom severity was noted at the 4-month time point alone (\( P = .05 \)). The authors noted that quality of life is a broad construct that can improve, even when a change in symptoms is lacking.

The randomized trials conducted by Temel et al\(^8\), Bakitas et al\(^9\), and Zimmermann et al\(^10\) provide key lessons for integrated practice, including (1) the benefits of normalizing the standard integration of palliative care for all patients, (2) the impact of integrating palliative care on the psychosocial domain of care, and (3) the need for sustainable management of palliative care resources and value-driven metrics.

**Normalizing Palliative Care**

Among the 3 randomized controlled trials presented, all patients in the intervention arms were connected to palliative or supportive consultation. Temel et al\(^8\) attributed some benefits of the intervention to immediate eligibility and enrollment of patients with a new diagnosis of advanced cancer. Also notable is that the study dropout rate was 1%, suggesting that, once initiated, utilization of palliative care may be driven by patient satisfaction, family member satisfaction, or both. A national poll conducted by the Center to Advance Palliative Care revealed that 7 out of 10 people are unfamiliar with palliative medicine, but, once it was described or offered to them, 92% said they would consider it as support to improve quality of life and symptom management. In addition, the results of a qualitative study from Schenker et al\(^24\) suggested that patients with unmet physical and psychosocial symptoms are likely to perceive a need for specialist palliative care. No significant association was seen between perceived need and likelihood to request palliative services. However, patients were more likely to see palliative specialists if their oncologist recommended the service. Based on these data, educating the public and establishing palliative care as a standard of care at the time of a cancer diagnosis is likely to be acceptable to patients and families. In addition, oncologists are key players in introducing patients to and supporting palliative care for those with an identified need.

**Psychosocial and Decision-Making Support**

Palliative medicine is traditionally associated with the management of physical symptoms and transitioning to end-of-life care. However, evidence suggests that palliative medicine can be a source of psychological and decision-making support. In the study by Temel et al\(^8\), the palliative care clinicians in...
the trial focused their attention on assessing psycho-
social symptoms, establishing goals of care, assisting
with decision-making regarding treatment, and
coordinating care. This focus was associated with
significant improvement in quality of life, decreased
depressive symptoms, and greater understanding of
prognosis among the study participants. Likewise,
Zimmerman et al realized a more pronounced im-
 pact on quality of life than on physical symptoms as
a result of the palliative care intervention. Bakitas
et al also found a positive effect on quality of life
and mood in the palliative care intervention group.

A summary of evidence in support of the early
integration of palliative care proposed the following
dominant mechanisms by which palliative care may
affect outcomes: psychological support, knowl-
gedge of illness, and coping behaviors (Fig 1). Car-
ing for psychosocial health, as well as empowering
decision-making skills for patients and families, is
integral to optimal cancer care.

**Sustainable Management of Palliative Resources**

Primary palliative care is defined as the “basic skills
and competencies required of all physicians and oth-
er health care professionals.” For example, primary
palliative care may include neuropathy management
by an oncologist during routine care. Secondary pal-
liative care refers to practices of “specialist physi-
cians and organizations that provide consultation and
specialty care.” Specialists may be consulted when

![Fig 1. — Hypothesized relationships between early palliative care interventions and clinical outcomes.](image)


symptoms are challenging to control with initial inter-
ventions (eg, complex pain syndromes, refractory anxiety; Fig 2).

Temel et al utilized a high-resource, specialist model in which patients met with their assigned palliative care clinicians in coordination with their oncologists. Alternatively, Bakitas et al described a
nurse-led approach that equipped the nursing team with palliative care skills, including didactic training and reference tools, and incorporated patient self-management. Both interventions realized significant improvements in quality of life and depression. Given the increased palliative care needs of people affected by cancer and the limited specialist workforce, models such as Project Educate, Nurture, Advise, Before Life Ends that utilize scripted interventions to build capacity for palliative care are critical to the sustainable provision of services. Scalable models for palliative care integration will require education of all health care professionals who provide primary palliative care as well as adequate support (eg, time, reimbursement). In addition, appropriate guidelines and referral criteria must be put into place for specialist support.

**Establishing Standard Measurements and Defining Value**

Integrating palliative care into oncology could have a higher likelihood of success if its value is clearly defined and accurately and consistently measured. In addition, clarity is needed on which components of a palliative care intervention affect which outcomes. For example, what interactions and with whom are absolutely necessary to achieve improved psychosocial well-being? The randomized studies by Temel et al, Bakitas et al, and Zimermann et al all included well-defined primary and secondary outcome measures. Comparisons between interventions and future investigations require an accepted common set of quality indicators that reflect the goals and scope of the specialty.

Several groups have proposed quality metrics for palliative care. ASCO’s Oncology Practice Initiative includes metrics on symptom measurement (pain, dyspnea, and constipation) as well as quality of end-of-life care (time on hospice, location of death). The Center to Advance Palliative Care also convened a panel to establish a common set of metrics to measure patient/family, clinical, operational, and financial outcomes (Table 1). Its consensus recommendations included metrics for symptom assessment, goals of care, family support, and transition management. It also recommended measurements of satisfaction among patients, their family members, and the health care team. Kamal et al reported on the landscape of quality measures relevant to palliative care utilizing domains defined by the National Quality Forum (Table 2). They identified metrics in physical, psychological, cultural, social, ethical, end of life, and spiritual care.

Metrics in some studies have focused on the alleviation of physical symptoms, quality of life, and the quality of end-of-life care. However, these measures are but a starting point; further delineation of cause and effect (eg, which component of the palliative care intervention affects which measure) is needed. Better understanding is needed of how patients, their families, and health care teams measure success in achieving optimal quality of living with a cancer diagnosis.

<table>
<thead>
<tr>
<th>Categories</th>
<th>Common Metrics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient/family</td>
<td>Satisfaction scores</td>
</tr>
<tr>
<td>Clinical</td>
<td>Symptom control scores, Psychosocial assessment scores</td>
</tr>
<tr>
<td>Operational</td>
<td>Demographics, Disease diagnosis and staging, Referring health care professional, Emergency department visits, Hospital admissions/readmissions, Hospital and intensive care unit lengths of stay, Hospice referral</td>
</tr>
<tr>
<td>Financial</td>
<td>Daily pre- and post-consultation hospital cost, Net loss/net gain for inpatient deaths</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Care Domain</th>
<th>Example Metrics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical</td>
<td>Symptom assessment and management (pain, dyspnea, fatigue, nausea)</td>
</tr>
<tr>
<td>Psychological</td>
<td>Psychosocial support, Caregiver depression, Depression, Grief and bereavement</td>
</tr>
<tr>
<td>Social</td>
<td>General management, Family satisfaction, Family preferences</td>
</tr>
<tr>
<td>Spiritual</td>
<td>Spiritual support, Value of life, Spiritual need</td>
</tr>
<tr>
<td>Cultural</td>
<td>Communication needs, Culturally sensitive care</td>
</tr>
<tr>
<td>End of life</td>
<td>Pain at end of life, Information at end of life, Death recognition, Peace at death</td>
</tr>
<tr>
<td>Ethical aspects</td>
<td>Respect, Insight into illness, Impaired capacity, Advance care planning, Patient preferences</td>
</tr>
</tbody>
</table>

Designing Sustainable Palliative Care: 2 Case Studies

Several organizations have been using innovative approaches to develop models of integration that incorporate knowledge from randomized trials as well as an understanding of local systems, culture, and stakeholders. Cancer Care Ontario (CCO; Toronto, Ontario, Canada) and Stanford Health Care (Palo Alto, California) are 2 case studies that offer strategies for integrating palliative care into cancer care beginning with routine screening and assessment. Both include efforts to define the roles and resources required for primary and specialist palliative care to accomplish this and manage the needs of patients and their families. CCO implemented a provincewide screening for symptoms, whereas Stanford Health Care is establishing value-based palliative care at a single academic medical center. Both are using a participatory, quality-improvement approach.

Cancer Care Ontario: Symptom Management

CCO, which is the provincial agency responsible for continually improving cancer services, launched the Provincial Palliative Care Integration Project (PPCIP) to improve care through systemwide screening, assessment, and management of cancer-related symptoms. CCO developed this quality-improvement initiative based on evidence that better symptom management and collaborative care “improves the patient experience across the cancer journey.” In the first iteration of the PPCIP, the Edmonton Symptom Assessment Scale (ESAS) was used to screen for physical and psychosocial symptoms, and toolkits were developed to facilitate follow-up assessment and symptom management. The project was pilot tested in 1 clinic, but it expanded throughout the province to include more than 25,000 symptom-intensity screenings. CCO established a consistent reporting mechanism, the Interactive System Assessment and Collection, which allowed regional cancer centers to track the success of ESAS as a tool and use patient data to inform treatment decisions. Interactive System Assessment and Collection is now embedded within electronic health records at 11 hospitals. It captures physical symptoms through ESAS and functional status using the Patient-Reported Functional Status tool.

In 2008, the results were publically reported and symptom screening became a quarterly performance indicator for each regional cancer care program. Survey results published in 2012 reported that 89% of patients thought ESAS was important to complete, 79% thought their health care professionals used the results to help formulate their care plan, and 78% reported that their symptoms had been controlled to a comfortable level. As the CCO initiative evolved, health care professionals outside of the initial PPCIP could view these results and request participation in the program. Participation increased from 6 hospitals in 2007 to 29 hospitals by 2013, and provincial screening has steadily increased, averaging 58% en route to their target of 70.

CCO provides a promising example of integrating at least 1 essential component of palliative care — symptom management — into oncology. It established a specific aim for symptom management, developed standard processes at the regional level, and created a transparent measurement system to track screening, symptom intensity, and functional status over time. In addition, it has normalized the integration of palliative care into routine cancer care from the point of diagnosis.

Stanford Health Care: Value-Based Palliative Care

In 2013, a patient with lymphoma receiving treatment at Stanford Health Care asked whether palliative care was supposed to be patient-centered. Indeed, the health care delivery model was not designed with a patient or family member in mind. The conversation prompted a design initiative at the Stanford Cancer Institute to improve quality of life for all 3 stakeholders — patients, their family members, and the health care team — by incorporating their values into the core processes and measures of palliative care delivery. This project is 1 component of the Stanford Cancer Institute Transformation Initiative, a joint project of the School of Medicine and Stanford Health Care to transform the experience of patients with cancer through comprehensive, coordinated, and compassionate care.

Stanford Health Care aims to routinely identify, assess, and manage the palliative care needs of patients and families from the point of diagnosis through survivorship and end of life. The institutional target is 100% screening for palliative care needs utilizing a global screening tool, the Patient Reported Outcomes Measurement Information System, which is a patient reporting tool that evaluates physical, emotional, social, spiritual, and functional needs. The hypothesis is that the primary oncology team can manage 50% of palliative care needs, and 50% will be referred to specialist services. Data will be gathered via electronic medical records of Stanford Health Care and will be documented on a dashboard visible to all stakeholders.

Stanford Health Care has engaged a diverse group (called the Core Innovation Team) of patients, family members, administrators, and physicians in oncology and palliative medicine to codesign strategies for primary and specialist palliative care. Baseline data to inform the work of the Core Innovation Team include interviews with patients and family members about their perceptions and knowledge of...
physicians to determine their understanding of palliative care, what components of palliative care they practiced, and when and how they integrated specialist palliative care. Physician values and goals were also assessed as well as how their own wellness might be improved in the context of their work.

An initial design session with the Core Innovation Team and several external stakeholders, including experts from health care consulting, marketing, and CCO, used the baseline data to identify high-impact areas for process improvement. Participants in the workshop defined quality of life as a key target from the outset and brainstormed how palliative care might promote improved quality of life for patients, families, and the health care team (Fig 3).

Similar to CCO, Stanford Health Care is utilizing rapid quality-improvement cycles to test new approaches. Solutions are selected based on feasibility and potential impact within the domains of primary, secondary, and specialist palliative care delivery (Table 3). Proposed solutions are being tested with disease-oriented, multidisciplinary practice teams (eg, gynecological oncology and hematology) before scaling across disease groups and the entire cancer center.

**Table 3. — Potential Solutions Being Piloted and Modified to Improve Quality-of-Life Care at Stanford Cancer Institute**

<table>
<thead>
<tr>
<th>Potential Solution</th>
<th>Description</th>
<th>Resources</th>
<th>Process</th>
<th>Education</th>
<th>Communicating Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two questions for quality of life</td>
<td>Oncologists are prompted to ask questions that help document goals and priorities in a patient’s health care plan.</td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>“What to expect” symptom management and transition tool series</td>
<td>Patients and family members are provided tailored symptom and adverse-event descriptions and management strategies at key stages along the care continuum.</td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>“Here when you need me” shadow and buddy system</td>
<td>Nurse navigators are paired with palliative care and oncology social workers for shadowing, communication role play, and ongoing “on-call” buddy support for complex needs.</td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Palliative Care Always (online course)</td>
<td>Oncology fellows, residents, nurse navigators, and social workers participate in a case-based, interactive course focused on patient experience, communication, and primary palliative competencies.</td>
<td></td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Standard screening, assessment, and referral</td>
<td>Oncology teams co-develop a standard screening process using the PROMIS global screening and referral algorithm for supportive services. Triggers are embedded to prompt discussion of PROMIS and potential specialist support. Focus is placed on social work as in-house support.</td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Specialist “hub” with triage support for noncurative needs</td>
<td>Specialist teams form a single service group and call center for complex needs. Screening, ad hoc oncology, and patient-initiated referrals are sent to the “hub” and connected with the appropriate specialist based on patient-centered referral criteria.</td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Core panel of quality metrics and reporting mechanism</td>
<td>Process and outcome measures for physical, emotional, spiritual, social, cultural, and ethical domains for quality of life are regularly reported to clinical teams, patients, and administration. Results help define future modifications.</td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

PROMIS = Patient Reported Outcomes Measurement Information System.

**Key Lessons for “Practical” Integration**

The PPCIP of CCO is one of the first of its kind to create a successful system for the real-time screening for palliative care needs. However, because of differences in culture and payment models, CCO’s processes must be modified to work within the US health care system. Thus, Stanford Health Care is
attempting to create a modified process by learning from CCO’s best practices and allowing areas for flexibility in order to maximize the likelihood of success within a different health care system. Both organizations share common strategies for integrating palliative care.

**Quality Improvement Strategy**

CCO and Stanford Health Care employ a structured, quality-improvement process to guide the integration of palliative care into the clinical workflow. CCO leadership coached regional teams in Canada to use the Institute for Healthcare Improvement’s model to create and test concepts that might “achieve significant results in quality and innovation”; the questions utilized appear in Fig 4.40

The central team at CCO and Stanford Health Care developed firm aims and target metrics (question 1 and 2; see Fig 4), and then local teams were given the flexibility to develop steps that could gain traction at their own institutions and lead to the desired improvements (question 3; see Fig 4).40 The teams test potential solutions using various cycles (see Fig 4) and visible, rapid reporting mechanisms to provide feedback to stakeholders.40 In the case of CCO, immediate data availability and visibility compelled additional hospitals to join the initiative.39 Reporting also revealed opportunities for improvement.33 Stanford Health Care is starting its program with limited test pilots with single clinical teams. Data will be reported back in real time to the physicians, thus allowing for rapid learning and refining of the initial care delivery prototypes.

**Screening Is Necessary But Insufficient**

Although a standardized process for screening is necessary, resources for assessment and management are also required. CCO created a symptom management toolkit with a mobile application as a resource for health care professionals. As the screening rate edges closer to the provincial target of 70%, symptom management of severe symptoms is still inadequate.38,39 For example, patients with severe pain do not always receive an opioid.39 Thus, CCO continues to work toward improved patient symptom assessment and treatment, including strategies to modify their reporting system, to better capture how clinical teams address severe symptoms, and further engage health care professionals.39 Stanford Health Care is harnessing these insights to establish an evidence-based process for screening and is also evaluating the assessment and management processes to ensure that palliative care needs are met.

**Stakeholder Engagement**

Physician engagement was a key strategy for CCO for managing process changes throughout Ontario.33 Regional and local teams recruited self-identified clinical champions who prioritized patient experience as a philosophy of care, and these champions participated in forums to assist the executive leadership with decisions about next steps for improved care delivery and evaluation.33 Stanford Health Care is also engaging physicians, patients, and families at every level of development and testing. Patient representatives are co-developing interventions and are involved in the implementation and evaluation. Stanford Health Care has taken this 1 step forward by ensuring that patients and families are also trained in leadership skills so as to more advocate for their needs during the process.
Conclusions

Although most US cancer centers report the existence of a palliative care program in their centers, palliative care remains limited to the inpatient setting in the majority of these centers. Even fewer centers have integrated practices, involve palliative care in tumor boards, or embedded educational opportunities. Barriers to integrated practice have been described and include knowledge and attitudes regarding palliative care, limited trained workforce, and lack of care and payment models that support early and regular palliative care. The early integration of palliative care into the treatment of patients with cancer is recommended.44-46

How best to integrate palliative care into cancer care is an area of active investigation and interest. Lessons from clinical trials, as well as examples from Cancer Care Ontario and Stanford Health Care, provide strategies for scalable integration.8-10,33,38,39 These strategies include:

- **Create reproducible outcomes with flexible structure:** Exact models for integration will evolve and vary by institution and patient population. However, even with model variability in care delivery, a consistent expectation is the early identification and assessment of palliative care needs for all patients with cancer, from the point of diagnosis through survivorship and end of life. Establishing this as a new standard of care will improve patient and family outcomes.

- **Start small and learn quickly:** Significant opportunity lies in the principles of quality improvement and rapid learning.37 Utilizing the Institute for Healthcare Improvement approach with a set aim, clear metrics, and rapid iterative cycles is feasible and necessary to create new and successful models for integration.

- **Leverage primary and specialist palliative care teams:** Understanding the role of primary teams for the provision of palliative care is critical for integrating palliative care into the continuum of cancer care. Providing education, training, and infrastructure to support the team’s role as palliative care providers is a promising strategy for meeting patient needs with a limited workforce. An interdisciplinary approach that includes social work and chaplaincy may further increase efficiencies in primary palliative care delivery in psychosocial and spiritual areas.

- **Measures matter:** Current metrics utilized in palliative care studies evaluate quality of care within a narrow framework primarily limited to quality of end-of-life care and assessment of mood and physical symptoms. The development of a broad range of metrics that align with the domains of palliative care (eg, decision-making, empowerment, connection) has the potential to demonstrate the anticipated increased value of integrated practice.

These strategies are a starting point for institutions and health care systems to begin their own processes for integrated care. This is crucial to improve quality of care for patients with a cancer diagnosis and their families. Routinely identifying palliative care needs early on and assessing such needs both have the potential to change the conversation between patients and health care professionals and create a health care paradigm in which the values of patients and their families come front and center in the delivery of cancer care.

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Quality-improvement collaborations will continue to grow in the field of palliative care.

Background: The measurement and reporting of the quality of care in the field of palliation has become a required task for many health care leaders and specialists in palliative care. Such efforts are aided when organizations collaborate together to share lessons learned.

Methods: The authors reviewed examples of quality-improvement collaborations in palliative care to understand the similarities, differences, and future directions of quality measurement and improvement strategies in the discipline.

Results: Three examples were identified that showed areas of robust and growing quality-improvement collaboration in the field of palliative care: the Global Palliative Care Quality Alliance, Palliative Care Quality Network, and Project Educate, Nurture, Advise, Before Life Ends. These efforts exemplify how shared-improvement activities can inform improved practice for organizations participating in collaboration.

Conclusions: National and regional collaboratives can be used to enhance the quality of palliative care and are important efforts to standardize and improve the delivery of palliative care for persons with serious illness, along with their friends, family, and caregivers.

Introduction
Over the last few years, use and acceptance of palliative care have been growing for the complex care and needs of patients with cancer and their loved ones. This reflects an increased understanding and acceptance of the care philosophy, the value of interdisciplinary teams that focus on the patient and his or her family as the unit of care, and the understanding that the goals of palliative care align with the priorities of all stakeholders. More patients are receiving palliative care because the scope of practice has expanded from community-based hospices to inpatient hospitals to the offices of primary care physicians, and the number of health care professionals seeking specialized continuing education and support to improve palliative care has increased. In parallel with this clinical growth,
collaborations to improve the quality of palliative care are also becoming more common, aiming to share data across sites and settings to translate quality improvement activities across the discipline.4

Quality-improvement collaborations aim to clarify how care is delivered and how care might be enhanced through realistic and sustainable interventions. The challenges to such collaborations vary by type and setting of practice, but capturing the diversity of care-delivery systems is paramount to understanding the variation of palliative care in settings, ranging from community-based organizations to large, academic medical centers. Collaborative initiatives to study the quality of care reflect our increasing reliance on data collection and analysis to understand broader patterns across health care, whether for program development, reimbursement, health services research, or quality assessment. Thus, this article will focus on 3 efforts to improve the quality of the delivery of palliative care at regional and national levels.

Global Palliative Care Quality Alliance

The Global Palliative Care Quality Alliance (GPCQA) is a novel, community/academic quality assessment and improvement collaboration for consultative palliative care that aims to:

• Collect data on the quality of care delivery using a standardized, point-of-care delivery approach
• Facilitate conversations between practices of all sizes and locations regarding challenges and sustainable solutions to improve care
• Use a Institute of Medicine–recommended rapid-learning health care approach to simultaneously inform clinical care, quality measurement, and outcomes research
• Monitor patients along the continuum of care
• Allow for benchmarking and sharing of best practices

The GPCQA originally began in 2007 as the Carolinas Consortium for Palliative Care. Realizing the need to test and adopt this model of quality improvement, its founders set out after initial planning in 2005 to establish an academic/community collaboration between Duke University (Durham, North Carolina) and community partners. The Carolinas Consortium for Palliative Care was originally composed of 5 sites throughout North Carolina: Duke University Medical Center (Durham) and 4 palliative care organizations, namely Four Seasons Compassion for Life (Flat Rock), Forsyth Palliative Care (Winston-Salem), Hospice of Wake and Horizons Palliative Care (Raleigh), and Charlotte Hospice and Palliative Care (Charlotte). Data from patients were collected by health care professionals near the point of care, entered into a local database, and intermittently transmitted to a centralized dataset maintained at Duke University for analysis and quality reporting. The information contributed to a growing data resource, the palliative care database (PCD), which is used for quality assessment and research purposes. From 2008 to 2011, a total of 6,957 unique patient data were collected. Data analyses also supported organizational, quality-improvement objectives and descriptive research about the population served by the Carolinas Consortium for Palliative Care, providing proof of concept that collecting data on quality is feasible in community settings and that these data can inform both clinical practice and institutional priorities in community-based palliative care.6 However, data collection processes were inefficient and the data collected did not always map to emerging quality measures. Further, a need exists to expand beyond the Carolinas to include partners from across the United States and the world so as to represent greater diversity in practice and patient needs. A contemporary-based solution was needed that could be electronically implemented in various institutions outside the region.7

In 2012, the Quality Data Collection Tool (QDACT) for palliative care was created, leveraging an iterative design in which modular components could be changed as quality measures in palliative care evolved. To develop a quality-assessment tool applicable to everyday practice, 6 steps were involved.

The first step was to review the experiences from participants of the PCD project.6 This proof-of-concept pilot confirmed that collecting data on quality was feasible in community settings.5

The second step was to perform a systematic review of all published quality measures relevant to palliative care, supportive oncology, and end-of-life care to identify measures from which the Consortium could choose to establish priorities for assessment.8

The third step was to develop a list of validated tools from a literature review that would inform these quality measures. We aimed to incorporate tools familiar to palliative care providers, when available, like the Palliative Performance Scale. In some instances, the Carolinas Consortium for Palliative Care added metrics and associated data elements based on group consensus.

The fourth step involved developing QDACT, an instrument that demonstrated scalability across expected future changes in the collection and sharing of data relating to palliative care. Electronic health systems and platforms for collecting data evolve and change, so it was important that the tool be generic and operable on different — rather than specific — operating systems, computer hardware, or Internet platforms and be compatible with diverse information technology resources used by palliative care programs nationwide. This process included the development of a data dictionary to support the quality measures.

The fifth step was to test the entire process, from
data collection to transmission, storage, analysis, and management; in addition, the process was tested to ensure that it conformed to the highest data security standards for protected health information, including those of the Health Insurance Portability and Accountability Act. This included thorough understanding of the challenges to data security that stem from both hardware and software used at the point of care as well as the potential risks of transmitting data over diverse networks to a shared database.

The sixth step was to expand the project and test its usability on a national scale.

The Carolinas Consortium for Palliative Care was renamed GPCQA in 2014, and it has 14 members who represent community and academic settings and span outpatient and inpatient palliative care programs. Reporting on quality metrics is performed each quarter for all sites, with a feedback loop to improve graphics and visual features. More than 33,000 patient encounters are represented in the database. The quality reporting has been used to support grant funding, to demonstrate the value of palliative care to hospitals and partnering organizations, to understand the patient population served at each participating institution, and to inform quality-improvement projects.

QDACT displays real-time, immediate feedback via a color-coded alert system while having built-in logic to help inform clinical decisions while health care professionals enter data. For example, a color-coded system reflects whether responses meet an alarm threshold, which is an evidence- or consensus-based parameter (e.g., pain score > 4 out of 10). At that point, a screen opens to prompt the user to input what treatments have been offered, if any, and a list of available evidence-based options are displayed. In this example, the alert color (red) will remain present until the pain is brought below the threshold. Other aggregate reports include longitudinal summaries customizable to the health care professional and his or her organization. Members of the GPCQA can request reports that provide both numerical and graphical presentations of descriptive statistics on patient needs, conformance to quality measures, comparative performance between reporting levels, and longitudinal changes. Reports under development include those aligned to national quality measurement initiatives (e.g., National Quality Forum, American Academy of Hospice and Palliative Medicine’s Measuring What Matters, Physician Quality Reporting Structure), financial projections, and cost-avoidance reports.

This infrastructure has been used to conduct several quality-improvement projects. One project simultaneously measured and assessed adherence to quality measures for timely assessment and management of pain, dyspnea, and constipation. Using reports tailored to the performance of individual health care professionals along with peer-related benchmarks, and then confidentially sharing those reports with those health care professionals, we observed an improvement of the timely management of these 3 important symptoms to levels above 95%. Longitudinal data collection will inform whether these results are long lasting.

Another quality-improvement project involved assessing spirituality and existential distress during the first palliative care visit in all care settings. Using a goal of more than 75% for the completion of the spiritual assessment, the results of the project demonstrated 80% compliance with completing the spirituality question across all of the providers within the GPCQA.

The GPCQA is also looking to expand its membership. Further plans include customized modular build-outs as part of QDACT, expansion of reporting features, integration with electronic health records (EHRs), introduction of a mobile application, and features that enable programs to pull data directly from the software platform. As the landscape of quality measure reporting increases in an era of value-based health care delivery, the GPCQA will look to continuously evolve its efforts to minimize the burden of data collection by health care professionals while maximizing the return on investment to health care professionals through reports, information to support program growth and sustainability, and financial benefits that reward health care professionals for actively promoting a culture of quality assessment and improvement.

**Palliative Care Quality Network**

The Palliative Care Quality Network (PCQN) is a continuous learning collaborative committed to improving the quality of palliative care services provided to patients and their families. The PCQN was established in 2009 by 20 established palliative care services in California with a shared vision for improving the quality and value of care. The PCQN developed a core dataset that includes care processes (e.g., psychosocial assessments) and patient level outcomes (e.g., symptom scores) that all members collect on every patient visit. Data are entered into the secure, web-based PCQN database that analyzes data and produces custom reports in real time for individual teams, with comparisons to the entire PCQN. PCQN data allow for coordinated, quality-improvement projects, benchmarking, and the identification of best practices.

The PCQN is composed of 34 palliative care teams from hospitals across the United States and includes community, academic, and public institutions. To date, 19 palliative care teams collect and submit data to the PCQN database and use those data to monitor and improve care. The PCQN database includes more than 13,000 patient encounters.

An important goal of the PCQN is to create and foster a professional community that contributes to the
growth and sustainability of palliative care teams and the professional development of the health care professionals that staff them. The PCQN achieves this goal by providing education in clinical care, leadership, team dynamics, and self-care, creating a forum for members to share successful strategies, offering a software program to calculate the financial impact of palliative care at each institution, and establishing a supportive network of like-minded health care professionals.

Guided by the goals of the prospective collection of operational and clinical outcomes data to support real-time patient care and quality improvement, efficiency, and adherence to national guidelines, including the NCP and NQF, the PCQN undertook a modified Delphi process to develop the PCQN core dataset. Overall, the 20 founding palliative care service members collected 96 unique data elements. Through a survey of all members, the PCQN identified 48 “must collect” elements. The PCQN data committee evaluated these elements against published preferred practices to create a 23-item core dataset that includes demographics, processes of care, and patient-level clinical outcomes, including daily symptom scores. The data committee also created a data dictionary to define each data element to ensure consistency across health care professionals and care sites.

A key goal of the PCQN was that the database would include all data that teams needed to collect; no PCQN member would need to maintain a secondary database. To that end, the PCQN adopted optional data elements requested by individual teams for monitoring care at their site. To date, the PCQN has added 22 optional data elements.

The PCQN then developed a secure, web-based database for convenient data entry. PCQN members directly enter data at the point of care into any Internet-connected device or on paper for later data entry. Teams can also collect PCQN data in the EHR, download those data to a spreadsheet file and then upload the file to the PCQN. When data are entered into the PCQN database, they are included in analyses.

The PCQN is collaborating with teams using several EHR platforms to fully integrate the collection of these data. Each member organization owns its data and can download all of the data at any time to a spreadsheet. Data are confidential; only member organizations know which data are theirs.

The PCQN database performs analyses that compare data from the entire network. Members can generate 4 types of summary reports in real time, including reports on demographics, processes of care, disposition and length of stay, and symptoms. Trend reports of data over time and member-comparison reports show the data of the member organization highlighted alongside the unidentified data of the other member organizations. The PCQN is also creating reports that will allow members to compare themselves with others in their health care system. In addition, members can submit information about the structure of their team and characteristics of their institution to compare themselves with similar teams as well as to the entire database.

The PCQN database also produces reports on data completeness and identifies missing data so that members can monitor data-collection efforts. PCQN data align with the Measuring What Matters measures of the American Academy of Hospice and Palliative Medicine/Hospice and Palliative Nurses Association have been used by members to achieve The Joint Commission advanced certification in palliative care.

The PCQN has developed a financial software program, CaseMaker PCS (San Francisco, California), to calculate the financial outcomes of palliative care at each member institution. CaseMaker PCS combines PCQN data with financial data supplied by member institutions to produce an editable summary of the financial impact of the palliative care team’s work. Combined with outcomes data demonstrating quality and comparative data on team composition, the financial analysis information provides palliative care teams information needed to demonstrate value and proof for sustaining and growing their service.

A PCQN quality-improvement collaborative was launched in 2014 with the goals of providing education in quality-improvement methods and using PCQN data to drive coordinated quality-improvement projects. Through quality-improvement workshops at biannual conferences, monthly conference calls, and ongoing mentoring, teams in the collaborative share strategies, challenges, and successes to advance a quality-improvement project. Nine PCQN teams are participating in the first PCQN quality-improvement project, which is focused on improving pain management (a patient-reported outcome).

PCQN data show that, at baseline, 69% (range, 62%–80%) of patients with moderate or severe pain on the day of their initial palliative care assessment had an improvement in their pain by the second palliative care assessment, but only when that assessment occurred within 72 hours of the first. Through the quality-improvement collaborative, participants have identified and tested a number of strategies aimed at improving pain management, including seeing patients with pain early in the day, contacting primary teams and nurses with recommendations or new orders immediately after seeing a patient in pain, and conducting follow-up visits in the afternoon to reassess pain and amend recommendations or orders. Members are monitoring these processes as well as their associated daily pain scores to determine the success of each test of change.

To date, improvements have been difficult to
achieve, but the variation in performance is helping to identify additional targets, including the value of addressing anxiety in patients with pain, and the project is ongoing. Members with better outcomes share strategies with others on each monthly conference call, struggling members are provided ideas about how to overcome stumbling blocks, and regular calls motivate all members to keep the project active and advancing.

Satisfaction with the quality-improvement collaborative is high, with 82% of respondents agreeing that their participation motivated their member organization to engage in quality improvement, and 83% indicating that they were interested in continuing their participation in the quality-improvement collaborative.

The PCQN is growing and is inviting additional palliative care teams to join. The more members, the greater the capacity to benchmark with like hospitals to determine with greater precision which structures and processes of care are associated with better outcomes. The PCQN is developing outpatient and home-based palliative care datasets to link with the existing PCQN database, allowing members to monitor and improve care across settings and over time. The PCQN is also working with vendors of EHRs to create systems for quality data collection within the EHR to be submitted to the PCQN database. The PCQN continues to refine its approach to quality improvement and will engage in additional quality-improvement projects involving more teams.

Improving palliative care is a key goal and, thus, a broad dissemination of effective strategies to improve care is a major focus of PCQN going forward. The PCQN is partnering with other organizations and quality initiatives within and outside of palliative care, including the GPCQA, to improve the quality of care across the field, with the mission of transforming health care by defining and promoting quality palliative care.

**Project Educate, Nurture, Advise, Before Life Ends**

Project Educate, Nurture, Advise, Before Life Ends (ENABLE) is an evidence-based, telehealth, upstream, palliative care model designed to improve care and quality of life for persons with newly diagnosed advanced cancer. First developed in 1999 as a demonstration project through the Robert Wood Johnson Foundation, Project ENABLE has undergone efficacy and effectiveness testing through 2 randomized controlled trials funded by the National Institutes of Health. Because of its demonstrated benefits to patient quality of life, symptoms, mood, rates of survival, and to family caregiver depression and burden, Project ENABLE is a scalable model of care. The project was developed and tested in primarily rural, community-based cancer practices; however, little guidance exists on how community cancer centers can integrate this model of early concurrent palliative care alongside standard, curative cancer therapies.

In 2013, through a research scholar grant from the American Cancer Society, we embarked on a 4-year dissemination/implementation project using a virtual-learning collaborative approach in 4 racially diverse settings. The project goals were to:

- Assess current palliative care practices and prepare for organizational/health care system change
- Tailor and implement the evidence-based, concurrent, palliative care model of Project ENABLE
- Use the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework to assess outcomes associated with health care institutions, patients and caregivers, and costs before and after implementation of the model

We chose a virtual-learning collaborative approach for 3 reasons because we wanted to increase access to nationwide sites in predominantly rural areas, examine the effectiveness and scalability of this model in racially and ethnically diverse settings, and modify and hone implementation strategies for future dissemination of the program. In addition, we chose RE-AIM because it is a well-tested framework to evaluate the impact of new public health programs.

The first step was to establish working relationships and procedures to launch a virtual collaborative between the School of Nursing at the University of Alabama at Birmingham, which was the coordinating center, and the 4 sites (Gibs Cancer Center [Spartanburg, South Carolina], Mitchel Cancer Center [Mobile, Alabama], Birmingham Veterans Administration Medical Center [Birmingham], and the Department of Gynecologic Oncology, Wallace Tumor Institute, University of Alabama at Birmingham). Over the last 2 years, the teams at each institution met every 2 weeks as a group with the coordinating center via video conferencing using an online learning platform. During the intervening weeks, the coordinating center team met to troubleshoot, develop, and refine processes.

Early steps included defining the essential elements of the Project ENABLE model and working with individual sites to tailor the model’s elements to specific institutional cultures and resources. Through dialogue and consensus with sites, we also established implementation measures guided by the RE-AIM framework. However, because RE-AIM was not previously used in the setting of palliative care or oncology, time was spent adapting the RE-AIM framework to suit our model and the population of newly diagnosed patients with advanced cancer and their caregivers.

To measure the capacity of organizational characteristics to implement and sustain Project ENABLE, we adapted the General Organizational Index scale. Data collection included a survey to measure the per-
ceptions of oncologists about early and concurrent palliative care, a tool to examine implementation costs, and a battery of patient and caregiver self-report measures similar to those used in our prior randomized controlled trials.11,12 Mixed methods were used to collect data, including in-person site visit interviews, web-based surveys, and phone interviews.

We have experienced challenges and successes related to the implementation of this model, and we have learned lessons along the way. For example, each site received a small yearly stipend to offset some initial implementation costs (eg, developing materials, fees related to Institutional Review Boards, salary support for conducting the program), but this stipend was not intended to fully support a new program. As such, institutions have had to envision strategies for supporting their programs beyond the grant period.

As a result of changes in institutional leadership, 2 sites were unable to continue and the 2 replacement sites had to quickly acclimate to the model during the planning year. Implementation studies are uncommon to many Institutional Review Boards, so there were many delays prior to acquiring Institutional Review Board approval in the 4 diverse community institutions (including 1 Veterans Administration medical center).19 One success included 2 functioning programs that introduced potentially sustainable models of early palliative care concurrent with standard cancer treatment, thus increasing access, as was defined in the original project aims. Another success was identifying promising implementation strategies (guided by the RE-AIM framework) for developing new palliative care programs. The important lessons learned, such as institutional barriers and facilitators of implementation, will serve as a foundation for future progress.

Our future goals within the context of this project are to refine all processes and measures to create a toolkit that could be used by other centers wishing to implement an early palliative care model, either in settings with existing palliative care teams without an outpatient or home-/community-based component or within systems without a functional palliative care model. In addition, we will use the current model and methods as pilot data for a larger implementation grant within an established practice network, such as across the US Veterans Administration health care systems, the Deep South Network for Cancer Control, or a research network such as the Palliative Care Research Cooperative Group.

**Discussion**

Quality-improvement initiatives reflect the natural evolution of the evidence base in palliative care. Use of palliative care has grown in the last decade, with its roots beginning in the hospice movement in the late 1970s. A defined subspecialty field, with an evidence base for practice that improves daily palliative care, should use implementation and dissemination approaches that routinely include elements of quality measurement (often with validated measurement tools). Federated database systems facilitate the simultaneous examination of both quality and research questions. Administrators, health care professionals, and researchers are beginning to recognize that robust data analytics are crucial for improving patient- and family-centered advanced illness care.

The 3 quality-improvement and dissemination efforts reviewed in this article all use a conceptual model of quality improvement in palliative care to guide their approach, highlighting the importance of collecting uniform data. For example, all 3 efforts require participants to use a federated set of primary data elements defined by a common database dictionary as part of the validated collection metrics. Given the variety of practice settings, clinician types, and stages of disease process represented, this allows for uniformity and interoperability that ensures that data can be aggregated, compared, and analyzed in the future to better characterize palliative care.

One significant, ongoing challenge for new and existing quality-improvement initiatives is how to make the effort as invisible and integrated as possible amid the fabric of usual clinical operations. As the GPCQA has found, the dual-entry of data elements — once into the EHR for clinical purposes, and once into a registry for aggregation and reporting — is a significant barrier to health care professional buy-in and effectiveness. The seamless integration of validated, quality metric data collection into EHRs is ideal but has major cost and time implications. However, overcoming these barriers is crucial to allow for increasingly robust reporting of data, which can then be used to aid palliative care program development, sustainability, and growth.

**Future Directions**

Quality-improvement collaborations are expected to continue to grow in the field of palliative care. For established efforts such as the 3 described in this article, this growth will manifest as a focus on how to sustain the initiative in terms of mutually beneficial outcomes, continued innovation, and financial viability. In turn, sustainability will allow for additional innovation, such as developing quality-improvement initiatives focused on patient-reported outcomes and caregiver outcomes. Programs may join forces and align with other initiatives to allow for larger learning networks and more robust data. By contrast, small, issue-specific collaborations may develop where practices are less unified, such as when palliative care is incorporated into alternative payment model structures (eg, medical homes, accountable care or-
oganizations). Similarly, local efforts may develop among health care professionals in a single region so that a single patient’s trajectory can be tracked — and quality of palliative care improved — across multiple care transitions and health care systems. As the push for meaningful use and interoperability of electronic health records continues, uniform and secure data collection and sharing (per the requirements of the Health Insurance Portability and Accountability Act) should continue to improve.

Conclusions
Health care leaders and those specializing in palliative care are faced with the challenge of providing consistent, high-quality care that meets the needs of patients and their family, friends, and caregivers. This challenge can be aided by belonging to a community of like-minded leaders focused on cooperative efforts to define, measure, and improve the quality of palliative care delivery. Clinical palliative care is a collaborative effort, so alliances and networks of engaged health care leaders and physicians are needed to prioritize the care processes that consistently improve the experiences of patients with serious illnesses.

Acknowledgment: The authors would like to recognize the dedication of our colleague clinicians and patients who make this work possible.

References
A systematic approach to managing symptoms related to advanced oncological illness can improve patient quality of life and lessen distress.

Palliative Pharmacotherapy: State-of-the-Art Management of Symptoms in Patients With Cancer

Eric E. Prommer, MD

**Background:** Advanced cancer produces multiple symptoms as patients progress through their disease trajectory. Identifying, measuring, and providing therapy for uncontrolled symptoms becomes important because disease-altering therapies may be no longer possible. Symptoms other than pain that cause distress in patients with cancer include delirium, dyspnea, anorexia, nausea, and fatigue. Precise management of these symptoms can lead to the best possible quality of life and lessen distress. This article reviews current management strategies of these symptoms.

**Methods:** The epidemiology, mechanisms, assessment, and therapies of common symptoms in the advanced cancer population are reviewed.

**Results:** Identifiable approaches facilitate symptom management in advanced illness.

**Conclusions:** Using a systematic approach to symptoms in advanced illness can improve the quality of life and lessen distress among patients with cancer and their families, friends, and caregivers.

**Delirium**

Delirium is a clinical emergency characterized by changes in consciousness, hallucinations, and changes in the sleep–wake cycle and language. Delirium is a frequent event in patients with advanced cancer, and factors predisposing patients with advanced cancer include drugs, infection, brain metastasis, and underlying dementia. Delirium differs from dementia in that dementia does not have acute alterations in consciousness. Delirium is classified according to level of agitation; for example, a patient who is agitated has hyperactive delirium and a patient who is withdrawn and somnolent has hypoactive delirium. Patients usually have mixed features. Prevalence rates for delirium range from 30% to 50% for hospitalized patients and is typical in the hours or days before death. Experiencing delirium is likely to cause distress in families. Patients who are delirious are unable to communicate levels of pain or other symptoms and cannot take part in health care decisions. Although delirium is often a harbinger of a poor prognosis, it is reversible in 50% of cases. Health care professionals use nonpharmacological as well as pharmacological interventions to treat delirium. Nonpharmacological approaches to delirium include using clocks to show the time, lighting the room, and frequent reorientation, whereas pharmacological interventions may include the use of antipsychotic medications, which can be used to palliate...
patients who are agitated (hyperactive delirium) as well as those experiencing hallucinations regardless of agitation level.

**Mechanisms**

Delirium results from underlying disorders that cause imbalances in brain neurotransmitters. Neurotransmitters involved in delirium include dopamine, glutamate, norepinephrine, acetylcholine, γ-aminobutyric acid, and serotonin. Cytokines (interleukin [IL]-1, IL-2, tumor necrosis factor [TNF], interferon) produced by the immune system, the tumor, or cancer treatment may mediate central nervous system effects, such as somnolence, agitation, and cognitive failure. Drug therapies for delirium target imbalances in neurotransmitters, which may play a role in developing delirium.

**Assessment**

A history of the patient’s baseline mental status prior to symptom onset should be obtained from his or her family, caregivers, or both parties. Fluctuating consciousness is the hallmark of delirium. Assessment tools can screen or rate delirium or do both. Commonly used tools include those for screening (Mini Mental State Examination, Confusion Assessment Method) or rating of severity (Memorial Delirium Assessment Scale, Disability Rating Scale). Some instruments will address more than 1 goal. Other important considerations are time constraints, the level of expertise and training of the investigator (the Mini Mental State Examination requires none), and constraints of the patient (eg, patient in the intensive care unit).

**Management**

**Nonpharmacological:** Identification of reversible causes is important. Investigations should be tailored to each individual patient’s goals of care because 50% of cases of delirium may be reversible. Health care professionals must look for infection, dehydration, and drug and metabolic abnormalities as potentially reversible causes of delirium. Patients with cancer should be evaluated for central nervous system metastasis. It is worth noting that fecal impaction and urinary tract infection are often overlooked as causes of delirium. Common drugs linked to delirium include opioids, anticholinergics, benzodiazepines steroids, and select chemotherapy agents. Inquiring about alcohol intake is prudent because alcohol withdrawal can precipitate delirium and responds to benzodiazepines. Nonpharmacological approaches to delirium include keeping room lights on, having calendars and pictures at the bedside, frequent redirection, and allowing patients to participate in their care.

**Pharmacological:** Antipsychotic drugs are the primary therapy for all forms of delirium, in particular hyperactive and mixed delirium. Table 1 reviews common agents used for delirium. Haloperidol remains the gold standard despite a paucity of clinical trials. Severity of delirium and patient age are both important considerations for dosing. In elderly patients (aged ≥ 60 years) and in patients with mild to moderate agitation, Canadian guidelines suggest that haloperidol be started at low doses (ie, 0.5 mg orally 2–3 times a day) and then be titrated to obtain an effect. Severe cases and younger patients may require more haloperidol, and, in severely agitated patients, rapid dosing is required. In this setting, parenteral doses are recommended and haloperidol doses such as 1 to 2 mg in young patients and 0.25 to 0.5 mg in elderly patients, repeated every 1 to 2 hours until the agitation resolves; protocols for rapid titration are available. Haloperidol is the least sedating of the antipsychotic class and can be intravenously or orally given.

Atypical antipsychotics may also be useful because they are less likely to cause extrapyramidal symptoms and have less potential for effects on cardiac conduction; however, these antipsychotics cannot be given via the parenteral route. Commonly used atypical antipsychotics include olanzapine, quetiapine, and risperidone. These types of antipsychotics are also appropriate for patients with underlying Parkinson disease. Benzodiazepines are not indicated for the management of delirium and are best used in the setting of de-

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**Table 1. — Common Drugs for Pharmacological Management of Delirium**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Adverse Events</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol</td>
<td>0.5 mg orally 2–3 times a day</td>
<td>Acute extrapyramidal events (eg, torticollis, oculogyric crisis, tongue and laryngeal spasm)</td>
<td>Mild to moderately agitated elderly patients</td>
</tr>
<tr>
<td></td>
<td>1–2 mg intravenous/subcutaneous every 30 min to 1 h until agitation resolved</td>
<td></td>
<td>Severe agitation in patients aged &lt; 60 y</td>
</tr>
<tr>
<td>Risperidone</td>
<td>1 mg orally each day or every other day</td>
<td>QT interval and cardiac arrhythmia</td>
<td>Potent dopamine blocker</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2.5–11 mg daily</td>
<td>QT interval and cardiac arrhythmia</td>
<td>Very anticholinergic</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>25–75 mg orally every day</td>
<td>QT interval and cardiac arrhythmia</td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>0.5–1 mg subcutaneous</td>
<td></td>
<td>Do not use alone Useful for severe agitation in conjunction with haloperidol</td>
</tr>
</tbody>
</table>

Information from reference 13.
Lirium associated with alcohol withdrawal. Benzodiazepines can be added to haloperidol when agitation does not respond to haloperidol alone.

**Chronic Nausea and Vomiting Unrelated to Chemotherapy**

Nausea and vomiting affects up to 70% of patients with advanced cancer; however, nausea is more common. Chronic nausea is defined as nausea that lasting more than 1 week without an identifiable precipitant, and its causes include underlying cancer and its progressive effects as well as medication use (eg, opioids).

**Mechanisms**

The nausea and vomiting reflex is governed by nuclei in the medulla. The nucleus tractus solitarius receives input from multiple sites, and then relays to the dorsal motor nucleus of the vagus to cause vomiting. Afferent input comes from the chemoreceptor trigger zone, vagus nerve, cortex, and vestibular pathways. Neurotransmitters populate these areas critical to the emetic reflex and include dopamine, serotonin, histamine, substance P, and acetylcholine. Blocking these neurotransmitters forms the basis for antiemetic therapy.

**Assessment**

Health care professionals should gather information about duration, frequency of vomiting episodes, and the ability of the patient to keep fluids down — all of which may affect the route of drug administration. Delayed nausea and vomiting due to chemotherapy should be considered. Large-volume emesis suggests gastric or bowel obstruction, whereas polydipsia, polyuria, and cognitive changes suggest metabolic causes. Health care professionals should inquire about the presence of constipation, which can also cause nausea. Mood should be assessed. Physical examination findings may provide clues. Papilledema suggests brain metastasis, whereas orthostatic changes suggest autonomic insufficiency. Numerical rating scales can be used to measure the severity of nausea.

**Management**

Recommendations support either antiemetic therapy based on proposed pathophysiology or a sequential trial of antiemetics. Response rates near 80% with these approaches. Table 2 lists select antiemetics that can be used in patients with advanced illness. Operative approaches are considered in cases of mechanical bowel obstruction. However, consideration for surgical interventions should be individualized, with health care professionals weighing the risks and benefits of the procedure. Use of acupuncture to treat nausea and vomiting in advanced illness has not been evaluated.

**Dyspnea**

Dyspnea is the uncomfortable awareness of breathing, and it is a frequent symptom in advanced illness with prognostic importance. The prevalence of dyspnea is between 20% and 80% in patients with advanced cancer. It has been described in various ways, including as air hunger, suffocation, and choking. Health care professionals typically have differing perspectives on dyspnea, and they often under-rate it as a symptom.

**Mechanisms**

Peripheral receptors involved in breathing play a role in the perception of dyspnea. Excessive input from receptors sensing oxygen and carbon dioxide levels contribute to dyspnea. The overactivity of mechano-receptors and respiratory muscle as well as lung and chest-wall receptors all contribute to the sensation of dyspnea. These receptors likely also stimulate the cortex, thus influencing cortical perception.

**Assessment**

Many tools exist to measure breathlessness, but few

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Route</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butyrophenone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.5–2.0 mg every 4–6 h</td>
<td>Intravenous</td>
<td>Useful with associated delirium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subcutaneous</td>
<td></td>
</tr>
<tr>
<td>Substituted Benzamide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>10 mg every 6 h</td>
<td>Intravenous</td>
<td>Prokinetic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Subcutaneous</td>
<td></td>
</tr>
<tr>
<td>Antihistamine</td>
<td></td>
<td></td>
<td>For vestibular component</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dronabinol</td>
<td>5 mg/m² every 6 h</td>
<td>Oral</td>
<td>Very long half-life (≤ 56 h)</td>
</tr>
<tr>
<td>Nabilone</td>
<td>1–2 mg twice daily</td>
<td>Oral</td>
<td>2-h half-life Not detected on urine testing</td>
</tr>
<tr>
<td>Glucocorticoid</td>
<td>Brain metastasis: 4–6 mg every 6 h</td>
<td>Intravenous</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>Atypical Antipsychotic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>2.5–7.5 mg daily</td>
<td>Oral</td>
<td>Single daily dose May require another antiemetic for breakthrough emesis</td>
</tr>
</tbody>
</table>

Information from reference 21.
cancer-specific tools exist; however, one such tool is the Lung Cancer Symptom Scale, and a scale, such as the visual analog scale, numerical pain scale, or cancer-specific tool, is recommended.32,33

**Management**

In advanced illness, treatment should focus on comfort and should include assessment of overall patient distress and work of breathing. Reversible causes of dyspnea and their treatment should be in keeping with the individual patient's goals of care.

**Oxygen Therapy:** Oxygen therapy can benefit patients with chronic obstructive pulmonary disease and hypoxia in domains such as exercise capacity, cognitive function, and survival; however, its benefits are not clear in the oncology setting.34 Oftentimes, patients with cancer are dyspneic but not hypoxemic. Randomized controlled trials have compared oxygen therapy with room air for relief of dyspnea.35,36 The results of 2 studies suggested that those with cancer who were hypoxemic on room air benefited from oxygen, and the results of another study showed that oxygen did not benefit those with cancer experiencing dyspnea who were not hypoxemic.36,37

**Opioids:** Opioids are the preferred treatment for refractory dyspnea, and patients typically benefit from oral or parenteral opioids.38 Sustained-release formulations are effective.39 All opioids as a class are effective for dyspnea because they decrease the perception of breathlessness. Results from a meta-analysis of 9 small, randomized studies (116 study patients) and 1 randomized crossover trial (48 study outpatients) showed that systemic opioids reduced mean chronic breathlessness by approximately 20% over baseline.40 No evidence suggests that nebulized opioids are effective.41

**Benzodiazepines:** Benzodiazepines are used for dyspnea and to relieve anxiety.42 Results from a meta-analysis of 7 studies (200 study patients) found that benzodiazepines did not relieve breathlessness and instead increased the risk of drowsiness; however, the studies were heterogeneous and the sample sizes were small.43 One controlled trial found that adding subcutaneous midazolam to an opioid enhanced dyspnea relief in patients with advanced cancer.44

**Antidepressants:** Current evidence for the use of antidepressants to decrease breathlessness is inconsistent.45

**Saline:** A randomized, single-blinded trial of 40 people with an exacerbation of chronic obstructive pulmonary disease showed no consistent relief of breathlessness from nebulized, isotonic saline compared with placebo.46

**Furosemide:** Exploratory studies are conflicting regarding the efficacy of inhaled furosemide on breathlessness.47 Thus, the level of efficacy of furosemide in this patient population requires confirmation in larger clinical trials.

**Cancer Anorexia/Cachexia**

Cancer anorexia/cachexia is defined as “a multifactorial syndrome defined by ongoing loss of skeletal mass (with or without loss of fat) that cannot be reversed by conventional nutritional support and leads to progressive functional impairment.”48 A cluster of symptoms characterizes the syndrome and includes weakness, early satiety, and anorexia.48 Criteria for diagnosing cachexia in patients with cancer are: weight loss of more than 5% in 6 months (in the absence of starvation), body mass index below 20 kg/m², and any degree of weight loss of more than 2% or appendicular skeletal muscle index consisting of sarcopenia (men: < 7.26 kg/m²; women: < 5.45 kg/m²).49 It has 3 stages: precachexia, cachexia, and refractory cachexia. The syndrome occurs in 50% of patients with cancer (many various types).49

Associated complications include poor performance status, poor quality of life, decreased survival, and poor response and tolerability to chemotherapy.48-50 Anorexia frequently accompanies the syndrome.51 Patients may manifest decreased muscle mass and decreased strength, and they may experience fluctuations in resting energy expenditure and increased psychosocial distress.52 Both lean body mass and muscle strength, as measured by handgrip strength, are predictive of survival and quality of life.53

Cancer anorexia/cachexia limits therapeutic options.54 Weight loss correlates with treatment toxicity, poor tumor response, and lower chemotherapy response rates.55 Loss of more than 10% of premorbid weight before chemotherapy predicts death and is independent of disease stage, tumor histology, and performance status.55 Anorexia is also a powerful predictor of early death, and this observation persists even after adjusting for several other prognostic parameters.56 Thus, both weight loss and anorexia predict poor prognosis for patients with advanced cancer.

**Mechanisms**

The mechanisms leading to the development of cancer anorexia/cachexia are not fully understood. Anorexia/cachexia results from abnormal host responses to cancer, and the syndrome appears to result from the interplay between tumor byproducts and host cytokine response.57,58 In animal studies, targeting cytokines with monoclonal antibodies relieves cachexia.59 The interplay between tumor byproducts and inflammatory mediators creates acute-phase proteins in the liver, and this, in turn, leads to the breakdown of muscle protein, lipolysis of fat, insulin resistance, and an elevated level of triglycerides.51 Inflammatory mediators enter the hypothalamus,
which is where they mimic anorexigenic neurotransmitters and cause anorexia.60

Assessment

Tools measuring cancer anorexia/cachexia include the Edmonton Symptom Assessment System, Bristol Meyers Anorexia/Cachexia Recovery Instrument, Patient Generated Global Assessment Instrument, and the cancer anorexia/cachexia subdomain of the Functional Assessment of Anorexia/Cachexia Therapy questionnaire.61-63 Clinical tools useful for assessment cancer anorexia/cachexia include weight, midarm circumference, and hand grip.61 It is worth noting that mid-arm circumference has prognostic value.64 Optimal methodology to assess muscle mass has not yet been determined. Computed tomography, dual energy x-ray imaging, and bioimpedance can all be used to measure muscle mass.48 Whole-body impedance and electro conductivity are based on the principle that lean tissue conducts electricity better than fat.

Management

Secondary reasons for weight loss should be addressed or ruled out. Health care professionals should look for nausea, constipation, taste alteration, depression, dyspnea, and deconditioning as possible causes. Other important patient factors contributing to cancer anorexia/cachexia include dry mouth, difficulty swallowing, any alteration in sense of smell, early satiety, mouth sores, dental issues, and anxiety.

Nutritional Support: Nutritional support early on is important and can include dietary advice, nutritional supplements, and consideration of an enteral diet. Dietitians may recommend foods tailored to preference, portions, and an individual patient’s ability to swallow. Pungent foods should be avoided. It is not clear whether nutritional supplements reverse weight loss and decline in quality of life.65

Psychosocial Intervention: Psychosocial interventions are important because patients and their friends, families, and caregivers may be experiencing distress. Information, support, and clinician interactions with the patient and his or her friends, family, and caregiver can help mitigate such distress.

Pharmacologic Intervention

Megestrol: Megestrol acetate has long been an option for cancer anorexia/cachexia.66 Results of the initial study (and subsequent studies) showed significant improvement over placebo with respect to appetite, nausea, weight gain, and food intake (megestrol acetate 800 mg/day).67 Bruera et al68 conducted a 15-day, blinded, placebo-controlled, crossover trial of megestrol acetate 480 mg/day and found statistically significant improvements in caloric intake, appetite, and weight gain among the study participants. Results of a meta-analysis that included 3,500 participants and 25 clinical trials comparing megestrol acetate with steroids, nandrolone, eicosapentanoic acid, and dronabinol suggested consistent improvement in appetite, weight gain, and quality of life.69 Megestrol acetate improves appetite and weight gain in approximately 30% of patients.69 The numbers of patients needed to treat are 8 patients for weight gain and 3 patients for anorexia.69 Megestrol acetate benefits patients with HIV/AIDS and geriatric cachexia.70,71 Adverse events that occur relatively infrequently include adrenal insufficiency, thrombosis, and hyperglycemia.72-74 Rash and menstrual disorders have similar frequency.67,75 Some evidence suggests that the drug improves fat-free body mass.71

Glucocorticoids: Glucocorticoids work by inhibiting markers of inflammation and also increase neuropeptide Y.70 Glucocorticoids, such as dexamethasone (3–6 mg/day), prednisone (15 mg/day), and methylprednisone (32 mg/day), can improve appetite and can cause weight gain.77 Their effects are rapid but are of short duration than megestrol acetate.78 Glucocorticoids can be used for patients in need of a rapid effect but are more appropriately used in patients with a short prognosis.

Cannabinoids: Dronabinol is the most-studied cannabinoid, with dosages ranging from 2.5 to 20 mg/day; compared with placebo, dronabinol reduces nausea, stabilizes weight, and increases appetite.79 Cannabinoids probably inhibit inflammatory mediators, and they also may influence leptin by activating the cannabinoid receptor. Toxicities include euphoria, hallucinations, tachycardia, and psychosis.79 A phase 2 study (N = 19) found that 5 mg/day dronabinol improved anorexia in 68% of study patients, but 16% of study patients discontinued the drug due to adverse events.79 With respect to appetite and weight gain, dronabinol is inferior to megestrol acetate and megestrol acetate/dronabinol combinations, and it is not recommended for cancer anorexia/cachexia.80,81

Anamorelin: Anamorelin is a novel, ghrelin, growth-hormone secretagogue taken orally for the treatment of cancer anorexia/cachexia because it improves appetite and muscle mass.82 Ghrelin is an orexigenic hormone that stimulates food intake in a dose-dependent manner in rodents and humans by stimulating growth hormone and neurotransmitters such as neuropeptide Y.83,84,85 Levels of ghrelin are elevated in fasting and reduced in obesity.86 It also stimulates the hypothalamus, thus causing food intake.87 The results of a phase 3 trial showed increased lean body mass and decreased symptoms of anorexia/cachexia in patients with stage 3/4 non–small-cell lung cancer.85

Nonsteroidal Anti-Inflammatory Drugs: Nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase 2 inhibitors, reduce the tumor-asso-
The results of 2 controlled clinical trials of patients with cancer anorexia/cachexia suggested that NSAIDs were effective for gaining weight and muscle mass in this study population, and this was especially true when NSAIDs were combined with progestogens. However, larger trials are required to further study their effect in this patient population.

**Thalidomide:** Thalidomide has multiple immune-modulating, anti-inflammatory, and TNF-α and IL-6–inhibiting properties. The results of 2 controlled clinical trials show that it increased appetite, weight, and feeling of well being in study patients with cancer anorexia/cachexia. These initial results are promising, but they may need to be confirmed by additional clinical trials.

**Melatonin:** Melatonin is an endogenous hormone secreted by the pineal gland and is used to treat sleep disorders. It inhibits cytokines and TNF-α. Two controlled clinical trials measuring the efficacy of melatonin in 1,600 study patients with advanced cancer found improvements in asthenia and anorexia compared with placebo. However, another controlled clinical trial comparing melatonin with placebo in study patients with cancer anorexia/cachexia (N = 48) did not find any differences between the 2 treatment groups. Thus, more studies are indicated to determine its effectiveness.

**Anabolic Steroids:** Oxymetholone, oxandrolone, nandrolone, and fluoxymesterone are anabolic steroids studied in cancer anorexia/cachexia. They act to increase muscle mass without changes in appetite or amount of food intake. They have been evaluated for cachexia with a nononcological origin (eg, AIDS, chronic obstructive pulmonary disease, renal impairment). One controlled clinical trial confirmed that the efficacy of fluoxymesterone in cancer anorexia/cachexia was comparable with that of megestrol acetate. However, its use is not recommended due to its high rate of hepatotoxicity.

**Combination Treatment:** Another approach to cancer anorexia/cachexia is using multiple drugs on different pathways that play a role in the disorder. A controlled clinical trial compared 5 treatments (megestrol acetate, eicosapentaenoic acid, L-carnitine, thalidomide, and combination megestrol acetate/eicosapentaenoic acid/L-carnitine/thalidomide) during a 4-month period. The results showed that the drug combination was superior to the drugs alone and improved appetite and asthenia, reduced energy expenditure at rest, increased fat-free mass, and reduced IL-6.

**Fatigue**

Patients with cancer commonly experience fatigue, which impacts the physical, emotional, and cognitive domains. Fatigue can impair concentration, often manifesting as lack of motivation. In addition, patients may perceive fatigue as decreased energy and weakness. Use of radiation, chemotherapy, biological therapies, and targeted therapies may cause fatigue. Moreover, fatigue can persist in cancer survivors and last for many years.

**Mechanisms**

Factors contributing to fatigue in patients with cancer can include tumor burden, oncology treatment, and the effect of cytokines. Cytokine production leads to symptoms of fever, pain, cachexia, and depression. Patient comorbidities can also exacerbate fatigue and may include chronic obstructive pulmonary disease, renal insufficiency, and electrolyte, endocrine, and pre-existing mood disorders.

**Assessment**

Fatigue should be evaluated like any other symptom, with the health care professional detailing its severity, temporal features, any exacerbating and alleviating factors, associated distress, and its impact on the patient's daily life. Tools for the measurement of fatigue include the Edmonton Symptom Assessment System, the Functional Assessment of Cancer Therapy-Fatigue Subscale, the Brief Fatigue Inventory, and the Memorial Symptom Assessment Scale Short-Form.

**Management**

Health care professionals can use nonpharmacological and pharmacological approaches to treat cancer-related fatigue. Identification of anemia, infection, hypogonadism, pain, depression, anxiety, cachexia, dehydration, metabolic abnormalities, other comorbidities, and medication use, as well as autonomic insufficiency and their attempted correction, are also important. Clear relationships exist between hemoglobin levels and symptoms of fatigue and functional and physical well-being. Treating anemia does improve energy and quality of life; however, transfusions can benefit patients with cancer approximately 60% of the time. Erythropoietin and other similar treatments are impractical in patients with advanced cancer because these treatments often take 4 to 8 weeks. As the disease progresses, the benefits of transfusions lessen.

**Nonpharmacological:** Exercise can be beneficial for cancer-related fatigue because it improves cardiovascular conditioning, helps patients maintain muscle mass, and can improve mood and sleep. Exercise can also benefit patients receiving chemotherapy and bone marrow transplants. However, it is important for the health care professional to set realistic expectations for patients when recommending exercise. Patients with cancer may experience metabolic changes, such as an excess lactate level, and morphological muscle changes, such as myofibrillar and sarcomeric abnormalities, even in tumor-free muscles. Decondition-
ing complicates exercise goals, and use of steroids can cause physical weakness. Thus, an ideal exercise pro-
gram appropriate for all degrees of performance status among patients with advanced illness remains to be
determined.

Pharmacological: Management options for cancer-related fatigue include corticosteroids and psy-
chostimulants. Glucocorticoids have been shown to improve fatigue in advanced illness, although their
benefits are short term. Steroids are best reserved for patients with a short prognosis. Doses equivalent to
dexamethasone 8 mg daily are appropriate. A meta-
analysis of psychostimulants for cancer-related fatigue suggested a benefit for this patient population. Psy-
chostimulants such as methylphenidate and modafinil can also be used.

Conclusions
Symptom management in patients with advanced cancer is more effective when health care professionals
use a systematic approach to assessment. Expert man-
agement requires understanding of the pathophysi-
ology of common symptoms in advanced cancer, use of
symptom assessment tools to measure symptom inten-
sity, and the application of proven symptom control in-
terventions.

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It is important that clinicians assess opioid responsiveness to determine whether adjuvant analgesics should play a role in the treatment plan.

Pharmacological Management of Cancer-Related Pain
Eric E. Prommer, MD

Background: Pain occurs in 50% of patients with cancer at the time of diagnosis, and nearly 80% of patients with advanced stage cancer have moderate to severe pain. Assessment of pain requires the health care professional to measure pain intensity, delineate opioid responsiveness, and clarify the impact of pain on a patient’s psychological, social, spiritual, and existential domains. To this end, the World Health Organization (WHO) has developed a 3-step pain ladder to help the health care professional effectively manage pain, classifying pain intensity according to severity and recommending analgesic agents based on their strength.

Methods: Health care professionals should follow the WHO guidelines to manage cancer-related pain in their patients. With regard to opioids, dosing, equianalgesic conversions, the management of adverse events, and the identification of new agents are discussed. Integrating adjuvant analgesics and interventional pain techniques into the management of cancer-related pain is also discussed.

Results: The WHO analgesic ladder is an effective tool for managing cancer-related pain. Successful pain management in patients with cancer relies upon the health care professional to pay attention to detail, especially during the introduction of new drugs and in identifying potential adverse events. Health care professionals must assess opioid responsiveness to determine whether adjuvant analgesics should also play a role in a patient’s treatment plan.

Conclusion: Adherence to the WHO pain ladder and understanding proper use of interventional pain techniques complement the pharmacological management of cancer-related pain.
cancer itself, oncology treatment, and coexisting nonmalignant pain.10 Cancer types determine pain prevalence; for example, patients with head and neck cancer have the highest prevalence of cancer pain.9 Age has also been shown to affect cancer pain; younger patients experience more pain and more pain flares than older patients.10 In addition, elderly patients receive less opioids than their younger counterparts.11 Patients with cancer most commonly experience pain in the back — prompting health care professionals to exclude spinal cord metastasis — as well as in the abdomen, shoulders, and hips.12

World Health Organization Pain Ladder
WHO guidelines form the basis of cancer pain management, recommending a step-by-step approach to managing cancer pain based on pain intensity.2 The pain ladder starts with nonopioid analgesics, such as acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs), for mild pain, then adds a so-called weak opioid if pain persists or increases, and then replaces the weak opioid with a step 3 opioid for severe pain. Morphine is recommended as a first-line opioid to relieve cancer-related pain; however, the evidence level for morphine as a first-line opioid is not particularly strong.3,6 Other step 3 options for moderate to severe pain include methadone, oxycodone, fentanyl, and hydromorphone. Successfully using the WHO pain ladder can help manage pain/provide effective analgesia in 90% of patients in certain settings, although results from randomized control trials show success rates of 70% to 80%.13-15

Step 1
Step 1 analgesics include acetaminophen and NSAIDs, which are both analgesic and anti-inflammatory; acetaminophen is only analgesic.16,17 Dosing of acetaminophen and NSAIDs is limited by a ceiling effect, meaning that further dose escalation will not improve analgesia. Acetaminophen dosing is limited by concerns of hepatic toxicity at a total dose of more than 4 g/day.18 Acetaminophen has several postulated mechanisms of action, including central inhibition of the cyclooxygenase system, nitric oxide synthetase, the endocannabinoid system, and the descending serotonin pathways.17 NSAIDs inhibit the enzyme cyclooxygenase, which produces inflammatory prostaglandins that cause sustained nociceptive responses by lowering pain thresholds in nociceptive, neuropathic, and possibly visceral pain through a process called peripheral sensitization.19 One major action of NSAIDs is the prevention of peripheral sensitization.20 When considering the use of NSAIDs, choices should be based on experience and the toxicity profile, which depends on the cyclooxygenase 1:2 ratio. There is no ideal NSAID. NSAIDs are orally administered, with the exception of ketorolac. Thus, loss of the oral route with advanced illness eliminates NSAIDs from consideration for analgesia in patients at the end of life.

At the end of life, NSAIDs are typically replaced by stronger analgesics in the setting of moderate to severe pain. It may be important to continue NSAIDs as long as possible, because clinical trials show additive analgesia when combined with opioids as well as an opioid-sparing effect.21 Ketorolac, diclofenac, and ibuprofen are parenteral NSAIDs, and ketorolac is useful for the treatment of cancer pain syndromes not uniformly responsive to opioid therapy.22 Ketorolac use in the advanced patient with cancer is not recommended for more than 1 week.23 Acetaminophen has not been shown to work synergistically with opioids but has not been shown to be opioid-sparing with opioid doses of more than 200 mg of morphine equivalents.24 NSAIDs are useful for pain originating in tissues such as connective tissue, joints, serous membranes, and the periosteum; in addition, visceral pain may also respond to NSAIDs.25

Step 2
Step 2 on the WHO pain ladder is for mild to moderate cancer pain and includes recommendations for acetaminophen products containing hydrocodone, oxycodone, codeine, and tramadol, as well as propoxyphene and dihydrocodeine (not available in the United States).2 Propoxyphene is not recommended for use in cancer pain.25

Hydrocodone: Hydrocodone is structurally similar to morphine, differing only in having a single bond at carbons 7 and 8 and a keto (=O) group at 6-carbon. Hydrocodone is metabolized by both cytochrome P450–dependent oxidative metabolism and glucuronidation. CYP3A4 and CYP2D6 play a role in the generation of hydrocodone metabolites: norhydrocodone and hydromorphone, respectively.26 Polymorphisms of CYP2D6 potentially affect hydrocodone metabolism and therapeutic efficacy.27 Hydrocodone has equivalent potency as morphine on a milligram-for-milligram basis.27 Adverse events of hydrocodone are similar to other opioids.

Rodriguez et al28 evaluated 118 study patients with chronic cancer pain and compared hydrocodone/acetaminophen with tramadol in a double-blind, randomized controlled trial. A total of 62 study patients received hydrocodone/acetaminophen and 56 received tramadol.28 Hydrocodone/acetaminophen decreased pain in 57% of participants at a starting dose of 25 mg/2500 mg/day (5 doses per day).28 Analgesic responses increased by 15% with dose doubling.28 Pain did not respond to hydrocodone/acetaminophen administration in 29% of study patients.28

Another multicenter, double-blind, randomized, parallel group study compared codeine/acetamino-
phen phosphate with hydrocodone/acetaminophen for moderate to severe pain. Study patients had chronic moderate to severe cancer pain (>3 on a 10-cm visual analog scale and >1 on a 4-point verbal intensity scale). A total of 88% of study patients had moderate pain and 12% had severe pain; 121 participants received either 1 tablet of codeine/acetaminophen 30/500 mg or hydrocodone/acetaminophen 5/500 mg orally every 4 hours (total daily doses, 150/2500 and 25/2500 mg, respectively) for 23 days. Dose escalation occurred after 1 week if participants experienced severe pain. The primary end point was the percentage of study patients achieving a decrease in their pain score by 1 point on a 5-point verbal intensity scale. The secondary end point was the percentage of study patients whose pain decreased by at least 3 cm on the 10-point scale. Of the 121 participants, 59 received codeine/acetaminophen and 62 received hydrocodone/acetaminophen. Of the total number of cases, 59 had ages ranging from 60 to 89 years. A total of 58% of patients in the codeine/acetaminophen arm of the study experienced pain relief, and an additional 8% achieved pain relief with a doubling of the dose. Approximately one-third had unresponsive pain. In the hydrocodone/acetaminophen arm of the study, 56% experienced pain relief with a starting dose of 25/2500 mg/day. A total of 15% more achieved pain relief doubling of the initial dose, and one-third of patients did not respond to hydrocodone/acetaminophen.

Tramadol: Tramadol is a synthetic opioid from the aminocyclohexanol group. Tramadol has opioid-agonist properties and prevents the uptake of norepinephrine and serotonin, making it useful for neuropathic pain. Tramadol possesses low affinity for opioid receptors, with an affinity to μ receptors 10 times weaker than codeine, 60 times weaker than dextropropoxyphene, and 6,000 times weaker than morphine. Tramadol requires conversion to an active metabolite by CYP2D6. This metabolite has affinity for opioid receptors, but less so than step 3 opioids. Patients who are poor metabolizers of CYP2D6 may experience poor analgesia. Adverse events of tramadol include constipation, dizziness, nausea, sedation, dry mouth, and vomiting.

Rodriguez et al evaluated 118 participants with chronic cancer pain and compared hydrocodone/acetaminophen and tramadol in a double-blind, randomized controlled trial. In addition, Wilder-Smith et al compared tramadol with morphine in a randomized, crossover, double-blind study for severe cancer pain (N = 20). Initially, participants received either tramadol 50 mg or morphine 16 mg every 4 hours, with dose titration to achieve pain control. After 4 days, pain intensities did not differ between the groups, although adverse events appeared to differ, with less-intense nausea and constipation noted in the tramadol group. The authors estimated equianalgesic doses of morphine and tramadol and found a ratio of morphine to tramadol of 1:4.

Tawfik et al compared oral tramadol with sustained release morphine for cancer pain in 64 participants with severe cancer pain in a randomized, double-blind study. Tramadol worked best in participants with lesser pain intensity, and morphine worked more effectively and was preferred for participants experiencing severe pain intensity. Good analgesia was achieved in 2 weeks of treatment in 88% of study patients receiving tramadol and 100% of study patients receiving sustained-release morphine. Participants receiving tramadol experienced fatigue (15%), nausea (8%), and sweating (8%). In those receiving morphine, adverse events included constipation (35%), rash (14%), and drowsiness (14%).

Bono and Cuffari compared tramadol with buprenorphine in a randomized, crossover trial in study patients with cancer pain. All 60 study patients received either drug for 1 week and then, after a 24-hour wash-out period, were switched to the other drug. The tramadol dose was 300 mg/day and the buprenorphine dose was 0.2 mg 3 times a day. Tramadol was better tolerated than buprenorphine and caused less frequent and milder adverse events, and more study drug withdrawals occurred in the buprenorphine arm.

Tapentadol: Tapentadol is structurally related to tramadol. Opioid receptor–binding studies show that tapentadol is a strong opioid with high-affinity binding to μ, δ, and κ opioid receptors. In human μ opioid receptor [35S]GTPγS–binding assays, tapentadol shows agonistic activity, with an efficacy of 88% relative to morphine; tapentadol provides potent inhibition of norepinephrine uptake and its bioavailability is lower than tramadol. Tmax is achieved in 1.25 to 1.5 hours, the half-life is 24 hours, and the plasma protein binding is 20%. Tapentadol metabolism is mainly by glucuronidation, with some contribution from CYP enzymes, especially CYP2D6. Tapentadol is not an inducer of CYP3A4. Tapentadol has no active metabolites. There is chiefly renal excretion. Tapentadol causes adverse events such as nausea, dizziness, vomiting, headache, and somnolence. The manufacturer recommends against using tapentadol in severe hepatic or renal failure, and dosing above 600 mg/day should be avoided. The current dosing recommendations are 50, 75, or 100 mg every 4 to 6 hours. Tapentadol does
not affect the QTc interval.\(^4^3\) Prolonged-release tapentadol (100–250 mg twice daily) is effective compared with placebo for managing moderate to severe, chronic, malignant tumor-related pain.

**Codeine:** Codeine is a prodrug whose analgesia is mediated through the \(\mu\) receptor by its metabolite, morphine. A total of 10% of codeine is broken down to morphine by CYP2D6, an enzyme lacking in 5% to 10% of white populations.\(^4^4\) Codeine use is not recommended in the setting of renal failure.\(^4^5\) One placebo-controlled study has evaluated codeine for cancer pain involving a sustained-release formulation.\(^4^6\) Thirty study patients with chronic cancer pain completed the study and received either sustained-release codeine every 12 hours or placebo in a double-blind study.\(^4^6\) Crossover occurred after 7 days.\(^4^6\) Pain intensity was measured using a visual analog scale as well as a 5-point categorical scale. Rescue analgesia (acetaminophen/codeine 300 mg/30 mg every 4 hours as needed) was recorded. The median doses of controlled-release codeine doses were 277 ± 77 mg (range, 200–400 mg). Pain intensity scores on a visual analog scale, categorical pain intensity scores when assessed by day of treatment and by time of day, and need for breakthrough pain were significantly lower in the codeine arm \((P < .0001)\).\(^5^3\)

**Step 3**

The WHO pain ladder recommends the use of step 3 opioids as first-line therapy for moderate to severe pain (morphine, oxycodone, hydromorphone, fentanyl, levorphanol, methadone).\(^4^7\) Step 3 opioids differ from those in step 2 medications in terms of potency and dosing. Although many step 2 medications often have a ceiling dose due to fixed formulations with acetaminophen, step 3 opioids do not have this ceiling. Dosing can increase to achieve adequate analgesia as long as adverse events are tolerated. Step 3 opioids interact with opioid receptors found throughout the central nervous system and peripheral tissues, resulting in analgesic effects, as well potential adverse events, including sedation, respiratory depression, and dependence. Opioid receptors exist throughout the intestinal tract and, when activated, slow bowel motility.\(^4^8\) Varying degrees of activation and affinity for each receptor subtype may account for the differences in efficacy and activity between opioids. In addition, interindividual variation is significant in analgesic response and toxicities based on genetic disparities.\(^4^9\) However, a reliable method to predict an individual patient’s response does not exist and a paucity of evidence suggests superiority of one opioid over another in terms of efficacy or tolerability.

**Morphine:** WHO considers morphine the drug of choice for moderate to severe cancer pain.\(^5^0\) The liver is the principal site of morphine glucuronidation.\(^5^1\) There is a minor contribution (30%) to glucuronidation from the kidneys.\(^5^2\) First-pass metabolism of oral morphine determines its systemic bioavailability. Three major metabolites are produced: normorphine, morphine-3-glucuronide, and morphine-6-glucuronide. The metabolites are principally eliminated by the kidney and accumulate in renal failure.\(^5^3\) The elimination half-life of morphine is approximately 2 hours and is independent of route of administration or formulation.\(^5^4\) Morphine administered by sublingual and buccal routes has a delayed onset of action compared with oral morphine (smaller peak plasma levels, lower bioavailability, and larger interpatient variability).\(^5^4\) Intrathecal morphine is 100 times as potent as its oral form, and epidural morphine is 10 times as potent (0.5 mg intrathecally equals 5 mg epidurally).\(^5^4\) Morphine dosing is minimally affected by hepatic failure but is greatly affected by renal failure. There is a linear relationship between creatinine clearance and renal clearance of morphine, morphine-3-glucuronide, and morphine-6-glucuronide.\(^5^5\) Kidney failure impairs glucuronide excretion more than morphine excretion, increasing the duration of action of morphine-6-glucuronide and morphine-3-glucuronide, thus leading to adverse events.\(^5^6\) Glucuronidation is largely unaffected by cirrhosis. Morphine doses must be carefully titrated or avoided when creatinine clearance is less than 30 mL/minute.\(^5^4\) Morphine continues to be considered the standard medication for the treatment of cancer pain partly due to familiarity with the product as well as cost effectiveness. However, it may not always be the ideal product due to issues associated with its metabolism and adverse-event profile.\(^1^1\) Almost all randomized controlled comparisons of potent opioids have shown equivalence (ie, noninferiority) to morphine.\(^6^,1^1,5^7-5^9\)

**Methadone:** Methadone has features that make it unique: It works at 3 levels to provide analgesia. It is a potent opioid with strong interactions with the \(\mu\)-opioid receptor, and it is a N-methyl-D-aspartate (NMDA) receptor antagonist, a receptor that is activated in chronic pain states and, when blocked, can enhance analgesia and reverse opioid tolerance. Methadone also works on neurotransmitters, such as noradrenaline and serotonin, which play a role in descending pain modulation.\(^5^9,6^0\)

Methadone is a second-line analgesic for pain that is poorly responsive to other opioids.\(^5^9\) It shows promise as a first-line analgesic for cancer pain, neuropathic pain, and as a breakthrough agent. Methadone is available in oral, sublingual, and intravenous formulations. Methadone has different pharmacokinetics from other opioids. Methadone has a long half-life that varies between 60 and 120 hours.\(^5^9\) High-dose intravenous methadone is associated with QT prolongation and torsades de pointes.\(^6^1\) In fact, a retrospective study found
that oral methadone can cause QT prolongation in 16% of patients. Dosing of methadone is complicated. Methadone shows an inverse relationship of its starting dose to the total morphine equivalent daily dose (MEDD). As the MEDD increases, the equianalgesic dose of methadone progressively decreases.

Clinical trials comparing methadone to morphine have not shown superiority of methadone; in fact, 3 studies have compared morphine and methadone as first-line therapy for cancer-related pain. Ventafriidda et al compared methadone with morphine for moderate to severe cancer pain in 54 study patients who had previously been taking step 2 opioids. Patients received either morphine or methadone by mouth for 14 days. Both therapies provided clear reductions in pain intensity. In one study, a double-blind, randomized comparison of sustained-release hydromorphone with sustained-release morphine showed equivalence in pain relief. Systematic reviews involving 11 studies and 645 study patients show that hydromorphone equals morphine in analgesic effect.

**Oxycodone**: Oxycodone is available as immediate-release and sustained-release formulations. (Intravenous formulations are available in Europe.) The immediate-release formulation has a half-life of approximately 2 to 4 hours and a bioavailability of 50% to 60%. The primary difference between oxycodone and morphine is its bioavailability: its half-life is longer than normal in renal failure and liver failure. Several trials comparing oxycodone with morphine show equal efficacy. Minor differences in adverse events have been described. Hallucinations and nausea are less common with oxycodone treatment. However, because of its cost and lack of versatility, morphine remains the preferred analgesic. Hallucinations and nausea are less common with oxycodone treatment. Hallucinations and nausea are less common with oxycodone treatment. However, because of its cost and lack of versatility, morphine remains the preferred analgesic.

**Oxymorphone**: Oxymorphone is a semisynthetic μ-opioid agonist 1.2 times as potent as morphine. Until recently, oxymorphone was available as parenteral injection and in suppository form; however, immediate-release and long-acting oral formulations were developed that make oxymorphone another option for treating moderate to severe pain. Trials in malignant and nonmalignant pain confirm its potential as another step 3 option. Oxymorphone is more lipid soluble than morphine. The oral bioavailability of oxymorphone is approximately 10%, which is the lowest of the oral step 3 opioids. In healthy volunteers, the half-life ranges from 7.2 to 9.4 hours. The half-life of immediate-release oxymorphone is longer than that of morphine, hydromorphone, and oxycodone. Immediate-release oxymorphone tablets may be given at 6-hour intervals, whereas the extended-release formula is dosed twice daily. Steady-state conditions are achieved after 3 to 4 days. Oxymorphone is subject to hepatic first-pass effects and is excreted by the kidneys. Oxymorphone accumulates in renal failure. Oxymorphone has a prolonged half-life in renal failure. In the setting of hepatic insufficiency, increasing the dosing interval is recommended.

Sloan et al conducted a pilot study comparing extended-release oxymorphone and controlled-release oxycodone in 86 study patients with moderate to severe cancer pain. The tolerability and safety profiles (e.g., nausea, drowsiness, somnolence) were similar between the 2 drugs, and no significant differences in daily pain intensity scores were seen between extended-release oxymorphone and oxycodone.
cross both the skin and oral mucosa. The transdermal formulation delivers fentanyl from the reservoir into the stratum corneum where it then slowly diffuses into the blood. Another formulation on the market is a matrix-delivery system in which fentanyl is dissolved in a polyacrylate adhesive. This formulation can be cut. Both the reservoir and matrix-based patches have similar kinetics and clinical effectiveness. Fen-
yl is metabolized to norfentanyl under the influence of CYP3A4. The concomitant use of fentanyl with potent CYP3A4 inhibitors (eg, ritonavir, ketoconazole) may affect its metabolism. Fentanyl is safe to use in patients with renal failure. The elimination half-life of transdermal fentanyl is approximately 12 hours. Con-
version to fentanyl are made by calculating the MEDD and the using the ratio of 2 mg:1 µg to reach the start-
ing fentanyl dose. Most experts do not recommend using transdermal fentanyl for acute titration. Compared with morphine, constipation is less frequent with fentanyl. Comparisons between morphine and transdermal fentanyl have shown equal analgesic ef-

ciency. When compared with morphine, daytime drowsiness and interference with daytime activity oc-

cur at lower rates.

The oral transmucosal administration of fentanyl has been extensively explored. In 1 study, 25% of the de-

livered drug was transmucosally absorbed, with another 25% delivered through the gastrointestinal tract. Randomized controlled trials of oral transmucosal fentanyl citrate show increased analgesic efficacy and patient preference over placebo and morphine. Administration of fentanyl is being explored through other routes (eg, intranasal). Rapid intravenous administration of fentanyl in the emergency department can result in rap-

id improvement in pain control.

**Buprenorphine:** Buprenorphine is emerging as another option for cancer pain. Well-known as a strong analgesic, the development of a transdermal formulation makes it a possible option for cancer pain. Buprenorphine is also available in intravenous and sublingual formulations, with the sublingual formulation having a bioavailability of 50% to 65% and a half-life of more than 24 hours. After application of the transdermal formulation, plasma concentrations steadily increase. The larger-dose transd-

ermal formulations achieve the minimum effective therapeutic dose sooner.

Open-label, randomized, parallel-group, multiple-
dose pharmacokinetic studies show that the minimum effective concentrations are reached after 31, 14, and 13 hours, respectively, with the 35, 52.5, and 70 mg/hour patches (not available in the United States). Patches reach steady state after the third consecutive application. Bioavailability of the transdermal formulation is 60% compared with the intravenous route. Effective plasma levels occur within 12 to 24 hours and last for 72 hours. It takes 60 hours to reach C_{max}. After patch re-

moval, concentrations decrease to one-half in 12 hours, then more gradually decline.

Metabolism by CYP3A4 and CYP2C8 converts buprenorphine to an active metabolite, norbuprenor-

phine, which is a weaker but full-opioid agonist. Buprenorphine and its metabolite later experience gluc-

uronidation. Liver disease affects buprenorphine metabolism. With involvement of both cytochrome 

oxidase system and glucuronidation in metabolism, severe liver disease potentially inhibits formation of norbuprenorphine through effects on the cyto-

chrome oxidase system. Liver disease does not affect glucuronidation as much. Buprenorphine is safe to use in the presence of mild to moderate liver failure as well as in the setting of renal insufficiency and dialysis.

Buprenorphine produces adverse events similar to other step 3 opioids and include constipation, urinary retention, sedation, and cognitive dysfunction. Buprenorphine causes less nausea than transdermal fentanyl.

Three phase 3, placebo-controlled studies of mixed study populations with cancer evaluated trans-
dermal buprenorphine for cancer pain. In these studies, buprenorphine acted as an opioid agonist. There was no dose ceiling or opioid antagonist activity.

**Levorphanol:** Levorphanol is a potent opioid considered to be similar to methadone. Morphologi-
cally similar to morphine, levorphanol has strong af-
finity for μ, δ, and κ opioid receptors. Levorphanol is a noncompetitive NMDA receptor antagonist and blocks NMDA with the same potency as ketamine. Levorphanol can be orally, intravenously, subcutaneous-
ously, and intramuscularly administered. Levorpha-
nol has poor absorption via the sublingual route com-
pared with other opioids such as morphine sulfate (18%), buprenorphine (55%), fentanyl (51%), and metha-

done (34%). The pharmacokinetics of levorphanol are similar to methadone with a duration of analgesia ranging from 6 to 15 hours and a half-life as long as 30 hours. First-pass metabolism produces a 3-gluc-
uronide metabolite, which may have neurotoxicity. Metabolites of levorphanol are renally excreted. The high volume of distribution and increased protein binding suggest that levorphanol should not be dialyz-
able. In the setting of renal disease, the dosing inter-
val should be increased. This differs from methadone. The predominant mode of metabolism is hepatic. In the setting of hepatic insufficiency, it is advisable to consider an increased dosing interval. Experience and clinical trial results suggest that the type and inci-
dence of adverse events are similar to those seen with strong opioids. Levorphanol has been studied as a treatment for chronic neuropathic pain and has been shown to be effective.
Interventional Pain Modalities

Clinicians consider “step 4” of the WHO pain ladder when there is an inadequate response to step 3 agents, adjuvants, or both. Treatment options include use of nerve blocks, as well as spinal administration of local anesthetics, opioids, and other adjuvants. Abdominal pain may be controlled by a blockade of the celiac plexus, which, if successful, can block nociceptive input from many structures in the upper abdomen, in particular the pancreas. Use of the superior hypogastric ganglion block for the treatment of malignant pelvic pain was first described by Plancarte et al.

Opioids
Receptor Interactions

Opioids interact with opioid receptors to produce analgesia (as well as adverse events). Opioids interact with receptors, leading to receptor phosphorylation by G protein-coupled receptor kinases. Arrestin then binds with the activation of distal pathways. Opioids intracellularly drive receptors by endocytosis, with the receptors ultimately resurfacing. Opioids differ in their G protein coupling and in their propensity to drive receptors into the cell. For example, compared with other strong opioids, morphine is inefficient in its ability to promote receptor internalization. Some postulate that noninternalized receptors continue to signal and promote adaptive responses, thus causing cellular tolerance.

Responsiveness

Opioid responsiveness is the “degree of analgesia achieved as the opioid dose is titrated to an endpoint, defined either by intolerable side effects or the occurrence of acceptable analgesia.” Pain poorly responsive to opioids exists when intolerable adverse events, inadequate analgesia, or both continue despite opioid escalation. Pharmacodynamic and nonpharmacodynamic factors affect opioid responsiveness. Identifying pain poorly responsive to opioids should lead the health care professional to consider using adjuvant analgesics or opioid switching, changing the route of administration, using NMDA antagonists, or interventional pain techniques.

Routes of Administration

Opioids are available in many dosage forms, including via the oral, rectal, subcutaneous, intramuscular, intravenous, transdermal, transmucosal, and intraspinal routes of administration. Oral administration is simple, cost effective, and is the preferred route of delivery. Both immediate-release and extended-release preparations are available. Clinicians use the subcutaneous, intravenous, rectal, transdermal, transmucosal, and intraspinal routes when patients cannot take oral medications. Intramuscular administration is contraindicated as it does not confer any pharmacokinetic advantages and is painful for patients. Subcutaneous delivery is relatively easy, effective, and safe. Intravenous routes are useful when pain is severe or pain levels have acutely increased. Transdermal fentanyl preparations are effective for patients unable to take oral medications and have stable pain control. Other short-acting opioids are used to control pain when transdermal fentanyl is used, because levels of fentanyl gradually increase during a 12- to 24-hour period until reaching steady state. Transmucosal fentanyl is similar to intravenous administration in its rapid onset, and it can be used for acute breakthrough pain. Historically, dosing of transmucosal fentanyl was not thought to be based on dose proportionality, but this consideration has been challenged. Intraspinal administration of opioids can either be epidural or intrathecal. This method is the most invasive technique and requires a specialist for initiation. This delivery confers advantages in patients with significant dose-limiting adverse events as systemic involvement is circumvented. Intraspinal delivery allows the addition of adjuvant medications to opioids that can be directly administered to the spinal cord.

Dose Titration

Clinicians adjust opioid analgesics to balance adequate pain control with their respective adverse events. Dosage requirements change with cancer progression. Most patients with cancer have chronic daily pain, so analgesics should be given on a scheduled basis. Breakthrough analgesics are ideally given according to the time it takes to reach Cmax. The Cmax depends on the route of administration. Cmax is 1 hour for the oral route, 30 minutes for the subcutaneous route, and 6 minutes for the intravenous route. Once Cmax is reached, another dose should be given if pain is not adequately controlled.

Multiple approaches to opioid initiation and titration exist. The European Association for Palliative Care recommends dose titration with immediate-release oral morphine every 4 hours, with breakthrough dosing of the same dose given every hour as needed. The scheduled dose should then be adjusted to account for the oral MEDD. Several studies have shown acceptable pain control and adverse-event profiles with use of 5 mg every 4 hours in study patients naive to opioids and 10 mg every 4 hours in patients previously using a step 2 drug. After acceptable pain control occurs, patients can use extended-release preparations as this is convenient and improves compliance. Breakthrough dosing is 10% to 20% of the MEDD.

Opioid titration with sustained-release formulations is slower than titration with immediate-release formulations. Titration with intravenous medications
is effective and tolerated.\textsuperscript{154} In patients on established opioid regimens, dosing adjustment should be made according to the level of pain. Adult cancer pain guidelines recommend an increase of 25\% to 50\% in the total MEDD for moderate pain (4–6 out of 10) and 50\% to 100\% for severe pain (7–10 out of 10).\textsuperscript{155}

**Equianalgesic Conversions**

When converting between opioids, equianalgesic guidelines should be followed, although they may be modified according to clinical judgment with regard to adequacy of a patient’s current pain medication regimen.\textsuperscript{155} Opioid rotation may be secondary to poor analgesia, excessive adverse events, convenience, or patient preference.\textsuperscript{156} Incomplete cross tolerance is a phenomenon that has been empirically observed.\textsuperscript{135} For various reasons, patients may develop less of a response (eg, poor analgesia, adverse events) to a particular opioid over time. Patients may not show these characteristics with a new opioid, despite similar action between opioids, and slight variations in opioid structures may account for this.\textsuperscript{137} When calculating the dose of the new opioid, new doses should be reduced by 25\% to 50\% to account for non–cross tolerance.\textsuperscript{155} This is not done for fentanyl or methadone, and equianalgesic guidelines should not to be used for these calculations.

**Adverse Events**

The development of adverse events varies between individuals based on age, comorbidities, stage of illness, and genetic differences.\textsuperscript{116} Impaired renal function also increases the risk of adverse events due to accumulation of active metabolites.\textsuperscript{116} The most common adverse events include constipation, nausea, vomiting, and altered cognition.\textsuperscript{116} Other adverse events may include xerostomia, urinary retention, respiratory depression, myoclonus, pruritus, and hyperalgesia.\textsuperscript{116} Most adverse events from opioid use subside within days to weeks, except for constipation for which patients do not develop tolerance and is not dose-related. For those symptoms that persist or are present during the initiation of opioid therapy, symptom management is a key element of care. Constipation is prophyllactically managed. Opioids inhibit gastrointestinal peristalsis; thus, all patients should receive a stimulant laxative such as senna, which can be combined with a stool softener such as docusate sodium or polyethylene glycol. Dietary recommendations, such as increasing fiber in the diet, are unrealistic in patients with advanced disease because hydration is necessary to facilitate the action of fiber, often something difficult to achieve in ill patients.\textsuperscript{126} Constipation is exacerbated by metabolic abnormalities, including diabetes, hypercalcemia, hypokalemia, and hypothyroidism, that should be corrected if possible.\textsuperscript{116} Increased physical activity is often helpful if possible. Use of quaternary opioid antago-
Use in the elderly may also be problematic due to adverse events, including orthostatic hypotension and sedation.146 Tricyclic antidepressants should also be cautiously used in patients with coronary artery disease or cardiac rhythm disorders, as well as those with a history of narrow anterior eye chambers or glaucoma. The anticholinergic properties of these drugs contribute to delirium in the elderly or anyone at risk for delirium such as patients whose cancer has metastasized to the central nervous system. These drugs should be started at the lowest dose with cautious escalation. Dose escalations are made every 3 to 4 days if analgesic response is suboptimal.

Selective serotonin reuptake inhibitors (SSRIs) have a limited role as adjuvants, although paroxetine and citalopram have been evaluated for nonmalignant neuropathic pain.147,148 No studies have been performed on cancer pain. Some SSRIs have unique mechanisms of action that may make them useful for cancer pain; for example, venlafaxine, which inhibits the uptake of serotonin and norepinephrine (important in the regulation of descending pain pathways), is effective for painful neuropathy and neuropathic pain associated with therapy used in breast cancer.148,149 Newer drugs, such as duloxetine, can be used to inhibit the uptake of norepinephrine, which is also effective in neuropathic pain, especially related to chemotherapy.150 Bupropion, a noradrenergic compound, has both analgesic and activating properties and can be effective in patients with depression and significant neuropathic pain.151

Corticosteroids
Corticosteroids can be used for patients with bone pain and to decrease swelling in the brain and spinal cord due to metastatic disease. Nerve root inflammation responds to corticosteroids. Corticosteroids are often considered for painful liver metastasis and obstruction of the ureter, although the evidence base for this use is not strong.152 The most commonly used corticosteroid is dexamethasone, which has low mineralcorticoid properties. Optimal dosing for palliation may be 8 mg as this dose has no more adverse events than placebo.153 In the case of spinal cord compression, recommendations exist for either high-dose (96 mg/day) or low-dose (16 mg/day) dexamethasone.154 The challenge with the higher dose of steroids is the occurrence of adverse events.155 The management of edema associated with brain metastasis can be treated with dexamethasone 4 to 6 mg every 6 hours with a taper during the last phases of palliative radiation therapy. The minimal effective dose for brain metastasis is 8 mg/day.156 Steroids can be useful to counteract the phenomenon of radiation “flare,” which can occur with radiation therapy when radiation is applied to painful bony sites.157

Anticonvulsant Drugs
Anticonvulsants can be used for managing neuropathic pain.158 The most often used anticonvulsant for neuropathic pain is gabapentin. Gabapentin is effective for cancer-related neuropathic pain.159 Gabapentin can have significant adverse events if it is started at too high a dose or titrated too fast. Dosing begins at 150 mg to 300 mg at bedtime, with escalations every 3 days if pain control is suboptimal. The maximum dose is 3600 mg/day. The chief adverse event is somnolence.160 Gabapentin must be dose adjusted for renal insufficiency. Another anticonvulsant that may be useful for cancer pain is phenytoin.161 Agents such as lamotrigine, oxcarbazepine, pregabalin, topiramate and levetiracetam have been used for nonmalignant neuropathic pain and are considered in the refractory case, but they have not been studied in the cancer pain population. Levetiracetam requires further study for cancer-related neuropathy.162 Lamotrigine is not effective in chemotherapy-related neuropathy.163

Oral and Parenteral Local Anesthetics
The most common parenteral anesthetic used for symptom management is lidocaine.164 Studies suggest its efficacy in refractory cases of neuropathic pain. One study in patients with cancer with refractory pain showed improved analgesia with a single dose of lidocaine.165 The recommended starting dose is 1 to 5 mg/kg infused for 20 to 30 minutes. In patients who are frail, lower doses may be needed. Lidocaine should be avoided in patients with coronary artery disease. One potential benefit of lidocaine is prolonged pain relief that occurs following its infusion. Lidocaine can be given subcutaneously in the home or hospice setting.166 Mexiletine, an oral cogener of lidocaine, has been used after lidocaine infusions.167 Clinical trial results suggest that mexiletine has a distinct adverse-event profile and may not be tolerated by all patients.168

Transdermal Analgesics
Transdermal lidocaine (5% patch) provides another route for local anesthetics. It can be used to treat postherpetic neuralgia, but use in other settings requires further study to clarify its role in cancer-related neuropathy. The patch has minimal systemic absorption, and it can be applied 12 hours per day; evidence suggests that increasing the number of patches and extended dosing periods may be safe.169,170 It may take several weeks to observe a maximal effect. The most frequently reported adverse events are mild to moderate skin redness, rash, and irritation at the patch application site.165

Ketamine
Chronic pain is associated with central nervous system
changes, including activation of the NMDA receptor, and can lead to opioid tolerance and the development of opioid resistance. The pharmacological blockade of the NMDA receptor offers a therapeutic approach in the setting of opioid resistance. Ketamine is a useful NMDA antagonist to consider in the management of cancer pain and its use often leads to reduced opioid requirements. Given at subanesthetic doses (< 1 mg/kg), ketamine is an effective analgesic in cancer-related neuropathic pain. Multiple routes exist for administration and include the oral, intravenous, subcutaneous, and topical routes. Ketamine is metabolized via CYP3A4. No significant drug interactions have been reported. Ketamine is recommended by the WHO for the management of refractory pain. The oral bioavailability is 17%, and onset of action of ketamine is 15 to 20 minutes. The half-life of ketamine is 2.5 to 3 hours. Ketamine has protein binding of 20% to 30%. Pharmacologically, no major differences exist in the characteristics between the isomers. Its intravenous onset of action is within seconds and, subcutaneously, the onset of action is 15 to 20 minutes. The half-life is 2 to 3 hours for both routes. The results of 1 trial of subcutaneous ketamine as an add-on option to opioids showed no efficacy in cancer-related nociceptive pain.

Cannabinoids
Formulations of cannabinoids, the cannabinoid extracts, have been studied for cancer-related pain. Johnson et al evaluated tetrahydrocannabinol (THC)/cannabidiol (CBD) in a 2-week, multicenter, double-blind, randomized, placebo-controlled, parallel-group trial of 177 study patients with cancer whose pain was inadequately controlled despite them being on opioid therapy. The cannabinoid extract contains THC 2.7 mg and CBD 2.5 mg per dose. It is formulated in ethanol/proplylene glycol with peppermint flavoring and is designed as a pump spray for self-administration and titration via the oromucosal route. The study patients received THC/CBD, THC extract, or placebo and continued their previous analgesics. The THC/CBD extract arm achieved a statistically significant improvement in pain when compared with placebo (P < .024) as measured on a numerical rating scale, a primary end point of the study. The THC extract showed no significant changes from baseline compared with placebo.

Neuroleptics
Second-generation (atypical) agents, such as olanzapine, have been shown to have antinociceptive activity in animal models. Clinical evaluation of its analgesic effects has been limited. Khojainova et al evaluated the analgesic activity of olanzapine in 8 study patients with severe cancer pain who did not respond to increased opioid dosing and who also received olanzapine for the treatment of associated anxiety and mild cognitive impairment. Participants did not meet diagnostic criteria for delirium and the cognitive impairment was classified as not otherwise specified. Study patients received 2.5 to 7.5 mg of olanzapine daily, and their pain intensity, sedation, and opioid consumption measurements were made before administering olanzapine and 2 days after olanzapine was given. Cognitive function was assessed daily. All participants experienced reduced pain scores, and the average daily opioid use significantly decreased in all study patients. Cognitive impairment and anxiety resolved within 24 hours of initiating olanzapine. The authors suggested that olanzapine may have an intrinsic analgesic action, but they also suggested that pain scores and opioid requirements may have resulted from improvement in cognitive function and the known anxiolytic effect of olanzapine.

Agents Specifically Used for Bone Pain
Bone pain is a common problem in the palliative care setting. Radiation therapy can be effective with localized pain. Systemic therapies with NSAIDs, corticosteroids, bisphosphonates, and radiopharmaceuticals can be useful for patients with multifocal lesions.

Bisphosphonates: Bisphosphonates are analogues of inorganic pyrophosphate that inhibit osteoclast activity and can be useful in many types of cancer in which bone resorption leads to complications. Bisphosphonates bind to calcium on bone, become ingested by osteoclasts, and then subsequently kill osteoclasts, thus preventing bone resorption. The end result of decreased osteoclast activity is increased bone stability and reduced pathological fractures. The most potent bisphosphonate is zoledronic acid, which has been shown to reduce pain and the occurrence of skeletal-related events in breast and prostate cancers, multiple myeloma, and a variety of solid tumors, including lung cancer. Denosumab is useful when renal insufficiency precludes the use of bisphosphonates.

Radiopharmaceuticals: Radionuclides are agents absorbed in areas of metastatic cancer activity. Strontium-89 and samarium-153 are effective for diffuse bony metastatic disease, such as in the case of prostate cancer.

Muscle Relaxants
Pain originating from connective tissue injury is common in patients with cancer. However, use of muscle relaxants as adjuvant agents has not been evaluated in patients with cancer.

Use for Malignant Bowel Obstruction
Pain, along with nausea and vomiting, is a common symptom associated with malignant bowel obstruction. Nonsurgical management of malignant bowel ob-
struction focuses on the management of pain and other obstructive symptoms, such as distension, nausea, and vomiting. The use of parenteral opioids, antiemetics, and antisyecretory agents, such as octreotide, are common methods of pharmacological symptom control. Octreotide has anecdotally been shown to have analgesic properties.190

**Combination Use**

The treatment of neuropathic pain frequently requires several adjuvants. For example, it is not unusual for a patient with a severe, cancer-related neuropathic pain to require an opioid or several additional adjuvants. When this occurs, the clinician should monitor the patient for potential drug interactions.191

**Conclusions**

Successful cancer pain management requires close attention to detail, particularly when introducing the drug; in addition, health care professionals must be watchful for the presence of adverse events. Assessing opioid responsiveness will help determine the role of adjuvant analgesic use. Adherence to the World Health Organization pain ladder and understanding proper use of interventional pain techniques complements the pharmacological management of cancer-related pain. New drugs are being introduced into the market and their roles in cancer-related pain control are being evaluated.

**References**


Clinical Implications of Opioid Pharmacogenomics in Patients With Cancer

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Background: Pain can be a significant burden for patients with cancer and may have negative effects on their quality of life. Opioids are potent analgesics and serve as a foundation for pain management. The variation in response to opioid analgesics is well characterized and is partly due to genetic variability.

Methods: We reviewed the results of clinical studies to evaluate the relationships between genetic variants and select genes involved in the pharmacokinetics and pharmacodynamics of opioids, with an emphasis on patients with cancer.

Results: In patients with cancer-related pain, genetic variation in OPRM1, COMT, and ABCB1 is associated with response to morphine, which is the most well-studied opioid. Although it has not been studied in patients with cancer-related pain, the effect of CYP2D6 variation is well characterized with codeine and tramadol. Evidence is limited for associating the genetic variation and pain response of oxycodone, hydrocodone, and fentanyl in patients with cancer.

Conclusion: The clinical availability of pharmacogenomic testing and research findings related to these polymorphic genes suggest that genotyping patients for these genetic variants may allow health care professionals to better predict patient response to pain and, thus, personalize pain treatment.

Introduction

Pain is one of the most burdensome symptoms associated with cancer and its treatment and is estimated to affect 49% to 57% of patients with curable cancer and 56% to 75% of patients with advanced disease. Uncontrolled pain can have significant adverse effects on function, mood, sleep, and quality of life, and studies suggest that pain is an independent prognostic factor for overall survival in cancer. A study of 2,761 patients with cancer reported that one-third of patients with initial pain had a significant reduction in pain at 1 month and one-fifth had an increase in pain scores. Opioids are the most potent analgesics available and remain the cornerstone of clinical pain management. The choice of opioid analgesic depends on a number of medical and nonmedical factors. Nonopioid and co-analgesics (eg, nonsteroidal anti-inflammatory drugs), as well as nonpharmacological measures, are often used to improve analgesic control, reduce opioid requirements, or both, as well as minimize adverse events related to opioid use.
Regardless of the analgesic type, effective pain management depends on achieving a favorable balance between adequate analgesia and adverse events.

It is well documented that patients vary considerably in their response to pain therapies, including medication. Response in analgesia and to adverse events may vary between patients with similar pain levels or disease status and may vary among patients at different stages of the care trajectory. Increasingly, research has been aimed at identifying the hereditary basis for interindividual differences in drug effects to explain altered efficacy and adverse events. Currently, genetic factors may be responsible for 12% to 60% of response variability in opioid therapy. Using genetic variation to help guide drug therapy choices may be helpful in balancing the exclusion of low-yield therapy, avoiding adverse events, and achieving pain control.

**Genes Modulating Opioid Response**

Many genes have been studied to identify pharmacogenomic markers in opioid therapy, including genes implicated in the pharmacodynamics (OPRM1, COMT) and pharmacokinetics (CYP2D6, CYP3A4/5, ABCB1) of opioids.

**Pharmacokinetics**

**Transporters**

One of the most studied transporters in opioids is a member of the adenosine triphosphate–binding cassette, sub-family B, member 1 (ABCB1), also known as P-glycoprotein or multidrug resistance protein 1. ABCB1 transporters are present in numerous locations, including the gastrointestinal tract, liver, kidneys, and the blood–brain barrier, and they facilitate the absorption, distribution, and elimination of medications, including opioids such as morphine and fentanyl and their metabolites. Impairment of these transporters may result in increased bioavailability of oral medications, decreased renal excretion, and increased central nervous system concentrations. Specifically, the transport of opioids into the brain through the blood–brain barrier may be affected by variations in ABCB1 transporters at this site. ABCB1 is highly polymorphic, with more than 100 single nucleotide polymorphisms (SNPs) identified, but C3435T (rs1045642) is the most widely studied. The 3435T variant is associated with decreased mRNA expression, protein expression, or both in some tissues. Although the results have been mixed, several studies report a difference in pain relief and opioid doses between reference and variant genotypes.

**Cytochrome P450 Enzymes**

Cytochrome P450s are a gene superfamily of catalytic proteins that fill important roles across the spectrum of cellular biochemical reactions, including endogenous hormone production and xenobiotic metabolism. This includes the activation of many opioids from a relatively inert compound to a pharmacologically active molecule. The enzyme CYP3A4 plays a role in the metabolism of numerous medications, including many opioids (eg, methadone, oxycodone, hydrocodone, fentanyl), but few studies link genetic variations to opioid response. The cytochrome P450 enzyme 2D6 (CYP2D6) influences the metabolism of 25% of all drug therapies, including codeine, hydrocodone, oxycodone, and tramadol, as well as tricyclic antidepressants. Genetic variation in the CYP2D6 enzyme is one of the most studied and well-understood of all the drug-metabolizing enzymes. The effect of variation on phenotype is typically classified into 4 major groups: poor metabolizers (5%–10%), intermediate metabolizers (2%–11%), extensive metabolizers (77%–92%), and ultra-rapid metabolizers (1%–2%). These percentages are based on data for whites and will vary for other ethnicities. Reports of therapeutic failure (lack of pain control, opioid-related adverse events, or both) in patients with specific genotypes receiving select opioids (codeine, hydrocodone, oxycodone, tramadol, fentanyl, methadone) suggest a significant impact of CYP2D6 genetic variants on drug efficacy and adverse-event profile. In addition, CYP2D6 metabolizer status becomes particularly important when concomitant medications affecting other pharmacokinetic pathways are used. Serious or fatal, inadvertent codeine overdose can occur when a patient with cancer and CYP2D6 ultrarapid metabolizer status is also treated with CYP3A4 inhibitors, such as clarithromycin and voriconazole. The “double hit” of hyperactivation to morphine via CYP2D6 and the reduced inactivation due to blocked CYP3A4 leads to life-threatening respiratory depression.

**Pharmacodynamics**

**OPRM1**

The µ-opioid receptor gene encoded by the genetic locus OPRM1 is the primary binding site for endogenous opioid peptides and opioid analgesics. As such, OPRM1 is a biologically plausible candidate for evaluating the role of polymorphism in the clinical effects of opioids. More than 100 SNPs have been described for OPRM1. The most prevalent and widely studied SNP is a nonsynonymous nucleotide substitution at position 118 (A118G; rs1799971). The frequency of this SNP widely varies among different races and ethnicities: 4.7% in Africans, 15.4% in Europeans, 48.5% in Japanese, and 14% in Hispanics. To assess the possible functional effect of each allele of this gene, persons are identified by 1 of 3 genotypes: homozygous G/G, homozygous A/A, or heterozygous G/A.
This SNP has been associated with variation in opioid response in a number of settings, including cancer-related pain. Numerous studies have examined the relationship of OPRM1 genetic variants to pain control in the oncology setting with mixed results.

**COMT**

COMT encodes an enzyme involved in the metabolism of catecholamines, including epinephrine, norepinephrine, and dopamine, which play a role in pain modulation. Impairment of the catechol-O-methyltransferase (COMT) enzyme, which results in increased concentrations of dopamine, can suppress the production of endogenous opioids (eg, enkephalin), which, in turn, cause subsequent opioid receptor expression upregulation. The COMT gene locus contains multiple SNPs; the most studied SNP is Val158Met, also known as rs4680. It has been postulated that this polymorphism leads to a 3- to 4-fold reduced activity of the COMT enzyme and has been associated in patients with cancer with increased sensitivity to painful stimuli (for the Val/Val genotype) and with lower doses of morphine required for satisfactory relief of pain (for the Met/Met genotype). Variation in COMT may also affect unwanted effects of opioid treatment such as sedation.

A limited number of studies have examined the relationship of variants in these genes to pain control in cancer, and nearly all of these studies have involved the acute postoperative period with outcomes related to cancer recurrence and progression. Few studies have involved patients with cancer, and patient-reported pain outcomes in relation to these genetic variants and pain relief is sparingly used. Commonly used opioids in patients with cancer and the genetic variants reported to modulate response are reviewed in the Table.

### Pharmacogenomics

**Morphine**

Because the µ-opioid receptor is the main site of action for morphine, numerous studies have evaluated the OPRM1 A118G variant in relation to pain response, adverse events, or both in patients with cancer and have had mixed results. Other variants commonly studied include COMT Val158Met and ABCB1 C3435T.

One study evaluated the relationship of 4 OPRM1 polymorphisms and pain control in 207 study patients with cancer pain. A total of 99 volunteers who completed the Brief Pain Inventory (BPI) survey and had adequate pain control were included in the final analysis. The A118G variant alone was related to morphine dose. Participants with G/G genotype (225 ± 143 mg/24 hours) required significantly higher doses of morphine when compared with participants with wild-type A/A (97 ± 89 mg/24 hours) and A/G (66 ± 50 mg/24 hours).

### Table. — Summary of Select Genetic Variants Associated With Response in Cancer Pain

<table>
<thead>
<tr>
<th>Opioid Agent</th>
<th>Study</th>
<th>Genetic Variant</th>
<th>No. of Patients</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>Reyes-Gibby²⁸</td>
<td>OPRM1 A118G COMT Val158Met ABCB1 C3435T</td>
<td>695</td>
<td>No difference in dose requirements for all variants</td>
</tr>
<tr>
<td>Morphine</td>
<td>Ross²⁵</td>
<td>CYP3A5*3 ABCB1 C1236T</td>
<td>60</td>
<td>Greater central adverse events with *3/*3 genotype</td>
</tr>
<tr>
<td></td>
<td>Belfer³³</td>
<td>COMT Val158Met ABCB1 C3435T</td>
<td>221</td>
<td>No difference in central adverse events (confusion, drowsiness, hallucination)</td>
</tr>
<tr>
<td></td>
<td>Kasai and Ikeda⁶⁹</td>
<td>OPRM1 A118G</td>
<td>99</td>
<td>Patients with G/G genotype required higher doses of morphine when compared with A/G and A/A genotypes</td>
</tr>
<tr>
<td></td>
<td>Lotsch¹⁶</td>
<td>OPRM1 A118G ABCB1 C3435T</td>
<td>137</td>
<td>Patients with OPRM1 A/A identified as having good responses indicated by decrease in numerical rating scale</td>
</tr>
<tr>
<td></td>
<td>Ravindranathan²⁵</td>
<td>OPRM1 A118G COMT Val158Met</td>
<td>207</td>
<td>Patients with OPRM1 A/A and COMT Met/Met combined required lowest morphine dose when compared with other combinations of genotypes</td>
</tr>
<tr>
<td></td>
<td>Reyes-Gibby²⁸</td>
<td>OPRM1 A118G COMT Val158Met ABCB1 C3435T</td>
<td>827</td>
<td>No difference in dose requirements for all variants</td>
</tr>
<tr>
<td></td>
<td>Ross³¹</td>
<td>COMT Val158Met</td>
<td>207</td>
<td>Patients with Val/Val genotype required higher dose of morphine compared with Val/Met and Met/Met</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Haji¹⁴</td>
<td>CYP2D6</td>
<td>450</td>
<td>No difference in pain intensity or adverse events (nausea, sedation, cognition) between metabolizer status</td>
</tr>
<tr>
<td></td>
<td>Reyes-Gibby²⁸</td>
<td>OPRM1 A118G COMT Val158Met ABCB1 C3435T</td>
<td>445</td>
<td>No difference in dose requirements for all variants</td>
</tr>
</tbody>
</table>

| ABCB1 C3435T | ¹¹⁰ | ¹³⁷ | ¹⁵⁶ | ⁶⁹ | ⁴⁴⁵ |

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had a good response. In this study, all participants were included in the analysis. Those with the Val/Val genotype received the highest dose of morphine (155 ± 160 mg/24 hours) followed by those with the Val/Met genotype (117 ± 100 mg/24 hours) and the Met/Met genotype (95 ± 99 mg/24 hour; P = .025).

Reyes-Gibby et al conducted a secondary analysis combining the results of the above-mentioned studies in the same patients to explore the joint effects of COMT Val158Met and OPRM1 A118G variants on the efficacy of morphine for cancer pain. Carriers of both wild-type OPRM1 A/A and COMT Met/Met genotypes had the lowest morphine dose (87 mg/24 hours; 95% confidence interval [CI]: 57–116), which significantly differed from study participants with neither Met/Met nor A/A who had the highest dose (147 mg/24 hours; 95% CI: 100–180). After controlling for demographic and clinical variables, such as age, sex, time from cancer diagnosis, and months using morphine, the joint-effect results remained.

Campe et al evaluated the relationship of OPRM1 A118G and ABCB1 C3435T variants to pain response in 137 study patients with cancer receiving treatment with morphine. Pain response was measured using an 11-point numerical rating scale (NRS) and the main endpoint was a change in NRS at the end of the first 7 days. At the end of the first 7 days, study patients with wild-type OPRM1 A/A genotype had a significantly greater change in NRS score (3.73; standard deviation [SD] ± 1.72) when compared with homozygous-variant study patients (0.30; SD ± 1.77). In addition, study patients with ABCB1 T/T genotype had a significantly greater change in NRS score (4.39; SD ± 2.21) than homozygous wild-type study patients (2.31; SD ± 1.73). Multivariate analysis assessed the joint effects of variation in the 2 genes. Study patients with at least 1 OPRM1 variant were the worst responders regardless of ABCB1 genotype; conversely, study patients with wild-type OPRM1 A/A genotype had a good response. Study patients with wild-type OPRM1 A/A and homozygous-variant ABCB1 T/T genotype were the best responders, with an NRS score of 4.8 ± 1.62.

Some studies report lack of association with numerous genetic variants. An observational, single time point trial with 156 study patients with cancer found no association with the OPRM1 A118G variant and response to morphine. This study evaluated numerous genetic variants in 4 genes (OPRM1, ARRB2, STAT6, and UGT2B7) and consisted of morphine responders (controlled on morphine for ≥ 1 month) and nonresponders (switched alternative agents due to inadequate analgesia with titrated doses or intolerable adverse events). No association was found with variants in OPRM1 and UGT2B7, but numerous variants in the other 2 genes were associated with response. One of the largest trials to date evaluated the influence of 112 genetic variants of 23 candidate genes on the efficacy of numerous opioids in 2,201 study patients with cancer: morphine (n = 827), oxycodone (n = 445), fentanyl (n = 695), and other opioids (n = 234). All drug doses were converted to equivalent morphine doses and pain intensity was measured using the BPI. Klepstad et al noted that all SNPs, including OPRM1 A118G, ABCB1 C3435T, and COMT Val158Met, failed to show a relationship with opioid dose. A case-control study of 221 participants with cancer treated with morphine reported no association with COMT Val158Met or ABCB1 C3435T variants and the central adverse events of confusion, drowsiness, and hallucination. Of note, other variants in COMT and ABCB1 were associated with central adverse events. Because of these conflicting data, concluding whether these variants predict morphine analgesia or adverse events is difficult. The most benefit will likely be derived from combining these markers to identify patients with a poor-response profile for which an alternative therapy may be preferred.

**Codeine**

The analgesic properties of codeine are derived from its conversion to morphine and morphine-6-glucuronide by CYP2D6 (Fig). Persons who are CYP2D6 poor metabolizers have little or no CYP2D6 enzyme activity and will not attain a meaningful degree of pain control. An important safety concern is that persons with extra copies of CYP2D6 convert codeine to morphine to a greater extent and may be at risk for adverse events such as sedation and even respiratory depression. The results of numerous studies (mainly in patients without cancer) suggest a difference in analgesia and adverse effects across CYP2D6 metabolizer statuses and these differences have been highlighted in a peer-reviewed guideline by the Clinical Pharmacogenetics Implementation Consortium. Therefore, CYP2D6 testing is useful in determining which patients will derive the most benefit from codeine use as well as patients who may be at increased risk for toxicity.

**Tramadol**

Similar to codeine, CYP2D6 is responsible for the conversion of tramadol to O-desmethyltramadol, which has a 200-fold greater affinity for the μ-opioid

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receptor target (see Fig).\textsuperscript{21} Several studies have reported that CYP2D6 poor metabolizers display decreased analgesic response with tramadol than those who are extensive metabolizers.\textsuperscript{37-39} No studies have focused on the pharmacogenomics of tramadol specifically in a cancer population; however, given the evidence in other pain populations, tramadol is likely to have reduced clinical benefit in patients who poorly metabolize CYP2D6.\textsuperscript{37-39}

**Oxycodone**

The majority of oxycodone is metabolized to noroxycodone by CYP3A4 (see Fig).\textsuperscript{40} A smaller percentage (11\%) is converted by CYP2D6 to the active metabolite oxymorphone, which has a 40-fold higher affinity and 8-fold higher potency for \( \mu \)-opioid receptors than oxycodone.\textsuperscript{21} Studies evaluating CYP3A4 variation to oxycodone response are scarce, whereas studies in healthy volunteers and postoperative patients have reported mixed results on CYP2D6 polymorphisms and response to oxycodone.\textsuperscript{15} In a cross-sectional study of 450 study patients with cancer treated with oxycodone, Andreassen et al\textsuperscript{22} reported no difference in pain intensity using the BPI or the incidence of adverse events (nausea, sedation, cognitive) between CYP2D6 metabolizer statuses.

In the large study of 2,201 study patients with cancer being treated with various opioids, including 445 of whom were treated with oxycodone, Klepstad et al\textsuperscript{31} could not determine an association with \( OPRM1 \), \( ABCB1 \), and \( COMT \) variants (as well as numerous other genes) and opioid requirements. Based on this evidence, little basis exists for the use of pharmacogenomics to personalize the use of oxycodone therapy in patients with cancer.

**Hydrocodone**

Hydrocodone is metabolized by CYP2D6 to the active metabolite hydromorphone, which has a 10- to 33-fold greater affinity for \( \mu \)-opioid receptors than hydrocodone (see Fig).\textsuperscript{40} Additional metabolism includes the formation of norhydrocodone by CYP3A4, and 40\% of clearance is attributed to non-CYP pathways.\textsuperscript{40} No studies have focused on the pharmacogenomics of hydrocodone specifically in a cancer population. Thus, little basis exists for the use of pharmacogenomics to personalize the use of hydrocodone therapy in patients with cancer.
**References**

Communication between patients, their relatives, and health care staff is very important when administered palliative sedation.

Palliative Sedation in Patients With Cancer
Marco Maltoni, MD, and Elisabetta Setola, MD

Background: Palliative sedation involves the use of sedative medication to relieve refractory symptoms in patients by reducing their level of consciousness. Although it is considered an acceptable clinical practice from most ethical points of view, palliative sedation is still a widely debated procedure and merits better understanding.

Methods: The relevant medical literature pertaining to palliative sedation was analyzed and reviewed from various technical, relational, and bioethical perspectives.

Results: Proportionate palliative sedation is considered to be the most clinically appropriate modality for performing palliative sedation. However, guidelines must be followed to ensure that it is performed correctly. Benzodiazepines represent the first therapeutic option and careful monitoring of dosages is essential to avoid oversedation or undersedation.

Conclusions: Proportionate palliative sedation is used to manage and relieve refractory symptoms in patients with cancer during their last days or hours of life. Evidence suggests that its use has no detrimental effect on survival. A different decision-making process is used to manage the withdrawal of hydration than the process used to determine whether proportionate palliative sedation is appropriate. Communication between patients, their relatives, and the health care staff is important during this medical intervention.

Introduction
Within the context of palliative medicine, the practice of drug-induced sedation for symptom control — the use of all possible antisymptomatic treatments notwithstanding — is called palliative sedation. Historically, palliative sedation was often known as terminal sedation because it was considered a last resort in the final phase of a patient’s life. However, terminal sedation is a confusing and inappropriate term because it implies that the practice is designed to shorten life; thus, more appropriate terminology was needed and, hence, the term palliative sedation. Its implementation into everyday clinical practice has led to the use of the term in the majority of studies focusing on this topic.1

By reducing the level of consciousness, palliative sedation uses sedative medication to control refractory symptoms in patients with cancer.2 As this approach became more widespread and was acknowledged as an important part of palliative care, procedural principles were needed to avoid malpractice. The guidelines created clarified the definition and practice of palliative sedation, also underlining its inherent and intrinsic difference from euthanasia.3-10 Various guidelines...

Photo courtesy of Lisa Scholder. Organic Walk, 16" x 24".
state that sedation in palliative care is a therapy mainly performed in the last days or hours of life, with an unambiguous aim, a precise procedure, and well-defined results — all of which are in contrast to those of euthanasia.9-12 In addition, use of palliative sedation does not hasten death when conducted in accordance with standard guidelines.13-15

**Methods and Types**

Some adjunctive characteristics of palliative sedation have been included in more detailed definitions of the practice.16 For example, the definition of palliative sedation as the “intentional administration of sedative drugs in dosages and in combinations required to reduce the consciousness of a terminal patient as much as necessary to adequately relieve one or more refractory symptoms,” considers a number of specific parameters, including short-term prognosis, proportionality of the intervention, effectiveness of the sedation through adequate monitoring, and refractoriness of symptoms.16 This definition also implies that palliative sedation is not a fixed intervention; rather, it is a dynamic process that can be adapted to the needs of the patient.16

Palliative sedation can vary in terms of depth of sedation and correlated level of unconsciousness, continuity, drugs used, and rapidity of implementation (Table 1). In that sense, palliative sedation is not necessarily deep continuous sedation or continuous sedation until death, which is the last step of a progressive process.

**“Proportionality” Theme**

When symptom-guided, dose-titrated, and result-assessed, palliative sedation can be a progressive or sudden procedure (see Table 1). Choice of sedation has a clinical basis and is oriented toward different clinical needs: rapid palliative sedation for catastrophic and acute symptoms compared with proportional sedation for progressively worsening symptoms. Thus, implementing palliative sedation is based on the suddenness of symptom appearance.

Different methods of palliative sedation exist, namely, the proportional method of palliative sedation (also called proportionate palliative sedation), and sustained, deep and continuous palliative sedation from the onset, regardless of the intensity of symptoms.17-21 The latter suggests that relational continuity between patients and relatives is not necessarily a value, that the concept of hastening or not hastening death is irrelevant (given the patient’s condition), and that the process of drug titration may delay the clinical effect of sedation. We consider that the supporters of this view are in favor of administering drugs in a “standardized” way, which leads to deep sedation, and interrupting all forms of hydration and nutrition. Taking this concept to an extreme, many patients in this setting would be candidates for deep continuous sedation or continuous sedation until death. In our opinion, those in favor of using palliative sedation in this way do not consider that this view is a departure from the original practice; indeed, such an approach could be counterproductive to its large-scale implementation.

By contrast, some proportional palliative sedation supporters view proportionality as a fundamental characteristic of palliative sedation and maintain that relational continuity is an important issue.6,14 They also argue that the effects of palliative sedation on refrac-

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td><strong>Depth</strong></td>
<td></td>
</tr>
<tr>
<td>Superficial</td>
<td>Patient conserves (at least partially) the ability to communicate with family or caregivers</td>
</tr>
<tr>
<td>Deep</td>
<td>Patient enters a state of total unconsciousness</td>
</tr>
<tr>
<td><strong>Continuity</strong></td>
<td></td>
</tr>
<tr>
<td>Intermittent</td>
<td>Sedation is performed for a limited period of time for a specific symptom and discontinued if a reduction (albeit slight) in the distress caused by the symptom has been obtained</td>
</tr>
<tr>
<td>Continuous</td>
<td>Drugs are administered without interruption to obtain a persistent effect, which more frequently occurs near death and in severe cases</td>
</tr>
<tr>
<td><strong>Use of Drugs</strong></td>
<td></td>
</tr>
<tr>
<td>Primary palliative sedation</td>
<td>Sedatives are used to lower the level of consciousness</td>
</tr>
<tr>
<td>Secondary palliative sedation</td>
<td>Dosage of drugs primarily used for symptom control (ie, morphine for pain or dyspnea) is increased to make use of an adverse event (eg, somnolence) to reduce the level of consciousness (not recommended)</td>
</tr>
<tr>
<td><strong>Rapidity of Administration and Effect</strong></td>
<td></td>
</tr>
<tr>
<td>Progressive</td>
<td>Most common method in which the dose of sedative drugs is monitored and modified according to patient needs</td>
</tr>
<tr>
<td>Sudden, rapid intervention method</td>
<td>Also called “emergency” sedation; required for a catastrophic event such as massive bleeding, severe dyspnea, agitated delirium, or acute pain</td>
</tr>
</tbody>
</table>
tory symptoms must be carefully monitored to avoid undersedation or oversedation and that the drug dosage should be individually titrated to the minimum effective dose level. Not every palliative sedation is deep continuous sedation or continuous sedation until death, and the latter approach is required in patients for whom a lower level of sedation is insufficient to control refractory symptoms. A survey carried out by Putman et al on intention and practice in US physicians reported that many of these physicians preferred the proportional method, because they did not wish to pursue full unconsciousness in patients without monitoring the effect of such sedation.

Moreover, some of the first articles published on palliative sedation were based on the use of a proportional, clinical, symptom-guided form of sedation. This form of palliative sedation is accepted by most ethical points of view, cultural perspectives, and procedural guidelines. ten Have and Welie used the term mission creep to describe the intention of shortening life — however small — by using deep sedation, concluding that such an approach cannot be considered palliative sedation. In a clinical context, mission creep occurs when a specific practice considered appropriate in a given situation is gradually extended for use with different indications, groups of patients, and different intentions.

Prevalence and Settings

The debates about the characteristics and how to define palliative sedation are reflected in the wide-ranging prevalence of the practice observed in the literature (1%–88%), which can be attributed to a number of factors:

- Different health care settings
  Higher prevalence in inpatient acute tertiary palliative care units compared with home-care hospice programs.

- Different case mixes in similar settings
  In a comparison between 2 Italian hospices, a statistically significant difference in prevalence of sedation initially observed in the 2 populations disappeared when the groups were corrected for age and duration of stay in hospice. This was interpreted as an indication that younger patients and those admitted for acute symptoms required more palliative sedation interventions than older patients admitted to the hospice for psychosocial reasons.

- Degree of adherence to palliative sedation guidelines or level of competence and expertise of health care professionals
  Little experience in managing difficult symptoms may increase the prevalence of palliative sedation. The decision to initiate palliative sedation should be taken together with a palliative care specialist to ensure that all other options have been explored. In the event of insufficient psychological support, the palliative care team may be at risk of burnout and, thus, might perform unnecessary palliative sedation.

- Adoption of wider or narrower definition of palliative sedation may influence prevalence
  However, the real frequency of palliative sedation has also been suggested to vary: possibly between 25% and 35% of all patients admitted to a hospice or palliative care unit. In home-care hospice programs, palliative sedation may be a feasible option. Mercadante et al reported that 13.2% of patients with cancer were sedated in their homes.

Symptoms and Refractoriness

Management of refractory symptoms is the single indication for use of palliative sedation. The definition of a refractory symptom, which was first proposed by Cherny and Portenoy, is still widely accepted: “Symptom for which all possible treatment has failed, or it is estimated that no methods are available for palliation within the time frame and the risk:benefit ratio that the patient can tolerate.” The concept of refractoriness has been associated with that of unbearable suffering, multidisciplinary evaluation, and a prognosis of short-term survival.

Prior to offering sedation, all other available medications, procedures, and interventions should be considered and offered as appropriate. When possible, discussions should take place with patients, their relatives, and their caregivers so that an agreement can be made about the action to be taken. All dimensions of the symptom (physical, psychological, social, emotional, existential/spiritual) must be taken into account and help offered for each component. Physical symptoms that are most prone to refractoriness include delirium and dyspnea; both are frequently present as death approaches, and their timely management is crucial. Pain and emesis may also become refractory, albeit this occurs less frequently. Palliative sedation...
is occasionally used for intractable seizures or terminal hemorrhage (Fig 1).

Psychological distress and existential suffering are complex and challenging. These terms encompass issues such as meaninglessness of life, sense of hopelessness, perception of self as a burden to others, feeling dependent on others, feeling isolated, grieving, loss of dignity and purpose, fear of death of self, or fear of the unknown. Multidimensional management directed at the physical, psychological, and existential aspects is recommended, with support provided by psychologists, psychiatrists, chaplains, ethicists, or palliative care specialists.

Psychological distress and existential suffering have many peculiarities. Psychological distress can occur at any time during the course of a disease, and supportive interventions, psychological interventions, or both types of interventions may be ineffective and do not completely resolve the problem; however, this does not mean that the distress is refractory. Rather, psychological distress may not have a progressive course similar to that associated with physical symptoms; its course is often unpredictable. For these reasons, frequent meetings with the palliative care team are needed; the same may be true of spiritual assistance. Intermittent or relief sedation, rather than continuous sedation, may also be beneficial.

Some authors have focused on the search for early determinants for continuous palliative sedation so that patients at risk can be identified in a timely manner and their symptoms managed by other strategies. Information on determinants that more frequently lead to use of palliative sedation could also be used to assess the need for advanced care planning. However, study results have suggested that implementing palliative sedation is more often linked to the attitudes and beliefs of physicians and to organizational settings than to the clinical needs of patients. Other studies found a correlation between palliative sedation and higher doses of opioids used prior to implementing palliative sedation as well as between palliative sedation and younger patient age.

**Duration**

The mean or median length of palliative sedation ranges from 0.8 to 12.6 days. One study observed an even larger range (0–43 days), despite mean and median times in line with the literature (4 and 2 days, respectively). In this study, 10.8% of patients underwent palliative sedation for more than 10 days and 3.4% of patients for more than 20 days. Patients requiring sedation for more than 10 days had fewer rates of delirium and dyspnea, milder and more frequent use of secondary palliative sedation, and higher rates of psychological distress than their counterparts.

**Drugs**

The most widely used drug for palliative sedation in the context of palliative care is midazolam, which is a benzodiazepine prescribed in 9 of the 11 studies evaluated (Fig 2). Midazolam is prescribed in a wide dose range; for example, in 1 study, 61% of patients used doses no more than 30 mg and 8% of patients used doses of at least 120 mg. The highest final daily dose of midazolam was correlated with age (the younger the patient, the higher the dose) and treatment duration (the longer the treatment, the higher the dose). Midazolam has a rapid onset of action and short half-life, and both of these pharmacokinetic features facilitate the titration procedure during the first phase of sedation. When an adequate minimum dose (or, in some settings, a loading dose) has been identified for symptom control, a maintenance dose should be started by continuous intravenous or subcutaneous infusion. Because midazolam has anticonvulsant, muscle-relaxant, hypnotic, and anxiolytic properties, it can be added to other sedative classes to achieve control of these specific symptoms.

Some studies advocate use of neuroleptics for delirium (eg, haloperidol). Haloperidol has less sedating power than midazolam, so it is typically used to attenuate delirium; thus, it is not the most appropriate choice of drug for achieving continuous sedation. Other drugs used for palliative sedation have included levomepromazine, chlorpromazine (especially when profound sedation is needed for acute agitated delirium), propofol, ketamine, and dronabinol. If a patient undergoing sedation is treated with an opioid for pain or dyspnea, then the opioid must not be interrupted. By contrast, opioids should not be used for sedation, because doing so would make use of their secondary effect (somnolence) and would be considered secondary palliative sedation, which is not recommended.

Guidelines for palliative sedation recommend close surveillance of patients with respect to the management and relief symptoms and suffering, depth of sedation (level of consciousness), and potential adverse events of sedation.\(^5\)\(^-\)\(^10\) Family members of patients and their health care team should be monitored for psychological and spiritual distress.\(^3\)\(^-\)\(^8\) Vital signs should be assessed in nonimminently dying patients undergoing short-term, intermittent, or light sedation.

Evaluating symptom relief or relief of suffering in unconscious patients can be difficult. Some scores monitoring verbal or facial expression, body movements, and response to nonpainful stimuli may be useful when deep sedation is performed, and some authors have suggested using the level of sedation as a proxy for evaluating symptoms.\(^3\)\(^-\)\(^25\)\(^-\)\(^31\)

Depth of sedation is a common theme in studies and the tools used to assess it can vary. For example, guidelines from the European Association for Palliative Care recommend the Critical-Care Pain Observation Tool or the Richmond Agitation-Sedation Scale (RASS).\(^52\)\(^-\)\(^55\) A prospective study performed by Arevalo et al\(^54\) evaluated the validity and reliability of 4 scales: the Minnesota Sedation Assessment Tool, the RASS, the Vancouver Interaction and Calmness Scale, and a sedation score proposed by the Royal Dutch Medical Association. The RASS was as reliable as the score proposed by the Royal Dutch Medical Association and study results claimed that the RASS was the least time consuming, clearest, and easiest to use of the 4 tools.\(^54\)\(^-\)\(^55\) Another study tested a modified form of RASS (RASS-PAL) for use in patients in the palliative care unit, observing that the tool was useful for assessing sedation; however, further validation studies are needed to confirm these results.\(^56\)

More objective methods to evaluate depth of sedation have been proposed because some sedated patients may continue to experience symptoms without being able to communicate their distress.\(^57\)\(^-\)\(^58\) Deschoppe\(^59\) proposed a mixed-evaluation method that combined use of a scale, a subjective assessment by professionals, as well as neuroimaging, electrophysiological techniques, or both. However, such an approach is impractical in end-of-life care and may be more suited to a research setting.\(^57\) A systematic review of the literature revealed that 5 clinical studies and 1 guideline-based article included use of a validated scale to evaluate the results of palliative sedation.\(^58\) During the titration phase of sedation, clinical parameters should be evaluated every 15 to 30 minutes, but the exact interval should be calculated on the basis of the drugs, doses used, and clinical conditions of the patient; once an appropriate level of sedation has been achieved, the frequency of assessment can be reduced to once every 24 hours.\(^3\) One Cochrane review evaluated the impact of palliative sedation on quality of life and participant well-being.\(^55\) None of the 14 studies included in the review took any of the above issues into consideration.\(^15\) The impact on symptoms was partially reported and with different methods, thus making data pooling impossible.\(^15\) Furthermore, the studies reviewed had numerous biases, with the authors concluding that the data are insufficient and the evidence is of poor quality with regard to the qualitative effectiveness of palliative sedation.\(^13\) They also recommended that studies on palliative sedation focus on qualitative, rather than quantitative, end points (ie, length of survival from the start of palliative sedation).\(^15\)

**Impact on Survival**

For some, the impact of palliative sedation on survival is not an issue that merits much attention, given that the priority of palliative sedation in the end-of-life setting is quality of life; thus, even a detrimental effect on survival may not be considered of particular relevance.\(^39\) By contrast, some physicians may consider it fundamental to know whether the sedation proposed has a high, medium, or low risk of hastening the death of their patient.\(^14\) However, this question cannot be studied with the highest evidence-based methodology. Although the authors of the Cochrane review were unable to pool data on qualitative outcomes of palliative sedation, they did provide reasonably good, quantitative evidence that palliative sedation does not have a detrimental impact on survival.\(^15\) The authors looked at 14 studies involving 4,167 adults — nearly one-third of whom were sedated.\(^13\) Survival time measured from admission or referral to death was not statistically significant between those who were sedated and those who were not.\(^15\) A prospective study of patients admitted to hospices matched patients who were sedated and those who were not for sex, age, reason for admission, performance status, and prognostic score.\(^13\) Survival from admission to death was compared between the 2 groups and no detrimental effect of palliative sedation on survival was found.\(^13\) Of note, even intensive procedures, deep continuous sedation or continuous sedation until death, did not hasten death when performed in a proportional, step-by-step manner.\(^13\) A subsequent systematic review also identified 11 studies totalling approximately 2,000 patients.\(^14\) No difference in survival was seen between patients receiving hospice care who underwent sedation (median, 7–27 days) and those who did not (median, 4–40 days).\(^14\)

Such results confirm that palliative sedation can be considered a legitimate clinical intervention from most ethical viewpoints and that the principle of double effect is unnecessary to justify its practice. This ethical criterion is appropriate in a small percentage of patients receiving sedation in whom respiratory or circulatory function depression is recorded following...
palliative sedation (3%–4%) and hypothesized as having potentially hastened death. In that sense, it may be appropriate to consider this effect a serious adverse event, which could occur after any medical or surgical procedure.

**Ethical Considerations**

If a survival impact of palliative sedation was ever demonstrated, then palliative sedation might have been equated with “slow” or “soft” physician-assisted suicide; however, absence of a detrimental impact on survival is sufficient to distinguish palliative sedation from physician-assisted suicide. The European Association for Palliative Care has identified 3 areas in which palliative sedation differs from euthanasia:

- The intention of palliative sedation is to provide relief from unbearable suffering caused by a refractory symptom, whereas euthanasia is designed to end the life of someone who is suffering.
- Palliative sedation is a proportionate and symptom intensity–guided procedure using the minimum useful dose of a sedative drug (eg, a benzodiazepine); it is individually oriented and monitored. Conversely, euthanasia uses neuromuscular relaxants and barbiturates and is not monitored on the basis of the symptom relief obtained.
- Success of palliative sedation is measured in terms of the relief it provides from distress.

Although palliative sedation does not play a role in hastening death, its use prevents many patients from maintaining verbal contact with their relatives, which makes it unique among medical interventions. Injudicious uses of palliative sedation include inadequate assessment of potentially reversible causes of severe symptoms, lack of involvement of specialists in the condition underlying the presenting symptoms, excessive use by overwhelmed health care professionals, performing the procedure at the request of the relative, and untimely start (ie, too early, too late).

Although some may view palliative sedation, deep continuous sedation, or continuous sedation until death as bringing patients to a sort of “living dead-like” state in which they are no longer considered persons, it is our opinion that patients who are sedated can be talked to, wanted, cared for, and loved by their relatives, sometimes “answering” with their presence in surprising and unexpected ways. The “innate” core of personhood (“individual component”) has been suggested to persist even after relational and societal components are severely reduced.

**Nutrition and Hydration**

Those who believe that palliative sedation plays a role in hastening death may place most of the responsibility for this “secondary effect” on the simultaneous interruption of artificial nutrition and hydration — both of which are considered medically assisted treatments or as vital support interventions, at least in this patient setting. However, medically assisted hydration is a topic more often discussed, given that artificial nutrition may be interrupted prior to palliative sedation due to its proven lack of impact on the duration and quality of life of patients with a terminal disease. The role of hydration in end-of-life care is subject to different perspectives and is widely discussed in the literature. In certain situations, excess hydration can lead to water retention and exacerbation of pleural or peritoneal effusion, among other problems; by contrast, interrupting liquids may provoke thirst and an increase in drug metabolites, worsening delirium, and agitation, thus making it difficult for patients to communicate distress. Thus, maintenance or withdrawal of hydration must be individually evaluated and managed.

Results from a large epidemiological study on 20,480 questionnaires completed by physicians experienced in deep continuous sedation or continuous sedation until death showed that, even in this “extreme” form of sedation, up to two-thirds of patients continued hydration for clinical reasons. The take-home message is that use of palliative sedation and evaluation of whether or not to continue hydration involve 2 different decision-making processes. Thus, hydration does not have to be automatically stopped because palliative sedation has begun.

**Communication and Decision-Making Process**

Talking about death with patients and their families is a delicate and challenging aspect of palliative care. Ideally, discussions of this kind should be initiated when a patient’s prognosis is years to months and then reevaluated when the patient’s life expectancy decreases to months to weeks. The conversation should be a balance between maintaining hope and realistic and achievable goals. Health care professionals must plan these end-of-life interventions by taking into account the goals, values, needs, and wishes of the patient. Patients should be asked where they prefer to die so that adequate plans can be made to respect their request. All decisions should be documented in the patient’s medical records. When a health care professional recognizes the imminence of suffering, he or she should discuss the possibility of sedation with the patient, outlining the aims, risks, and benefits of the procedure. The patient may not want to broach the subject and may authorize the health care professional to make decisions on his or her behalf or delegate a caregiver to do so. If the patient is no longer capable of making an autonomous decision, then the health care professional may approach a family member or a surrogate decision maker to clarify the patient’s wishes.
A multidisciplinary team of oncologists, palliative care specialists, psychologists, psychiatrists, nurses, chaplains, or spiritual advisors, among others, may also form the decision-making group, together with the patient and his or her family.\(^5\) In particular, such a team can help ensure that all conditions have been met for palliative sedation, that informed consent is obtained, that the type of intervention has been planned, and then modify any plans, when and if necessary, during the course of sedation. Further therapeutic interventions may also be performed if other conditions arise (eg, urinary retention, constipation, myoclonus, “death rattle”).

Keeping an open dialog with relatives and the patient’s loved ones throughout the palliative sedation process is fundamental so that they understand the characteristics of this medical intervention (ie, it is performed in the absence of other means to manage refractory and unbearable symptoms; it neither hastens nor postpones death; it reduces or eliminates the possibility of verbal communication with patients; clinical conditions permitting, it is reversible in nature; it is carefully monitored to avoid oversedation or undersedation; it is performed for the well-being of patients).\(^{68,69}\)

Although some relatives experience psychological distress, Bruinsma et al\(^69\) reported that most are comfortable with palliative sedation if they are appropriately informed about the procedure and actively involved in the decision-making process. A study of Swiss caregivers of patients who died while undergoing palliative sedation found that most caregivers agreed about the timing of the initiation of palliative sedation and confirmed that it led to a substantial improvement in refractory symptoms.\(^70\) In a small study of Dutch relatives of patients receiving palliative sedation until death, many of the relatives acknowledged that palliative sedation was indicated, but they felt that communication between the health care professionals and the relatives was poor.\(^71\)

Although an open dialog between the health care team, the patient, and his or her family members and loved ones is important, we do not feel that such open communication is always respected. In an Italian study of communicative behavior in 2 different hospice settings, family involvement in the decision-making process with regard to palliative sedation was 100% in both hospices, but the rate of patient participation in such decision-making varied from 24% to 59%.\(^35\) Another study of Dutch and US physicians revealed that open discussion among physicians, patients, and families was more diffuse in The Netherlands than in the United States.\(^72\) However, the study involved too few cases to conclude that an international difference exists when communication about sedation due to different cultural approaches.\(^72\) In a group of 27 sedated patients, a Portuguese case study determined that the decision to begin sedation was made by health care professionals alone in 21 cases.\(^39\) The authors attributed this result to the fact that 76% of study patients required urgent and nonpostponable sedation.\(^38\)

Nurses also play an essential role in the decision-making process. A survey of 576 nurses from The Netherlands showed that most responders had cared for at least 1 patient who received palliative sedation.\(^73\) Nearly all of the nurses indicated that they had been involved in the decision to perform palliative sedation and were present when palliative sedation was started, unlike the physicians who were present in fewer than 50% of cases.\(^73\) A study of Flemish nurses also revealed that the majority of the nurses supported use of palliative sedation for refractory symptoms.\(^74\) Patel et al\(^75\) studied the attitudes and perspectives of nurses working with patients receiving palliative sedation in 3 different settings (oncology, intensive care, and hospice), highlighting their ability to define palliative sedation, their skill set for administering palliative sedation, policy, and procedural guidelines, and their education on palliative sedation and end-of-life care.

**Guidelines**

Many clinical associations and international agencies have produced procedural guidelines for use of palliative sedation so as to provide health care professionals with a framework on which to base the clinical decision-making process.\(^3-10\) Key issues in palliative sedation were also addressed in a 10-item framework created by the European Association for Palliative Care (Table 2).\(^5,6\) An audit performed in a single center to assess adherence to guidelines on palliative sedation in

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<th>Description of necessary evaluation and consultation procedures</th>
<th>Indications for informed consent requirements</th>
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<tr>
<td>Indications for need to discuss decision-making process with patient’s family</td>
<td>Indications for selecting method of sedation</td>
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<td>Indications for dose titration, patient monitoring, and care</td>
<td>Indications for needs of the patient’s family</td>
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**Table 2. — European Association for Palliative Care 10-Item Framework for Guidelines in Palliative Sedation**

<table>
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<th>Need for preemptive discussion of potential role of sedation in end-of-life care and contingency planning</th>
<th>Description of when sedation is indicated</th>
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a palliative care unit confirmed an adherence rate of 100%. Conversely, a survey of Dutch general practitioners revealed a high resistance to following guidelines, and this was particularly true with regard to the inadvisability of using palliative sedation without previous expert consultation and to the recommendation of the involvement of a multidisciplinary palliative care team. Without such an approach, misconceptions about palliative sedation may be further misconstrued and perpetuated.

Conclusions

Some patients with cancer experience refractory symptoms during the last hours or days of their life and are no longer responsive to antisymptomatic treatments. Managing such symptoms is the objective of palliative sedation, a proportional medical approach that must be individually tailored to each patient and closely monitored. Under sedation and oversedation can be avoided by titrating the level of sedating drugs to the minimum useful dose (termed proportionate palliative sedation). A different approach involving standardized drug dosages and deep continuous sedation or continuous sedation until death risks being performed with the total or partial intention to hasten death. However, palliative sedation should only be used in a proportional way; such a view has been accepted by many bioethical viewpoints.

Although evidence suggests that proportionate palliative sedation does not have a detrimental impact on survival, further research is needed to monitor the qualitative results of the procedure. Benzodiazepines — in particular, midazolam — are the first choice of drugs for this type of sedation. The decision-making process to initiate proportionate palliative sedation is complex and should involve patients, their relatives and loved ones, and the healthcare team. This process varies from those used for other clinical decisions such as maintenance or withdrawal of artificial nutrition and hydration. Proportionate palliative sedation is a universally accepted medical intervention that differs from physician-assisted suicide in terms of intention, procedure, and results.

Acknowledgments: The authors thank Gráinne Tierney and Ursula Elbling for editorial assistance.

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10. Tierney and Ursula Elbling for editorial assistance.


Progress has been made in recent years for integrating psychosocial care into routine cancer care, but more work is needed.

Integrating Psychosocial Care Into Routine Cancer Care

Paul B. Jacobsen, PhD, and Morgan Lee, MA

Background: Despite growing recognition that psychosocial care is an essential component of comprehensive cancer care, evidence suggests many patients with cancer do not receive needed psychosocial care.

Methods: Four areas were identified as potentially increasing the number of patients with cancer who receive needed psychosocial care: (1) formulating care standards, (2) issuing clinical practice guidelines, (3) developing and using measurable indicators of quality of care, and (4) demonstrating projects designed to improve the delivery of care.

Results: Standards for psychosocial care are identified, including a standard issued in 2015 by an accrediting organization. Three clinical practice guidelines for provisioning psychosocial care are also identified and reviewed. Methods for monitoring the quality of psychosocial care are characterized and the impact of monitoring changes in quality are evaluated in relation to existing evidence. Examples are provided of 2 large-scale efforts designed to improve the delivery of psychosocial care in community settings.

Conclusions: Although considerable progress has been made in integrating psychosocial care into routine cancer care, work must still be done. Additional progress will be fostered by continued efforts to promote adherence to clinical practice guidelines and care standards for psychosocial care and by the development and dissemination of models that demonstrate how practices can implement these guidelines and standards.

Introduction

Recognition is growing that psychosocial care is an essential component of the comprehensive care of people diagnosed with cancer. In addition to attempting to extend survival rates in people following a cancer diagnosis, the oncology community is recognizing the value of quality of life. Psychosocial care, with its goals of relieving emotional distress and promoting well-being, is central to efforts to improve quality of life. However, evidence suggests that many patients with cancer who might benefit from psychosocial care do not receive it.

Four areas of activity have the potential to increase the number of patients who receive needed psychosocial care:

1. Formulating care standards that address the psychosocial component of care
2. Issuing clinical practice guidelines for the psychosocial care of patients with cancer
3. Developing and using measurable indicators of quality of psychosocial care in oncology settings
4. Demonstrating projects designed to promote the greater implementation of standards for psychosocial care
Definitions
Standards in medical care refer to diagnostic or treatment processes that health care professionals should follow for certain classes of patients, illnesses, or clinical circumstances. Standards may be developed based on evidence, expert consensus, and/or ethical and safety considerations. With regard to the psychosocial domain, standards of care represent recommendations for the organization and delivery of psychosocial care that apply to patients seen in the oncology setting.

Clinical practice guidelines are systematically developed statements designed to assist health care professionals and patients in making decisions about appropriate health care based on specific characteristics of the patient (eg, age, comorbidities), illness (eg, disease severity), or clinical circumstances (eg, symptom presentation). Similar to standards, clinical practice guidelines can be developed based on evidence, expert consensus, and/or ethical and safety considerations.

In general, measuring the quality of care involves assessing the extent to which an organization and delivery of care conforms to standards of care and clinical practice guidelines. A widely used model dating from the 1960s differentiates 3 components important to consider in evaluating quality, namely: (1) the structure of care (eg, resources or personnel), (2) the processes of care (eg, performance of specific diagnostic procedures or treatments), and (3) outcomes of care (eg, survival rates). Methods for assessing the quality of psychosocial care have primarily focused on evaluating processes of care.

Standards
Efforts to promote greater awareness of the importance of psychosocial care for patients with cancer received a boost following a 2008 publication from the Institute of Medicine (IOM) summarizing evidence regarding the deleterious effects of unmet psychosocial needs and benefits of providing psychosocial services. Despite evidence supporting the effectiveness of psychosocial services, the IOM concluded that many patients do not receive help for problems that might benefit from this type of care. To address this problem, the report included a list of recommended actions, including that all entities establishing or using standards for the quality of cancer care adopt a standard that calls for the provision of appropriate psychosocial health services. The recommendation further identifies certain processes and goals of care as being components of this standard (Table).

Several initiatives predate the IOM report in proposing standards that address psychosocial care. For example, the National Comprehensive Cancer Network (NCCN) included standards of care as part of its clinical practice guidelines for the management of cancer-related distress first published in 1999. In addition to identifying policies and procedures related to screening for and managing distress, the NCCN standards call for the formation of interdisciplinary committees

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<th>Summary and Comments</th>
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<td>American College of Surgeons Commission on Cancer</td>
<td>Specifies standards for organizing, delivering, and monitoring of oncology services. Presented as requirements evaluated during accreditation review. Key example of standards for psychosocial care: • Cancer committee develops and implements a process to integrate and monitor on-site psychosocial distress screening and referral for psychosocial care.</td>
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<tr>
<td>Canadian Association of Psychosocial Oncology</td>
<td>Specifies standards of care for organizing and delivering psychosocial health services. Presented in sections (key principles, organization and structure, educational standards for providers, standards of care) Key examples of standards for psychosocial care: • People at risk for or living with cancer are entitled to psychosocial screening using a standardized approach. • People affected by cancer are entitled to access appropriate levels of treatment to address their needs.</td>
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<tr>
<td>Institute of Medicine</td>
<td>Specifies standards for providing appropriate psychosocial services. Presented as processes and goals of care. Key examples of processes and goals of psychosocial care: • Facilitate effective communication between patients and health care professionals. • Identify psychosocial health needs of each patient. • Design and implement a plan to link patient with needed services. • Follow-up on, re-evaluate, and adjust plan.</td>
</tr>
<tr>
<td>National Comprehensive Cancer Network</td>
<td>Specifies standards of care for distress management. Presented as imperatives focused on distress management. Key examples of standards for distress management: • Distress should be recognized, monitored, documented, and promptly treated. • Screening should identify the level and nature of distress. • Distress should be assessed and managed according to clinical practice guidelines. • Interdisciplinary institutional committees should be formed to implement standards for distress management. • Experienced licensed mental health professionals and certified chaplains should be available as staff members or by referral.</td>
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at each institution to implement guidelines for distress management and for the availability of trained, on-site professionals or by referral to deliver psychosocial care (see Table).2,4-6

Initiatives promoting standards for the psychosocial care of patients with cancer are not limited to the United States. For example, the Canadian Association of Psychosocial Oncology developed standards in 1999 and updated them again in 2010.4,8 In addition to identifying procedures for psychosocial screening and treatment, these standards cover the organization and structure of psychosocial services and the education and training of psychosocial care providers.4

Most standards for psychosocial care are developed by organizations and committees composed of members of the psychosocial oncology clinical and research communities. Thus, concerns exist about the extent to which the wider oncology community has been cognizant of these standards and has adopted them.9 Efforts to promote the adoption of such standards would benefit patients if major accrediting organizations included psychosocial care among their standards.

One such organization is the American College of Surgeons (ACS) Commission on Cancer (CoC), which is a consortium of 47 professional organizations.10 The ACS CoC establishes cancer care standards and monitors the quality of care at approximately 1,500 hospitals, which are estimated to provide care to 70% of patients with cancer in the United States.10 In 2012, the ACS CoC released several standards for patient-centered care.5 Among them is a standard specifying that a local oversight committee should develop and implement a process for psychosocial distress screening and referral for psychosocial care (see Table).2,4-6 These standards are being evaluated in 2015 as part of the ACS CoC accreditation process.11

**Clinical Practice Guidelines**

Worldwide, numerous organizations have proposed clinical practice guidelines that include recommendations for the psychosocial care of people with cancer.12 For brevity, only the details of 3 North American–based guidelines for psychosocial care will be covered in this article.

**National Comprehensive Cancer Network**

Clinical practice guidelines from the NCCN for distress management were first issued in 1999; they are updated every year and include recommendations for psychosocial screening, evaluation, treatment, and follow-up primarily presented in the form of algorithms or decision pathways.6 Most of the recommendations represent uniform consensus among experts from NCCN member institutions based on lower-level evidence (eg, clinical experience of expert providers) rather than higher-level evidence (eg, results of randomized controlled trials).

Recommendations for the management of mood disorders (eg, major depression) help illustrate how the clinical practice guidelines are organized. For example, the NCCN guidelines recommend that all patients undergo brief psychosocial screening for distress using a valid and reliable self-report tool.6 The importance of systematic screening is underscored by research indicating that oncologists typically underestimate the level of distress in their patients.13-15 For patients who have moderate to severe distress, referral to psychosocial care professionals is recommended.6 If patients are displaying signs and symptoms of a mood disorder, the initial recommendation is further evaluation, diagnostic studies, and modification of the factors potentially contributing to the symptoms (eg, concurrent medications, pain).6 Based on these findings, subsequent recommendations may include initiating psychotherapy and antidepressant medication, possibly in combination with anxiolytic medication. Consideration of referral to social work or chaplaincy services is also recommended before follow-up and re-evaluation.6

**Pan-Canadian**

In 2010, the Canadian Partnership Against Cancer and the Canadian Association of Psychosocial Oncology jointly issued the Pan-Canadian guidelines based on methodology developed by the ADAPTE Collaboration.16 Development of the guidelines began with a systematic search to identify other relevant guidelines, systematic reviews, and guidance documents—a process that led to the formulation of a guideline presented in the form of recommendations (accompanying by information on the level of supporting evidence) and an algorithm describing the process for screening, assessing, and managing depression and anxiety.16 Unlike the NCCN guidelines that address a wide range of psychiatric disorders and psychosocial problems, the Pan-Canadian guidelines focus on depression and anxiety.6,16

Using depression as an example, the guidelines include specific recommendations for screening, assessing, and treating depression.16 These recommendations are similar in many respects to those in the NCCN guidelines, in part because the NCCN guidelines were part of the systematic search during the creation of the Pan-Canadian guidelines.16 However, the algorithm does differs from the NCCN algorithm; for example, the Pan-Canadian algorithm recommends screening for depression rather than distress, and it identifies separate care pathways based on the severity of depression rather than on the type of mood disorder.16

**American Society of Clinical Oncology**

The American Society of Clinical Oncology (ASCO)
issued clinical practice guidelines in 2014 for the screening, assessment, and care of anxiety and depressive symptoms in adults with cancer.\textsuperscript{17} The ASCO guidelines were adapted from the Pan-Canadian guidelines, so they also used ADAPTE methodology and many of the ASCO recommendations and algorithms mirror those in the Pan-Canadian guidelines.\textsuperscript{17} However, the ASCO panel modified the Pan-Canadian guidelines in several instances and developed new recommendations based on additional evidence and expert opinion.\textsuperscript{17}

Using the recommendations on depression as an example, the ASCO guidelines specify distinct care pathways based on the severity of depression.\textsuperscript{17} By contrast to the Pan-Canadian guidelines, which recommend use of the Edmonton Symptom Assessment System to screen for depression, the ASCO guidelines recommend the Patient Health Questionnaire.\textsuperscript{16,17} In addition, the ASCO guidelines include detailed recommendations for follow-up of patients identified as having depression.\textsuperscript{17}

**Guideline Harmonization**

Having 3 or more clinical practice guidelines from Canada and the United States, along with numerous other guidelines from other countries, may cause confusion among health care professionals and patients with cancer seeking guidance about when and how psychosocial care should be delivered.\textsuperscript{12} A possible solution to this problem is a process known as guideline harmonization. One such example of guideline harmonization is the ongoing, worldwide collaboration designed to standardize various clinical practice guidelines for the long-term follow-up of children and young adults with cancer; this collaboration has resulted in harmonized guidelines for breast cancer surveillance in women with cancer who have received chest irradiation.\textsuperscript{18,19} Similar to this approach, relevant stakeholders should seek to develop a set of harmonized guidelines that address the screening, assessment, and management of more common psychosocial problems encountered by people with cancer, beginning with depression and anxiety.

**Measuring Quality**

A paucity of data exists about the extent to which standards and clinical practice guidelines for psychosocial care of patients with cancer are being implemented. One source of evidence is a survey of 20 NCCN member institutions completed by a representative of each institution.\textsuperscript{20} Although psychosocial services were available at 19 of these institutions, only 12 institutions (60\%) were conducting routine outpatient screening for distress, as stipulated in the NCCN standards of care and clinical practice guidelines for distress management.\textsuperscript{6,20} Among these 12 institutions, 6 reported routinely screening all outpatients as recommended and 6 reported routinely screening select patients (eg, candidates for transplant).\textsuperscript{20} Of the 14 institutions conducting any routine inpatient or outpatient screening, 13 (93\%) reported that, consistent with NCCN guidelines, patients identified as being in distress were referred to a mental health professional.\textsuperscript{6,20}

The IOM report and the findings of an NCCN survey suggest the need to foster greater implementation of recommendations for the psychosocial care of patients with cancer.\textsuperscript{2,20} One way to foster greater implementation might be to measure and provide feedback to health care professionals about the quality of the psychosocial care their patients with cancer receive. Research has shown that medical oncology practices provided with feedback demonstrating their poor performance on quality indicators will improve over time on those same indicators.\textsuperscript{21} Could psychosocial care for patients with cancer likewise be improved by measuring and reporting to oncology practices their performance on indicators of the quality of psychosocial care? To help answer this question, the IOM recommended that organizations setting standards for cancer care use performance measures for psychosocial care as part of quality-oversight activities.\textsuperscript{2}

The first step in this process is to develop measurable indicators of the quality of psychosocial care. Toward this end, the American Psychosocial Oncology Society formed a workgroup in 2007 charged with developing quality indicators.\textsuperscript{22} Members of the workgroup included 5 mental health professionals (psychologists, psychiatrists, and social workers) with extensive experience in the delivery of psychosocial care to patients with cancer. The committee focused on developing process measures of the quality of psychosocial care that could be evaluated by medical record abstraction.\textsuperscript{22} Following a review of the relevant literature, including the IOM report and the NCCN guidelines, committee members identified several potential indicators that were then reduced in number using a modified Delphi method.\textsuperscript{2,6,22} This process resulted in selection of measures assessing 2 components considered to be necessary (although not sufficient) for providing quality psychosocial care.\textsuperscript{22}

The first quality indicator specifies evidence should exist in the patient's medical record that his or her current emotional well-being was assessed within 1 month of the patient's first visit with a medical oncologist.\textsuperscript{22} The second quality indicator stipulates that, if a problem with emotional well-being was identified, then evidence should exist in the patient's medical record supporting that action was taken to address the problem or an explanation provided for why no action was taken.\textsuperscript{2} Measuring these indicators is operationalized by formulating questions that can be answered “yes” or “no” based on the review of an individual pa-
Two sources offer preliminary evidence that suggests providing feedback on the quality of psychosocial care might lead to improvements in care. One source is ASCO's Quality Oncology Practice Initiative, a voluntary, practice-based quality improvement program. In 2008, 2 quality indicators for psychosocial care were added to its core set of measures completed by all participating practices. Practices participating in the practice initiative have the opportunity to submit chart audit information at 6-month intervals. Following submission of their data, practices are given feedback on the quality of psychosocial care and data from approximately 15,000 patients at each time point. The average rate per practice for performing an assessment of emotional well-being improved over time, from 64% to 73% (P < .001). By contrast, the average rate per practice for taking action if a problem with emotional well-being was identified increased from 74% to 76% (P = .41).

Additional evidence comes from the Florida Initiative for Quality Cancer Care. As part of a larger project examining quality of cancer care, performance rates for the 2 psychosocial indicators were available for 10 practice sites in Florida that completed chart audits of patients with colorectal, breast, or non–small-cell lung first seen by a medical oncologist in 2006 (n = 1,609) and 2009 (n = 1,720). Following the 2006 chart audit, all 10 practices received feedback on their performance and were encouraged to develop their own quality improvement efforts if performance rates were below 85%. The mean percentages of patients whose emotional well-being was assessed were 53.1% in 2006 and 51.3% in 2009, reflecting a nonsignificant decrease (P = .661). However, significant increases were seen in the prevalence of documented problems in emotional well-being among all patients (from 13.0% to 16.0%) and among patients whose emotional well-being was assessed (from 24.5% to 31.3%; P ≤ .021). The percentages of patients for whom action was taken to address a problem in emotional well-being were 57.4% in 2006 and 45.3% in 2009, thus reflecting a nonsignificant decrease (P = .098).

Taken together, these findings suggest that providing feedback alone may be more effective in promoting psychosocial screening, identifying distressed patients, or both, than improving the delivery of psychosocial care to patients in need. Efforts to improve the delivery of psychosocial care to patients in distress are likely to face a number of additional barriers, including competing clinical priorities, poor reimbursement for mental health services, and lack of psychosocial staff to accept referrals. This situation points to the need to conduct demonstration projects that seek to identify and test different approaches to improving the quality of psychosocial care in oncology settings. Consistent with this view, the IOM included a recommendation that federal funding agencies support a large-scale demonstration and evaluation of how standards for psychosocial care could be implemented across diverse treatment settings.
recommendation that psychosocial needs of patients be identified.35 A level 1 rating reflects no systematic screening process in place, and a level 5 rating reflects consistent systematic screening on multiple occasions from diagnosis through follow-up, accompanied by a comprehensive assessment for patients who screen positive.35 It should be noted that the NCCCP developed a similar tool for evaluating and improving palliative care services.34 Results suggest the CPCM was useful in evaluating the progress NCCCP sites had made in their goal to improve the quality of psychosocial care provided to their patients.35

In 2010, 16 NCCCP sites used the CPCM to provide retrospective ratings of their psychosocial program characteristics upon entry into the NCCCP as well as current ratings approximately 2 years later.53 Findings indicated that most of the baseline responses (60%) of the sites reflected level 1 responses (ie, lowest possible level of service delivery).35 Two years later, the majority of responses (59.4%) reflected level 2 to 4 responses (ie, intermediate levels of service delivery).35 In addition to quantifying progress in improving care, anecdotal findings indicated that the CPCM served at most sites to promote intentions to improve psychosocial services and that the ordered response options facilitated incremental growth toward a desired practice.35

The other example is a project that evaluated the feasibility of a quality improvement strategy for integrating psychosocial care at 27 medical centers in Italy.55 The strategy relied on context analysis and problem solving to facilitate implementation and involved 4 to 6 visits conducted in each center by the project team to assist clinic staff in identifying obstacles, finding solutions, and strengthening motivation to carry out recommended changes. Following an implementation period, the authors assessed adherence to each of the 6 recommendations and considered the objective to be met if the center’s adherence percentage was at least 75%.55 Implementation was generally successful, as indicated by the relatively few centers with adherence rates that fell below this criterion for each of the following 6 recommendations: clinician participation in communication skills training (1 center), provision of a question prompt list to each patient (7 centers), assignment of a specialist nurse to each patient (2 centers), completion of at least 1 psychosocial distress screening for each patient (3 centers), completion of at least 1 social need screening for each patient (3 centers), and an offer to visit an information and support center for each patient (3 centers).55 Although these results are promising, the participating medical centers were primarily leading centers of excellence, the sustainability of these outcomes was not assessed, and the evidence of improvement was limited to process indicators and not outcome indicators of quality (eg, patient psychological well-being).35

Future Directions
In retrospect, the IOM report can be seen as a turning point in the efforts to promote the integration of psychosocial care into routine cancer care.2 Although the IOM’s report was useful in summarizing the benefits of addressing psychosocial needs and the liabilities of not addressing them, its major impact has been to draw attention to the fact that many patients who might benefit from psychosocial care are not receiving it.2 In addition to focusing attention on the problem, the report included a number of recommendations that have served as an effective action plan for efforts to address the problem.2

Among the IOM report’s most important recommendations was one stipulating that entities establishing or using quality standards in oncology should include a provision of appropriate psychosocial health services among their standards.2 Although clinical practice guidelines for psychosocial care have been available since 1999, many reasons exist to believe that developing and disseminating guidelines are necessary steps but are insufficient when it comes to changing clinical practice.7 The development of standards of care is also required but experience suggests that, for this approach to be successful, the issuance of standards must move beyond initiatives developed and directed primarily by members of professional societies.

A critical milestone occurred in 2012 when the ACS CoC issued standards requiring the development and implementation of processes for psychosocial distress screening and referrals for psychosocial care.5 Adherence to these standards is being evaluated in 2015 as part of the ACS CoC accreditation, so considerable motivation exists for many oncology care sites to evaluate and, if needed, improve their processes in this area.10 In anticipation of this new standard taking effect, several major professional societies involved in psychosocial care have collaborated to issue recommendations that address the 6 components of the standard56:

1. Overall plan for screening
2. Timing of screening
3. Method and mode of screening
4. Tools for screening
5. Assessment and referral
6. Documentation of screening and related actions in the medical record

These recommendations build on published clinical practice guidelines.6

Another important recommendation that came out of the IOM report stipulated that the organizations setting standards for cancer care should implement performance measures for psychosocial care as part of quality oversight activities.2 The Quality Oncology Practice Initiative of ASCO is one of the largest cancer-related quality monitoring systems in the United States,
with more than 900 registered practices. Spurred in part by the IOM report, the initiative adopted indicators of the quality of psychosocial care for its core module that are required of all participating practices. Findings based on audits of the Quality Oncology Practice Initiative and the Florida Initiative for Quality Cancer Care suggest that providing feedback about the quality of psychosocial care can have a positive impact on rates of psychosocial screening. However, change is lacking for taking action in cases where problems in emotional well-being were identified; thus, this finding suggests feedback alone is insufficient for improving the delivery of psychosocial services. Possible explanations for such findings include lack of referral procedures for psychosocial care, lack of identified resources for providing psychosocial care, or both.

Oncology practices seeking to address these issues would benefit from knowing how other practices have responded to similar challenges. One source of information might be case studies describing how practices improved their provision of psychosocial care. An example of this type can be found in a publication that provided a description of how a regional cancer center developed counseling services to address the unmet psychosocial needs of its patients.

The IOM report also recommended that funding agencies support a large-scale demonstration and evaluation of how standards for psychosocial care can be implemented across diverse treatment settings. This recommendation was addressed as part of the federally funded NCCCP. Based on guidance provided by the IOM, participating sites implemented planning efforts that resulted in substantial improvements in psychosocial care delivery. Additional reports have provided more in-depth descriptions of efforts to implement distress screening and psychosocial referral and the acceptability and impact on processes of care in those efforts. Work in this area would also benefit from published findings from rigorously designed, quality improvement projects designed to document the processes used to improve psychosocial care and the outcomes achieved, including the impact on patient quality of life. Such studies should also consider relevant conceptual frameworks such as the PRECEDE–PROCEED model, which focuses on identifying and influencing predisposing, enabling, and reinforcing factors for implementing changes. Reports of this type have yet to appear in the literature and should be considered a high priority for future efforts to promote psychosocial care for patients with cancer.

Conclusions

Although considerable progress has been made in recent years in integrating psychosocial care into routine cancer care, much work remains to be done. Additional progress will be fostered by continued efforts to promote adherence to clinical practices guidelines and care standards for psychosocial services and through the development and dissemination of models demonstrating how practices can effectively implement these guidelines and standards.

References

Integrating palliative care has not always extended to rural areas; however, some research is focusing on future progressive solutions.

Systematic Review of Palliative Care in the Rural Setting

Marie A. Bakitas, DNSc, CRNP, Ronit Elk, PhD, Meka Astin, MPH, Lyn Ceronsky, DNP, GNP, Kathleen N. Clifford, MSN, FNP-BC, J. Nicholas Dionne-Odom, PhD, RN, Linda L. Emanuel, PhD, MD, Regina M. Fink, RN, PhD, Elizabeth Kvale, MD, Sue Levkoff, ScD, MSW, Christine Ritchie, MD, MSPH, and Thomas Smith, MD

Background: Many of the world’s population live in rural areas. However, access and dissemination of the advances taking place in the field of palliative care to patients living in rural areas have been limited.

Methods: We searched 2 large databases of the medical literature and found 248 relevant articles; we also identified another 59 articles through networking and a hand search of reference lists. Of those 307 articles, 39 met the inclusion criteria and were grouped into the following subcategories: intervention (n = 4), needs assessment (n = 2), program planning (n = 3), program evaluation (n = 4), education (n = 7), financial (n = 8), and comprehensive/systematic literature reviews (n = 11).

Results: We synthesized the current state of rural palliative care research and practice to identify important gaps for future research. Studies were conducted in the United States, Australia, Canada, Africa, Sweden, and India. Two randomized control trials were identified, both of which used telehealth approaches and had positive survival outcomes. One study demonstrated positive patient quality of life and depression outcomes.

Conclusions: Research to guide rural palliative care practice is sparse. Approaches to telehealth, community–academic partnerships, and training rural health care professionals show promise, but more research is needed to determine best practices for providing palliative care to patients living in rural settings.

Introduction

In 1990, the World Health Organization revised its comprehensive Cancer Pain Relief and Palliative Care report to include palliative care.1 Since then, strides have been made worldwide in providing patients with cancer access to palliative care, and professional medi-
cal organizations have recommended early palliation for patients with advanced cancer. However, access and the dissemination of palliative care advances to the 40% to 60% of the global population who live in rural areas have been limited.

Although persons with cancer are more likely than those with other, nononcological, progressive, and life-limiting illnesses to receive palliative care, those with cancer living in rural communities continue to be underserved. The limited focus on palliative care in the rural setting is evident in the lack of guidance by national organizations to address the unique challenges and barriers faced by these patients and health care professionals. Clinical guidelines on quality palliative care from the National Consensus Project do not contain the term rural nor do they address how these standards should be applied in rural settings. Not only must performance indicators of palliative care need to be modified, but the reality is that many rural health care facilities do not have access to any type of specialty oncology or palliative care resources.

Thus, the purpose of this paper is to synthesize empirical evidence, much of which has focused on persons with cancer, to describe the current practice and state of research relating to palliative care in the rural setting, and to identify important gaps for future research.

Methods
We conducted a systematic review of 2 large databases from January 1990 to February 2014. The search revealed 248 relevant articles and we identified an additional 59 articles through networking and a hand search of reference lists. We screened titles and abstracts of 307 articles and assessed the full text (focused on methodology sections to identify original research) of 225 articles. Thirty-nine articles met the inclusion criteria of being a research study or systematic review and had a rural focus. Papers meeting the inclusion criteria were included regardless of study quality so we could obtain the broadest possible representation of the state of research.

Articles were grouped into 7 categories and 1 or 2 authors reviewed and synthesized each category. Studies reports represented the United States (n = 13), Australia (n = 7), Canada (n = 4), Africa (n = 2), Sweden (n = 1), and India (n = 1). Category definitions and summaries of the studies are described in Tables 1 and 2.

Intervention Studies
Four papers representing 2 randomized controlled trials (RCTs) were identified. Both RCTs offered early palliative care approaches to patients with advanced cancer and their family caregivers using a telehealth/telephonic intervention. The settings, which were rural New Hampshire and Vermont outpatient cancer clinics that included a US Veterans Affairs Medical Center, were the same for both studies. Each study generated separate papers focused on patient or caregiver outcomes. Positive patient quality of life (QOL), depression and survival and positive caregiver outcomes were reported.

Needs Assessment
Two US studies focused on needs assessments and the development of rural palliative care. Ceronsky et al focused on palliative care quality practices and utilized a learning collaborative methodology to assist communities to establish and strengthen palliative care capacity in rural Minnesota. A program-development evaluation survey assessed the benefits of the Minnesota Rural Palliative Care Initiative and satisfaction with participation. All the program components were rated well and an increase was seen in participant knowledge of pain management and goals of care discussions.

Program Planning
Three studies addressed program planning for rural palliative care services and programs; 2 were conducted in Australia and 1 in Canada. The Australian studies found that palliative care had moved from being marginalized to a key component of rural health care delivery. Blackford and Street developed and evaluated the effectiveness of a model to improve advance-care planning in the community setting. Their model consisted of 5 domains: service-level governance, advance-care planning education, advance-care planning documentation, community engagement, and quality processes. They found that an advance-care planning model is feasible in the rural community and should focus on advance-care planning conversations and involve families rather than just advance-care planning completion rates. Phillips et al evaluated the applicability of the Predisposing, Reinforcing, Enabling, Causes in, Educational Diagnosis and Evaluation (PRECEDE) and Policy, Regulatory, Organizational Constructs in Educational and Environmental Development (PROCEED) model in the development of targeted, nursing-led chronic illness interventions. They studied an aging population with rural, unmet palliative care needs and a disadvantaged urban community at high risk for cardiovascular dis-
## Table 1. — Selected Studies of Palliative Care in Rural Settings

<table>
<thead>
<tr>
<th>Study</th>
<th>Design/ Intervention</th>
<th>Sample</th>
<th>Setting</th>
<th>Measure</th>
<th>Outcome</th>
<th>Comment</th>
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<tbody>
<tr>
<td><strong>Intervention</strong></td>
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<tr>
<td>Bakitas12</td>
<td>Prospective RCT</td>
<td>322</td>
<td>NH/VT Outpatient cancer clinics and VAMC</td>
<td>FACIT-Pal CES-D Edmonton Symptom Assessment Scale Resource Use</td>
<td>Improved QOL and depression (both ( P = .02 )) and trend toward improved symptoms (( P = .06 ))</td>
<td>One of the first studies to describe benefits of early palliative care</td>
</tr>
<tr>
<td>Bakitas13</td>
<td>Prospective, wait-control RCT ENABLE phone-based coaching at diagnosis vs 3-mo delayed</td>
<td>207</td>
<td>NH/VT Outpatient cancer clinics and VAMC</td>
<td>CES-D FACIT-Pal QUAL-E Survival Resource use</td>
<td>Immediate group had improved survival (15%, ( P = .38 )) compared with delayed group at 1 y</td>
<td>Failure to achieve recruitment target may have impacted ability to demonstrate differences between groups</td>
</tr>
<tr>
<td>O’Hara14</td>
<td>Prospective RCT</td>
<td>222</td>
<td>NH/VT Outpatient cancer clinics and VAMC</td>
<td>Caregiver burden MBCBS After-death interview Complicated grief</td>
<td>No differences in caregiver burden</td>
<td>Higher caregiver objective and stress burden related to lower patient QOL</td>
</tr>
<tr>
<td>Dionne-Odom15</td>
<td>Prospective, wait-control RCT ENABLE phone-based coaching at diagnosis vs 3-mo delayed</td>
<td>122</td>
<td>NH/VT Outpatient cancer clinics and VAMC</td>
<td>QOL-CG CES-D MBCBS</td>
<td>Immediate group had improved depression at 3 mo (( P = .02 )); decedent caregivers had improved depression and subjective burden (both ( P = .01 ))</td>
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<tr>
<td><strong>Needs Assessment</strong></td>
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<tr>
<td>Ceronsky17</td>
<td>Quality improvement/learning collaborative to assist communities to establish/strengthen palliative care in rural Minnesota using theory and NQF preferred practices</td>
<td>10</td>
<td>Rural Minnesota MRPCI</td>
<td>Program development Evaluation survey to assess benefit of MRPCI and satisfaction with participation</td>
<td>Teams grew from 1 to 6 All components of program rated well Increased knowledge of pain management by 73% and goals of care discussion by 81%</td>
<td>10 teams represented 64 organizations; used community capacity development theory</td>
</tr>
<tr>
<td>Fink16</td>
<td>Descriptive, determine awareness, knowledge, barriers, and resources of palliative care services in rural hospitals</td>
<td>374</td>
<td>236 Rocky Mountain rural hospitals (&lt; 100 beds) in Montana, Wyoming, Utah, New Mexico, Colorado, Kansas, and Nebraska</td>
<td>Investigator-developed qualitative/quantitative 7-section needs assessment instrument covering current palliative care services, professional education programs, desired learning methods, satisfaction with and barriers to palliative care, community resources, and populations needing assistance</td>
<td>99% familiar with palliative care concept 76% had a contract with hospice 72% participated in advance-care planning program 56% had access to palliative care resources 9% had board certified physicians in hospice and palliative medicine 72% offered palliative care education in past year Ethical issues and psychosocial support least satisfied</td>
<td>36 surveys did not list location 40% response rate</td>
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### Table 1. — Selected Studies of Palliative Care in Rural Settings (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design/ Intervention</th>
<th>Sample</th>
<th>Setting</th>
<th>Measure</th>
<th>Outcome</th>
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<tbody>
<tr>
<td><strong>Program Planning</strong></td>
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<tr>
<td>Blackford18</td>
<td>Multisite, action research to design and evaluate the feasibility of an advance-care planning program</td>
<td>3 community sites n = 611 (urban) n = 460 (urban) n = 186 (regional)</td>
<td>3 community palliative care services: 1 regional and 2 metropolitan, urban in Victoria, Australia</td>
<td>Client and service management audits (pre- and post-implementation of the program/model) Key informant interviews (n = 9) Development and evaluation of efficacy of a model to improve advance care planning in the community setting</td>
<td>Model to implement advance care planning in the community is feasible Documentation of advance care planning discussions with clients and families is a more useful outcome than completing advance-care planning Community palliative care services needs to engage with local communities Leadership essential ingredient to change the process</td>
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<tr>
<td>Phillips19</td>
<td>Reflective case study approach to demonstrate the applicability of model to the development of nursing-led chronic illness interventions</td>
<td>2 case studies/populations</td>
<td>Regional coastal Australian aging population with rural, unmet palliative care needs Urban area in Sydney, Australia: Disadvantaged urban community at high risk for cardiovascular disease</td>
<td>PRECEDE-PROCEED model used Needs assessment conducted (social, epidemiological, behavioral, environmental, educational, and ecological)</td>
<td>Data shaped development of a multifaceted intervention focusing on increasing aged care personnel’s palliative care capacity, access to resources, development of evidence-based guidelines, and evaluation</td>
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<tr>
<td>Watanabe20</td>
<td>Assess feasibility of pilot study and explore symptom, cost, and satisfaction outcomes</td>
<td>44 initial consultations and 28 follow-up visits</td>
<td>Canada</td>
<td>Videoconferencing to provide specialist palliative care and radiotherapy consultation to those with cancer living in rural settings and explore symptoms, cost, and satisfaction outcomes</td>
<td>Videoconferencing is feasible, may improve symptoms, results in cost savings, and satisfactory to patients and HCPs</td>
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<tr>
<td><strong>Program Evaluation</strong></td>
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<tr>
<td>Hatton21</td>
<td>2-y pilot project delivering palliative care services</td>
<td>1 case study</td>
<td>Rural and remote Griffith, Australia</td>
<td>Evaluation of Griffith Area Palliative Care Service model Key elements included: • 24-h access • Governance and staffing • Case management review • Enhanced primary care • Information management • Outcomes and evaluation • Weekly multidisciplinary team meeting</td>
<td>Coordinated integrated application of existing resource Investment of new resources Formal evaluation</td>
<td>Plans for future dissemination identified</td>
</tr>
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</table>
Table 1. — Selected Studies of Palliative Care in Rural Settings (continued)

<table>
<thead>
<tr>
<th>Study</th>
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</table>
| Wilkes22 | Descriptive evaluation of a pilot project of a palliative care telephone call service | 48 HCPs 21 after-hours telephone support nurses | New South Wales, Australia | Telephone logbook (12 calls), text analysis of reflective journals, questionnaire, interviews | Major themes:  
  - Program preparation and introduction  
  - After-hours telephone support service for families and HCPs  
  - Nurse experiences (personal impact and support) | Lack of HCP knowledge about service |
| Bensink23 | Evaluation of the acceptability of videotelephony/webcam | 17 Tertiary pediatric oncology service in Brisbane, Australia | Interview (face to face or telephone) | Cost analysis | 92% participation rate  
Families receiving videotelephone calls found them to be more useful than a telephone call | 2 RCTs previously attempted and abandoned following difficulty with family recruitment  
Evaluation of videotelephony was conducted |
| Logie24 | Program evaluation | 8 5 hospices 3 home-based care organizations | Zambia | Multiple methods rapid field evaluation:  
  - Desk surveys  
  - Facility interviews  
  - Data from 2 field visits (practice observation, trainee feedback, interviews with key personnel and funders) | Program enhancement with modest funding included:  
  - Training program (rural and urban)  
  - Improved access to morphine and other drugs  
  - Increased government lobbying to support palliative care and hospice and to improve standards | For palliative care to thrive in a resource poor country, public health system integration is crucial and long-term funding needed |
| Smith31 | Qualitative program evaluation of providing specialists in 2 rural community hospitals | 6,958 audited patient charts pre-RCOP and 7,572 post-RCOP | RCOP of the Massey Cancer Center Medical College of Virginia | No formal measurement; anecdotal observations include ability to keep patients with cancer in their local communities | Rural practitioners able to safely administer cancer therapy | Focused on outcomes for local clinicians |
| Thulesius25 | Comparison of learner-centered education program and control group | 460 Rural areas in Sweden | Intervention and control groups sepa-rated by 20-mile-wide rural district Matched in terms of demography and home care structure | 20-item attitude questionnaire HADS administered to staff | Postintervention: Significant differences on 17 of 20 items between 2 groups  
Preintervention: Significantly higher in education group  
Postintervention: Significantly lower in education group  
Improved attitude about care and improved mental health well-being of staff | Education program was evidence-based, mixing small group work with lectures, seminars, and discussion  
Objective was to produce local guidelines for end-of-life care  
Only study reviewed with control group |

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### Table 1. — Selected Studies of Palliative Care in Rural Settings (continued)

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<tr>
<th>Study</th>
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<th>Measure</th>
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<tbody>
<tr>
<td>Kelley26</td>
<td>Retrospective analysis of the Ontario Ministry of Health educational palliative care program delivered in last 8 y</td>
<td>353 Ontario</td>
<td>Questionnaires (26 questions)</td>
<td>83% said training very significant compared with other sources of learning 87% reported practice of palliative care changed 91% shared palliative care knowledge with others 68% reported palliative care delivery in their community much better than prior to training 70% now had palliative care team (compared with 9% prior to training)</td>
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<tr>
<td>Reymond27</td>
<td>Pre- and post-design 14 workshops for general practitioners tailored to specific patient symptoms</td>
<td>149 Remote areas in Australia</td>
<td>Cost of training Evaluation of education and clinical objectives</td>
<td>Goal to evaluate intervention aimed at increasing knowledge and capacity of palliative care 95% general practitioner satisfaction with workshop in teaching palliative care skills (91% for nurses and other HCPs) Confidence in managing palliative care cases increased from 2.9 to 3.9 (5-point scale) HCPs reported improvement in confidence at 3 mo</td>
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<tr>
<td>Kaufman28</td>
<td>Prospective design study of educational presentations to HCPs (nurses = half-day conference; physicians = grand rounds)</td>
<td>27 New Mexico</td>
<td>Change in hospice utilization pattern: • Subsequent referral to hospice • Patient referral pattern • Length of stay • Diagnosis at admission • Nursing home referral pattern</td>
<td>Significant increase in hospice utilization (33 to 61) 113/254 eligible for hospice were referred (65%) Increase in referrals by community nursing homes (but not other sources) • Not significant in time in days in hospice • Not significant in terms of diagnosis • Significant increase in frequency of referral from 2 nursing homes</td>
<td>Goal to increase hospice utilization in rural community Effective for changes in referral by nursing homes alone (no change in physician referrals) Training conducted by local HCPs at very low cost</td>
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</tr>
<tr>
<td>Easom29</td>
<td>Pre- and post-design study of educational presentations to rural nurses and licensed practical nurses in assisted-living and nursing home environments</td>
<td>9 Assisted living facility in southeastern United States</td>
<td>End-of-life attitudes survey End-of-life knowledge assessment Open-ended questions</td>
<td>Post-test results significantly higher than pre-test knowledge on end-of-life care Most knowledge growth on response to pain medication, administration of opioid analgesics for pain, and interventions to relieve nausea Significant difference in attitudes</td>
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Education (continued)

Kortes-Miller\textsuperscript{30}
Determine staff needs for palliative care education, then develop 15-h interprofessional curriculum Program piloted in 3 facilities
128
Ontario (remote, rural, and long-term care facilities)
Identify 3 most important learning needs and preferred format
Highest ranking topics: stress management for staff (73%), for individual and family (71%), understanding emotional needs of dying person (67%) Majority preferred education in face-to-face format, liked interdisciplinary focus, teambuilding, felt empowered by program
Approach can serve as a model for palliative care education in other rural areas

Financial

Smith\textsuperscript{31}
Pre- and post-financial analysis of RCOP
1 site
3 rural clinics serving 3–5 counties in Virginia
Chart audits after 3 y of operation (post-RCOP) compared with 2-y results (pre-RCOP)
Profitable for rural hospitals Revenue-neutral for academic centers Cost saving for society
Successful enough to be a required part of all comprehensive cancer center programs

Desch\textsuperscript{32}
Pre- and post-financial data analysis of RCOP
1 site
Low-income areas in rural Virginia
Main outcome measures:
• Costs (estimated reimbursement from all sources)
• Revenues
• Contribution margins
• Profit (or loss)
Rural hospitals generated > $500,000 USD/y after RCOP Total cost per patient in network decreased from $10,233 USD to $4,392 USD (57% decrease)
Programmatic part of all National Cancer Institute centers

Uys\textsuperscript{33}
3-mo, multisite home-based care project providing palliative care for patients with AIDS
7 sites rural = 2 peri-urban = 2 urban = 3
Underserved in South Africa
Evaluation of costs:
• Setup (training, equipment, and planning)
• Cost per site
• Site operating cost (total and average per patient)
• Average hospital inpatient
• Hospital outpatient
• Primary care clinic costs per participating patient
Palliative home-based care increased in rural areas where a vehicle is required for staff transport
Impossible to know whether home-based care adds services or can cost-effectively substitute for hospital services

Cassel\textsuperscript{34}
Analysis of Rappahannock Rural Palliative Care Program
1 site
Northern Virginia, located in a 5-county rural farming area Seacoast area on Chesapeake Bay
Collected data from consults, physician billing, and receipts to calculate hospital charges for patients treated with concurrent palliative care
Cost per day decreased to $400 USD/y (25% of total) Generated $80,000–100,000 USD in savings in reduced hospital charges and cost per year

Emanuel\textsuperscript{38}
Single site pilot survey of patient-caregiver dyads
11
Trivandrum, Kerala, India Southwest coast of India
Pilot study of economic impact and openness to training
100% reported decreased family earnings Families surveyed averaged $1,082 USD of debt 8 of 11 caregivers open to training
They suggested the PRECEDE-PROCEED model could be used to guide nursing-led interventions in existing health care environments. They evaluated the feasibility of videoconferencing to provide specialist palliative care, radiotherapy consultations, and to explore symptoms in rural Canadian persons with cancer. They found videoconferencing to be feasible, suggested that its use may improve symptoms and result in cost savings, as well as increase satisfaction for patients, families, and health care professionals.

Program Evaluation

Three Australian studies and 1 Zambian study evaluated various, rural, palliative care delivery approaches. Hatton et al evaluated a pilot collaborative project among multiple agencies in Australia to meet the challenges of providing palliative care services in rural and
Table 2. — Selected Systematic Reviews of Rural Palliative Care in Rural Settings

<table>
<thead>
<tr>
<th>Study</th>
<th>Purpose</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Evans39</td>
<td>Conduct systematic literature review of studies examining organization of rural palliative care and views of professionals in rural areas</td>
<td>No case-control, cohort, randomized controlled trials, or meta-analyses were found Majority of studies based out of Australia (n = 16) Role of primary care discussed in 12 studies Problems reported in the provision of symptom control for patients Issues with education, training, and emotional support for professionals providing palliative care in rural settings Accessing specialist services was reportedly difficult for professionals Professionals and rural families described difficulties in accessing information Developments in information technology were mentioned in a few studies as possible solutions Need perspectives from rural primary care professionals about the optimal organization of palliative care in the rural setting</td>
</tr>
<tr>
<td>Hughes40</td>
<td>Identify needs of rural-dwelling patients with cancer and their caregivers in delivery of palliative care</td>
<td>All studies from developed countries No studies specifically about ethnic minorities Noted difficulty of comparing studies due to differing methodologies and contexts Rural caregivers may have additional care demands placed on them Information needs may be higher in rural vs urban patients Geographical distance a major variable in care</td>
</tr>
<tr>
<td>Jennett 41</td>
<td>Review of readiness models for rural telehealth</td>
<td>Four distinct models identified for readiness assessment Each model discussed various themes essential for telehealth readiness Three themes common to each discussion: appreciation of practice context, strong leadership, perceived need to improve practice Combining e-health and telehealth with health informatics Theories of change, diffusion of innovations, components of telehealth readiness tools (eg, patient, public, health care professional, organization, system) could be reviewed and refined for application to e-health</td>
</tr>
<tr>
<td>Wilson42</td>
<td>Assess challenges and other important issues/ circumstances involving planning and providing EOL care in rural areas</td>
<td>Most research was single site, small sample, and exploratory Identified and described differences between EOL care in urban and rural settings, assessed EOL needs and wishes of terminally ill or dying persons, their family members, and health care professionals in rural areas, explored EOL education for rural EOL specialists EOL care as an essential service in rural communities Integration of EOL care into rural health care settings Family caregivers must be provided with more information and support (eg, home-based nursing care) Improved linkages to specialized palliative care necessary for continuing education Prepare and support rural health care professionals while delivering EOL care</td>
</tr>
<tr>
<td>Steers 43</td>
<td>Determine role played by UK community hospitals in provision of palliative care</td>
<td>Many UK community hospitals have resources to counter inequalities in access to general palliative care More prospective research using qualitative methods involving patients, caregivers and nurses required to understand complexities of providing palliative care</td>
</tr>
<tr>
<td>Cox44</td>
<td>Literature review of quality of care in rural areas</td>
<td>Rural communities more different than alike Rural issues differ from those in urban settings Research in rural health facilities to determine best practices for patient safety and outcomes Must determine best practices for mental health and effective smoking cessation programs and technological interventions Identification of mental health programs and services providing cost-effective quality care</td>
</tr>
<tr>
<td>Robinson 45</td>
<td>Identify, evaluate, and synthesize literature on rural palliative care</td>
<td>Grouped into patient and caregiver perspectives, professional attitudes, knowledge, and practice issues, and health care services Body of research is small and eclectic Little evidence to inform palliative policy and service development in rural settings Coordinated programs required to develop adequate body of knowledge to support effective service and policy development</td>
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remote areas of Australia. Key elements of the model included enhanced primary care, 24-hour palliative care access, weekly multidisciplinary team meetings, case management review, and a formal outcomes evaluation of existing resources. Barriers comprised inequity in community palliative care support and access to ambulatory and home services for patients with cancer compared with those without cancer, but with no formal system for after-hours home nursing support, and lack of dedicated palliative care beds. Two studies evaluated technological support for palliative care in rural areas. Wilkes et al evaluated an after-hours, nurse-driven telephone support service and found that its availability reduced isolation for families caring for rural palliative care patients at home. Physicians and nurses were satisfied with its accessibility because they believed it decreased rehospitalization rates for seriously ill patients. Bensink et al researched the acceptability of video telephone services to pediatric patients in regional and remote areas. This study team attempted 2 RCTs with this patient population; however, due to ethical constraints (eg, family reluctance to participate, patients too sick to participate) and technological issues (eg, blurred video, internet connection problems) the RCTs were not fully carried out. They suggested future research might include integration of a videotelephony model at the time of diagnosis with a life-threatening illness, rather than at the time of palliative care.

One study evaluated a synergistic, multipronged palliative care initiative in Zambia, a country with a high HIV prevalence rate and poor access to care. Eight hospices and palliative care organizations in poor and rural areas were partially funded for 2 years, and an extensive training program of staff was ini-

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**Table 2. — Selected Systematic Reviews of Rural Palliative Care in Rural Settings (continued)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Purpose</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Downing</td>
<td>Explore global developments in palliative care provision in rural settings since 2010, highlighting models, including challenges faced in establishing services</td>
<td>Provision of care based on premise that individuals wish to die at home Communication is a key concept to palliative care Community volunteers and networks intrinsic to palliative care models of rural Sub-Saharan Africa Challenges to recruitment and sustainability of main clinical team Lack of rural generalist providers having access to specialist support Major challenge is the cost and time of travel to access care Care services need to be individually tailored to specific rural communities Use of community volunteers in care delivery may be effective Practical issues related to access and traversing geographical distances remain challenging</td>
</tr>
<tr>
<td>Phillips</td>
<td>Review published studies evaluating impact of continuing professional development programs on ability of rural nurses to provide palliative care; inform the development of targeted learning activities for this population</td>
<td>Evaluated programs involving rural nurses and focused on increasing care capabilities Evidence limited by the absence of randomized controlled trials Valuable insights into barriers and facilitators to engaging rural nurses in learning opportunities Continuing education to positively impact patient and family outcomes Optimize opportunities for web-based technologies by developing and maintaining computer competencies Investigation needed of impact of specialist clinical placements capabilities to provide palliative care among nurses</td>
</tr>
<tr>
<td>Jang</td>
<td>Examine opioid availability, caregiver burden, and use of health care resources at patient EOL by setting to determine optimal setting for palliation in Africa</td>
<td>Recognizing and treating symptoms occurring at the EOL Research in Africa sparse; most from South Africa and Uganda Use of health care resources for palliative care at EOL More research on nurse prescribing training program, which is part of Uganda's public morphine program</td>
</tr>
<tr>
<td>O’Brien</td>
<td>Discuss palliative care and EOL models of care for Aboriginal people in New South Wales, Australia</td>
<td>Resistance to the idea of inpatient care due to Aboriginal Australians from their homeland and community Ceremonies that assist the spirit to leave the physical body and return to its sacred place common among Aboriginal people Lack of understanding of Aboriginal belief systems and their links to the land lead to a disconnect for health care professionals Aboriginal people must have culturally appropriate and locally accessible palliative care services because they have a sense of isolation and are disconnected culturally from accessing mainstream services Clarification of the social, emotional, spiritual, and cultural factors that influence decision making about accessing palliative care among Aboriginals</td>
</tr>
</tbody>
</table>

EOL = end of life.
tiated. A mixed-method analysis of outcome was conducted and determined that the palliative care environment in Zambia was strengthened with this approach. Funding enabled agencies to expand their services, more reliably offer morphine, provide gas for transportation, and support patient caregivers. Training enhanced staff confidence in caring for very ill and dying patients and their families, and raised competence and confidence rates were sustained 2 years later. However, once funding ended, services had to be curtailed, which led to the determination that the need for sustainable, long-term funding is essential to maintain success.

**Education**

Six studies evaluated palliative care services and education in rural patient settings. One study used a retrospective design and a control group. The studies used various education methods (didactic or experiential) and time allocation (half-day to multiple days). One study developed training methods by assessing the needs of staff and another tailored the training to specific patient symptoms (eg, pain, constipation, dyspnea, delirium). Training resulted in enhanced knowledge, and changes to the palliative program, including initiation of a palliative care team, increased hospice utilization, improved staff attitudes, and improved confidence in providing care. Most educational programs were low cost but yielded significant changes in study outcomes.

**Financial**

Eight studies analyzed financial data from rural-area palliative care programs: 4 were conducted in the United States, and 1 each in Canada, South Africa, Australia, and India. Smith et al conducted pre- and post-financial analyses of the Rural Cancer Outreach Program (RCOP) in 3 clinics that served 3 to 5 counties in Virginia. Chart audits were performed after 3 years of operation (post-RCOP) and results were compared with the 2 years preceding the study (pre-RCOP). Outcome measures included costs (estimated reimbursement from all sources), revenues, contribution margins, and profit (or loss) of the program. RCOP generated at least $1 million in profit for the rural hospital, even while expanding cancer and palliative services, and reduced the net cost per patient by about 40% due to better coordination. RCOP was deemed profitable for the rural hospitals, revenue-neutral for the academic centers (a marked increase in referrals, including 9% in nononcological cases, from the rural areas was offset by the poor payer mix, which included uninsured and underinsured patients), and cost saving for society; it has also continued for 25 years.

Cassel et al performed an analysis of the Rapahannock Rural Palliative Care Program located in a 5-county rural farming and seacoast area in northern Virginia. This study collected data from consultations, physician billing, and receipts, and the researchers calculated hospital charges for patients treated with concurrent palliative care.

Klinger et al analyzed resource utilization and costs of the Niagara West End-of-Life Care Project during a 15-month period in rural Ontario, Canada. The project was a success because hospital costs decreased by more than $400 per day when palliative care was involved, the in-hospital death rate decreased, and hospice discharges increased. The net effect was a sustainable program with $80,000 to $130,000 savings per year (although this number does not include avoided rehospitalizations).

Uys et al conducted a 3-month, multisite, home-based care project providing palliative care for South African patients with AIDS living in underserved areas. Evaluation of costs included setup (training, equipment and planning), cost per home-based care site, home-based care operating cost (total and average per patient), and average hospital inpatient, hospital outpatient, and primary care clinic costs per participating patient. It was not clear whether home-based care added services or was a cost-effective substitute for hospital services.

Bradford et al conducted a cost-minimization analysis to determine the cost of a home telehealth consultation for pediatric palliative care patients compared with costs of either a face-to-face consultation at a hospital or a home visit from a palliative care service. The cost for the home telehealth consultation was cheaper than the other 2 options because the telehealth option required no travel (which substantially increased costs). For families living in rural areas who must sometimes travel long distances to get to a hospital, video consultation can help ensure equity in access to quality palliative care.

Two studies from the same team — one focusing on India and the other in the United States — focused on the economic impact of a terminal illness and the feasibility of training caregivers as a means of stemming illness-related poverty. The pilot study conducted in India found that patients were forced to give up work as a result of their illness and, in the majority of families, caregivers had to change their work habits and many had to sell assets. Most families indicated that a trained caregiver would have reduced or prevented some of the household's illness-related change, and most caregivers said they would be interested in becoming a trained caregiver. The second paper proposed a strategy that would simultaneously mitigate household financial pressure as a result of illness as well as train caregivers to provide care that would in turn address the workforce talent shortage.
Systematic Reviews

Eleven papers were systematic reviews (see Table 2).39-49 Six of the reviews directly assessed palliative care in rural settings, and 5 assessed some aspect of rural palliative care, though this was not specifically part of the study purposes.39,49 Robinson et al50 identified and evaluated 79 studies to ascertain the strength of evidence available to inform public policy and guidelines and identify direction for future research. Identified studies were grouped into 3 categories: patient and caregiver perspectives (n = 24), professional attitudes, knowledge, and practice issues (n = 28), and health care services (n = 27).50 Our review of these studies concluded that little is known about experiences of rural patients and their caregivers because only 6 of the 24 studies directly assessed these perspectives. In addition, a need exists to better operationalize how palliative care specialists should integrate with rural primary care physicians. We also concluded that the medical literature is eclectic and lacks focused and sustained programs of research specifically part of the study purposes. 39-49 Robinson et al50 identified and evaluated 79 studies to ascertain the strength of evidence available to inform public policy and guidelines and identify direction for future research. Identified studies were grouped into 3 categories: patient and caregiver perspectives (n = 24), professional attitudes, knowledge, and practice issues (n = 28), and health care services (n = 27).50 Our review of these studies concluded that little is known about experiences of rural patients and their caregivers because only 6 of the 24 studies directly assessed these perspectives. In addition, a need exists to better operationalize how palliative care specialists should integrate with rural primary care physicians. We also concluded that the medical literature is eclectic and lacks focused and sustained programs of research specifically focus on developing and testing models of palliative care delivery in the rural setting.50

Discussion

When death is imminent, no second chance exists to improve the quality of care for the patient and family.51 Nationally, a significant increase has been seen in palliative care programs attempting to “get it right the first time”; however, rural areas still have limited palliative services, thus resulting in an important disparity for seriously ill patients with cancer and those without cancer.9 Nevertheless, as is evident from this review, through community support, academic support and partnerships, telehealth, community advisers, and other creative strategies, providing expert care to seriously ill patients may be feasible, even in the most remote locations. Such success occurs not by bringing the patient to the urban experts, but by bringing palliative care expertise to the patient and/or ensuring that palliative care support becomes imbedded into the fabric of the rural community.17,18,21,24 Tailoring studies and methods to the unique aspects of a rural community likely resulted in most studies using a quality-improvement design because the primary goal of the initiative was to improve care in a particular area or system rather than for the purpose of creating generalizable knowledge.

We acknowledge that publication bias is a limitation in our review, and we are aware of many unpublished examples of the successful integration of palliative care into rural communities. For example, 10 years ago, the Center to Advance Palliative Care, the National Hospice and Palliative Care Organization, and the National Rural Health Association partnered to compile Providing Hospice and Palliative Care in Rural and Frontier Areas, a comprehensive toolkit with exemplars of rural palliative care programs.52 Key informants from 31 programs were interviewed, representing 5 rural regions across the United States.52 Yet, our literature search yielded few added information about their programs since that monograph was published.52 Nonetheless, the body of published work that we reviewed has yielded a number of important pearls and lessons.

The first of the 2 RCTs, which used a telehealth/telephonic approach in patients newly diagnosed with advanced cancer, was also the first RCT to demonstrate the benefits of palliative care in any locale compared with usual cancer care.12 Despite the positive rates of patient QOL, mood, and survival outcomes in the first RCT and positive care giver outcomes in the subsequent RCT, the results are difficult to generalize due to the racial/ethnic homogeneity of the study participants.15

Quality-improvement efforts have also demonstrated positive results in rural settings. In the Minnesota Rural Palliative Care Initiative, a needs assessment was combined with an active quality improvement project.17 These rural communities identified diverse community resources and a strong commitment to developing palliative care programs.17 Although palliative specialists were commonly not available, hospice programs were identified as a primary resource for enhancing clinical knowledge.17 Improving processes of care was an identified need and teams worked across settings to meet quality guidelines.17

One finding in this review is that the community is pivotal to any future plans for developing primary palliative care services in the rural area. This includes enhancing education within the community so that primary care clinicians may have the knowledge to integrate 24-hour palliative care access in the rural area to all patients with life-threatening illness, not only patients with cancer. Educational offerings for rural practitioners may be web-based or onsite intensives. Partnering with local hospices to assist with palliative care education for clinicians may be helpful because the ability of rural health care professionals to travel to conferences can be a barrier due to lack of time and insufficient workload relief.9 Cancer Care Manitoba maintains a website (www.cancercare.mb.ca) describing its long-standing Community Cancer Program Network. According to its website, the Community Cancer Program Network, in partnership with regional health authorities, has helped rural patients outside of Winnipeg, Canada, receive oncology care close to home in 15 community cancer programs.

A primary palliative care model geared toward the rural setting might include the provision of palliative care through an existing home nursing–care agency, interdisciplinary team involvement as needed, difficult case review with access to tertiary palliative care ser-
vices through videoconferencing, a formal assessment of existing resources, and subsequent outcomes evaluation. Of interest, in the rural Virginia Cancer/Palliative Outreach Program, educating rural health care professionals was a compelling reason for the retention of health staff. In addition, strategic alliances between rural health care professionals and academic centers made access to up-to-date consultations, telehealth, and experts easier.

Limited studies, many of which have focused on cancer programs, have documented the cost savings/avoidance of employing palliative care services in rural areas. This body of work suggests that the impact of palliative care on health care costs and services is similar for both rural and urban populations. For example, the $400/day savings observed in the rural Virginia study is very similar to the $279 to $374/day savings observed in contemporary, urban hospital studies. Furthermore, the increased use of home hospice always follows palliative care consultations; the only concern may be that reduced occupancy may stress rural hospitals, especially if they cannot maintain a census of adequately insured patients. Palliative care may also positively impact household economics in rural and urban settings by keeping the patient and family caregivers economically productive, requiring less need for travel and time off from work.

The 11 systematic reviews addressed some component of rural palliative care (either alone or combined with urban studies), but the purposes, quality, and methodological rigor considerably varied among them. Thus, any direct comparison, compilation, and formal ratings of evidence strength among the reviews were problematic. Nevertheless, a few common themes were noted:

- Small and insufficient literature base to guide palliative care policy development in rural areas
- Geographical distance and lack of access to palliative care specialists limit the integration of quality palliative and end-of-life care in rural health care settings
- Stakeholder perspectives and “on-the-ground” involvement are essential to incorporating palliative care services to rural settings that are more dissimilar than homogeneous
- Policy and delivery models of rural palliative care have yet to be fully developed and tested
- Although promising, emerging telehealth and e-health methods need further testing, with emphases on improving health technology, connectivity, and competencies of rural health care professionals

Notable gaps in these reviews included assessments of symptom management practices in rural settings and palliative care for specific illness subtypes.

Use of telehealth strategies was prominent as a way to bring palliative support to patients. This technology is ushering in a new era of medicine in which health care will move toward becoming a commodity among others that people can access from their home or mobile devices. It is powerful and will entail rethinking the core of medicine, namely the doctor–patient relationship. Its decentralized and electronically mediated nature and the likelihood of scaling up due to its convenience (thus driving greater use) is likely to make quality control and transparent accountability both more challenging and easier. The types of medical errors that can occur while using mobile health technologies will morph, and methods for reducing medical errors must be revised to keep up. The roles of family caregivers and local unskilled, semi-skilled, and professional providers and distance providers will all change, entailing adjustments to credentialing and maintenance of professional certification. The economics of care delivery and the form of reimbursement will likely change, requiring revised models for billing and insurance. Emerging new issues that can scarcely be predicted will require assessment of concomitant regulatory issues. Policymakers will need to keep a close eye on telehealth to keep pace with its rapid development. Given the ability of integrated care-delivery networks to increase access to high-quality, person-centered care, the time is now to develop and evaluate comprehensive models of telemedicine that include standardized telephone support, use of peripherals to assess vital signs and oxygenation status, and video care to assess and interact with patients who are in a place of crisis. These models warrant rigorous testing and attention to the unique challenges and needs faced by patients in rural areas.

Other successful initiatives to expand palliative care expertise in low-resource and rural areas have included community partnerships and training local community clinicians, community health advisers, community health workers, and communication, behavioral health, and palliative care specialists. These initiatives can be time intensive due to the time and need for developing relationships with the cultural leaders and within the norms of the community. However, attempting to skip this critical step could result in efforts not relevant to or not embraced by community members. Regardless of the strategies employed, expanding palliative care into rural areas will take explicit planning and multicomponent, unique strategies.

Conclusions
Research has informed the development of professional guidelines and integration of the principles of palliation into oncology care, from the time of diagnosis to end of life among patients with curable cancers, high-symptom burden, and metastatic disease alike. However, the rural setting has created a barrier for these
advances to reach patients not located near specialty centers. This global issue has been recognized and efforts are being initiated to discover novel strategies to ensure that high-quality palliative and end-of-life care can reach those living in rural communities.

Telehealth, community health workers, specialists trained in various health care fields, and other volunteers trained in the approaches of palliative care have shown promise in bringing complex strategies to remote regions of the world. In addition, the ability to educate all of the health care professionals working in rural settings presents challenges that are surmountable. Organized efforts do exist for bringing palliative care skills to rural health clinicians and care settings. Shortages of palliative care specialists are a reality, even in urban areas. Hence, every clinician should have a basic set of primary palliative care skills of communication, advance care planning, and symptom control to ensure high-quality care for all persons with cancer and their families.

Acknowledgments: The authors wish to thank Karen Herman for coordinating the search and Kristen Allen and Claire Bourgeois for assistance with manuscript preparation.

References


Palliative care benefits patients with cancer in the outpatient setting, and such care should be concurrently and routinely provided with oncology treatment.

New Frontiers in Outpatient Palliative Care for Patients With Cancer

Michael W. Rabow, MD, Constance Dahlin, ANP-BC, ACHPN, Brook Calton, MD, Kara Bischoff, MD, and Christine Ritchie, MD, MSPH

Background: Although much evidence has accumulated demonstrating its benefit, relatively little is known about outpatient palliative care in patients with cancer.

Methods: This paper reviews the literature and perspectives from content experts to describe the current state of outpatient palliative care in the oncology setting and current areas of innovation and promise in the field.

Results: Evidence, including from controlled trials, documents the benefits of outpatient palliative care in the oncology setting. As a result, professional medical organizations have guidelines and recommendations based on the key role of palliative care in oncology. Six elements of the practice sit at the frontier of outpatient oncology palliative care, including the setting and timing of palliative care integration into outpatient oncology, the relationships between primary and specialty palliative care, quality and measurement, research, electronic and technical innovations, and finances.

Conclusions: Evidence of clinical and health care system benefits supports the recommendations of professional organizations to integrate palliative care into the routine treatment of patients with advanced cancer.

Introduction

In fundamental ways, the field of palliative care has developed in the context of oncology, and the majority of both clinical palliative care service and palliative care research involves patients with cancer and is conducted in health care centers focused on providing oncology care. Although the development of palliative care began in the hospital setting for patients during their last days of life, end-of-life hospital care is but a part of the much broader approach to care defined by palliative care. Most patients spend most of their time outside of the hospital, either at home, in other residences such as assisted-living centers, rehabilitation facilities, and in outpatient medical offices.

Thus, outpatient or community-based palliative care is recognized as a key frontier in palliative care, and palliative care in the setting of oncology care is the core of that frontier.1 Six elements at the frontier of outpatient oncology palliative care are reviewed, including the (1) setting and timing of integrating palliative care into outpatient oncology, (2) the relationship between primary and specialty palliative care, (3) quality...
and measurement, (4) research, (5) electronic and technical innovations, and (6) finances.

**Background**

Palliative care is defined by the Center to Advance Palliative Care as “specialized medical care for people living with serious illness.” This type of care focuses on providing relief from the symptoms and stress of a serious illness, regardless of the diagnosis. The goal of such care is to improve the quality of life for both the patient and his or her family. A team of palliative care specialists, nurses, social workers, and other health care professionals collaborate to provide “an extra layer of support.” Because palliative care is appropriate for any patient, regardless of age or disease stage, it can be provided along with curative treatment. The National Cancer Institute defines supportive care as “care given to improve the quality of life of patients who have a serious or life-threatening disease.” We conceive of much of traditional oncology supportive care as included in the constellation of services offered as part of the field of palliative care. Others have argued that supportive care is a broader model than palliative care; however, many medical organizations, including the American Cancer Society and the National Cancer Institute, interchangeably use these terms.

The field of palliative care grew out of the tradition of supporting patients facing the symptoms and distresses of illness within healing traditions generally and Western medicine specifically. With the failure of the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment trial to improve the care of hospitalized patients at the end of life, the Robert Wood Johnson Foundation, the Soros Foundation, and others supported the development and growth of the field of palliative care. In 2006, palliative care was recognized by the American Board of Medical Specialties as a subspecialty of numerous boards of medicine and surgery. The American Academy of Hospice and Palliative Medicine and the Hospice and Palliative Nurses Association have offered a joint annual assembly since 2004, and the technical support provided by the Center to Advance Palliative Care has spurred on the development of an increasing number of inpatient palliative care services. The National Palliative Care Research Center (NPCRC) and the National Institute of Nursing Research (NINR)–funded Palliative Care Research Cooperative Group have fostered research in palliative care, with the NPCRC registry having compiled national operational data for inpatient services. In addition to the Palliative Care Leadership Center Initiative from the Center to Advance Palliative Care, other major international palliative care education is led by the End-of-Life Nursing Education Consortium. The California State University Institute for Palliative Care also offers online education for palliative care–related disciplines.

Professional medical organizations have offered guidelines and recommendations about the role of palliative care in oncology. The National Comprehensive Cancer Network (NCCN) is conducting a study of palliative care services among its member organizations (personal communication, Jessica Sugalski, MPPA). Marking the philosophical, clinical, and financial alignment of palliative care and oncology, the American Society of Clinical Oncology (ASCO) launched the first annual Palliative Care in Oncology Symposium in October 2014.

**Benefits**

The benefits of outpatient palliative care to patients with cancer and their families and health care professionals, in addition to the health care system, have been well documented in a series of studies. One review catalogued these benefits, noting that much of the research referenced came from studies in oncology. The most rigorous study designs include the randomized trials of early palliative care in non–small-cell lung cancer, telephonic palliative care for rural patients in a cancer center, and palliative care across 24 medical oncology clinics in Canada. Randomized studies demonstrate improved satisfaction, clinical outcomes, mortality, and health care utilization. In aligning patient care with individual patient preferences, palliative care helps to prevent unwanted, burdensome, and potentially ineffectual oncology-directed treatments at the end of life. The result of this impact on utilization is a demonstrated decrease in the overall cost of care in the setting of improved quality care in outpatient palliative care for patients with cancer. Palliative care in the oncology setting is helping to align quality and cost.

**Guidelines**

In light of data demonstrating the benefits of palliative care for patients with cancer, ASCO issued a provisional clinical opinion that “combined standard oncology care and palliative care should be considered early in the course of illness for any patient with metastatic cancer and/or high symptom burden.” Thus, ASCO is signaling that palliative care is a routine part of standard oncological care for patients with advanced disease. The American College of Surgeons Commission on Cancer (CoC), which issues basic regulations for oncology centers in the United States, issued standard 2.4 in 2011 that requires these centers to have palliative care services on site or by referral. Although the CoC is not explicit about how this standard is enforced, the directive is a powerful statement about the central role of palliative care in standard oncological care.

The Institute of Medicine (IOM) also focuses on palliative care and has addressed palliative care in the
A palliative focus underlies the recommendation of the IOM and directive of the CoC to oncology centers for universal psychosocial distress screening. In addition, palliative care is part of the supportive care guidelines updated every year by the NCCN, and palliative care is included as a recommended resource in many of the other NCCN guidelines, including adult cancer pain and ovarian cancer, among others.

Prevalence and Characteristics of Care Services

Given the fundamental role of palliative care in oncology care and other care programs, relatively little is known about the prevalence and characteristics of outpatient oncology palliative care services on a national scale. In 2010, Hui et al assessed the institutionally reported prevalence of outpatient palliative care at US National Cancer Institute (NCI)-designated and non-NCI-designated comprehensive cancer centers. They reported that 59% and 22% of all NCI-designated cancer centers and non-NCI-designated centers reported an outpatient palliative care clinic, respectively. Rabow et al reported on established outpatient palliative care practices in the United States, noting that 80% of patients referred had cancer, and oncologists accounted for 76% of the overall referrers. In 2013, Smith et al described the general landscape of outpatient palliative care in the United States and found that the majority of referred patients had cancer. Unpublished data also add to our understanding of outpatient oncologic palliative care practice. In 2014, the NCCN obtained information about the presence of palliative care services from 18 of their 23 member institutions at that time, and all had inpatient palliative care services and 16 (89%) reported offering outpatient palliative care (personal communication, Jessica Sugalski, MPPA).

Although national data are limited, some individual states have sought to document the prevalence of outpatient palliative care services. Rabow et al studied outpatient palliative care practices affiliated with California hospitals and found that 7% of hospitals within California had affiliated outpatient practices (a proportion not significantly changed compared with a survey conducted 4 years earlier), with nearly one-half of referrals from oncology.

Many problems exist with these prevalence data. Prevalence estimates for the penetrance of palliative care in oncology centers may be overestimated due to inconsistent definitions of what constitutes outpatient oncology palliative care and the potential inaccuracies of self-reported survey data. Except for NCCN data, as yet unpublished, much of the data are not recent. Although increasing attention is being paid to outpatient palliative care and many institutions appear to be developing services, the evidence for rapid growth is scant. The study of outpatient palliative care affiliated with California hospitals suggested that, although new palliative care programs are developing, established programs are also disappearing to the point that the prevalence of outpatient palliative care may not be changing as many expect.

Regardless of the specific prevalence figures on local and national scales, the issue of greatest practical importance is how the capacity of outpatient oncologic palliative care compares to the need. ASCO’s recommendation for routine palliative care for all US patients with metastatic cancer or high symptom burden suggests shortages of workforce and clinical capacity. With the support of the California HealthCare Foundation, Kerr et al assessed the outpatient palliative care capacity in California, including information about the presence of outpatient palliative care services from oncology centers. They estimated a range of need for palliative care based on estimates of the number of all deaths in California and the number of deaths from 7 illnesses, including cancer, thus accounting for the majority of nontraumatic deaths in the state. Their estimate suggests that the current capacity for outpatient palliative care (oncological and nononcological) in California is 24% to 37% of the need, with no type of palliative available in nearly 40% of California counties. An international study demonstrated that most oncology palliative care specialists felt their institutions were unlikely to expand palliative care services due to financial constraints.

Although the national prevalence and sustainability of outpatient oncological palliative care programs is not precisely known, interest in the field exists and there are many exciting areas of innovation and growth. Six of these areas are reviewed below.

Integration of Care Setting

Palliative care specialists seek to integrate palliation within routine oncology care to improve clinical quality. However, despite widespread calls for integration, no consensus exists about how this is best done. We do not have a clear vision of what constitutes integration or the added value of various elements of integration. At a basic level, integration is influenced by the setting of palliative care. Although stand-alone palliative care clinics in academic medical centers were some of the first outpatient palliative care services offered to patients with cancer, palliative care services are “embedding” into oncology practices. Embedded clinics improve the potential for palliative–oncological integration and collaboration, and they increase convenience for patients able to avail themselves of “one-stop” clinical care. Embedded care requires enhanced palliative care competencies for nurses and social workers. Additionally, the integration of ambulatory care and hospice care is important for patients who lack access to hospital-based palliative care. This integration helps to expand access to palliative care and improve patient outcomes.

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Outpatient palliative care is beneficial.\(^2\)\(^{-25}\),\(^2\)\(^9\),\(^5\)\(^0\) Three conversations on the understanding of illness, prognostic understanding, and transitions of care as agreed upon by the health care team.

Although patients who are homebound due to advanced cancer may also be too disabled to benefit from chemotherapy, oncologists may be able to extend the care of homebound patients with orally targeted therapies and home-based palliative care. In fact, home-based palliative care is increasingly recognized as key for patients who are homebound or nearly so and have significant symptomatology but do not qualify for home hospice because of a prognosis longer than 6 months, patient refusal of hospice, or the desire to receive concurrent oncological or other disease-management services (eg, blood transfusions, artificial nutrition) along with palliative care.\(^4\)\(^9\) This includes specialty oncology home services that offer monitoring of home infusion of chemotherapy and other fluids.\(^4\)\(^9\) Given resource and workforce limitations, innovative palliative care programs are collaborating with hospice organizations or home-based medical and assisted-living services that often have the expertise and capabilities to provide palliative care at home, including in rural and challenging urban settings.\(^4\)\(^9\)

**Timing**

Outpatient palliative care allows patients with cancer to be seen early in the course of their illness.\(^2\)\(^9\) Potential benefits of early outpatient oncology palliative care include aggressive management of adverse events and symptoms, longitudinal psychosocial support for patients and their caregivers, and the facilitation of conversations on the understanding of illness, prognostic understanding, and transitions of care as agreed upon by the health care team.

A growing body of literature suggests that early outpatient palliative care is beneficial.\(^2\)\(^{-25}\),\(^2\)\(^9\),\(^5\)\(^0\) Three randomized control trials of early, integrated palliative care plus oncological care compared with standard oncological care alone reported improvements in quality of life, depression, and satisfaction among patients with advanced cancer and limited prognoses.\(^2\)\(^{-24}\),\(^5\)\(^0\) Temel et al\(^2\)\(^2\) found that 151 patients with newly diagnosed non–small-cell lung cancer had a 2.5-month longer survival rate when they were randomized to early palliative care. Early palliative care has also been associated with reduced health care utilization in studies comparing early palliative care with usual oncology care and late palliative care (ie, > 90 days or < 90 days before death).\(^2\)\(^2\),\(^2\)\(^5\)

However, the optimal timing of outpatient palliative care involvement to maximize clinical benefit remains unknown. A recent study randomizing patients with advanced cancer to early in-person outpatient palliative care consultation plus nursing telephonic coaching sessions (within 30–60 days of diagnosis) or late sessions (approximately 4 to 5 months after diagnosis) found no improvements in patient outcomes (eg, quality of life) or health care utilization.\(^2\)\(^3\) However, the same study found a 15% improvement in rate of survival for patients receiving early palliative care.\(^2\)\(^3\) The results of this study raise questions regarding the optimal timing of palliative care interventions along with the mechanisms that contribute to increased survival rates.\(^2\)\(^3\) Further complicating the question of timing is that the benefits of palliative care may differ by cancer type and prognosis. Additional research is needed to guide when, along a patient’s cancer journey, palliative care can have the most reliable and effective impact.

In most referral systems, outpatient oncologists play a crucial role in deciding on the need for and timing of palliative care referral.\(^5\)\(^1\) Although a significant increase has been seen in the use of palliative care by oncologists overall, data from a national survey suggest that a minority of oncologists frequently refer their patients to pain or palliative care specialists.\(^5\)\(^2\),\(^5\)\(^3\) Furthermore, when referrals do occur, they tend to be late in the patient’s illness course, typically 30 to 60 days before death.\(^5\)\(^4\) Potential explanations for the lack of referrals or late referrals include the misperception by the oncology team members that palliative care means end-of-life care, concern that referral will cause patients to feel defeated, frightened, or lose hope, limited access to services, not knowing the appropriate time to refer, and under-recognition of the patient concerns that might benefit from palliative care consultation. One study found significant differences between the reasons an oncologist referred to palliative care compared with a comprehensive screening system.\(^5\)\(^5\)

Currently, no national standards for outpatient palliative care referral exist. Identifying reliable markers and developing standardized screening tools to trigger timely outpatient palliative care referral would likely address some barriers to referral and help integrate palliative care into oncology care. Potential indicators could include prognosis using validated prognostic models, index hospitalization for symptom management or loss of function, development of increased symptom burden, referral of patients with cancers with historically poor prognoses and/or high symptom burden, or progression after first-line chemotherapy.
Primary vs Specialty Palliative Care

The future of comprehensive cancer care includes palliative care beginning at diagnosis and, in particular, for advanced disease. Given both the need for and benefits of providing palliation in the oncology setting, as well as the shortages of health care professionals specializing in palliative care, the development of primary palliative care training and competence among oncologists is key. With mandates from ASCO, CoC, NCCN, and IOM for palliative care as part of comprehensive cancer care, outpatient oncology care necessitates that all health care professionals providing oncology care have primary palliative care skills as well as access to palliative care specialists.13-19 All oncologists must learn to understand basic palliative care concepts and to appropriately utilize palliative care as part of comprehensive, patient- and family-focused care.

A distinction is emerging between primary palliative care and specialty palliative care within oncology care.66 Although both settings pertain to pain and symptom management and communication, clear delineations exist in skills (Tables 1 and 2).66-59 Primary palliative care addresses relief of symptoms, including basic management of pain and symptoms (eg, depression, anxiety) and communication skills (eg, goals of care inclusive of prognosis, advance care planning, code status). All oncologists can and must learn palliative care skills. Depending on the clinician’s discipline, options exist for primary palliative care education. Nurses, physicians, and social workers may obtain some palliative care competency through their routine education and training; however, this is usually insufficient.60 Oncology physician fellowships offer an overview of palliative care, symptom management, and communication skills. Oncology nurses may receive education in common symptoms for specific cancers and management of those symptoms. Other specialized programs, such as End of Life Nursing Education Consortium and Education in Palliative Care and End-of-Life Care for Oncology, focus on the care of patients with cancer.57,61 Another program for psychologists, social workers, and spiritual care professionals is the Advocating for Clinical Excellence: Transdisciplinary Palliative Care Education.62 In real time, the collaboration around individual patients between specialty palliative care teams and oncology teams can create opportunities for cross education. In clinical work together, oncologists can learn primary palliative care concepts and palliative care specialists can learn about primary oncology concepts.

Beyond education, new paradigms of primary palliative care in oncology are evolving. One model is an oncology nurse navigator who employs primary palliative care skills to address patient symptom needs, engage patients in their care through advance care planning, provide emotional support, and communicate

| Table 1. — Primary and Specialty Palliative Care in Oncology Care |
|-----------------|-----------------|
| **Primary**     | **Specialty**   |
| Basic symptom management of physical and psychological symptoms | Complex symptom management of refractory symptoms |
| Cancer-related pain | Complex pain |
| Depression       | Complex depression |
| Anxiety          | Existential distress |
| Relief of symptoms |      |
| **Communication** |                |
| Cancer prognosis Goals of treatment | Communication |
|                      | Conflict management within the circle of patients, families, and health care team |
| **Advance care planning** | Ethics (in particular, medical futility) |


| Table 2. — Importance of Palliative Care as Part of Cancer Care |
|-----------------|-----------------|
| **Goals**       | **Action**      |
| **Primary Palliative Care Recommendations** |                |
| The cancer care team should provide patients and their families with understandable information on cancer prognosis, treatment benefits and harms, palliative care, psychosocial support, and estimates of the total and out-of-pocket costs of cancer care. | The cancer care team should collaborate with their patients to develop a care plan that reflects their patients’ needs, values, and preferences, and considers palliative care needs and psychosocial support across the cancer care continuum. |
| In the setting of advanced cancer, the cancer care team should provide patients with end-of-life care consistent with their needs, values, and preferences. | Professional educational programs for members of the cancer care team should provide comprehensive and formal training in end-of-life communication. |
| **Specialty Palliative Care Recommendation** |                |
| Members of the cancer care team should coordinate with each other and with primary/geriatrics and specialist care teams to implement patient care plans and deliver comprehensive, efficient, and patient-centered care. | Academic institutions and professional societies should develop interprofessional education programs to train the workforce in team-based cancer care and promote coordination with primary/geriatrics and specialist care teams. |
| All individuals caring for patients with cancer should have appropriate core competencies. | Cancer care delivery organizations should require that the members of the cancer care team have the necessary competencies to deliver high-quality cancer care, as demonstrated through training, certification, or credentials. |

with the oncology team about care needs.65 Other palliative care teams have reported on their primary palliative care education for oncologists.64

Even in the setting of primary palliative care by oncologists, specialist palliative care teams can improve the overall care of patients with cancer.65-72 Specialty palliative care includes the complex management of refractory pain and symptoms, addressing grief and existential distress, and medical futility, as well as more advanced communication such as management of conflict among patients, families, and the health care team. A qualitative review of a small sample of patients with lung cancer who had early intervention specialty palliative care received a range of services, including psycho/spiritual/emotional support, symptom management, advance care planning, and promotion of illness understanding.65 Other studies have demonstrated better symptom control and earlier referral to hospice with specialty palliative care.66,67 By reducing and relieving the stress of care, specialty palliative care saves oncologists time and allows the oncology team to focus on cancer treatment.68,69 Implementation of specialty palliative care within oncology varies and can include palliative care teams that have clinical space in the oncology clinic and are embedded into care delivery, advanced-practice oncology nurses or oncologists who provide oncology care on one day and specialty care on other days, and specialty palliative care clinics within the community.70-72

The relative roles and balance of responsibilities between primary and specialty palliative care teams in the outpatient setting remain to be clarified, but they will need to individualized based on resources, expertise, and access to specialty health care professionals. Integration of primary and specialty palliative care is likely to vary depending on whether the oncology practice is part of an independent practice, hospital, or large health care system.

Quality and Metrics
The theoretical benefits of outpatient palliative care services or an informal sense of patient and clinician satisfaction were historically sufficient to justify support for services. However, increasingly, outpatient palliative care is being challenged to demonstrate its quality objectively, similar to other fields of medicine. This has ignited a broad conversation about how the quality of outpatient palliative care can be best measured.

The American Academy of Hospice and Palliative Medicine and Hospice and Palliative Nurses Association convened a working group to review the existing literature about quality measures in palliative care and to select 10 measures considered to be the highest priority because of their scientific validity and clinical utility to promote across the field.73 The majority of quality metrics prioritized by this initiative pertained to either hospice or inpatient palliative care, because these are the settings in which most of the research has been done.74 An important next step will be to determine how they should be extrapolated to the outpatient palliative care in oncology centers. Similarly, the National Quality Forum formally endorsed 13 quality measures for palliative care in 2012, but the majority of these pertain to patients in the hospital or hospice settings; 1 measure is specifically tailored to measure the quality of outpatient palliative care at oncology centers.75 The Quality Oncology Practice Initiative is an oncologist-led quality assessment program that has promoted a unified set of quality measures for oncology since 2011.76 Its list of metrics includes several that pertain to palliative care, including pain assessment and management, dyspnea assessment, constipation assessment, management of nausea and emesis, provision of hospice and palliative care, and location of death.77 Although evidence for these activities is abstracted from oncologist notes, more complete information about the quality of care that patients with cancer receive could be determined by also examining the work of palliative care specialists. The American College of Surgeons CoC set a new standard to be implemented by 2015 stating that all patients with cancer must be screened at least once for distress and social concerns using a survey instrument (eg, distress thermometer).18,78 The role of palliative care specialists in performing or responding to screening has not yet been determined, but having a robust plan will be critical to respond to the distress identified.

Traditionally, quality metrics considered for outpatient palliative care are intended for patients being evaluated by palliative care specialists. However, an even larger — and unanswered — question is how to measure and improve the quality of the primary palliative care that oncology teams provide to patients.

In addition to establishing consensus quality metrics for palliative care, methods must be developed to collect and share standardized data across outpatient palliative care programs to benchmark and drive improvement. The Palliative Care Quality Network and the Quality Data Collection Tool provide 2 formats for the prospective collection and comparison of standardized palliative care data.79,80 Prospective data collection makes it possible to obtain patient-reported outcomes in a standardized way, thus allowing for quality improvement efforts that target clinical outcomes (eg, constipation improvement) rather than just processes of care (eg, treatment of constipation). These organizations also provide opportunities for the collaboration of coordinated quality improvement projects across sites that may enable greater gains in quality and safety than any single program could make alone.79,80

Robust measurement, reporting, and quality improvement are important next steps for outpatient pal-
livative care to help ensure the best care for our patients and to continue to earn the confidence of oncology specialists.

Research
Recognizing its growing importance, prominent entities such as the IOM, the Patient Centered Outcomes Research Institute, and the National Institutes of Health have recommended that palliative care research become a national priority. Many unanswered questions warrant research in outpatient oncology palliative care. The study by Temel et al. raised a number of key questions, including whether the benefits seen in patients with non–small-cell lung cancer can be generalizable to patients with other cancers, whether their study results can be generalizable to other oncology centers, whether palliative care focused on those with metastatic disease would show the same benefit in if provided to those without metastases, and, of the 7 key elements of palliative care in their intervention, which one would account for the most benefit and which ones are true across different cancers in different settings.

Other important research questions in outpatient oncology palliative care include which models of care offer the most effective patient-centered approach to care and which patient and treatment factors contribute most to poor quality of life and how these factors can be modulated to improve patient wellbeing. In 2013, the National Institute of Nursing Research launched the Innovative Questions initiative. The goal of this initiative was to initiate a dialogue with the National Institute of Nursing Research stakeholders to identify novel scientific questions. Two of the topic areas were of particular relevance to outpatient oncology palliative care: symptom science and end-of-life/palliative care. A number of these questions directly related to outpatient oncology palliative care research (Table 3).

Investigators, health care systems, and national organizations are seeking to facilitate research into these questions. The NPCRC promotes palliative care research in an era where many palliative care researchers work in isolation with few other collaborators in their institution. The NPCRC also helps to develop junior investigators and supports research that can be rapidly and directly translated into improved clinical practice. The Palliative Care Research Cooperative Group focuses on answering research questions that cannot be easily answered at a single site. It provides infrastructure for efficient, multisite palliative care research by offering a network of motivated, coordinated, investigators/sites that create capacity for multisite research, as well as methods, tools, and processes that promote the timely and valid conduct of robust cooperative group research. These 2 organizations support oncology palliative care research and seek to facilitate investigator development in research oriented toward oncology palliative care.

Technology
To comprehensively care for patients across the continuum of oncology care (in hospitals, clinics, home, and in the community), the future of outpatient palliative care in the oncology setting will depend on technological innovations. Technology is beginning to address barriers of space, time, and the limited clinical availability of specialty expertise, and it will be useful as part of a number of the elements of outpatient palliative care in the oncology setting.

Technology can provide patient education and support. Beyond how patients and families use social media, support groups are available online with and without professional facilitation, and smart phone applications and websites exist to assist patients and families with symptom assessment, advance care planning, and family caregiver support. The applicability and benefits of a select number of these services have been evaluated. Telephonic and video health technology can provide effective clinical care for patients unable to travel due to disability or distance. Few interventions have been rigorously evaluated. Patient outcomes electronically reported are the core to some of these technologies and this will be facilitated by developments in what has been called the “quantified self.”

Table 3. — Selected Items From the Innovative Questions Initiative

<table>
<thead>
<tr>
<th>Question</th>
<th>Example</th>
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</thead>
<tbody>
<tr>
<td>How do we overcome barriers in underserved, hard-to-reach populations</td>
<td>Implement culturally congruent, patient-, and caregiver-centered palliative care strategies</td>
</tr>
<tr>
<td>What oncology palliative care interventions/strategies best align</td>
<td>with patient and caregiver goals?</td>
</tr>
<tr>
<td>How do type, intensity, complexity, and fluctuation of symptom burden</td>
<td>in oncology patients impact individual and family goals for care?</td>
</tr>
<tr>
<td>What are the best models for community-based oncology palliative care?</td>
<td></td>
</tr>
<tr>
<td>What are the strategies for assessing caregiver preparedness and self-</td>
<td>care abilities for oncology palliative care early in the illness trajectory?</td>
</tr>
<tr>
<td>For symptom management at the end of life, what are the best</td>
<td>minimally invasive methods to monitor functional status, physiological status, and patient</td>
</tr>
<tr>
<td>What electronic data collection methods can be used by health care</td>
<td>reported outcomes?</td>
</tr>
<tr>
<td>What are the best ways to measure patient reported outcomes using</td>
<td>standardized, widely used instruments or common data elements?</td>
</tr>
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life-sustaining treatment paradigms and advance directives, can be stored and accessed online, improving care across the continuum of sites over time. Patient privacy and Health Insurance Portability and Accountability Act concerns must be addressed as clinical care, patient-reported outcomes, and storage of these data and other health documents occur electronically and move online and, thus, outside the physical boundaries of individual medical centers and across state and national lines. The potential for better care from analysis and research using “big data” is profound. Technology can also increase the efficiency of primary palliative care education and consultation. Educational curricula can be shared within computerized health systems and electronic medical records, as well as online. Palliative care specialists can provide e-consults to treating oncologists at a distance.

Financing
In a fee-for-service system for oncology care, the incentives of individual oncologists and hospitals are aligned with the provision of multiple treatments and services (volume-based payment) without respect to the value of those treatments and services. The future of oncology care likely involves the ongoing development and penetration of more global health care budgets, including for oncology care, in which efficiency and value (both clinical benefits and cost) are scrutinized and incentivized. ASCO recommends the early integration of palliative and oncology care as a means to improve quality and value, thus reducing the rising costs of oncology care at the end of life. Although most research documenting the cost-effectiveness of palliative care has been conducted in the inpatient setting, outpatient oncology palliative care has demonstrated its role as part of comprehensive oncology care to improve the efficiency of health care utilization, thereby helping to control costs. Palliative care in the outpatient oncology setting will continue to be defined by the historical alignment of quality and cost in today’s environment of health care reform.

Conclusions
Evidence suggests that palliative care in the outpatient oncology setting is beneficial. As a result, professional organizations have issued guidelines and recommendations about the role of palliative care in oncology. Palliative care is integral to quality comprehensive care for patients with symptoms from cancer, advanced disease, or other serious illness. Six areas are at the forefront of outpatient palliative care for patients with cancer, including (1) the setting and timing of palliative care integration into the outpatient setting, (2) the relationship between primary and specialty palliative care, (3) quality and metrics, (4) research, (5) electronic and technology innovations, and (6) health care financing. Experts in these frontiers have also begun to address the profound challenge of workforce shortages in specialty palliative care. Through the successful integration of oncology and palliative care, all patients with cancer should be able to receive standard, comprehensive, integrated care that allows them to live as long and as well as possible.

References
Oncologists should collaborate 
early with palliative care 
specialists to help care for AYA 
patients with cancer.

Palliative Care in Adolescents and Young Adults With Cancer
Kristine A. Donovan, PhD, Dianne Knight, MD, and Gwendolyn P. Quinn, PhD

Background: Cancer survival rates for adolescents and young adults (AYA) have not improved over time relative to children or adults older than 39 years of age. Palliative care is specialized medical care focused on the control of symptoms and relief of suffering with the goal of improving quality of life for the patient and his or her family. To date, the integration of palliative care in AYA patients with cancer remains suboptimal.

Methods: We explore the role of palliative care in the continuum of clinical care for AYA patients with cancer.

Results: Clinical practice guidelines highlight the need for integrating palliative care for all patients with cancer, including the AYA population. Despite this, a paucity of evidence exists regarding the use of palliative care with AYA patients with cancer. Graduate clinical education represents an opportunity to promote the full inclusion and early integration of palliative care in the care of AYA patients with cancer. Advance care planning is one area where some agreement exists on the unique needs of AYA patients and their families.

Conclusions: In general, palliative care is seen as being synonymous with end-of-life care for patients with cancer. However, the emerging trend toward standardizing oncology care to meet the unique medical, psychosocial, and supportive care needs of AYA patients with cancer and their families represents an opportunity for health care professionals to collaborate early with palliative care specialists to control symptoms and relieve suffering in this vulnerable population.

Introduction
Defined on the basis of age and cancer biology, cancer in adolescents and young adults (AYA) accounts for approximately 6% of all invasive cancers diagnosed on a yearly basis.1 Each year, nearly 70,000 AYA patients in the United States receive a cancer diagnosis.2 The incidence of specific cancers in the AYA population varies across the age span, which is typically defined as between 15 and 39 years.3 In the last 30 years, survival rates for AYA patients have not improved relative to younger and older age groups, and cancer is the leading cause of disease-related death in this population.4-6

This lack of improvement in survival has been attributed to numerous factors, including the unique biology of AYA cancers, limited access to care, delays in diagnosis and treatment, lack of consistency in treatment approaches, patient nonadherence to treatment, and low rates of access to and participation in clinical trials, as well as the unique medical, psychosocial, and supportive care needs of this patient population.7-10

Recent study results suggest that implementation of the Affordable Care Act will positively affect the AYA population; however, whether the applicable regulations will result in improved rates of cancer survival

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remains to be seen.\textsuperscript{11,12}

Although the continuum of AYA development is different across its age span, many issues have been identified that distinguish AYA from pediatric and adult populations.\textsuperscript{13-16} Such issues include the transition away from parental dependence toward dependence on peers and social networks, concerns about future family and life plans, limited access to mental health services and social and peer support networks, and disruptions in school or work life with the associated financial challenges.\textsuperscript{13-15} Although the specific needs of individual AYA patients may vary, as a group, these patients have more in common than not.\textsuperscript{7}

Cancer and its treatment confound the AYA patient’s ability to establish autonomy and make independent decisions about education, employment, relationships, and starting a family.\textsuperscript{15} In a recent review of palliative care in AYA, Clark and Fasciano\textsuperscript{17} distinguish AYA patients as a vulnerable population and highlight the chasm between pediatric and adult oncology care where the AYA patient is often lost. This should be alarming to those who care for AYA patients, because research suggests that, as a group, AYA patients tend to experience more complex, more severe, and longer-lasting distress than children or adults with similar diagnoses.\textsuperscript{18-20}

**Palliative Care**

Palliative care is specialized medical care for individuals with serious illnesses. It focuses on control of symptoms and relief of suffering with the goal of improving quality of life (QOL) for patients and their families. Palliative care in cancer is appropriate at any age and at any stage and can be provided along with curative treatment.\textsuperscript{21}

Palliative medicine is a recognized medical specialty in the United States, and current models of palliative care suggest interdisciplinary approaches that include both the primary oncology team and a specialized palliative care team facilitate optimal patient and family care.\textsuperscript{22,23} In 2012, the American Society of Clinical Oncology issued a provisional clinical opinion calling for the integration of palliative care into standard oncology care for patients with metastatic cancer, high symptom burden, or both.\textsuperscript{21} This opinion derives from expert consensus and the results of several randomized controlled trials demonstrating the benefits of integrating palliative care into standard oncology care, including a trial of early palliative care in patients with cancer that found an increased survival benefit for those who received palliative care.\textsuperscript{21,24} Studies also have demonstrated a beneficial effect of early palliative care on QOL in patients with advanced cancer.\textsuperscript{25-26} By referencing the potentially practice-changing data from these studies, the opinion highlights the increasing relevance of palliative care for the care of all patients with cancer.\textsuperscript{21} Consistent with the opinion of the American Society of Clinical Oncology, many professional organizations now recommend that patients with cancer be screened for palliative care needs.\textsuperscript{21,23,27,28} For example, guidelines from the National Comprehensive Cancer Network recommend that all patients with cancer be routinely screened and rescreened at appropriate intervals for palliative care needs.\textsuperscript{23} The guidelines also recommend early collaboration with palliative medicine specialists to improve QOL.\textsuperscript{25}

**Cancer Treatment**

Despite the focus on symptom control and QOL at any stage of disease or treatment, palliative care teams have historically been more often involved in the care of patients with cancer deemed challenging or at or near the end of life.\textsuperscript{7,29} The result is that, among oncology care providers, palliative care is generally synonymous with end-of-life care.\textsuperscript{29} Thus, integrating palliative care into standard oncology care for AYA, like that for pediatric and adult patients with cancer, remains suboptimal.\textsuperscript{30} To the best of our knowledge, no trial has integrated early palliative care into the care of AYA patients with cancer receiving treatment.

Data on symptom burden in AYA patients, especially at the end of life, are limited. Data on AYA patients with cancer are often contained within the adult and pediatric oncology literature, making it difficult to discern the potential effects of palliative care in the vulnerable AYA population.\textsuperscript{31-33} Nevertheless, data indicate most AYA patients with cancer experience multiple physical and psychological symptoms and often spend their last days of life within an acute care setting, with end-of-life discussions often occurring only when death is imminent.\textsuperscript{34-36}

In one of the few studies to date of symptom burden in AYA patients with advanced cancer, Cohen-Gogo et al\textsuperscript{35} conducted a retrospective review of the medical records of 45 AYA patients with cancer treated in a specific AYA oncology unit who died as a result of progressive disease during a 2-year period. Diagnoses of sarcoma or a brain tumor predominated and accounted for 78% of diagnoses.\textsuperscript{35} A total of 40% of patients received palliative chemotherapy during the last month of life.\textsuperscript{35} The median time between the last cycle of chemotherapy and death was 30 days (range, 2–457 days).\textsuperscript{35} A total of 24% of patients received radiotherapy in the last month of life, mostly for pain and symptoms related to tumor volume.\textsuperscript{35} One-third of patients received artificial nutrition during the last week of life.\textsuperscript{35} The median number of physical symptoms was 4 (range, 1–7).\textsuperscript{35} Pain and dyspnea were the most common symptoms, particularly among patients with sarcoma, whereas patients with a brain tumor were more likely to experience paralysis, confusion, or coma.\textsuperscript{35} With respect to psychological symptoms, during the last month of life, all pa-
Patients reported sadness, anxiety, fear of being alone, fear of death, fear of pain, and guilt. A total of 77% of patients met with the psychologist on staff at the AYA unit during their initial anticancer treatment; of these patients, 83% continued to receive care from the psychologist during the last month of life. In addition, most of the patients admitted to the unit spent more than 2 weeks in the hospital (median, 16 days; range, 0–30 days) during the last month of life.

Although this study provides only general baseline information about symptoms and patterns of end-of-life care of AYA patients treated in 1 specific AYA unit, it is noteworthy that in most of the patients, end-of-life care continued to be an active period of care. Many of the patients experienced substantial physical and psychological symptoms during the last week of life, a finding that supports the need for a well-trained, multidisciplinary palliative care team to collaboratively work with other members of the health care team.

Data on QOL among AYA patients with advanced cancer are also scarce, either from descriptive observational studies or randomized controlled trials of interventions aimed at enhancing QOL at any point along the disease trajectory. In a systematic review of the literature regarding QOL in AYA patients with cancer, Quinn et al identified 35 studies whose outcomes were any psychosocial factors affecting QOL in AYA patients. Most of the studies they reviewed focused on the post-treatment survivorship period and, broadly defined, the psychosocial supportive care needs of AYA cancer “survivors.” Only 1 study involved AYA patients with advanced cancer with an eye toward palliation of symptoms — in this case, at the end of life to improve QOL. In their review, Quinn et al note lack of sufficient QOL measurement tools and lack of evidence-based interventions to improve QOL in AYA at any point in the cancer care trajectory. They conclude by commenting on the unique needs of the AYA population and the emerging trend toward standardizing oncology care for this population (for additional commentary, see Thomas et al).

Palliative care has not been established in standard oncological care for AYA patients with cancer. However, clinical practice guidelines aimed at the care of AYA patients with cancer across the continuum of care — from diagnosis to survivorship, or end of life — have begun to reflect the need for integrated palliative care. For example, consistent with the recommendation that oncology care providers collaborate early with palliative medicine specialists to control symptoms and reduce suffering in all patients with cancer, guidelines from the National Comprehensive Cancer Network include several considerations for palliative care. The guidelines note that referral to palliative care is appropriate when patients are being treated with curative intent, that palliative care may be initiated at diagnosis (to provide the best possible care for patients), and that interdisciplinary members of the palliative care team should have expertise in understanding the psychosocial, emotional, and developmental issues unique to the AYA cancer population. The guidelines also specifically note the importance of creating an AYA team that includes palliative care as a means of improving early referrals, research, and patient-centered care.

Clinical Education

The creation of an AYA team that includes a palliative care clinician knowledgeable about the unique needs of AYA patients with cancer highlights a critical fact. As Wiener et al note in their review of factors that make the provision of palliative care particularly challenging in AYA, a dearth of clinicians exists, both in medicine and nursing, who have the requisite training and skills in palliative care needed to care for AYA patients with cancer. Formal palliative care training is limited in the average US medical school curriculum. Furthermore, training in adolescent medicine in the United States has been described by many graduates of subspecialty medical residency programs as inadequate for clinical practice. Some commentators, who are aware of the chasm that exists between pediatric and adult oncology care, have suggested that the key to appropriate symptom palliation among AYA patients with cancer is to transition the AYA patient to the adult oncology setting. Others have emphasized the need for specialized AYA multidisciplinary palliative care teams that can work in both pediatric and adult facilities. However, the most convincing commentators are those who seek to integrate palliative care into AYA oncological care by offering educational strategies for teaching clinicians about palliative care in the AYA population.

To this end, Wiener et al have proposed an educational and conceptual model for education aimed at palliative care in the AYA population that acknowledges existing contextual barriers, such as the limited exposure of clinicians-in-training to functional multidisciplinary teams. The model addresses key aspects of clinician development: knowledge (eg, of human development), skills (eg, symptom management, ability to work in teams), and attitudes (eg, about patient dignity). Weiner et al also advocate for the teaching of palliative care concepts via educational strategies and mentorship with the greatest potential to improve AYA outcomes. With respect to outcomes, their model highlights social outcomes, such as receiving respect, feeling understood, and trusting the system, and physical outcomes.

Advance Care Planning

In comprehensive palliative care, discussions about end-of-life care are paramount, and advance care plan-
ning documents are often used to facilitate these discussions.23 Several advance care planning guides are available for adults, including Five Wishes (Age With Dignity, Tallahassee, Florida; https://fivewishesonline.agingwithdignity.org), which is a document that appoints a legal health care decision-maker at the end of life and specifies an individual's desired therapies for medical care (eg, palliative care). Five Wishes largely focuses on the expressed desire of adults to participate in medical decision-making regarding treatment at the end of life.

Researchers have begun to explore whether AYA patients with cancer are similarly motivated to participate in end-of-life discussions and whether they consider these discussions to be beneficial.31,47-52 Evidence does suggest that AYA patients with cancer are interested in having end-of-life discussions and that the patients, their families, and their health care professionals all benefit from such discussions.48,51 Although adult patients with cancer tend to focus on decision-making related to their end-of-life care, AYA patients with cancer appear to be more concerned with how they want to be treated and remembered than about decision-making.57

Whether this finding is related to developmental differences (eg, many adolescent patients may depend on their parents to make treatment-related decisions for them) or to a limited understanding of life-support treatment options and the legal aspects of end-of-life care is unclear. Regardless, such findings suggest that advance care planning documents used to facilitate end-of-life discussions with AYA patients should include developmentally appropriate language and terminology and must also reflect AYA patient values and beliefs.47 Thus, advance care planning guides developed for adult patients are not suitable for AYA patients with cancer and their families.

Voicing My Choices (Aging With Dignity; www.agingwithdignity.org/voicing-my-choices.php) is an advance care planning guide designed for AYA patients to help them communicate their end-of-life preferences to family, caregivers, and friends. The guide was developed by investigators at the National Cancer Institute and National Institute of Mental Health via iterative formative research using Five Wishes in a population of patients with cancer and pediatric patients infected with HIV.47-49,53

Similar to Five Wishes, Voicing My Choices is designed to facilitate communication between AYA and their families and health care professionals, including care providers from the fields of medicine, nursing, social work, chaplaincy, psychiatry, and psychology. It consists of an introduction followed by 9 sections, each one a separate module, that addresses topics such as how patients wish to be supported so they do not feel alone, who they would want to make their medical care decisions if they cannot make them on their own, and what they wish their friends and family to know about them. Five Wishes is legally binding. By contrast, Voicing My Choices is designed to be a legacy document that is not legally binding but that fulfills the patient's final wishes. The effectiveness of Voicing My Choices is predicated on the skills and attitude of the health care professional.53 The guide brings family members or a surrogate decision-maker into the discussion.53 However, it has not been systematically evaluated. Thus, although it is likely to enhance and facilitate discussion between the AYA patient and his or her health care professional, whether the guide serves to facilitate discussion between the AYA patient and his or her family is not yet known. These and other issues are currently being explored in a multi-institutional trial (NCT02108028), so more information about the utility of the guide should be forthcoming.

Conclusions

Cancer survival rates for adolescents and young adults (AYA) have not improved over time relative to younger and older age groups.4-6 Palliative care is specialized medical care that focuses on control of symptoms and relief of suffering with the goal of improving quality of life for the patient and his or her family. Palliative care is appropriate at any age and at any stage of cancer and can be provided along with curative treatment.21 To date, the integration of palliative care in AYA cancer care remains suboptimal.30 Existing clinical practice guidelines highlight the need for the integration of palliative care into the care of all patients with cancer, including the AYA population.21,23,47,48 Despite this, a paucity of evidence exists regarding the use of palliative care in AYA patients with cancer beyond care in the last few weeks or months of life.35 Graduate clinical education represents an opportunity to promote the full inclusion and early integration of palliative care in the care of AYA patients with cancer.99,42,43 Advance care planning is one area where some agreement exists on the unique needs of AYA patients and their families. Although palliative care is generally still synonymous with end-of-life care in cancer care, the emerging trend toward standardizing oncology care to meet the unique medical, psychosocial, and supportive care needs of AYA patients and their families represents an opportunity for health care professionals to collaborate early with palliative care specialists to control symptoms and reduce suffering in this vulnerable population.15,29,37

References

478 Cancer Control


In conjunction with palliative care, life expectancy, functional reserve, and the treatment goals of patients with cancer should be continually reviewed and assessed throughout the course of treatment.

Photo courtesy of Lisa Scholder. Duality. 18" × 24".

Palliative Care in Older Patients With Cancer
Lodovico Balducci, MD, Dawn Dolan, PharmD, and Sarah E. Hoffe, MD

Background: In general, cancer is a disease of aging, and palliative care is an essential step in the management of cancer in patients who are older. The goal of this article is to review common symptoms of cancer and oncology treatment and their management.

Methods: The pertinent medical literature was reviewed.

Results: The scope of palliative care includes personalized cancer treatment. This involves choosing treatment options that best fit the needs of each individual patient. Balancing treatment benefits and risks may be challenging in older patients, many of whom have limited life expectancies and decreased functional reserves. The benefits of treatment may diminish, and the risks of such treatment options increase with age. Thus, the first step toward personalized treatment includes determining physiological age, which is best estimated with a comprehensive geriatric assessment. Prevention of common complications, which include neutropenia and mucositis, allows the administration of treatment in full and effective doses. Fatigue is a chronic symptom related to cancer and its treatment and may lead to functional dependence and an increased risk of death. Fatigue might be prevented by daily exercise even during treatment. Other symptoms include pain and feelings of memory loss.

Conclusions: The scope of palliative care encompasses more issues that symptom management and, for this reason, palliative care should be provided once the diagnosis of cancer is established. Determining treatment goals is essential to improve the treatment experience. Symptom management is similar in older and young patients, but symptoms in the older population may be associated with more frequent and severe complications. Many options exist to prevent and ameliorate the complications of oncology treatment in the aged. However, more studies should be conducted on the long-term care of older patients who have survived cancer.

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Introduction
The goal of palliative care is to improve the disease experience for all patients, irrespective of the outcome. In addition to symptom management, the scope of palliative care includes emotional, spiritual, and social needs of patients, their families and friends, and their caregivers. Many palliative care specialists believe that healing is always achievable even when cure is out of reach, because healing involves patients coming to terms with their disease and its symptoms and outcome.

Palliative care in older patients with cancer is important because integrating palliative care into stan-
dard oncological care can improve rates of survival and quality of life as well as reduce the cost of treatment.\(^3\) By the year 2020, more than 50% of patients diagnosed with cancer will be aged 70 years and older.\(^4\) In addition, older individuals may present different issues unrelated to cancer than their younger counterparts that make palliative care both urgent and challenging.\(^4\)

**Assessing Physiological Age**

Aging may be defined as a progressive loss of functional reserve in multiple organ systems that eventually leads to disability and death.\(^5\) Thus, social support becomes important to the welfare and survival of persons who are elderly when they are unable to accomplish instrumental or basic activities of daily living.

Aging is universal but highly individualized, and physiological age is poorly reflected in chronological age.\(^5\) Thus, assessing physiological age is paramount to any medical decisions related to older individuals. In the case of cancer management, the questions facing the health care professional may include:

- Will the patient die of cancer or with cancer?
- Is the patient likely to experience consequences of cancer during his or her lifetime?
- Will the patient tolerate the treatment proposed?
- What might be the long-term consequences of cancer and its treatment in this patient?

The assessment of physiological age is founded on the comprehensive geriatric assessment (CGA), which encompasses medical, emotional, and social domains, because aging is multidimensional and the assessment of several domains is necessary to estimate life expectancy and stress tolerance (Table 1).

Several models integrating the CGA with clinical and laboratory parameters allow estimates of tolerances of surgery, cytotoxic chemotherapy, and life expectancy independent of cancer.\(^6\)-\(^9\) This information may be used in negotiating and determining the most appropriate treatment for each patient.

Function is assessed in the CGA as a patient’s ability to perform instrumental and basic activities of daily living, because they have prognostic value independent of performance status. No consensus exists concerning the best way to assess polymorbidity and polypharmacy. Several comorbidity scales that account for the number and the severity of comorbid conditions are in use.\(^10\) The definition of polypharmacy may include the number of daily drugs, medication redundancy, drugs contraindicated in older individuals, risk of at least a type 1 drug interaction, and the absence of drugs that may be appropriate.\(^11\) Depression, including subclinical depression, has been associated with increased risk of mortality if it is left untreated; depression can be assessed with a number of screening tests.\(^12\) Many older individuals may be malnourished or at risk of malnutrition; cancer alone is a cause of malnutrition.\(^13\),\(^14\) Both forms of malnutrition can be estimated with the Mini Nutritional Assessment, a commonly used tool. Malnutrition is associated with increased mortality rates, surgery risks, and chemotherapy-related complications.\(^15\) A number of simple tests may be utilized to screen a patient for memory disorders associated with decreased rates of survival. Of these, the Minimental status, Montreal Cognitive Assessment, and Saint Louis University Mental Status Exam are commonly used tools.\(^16\) Assessment of social support status includes available resources, the need for a caregiver, and the caregiver’s availability and effectiveness.\(^17\) Geriatric syndromes involve several conditions that become more common with age, although they are not unique of aging, and purport decreased life expectancy and increased risk of functional dependence.\(^18\)

In addition to estimating cancer-independent life

<table>
<thead>
<tr>
<th>Domain</th>
<th>Element Assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Function</td>
<td>Zubrod performance status&lt;br&gt;Activities of daily living&lt;br&gt;Transferring&lt;br&gt;Bathing&lt;br&gt;Grooming&lt;br&gt;Feeding&lt;br&gt;Dressing&lt;br&gt;Going to the bathroom&lt;br&gt;Maintaining continence&lt;br&gt;Instrumental activities of daily living&lt;br&gt;Use of transportation&lt;br&gt;Ability to take medication&lt;br&gt;Use the phone&lt;br&gt;Manage finances&lt;br&gt;Go shopping&lt;br&gt;Provide one’s own meals</td>
</tr>
<tr>
<td>Polymorbidity</td>
<td>Number and severity of medical conditions (excluding cancer)</td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>Number of medications (generally ≥ 5)&lt;br&gt;Redundancy and duplications&lt;br&gt;Medications inappropriate for use in the elderly&lt;br&gt;Risk of drug interactions&lt;br&gt;Lack of necessary medications</td>
</tr>
<tr>
<td>Emotional status</td>
<td>Screening for depression</td>
</tr>
<tr>
<td>Memory disorders</td>
<td>Assessment of memory impairment (common use is Minimental status)</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Presence and risk of malnutrition: Mini Nutritional Assessment</td>
</tr>
<tr>
<td>Geriatric syndromes</td>
<td>Dementia&lt;br&gt;Severe depression&lt;br&gt;Delirium during mild infection or with medications that generally do not cause delirium&lt;br&gt;Repeated fails&lt;br&gt;Continuous dizziness&lt;br&gt;Indolence&lt;br&gt;Severe osteoporosis</td>
</tr>
</tbody>
</table>
expectancy and risk of treatment-related toxicity, the CGA helps to determine the existence of unsuspected conditions that could interfere with antineoplastic treatment, including various diseases, depression, initial memory disorders, inadequate resources, and inadequate caregiver support.19

Many other instruments have been proposed to assess life expectancy and risk of disability but none has been validated in patients with cancer; however, the “inflammatory index” has been validated in 2 large cohort studies of aging populations.20 Age-related inflammation may be considered chronic and progressive, and the concentration of inflammatory markers, such as cytokines and fibrinolytic products, has been associated with decreased life expectancy and increased risk of disability. The inflammatory index, ie, the sum of the logarithm of interleukin 6 and tumor necrosis factor-α receptor 1 in the circulation, is the most reliable predictor of long-term mortality.20 It is unclear how cancer-related inflammation might affect the inflammatory index.

Frailty is a term often used in the geriatric and geriatric oncology literature.21 Frailty can be interpreted in 2 ways. In one case, it is considered a threshold, a critical loss of functional reserve beyond which any stress, even minimal, may have catastrophic consequences. In the other case, it is considered a continuum, a measurement of the degree of aging.

Pharmacology of Aging
Aging is associated with changes of pharmacokinetics and pharmacodynamics that may affect oncology treatment and the symptoms of cancer (Table 2).22 Reducing the volume of distribution of hydrosoluble agents may be related to reduced total body water, reduced concentration of plasma proteins, and reduced mass of red blood cells, leading to increased area under the curve and toxicity measures of these hydrosoluble medications. It may be mitigated with the correction of anemia.

CYP450 hepatic reactions are the most common site of drug interactions. Patients who are elderly are at increased risk for these interactions due to decreased activity of these reactions and polypharmacy.

Reduced glomerular filtration rate appears to decrease the excretion of medications as well as their active metabolites. For example, although anthracyclines are excreted with bile, some of these anthracyclines give rise to active metabolites (daunorubicinol, idarubicinol) excreted from the kidneys. When the glomerular filtration rate is reduced, compound toxicity, including myelotoxicity, cardiotoxicity, and mucositis, may be increased. Morphine and its congeners are partly metabolized to 6-glucuronides that are active and renally excreted. The increased area under the curve of these metabolites may partly explain the increased effectiveness and toxicity of opioids in older individuals.

Aging is associated with increased risk for myelo-

### Table 2. — Select Pharmacological Changes of Aging

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Age-Related Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacokinetics</strong></td>
<td></td>
</tr>
<tr>
<td>Absorption</td>
<td>Uncertain</td>
</tr>
<tr>
<td></td>
<td>May be reduced due to decreased absorptive surface, decreased gastric secretions and motility, and decreased splanchnic circulation</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>Decreased for water-soluble agents</td>
</tr>
<tr>
<td></td>
<td>Increased for lipid-soluble agents</td>
</tr>
<tr>
<td>Hepatic uptake and metabolism</td>
<td>Decreased hepatic uptake due to decreased splanchnic circulation and decreased liver weight</td>
</tr>
<tr>
<td></td>
<td>Decreased activity of CYP450-dependent reactions</td>
</tr>
<tr>
<td></td>
<td>No apparent change in glucuronidation reactions</td>
</tr>
<tr>
<td>Excretion</td>
<td>Renal excretion</td>
</tr>
<tr>
<td></td>
<td>Decreased due to reduction of both glomerular filtration rate and tubular excretion</td>
</tr>
<tr>
<td></td>
<td>Biliary excretion Unchanged</td>
</tr>
<tr>
<td><strong>Pharmacodynamics</strong></td>
<td></td>
</tr>
<tr>
<td>Organs and systems</td>
<td>Age-related changes and clinical consequences</td>
</tr>
<tr>
<td>Hemopoietic system</td>
<td>Decreased hemopoietic reserve due to reduced number and function of hemopoietic precursors that may lead to increased risk of myelosuppression by cytotoxic drugs</td>
</tr>
<tr>
<td>Mucosa</td>
<td>Increased susceptibility to cytotoxic agents to decreased stem cells and increased proliferation of cryptal cells</td>
</tr>
<tr>
<td>Heart</td>
<td>Decreased number of cardiomyocytes and increased susceptibility to cardiotoxic drugs</td>
</tr>
<tr>
<td>Lungs</td>
<td>Decreased respiratory reserve</td>
</tr>
<tr>
<td></td>
<td>Possibly increased susceptibility to cytotoxic agents</td>
</tr>
<tr>
<td>Brain</td>
<td>Decreased brain volume and circulation may lead to increased susceptibility to medication-related damage</td>
</tr>
<tr>
<td></td>
<td>Possible altered μ:δ receptors may lead to decreased effectiveness and increased toxicity of opioids</td>
</tr>
<tr>
<td>Peripheral nervous system</td>
<td>Increased susceptibility to neurotoxic drugs</td>
</tr>
<tr>
<td>Kidney</td>
<td>Decreased glomerular filtration rate and tubular function may lead to increased susceptibility to nephrotoxic drugs</td>
</tr>
</tbody>
</table>
management, prolonging survival, and preserving quality of life, as well as prolonging active life expectancy — that is, maintaining functional independence and preventing functional decline in older individuals. Loss of independence is universally recognized as the worst threat to quality of life in older patients.

Treatment goals may be at odds with each other. For example, adjuvant treatment improves the likelihood of cure for cancers of the breast, lung, large bowel, and bladder, but it may be associated with intolerable complications. Aromatase inhibitors that represent the hormonal treatment of choice for hormone-sensitive breast cancer can cause severe joint pain and, thus, lead to functional decline, as well as vaginal dryness and dyspareunia. Approximately 15% of older women decide to forgo a higher likelihood of cancer control because of these complications. Peri-

Peripheral neuropathy is a disabling complication of chemotherapy for older individuals and may be caused by drugs commonly used for adjuvant treatment, such as platinum derivatives and taxanes. In most cases, the decisions of forgo chemotherapy is made following exposure to one of these agents, and, in some cases, the decision may be made due to compelling reasons prior to initiating treatment (eg, patients involved in activities that require manual dexterity).

Realistic treatment goals should be established prior to initiating treatment and revisited during the course of the treatment. Initial goals should be based on patient desires, cancer stage, aggressiveness and responsiveness to treatment, life expectancy, risk of complications, and available resources (Fig). However, it is important to remember that the values and desires of the patient are paramount in situations in which prolonging survival might be achieved at significant personal cost.

The role of the caregiver when he or she is unable or unwilling to provide necessary care is an unresolved and vexing problem. Caregivers should provide timely access to health care professionals and to emergency care, provide assistance at home (eg, symptom management, aid in instrumental activities of daily living that the patient is no longer able to perform), and emotionally support the patient. In some instances, the caregiver may act as the family spokesperson within the health care system and may help manage conflicts within the family relating to the patient. In general, the primary caregiver of an older patient with cancer is an elderly spouse with health conditions of his or her own or an adult child who has professional and family responsibilities of his or her own (“Aeneas syndrome”).

Thus, assessment of the caregiver should be part of the initial evaluation of an older patient undergoing any form of antineoplastic treatment; the health care professional can be aided by a social worker to evaluate the availability, the capability, and the willingness of the caregiver. If the results of such an assessment prove inadequate, then alternative solutions should be sought (eg, involvement of other family members or other caregivers).

The caregiver represents a valuable ally for the health care team and is likely to make a difference in the patient’s experience; however, caregivers may be susceptible to severe emotional and physical stress that may lead to disease, including depression, disability, and increased mortality. This stress may impact the family of the caregiver as well as compromise the work quality and productivity of the caregiver. By contrast, caregiving can be a rewarding emotional and spiritual experience that inspires self-worth. Thus, the health care professional must train and support the caregiver by providing a realistic outline of the likely course of the disease and of the difficulties that may emerge, as well as potential solutions, by allowing caregivers to express concerns and show sympathy for them, and by directing caregivers to available resources (eg, support groups). In each encounter with the health care team, the patient and caregiver should be recognized as a dyad held together by the patient’s disease and treatment.

**Management**

**Treatment-Related Complications**

Complications of radiation therapy and systemic cancer treatment, including hormonal therapy, cytotoxic

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**Fig. — The structure of a medical decision.**

Cancer
- Stage
- Aggressiveness
- Responsiveness

Treatment Decisions

Patient
- Life expectancy
- Treatment tolerance
- Resources

Treatment
- Effectiveness
- Toxicity
- Cost

---
chemotherapy, and targeted therapy, are shown in Table 3.

Osteoporosis is a complication of aromatase inhibitors that may be used for the treatment of breast cancer, and androgen deprivation treatment (ADT), which may be used for prostate cancer; the risk for osteoporosis may offset the potential benefits.31 For example, in an older woman prone to falls, aromatase inhibitors may prove more hazardous than the recurrence of breast cancer. Select patients with prostate cancer may undergo ADT for a small increase of prostate-specific antigen in the serum after definitive treatment of the cancer; however, no evidence suggests that this practice is beneficial in the absence of disease (based on imaging results), whereas evidence suggests that the risk of bone fractures increases by 50% after 1 year of ADT.34

Health care professionals must check bone density at the beginning of a patient’s treatment; if the value is normal, then it should be maintained with adequate intake of calcium and vitamin D. In the presence of osteopenia and osteoporosis, then more aggressive treatment with bisphosphonates or denosumab may be indicated. Some studies have shown that an intensive schedule of intravenous zoledronic acid may prevent osteoporosis and cancer recurrence in postmenopausal women receiving adjuvant treatment with an aromatase inhibitor.32,33 Thus, the potential benefit of zoledronic acid should be weighed against its inconvenience, cost, and risk for osteonecrosis of the jaw.

Myelodepression from cytotoxic chemotherapy is more prolonged and more severe in older individuals, and it may be further aggravated by combination chemotherapy/radiotherapy to the chest.22 The risk and duration of neutropenia and of neutropenic infections increases with age, and patients aged 65 years or older are at increased risk for such complications. In addition to severe and sometimes lethal infections, another risk of neutropenia includes treatment delay, and both may cause decreased therapeutic benefits. When myelodepression is managed with dose reduction and delayed treatment administration, neutropenia can lead to a decrease in the treatment dose and intensity, which may result in reduced effectiveness. Myelopoietic growth factors (filgrastim and pegfilgrastim) are effective in older individuals.22 Guidelines recommend that patients treated with a chemotherapy dose in an intensity comparable with cyclophosphamide/doxorubicin/vinorelbine may undergo ADT for a small increase of prostate-specific antigen in the serum after definitive treatment of the cancer; however, no evidence suggests that this practice is beneficial in the absence of disease (based on imaging results), whereas evidence suggests that the risk of bone fractures increases by 50% after 1 year of ADT.34

Several techniques reduce the damage of radiation to normal tissues. The most serious complications of radiation damage are seen from combination chemotherapy/radiotherapy in the management of cancer of the upper airways, the esophagus, and the lungs.36 Severe mucositis may lead to dysphagia, malnutrition, and dehydration. Given the limited nutritional and hydric reserve of the elderly, these complications may be more severe and lethal for older individuals. The prophylactic insertion of a gastric or jejunal tube helps

**Table 3. — Select Complications of Oncology Treatment in Older Patients**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Causes</th>
<th>Possible Prevention/Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis</td>
<td>Aromatase inhibitors (breast cancer) androgen deprivation therapy (prostate cancer)</td>
<td>Calcium and vitamin D supplementation, Bisphosphonates, Denosumab</td>
</tr>
<tr>
<td>Myelosuppression</td>
<td>Most forms of cytotoxic chemotherapy</td>
<td>Dose reductions, Prophylactic use of myeloid growth factors (cytotoxic chemotherapy alone)</td>
</tr>
<tr>
<td></td>
<td>Select forms of targeted therapy (palbociclib, idelalisib, rituximab, ibrutinib, lenalidomide, TKI [chronic myeloid leukemia])</td>
<td>Blood transfusions, Erythropoiesis-stimulating agents (cytotoxic chemotherapy alone) Platelet transfusions</td>
</tr>
<tr>
<td>Mucositis</td>
<td>Cytotoxic chemotherapy (fluorouracil, methotrexate, anthracycline)</td>
<td>Prophylactic treatment with supersaturated solutions of calcium, phosphate, and bicarbonates Management of mucosal infections Prophylactic positioning of gastric or jejunal tube (for radiation therapy and chemotherapy combinations) IV hydration</td>
</tr>
<tr>
<td></td>
<td>Cytotoxic chemotherapy in combination with radiation Select targeted agents (everolimus)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Cytotoxic chemotherapy (fluorouracil, methotrexate, irinotecan) Radiation therapy to the pelvis TKIs Anti-EGFR antibodies Immune check-point inhibitors Anti-PD and anti-PD-L1 antibodies Anti-CTLA-4 antibodies</td>
<td>Antidiarrheal medications Octreotide for severe/resistant cases IV hydration Steroids (for check-point inhibitors alone)</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>Anthracyclines Trastuzumab</td>
<td>For anthracyclines, dexrazoxane</td>
</tr>
</tbody>
</table>

CTLA-4 = cytotoxic T-lymphocyte-associated protein 4, EGFR = epidermal growth factor receptor, IV = intravenous, PD = programmed cell death, PD-L1 = programmed cell death ligand 1, TKI = tyrosine kinase inhibitor.
provide the patient with nutrition and fluids throughout treatment. In addition, the prophylactic use of hyper-saturated calcium solution may assuage the pain of mucositis in the upper digestive tract. Laser and light therapy as well as cryotherapy represent promising treatment options for oral mucositis. When mucosal infections are present, they must be treated, otherwise management consists of temporarily discontinuing oncology treatment and managing pain with opioids. Even in the absence of radiotherapy, mucositis may result from cytotoxic chemotherapy, particularly fluorouracil, methotrexate, and doxorubicin. The management is the same as that recommended for combined chemotherapy/radiotherapy. A keratinocyte-stimulating factor may reduce the risk of mucositis, but it is expensive and cumbersome to administer. Its prophylactic use is not recommended.

Diarrhea is a common complication of the same drugs that cause mucositis, tyrosine kinase inhibitors, and radiotherapy to the pelvis, although the use of image-modulated radiation therapy or protons can reduce the risk of diarrhea. In addition to the use of antidiarrheal medication, maintaining proper hydration is paramount. In some resistant cases, octreotide may be used. Lactobacillus may be useful in chemotherapy/radiotherapy. A keratinocyte-stimulating factor may reduce the risk of mucositis, but it is expensive and cumbersome to administer. Its prophylactic use is not recommended.

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Diarrhea is also a common complication of immune check-point inhibitors, such as ipilimumab, nivolumab, and pembroluzimab. In such a case, diarrhea is auto-immune related and may respond to steroids.

Many different medications can cause peripheral neuropathy, which is common in patients treated with platinum derivatives (eg, oxaliplatin) and taxanes. Peripheral neuropathy may cause symptoms such as loss of sensation, paresthesias, shooting pain, burning pain, weakness, and paresis. One prophylaxis for neuropathy is effective, and that is the timely discontinuance of the offending agents. In some cases, neuropathic pain may respond to high-dose gabapentin or pregabalin, but these drugs may cause somnolence and confusion in older individuals. Numbness may be associated with difficulty performing basic and instrumental activities of daily living as well as unstable gait and falls.

Cardiomyopathy is a complication of anthracyclines, anthracenediones, and cyclophosphamide in high doses. Anthracycline-related cardiomyopathy may be due to progressive damage of the myocardium by free radicals, and it may be irreversible. It is rare prior to a total dose of doxorubicin of 300 mg/m² (and equivalent doses of other anthracyclines). Several approaches may prevent this complication and include concomitant administration of dexrazoxane to prevent the formation of free radicals, administration of doxorubicin as a continuous intravenous infusion, or taken as a low daily dose, and use of liposomal pegylated preparations. Dexrazoxane may enhance other treatment complications, including myelosuppression and mucositis. According to the results from 1 study, dexrazoxane may diminish the antineoplastic effect of doxorubicin. In general, dexrazoxane is recommended only after at least 2 doses of anthracycline. Administering doxorubicin via continuous infusion may be cumbersome outside of major academic centers, and its effectiveness has been confirmed only in sarcomas and in myeloma. Data are insufficient for recommending low daily doses of anthracyclines. Pegylated liposomal doxorubicin may be used in lieu of doxorubicin in patients at high risk of cardiomyopathy, but whether its effectiveness is comparable with doxorubicin is unknown.

A different form of cardiac toxicity that is, in most cases, reversible can be caused by the monoclonal antibody trastuzumab, which causes a condition of frozen myocardium; discontinuing the drug reverses the effect. Risk of cardiac toxicity with trastuzumab also increases with age, and management consists of suspending the administration of trastuzumab, although the drug may be safely restarted when myocardial function has been restored.

**Cancer-Related Complications**

The most common symptom of cancer in older individuals is fatigue. Other important manifestations include pain and malnutrition.

**Fatigue:** Fatigue is a condition of exhaustion that does not improve with rest and that interferes with individual functions. The prevalence of fatigue, even in the absence of cancer, increases with age; in older individuals, fatigue is associated with increased risk of functional deficiency and death. The mechanisms of fatigue are multiple and not fully understood; they may include increased concentration of inflammatory cytokines in the circulation, tissue hypoxia from anemia, hypogonadism-associated ADT, and sarcopenia, a catabolic condition associated with aging that may be related to a combination of inflammation, malnutrition, and endocrine senescence. Radiotherapy and cytotoxic chemotherapy may cause fatigue at least in part through treatment-related anemia.

Management of fatigue is controversial and unsatisfactory. There is consensus that exercise prevents fatigue, but only if the patient is able to follow an exercise program during cancer treatment. Correction of anemia with erythropoiesis-stimulating agents may improve energy level. Although concern exists that erythropoiesis-stimulating agents may stimulate tumor growth, these agents appear safe when the hemoglobin level is not above 12 g/dL and they are used only in patients receiving cytotoxic chemotherapy. Blood transfusions may also relieve fatigue but only for a limited time.
Pain: The perception of somatic and visceral pain may decrease with age. For example, it is not uncommon in older individuals to experience silent myocardial infarction or silent intestinal perforation. Older individuals may have a higher tolerance of pain, because they may consider pain an expected consequence of aging. However, bone pain, in particular, may represent a serious limitation to patient activity and independence.

As in any other individual, the assessment of pain of older individuals includes:

- Type of pain (eg, dull, aching, burning, spasmodic, shooting)
- Localization
- Conditions that elicit pain (eg, particular movements, positions)
- Grade of pain on a pain scale

It is important to note that pain may have some atypical manifestations in older individuals; of these, delirium is one of the most common manifestations.

Another age-related challenge is assessing pain in individuals with dementia or in those unable to communicate. However, select behavioral manifestations, including grimaces, grunting, screaming, or withdrawal, may suggest the need to manage pain.

The management of pain depends on many factors, including the type, location, and intensity of the pain. The most common form of pain is bone pain from metastases. When the pain is localized to a single area, local radiotherapy may suffice. If bone metastases are numerous, then relief of pain in one area may result in the emergence of pain in different areas. Systemic cancer treatment, if effective, represents the most definitive and lasting treatment of pain. Timely use of intravenous bisphosphonates or denosumab may mitigate the symptoms and delay the development of pain. Select radioisotopes are available for the management of bone pain; of these, radium 223 has been shown to relieve pain, with minimal marrow damage, in patients with castrate-resistant prostate cancer.

Pharmacological management is the mainstay of acute pain control. Tapering doses of steroids may provide temporary relief of bone pain. Nonsteroidal anti-inflammatory drugs have limited use in older patients due to their risks of gastritis and renal insufficiency. Opioids represent the most beneficial class of drugs, but their dose should be slowly titrated because the risk of complications may increase with age. Intrathecal administration of opioids may prevent most other types of complications, but this route of administration is cumbersome, expensive, and associated with the risk of spinal infections. Administration of opioids should be complemented by a prophylactic bowel regimen to prevent constipation. Methylnaltrexone relieves opioid-related constipation without interfering with analgesic activity.

Malnutrition: Malnutrition is common, especially in most advanced cancer stages. In patients with cancer of the esophagus and upper digestive tract, malnutrition is often present at diagnosis. Malnutrition is due to a combination of factors, including the consumption of tissues by the cancer, decreased food intake, and absorption. Anorexia may be prominent during the last phases of cancer and appears to be mediated by increased concentration of 5HT3 and tryptophan in the brain stem.

Nutritional support is an essential treatment component for patients with a treatable neoplasm, because malnutrition increases the risk of complications of surgery, radiotherapy, and cytotoxic chemotherapy. Enteral nutrition is more effective than parenteral nutrition and is preferred in the presence of a functional gastrointestinal tract. Prophylactic insertion of gastric or jejunal tubes in the presence of an impending obstruction of the esophagus and upper digestive tract and the aggressive prevention and management of mucositis, nausea, and vomiting are effective and recommended. The management of anorexia is not well established. The effectiveness of cannabinoids is controversial; use of medroxyprogesterone at a high dose appears to stimulate the appetite, but it may not increase the lean body weight of patients. Anamorelin, which is a synthetic analog of the gastric hormone ghrelin, appears promising in early clinical trials.

Nutritional support of any type fails to improve the lean body weight of patients whose neoplasm is advanced and untreatable and does not affect the survival of such patients. Hyperalimentation may have a detrimental effect on survival. For these patients, nutritional support is indicated only if it is necessary to maintain quality of life.

Survivor Care

The survival rates of most cancers have improved for patients of all ages; however, a consensual definition of “survivor” is needed. Few data relate to elderly patients who have survived cancer. It is well known that age is a risk factor for developing acute leukemia after cytotoxic chemotherapy, and older cancer survivors are at increased risk of developing a second cancer that may be related or unrelated to the original one. At present, evidence is insufficient to suggest that elderly patients who are survivors of cancer may benefit from additional cancer screening.

The main concerns related to elderly cancer survivors include functional dependence and memory disorders. Functional dependence may result from a combination of factors, including peripheral neuropathy, sarcopenia, and fatigue. Fatigue appears to play a major role because it is associated with increased risks of functional dependence and mortality among older patients. The most effective treatment of fatigue
appears to be prevention through regular exercise, nutritional preservation, correction of anemia, and depression management, beginning at the time oncology treatment is initiated.

Whether cancer and its treatment are associated with full-blown dementia is controversial; however, cognitive function has been shown to decline as a result of treatment, and this decline may cause distress in patients and their loved ones. Distress may be prevented by anticipating the possibility of cognitive decline, but reassuring the patient might include performing a neuropsychological evaluation. The fear of cognitive decline appears to be a major cause of distress, and, thus, normal findings may reassure the patient that decline has not occurred.

Conclusions

The goal of palliative care is to improve the patient experience; thus, palliative care is most effective when administered together with antineoplastic treatment. After the evaluation of the disease, life expectancy, functional reserve, and treatment goals of the patient should be reviewed and assessed — a process that should be continually reviewed throughout the course of treatment. When feasible, common treatment complications, such as neutropenia and neutropenic infections, should be prevented. Management of fatigue, pain, and malnutrition are paramount to the success of treatment. More information is needed on the elderly cancer survivors, particularly as to whether elderly patients should undergo additional cancer screening and determining the most effective management options for fatigue and cognitive decline in elderly patients.

References


Despite their limited accuracy, clinician prediction of survival, prognostic factors, and prognostic models can help health care professionals estimate survival and inform clinical decision-making.

Prognostication of Survival in Patients With Advanced Cancer: Predicting the Unpredictable?

David Hui, MD, MSc

Background: Prognosis is a key driver of clinical decision-making. However, available prognostication tools have limited accuracy and variable levels of validation.

Methods: Principles of survival prediction and literature on clinician prediction of survival, prognostic factors, and prognostic models were reviewed, with a focus on patients with advanced cancer and a survival rate of a few months or less.

Results: The 4 principles of survival prediction are (a) prognostication is a process instead of an event, (b) prognostic factors may evolve over the course of the disease, (c) prognostic accuracy for a given prognostic factor/tool varies by the definition of accuracy, the patient population, and the time frame of prediction, and (d) the exact timing of death cannot be predicted with certainty. Clinician prediction of survival is the most commonly used approach to formulate prognosis. However, clinicians often overestimate survival rates with the temporal question. Other clinician prediction of survival approaches, such as surprise and probabilistic questions, have higher rates of accuracy. Established prognostic factors in the advanced cancer setting include decreased performance status, delirium, dysphagia, cancer anorexia–cachexia, dyspnea, inflammation, and malnutrition. Novel prognostic factors, such as phase angle, may improve rates of accuracy. Many prognostic models are available, including the Palliative Prognostic Score, the Palliative Prognostic Index, and the Glasgow Prognostic Score.

Conclusions: Despite the uncertainty in survival prediction, existing prognostic tools can facilitate clinical decision-making by providing approximated time frames (months, weeks, or days). Future research should focus on clarifying and comparing the rates of accuracy for existing prognostic tools, identifying and validating novel prognostic factors, and linking prognostication to decision-making.

Introduction

In the last months, weeks, and days of life, patients with advanced cancer may face numerous decisions regarding their personal affairs and health care, many of which depend on how long they will live. For example, patients were less likely to choose chemotherapy at the end of life if they understood that they had a short survival rate.1,2 Similarly for health care professionals, prognosis is a key determinant of clinical decision-making because the risk:benefit ratio for many interventions increases as patients approach the last weeks of life. Chemotherapy given to a patient with months...
of life expectancy may result in tumor response, symptom control, and improved survival; however, the same chemotherapy regimen could cause life-threatening complications if administered to a patient with a poor performance status and a short survival rate.\textsuperscript{5,4} Moreover, palliative resection, total parenteral nutrition, and insertion of an indwelling pleural catheter are generally appropriate for patients with at least a few months of life expectancy.\textsuperscript{3} Moreover, hospice eligibility is based on a survival of 6 months or less.\textsuperscript{6} One study showed that patients were more likely to be referred earlier to hospice if their health care professionals made an accurate prediction of survival.\textsuperscript{7}

Prognosis-based decision-making depends on an ability to accurately estimate survival, which has been a challenge for health care professionals and researchers alike.\textsuperscript{8} The process of prognostication can be divided into formulation (foresighting) and communication (foretelling).\textsuperscript{9,10} Clinicians may formulate prognosis either subjectively (ie, clinician prediction of survival based on intuition) or objectively (ie, actuarial prediction of survival based on prognostic factors and models). Despite the availability of validated prognostic factors and tools, most health care professionals rely on clinician prediction of survival to estimate prognosis because clinician prediction of survival is instantaneous, convenient, and easy to understand. Although clinician prediction of survival often incorporates many known prognostic factors in its determination, each may be assigned a variable weight by different health care professionals. Coupled with variable knowledge, clinical experience, and personality, this results in heterogeneous and often optimistic estimations of life expectancy.\textsuperscript{11,12}

Progress has taken place in the science of prognostication. In this article, some important principles of survival prediction are discussed and the medical literature on clinician prediction of survival, prognostic factors, and prognostic models are reviewed, focusing on patients with advanced cancer with a survival rate of months or less. The implications for clinical decision-making and future research directions are also explored.

**Principles of Prognostication**

Prognostication is a process instead of an event. A patient’s prognosis may change based on treatment response, development of acute oncological complications (eg, hypercalcemia, spinal cord compression, pulmonary embolism), or competing comorbidities (eg, heart failure). In a study of 352 patients admitted to acute palliative care units who had a median survival of 10 days, the presence of acute symptomatic complications, such as pneumonia, peritonitis, metabolic acidosis, and gastrointestinal bleed, was associated with a higher risk of mortality.\textsuperscript{13} Patients with a larger number of acute complications also had a shorter survival.\textsuperscript{13} Thus, it is important for health care professionals to revisit prognosis with patients over time. Sentinel events such as cancer diagnosis, disease progression, and hospitalizations should trigger a prognostic discussion.

Prognostic factors may vary by the stage of disease. In patients with early stage cancer, prognosis may be driven by cancer biology such as tumor stage, histological grade, and mutation status (Table 1). By contrast, prognostic variables in patients with far advanced disease typically consist of patient-related factors such as performance status, dyspnea, delirium, and cancer anorexia–cachexia.\textsuperscript{14} In the last days of life, distinctive, bedside physical signs may signal that death is imminent.\textsuperscript{15,16} Thus, it is important to understand the inception cohort for which the prognostic factors/models were derived and apply the study findings to the appropriate patient population. Terms used to describe the inception cohort in the literature, such as end of life and terminally ill, have been heterogeneously defined.\textsuperscript{17} A systematic review of the literature clarified that both of these terms refer to patients with “months or less of life expectancy,” which represent the target population of this review.\textsuperscript{18}

Accuracy is an elusive concept in prognostication research. This is because not all prognostic studies consistently report accuracy; and, when reported,
different investigators may use different metrics to assess accuracy, the accuracy of a prognostic tool varies by patient population and the time frame of prediction, and very few studies examining novel prognostic factors have incorporated a comprehensive list of known prognostic variables for benchmarking and examined reclassification. Discrimination and calibration are 2 key aspects of accuracy. Discrimination reflects how well a prognostic tool differentiates between patients who died and remained alive by a specific time frame. The Concordance statistic (C-statistic) is often used to examine discrimination, with a value between 0.5 and 1. For a C-statistic to be significant, the 95% confidence interval should not cross 0.5. Because the C-statistic is less sensitive to the addition to a novel prognostic marker to an existing model, reclassification statistics, such as the reclassification calibration statistic, net reclassification improvement, and integrated discrimination improvement should be used to assess the degree of improvement with addition of the new factor. Calibration represents how well the predicted probability of survival based on a prognostic model matches the actual outcomes. A model is considered to have satisfactory calibration (or goodness-of-fit) if the Hosmer–Lemeshow test gives a P value greater than .05. Furthermore, the prognostic accuracy could be estimated with sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy. To advance the science of prognostication, the accuracy of existing and novel prognostic markers and models need to be routinely assessed.

It may not be possible to prognosticate with 100% accuracy (ie, 100% sensitive and 100% specific). Because death is a probabilistic event, its exact timing cannot be predicted with certainty. With disease progression, the likelihood of acute catastrophic complication increases, such as myocardial infarction, pneumonia, and massive bleeding. Some patients may survive longer than expected, whereas some may die earlier than expected. Thus, health care professionals may want to avoid providing specific numbers when discussing prognosis, because doing so could be misleading. Instead, they can acknowledge the uncertainty, guide decision-making by providing general time frames (eg, weeks to months), and advise patients and families to expect the unexpected.

If we can make decisions based on approximations, why should we still strive to improve the accuracy of survival prediction? It is because higher accuracy can offer health care professionals greater confidence when communicating with patients and families while also bringing greater clarity to decision-making.

**Clinician Prediction of Survival**

Over the last decades, clinician prediction of survival has evolved from the classic, temporal question, “How long do I have?” to the surprise and probabilistic questions. Table 2 highlights the question formats and advantages and disadvantages for each approach. The results of some studies also suggest that how the question about prognosis is asked may impact its rate of accuracy.

**Temporal Question**

With the temporal approach, the health care professional is asked the question, “How long will this patient live?” The answer may be provided as a specific time frame. This approach is simple and quick, but it is subjective and unclear if the time frame represents the average/median, maximal or minimal. It may be difficult emotionally to provide a specific number.

**Surprise Question**

With the surprise approach, the health care professional is asked the question, “Would I be surprised if this patient died in (specific time frame)?” This approach is simple, quick, and intuitive to provide. It is subjective and time frame dependent. The threshold for “surprise” may vary by individual. Yes/no answer only.

**Probabilistic Question**

With the probabilistic approach, the health care professional is asked the question, “What is the probability of survival within a specific time frame?” This approach is simple, quick, and intuitive to provide. It is subjective and time frame dependent. Probability needs to be interpreted.
time frame (eg, 3 days, 6 months). This is the most commonly used approach to estimate the rate of survival. The answer is relative easy to formulate, communicate, and understand. However, it is often not specified if the answer represents the average, median, maximal, or minimal expected survival, possibly resulting in confusion among health care professionals and patients. Furthermore, some health care professionals may find it psychologically challenging to provide a number and communicate with patients an “expiration date.”

Temporal clinician prediction of survival often results in systematically overestimation and has a 20% to 30% rate of accuracy, defined as a predicted survival rate of within ±33% of actual survival.11,12 Christakis et al13 asked 343 physicians to estimate the survival for 468 patients at the time of hospice referral; the median survival in this cohort was 24 days. A total of 20% of predictions were accurate, 63% were overly optimistic, and 17% were overly pessimistic.31 Female patients, certain medical subspecialties, lack of clinical experience, and a longer duration of the doctor–patient relationship were associated with less accurate predictions.31 Another study that included advanced patients with cancer with a median survival of 12 days found that younger patient age was associated with less accurate, temporal clinician prediction of survival.11

**Surprise Question**
The surprise question poses the following to the health care professional: “Would I be surprised if this patient died in (specific time frame)?” The health care professional can answer “no” if he or she would not be surprised that the patient would die within the predefined period of time and “yes” if he or she felt otherwise. Rather than a number with infinite possibility, as in the temporal question, the answer is binominal (yes or no), which may help to reduce the likelihood of error. However, each health care professional may have a different threshold for “surprise.”

Moss et al29 asked 4 oncologists to estimate the 1-year survival rate of 853 patients with cancer using this surprise question. The positive predictive value was 41%, the negative predictive value was 97%, and the accuracy rate was 88%.29 In other words, the surprise question was helpful in identifying patients who would live beyond 1 year but less able to identify patients who were going to die within that time frame. In another study, 42 general practitioners in Italy answered the surprise question for 1-year survival in 231 patients with advanced cancer.32 The positive predictive value was 84%, negative predictive value was 69%, and accuracy was 76%.32 Most recently, Hamano et al33 examined the prognostic accuracy rate of the surprise question in 2,361 patients of Japanese descent who had a median survival of 33 days. With the “7-day” surprise question, the rates of sensitivity and specificity were 85% and 68%, respectively, the positive predictive value was 30%, the negative predictive value was 96%, and the rate of accuracy was 70%.33 By contrast, the “30-day” surprise question had sensitivity and specificity rates of 96% and 37%, respectively, and a positive predictive value of 58%, a negative predictive value of 90%, and a rate of accuracy of 65%.33

The surprise question has been used to identify patients who have a limited survival and, thus, may benefit from various services such as palliative care referral and advance care planning discussions; however, the usefulness of this approach needs to be further validated. One qualitative study examining the use of the surprise question among general practitioners identified some potential concerns, including its subjective nature, difficulty in defining a precise time or event when the health care professional would switch the answer from “yes” to “no,” and disagreement that a “no” answer represents the ideal time for specific actions such as advance care planning discussions.34

**Probabilistic Question**
The third approach to clinician prediction of survival employs the probabilistic question. Instead of the “surprise” wording, it asks the health care professional to state the probability of survival within a specific time frame (at 10% increments from 0% to 100%). The response is considered accurate if the health care professional provided a probability of at least 70% and the patient was alive by the prespecified time frame, or if health care professional provided a probability of up to 30% and death occurred within the time frame. By definition, any probability between 40% and 60% is considered inaccurate because the health care professional expressed ambivalence. The probabilistic approach has a potential advantage over the surprise question because it is not dependent on how “surprise” is interpreted.

The probabilistic approach was tested in a cohort of 151 patients with advanced cancer admitted to an acute palliative care unit.11 The median survival was 12 days.11 Both physicians and nurses were asked to provide their estimation of survival from the time of admission related to the following time frames: 24 hours, 48 hours, 1 week, 2 weeks, 1 month, 3 months, and 6 months, and the respective accuracy rates were 71%, 66%, 58%, 56%, 67%, 86%, and 96% for physicians and 91%, 86%, 61%, 53%, 60%, 79%, and 88% for nurses.11 By contrast, the rate of accuracy was significantly lower with the temporal approach (32% for physicians and 18% for nurses).11 Because the same group of health care professionals made predictions in the same cohort of patients, the findings from this study suggested how we pose the question may yield answers with different accuracies.11
In another study, physicians and nurses provided daily prognostication in 311 patients from the time of admission to an acute palliative care unit until death or discharge using both the probabilistic approach (24- and 48-hour time frames) and the temporal approach. The rate of accuracy of the probabilistic approach (40% to 100%) was consistently higher than the temporal approach (10% to 30%) among both professions, although its rate of accuracy decreased as death approached. Nurses were more accurate than physicians with the probabilistic approach but not with the temporal approach, suggesting that the rate of prognostication, the type of health care professional, and the method of clinician prediction of survival are all determinants of the rate of accuracy. Finally, the result highlights the difficulty in identifying patients who are imminently dying even among experienced palliative care physicians and nurses.

**Actuarial Estimation of Survival**

Prognostic factors can generally be classified as disease- and patient-related factors. Patient-related factors have a prominent role in prognostication in the last months or weeks of life. Many tumor-related markers, such as circulating tumor cells, have been shown to have prognostic and predictive utility in patients with metastatic disease; however, their role in patients with only months or weeks of survival need to be further examined. For the purpose of this review, the discussion is focused on the most validated prognostic factors and models as well as on several novel prognostic factors.

**Prognostic Factors**

Among the multiple symptoms with prognostic significance in the advanced cancer setting are the 4 Ds: decreased performance status, dysphagia and cancer anorexia–cachexia syndrome, delirium, and dyspnea. Performance status declines in the months before death, with a steeper deterioration in the weeks and days preceding death. Patients with a lower performance status had a higher likelihood of developing serious adverse events when receiving systematic therapy. In a study involving 1,655 patients with advanced cancer, Eastern Cooperative Oncology Group performance scale, Palliative Performance Scale (PPS), and Karnofsky Performance Scale were strongly associated with survival, with C-statistics of 0.64, 0.63, and 0.63, respectively. A web-based program (Prognostat [University of Victoria, British Columbia, Canada]) is available that provides the historical rates of survival based on PPS, age, sex, and cancer diagnosis; however, further validation is required.

Cancer anorexia–cachexia is another prognostic factor seen in patients with advanced cancer and is associated with elevated inflammatory response and poor nutritional status; loss of appetite is a poor prognostic marker. Malnutrition assessed by either subjective global assessment or other nutritional indices has also been found to be associated with shortened rates of survival. A multicenter study showed that a lower baseline body mass index and higher percentage of weight loss were both associated with shorter rates of survival, thus forming the basis for a prognosis-based staging system for cancer anorexia–cachexia. Moreover, decreased lean body mass, a hallmark of anorexia–cachexia, has prognostic significance independent of the palliative prognostic score.

Delirium is another syndrome associated with a shortened rate of survival. Although delirium is potentially reversible in some patients, many patients with cancer develop irreversible or terminal delirium in the last weeks or days of life. Multiple studies have also confirmed the prognostic role of dyspnea; in particular, patients with dyspnea at rest have a shorter rate of survival than those with episodic dyspnea alone. Other objective, physiological measures also have prognostic utility. Phase angle, a marker of cellular membrane integrity and hydration, is lower in patients with shorter survival. A prospective study of 222 patients with advanced cancer and a median survival rate of 106 days found that phase angle was a significant prognostic factor independent of Palliative Prognostic Score (PaP), hypoalbuminemia, and decreased lean body mass. Hand-grip strength and maximal expiratory pressure that assess skeletal muscle and respiratory muscle functions, respectively, were also associated with survival in patients with advanced cancer. These objective measures show some promise in survival prediction because they are reproducible, noninvasive, easy to use, portable, and inexpensive. However, they need to be further validated before they can be applied in routine practice.

Several laboratory abnormalities have prognostic significance in the advanced cancer setting. Markers of inflammatory response, such as elevated C-reactive protein, erythrocyte sedimentation rate, leukocytosis, lymphopenia, and neutrophil:lymphocyte ratio were associated with poor nutritional status and survival. Other markers of decreased survival include hypoalbuminemia (indicative of malnutrition), hypogonadism (associated with decreased lean body mass and performance status), hypercalcemia (often related to tumor progression), hyponatremia, and elevated lactate dehydrogenase. For example, patients with advanced solid tumors who presented with hypercalcemia have a median survival rate of 2 months.

**Prognostic Models**

Multiple prognostic scoring systems have been developed for patients with advanced cancer. These prog-
nostic models typically include many of the established prognostic factors discussed above. Table 3 illustrates several of the well-validated prognostic models in the advanced cancer setting, including PaP, the Palliative Prognostic Index (PPI), and the Glasgow Prognostic Score.

General time frames are provided by risk score categories for these 3 prognostic models. The original PaP score does not include delirium, although the addition of this variable to create the Delirium-PaP score results in only slight improvement in its performance. A modified version of the Glasgow Prognostic Score assigns no points (instead of 1 point) to hypoalbuminemia alone without an elevated level of C-reactive protein.

In all of these models, total score is calculated based on the number of prognostic factors (ie, higher score = worse survival) and a probability of survival by a defined time frame is provided based on the risk group category.

Other prognostic models have been derived from patients with only months or weeks of survival, including the Objective Prognostic Score, the B12/C-reactive protein Index, the Japan Palliative Oncology Study-Prognostic Index, the Chuang Prognostic Score, the Terminal Cancer Prognostic Score, and the Poor Prognosis Indicator.

Despite the plethora of prognostic models, the one that is the most accurate or superior to clinician prediction of survival alone remains unclear. In a prospective study of 549 patients with advanced cancer and a median survival of 22 days, Maltoni et al reported that PaP, Delirium-PaP, PPI, and PPS had respective C-indices of 0.72, 0.73, 0.62, and 0.63 and accuracy rates of 88%, 80%, 72%, and less than 50%. However, the PPI cutoffs used were different from earlier studies. In a separate study, Stiel et al examined the performance of PPI, PaP, and clinician prediction of survival in 84 patients with cancer. PPI had the highest correlation coefficient with actual rate of survival (0.68), followed by PaP (0.58) and clinician prediction of survival (0.56). Clinician prediction of survival was examined as a categorical variable instead of as a continuous variable. In a large prospective study in Japan, Baba et al examined the feasibility and accuracy of PaP, Delirium PaP, and PPI in 2,361 patients in both hospital and home settings. Although PPI was completed more often, PaP and Delirium PaP scores had higher rates of accuracy than PPI for predicting 21-day survival rates (C-statistic, 0.79–0.89 vs 0.75–0.84; P < .05) and 42-day survival rates (C-statistic, 0.81–0.88 vs 0.75–0.85; P < .05).

The change in a prognostic score may also be useful for predicting survival, with the understanding that patients who deteriorate often have a worse prognostic score over time and vice versa. In a study of 2,392 patients with advanced cancer, Kao et al found that the median PPI increased from 6 on day 1 to 7 on day 8 (P < .001). The median survival rate was 53 days with an improvement in PPI score, 36 days with a stable PPI score, and 22 days with PPI deterioration over the 1-week period. The C-statistic for 30-day survival was 0.65 for a baseline PPI score, 0.64 for a PPI change score, and 0.71 for the combined baseline and change in PPI. When only patients with a higher baseline PPI (ie, > 6) were included, the C-statistics for 30-, 60-, and 90-day survival rates were 0.66, 0.64, and 0.63 for the baseline PPI, respectively, and 0.72, 0.76, and 0.79 for the magnitude of PPI change between baseline and day 8. The corresponding accuracy rates were 61%, 57%, and 55% for baseline PPI, and 71%, 79%, and 83% for PPI change, respectively.

### Table 3. — Prognostic Models for Patients With Advanced Cancer

<table>
<thead>
<tr>
<th>Model</th>
<th>Variable</th>
<th>Scoring</th>
<th>Survival Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Palliative Prognostic Score</strong></td>
<td>Clinician prediction of survival (0–8.5) K Karnofsky performance scale ≥ 50% (2.5) A Anorexia (1.5) D Dyspnea (1) L Lymphopenia (0–2.5)</td>
<td>Total score 0–17.5 points Higher score = worse survival</td>
<td>Risk group A (0–5.5 points); months of survival Risk group B (5.6–11 points); weeks of survival Risk group C (11.1–17.5 points); days of survival</td>
</tr>
<tr>
<td><strong>Palliative Prognostic Index</strong></td>
<td>Palliative performance score (0–4) D Delirium (considered absent if caused by a single medication and potentially reversible) (4) O Oral intake (0–2.5) E Edema (1)</td>
<td>Total score 0–15 points Higher score = worse survival</td>
<td>Risk group A (0–4 points); months of survival Risk group B (4.1–6 points); weeks of survival Risk group C (6.1–15 points); days of survival</td>
</tr>
<tr>
<td><strong>Glasgow Prognostic Score</strong></td>
<td>Albumin &lt; 35 g/L (1) C-reactive protein &gt; 10 mg/L (1)</td>
<td>Total score 0–2 Higher score = worse survival</td>
<td>Score = 0: months to years of survival Score = 1: months of survival Score = 2: weeks to months of survival</td>
</tr>
</tbody>
</table>
change score could only be used in patients who re-
maind alive 1 week after the initial assessment, which
may limit its utility to a certain extent; nevertheless, a
change in PPI over only 1 week had prognostic value.74
Further studies are needed to examine the prognostic
utility of change over different time periods and with
different prognostic scores.

Future Directions

Accuracy Reporting

The discrimination and calibration of prognostic mark-
erators (eg, clinician prediction of survival, prognostic fac-
tors and models) should be consistently reported using
standardized, predefined, and practical time frames
(eg, 1 week, 1 month, 2 months, 3 months, 6 months)
that would allow comparison across studies.

Clinician Prediction of Survival

How we pose the questions matters. In addition, the
rate of accuracy of clinician prediction of survival var-
ies by clinician factors, patient characteristics, and
time frame of prediction. To date, the surprise ques-
tion has only been tested with the 1-year, 30-day,
and 7-day survival time frames in advanced patients
with cancer.53 The probabilistic question has been ex-
amined with the time frames of 24 hours, 48 hours,
1 week, 2 weeks, 1 month, 3 months, and 6 months;
however, this was only conducted in patients admitted
to palliative care units.11,50 Thus, these rates of clinici-
nian prediction of survival must be further validated.
A direct comparison of the accuracy rate of these ap-
proaches is also needed.

Prognostic Factors/Models

Existing: Validation of existing prognostic factors/
models is important. Furthermore, comparison of the
performance of these prognostic tools is warranted to
help health care professionals identify the most appro-
priate model(s) for clinical practice.

Novel: A better understanding of the physiological
and pathological processes in patients with cancer may
help develop novel prognostic markers. Research stud-
ies of novel prognostic markers should aim at improv-
ing the rate of accuracy of established prognostic mod-
el; thus, reclassification statistics should be consistently
reported. The role of serial prognostication should also
be further examined.

Diagnosis of Impending Death

Recognition that a patient has entered the last days of
life presents a unique area for research. Instead of a
prognostic question, this may be a diagnostic issue be-
cause the process of dying is irreversible. The results of
some studies have suggested that several bedside clini-
cal signs have very high specificity rates for impending
death; however, further validation is required.15,16

Web-Based Programs

Few web-based prognostication programs are avail-
able for patients with advanced cancer. Thus, web-
based programs should be developed to facilitate the
use of validated prognostic models for clinical deci-
sion-making. Existing programs (eg, Prognostat) have
limited use.40,41

Communicating Prognosis

Although it is beyond the scope of this review, how
health care professionals discuss prognoses with pa-
tients and families also warrants further research.
Should we give the maximum, minimum, and/or me-
dian survival times (as in the temporal approach), the
probability of survival at various time points (as in the
probabilistic question and prognostic models), or gen-
teral time frames (eg, days, weeks, months)? Given that
the rate of accuracy is below 80% for a vast majority
of prognostic tools, perhaps communicating pro-
gnosis using general time frames would provide adequate
information for decision-making while not being mis-
leading. Ultimately, research studies are needed in this
area.

Prognostic Factors

Clinical Decision-Making: More studies are needed
to examine how prognostic tools can be used to guide
clinical decisions, such as palliative care referral or
chemotherapy discontinuation.

Clinical Trials: In addition to clinical decision-
making, prognostic factors and models may be incorpo-
rated as eligibility criteria or stratification factors in clini-
tals of oncology treatment. Currently, performance
status is commonly included. Some prognostic markers
may have both predictive and prognostic utility.

Conclusions

Clinician prediction of survival remains the most com-
monly used approach to formulating a prognosis, a fact
that can be attributed to convenience (clinician predic-
tion of survival already incorporates many existing
prognostic factors), and few studies have demonstrat-
ed that use of prognostic models can significantly im-
prove rates of accuracy. However, health care profes-
sionals often overestimate survival with the temporal
question, and other clinician prediction of survival ap-
proaches, such as the surprise question and the proba-
ibilistic question, may estimate survival with a defined
time frame and have moderate to high accuracies.

Prognostic factors in the advanced cancer set-
ting include symptoms (eg, decreased performance
status, delirium, dysphagia, cancer anorexia–cachex-
ia, dyspnea), physiological changes (eg, decreased
muscle function, lean body mass), and laboratory ab-
normalities (eg, increased C-reactive protein, hypoal-
buminemia). Multiple prognostic models have been
References


Is **DOG1** Immunoreactivity Specific to Gastrointestinal Stromal Tumor?

William Swalchick, MA, Rania Shamekh, MD, and Marilyn M. Bui, MD, PhD

**Background:** **DOG1** is a novel gene on gastrointestinal stromal tumors (GISTs) that encodes the chloride channel protein anoctamin 1, also known as discovered on GIST-1 (DOG1) protein. **DOG1** antibodies are a sensitive and specific marker against GIST positive for CD117 and CD34 and negative for CD117 and CD34. **DOG1** is also independent of **KIT** or **PDGFRA** mutation status and considered specific for GIST when it was first discovered in 2004.

**Methods:** The previous 10 years of literature was searched for articles relating to **DOG1**. We critically reviewed 12 studies that showed **DOG1** was positive in 250 cases of 2,360 tested non-GIST neoplasms (10.6%) at different anatomical sites using monoclonal, polyclonal, or nonspecified antibodies. Criteria for positivity varied between the studies.

**Results:** Monoclonal and polyclonal **DOG1** antibodies were reactive in various different non-GIST tumor types spanning 9 organ systems in addition to normal salivary and pancreatic tissues. The tumors included were renal oncocytoma (100%), renal cell carcinoma chromophobe type (86%), solid pseudopapillary neoplasm of the pancreas (51%), neoplastic salivary tissue (17%), synovial sarcoma (15%), leiomyoma (10%), pancreatic adenocarcinoma (7%), and leiomyosarcoma (4%).

**Conclusions:** By contrast to the original concept that **DOG1** antibodies are specific to GIST neoplasms, the studies reviewed showed that the data suggest **DOG1** positivity in select non-GIST tumors. Only in the appropriate clinical and pathological context is **DOG1** positivity specific and helpful in the diagnosis of GIST.

**Introduction**

A 58-year-old woman who did not smoke was found to have a 1-cm left upper lobe lingula lung nodule discovered on a screening radiograph as part of a routine physical examination. The patient denied fever, chills, sweats, anorexia, or weight loss. She had a past medical history of thyroid nodule. Her family history was positive for hypertension, heart disease, and lung cancer. She was taking chlorthalidone for hypertension and ibandronate for osteoporosis as well as multivitamin supplements. Subsequent positron emission tomography showed the hypermetabolic uptake of fluorodeoxyglucose in the nodule with a standard uptake value of 7, which is suspicious for a neoplasm. She underwent wedge resection of this lung nodule. Gross examination showed a 1-cm, grey-tan, firm nodule 0.5 cm from the resection margin. Microscopic examination revealed sheets of oncocytic tumor cells with abundant pink, granular cytoplasm, ovoid nuclei, small nucleoli (Fig 1A), and negative surgical margins. Immunohistochemistry was strongly and diffusely positive for **DOG1** (Fig 1B) but negative for **CD10**, **CD34**, **CD117** (C-kit), **CD163**, cytokeratin (CK) 7, CK20, CK AE1/AE3, thyroid transcription factor 1, epithelial membrane antigen, renal cell carcinoma, thyroglobulin, and **ERG**.

Based on these findings, a preliminary diagnosis of epithelioid gastrointestinal stromal tumor (GIST) was made. Magnetic resonance imaging of the abdomen was obtained and was within normal limits. The patient came to the H. Lee Moffitt Cancer Center & Research Institute (Tampa, FL) for treatment.

After performing a thorough history and physical examination and reviewing her imaging and pathology findings, her physician indicated that the findings were inconsistent with a diagnosis of GIST. Criteria for diagnosing GIST are reviewed in Table 1.1 After our pathological review of the case, the **DOG1** immunostain (SP31 clone, prediluted via a dispenser) was repeated and it was diffusely but weakly positive (Fig 1C).

**Is This Gastrointestinal Stromal Tumor?**

To practice evidence-based medicine, it is necessary to work-up the case in a systemic approach. The steps include:

1. Clinical and radiological correlation with pathology findings: In this case, the overall his-
tological features are not typical for epithelioid GIST; however, the immunoreactivity of DOG1 was puzzling. Primary GIST of the pleura has been reported in a single case report; however, primary GIST originating in the lung has not been reported.

2. Review the literature and investigate if DOG1 immunoreactivity is specific for GIST alone and what other tumors are positive for DOG1 and could be a potential diagnosis. The literature review revealed an interesting result, and our findings are included below so other pathologists may find them useful when dealing with tumors and GISTs positive for DOG1.

3. Conduct judicious ancillary testing to rule in or out differential diagnoses (eg, carcinoma, melanoma, granular cell tumor, and epithelial sarcoma).

4. If in doubt, seek an expert opinion.

After pertinent differential diagnoses were ruled out, we felt this was not a case of epithelioid GIST, but rather a primary lung tumor that warranted further subtyping. Christopher D.M. Fletcher, MD, at Brigham & Women’s Hospital (Boston, MA) was consulted. Other pertinent stains as well as repeat immunostains were negative for DOG1. The tumor was deemed to be an atypical epithelioid neoplasm of the lung; however, this entity is not an established World Health Organization classification but instead is a descriptive diagnosis that reflects the uncertain histogenesis, clinical behavior, and outcome of this type of tumor.

Table 1. — Diagnostic Criteria of GIST

<table>
<thead>
<tr>
<th>Site of Involvement</th>
<th>Stomach: 54%</th>
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<tbody>
<tr>
<td></td>
<td>Small intestine and duodenum: 32%</td>
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<tr>
<td></td>
<td>Colon and rectum: 1%</td>
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<tr>
<td></td>
<td>Others: 9%</td>
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<tr>
<td>Histology</td>
<td>Spindle cell tumor, in most</td>
</tr>
<tr>
<td></td>
<td>Epithelioid: 20%–25%</td>
</tr>
<tr>
<td></td>
<td>Mixed spindle and epithelial cells</td>
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<tr>
<td>Differential Diagnosis</td>
<td>Smooth muscle tumor</td>
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<tr>
<td></td>
<td>Nerve sheath tumor</td>
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<tr>
<td></td>
<td>Other spindle or epithelial tumor</td>
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<tr>
<td>Immunophenotype</td>
<td>CD117 (C-kit) strongly positive, except in 5% of GIST cases with mutant PDGFRA</td>
</tr>
<tr>
<td></td>
<td>CD34 is positive in most cases of spindle-cell GIST; less consistent in epithelioid histology</td>
</tr>
<tr>
<td></td>
<td>DOG1 is positive in most cases of GIST (CD117+/DOG1+); often positive in CD117- GIST (CD117-/DOG1-)</td>
</tr>
<tr>
<td>When to Diagnose GIST?</td>
<td>CD117 positivity in context with correct clinical and pathological setting</td>
</tr>
<tr>
<td></td>
<td>DOG1 more sensitive than CD117 in detecting GIST of gastric origin, epithelioid morphology, and GIST harboring PDGFRA mutation</td>
</tr>
<tr>
<td></td>
<td>CD34 alone not used to diagnose GIST</td>
</tr>
</tbody>
</table>

GIST = gastrointestinal stromal tumor.

and our current scientific understanding of the lesion. The recommended management is judicious follow-up. At the time of publication, the patient is under surveillance.

DOG1 has shown rates of high sensitivity and specificity in the detection of GISTs, and 74% of GISTs exhibit a positive DOG1 and CD117 immunoprofile.5 Discovered on GIST-1 (DOG1) protein antibodies are more sensitive than CD117 antibodies in detecting tumors of gastric origin, epithelioid tumors, and tumors harboring PDGFRA.4 Although DOG1 positivity is generally required for the diagnosis of GIST, the results should be interpreted alongside morphological findings of the tumor and the clinical picture, as shown in the current case. From this, we intend to explore the immunoreactivity of DOG1 in non-GIST neoplasms to provide useful information for practicing pathologists and other health care professionals.

Methods
A search of the English-speaking medical literature was conducted to identify original articles published from 2004 to 2015 regarding the use of the DOG1 antibody for the pathological diagnosis on formalin-fixed and paraffin-embedded human tissue. We reviewed the relevant studies to examine the results of the clones of DOG1 antibodies as well as immunoreactive and tissue types. The clone refers to DOG1 antibodies made by identical immune cells copies of a unique parent cell (K9, SP31, DOG1.1). These clones were developed from mice and rabbits. Documentation of the findings, a critical review of the results, and the application of this information in the work-up of the index case are discussed.

Results
Antibodies
Twelve relevant studies were identified. The DOG1 antibody used in these studies included monoclonal (SP31, K9, DOG1.1), polyclonal, or nonspecified antibodies. Criteria for positivity varied among the studies.

DOG1 Expression

DOG1 is expressed in normal salivary acini gland and pancreatic endocrine tissue (Table 2).5-6 Table 3 summarizes DOG1 expression in 250 cases out of 2,360 non-GIST neoplasms tested at different anatomical sites.5-7-17 Of the 2,360 tumors tested, the average rate of DOG1 positivity was 10.6%.

As illustrated in Fig 2,12-14 DOG1 is 100% positive in cases of renal oncocytoma and chondroblastoma,8% to 72% positive in acinic cell carcinoma, chromophobe renal cell carcinoma, fibroadenoma, adenoid cystic carcinoma, and squamous cell carcinoma7,11,12,14; 22% to 53% positive in epithelial-myoid epithelial carcinoma, pseudopapillary neoplasm, neoplastic salivary tissue, endometrial adenocarcinoma, gastric adenocarcinoma, and glomus tumor5,8,10-11,7% to 17% positive in cholangiocarcinoma, synovial sarcoma, colonic adenocarcinoma, leiomyoma, and pancreatic adenocarcinoma8,10-12,14,15, and 1% to 5% positive in leiomyosarcoma, angiosarcoma, Ewing sarcoma, malignant peripheral nerve sheath tumor, neuroendocrine tumor, melanoma, and schwannoma5,8,10-12,14-16. Reports regarding solid pseudopapillary neoplasm of the pancreas are conflicting.6,8

Except in cases of renal oncocytoma and chondroblastoma, the tumors mentioned above have various levels of DOG1 expression. However, of the 2,360 cases, a total of 959 tumors, other than those listed in Table 3, are nonresponsive to DOG1 immunohistochemistry. The list of these tumors is summarized in Table 4.7-12,14

Discussion
This first clue that this lung tumor may not be GIST is that primary GIST has never been reported.2 If this case was the first discovered primary lung GIST, then molecular confirmation would have been warranted. GIST does not appear to metastasize to the lung, other than in the setting of many years of treatment with tyrosine kinase inhibitors. To the best of our knowledge, primary GISTs in the lung have not been documented in the English literature. The second clue lies in the specificity of DOG1 immunoreactivity in GIST.

DOG1 was shown to be independent of the KIT/PDGFRA mutation status and was considered specific for GIST when it was first discovered in 2004.18 In other words, DOG1 should be tested when the tumor is of gastric origin, has epitheloid morphology, and in cases harboring the PDGFRA mutation. Data are emerging regarding the expression of DOG1 in non-GIST tissue. Studies that have reported higher rates of DOG1 specificity

<table>
<thead>
<tr>
<th>Study</th>
<th>Anti-DOG1 Antibody Type</th>
<th>Site</th>
<th>Tumor Type</th>
<th>DOG1 Expression, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chenevert5</td>
<td>DOG1.1</td>
<td>Salivary gland</td>
<td>Salivary tissue</td>
<td>109/109 (100)</td>
</tr>
<tr>
<td>Ardeleanu6</td>
<td>Polyclonal</td>
<td>Pancreas</td>
<td>Endocrine tissue</td>
<td>11/11 (100)</td>
</tr>
</tbody>
</table>

Representative of 135 cases.

GIST = gastrointestinal stromal tumor, IHC = immunohistochemistry.
have had small sample sizes, whereas larger studies (> 83 cases) have reported that a small percentage of non-GIST tumors were positive for DOG1 (see Fig 2).8,10-12,14

As shown in Fig 2, neoplastic salivary gland may show DOG1 expression. As shown in Table 3, the average DOG1 specificity rate for neoplastic salivary tissue was 17%.5,11,14 DOG1 expression in synovial sarcoma was reported by 4 different studies to have various specificity rates.10-12,14 The average rates of DOG1 specificity for synovial sarcoma was 14.8%.

Gastric adenocarcinoma has 28% positivity for DOG1 compared with 13% for colonic adenocarcinoma (see Fig 2).12,14 Even though the location of these tumors may overlap with GIST, they rarely overplay histologically with GIST and do not pose diagnostic challenges.

Smooth muscle tumors were reported in 5 studies.10,12,14,15 The average rates of DOG1 specificity for leiomyoma and leiomyosarcoma were 10.7% and 4.2%, respectively (see Fig 2). When the smooth muscle tumor occurs in the gastrointestinal tract, it may be diagnostically challenging to be differentiated from GIST. As shown in Fig 2, nerve sheath

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**Fig 2.** — DOG1 tumor specificity rates. GIST = gastrointestinal stromal tumor.

Non-GIST Neoplasm

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- Renal oncocytoma (n = 21)
- Chondroblastoma (n = 9)
- Acinic cell carcinoma (n = 33)
- Fibroblastoma (n = 11)
- Adenoid cystic carcinoma (n = 37)
- Squamous cell carcinoma (n = 28)
- Encephalomyoepithelial neoplasm (n = 15)
- Endometrioid adenocarcinoma (n = 10)
- Gastric adenocarcinoma (n = 27)
- Glomus tumor (n = 83)
- Synovial sarcoma (n = 115)
- Cholangiocarcinoma (n = 6)
- Colonic adenocarcinoma (n = 112)
- Leiomysarcoma (n = 214)
- Colonic adenocarcinoma (n = 112)
- Pancreatic adenocarcinoma (n = 112)
- Ewing sarcoma (n = 34)
- Neuroendocrine tumor (n = 99)
- Melanoma (n = 181)
- Schwannoma (n = 83)
Table 3. — *DOG1* IHC in Neoplastic Non-GISTs

<table>
<thead>
<tr>
<th>Study</th>
<th>Anti-<em>DOG1</em> Antibody Clone Type</th>
<th>Site</th>
<th>Tumor Type</th>
<th><em>DOG1</em> Expression, n/N (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhao</td>
<td>Not specified K9</td>
<td>Kidney</td>
<td>Renal oncocytoma</td>
<td>21/21 (100)</td>
</tr>
<tr>
<td>Hemminger</td>
<td></td>
<td></td>
<td>Chromophobe renal cell carcinoma</td>
<td>32/37 (86)</td>
</tr>
<tr>
<td>Akpalo</td>
<td>SP31 K9</td>
<td>Bone</td>
<td>Chondroblastoma</td>
<td>9/9 (100)</td>
</tr>
<tr>
<td>Wong</td>
<td></td>
<td></td>
<td>Glomus tumor</td>
<td>6/27 (22)</td>
</tr>
<tr>
<td>Lopes</td>
<td></td>
<td></td>
<td>Ewing sarcoma</td>
<td>1/34 (3)</td>
</tr>
<tr>
<td>Miettinen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bergman</td>
<td>Not specified K9</td>
<td>Pancreas</td>
<td>Pseudopapillary neoplasm</td>
<td>15/29 (51)</td>
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<tr>
<td>Hemminger</td>
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<td></td>
<td>Adenocarcinoma</td>
<td>8/112 (7)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Neuroendocrine tumor</td>
<td>2/99 (2)</td>
</tr>
<tr>
<td>Chenevert</td>
<td><em>DOG1.1</em> K9</td>
<td>Head and neck</td>
<td>Acinic cell carcinoma</td>
<td>32/33 (97)</td>
</tr>
<tr>
<td>Lopes</td>
<td></td>
<td>Salivary gland</td>
<td>Adenoid cystic carcinoma</td>
<td>20/28 (71)</td>
</tr>
<tr>
<td>Hemminger</td>
<td></td>
<td></td>
<td>Epithelial-myoepithelial carcinoma</td>
<td>8/15 (53)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neoplastic salivary tissue</td>
<td>14/83 (17)</td>
</tr>
<tr>
<td>Lopes</td>
<td><em>DOG1.1/K9</em></td>
<td>Breast</td>
<td>Fibroadenoma</td>
<td>9/11 (82)</td>
</tr>
<tr>
<td>Wong</td>
<td></td>
<td>Soft tissue</td>
<td>Synovial sarcoma</td>
<td>17/115 (15)</td>
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<tr>
<td>Sah</td>
<td></td>
<td></td>
<td>Leiomyosarcoma</td>
<td>9/214 (4)</td>
</tr>
<tr>
<td>Miettinen</td>
<td></td>
<td></td>
<td>Angiosarcoma</td>
<td>1/32 (3)</td>
</tr>
<tr>
<td>Hemminger</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sah</td>
<td>K9</td>
<td>Esophagus</td>
<td>Squamous cell carcinoma</td>
<td>9/15 (60)</td>
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<tr>
<td>Wong</td>
<td></td>
<td>Stomach</td>
<td>Adenocarcinoma</td>
<td>11/39 (28)</td>
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<tr>
<td>Lopes</td>
<td></td>
<td>Liver</td>
<td>Cholangiocarcinoma</td>
<td>1/6 (17)</td>
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<td>Miettinen</td>
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<td>Abdomen</td>
<td>Leiomyoma</td>
<td>11/103 (11)</td>
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<tr>
<td>Hemminger</td>
<td></td>
<td>Colon</td>
<td>Adenocarcinoma</td>
<td>4/30 (13)</td>
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<tr>
<td>Wong</td>
<td>K9</td>
<td>Uterus (endometrium)</td>
<td>Endometrioid adenocarcinoma</td>
<td>4/10 (40)</td>
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<tr>
<td>Lopes</td>
<td></td>
<td>Central nervous system</td>
<td>Malignant peripheral nerve sheath tumor</td>
<td>1/34 (3)</td>
</tr>
<tr>
<td>Miettinen</td>
<td></td>
<td></td>
<td>Schwannoma</td>
<td>1/83 (1)</td>
</tr>
<tr>
<td>Hemminger</td>
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<td>Skin</td>
<td>Melanoma</td>
<td>3/181 (2)</td>
</tr>
<tr>
<td>Gonzalez</td>
<td>K9/SP31</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wong</td>
<td></td>
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<tr>
<td>Lopes</td>
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<tr>
<td>Miettinen</td>
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<tr>
<td>Tang</td>
<td>K9</td>
<td>Prostate</td>
<td>Stromal sarcoma</td>
<td>1/1 (100)</td>
</tr>
</tbody>
</table>

Representative of 1,401 cases.

<sup>a</sup>Combined data from multiple studies.

GIST = gastrointestinal stromal tumor, IHC = immunohistochemistry.

tumors also have a small rate of *DOG1* positivity (<5%). In these situations, other markers for GIST, such as CD117, CD34, or mutational analysis for CD117 and *PDGFR*, can be used to help definitively diagnose GIST.

**Limitations**

The various studies we reviewed used different antibodies and various scoring criteria for *DOG1* immunoreactivity. Although no specific practice guideline exists for the diagnosis of GIST, strong, diffuse, and membranous *DOG1* immunoreactivity was generally accepted for the diagnosis. The heterogeneous result of *DOG1* immunoreactivity by various laboratories may present a challenge. For example, in our index case, *DOG1* was tested in 3 different laboratories with 2 different antibodies and yielded different results. If the *DOG1* immunostain was negative, then this lung mass would never have been diagnosed as GIST.

**Conclusion**

In addition to *DOG1* being detected in cases of gastrointestinal stromal tumor, *DOG1* positivity can be detected in other non-neoplastic and neoplastic tissue; however, only in the appropriate clinical and pathological...
Table 4. — IHC Negative for DOG1 in Neoplastic Non-GISTs

<table>
<thead>
<tr>
<th>Study</th>
<th>Anti-DOG1 Antibody Clone Type</th>
<th>Tumor Type</th>
<th>Case, n (N = 959)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhao&quot; Hemminger&quot;14</td>
<td>Not specified K9</td>
<td>Clear-cell renal cell carcinoma</td>
<td>35</td>
</tr>
<tr>
<td>Akpalo9 Lopes11</td>
<td>SP31 K9/DOG1.1</td>
<td>Chondromyxoid fibroma</td>
<td>12</td>
</tr>
<tr>
<td>Wong10 Lopes11 Miettinen12 Hemminger14</td>
<td>K9 K9/DOG1.1 K9 K9</td>
<td>Dedifferentiated liposarcoma</td>
<td>27</td>
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<tr>
<td></td>
<td></td>
<td>Desmoid tumor</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Desmoplastic small round cell tumor</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endometrial stromal sarcoma</td>
<td>28</td>
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<td></td>
<td></td>
<td>Extraskeletal myxoid chondrosarcoma</td>
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<td></td>
<td>Gastrointestinal ganglieneuroma</td>
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<td></td>
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<td>Inflammatory fibroid polyp</td>
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<td>Inflammatory myofibroblastic tumor</td>
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<td></td>
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<td>Kaposi sarcoma</td>
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<td>Neurofibroma</td>
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<td>Perivascular epithelioid cell tumor/angiomyolipoma</td>
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<td>Sarcomatoid carcinoma</td>
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<td>Small cell carcinoma</td>
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<td>Solitary fibrous tumor</td>
<td>49</td>
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<tr>
<td>Hemminger8</td>
<td>K9</td>
<td>Serous cystadenoma</td>
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<tr>
<td>Lopes11</td>
<td>K9/DOG1.1</td>
<td>Mesenchymal tumors other than GIST</td>
<td>261</td>
</tr>
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<td>Miettinen12 Lopes11</td>
<td>K9</td>
<td>Extramedullary myeloid tumor</td>
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<td>Mastocytoma, skin</td>
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<td>Neuroblastoma</td>
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<td>Undifferentiated sarcoma</td>
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<td>Small intestine carcinoid tumor</td>
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<td>Undifferentiated sarcomatoid carcinoma</td>
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<td>Alveolar soft-part sarcoma</td>
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<td>Prostate adenocarcinoma</td>
<td>10</td>
</tr>
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</table>

Combined data from multiple studies.
GIST = gastrointestinal stromal tumor, IHC = immunohistochemistry.

context is DOG1 positivity specific and helpful for diagnosing true cases of gastrointestinal stromal tumor.

References

4. Lee CH, Liang CW, Espinosa I. The utility of discovered on gastro-
10. Wong NA, Shelley-Fraser G. Specificity of DOG1 (K9 clone) and protein kinase C theta (clone 27) as immunohistochemical markers of gastrointestinal stromal tumour. Histopathology. 2010;57(2):250-258.
Occurrence of Multiple Tumors in a Patient
Elaine Tan, Mark Friedman, MD, and Domenico Coppola, MD

Summary: An 81-year-old man initially presented with a right forearm mass that was found to be myxofibrosarcoma. In addition, he was found to have gastric and intragastric masses identified as neuroendocrine tumor (NET) and gastrointestinal stromal tumor (GIST; presenting synchronously), respectively, as well as a new left upper quadrant mass identified as desmoid tumor in the colon. The patient complained of melena, which was found to be due to metastatic myxofibrosarcoma in the transverse colon. Several reports have associated GIST with NET and some reports have associated GIST with sarcomas and NET with sarcomas; however, this is the first report to document all these tumors in a single patient. Several factors may have contributed to the development of these tumors, including growth factors secreted by NET, KIT mutation of GIST predisposing to additional tumors, immunosuppressed state, or an underlying genetic syndrome. This case highlights the importance of investigating for additional malignancies when a primary malignancy is discovered.

Case Report
An 81-year-old man with a past medical history significant for multifocal lipomas and prostate cancer, for which he underwent prostatectomy, presented for removal of a mass on his right forearm. Excision was performed and pathology revealed high-grade myxofibrosarcoma. The resected tumor was 5 cm in size. Histologically, the tumor was poorly differentiated and involved the surgical resection margins. The tumor was composed of large epithelioid cells and spindle cells with scattered multinucleated cells. Nuclear pleomorphism was present, and the surrounding stroma was myxoid and desmoplastic. The patient underwent wide resection and radiotherapy.

Positron emission tomography/computed tomography demonstrated a large, hypermetabolic, soft-tissue mass in the subcutaneous fat of the posterior thigh and a hypermetabolic mass in the left upper quadrant of the abdomen. Wide excision of the mass of the posterior thigh revealed a 6-cm, metastatic, high-grade myxofibrosarcoma with positive margins. The patient underwent radiotherapy.

Later the same year, the patient underwent esophagogastroduodenoscopy, which revealed a gastric mass seen at the greater curvature; partial gastrectomy was performed. Macroscopically, a $3.7 \times 3.2 \times 3.2$ cm well-circumscribed, soft, tan-colored, lobulated gastric mass was identified. The tumor was composed of a monomorphologic population of cells with granular pink cytoplasm and round vesicular nuclei with nucleoli (Fig 1A). Immunohistochemically, the tumor was diffusely positive for cytokeratin (Fig 1B), chromogranin, and synaptophysin (Fig 1C), and Ki-67 revealed 4% positivity in 4% of the tumor (Fig 1D). These findings supported a diagnosis of well-differentiated, grade 2 neuroendocrine tumor (NET). One of 4 regional lymph nodes was positive for metastatic NET.

In addition, a $2.5 \times 1.3 \times 1.1$ cm, well-circumscribed, firm, tan-colored intragastric mass composed of spindle cells, arranged in intersecting fascicles and focally exhibiting paranuclear vacuoles (Fig 2A), was seen. These cells were diffusely positive for CD117 (Fig 2B) and CD34 (Fig 2C) but negative for actin (Fig 2D) and S100 by immunohistochemistry. The Ki-67 proliferation index was 1%. Genetic analysis of the mass revealed a mutation in exon 11 of KIT. Based on these findings, the diagnosis of gastrointestinal stromal tumor (GIST) was made.

More than 2 years after the patient originally presented, computed tomography of his abdomen and pelvis showed a new mass in the left upper quadrant of his abdomen, so segmental colectomy with primary colocolostomy was performed. The tumor was 3 cm in its largest diameter and had negative margins. Gross examination revealed a white, dense mass invading the muscularis propria of the large bowel. Macroscopically, the tumor was composed of plump, fibroblastic spindle cells infiltrating the smooth muscle of the muscularis propria (Fig 3A). No necrosis or mitotic activity was present. The lesion was completely resected. The lesional cells were immunohistochemically positive for beta-catenin (Fig 3B) and negative for S100, CD117, ac-
tin, and desmin. These results supported the diagnosis of a desmoid tumor (fibromatosis).

Nine months later, the patient represented with melena, and subsequent colonoscopy revealed a polypoid lesion in the transverse colon measuring 3.5 cm in its largest diameter. Histologically, the tumor was similar to this patient’s primary high-grade myxofibrosarcoma located in his right forearm and had infiltrated the colonic wall, including the colonic mucosa (Fig 4).

**Discussion**

GISTs have been well documented to be associated with the development of synchronous primary tumors, and this rate of association can be as high as 11.5% to 33.3%.1 Oftentimes, GIST coexists with adenocarcinoma of gastric, colonic, or pancreatic origin, as well as breast, prostate, and lung cancers.2,5

In our patient, GIST was found in association with gastric NET, a finding that has been reported a handful of times. In 1 case report, a 69-year-old man with well-differentiated NET in the corpus was also found to harbor submucosal borderline GIST.4 In another case, a 65-year-old woman with GIST of the gastric corpus was diagnosed with concomitant, well-differentiated NET in the same location.5 Although these 2 cases are examples of GIST being synchronous to NET, other cases have described a single tumor type that predated the occurrence of the second tumor by years; however, no clear predisposition of one tumor leading to the other has been established.2,6

GISTs have also been found in association with sarcomas. Arnogiannaki et al1 reported the simultaneous occurrence of gastric GIST with uterine leiomyosarcoma. Similarly, Sharma et al7 reported a case of a 50-year-old woman with ileal GIST and synchronous, high-grade breast sarcoma with heterologous cartilaginous, osseous, and rhabdomyoblastic differentiation. An association with NET and sarcoma has also been described by Adams et al8 who reported the occurrence of embryonal rhabdomyosarcoma of the cervix and appendiceal carcinoid tumor in a 43-year-old woman. However, our patient had a unique combination of myxofibrosarcoma, GIST,
NET, and desmoid tumor. To our knowledge, no other case of this kind has been previously reported in the English literature.

Several hypotheses have been postulated to explain the development of synchronous and metachronous primary tumors in the same patient. Two studies were unable to establish an immunohistochemical or molecular profile difference between single GISTs and GISTs coexisting with other tumors. The secretion of growth factors from NETs could contribute to the development of concurrent primary tumors. Growth factors such as platelet-derived growth factor, transforming growth factor β, and basic fibroblast growth factor are secreted from NETs and are all tumorigenic. GISTs are characterized by the KIT mutation that may predispose them to the development of other tumors; moreover, impaired KIT expression has been noted in carcinomas of the breast and colon. In addition, a primary malignancy may create an immunosuppressed state, thus causing patients to be more susceptible to developing secondary tumors.

The presence of genetic mutations could also lead to the simultaneous occurrence of these tumors, similar to how cancer syndromes like Li–Fraumeni syndrome, von Hippel–Lindau syndrome, and multiple endocrine neoplasia syndromes result from genetic mutations. Exposure to carcinogenic agents might also lead to the development of these synchronous tumors or, possibly, the synchrony happened by pure coincidence.

**Conclusion**

Gastrointestinal stromal tumors (GISTs) tend to present with synchronous tumors. When a patient is diagnosed with a non-GIST malignancy, the health care professional must consider the possibility of a synchronous or metachronous GIST, among other types of tumors. More research is needed on the pathophysiology of these synchronous and metachronous tumors.

**References**


Association of Cancer Stem Cell Markers With Aggressive Tumor Features in Papillary Thyroid Carcinoma

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Background: Identifying accurate prognostic molecular markers for papillary thyroid carcinoma (PTC) is important because many patients with PTC may be erroneously considered to have low-risk tumors. Evidence is also accumulating to support the existence of cancer stem cells in PTC.

Methods: Thirty controls and 167 patients with PTC were selected to establish a tissue microarray to investigate cancer stem cell marker expression in samples from an established pathological database. The protein expressions of CD44, CD133, epithelial cell adhesion molecule (EpCAM), CD45, and CD90 were evaluated by immunobistochemical assay in the tissue microarray.

Results: The protein levels of CD44, CD133, and EpCAM were significantly increased in PTC tissue compared with tissue from the controls. A positive correlation was found between cancer stem cell markers and tumor, node, and metastasis staging.

Conclusions: Among a subset of patients with PTC, cancer stem cells detected by immunohistochemistry can be used as prognostic markers to screen for potential tumor dissemination. Whether these cancer stem cell markers are potentially therapeutic targets — and, thus, could be used for effective adjuvant treatment strategies — remains to be seen, and more data are needed.

Introduction

Papillary thyroid carcinoma (PTC) is the most common endocrine malignancy, and an estimated 62,450 new cases of thyroid cancer will be diagnosed in 2015 in the United States alone; of these diagnoses, 3 out of 4 cases will occur in women. In general, PTC has a favorable prognosis, the overall 10-year survival rate of patients with PTC is about 90%, however, approximately 10% and 20% of patients with stage 1 or 2 PTC, respectively, have disease recurrence. Tumor recurrence affects the quality of life of patients; among those who develop local recurrence, some will die from the disease, indicating the existence of more aggressive variants of PTC. Up to 30% of patients with differentiated thyroid carcinoma may have tumor recurrence within several decades; 66% of recurrences occur within the first decade following initial therapy. Therefore, identifying the subpopulation at high-risk for disease recurrence is necessary.

Based on clinical and pathological studies, various factors, such as age, sex, tumor size, extrathyroidal extension, and distant metastasis, have been investigated to determine whether an association exists between them and PTC recurrence; however, the matter is controversial. Molecular and cellular events have been shown to be associated with PTC, and the cancer progenitor/stem cell is considered by some as a common cellular alteration detected in patients with PTC. Cancer stem cells, a small subpopulation of cells with stem-like properties, are key factors for tumor initiation and recurrence. Evidence supporting the existence of cancer stem cells in PTC is rapidly accumulating.

Recent research indicates that increased cancer stem cell–like features play an important role in the progression of PTC. The cancer stem cell theory was established based on the observation that cancer cell populations are heterogeneous. The identification and characterization of cancer stem cells in tumors largely depend on the surface markers shared with normal stem cells. These populations have been identified and isolated using the surface markers CD44 and CD24 in a human PTC cell line, TPC-1 (BHP10-3). Research shows that POU5F1, a stem cell marker, is significantly higher in CD44+ (high levels of CD44) and CD24 Lin (low levels of CD24) cells, supporting the hypothesis that CD44+CD24-Lin− cells are potential cancer stem cells in PTC.
stem cells. Further study suggests that CD44+CD24−Lin− PTC cells can form thyrospheroids, which are important in vitro features of cancer stem cells; moreover, data indicate that thyrospheroids can initiate a tumor in immunodeficient mice. Several other potential stem cell markers have been used by others in thyroid cancer stem cell research, such as CD133 and epithelial cell adhesion molecule (EpCAM).

Although the prognostic influence of cancer stem cells in PTC is unclear, the use of cancer stem cell markers may help histopathologically determine the existence of cancer stem cells in PTC tissue, possibly impacting patient prognosis. Traditional immunohistological examination consists of single-sectioning paraffin blocks and is amenable to routine pathology; however, a wide variety of the staining condition by traditional assay may limit its utility for detecting cancer stem cell markers in resected PTC samples. Tissue microarray is a high-throughput technology used for analyzing molecular markers in oncology. It offers added benefit with respect to decreased technical variability during the staining and interpretation process.

In our study, we established a tissue microarray process to investigate the expressions of cancer stem cell markers in tissue samples from a pathological database of patients with PTC. The specimens used in the tissue microarray consisted of different pathological stages of PTC and were stained by immunohistochemical assay. The protein expressions of CD44, CD133, EpCAM, CD45, and CD90 were then evaluated for each pathological stage of PTC. Furthermore, we set forth to determine the correlation between cancer stem cell markers and the pathological stages of PTC.

Materials and Methods
Thyroid nodule tissue from 670 patients was collected from a pathological database maintained by the Third Affiliated Hospital of Wenzhou Medical University (Ruian, Zhejiang, China). All specimens with a diagnosis of PTC were collected following surgical excision.

In this retrospective study, we reviewed the database for patients undergoing thyroid nodule resection between August 2012 and September 2013. This study was approved by the Institutional Review Board at Wenzhou Medical University.

Patient Selection
Patients were excluded if they had radiotherapy, chemotherapy, or both, either preoperatively or postoperatively. Patients also met exclusion criteria if they had certain types of conditions, including autoimmune disease, cerebrovascular accident, coronary artery disease, viral hepatitis, or another type of cancer. Overall, 167 patients postoperatively diagnosed with PTC, along with 30 benign, non-PTC controls, met inclusion criteria based on the completeness of their data. Dates of diagnoses and collection times ranged from August 2012 to September 2013.

Patients were divided into 4 treatment groups according to tumor, node, and metastasis (TNM) staging per the classification of thyroid cancer by the American Joint Committee on Cancer. PTC stage 1 was defined as papillary carcinoma localized to the thyroid gland. PTC stage 2 was defined as either (a) papillary carcinoma that has spread distantly in patients younger than 45 years, or (b) papillary carcinoma larger than 2 cm but no larger than 4 cm, and was limited to the thyroid gland in patients older than 45 years. PTC stage 3 was defined as papillary carcinoma occurring in patients older than 45 years that was larger than 4 cm and was limited to the thyroid or with minimal extrathyroidal extension, or positive lymph nodes limited to the pretracheal, paratracheal, or prelaryngeal/Delphian nodes. PTC stage 4 was defined as papillary carcinoma in patients older than 45 years that extended beyond the thyroid capsule to the soft tissues of the neck, cervical lymph node metastases, or distant metastases.

Of the 167 patients, 139 (83.2%) were women and 28 (16.8%) were men. Of the non-PTC controls with resected thyroid nodules, 26 (86.6%) were women and 4 (13.3%) were men. The mean age of the 167 study patients was 50.21 ± 11.65 years compared with 48.9 ± 11.34 years for the controls. Of the patients with PTC, 11 had a family history of diabetes mellitus, 26 had a family history of hypertension, 24 had a history of Hashimoto thyroiditis (chronic lymphocytic thyroiditis), and 3 were former smokers; by contrast, no controls had family histories of diabetes mellitus, hypertension, and smoking, and 1 had a history of Hashimoto thyroiditis history. Medical records were also reviewed (Table 1).

Tissue Microarrays
The surgical resection of PTC samples provided ample tissue for paraffin-embedded tissue blocks, and tissue array was constructed from the paraffin blocks. Prior to constructing the tissue arrays, the blocks were categorized into 5 groups: non-PTC (“benign controls”) and stages 1 to 4. The categorization was made according to each study patient's clinical history and diagnosis.

To avoid sample-selection bias, 2 pathologists reviewed the hematoxylin and eosin–stained tissue sections to identify areas of PTC and select the regions in blocks as donor core tissues. The reviewers were blinded to the study patients' clinical history. Donor core tissues with a diameter of 1 mm were obtained from corresponding regions in the donor paraffin block and embedded into a recipient block. Cores from archived specimens of normal thyroid tissue adjacent to
Single-donor core tissue samples from each specimen consisting of non-PTC (“benign controls”) and stages 1 to 4 were sampled and designed as 4 rows × 6 columns per block. The donor cores from all study patients were embedded in a tissue microarray recipient block. Nine tissue microarray recipient blocks were prepared consisting of tissue cores obtained from PTC and non-PTC samples.

**Immunohistochemical Assay**

Immunohistochemical staining was obtained on the paraffin-embedded blocks of tissue arrays using the DAKO EnVision+ System Kit (DAKO, Carpinteria, California). In brief, the sections were deparaffinized and hydrated. The slides were washed with a Tris buffer, and peroxidase blocking was performed for 5 minutes. After rewashing, the monoclonal antibodies, CD44 and EpCAM, and polyclonal antibodies, CD45, CD90, and CD133, were applied for 60 minutes at room temperature. The slides were rinsed and incubated with labeled polymer for 30 minutes at room temperature. The substrate-chromogen solution (diaminobenzidine) was added as a visualization reagent. As a final step, the slides were counterstained with hematoxylin. A negative control, using the same experimental procedure as the tested slides, except for the primary antibody, was included in each run.

**Computer Image Analysis**

Computer image analysis was performed to quantify the expressions of the cancer stem cell markers in 167 study patients with PTC and 30 benign controls. Two pathologists performed a pathological reading to confirm the PTC diagnosis for each tissue microarray slide before the digital image was captured. The imaging fields were randomly chosen from each core tissue to ensure sampling objectivity. Five imaging fields were scanned for each specimen sample. All digital images were acquired with the Olympus Microscope IX51 (Olympus, Pittsburgh, Pennsylvania) at 200 magnification using the Spot camera via the Image-Pro Plus Imaging System (Media Cybernetics, Warrendale, Pennsylvania) and stored as jpg data files (resolution was fixed at 200 pixels per inch).

The acquired color images from immunohistochemical staining were defined as standard threshold according to software specifications. The software quantified the threshold area represented in these images. Either the PTC images or normal thyroid images were delineated from the obtained tissues as a region of interest (ROI) using the set color threshold subroutine of the image analysis software. Because of the existence of the duct structure of PTC — in particular, the benign thyroid tissue — the “no tissue” regions were excluded within the ROI to avoid faulty measurement.

The integrated optical density measured for positive staining was a representation of the mass and a measurement of the total amount of positive staining in the delineated regions. Values of integrated optical density were normalized by dividing by the area of the threshold ROI of the positive staining. Positive expression was represented as the digital values of the integrated optical density/area, allowing us to analyze the statistical significance among the study groups.

**Statistic Analysis**

Analysis of variance was performed using SPSS16.0 (IBM, New York, New York) to determine the statistical significance of the level of expression of the cancer stem cell markers, if any, between TNM staging and controls. Spearman rank correlation coefficient was performed to analyze the correlation between cancer stem cell markers and TNM staging. Values are reported as mean plus or minus standard deviation. Differences between groups were regarded as statistically significant when P values were less than .05.

**Results**

**Protein Expressions of CD44, CD133, EpCAM, CD45, and CD90**

The expression pattern of CD44 showed that the positive staining mainly presented on the cell

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**Table 1. — Demographics of Study Patient and Control Groups (N = 197)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Papillary Thyroid Carcinoma (n = 167)</th>
<th>Control (n = 30)</th>
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<tbody>
<tr>
<td>Men:women</td>
<td>28:139</td>
<td>4:26</td>
</tr>
<tr>
<td>Age, y</td>
<td>50.21 ± 11.65</td>
<td>48.9 ± 11.34</td>
</tr>
<tr>
<td>Family history of diabetes mellitus, number ratio</td>
<td>11 (167)</td>
<td>0 (30)</td>
</tr>
<tr>
<td>Family history of hypertension, number ratio</td>
<td>26 (167)</td>
<td>0 (30)</td>
</tr>
<tr>
<td>History of smoking, number ratio</td>
<td>3 (167)</td>
<td>0 (30)</td>
</tr>
<tr>
<td>History of Hashimoto thyroiditis, number ratio</td>
<td>24 (167)</td>
<td>1 (30)</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone, mU/L</td>
<td>2.02 ± 6.87</td>
<td>1.26 ± 0.85</td>
</tr>
<tr>
<td>Total thyroxine 3, nmol/L</td>
<td>1.16 ± 0.26</td>
<td>1.12 ± 0.28</td>
</tr>
<tr>
<td>Total thyroxine 4, nmol/L</td>
<td>78.86 ± 36.92</td>
<td>88.61 ± 21.83</td>
</tr>
<tr>
<td>Free thyroxine 3, pmol/L</td>
<td>3.09 ± 0.62</td>
<td>2.93 ± 0.45</td>
</tr>
<tr>
<td>Free thyroxine 4, pmol/L</td>
<td>8.66 ± 4.84</td>
<td>9.13 ± 3.05</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.65 ± 1.86</td>
<td>5.39 ± 0.63</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.95 ± 1.44</td>
<td>1.59 ± 0.71</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.09 ± 0.99</td>
<td>5.25 ± 0.97</td>
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ly increased in the PTC tissue samples with stage 1 (152.2 ± 52.72; P > .05) but significantly increased in the PTC tissue samples with stage 2 (201.18 ± 60.33; P < .01), stage 3 (242.49 ± 66.81; P < .01), and stage 4 (284.81 ± 87.63; P < .01; Fig 2).

EpCAM showed a similar expression pattern as CD133, in which the positive staining mainly presented in the cytosol of PTC cells. Strong staining of EpCAM was seen in all PTC malignant tissue samples but weak and negative staining was seen in the benign controls. The computer quantification of EpCAM expression in control specimens was 48.30 ± 27.07. Compared with the controls, EpCAM expression increased in the stage 1 (157.48 ± 56.48; P > .05) PTC tissue samples but significantly increased in the PTC tissue samples with stage 2 (191.33 ± 51.12; P < .01), stage 3 (201.83 ± 58.20; P < .01), and stage 4 (226.75 ± 81.44; P < .01; Fig 3). The expressions of CD45 and CD90 showed weak (CD45) and mild staining (CD90) in the PTC tissue samples from all stages as well as the tissue samples from the benign controls. Analysis of variance did not indicate a statistical significance among the TNM stages and controls (Table 2).

**Correlation of CD44, CD133, and EpCAM**

We further analyzed the correlation between the 3 cancer stem cell markers (CD44, CD133, and EpCAM) and TNM staging. Positive correlations were
Fig 2A–F. — Detection of CD133 expression by immunohistochemistry and computer image analysis of positive staining in the papillary thyroid carcinoma tissue of 4 TNM stages and benign controls. (A) Stage 1 tumor. (B) Stage 2 tumor. (C) Stage 3 tumor. (D) Stage 4 tumor. (E) Benign controls. (F). CD44 expression. 
*P < .05 vs benign controls. **P < .05 vs stage 1.
IOD = integrated optical density, TNM = tumor, lymph mode, metastasis.

Fig 3A–F. — Detection of EpCAM expressions by immunohistochemistry and computer image analysis of positive staining in the papillary thyroid carcinoma tissue of TNM stages as well as in the tissue of benign controls. (A) Stage 1 tumor. (B) Stage 2 tumor. (C) Stage 3 tumor. (D) Stage 4 tumor. (E) Benign controls. (F). CD44 expression. 
*P < .05 vs benign controls.
EpCAM = epithelial cell adhesion molecule, IOD = integrated optical density, TNM = tumor, lymph mode, metastasis.
progenitor cells, have been widely explored as reliable markers for isolating cancer stem cells in many tumor types. Interest in these cancer stem cell markers has increased with the observation that the overexpression of cancer stem cell surface markers in tumor cells is associated with therapeutic failure and tumor recurrence. In PTC, immunohistochemical staining of CD44 has been shown to have a strong membranous expression pattern, which is consistent with our results. In addition, other studies show that the protein levels of CD44 significantly increase in biopsy tissue samples of most patients with PTC. Accordingly, in our study, the overall expression of CD44 was increased among all patients with PTC.

Research has shown that a CD133-positive subpopulation, such as cancer-initiating cells, can reproduce an original tumor and serially transplant it for several generations in immunodeficient mice, whereas CD133-negative cells cannot form tumors. Despite CD133 being known as a cancer stem cell marker in many tumors and tissue, CD133 expression in PTC was detected at a lower level in PTC cell lines and in patients with PTC; however, it was detected at a higher level in patients with anaplastic thyroid carcinoma, which is a highly aggressive neoplasm.

With regard to subcellular compartmentalization, we found CD133 expression to be predominantly cytoplasmic, which is consistent with previous observations. In our observations, very weak CD133 expression was detected in normal human thyroid tissue, and a lower level of CD133 expression was detected in patients with stages 1 and 2 PTC. However, a high level of CD133 expression was detected in patients with stages 3 and 4 PTC. Cytomorphological features of stages 3 and 4 PTC showed poor polarity, which is consistent with its aggressive growing pattern, in which tumor growth was found beyond the thyroid capsule, including metastasis to the soft tissues of the neck, cervical lymph node metastases, and distant metastases.

Although lymphatic spread is the most common form of PTC progression, the existing residual micrometastatic tumor cells in fact contribute to the

Table 2. — Expressions of CD45 and CD90 in Study Patients With Papillary Thyroid Carcinoma

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients</th>
<th>Intensity of IOD (mean ± SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CD45</td>
<td>CD90</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 45</td>
<td>57</td>
<td>54.43 ± 60.28</td>
<td>1.63 ± 2.07</td>
</tr>
<tr>
<td>≥ 45</td>
<td>110</td>
<td>65.14 ± 79.93</td>
<td>1.74 ± 2.34</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28</td>
<td>60.47 ± 66.1</td>
<td>2.38 ± 2.75</td>
</tr>
<tr>
<td>Female</td>
<td>139</td>
<td>61.69 ± 75.48</td>
<td>1.57 ± 2.11</td>
</tr>
<tr>
<td>TNM stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>101</td>
<td>59.95 ± 71.31</td>
<td>1.76 ± 2.26</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td>81.30 ± 103.95</td>
<td>1.00 ± 1.24</td>
</tr>
<tr>
<td>3</td>
<td>48</td>
<td>60.23 ± 72.06</td>
<td>1.66 ± 2.22</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>45.75 ± 37.97</td>
<td>3.36 ± 4.36</td>
</tr>
<tr>
<td>Controls</td>
<td>30</td>
<td>8.14 ± 7.7</td>
<td>1.41 ± 1.73</td>
</tr>
</tbody>
</table>

IOD = integrated optical density, SD = standard deviation, TNM = tumor, lymph node, metastasis.

found between CD44 and TNM staging ($r^2 = 0.5138; P < .01; \text{Fig } 4\text{A}$), between CD133 and TNM staging ($r^2 = 0.6107; P < .01; \text{Fig } 4\text{B}$), and between EpCAM and TNM staging ($r^2 = 0.27; P < .01; \text{Fig } 4\text{C}$).

Discussion

The results from this study demonstrate significant increases of expressions of CD44, CD133, and EpCAM in PTC tissue samples compared with the tissue samples from the benign controls. The increased amounts of these cancer stem cell surface markers were moderate in stage 1 but were the most pronounced in stages 2 to 4 of PTC. To our knowledge, this is the first study to examine the relationship between cancer stem cell surface markers and TNM staging of PTC.

To date, CD44, CD133, and EpCAM, which were initially described as surface markers for malignant

![Fig 4A–C. — Positive correlation of (A) CD44, (B) CD133, and (C) EpCAM expression in TNM staging. EpCAM = epithelial cell adhesion molecule, TNM = tumor, lymph node, metastasis.](image-url)
relapse.\textsuperscript{29} Residual, micrometastatic tumor cells are undetectable by conventional histopathological examination. Previously, immunohistochemistry using the monoclonal anti-EpCAM antibody (Ber EP4) for visualizing disseminated tumor cells in “tumor free” lymph nodes was performed by others.\textsuperscript{18} In that study, positive EpCAM tumor cells were revealed among “tumor-free” lymph nodes in 12.5% of cases.\textsuperscript{18} EpCAM is a 40kDa transmembrane glycoprotein frequently overexpressed in cancer progenitor cells, which are cancer-initiating cells in many human malignancies, including PTC and — although at very lower levels — in normal epithelia.\textsuperscript{18,30,31} Thus, the finding of positive EpCAM expression in tumor cells among “tumor free” lymph nodes may be clinically significant in relation to increased risk of local recurrence and distant metastases. However, a follow-up analysis (mean observation, 72 months) indicated no prognostic significance in cases with positive EpCAM expression because these patients underwent treatment of radioiodine, which can eliminate microdisseminated tumor residue.\textsuperscript{18} Nevertheless, detection of EpCAM is clinical significant. The concept is supported by 2 studies that identified the nucleus localization of EpCAM as an aggressive marker for poor prognosis among patients with thyroid cancer.\textsuperscript{17,32} In our study, the pattern of EpCAM expression showed weak staining in normal human thyroid tissue and strong staining in PTC tissue, with the staining increasing from stage 1 to stage 4. We also found that increased levels of cancer stem cell markers (CD44, CD133, and EpCAM) were positively related to the TNM staging of PTC. However, future studies are needed to define the specificity of cancer stem cell markers in PTC.

Conclusions
Identification of accurate prognostic molecular markers for papillary thyroid carcinoma (PTC) is important because most patients with PTC may be erroneously diagnosed as having low-risk tumors. Our findings suggest that, compared with traditional histopathological examination, tissue-array based immunohistochemistry for cancer stem cell marker detection can more accurately evaluate the biological characteristics of PTC. Thus, locating cancer stem cells in a subset of patients with PTC may be molecular markers that can be used as prognostic markers and to screen for tumor dissemination. However, whether these cancer stem cells markers are potential therapeutic targets for effective adjuvant treatment strategies requires additional evaluation.

References
Should Vital Signs Be Routinely Obtained Prior to Intravenous Chemotherapy? Results From a 2-Center Study

Smitha Menon, MD, Nathan R. Foster, MS, Sherry Looker, RN, Kristine Sorgatz, RN, Pashtoon Murtaza Kasi, MBBS, Robert R. McWilliams, MD, and Aminah Jatoi, MD

Background: The American Society of Clinical Oncology and the Oncology Nursing Society have issued guidelines stating that the vital signs of patients should be routinely checked on days that intravenous chemotherapy is administered. This study sought evidence to justify this approach.

Methods: This trial focused on consecutive patients with cancer from 2 institutions and evaluated outcomes during the first cycle of gemcitabine-based chemotherapy. The primary end point of the study was a visit to the ED, hospitalization, or death during the first cycle of chemotherapy.

Results: Medical records from 1,158 patients were reviewed, and vital signs were checked in 589 patients on day 1 and in 486 on day 8. A total of 148 patients (12.8%) were evaluated in the emergency department (ED), 145 (12.5%) were hospitalized, and 11 (0.9%) died during their first cycle of chemotherapy. In multivariate analyses, which were adjusted for age, sex, cancer type, role of chemotherapy, number of chemotherapy drugs administered on day 1, and institution, checking vital signs on day 1 was associated with neither higher rates of ED visits nor with increased hospitalization; however, checking vital signs on day 8 was associated with higher rates of ED visits (odds ratio [OR]: 3.71; 95% confidence interval [CI]: 2.18–6.22; \(P < .0001\)) and higher rates of hospitalizations (OR: 3.98; 95% CI: 2.34–6.73; \(P < .0001\)).

Conclusion: This study suggests a need for additional, evidence-based data to support the routine checking of vital signs prior to administering cancer chemotherapy.

Introduction

The American Society of Clinical Oncology and the Oncology Nursing Society have issued joint guidelines stating that the vital signs (blood pressure, pulse, respiratory rate, and temperature) of patients with cancer should be routinely and consistently checked on the day that intravenous chemotherapy is administered.1 Yet, to our knowledge, data to justify — or refute — this recommendation are lacking.

At least 2 factors point to the need to investigate the value of checking vital signs prior to the administration of intravenous chemotherapy in patients with cancer. In the nononcological setting, this issue is an important focus of ongoing research. Storm-Versloot et al2 performed a meta-analysis of the routine monitoring of vital signs in hospitalized patients and observed that, among 15 studies (N = 42,565 patients), conclusions were highly mixed. The investigators noted that studies appeared flawed and suggested a need for rigorous research “specifically intended to investigate the clinical relevance of routinely measured vital signs.”2 In addition, health care professionals are beginning to question the role of routinely checking vital signs of patients in nononcology settings, a finding that suggests similar questioning should occur in oncology settings.3-5 In view of a paucity of data on this topic in the oncology setting, the need to establish a role for the routine checking of vital signs prior to the administration of chemotherapy is important.

Second, checking vital signs prior to the administration of chemotherapy has enormous, onerous implications. If one assumes that checking vital signs takes about 5 minutes and if one works in a chemotherapy unit that treats approximately 150 patients per day, as is currently the case at the Mayo Clinic (Rochester, Minnesota), checking vital signs requires at least 1 full-time staff member whose only task is to check patient vital signs. Thus, acquiring evidence to support or refute the importance of this practice offers more than academic interest and is in keeping with Elshaug et al,6 who describe that a “groundswell of activity is seeking to identify and reduce the use of health care service that provide little or no benefit — whether through overuse or misuse.”

Thus, the primary goal of this 2-institution study was to generate and analyze data to better understand whether the routine checking of vital signs prior to the administration of intravenous chemotherapy is...
associated with fewer complications — specifically, with lower rates of emergency department (ED) visits and hospitalizations.

Methods
Overview
This study was undertaken at the Medical College of Wisconsin (Milwaukee, Wisconsin) and the Mayo Clinic. The Institutional Review Board of each institution reviewed and approved the study protocol prior to data acquisition and analyses. These institutions were chosen because, historically, one routinely checked vital signs prior to the administration of chemotherapy (the former) and the other did not.

An ED visit, hospitalization, or death during the first cycle of chemotherapy was considered a complication, which was the primary end point of the study.

Routine Nursing Assessment
Both institutions incorporated routine clinical assessment prior to the administration of chemotherapy on days when a prescribing health care professional had not seen the patient. This prechemotherapy nursing assessment consisted of asking patients about their general well-being and about specific signs and symptoms such as fever, fatigue, nausea, and vomiting. Concerns raised during the nursing assessment could conceivably trigger a vital-sign check based on clinical judgment and the temporal incidence and severity of the signs or symptoms.

Rationale for Focusing on Patients Treated With Gemcitabine
This study focused on patients with cancer about to receive their first cycle of gemcitabine-based chemotherapy. Pharmacy records were used to identify patients. The rationale for focusing on gemcitabine-treated patients is as follows: (1) gemcitabine is typically administered on day 8 in the chemotherapy cycle, and this day often does not entail a visit with a prescribing health care professional who likely would have checked vital signs as part of a routine physical examination, (2) this chemotherapy agent is used to treat a variety of cancers, leading to greater generalizability of findings, and (3) the adverse events of this agent are characteristic of those observed with classical, conventional chemotherapy (nausea, vomiting, myelosuppression, diarrhea), a profile that leads to greater generalizability of findings. We decided to focus on the first cycle of gemcitabine-based chemotherapy alone because the risk of adverse events generally increases with subsequent cycles, and this restriction would potentially enhance the homogeneity of the study population.

Data Abstraction
Consecutive medical records of patients with cancer treated with gemcitabine were reviewed, starting with the most recent and proceeding back in time. The following information was abstracted: patient date of birth, sex, date of administration of the first cycle of gemcitabine-based chemotherapy, cancer type, whether chemotherapy was given for metastatic disease or as adjuvant treatment, number of drugs administered within the regimen, institution of chemotherapy administration, whether vital signs were checked on days 1 and 8 of the chemotherapy cycle (these data were gathered irrespective of which health care professional performed the check), ED visit or hospitalization during the first chemotherapy cycle, and death during the first chemotherapy cycle.

Sample Size and Analyses
In calculating sample size, the study team estimated that approximately one-third of study patients would have had their vital signs routinely checked based on the anticipated patient representation from the Medical College of Wisconsin. Based on prior reported rates of adverse events in clinical trials, 5% of patients who had their vital signs checked were estimated to have a major complication during their first dose of gemcitabine-based chemotherapy. We estimated that this rate would increase to 10% in the absence of checking vital signs; this 5% effect size was derived from other clinical settings in which this increased complication rate approximates the upper limit of acceptability.7-9 We estimated that a target sample size of 1,015 study patients would enable us to detect the above with 80% power, assuming a 2-sided significance level of .05.

Analyses consisted of direct comparisons of complication rates between study patients who did and did not have their vital signs checked at specific time points. If chemotherapy was not administered on a particular day, then the complication data from that study patient were still included in the analyses relevant to that day. For univariate and multivariate analyses, logistical regression models were constructed to determine which variables were associated with ED visits and hospitalizations (in the event of a very low complication rate [eg, low death rate], this analysis was not performed). A 2-sided P value of less than .05 was considered statistically significant. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina) and JMP software (SAS Institute).

Results
Patient Demographics
We reviewed the medical records of 1,158 study patients. Vital signs were checked for 589 study patients on day 1 and for 486 study patients on day 8. Based on whether vital signs had been checked, patient characteristics were similar, although cancer type, number of drugs administered, and whether patients received
adjuvant treatment or treatment for metastatic cancer differed between groups, at times, based on vital-sign assessment and institution (Table 1).

Complications and Vital-Sign Checks
A total of 148 study patients (12.8%) were evaluated in the ED, 145 (12.5%) were hospitalized, and 11 (0.9%) died during their first cycle of chemotherapy. Subgroup analyses found no statistically significant differences in these complication rates based on institution, except for a trend toward a greater number of ED visits in patients from the Medical College of Wisconsin: 60 visits (15%) compared with 88 visits (12%; \(P = .08\)).

Checking vital signs on day 1 was associated with a trend toward more ED visits (85 visits [15%]) compared with patients whose vitals signs were not checked (63 [11%]; \(P = .09\)). By contrast, hospitalizations and deaths were not statistically different based on day 1 vital sign checks. Checking vital signs on day 1 was associated with a trend toward more ED visits (85 visits [15%]) compared with patients whose vitals signs were not checked (63 [11%]; \(P = .09\)). By contrast, hospitalizations and deaths were not statistically different based on day 1 vital sign checks.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Institution</th>
<th>(P) value</th>
<th>Day 1 Vital Signs Checked?</th>
<th>Day 8 Vital Signs Checked?</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wisconsin a</td>
<td>Mayo</td>
<td>Yes ((N = 5690))</td>
<td>No ((N = 589))</td>
</tr>
<tr>
<td>Median age, y (range)</td>
<td>62 (42–91)</td>
<td>63 (22–95)</td>
<td>62 (22–95)</td>
<td>63 (22–95)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>204 (52)</td>
<td>369 (48)</td>
<td>283 (50)</td>
<td>290 (49)</td>
</tr>
<tr>
<td>Female</td>
<td>192 (49)</td>
<td>393 (52)</td>
<td>286 (50)</td>
<td>299 (51)</td>
</tr>
<tr>
<td>Cancer type, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>73 (19)</td>
<td>89 (12)</td>
<td>61 (11)</td>
<td>101 (17)</td>
</tr>
<tr>
<td>Lung</td>
<td>59 (15)</td>
<td>141 (19)</td>
<td>102 (18)</td>
<td>98 (17)</td>
</tr>
<tr>
<td>Breast</td>
<td>17 (4)</td>
<td>47 (6)</td>
<td>31 (5)</td>
<td>33 (6)</td>
</tr>
<tr>
<td>Gynecological</td>
<td>38 (10)</td>
<td>115 (15)</td>
<td>76 (13)</td>
<td>77 (13)</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>99 (25)</td>
<td>166 (22)</td>
<td>146 (26)</td>
<td>119 (20)</td>
</tr>
<tr>
<td>Other</td>
<td>109 (28)</td>
<td>204 (27)</td>
<td>153 (27)</td>
<td>160 (27)</td>
</tr>
<tr>
<td>Chemotherapy, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjuvant</td>
<td>38 (10)</td>
<td>72 (9)</td>
<td>56 (10)</td>
<td>54 (9)</td>
</tr>
<tr>
<td>Metastatic</td>
<td>316 (80)</td>
<td>658 (86)</td>
<td>486 (85)</td>
<td>488 (83)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>39 (10)</td>
<td>32 (4)</td>
<td>27 (5)</td>
<td>44 (8)</td>
</tr>
<tr>
<td>Drugs given on day 1, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>76 (19)</td>
<td>196 (26)</td>
<td>143 (25)</td>
<td>129 (22)</td>
</tr>
<tr>
<td>2</td>
<td>320 (81)</td>
<td>499 (66)</td>
<td>384 (68)</td>
<td>435 (74)</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>65 (9)</td>
<td>41 (7)</td>
<td>24 (4)</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>2 (0)</td>
<td>1 (0)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Drugs given on day 8, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>74 (19)</td>
<td>150 (20)</td>
<td>111 (20)</td>
<td>113 (19)</td>
</tr>
<tr>
<td>2</td>
<td>160 (40)</td>
<td>380 (50)</td>
<td>288 (51)</td>
<td>252 (43)</td>
</tr>
<tr>
<td>3</td>
<td>162 (41)</td>
<td>220 (29)</td>
<td>165 (29)</td>
<td>217 (37)</td>
</tr>
</tbody>
</table>

*Parentheses do not always sum to 100% because of rounding or missing data.
day 8 was associated with more patients visiting an ED (85 [18%] compared with 62 [9%]; \( P < .0001 \)) and more patients being hospitalized (81 [17%] compared with 63 [9%]; \( P = .0002 \)).

Multivariate logistic regression analyses are shown in Table 2 and show that checking vital signs on day 1 was neither associated with a higher rate of ED visits nor an increased rate of hospitalization. However, checking vital signs was associated with a higher rate of ED visits and higher hospitalization rates when checked on day 8.

### Discussion

This study was undertaken to assess whether or not checking vital signs on the day of chemotherapy administration is associated with higher complication rates (eg, ED visits, hospitalizations). Our study findings indicate this was not the case. Rather, the opposite was found: Checking vital signs on the day of chemotherapy administration appears to be associated with higher rates of ED visits and hospitalizations. However, these findings do not indicate that checking vital signs leads to higher rates of complications; rather, patients who appeared ill presumably had their vital signs checked only because they appeared ill; these patients were subsequently referred to the ED or were hospitalized. Thus, the findings of this study suggest that not checking vital signs routinely prior to the administration of intravenous chemotherapy does not have adverse consequences.

The role of routinely checking vital signs is also being questioned in other areas of clinical medicine. Historically, checking vital signs was an essential, mandatory component of patient care. However, more recent studies — some of which include the routine monitoring of vital signs in hospitalized patients — have questioned the value of this practice and suggest that patients present with other symptoms or signs well before they manifest a concerning change in their vital signs.2,3 In hospital settings, the concern for compromising patient sleep, as well as escalating health care costs, has also led to the omission or curtailing of routine vital sign checks.4,5 Although the role of routinely checking vital signs continues to remain controversial, emerging trends show that this practice has been discontinued in some circumstances.10,11

A critical distinction should be made between routinely checking vital signs and checking vital signs when patients appear ill or when patients are receiving antineoplastic agents that put them at risk for hypertension. Patients who fall within these latter 2 categories should continue to have vital signs checked. We acknowledge that patients with cancer who are ill or asymptomatic but who are receiving a medication such as bevacizumab should have at least a partial set of vital signs obtained.

### Limitations

The retrospective nature of this study makes it impossible to determine why the checking of vital signs occurred or did not outside the routine practice of each specific institution. On day 1, or close to day 1, patients are likely to see their health care professional, who has performed an in-depth assessment of their status. Therefore, one might suggest that nurses can forgo checking vital signs if a physician had seen the patient at some very recent time point. Furthermore, patients with abnormal vital signs during their visit with their oncologist might have been deflected from receiving chemotherapy, resulting in a bias toward seeing normal vital signs on day 1 prior to administering chemotherapy. Of note, the foregoing is speculative, thus emphasizing the limitations of the design used in this study.

This study might have been underpowered with respect to determining whether early interventions, such as hospitalization, based on abnormal vital signs would have prevented more serious complications. We were unable to derive such information from a retrospective study.

In addition, the data from the current study are not derived from a randomized trial. As a result, comparative participant groups might be imbalanced with respect to institutional practices that could have influenced complication rates or patient predisposition for chemotherapy toxicity. If a prospective trial were to be performed, then the focus of that study should be on asymptomatic patients alone, with the exclusion of those receiving chemotherapy agents that might increase blood pressure. It would also be important to balance study arms based on the extent of prior cancer therapy and other factors that tend to lead to greater chemotherapy toxicity. One might argue that the great challenges of performing such a trial add to the importance of the data presented in this paper.

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**Table 2. — Multivariate Logistic Regression Model**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Checking Vital Signs</th>
<th>OR (95% CI)a</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED visits</td>
<td>Day 1 (yes vs no)</td>
<td>1.2 (0.72–1.97)</td>
<td>.48</td>
</tr>
<tr>
<td></td>
<td>Day 8 (yes vs no)</td>
<td>3.71 (2.18–6.22)</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>Day 1 (yes vs no)</td>
<td>1.32 (0.80–2.14)</td>
<td>.27</td>
</tr>
<tr>
<td></td>
<td>Day 8 (yes vs no)</td>
<td>3.98 (2.34–6.73)</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

\( ^a \)Analyses were adjusted for adjusted for age, sex, cancer type, chemotherapy type (adjuvant vs for metastatic disease), and number of drugs prescribed on day 1 or 8 (day 1 for the day 1 vital signs predictor and day 8 for the day 8 vital signs predictor), and institution. CI = confidence interval, ED = emergency department, OR = odds ratio.
Conclusion

Our findings question whether the absence of evidence to support the checking of vital signs should lead to the conclusion that vital signs should be obtained. At the very least, these study results call for further evidence-based data to assess this routine, expense-generating clinical practice.

References

Background: Few national registries exist in the Caribbean, resulting in limited cancer statistics being available for the region. Therefore, estimates are frequently based on the extrapolation of mortality data submitted to the World Health Organization. Thus, regional cancer surveillance and research need promoting, and their synergy must be strengthened. However, differences between countries outweigh similarities, hampering registration and availability of data.

Methods: The African-Caribbean Cancer Consortium (AC3) is a broad-based resource for education, training, and research on all aspects of cancer in populations of African descent. The AC3 focuses on capacity building in cancer registration in the Caribbean through special topics, training sessions, and biannual meetings. We review the results from selected AC3 workshops, including an inventory of established cancer registries in the Caribbean region, current cancer surveillance statistics, and a review of data quality. We then describe the potential for cancer research surveillance activities and the role of policymakers.

Results: Twelve of 30 Caribbean nations have cancer registries. Four of these nations provide high-quality incidence data, thus covering 14.4% of the population; therefore, regional estimates are challenging. Existing research and registry collaborations must pave the way and are facilitated by organizations like the AC3.

Conclusions: Improved coverage for cancer registrations could help advance health policy through targeted research. Capacity building, resource optimization, collaboration, and communication between cancer surveillance and research teams are key to obtaining robust and complete data in the Caribbean.

Introduction
Cancer is increasing in frequency and is a leading cause of death worldwide. As such, it is a principal priority for health authorities of many countries. An estimated 14 million new cancer cases occurred in the world in 2012. Lung, female breast, colorectal, pros-
tate, and stomach cancers accounted for nearly 50% of all cases diagnosed and of cancer-related deaths worldwide. The Caribbean, whose location is detailed in Fig 1, is no exception, with malignant neoplasms being the leading cause of mortality for those living in the Caribbean.

Although Caribbean nations share the same urgency in the fight against cancer in terms of surveillance and research, important limitations exist in addressing this issue. For example, although different countries share many similarities in terms of environmental, ethnic predominance (most English-speaking Caribbean countries comprise majority African-origin populations), and other common risk factors, geographical, demographic, and ethnic differences are also present. Not all Caribbean countries are islands, and their populations vary in size: from more than 11 million in Cuba to about 5,000 for Montserrat. Some countries have majority populations of East Indian ethnic origin, and many have an increasing proportion of their population of mixed ethnic background.

Economic differences also exist, with some Caribbean countries classified as high- (eg, Barbados, Bahamas), upper-middle (eg, Jamaica, Suriname), lower-middle (eg, Guyana), or low-income economies (eg, Haiti). Although ethnic and environmental factors influence trends in rates of cancer incidence and mortality, such factors are generally correlated with economic development. Variation in economic development throughout the Caribbean also means a range of access to and quality of health care across different countries; in some communities, insufficient or inadequate health insurance, or geographical remoteness, or estrangement from adequate specialized health infrastructure has resulted in a higher frequency of cancers with poor prognoses (due to diagnosis and treatment at advanced stages) and more deaths.

It is necessary to monitor epidemiological trends in cancer (eg, through surveillance), particularly in low-resource countries undergoing demographic transition with increasingly aging populations like those in the Caribbean. This is even more important because high-quality data on cancer are lacking from low- and medium-resource countries, and, con-
considering the differences between countries across the Caribbean, generalizations have been difficult. In addition, research is vital for understanding the specific determinants of most cancers, especially those affecting high-risk populations such as African Caribbean or indigenous populations, such as Amerindians, and to provide better guidance and evaluation of cancer control policies to develop targeted and efficient programs for cancer prevention and care. Although the distinction between surveillance and research is important, the synergy between them is often overlooked. Surveillance is necessary for continued disease monitoring, and its data analysis may hint at previously unknown insights. By contrast, the value of research lies in the ability of researchers to examine what can only be alluded to, but not proved, using surveillance data. Therefore, surveillance is often termed hypothesis generating and research hypothesis testing. Collaboration between researchers using these different methods for generating information on a subject can be powerful, although often they run along parallel paths.

However, considering the intra-Caribbean variation, countries in the region cannot be “equal in arms” against the cancer epidemic. Not all Caribbean countries possess sufficient essential health surveillance infrastructure to provide efficient cancer registration and quality cancer data. Where established and efficient cancer surveillance is present, little optimization of cancer registration exists to help make progress through cancer research. In addition, knowledge, resources, and collaboration may be too limited to utilize and address research needs overall, including via cancer registries.

Several prior regional scientific workshops and conferences have identified the few existing cancer surveillance systems of the Caribbean and have highlighted the ongoing scientific collaborations implicating cancer registries. These workshops advocate for more dynamic and productive communication between relevant partners while also emphasizing the growing importance of, and need for, cancer registration to address the increasing cancer burden through targeted research.

Herein we describe the latest 2013 and 2014 workshops coordinated by the African-Caribbean Cancer Consortium (AC3), which facilitates and promotes the collaboration between cancer research and surveillance. We also join the AC3 and other concerned cancer surveillance and research stakeholders in the Caribbean in calling for the reinforcement of cancer registration in the Caribbean to expand population-based coverage by cancer registries and obtain more complete and reliable data for their strategic use in guiding requisite cancer control interventions and collaborative research.

**Caribbean Nations**

The Caribbean region refers to the 15 Caribbean nations members and 5 associate members of the Caribbean Community (CARICOM), in addition to 10 other Caribbean nations (French Martinique, Guadeloupe, and French Guiana, as well as other Caribbean islands of the Greater and Lesser Antilles; see Fig 1). The 30 Caribbean nations referred to in this paper include Anguilla, Antigua and Barbuda, the Bahamas, Barbados, Belize, Bermuda, the British Virgin Islands, the Cayman Islands, Cuba, Dominica, the Dominican Republic, French Guiana, Grenada, Guadeloupe, Guyana, Haiti, Jamaica, Martinique, Montserrat, The Netherlands Antilles (Aruba, Bonaire, Curacao, Saba, St Eustatius, and the Dutch half of St Martin and St Maarten), Puerto Rico, St Barthélemy, St Kitts and Nevis, St Lucia, St Martin (the French half of St Martin and St Maarten), St Vincent and the Grenadines, Suriname, Trinidad and Tobago, the Turks and Caicos, and the US Virgin Islands. Although they predominantly comprise islands in the Caribbean Sea for which the official language is English, notable exceptions exist. French Guiana, Suriname and Guyana are on mainland South America while Belize is on mainland Central America; French Guiana, Haiti, Martinique, Guadeloupe, Saint Barthélemy and Saint Martin are French-speaking, while the official language of Suriname, Aruba, Bonaire, Curacao and Sint Maarten is Dutch, and that of Cuba, the Dominican Republic, and Puerto Rico is Spanish.

**African-Caribbean Cancer Consortium**

The mission of the AC3 is to study viral, genetic, environmental, and lifestyle factors for cancer risk and outcomes in populations of African descent. The consortium is part of the Epidemiology and Genomics Research Program consortia of the National Cancer Institute (NCI), which is composed of 3 connected networks of investigators in the United States, Africa, and the Caribbean region. The AC3 has 120 members and is a broad-based resource for education, training, and research on the etiology, screening, prevention, treatment, and survivorship related to cancer in populations of African descent. Within the AC3, 7 Caribbean cancer registries are represented (5 are national: Barbados, Guyana, Guadeloupe, Martinique, and Trinidad and Tobago; 2 are subnational: Cayman Islands and Jamaica). The AC3 focuses on capacity-building efforts in the field of cancer registration in the Caribbean by hosting a series of special topics and training sessions during biannual scientific meetings and other supporting...
Five scientific meetings have been conducted to date since 2007. During the 2007 and 2008 AC3 meetings, presentations by cancer registrars provided an overview of the cancer burden in the Caribbean region. During the 2010 meeting, rationale for cancer registration, the different types of cancer registries, and the relevant steps for planning and implementation of a cancer registry were discussed. The 2012 meeting provided another opportunity for presentations of national cancer registry data from 4 cancer registries in lower-middle-income countries (Kenya, Guyana, Jamaica, and Trinidad and Tobago). Cancer statistics were presented that revealed the reality of cancer burden in these Caribbean countries.

Cancer registration activities concluded with a satellite meeting with the NCI.

To continue what the AC3 has accomplished, the information learned thus far, and to address current needs, an AC3 cancer registry workshop was organized in 2013 as a preconference to the annual meeting of the Caribbean Public Health Agency (CARPHA). The primary purpose of the 1-day meeting was to amplify, promote, and sustain Caribbean scientific research through collaborations with cancer registries. The objectives of the workshop were to describe the applications and utilization of cancer registry data in collaborative research and to discuss the importance of policy decision-making and its impact on existing or developing national cancer registries and cancer control. The workshop united existing and aspiring cancer registrars, pathologists, clinical and biomedical scientists, representatives of public health organizations, and cancer advocates. It also presented opportunities for dialogue and collaboration between English- and French-speaking Caribbean nations.

This initiative was further reinforced by the 2014 Cancer Surveillance in the Caribbean meeting, a joint effort of several stakeholders that included the NCI, the CARPHA, the US Centers for Disease Control and Prevention, the International Agency for Research on Cancer (IARC), the Pan American Health Organization (PAHO), the US Northern Command, and the AC3. As of this publication, the AC3 2014 scientific meeting was the most recent gathering to discuss strategies in the way forward toward better cancer registration and collaborative research for the Caribbean region.

### Established Cancer Registries

Of the 30 nations and territories in the Caribbean region, 12 have established cancer registries, 6 of which have existed for more than 30 years (Puerto Rico, Jamaica–Kingston, Cuba, The Netherlands Antilles, Bermuda, and Martinique) and 1 for 20 years (Trinidad and Tobago), whereas all others have been in operation for 5 to 15 years (Table 1). Of these, 4 cancer registries (Cuba, Jamaica–Kingston, Martinique, and Puerto Rico), representing 14.4% of the regional population, have contributed high-quality incidence data published by the World Health Organization (WHO).

Based on discussions from the workshop, emerging cancer registries in other countries (eg, Anguilla, St Kitts and Nevis, St Lucia, the Bahamas and the Cayman Islands) may be hampered by challenges, including limited training opportunities, limited staff availability and qualifications, inadequate information technology support, and transportation difficulties for data retrieval. Other challenges include lack of diagnostic facilities, lack of pathologists, and long reporting delays compounded by poor verification of data, lack of formal death certification, and lack of support from ministries of health. The latter is critical to ensure sustainability of cancer registries and their role in developing and evaluating cancer control strategies.

### Table 1. — Inventory of Established Cancer Registries in the Caribbean

<table>
<thead>
<tr>
<th>Country</th>
<th>Type of Registry</th>
<th>Year of Establishment</th>
<th>Estimated Midyear Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puerto Rico</td>
<td>National</td>
<td>2000</td>
<td>3,688,000</td>
</tr>
<tr>
<td>Jamaica</td>
<td>Urban</td>
<td>2000</td>
<td>1,453,248</td>
</tr>
<tr>
<td>Cuba</td>
<td>National</td>
<td>1964</td>
<td>11,266,000</td>
</tr>
<tr>
<td>Netherlands Antilles</td>
<td>National</td>
<td>1977</td>
<td>199,929</td>
</tr>
<tr>
<td>Bermuda</td>
<td>National</td>
<td>1979</td>
<td>69,000</td>
</tr>
<tr>
<td>Martinique</td>
<td>National</td>
<td>1983</td>
<td>404,000</td>
</tr>
<tr>
<td>Trinidad and Tobago</td>
<td>National</td>
<td>1994</td>
<td>1,341,000</td>
</tr>
<tr>
<td>Guyana</td>
<td>National</td>
<td>2000</td>
<td>800,000</td>
</tr>
<tr>
<td>French Guiana</td>
<td>National</td>
<td>2005</td>
<td>249,000</td>
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<tr>
<td>Guadeloupe</td>
<td>National</td>
<td>2008</td>
<td>466,000</td>
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<td>Barbados</td>
<td>National</td>
<td>2010</td>
<td>289,000</td>
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<tr>
<td>Cayman Islands</td>
<td>National</td>
<td>2010</td>
<td>54,000</td>
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</table>

The Caribbean region ranks fifth worldwide for cancer incidence and fourth for mortality (185.4 and 102.0 per 100,000 per year, respectively; Fig 2). However, disparities exist in the quality of available cancer data, because 4 Caribbean nations have high-quality national or regional cancer incidence data, whereas 2 nations have complete, high-quality cancer mortality data (Table 2). Furthermore, for countries without existing surveillance initiatives,

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\[\text{Table 1. — Inventory of Established Cancer Registries in the Caribbean}\]

<table>
<thead>
<tr>
<th>Country</th>
<th>Type of Registry</th>
<th>Year of Establishment</th>
<th>Estimated Midyear Population</th>
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<tr>
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<td>National</td>
<td>2000</td>
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<td>1979</td>
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<td>1,341,000</td>
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<td>National</td>
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<td>2005</td>
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<td>National</td>
<td>2010</td>
<td>54,000</td>
</tr>
</tbody>
</table>

*This registration occurs in urban areas alone (Kingston and St Andrew).*

*Includes 6 Dutch-Caribbean islands: Curacao, Aruba, Bonaire, Saba, St Eustatius, and St Maarten.*

*Underwent restructuring in 2004 and relaunched in 2008.*
cancer registries or those with newly established registries, cancer statistics are typically derived from estimates of the WHO compiled from a combination of nationally reported mortality data and hospital-based data. Therefore, it is possible that under-reporting is occurring for some Caribbean nations, thus underlying the need for indigenous cancer registry data to accurately reflect the burden of cancer in the region.

Available Research Data
Deeper insight into cancer registration in the Caribbean and its potential perspectives was achieved through a description of available data provided by countries to CARPHA. Highlights from these data included the high prevalence of smoking in some countries (although the general belief is that smoking has a very low prevalence throughout the Caribbean) and a high prevalence of alcohol intake. Taken altogether, the data suggest an increased risk for the development of noncommunicable diseases, including cancer, with these conditions representing the top 10 causes of death during the last decade in the Caribbean. Although some research on environmental carcinogens has been documented, such as the prostate case-control study in Guadeloupe, the region still lacks research in this domain. Other gaps in the data include cancer morbidity and survival rates, clinical management, and population screening rates for specific cancers (cervical, breast, and colon).

Usefulness of Cancer Surveillance Data in Research Collaborations
The usefulness of cancer registries in collaborating with research for population-based case-control stud-
ies was also described (Fig 3). For example, data from registries allow researchers to plan or estimate the number of expected cases, identify the main hospitals where cases may be found, or identify patients for recruitment into research studies. During the study, data can be cross-checked with the registry to ensure coverage. Registry data are also useful for checking on selection bias in research studies. If the registry also conducts follow-up for cases, then it can provide the study with additional data on outcomes. Examples of such collaborative work were illustrated by an ongoing study investigating socioeconomic inequalities in cancer incidence and mortality in Martinique and Guadeloupe as well as AC3 collaborations involving the cancer registries in Trinidad and Tobago and Guyana. Analyses of data, issuing from these AC3 collaborations, have been conducted or are near completion for prostate, breast, and head and neck cancers. Such findings have helped shed insight into the burden of cancer and differences in outcomes in comparison with US or global cancer statistics. Furthermore, the important role played by cancer registries, in terms of research or public health intervention, was illustrated by the French Caribbean island of Martinique. There, long-existing, precise registry data have informed analytical studies on several cancers and have helped assess the environmental and occupational health risks or evaluation of medical practice and local screening programs for major sites.

Optimizing fruitful surveillance and research collaboration requires certain legal and ethical environments, as well as specific infrastructure and organization. Of particular importance is a properly defined and functioning information system. This should not...
necessarily be electronic, but indicators must be well defined, with appropriate resources for sustaining data collection and reporting from both public and private health care sectors. In addition, standard protocols, and best practices, relying on evidence-based medicine, should be implemented. Several presenters during the workshop provided evidence for using cancer registries as building blocks for collaborative research, with particular emphasis on capacity building in developing regions. Surveillance data were also demonstrated to have use in driving research studies. For example, the purpose of any cancer registry should include producing more stable and accurate rates, greater access to data, and the possibility to investigate geographical variability (Fig 3). However, a registry would also be valuable to investigate the quality of care, possibly by looking at stage at diagnosis, or whether screening is being performed, as well as examinations of social issues and barriers to screening and treatment. Although separate research studies may be required for some of these, by working with registry teams, the data could be combined to provide a broader picture. Population-based cancer registries represent the gold standard, but they can also be used to examine rates standardized by age, age-specific incidence, sex ratios, rates in different ethnic groups and migrants, time trends, and survival. These data could then be used in health care planning and monitoring, as well as to inform policies, guide planning, and, once the knowledge of trends is available, to project treatment outcomes. When they are used to help validate current cancer mortality data, cancer registry data can also illuminate areas for research.

Proving the usefulness of the data from a cancer registry is a powerful way to influence the public and to help ensure continued future funding. Linking surveillance with research outcomes is another way to guarantee continued collaboration and, perhaps, registry sustainability. For example, registry data can be used to evaluate improved outcomes from a range of research projects: public health interventions, comorbidity investigations, examination of the quality of diagnosis, treatment and follow-up care, epidemiological research, genetics, community impact, and survivorship, among others.

Policy Decision-Making and Its Impact
A general consensus suggested that the role of policy makers in institutions and governments is vital, because financial resources are essential to sustain a registry, especially in the current economic climate. This must be considered at a time when countries are grappling with salary payments and consideration of the sustainability of a registry may not be seen as a priority. Barbados represents an example of how sur-

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laborative research between registries and medical/research teams still remains limited and policymakers are not fully convinced of the need to promote such endeavors.27

Population-based cancer registries allow a specific type of surveillance vital for delivering quality national data to provide a precise description of the degree of cancer burden in a country. Without such data, knowledge about the degree of cancer burden may be very limited. Furthermore, it would be difficult, if not impossible, to develop, implement, monitor, and evaluate cancer strategies for prevention and disease management without cancer registries due to their continuous provision of national data.14,27-29 These data are important for cancer control and essential to better guide research.14,27-29

Most Caribbean nations with registries have managed to achieve an infrastructure that encourages collaboration with research; however, major challenges still exist to sustaining registry activity, addressing confidentiality concerns in a small island setting, maintaining economic viability and optimizing the quality of their data due to a combination of poor documentation and lack of electronic health information systems.22,24 For example, in Barbados, existing challenges include incomplete or poorly documented medical records, limitations in retrieval of death records, and suboptimal passive reporting from the private medical sector.22 One of the fundamentals will be stimulating better awareness of available tools and resources as well as resource optimization between existing Caribbean research networks, cancer registries, and international organizations.

Other Caribbean countries, despite acknowledging their need, experience challenges from limited cancer registry expertise or infrastructure, and/or a lack of support from governmental bodies.22,24 Many of these countries have important cancer burdens despite their small geographical and population sizes.2,4,5,17,18,22,24 For example, in St Lucia, which has had a hospital-based cancer registry in operation since 1997, almost one-half of the cases registered in 2002 were identified from death certificates alone, and cancer has been the leading cause of death on the island since 2006.22 Fully registered cases often lack follow-up information, partly due to decentralization and duplication of patient records within the public health care sector and partly because of the number of patients sent overseas for treatment.22 In addition, despite being operational for more than 15 years, the St Lucian registry is not perceived as being indispensable.22 Implementation of a national cancer control program through a multisectoral approach, including more collaboration with international agencies and more experienced registries, may help address some of these issues.

To help advance the cancer registry agenda, fledgling registries can take advantage of civil society organizations. For example, in the Cayman Islands, the Cayman Islands Cancer Society has played a significant role in lobbying for the registry.22 In Barbados, local civil society organizations have been strong supporters of the national cancer registry, working in partnership with them to ensure comprehensive data capture.22,24 The potential role that civil society organizations can play in reaching communities to build awareness and create grass roots advocates for registries is important. They also provide a valuable link between potential community advocates and decision-makers in ministries of health.

Further solutions lie in developing a strategic plan that includes setting standards for reinforced sustainable population research for the Caribbean. This implies identifying intercountry and intracountry specificities, needs, and priorities as well as existing tools, resources, and stakeholders. Developing standards also requires improved use of existing information systems, the generation of higher-quality cancer data, the implementation of best practice protocols, and more efficient communication. Because of the strong advocacy for surveillance guiding targeted research, the strategic regional research plan will also need to stimulate the development of collaborations in the region. Such collaborations, initiated between the various stakeholders/actors in the field of oncology (existing/aspiring cancer registries, research and medical teams, governmental and institutional policy makers and other cancer advocates/research teams at the local, regional and international levels), will create opportunities for dialogue on the rationale and role of cancer registration, the value, application, and utilization of cancer registry data in collaborative research, the illustration of the outcomes of cooperative work, and the importance and impact of policy decision-making.

Capacity building will be imperative to facilitate research collaboration through linkages between cancer registries, clinical personnel, research teams, and diverse data sources (eg, histopathology, comorbidity), because even well-established cancer registries experience underutilization of their data as a research resource.22,24 For example, the French Caribbean islands of Martinique and Guadeloupe need to promote their scientific activities to develop collaboration between these French Caribbean registries and other Caribbean islands with populations of similar ethnic and environmental patterns.22,24 Another important issue for some islands is their small population sizes, which make it difficult to examine less common cancer sites.22 Collaborative studies involving several Caribbean nations can overcome this limitation; however, differences in social and cultural contexts, in economic development, and lack of data on ethnicity in the French registries may be significant barriers to implementation of such collaborative studies.
To overcome some of these barriers, the AC3 has integrated cancer registries (7 Caribbean and 2 African) as members of their network and has constituted a broad-based platform for education, training, and research on all cancer aspects (etiology, screening, prevention, treatment, and survival) in populations of African descent. During the 2012, 2013, and 2014 AC3 Caribbean meetings, the desire to see an increase in indigenous cancer statistics reports from the region was unanimous and regional analyses of cancer statistics were prioritized as one of its planned activities. Collaborative efforts between the cancer registries represented within the AC3 are currently in motion. At the forefront of collaborative research in the region with 45 published articles, the AC3 has several initiatives in progress for regional cancer data analyses, foundations for research biospecimen banks, networking, collaborating, standardizing, supporting, and optimizing existing cancer surveillance and research opportunities, with the main objective of establishing a global cancer network within the Caribbean region. The 2013 and 2014 AC3 cancer registration meetings in Barbados and Martinique provided a much-needed opportunity for networking between research investigators, cancer registrars, and health care professionals, providing insight into the possibility of collaborative opportunities between cancer registries within the wider Caribbean region. These meetings also emphasized the importance of a regional cancer network in the Caribbean to help promote collaborative research and to obtain more effective and efficient cancer control, as the Caribbean moves toward optimization of these registries for scientific excellence in cancer research.

Existing research–cancer registry collaborations are paving the way, and organizations like the AC3, NCI, IARC, and PAHO facilitate and promote such endeavors. In 2011, heads of state and government representatives assembled for a high level UN meeting on the prevention and control of noncommunicable diseases. The meeting culminated with a political declaration, thus highlighting the need to reduce risk factors, strengthen national policies and health systems, build international cooperation, including collaborative partnerships, promote research and development, as well as implement systems for monitoring and evaluation to lessen the growing burden of noncommunicable diseases.

Because cancer is a major noncommunicable disease that impacts morbidity and mortality in the Caribbean, cancer surveillance must be included as a key component in the global monitoring framework for noncommunicable disease prevention and control developed as a result of the political declaration of the United Nations on noncommunicable diseases. Therefore, Caribbean countries are obligated to collect reliable data on cancer to facilitate reporting on these global indicators for noncommunicable diseases. Research on cancer is also limited in the Caribbean region and is greatly needed to facilitate a better understanding of this problem in the area, with a view to improving care and treatment as well as to guide the implementation of interventions for cancer prevention and control.

The regional agency, the CARPHA, supports public health surveillance and research in the English- and Dutch-speaking Caribbean. Working with its 23 member states, as well as with international partners, the agency is committed to strengthening the scientific evidence on cancers and other diseases of public health importance as a means of improving public health in the region.

The NCI has made significant investments to international cancer research, training, and other programs, with the goal of reducing the global cancer burden. In 2011, these activities were formalized and coordinated via the creation of the Center for Global Health, which works to address the complex global challenges of cancer. One of the top priorities of the Center for Global Health is strengthening US national and international partnerships for collaborations in global health research, cancer research, prevention, and control relevant to developing countries.

To pursue these goals, the NCI performed several site visits in the Caribbean with the aim of learning about the available infrastructure and priorities for cancer control planning. As a result, the NCI partnered with national, international, and regional stakeholders to plan initiatives to address the issue of cancer surveillance and registration for the Caribbean. The NCI is also a partner in the global initiative for developing cancer registries in low- and middle-income countries, which is led by the IARC and implemented through regional hubs that provide technical and scientific support, deliver tailored training for population-based cancer registration, advocate for cancer registration, affiliated associations and networks, and coordinate international research projects. Furthermore, the US NCI has partnered with the CARPHA, the PAHO, other US federal agencies as well as the AC3, to plan a stakeholder meeting for cancer surveillance to stimulate the strengthening of cancer registration and collaborative research in the Caribbean, to encourage the strategic use of information for national cancer control plans and programs, and to discuss strategies for moving forward. All of these activities will contribute to an overall strategic plan for the development and strengthening of cancer registration for the region.

Conclusions
Capacity building, resource optimization and sustainment, as well as collaboration and communication be-
between cancer surveillance and research teams, are key to obtaining robust and complete cancer surveillance data for the Caribbean region and advancing cancer control through collaborative research. The motto remains that we must collaborate to grow.

Acknowledgments: The authors would like to thank the National Cancer Institute, Center for Global Health and Donald T. Smeon, MSc, PhD, Caribbean Public Health Agency, for support of the AC3 Cancer Registry Workshop during the CARPHA 2011 annual meeting.

References

Cancer Clustering [in French]. Martinique, France: Cellule Interrégionale d’Épidémiologie; 2006.


Evidence relating to the effectiveness of palliative sedation in terms of symptom control or quality of life was insufficient. However, evidence suggests that death is not hastened by palliative sedation, but these data come from low-quality studies. Therefore, further studies are needed to specifically measure the effectiveness and quality of life in sedated people compared with non-sedated people as well as the potential for adverse events.


This provisional clinical opinion addresses the integration of palliative care services into standard oncology practices when a patient is diagnosed with advanced or metastatic cancer.


Studies have revealed promising results regarding use of pharmacogenetics as a diagnostic tool in the experimental setting; however, use of pharmacogenetics is a more complex task to accomplish in the clinical setting.


The aim of this review was to study contemporary conceptual models and clinical approaches for integrating oncology with palliative care. The authors suggest that additional research is needed to advise best practices for integrating palliative care into various health care settings.


These authors review a large group of measures used for assessing the quality of palliative care in patients with cancer and suggest that oncology-driven quality and outcomes studies are needed to broaden the connection between quality-based care and improved patient experiences.


Early evidence demonstrates the positive impact that population-based symptom screening has on patient care in Ontario, Canada. Expansion outside of hospitals and cancer centers accompanied by increased clinician engagement and education throughout the system is necessary to ensure the long-term success of the program.


Five very specific physical signs associated with death within 3 days of onset in patients with cancer may aid in the diagnosis of impending death. In this study, the authors discuss the frequency and onset of 52 other bedside physical signs and examine their diagnostic performance.


Researchers investigated the effect of early compared with delayed palliative care on symptom impact, quality of life, mood, resource use, and 1-year survival rates. They suggest that understanding the complex mechanisms by which palliative care may improve survival rates remains an important research priority.


Focus groups were conducted with palliative care clinicians who participated in randomized control trials of early palliative care for metastatic lung cancer. These data have become the foundation for training programs for clinicians.


This report summarizes panel discussions from the National Comprehensive Cancer Network and updates to its guidelines from 2013 and 2014. The most updated version of these guidelines can be found at http://www.nccn.org/professionals/physician_gls/pdf/palliative.pdf.
Peer review is the indispensable and critical element in the evaluation of all manuscripts being considered for publication in our journal. The oncology professionals who took part in our peer review process last year are listed below, and we thank them for their invaluable efforts on behalf of Cancer Control.

— The Editor

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Sam Donaldson
Former ABC news correspondent and member of the Moffitt Board of Advisors conducts a conversation with Dr. Belldegrun about the exciting immunotherapy field for cancer treatment.