A Review of Cost-Effectiveness Studies in Ovarian Cancer

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Background: Ovarian cancer is the fifth leading cause of all cancer-related deaths among women. While the costs of diagnosis and treatment impact the affected individual and the health system, the most important costs for the patient are often the pain and suffering associated with ovarian cancer. The quality of life associated with any management decision should be closely examined. Cost-effectiveness models take into account costs, effects, and quality of life and provide clinicians with useful tools to aid in making these difficult decisions.

Methods: A comprehensive review of cost-effectiveness analyses was undertaken concerning screening for and treatment of ovarian cancer.

Results: Screening methods to detect ovarian cancer are unproven, and the majority of women present with advanced-stage disease. Multimodal screening strategies with high specificities targeted at the highest-risk individuals are the most likely strategies to be cost-effective. Primary treatment with intravenous paclitaxel and platinum regimens has proven to be cost-effective in multiple studies. Studies evaluating intraperitoneal chemotherapy show that this strategy is potentially cost-effective over a long-term time horizon. A cost-effectiveness analysis of the management of recurrent platinum-sensitive ovarian cancer showed that treatment with carboplatin and paclitaxel is cost-effective compared to single-agent therapy. However, the preferred option for patients with recurrent platinum-resistant ovarian cancer appears to be supportive care (no chemotherapy) or single-agent therapy.

Conclusions: Many therapeutic choices are cost-effective in the treatment of ovarian cancer. Cost-effectiveness models offer one way to examine options in the management of a disease. The quality of life of the patient should be the most important factor in any management decision and is incorporated into well-designed studies on cost-effectiveness.

Introduction

Ovarian cancer is the leading cause of death among gynecologic cancers and the fifth leading cause of all cancer-related deaths among women. The American Cancer Society estimates that 21,880 new cases of ovarian cancer were diagnosed and 13,850 women died of the disease in the United States in 2010. The lifetime risk of invasive ovarian cancer in the United States is approximately 1.4% (1 in 71), and the lifetime risk of dying of invasive ovarian cancer is 1.1% (1 in 95).

Unfortunately, screening methods to detect ovarian cancer are currently unproven, and the majority of women present with advanced disease. Overall 5-year survival rates are approximately 49%. The majority of women present with stage III or IV disease, with survival...
rates of only 19% to 47%. In contrast, stage I ovarian cancer has a favorable 5-year survival rate of 90%2,3. The standard approach to primary management is surgery followed by platinum-based chemotherapy. Despite advances in chemotherapy, treatment for recurrent ovarian cancer is almost never curative, and most women will eventually die of this disease.

The costs associated with cancer impact both the affected individual and the health system. Healthcare costs have risen dramatically and now exceed 17% of the United States gross domestic product (GDP).4 Ovarian cancer treatment in particular is susceptible to rising costs due to the constant influx of novel chemotherapeutics and biologics, most of which are more costly than the established front-line therapies but have limited proven benefit. The costs associated with care of ovarian cancer patients are considerable and are highest during the first year of diagnosis and the last year of life.5

This article reviews the relevant cost-effectiveness analyses that have informed decisions about screening for and treatment of ovarian cancer.

Cost-Effectiveness Analyses
Cost-effectiveness analyses compare the relative value of various clinical strategies. These analyses offer a unique way to examine options in the management of disease. A cost-effectiveness analysis is defined by the United Kingdom’s National Institute for Health and Clinical Excellence (NICE) as an economic study design in which the consequences of different interventions are measured using a single outcome, usually in “natural” units (eg, life-years gained, deaths avoided, heart attacks avoided, or cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.6 Such an analysis should compare the health intervention of interest to the existing standard of care. If the standard practice does not appear to be a cost-effective option relative to other available options, the analyst should incorporate other relevant alternatives into the analysis. For example, a “do nothing” alternative or a viable lower-cost alternative might be used.

Costs that are generally accounted for in a cost-effectiveness model include medical costs (eg, hospitalization, physician, drugs, copayments) and nonmedical costs (eg, transportation, time costs of giving or receiving care, and out-of-pocket expenses). Costs of lost productivity include the cost of lost leisure time or work time. Intangibles include pain, suffering, and adverse events. Effectiveness data for each management strategy are preferably derived from randomized controlled trials (RCTs), but this is not always possible. The most commonly reported result of a cost-effectiveness analysis is the incremental cost-effectiveness ratio (ICER), which expresses a comparison of an intervention or strategy to an alternative strategy. The ICER for comparison of novel intervention A compared to standard intervention B is defined as:

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\text{ICER} = \frac{\text{Cost}_A - \text{Cost}_B}{\text{Effect}_A - \text{Effect}_B}
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Strategies are usually compared using either the cost per year of life saved, which quantifies improvements in survival, or the cost per quality-adjusted life year (QALY), which quantifies improvements in survival while also accounting for differences in quality of life associated with different strategies. Of the two, QALYs are the recommended outcome for cost-effectiveness analyses.7 In order to report results in QALYs, a utility must be assigned to the health state of interest. A utility is a number between 0 and 1, where 1 represents perfect health and 0 represents death. Accepted methods for calculating a utility include the time trade-off and standard gamble methods, which are usually performed via an extensive interview designed to determine an individual's preferences for one health state (eg, progressive metastatic ovarian cancer) compared with another (eg, perfect health).8 QALYs capture both the quantity (length) of life and its quality; the ideal treatment should maximize both.9 The ICER represents the additional cost of one unit of outcome gained (life-years saved or QALY) by a health care intervention or strategy when compared to the next best alternative, mutually exclusive intervention or strategy.9

The term “cost-effective” does not mean that the strategy saves money, but rather that the additional cost of the intervention is worthwhile. The concept of cost-effectiveness requires a value judgment — what one person believes is a good price for an additional outcome, someone else may not. Cost-effectiveness analyses in ovarian cancer typically focus on the costs of treatments, the survival outcomes, and the toxicities related to each treatment.10 An intervention is generally considered cost-effective relative to an alternative strategy if it costs less than US $50,000 per QALY.11 However, social norms may raise this value such that interventions costing $100,000 or more per QALY have sometimes been considered cost-effective.5 The sensitivity analysis, in which the impact of varying key assumptions or estimates on the model’s results is assessed, is as important as the absolute value of the ICER in a cost-effectiveness analysis. In combination, the base case (or main) outcome and the relevant sensitivity analyses allow us to draw appropriate conclusions from a decision model.

Ovarian Cancer Screening
The ability to accurately detect early-stage disease may have the potential to dramatically improve survival from ovarian cancer. However, the low prevalence of ovarian cancer may limit the achievable effectiveness and cost-effectiveness of general population screening. The combination of a specificity of a screening test and the disease prevalence determines the positive predic-
tive value (PPV) of a screening test, which is a measure of the number of diagnostic procedures necessary to diagnose one case of cancer. A PPV of at least 10% is generally considered clinically acceptable for a screening test.12 The tests that have been most extensively evaluated as screening methods include pelvic examination, the measurement of serum levels of CA-125, and ultrasound scanning.

Prospective evaluation of CA-125 in the general population reveals that its specificity for early-stage disease is fairly high (96% to 100%), but the sensitivity was as low as 57% in one study.13-16 In a prospective study of women over 50 years of age, a PPV of 4.6% was achieved using CA-125 alone.14 Transvaginal ultrasound has also been evaluated; in the largest study of women at average risk, mostly early-stage carcinomas were detected. However, most of these carcinomas were of nonserous epithelial origin.17 Menon et al18 evaluated patients with an elevated CA-125 and an abnormal transvaginal ultrasound and determined that the risk of developing a cancer in the subsequent year was increased approximately 300-fold. This supports the use of these screening tests in combination. However, a pilot RCT of multimodality screening in which women were randomized to a control group or screening that involved measurement of serum CA-125, pelvic ultrasonography if CA-125 was greater than or equal to 30 U/mL, and referral if ovarian volume was greater than 8.8 mL on ultrasound failed to demonstrate a significant difference in the number of deaths from ovarian cancer between the control and screened groups.19

Several groups have developed models to predict the success of population-based screening strategies. Skates and Singer20 developed the first mathematical model of the natural history of ovarian cancer, using stochastic progression across the four clinical stages to estimate the effectiveness of annual screening of postmenopausal women using CA-125. Their model predicted that screening could save at least 3 years of life per case detected. Urban et al21 modified the Skates and Singer model in examining single modality and multimodality strategies that involved both CA-125 and ultrasound. A multimodal strategy involving CA-125 with a threshold for positivity of either elevation above 35 U/mL or doubling since the previous screen, followed by transvaginal ultrasound only if CA-125 is positive, was found to be efficient in that no other strategies saved as many years of life at lower cost per year of life saved. They estimated the cost-effectiveness of different screening strategies for a population of 1 million women over age 50 years over a period of 30 years using a stochastic simulation model. All costs were measured in 1990 dollars, and all costs and benefits were discounted by 5% to 1990. Used annually, they predicted that a multimodal strategy would cost US $51,000 per year of life saved and would be potentially cost-effective. Both of these models assumed a fixed duration for each disease stage based on expert opinion (stage I: 9 months; stage II: 4.5 months; stage III: 12 months; and stage IV: 3 months).

A third ovarian cancer natural history model22 used a Markov transition state design that allowed direct progression from stage I to either stage II or stage III disease, which is consistent with the common clinical presentation and stage distribution of the disease. We utilized a hypothetical screening test whose characteristics and cost could be adjusted to reflect different potential screening modalities, and we assigned costs to false-positive results. The model was calibrated against data from the Surveillance, Epidemiology, and End Results (SEER) program for ovarian cancer incidence, stage distribution, and mortality. The model predicted that an annual screening test with a sensitivity of 85% and a specificity of 95% would have a PPV of 0.55%. At screening test specificities of up to 99%, the model-predicted PPV of annual testing did not exceed 4%. However, at a specificity of 99.9%, the PPV for annual screening was 22%. Annual screening of a population of women aged 50 to 85 years at average risk of ovarian cancer was predicted to improve life expectancy by 2.92 days on average, with an ICER of $73,469 (2007 US dollars) per year of life saved compared with no screening. However, simulated screening of a “high-risk” population of women aged 50 to 85 years with a relative risk of developing ovarian cancer of 2 resulted in an improvement in the ICER to $36,025 per year of life saved compared with no screening. Costs and outcomes were discounted at an annual rate of 3%. Based on this model, annual screening for ovarian cancer might be cost-effective in high-risk populations, and the specificity of a screening test would need to exceed 99% to achieve clinically acceptable PPVs of greater than 10%.22

Two RCTs in progress are the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) and the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial in the United States. The PLCO study is an RCT that randomized women aged 55 to 74 years to either screening with annual ultrasound and CA-125 (intervention group) or a control group who received usual care (no screening). Recently, an analysis on the first four rounds of screening revealed that the highest PPV achieved with screening was 1.3%, and 72% of the screen-detected cases were late-stage disease (III or IV). The effect of screening on mortality is not yet known, but initial results are not encouraging.23 Between 2001 and 2005, the UKCTOCS randomized 202,638 postmenopausal women aged 50 to 74 years to three arms: (1) no treatment (n = 101,359), (2) a multimodal screening consisting of annual CA-125 screening (interpreted by a risk of ovarian cancer algorithm) and transvaginal ultrasound scan as a second-line test (n = 50,640), or (3) annual screening with transvaginal ultrasound (n = 50,639). The initial round of “prevalence” screening resulted in a sensitivity, specificity, and PPV of 89.5%, 99.8%, and 35.1%, respectively, for multimodal screening.
and 75.0%, 98.2%, and 2.8% for ultrasound for primary invasive epithelial ovarian and tubal cancers. The trial is ongoing, with the final screening tests taking place in 2011, and all women will be followed until the end of 2014. The initial screen has established that these screening strategies are feasible. While the improved specificity, PPV, and stage distribution of cancers reported in this trial are encouraging, both mortality data and final analysis of the costs of the multimodality screening algorithm are critical to any assessment of the costs, benefits, and potential cost-effectiveness of screening. Moreover, quality of life has not been taken into account in any of these economic models.

### Chemical for Newly Diagnosed Ovarian Cancer

The recommended treatment for ovarian cancer entails primary surgery for diagnosis, staging, and cytoreduction followed by chemotherapy. Intravenous chemotherapy usually consists of a taxane and a platinum agent for 3 to 6 cycles; patients with advanced intraperitoneal (IP) disease are often candidates for IP chemotherapy. Based on the National Comprehensive Cancer Network (NCCN) 2009 guidelines, patients who are eligible for chemotherapy should be informed about the options of either intravenous (IV) chemotherapy or a combination of IV and IP chemotherapy. IV chemotherapy should consist of a taxane and a platinum agent for 3 to 6 cycles, while IP chemotherapy should be given in combination with IV chemotherapy utilizing taxane and platinum agents. The first cost-effectiveness studies in ovarian cancer chemotherapy were performed in response to the introduction of taxanes into the front-line chemotherapy regimen for this disease. Two independent RCTs, one by the Gynecological Oncology Group (GOG 111) and another by the European-Canadian Intergroup (OV-10), demonstrated that cisplatin plus paclitaxel as primary chemotherapy is superior to previous therapy of cisplatin plus cyclophosphamide in clinical response rate, progression-free survival, and overall survival. Three phase III RCTs subsequently showed similar efficacy of paclitaxel in combination with either carboplatin or cisplatin for the adjuvant treatment of ovarian cancer. The carboplatin combination was better tolerated and has subsequently become a standard first-line treatment.

When first introduced, paclitaxel plus cisplatin was a more expensive therapy than the old standard of cyclophosphamide plus cisplatin. A number of cost-effectiveness investigations using GOG 111 data based on cisplatin plus paclitaxel vs cisplatin plus cyclophosphamide were performed. From the perspective of a US oncology practice, the total drug costs for cisplatin plus paclitaxel were four times higher than those for cisplatin plus cyclophosphamide (US $9,918 vs $2,527; 1996 costs). Compared with cisplatin plus cyclophosphamide, the incremental costs per year of life gained for cisplatin plus paclitaxel therapy were US $19,820 for inpatient treatment and $21,222 for outpatient treatment. These incremental costs fall well within the generally accepted cost-effective range for new therapies.

From a Canadian health system perspective, cisplatin plus paclitaxel had an ICER of $32,213 (1993 costs for drug and hospital costs in Canadian currency [CaD]) per life-year gained compared to cyclophosphamide plus cisplatin. The investigators originally concluded that it may not be possible to adopt this as first-line therapy for all advanced-stage ovarian cancer patients because it would cost the province of Ontario an additional CaD $9 million annually. Ontario has a fixed budget for cancer care, and this new therapy would mean that fewer resources would be available for treating patients with recurring disease. However, initial adjuvant chemotherapy in Canada now often includes a platinum agent in addition to paclitaxel. Berger et al investigated the cost-effectiveness of cisplatin plus paclitaxel from the perspective of the national health services of various European countries. The incremental costs of cisplatin plus paclitaxel per life-year saved were evaluated for Germany (US $9,362), Spain (US $6,395), France (US $6,642), Italy (US $11,420), the Netherlands (US $7,796), and the United Kingdom (US $6,403). Of note, carboplatin and paclitaxel are now both marketed as generic agents, and therefore these prior studies are less applicable than when first published.

The NCCN 2009 guidelines for ovarian cancer recommend IP chemotherapy as primary/adjuvant therapy for optimally debulked (< 1 cm) stage II or greater ovarian cancer treatment. Three phase III clinical trials identified advantages to the use of IP chemotherapy for adjuvant treatment of stage III ovarian cancer. The most recent of these studies demonstrated an overall survival advantage of 16 months in the IP arm at the expense of increased adverse events and a significant reduction in quality of life.

Two analyses have evaluated the cost-effectiveness of IP chemotherapy for the primary treatment of stage III ovarian cancer. When comparing IP to IV chemotherapy, Bristow et al reported that IP chemotherapy was potentially cost-effective compared with IV, with an ICER of $37,454 per QALY (2006 US dollars). Havrilesky et al reported an estimate of $180,022 per QALY (2006 US dollars) when using a 7-year time horizon, which was consistent with the current duration of survival results from GOG 172. However, when the time horizon was extended to a lifetime under the assumption that any survival advantage realized with IP chemotherapy would persist over that period, the ICER of IP chemotherapy dropped to US $32,053 per QALY. Also of note, under the assumption that IP chemotherapy is equally effective as an outpatient regimen, the ICER of IP vs IV chemotherapy becomes even more attractive. While both studies informally incorporated quality of life based on the surveys administered to...
patients enrolled on GOG trials of chemotherapy, neither performed a validated utility assessment. Our conclusions are that IP chemotherapy is potentially cost-effective for women with stage III disease, but that more formal incorporation of quality of life, longer-term follow-up of the results of the last phase III study, and investigation of outpatient IP regimens would strengthen this conclusion.

Finally, the recent addition of biologic agents such as bevacizumab to first-line chemotherapy regimens for ovarian cancer has shown promise, as reported at the 2010 meeting of the American Society of Clinical Oncology (ASCO). No formal cost-effectiveness studies incorporating this therapy have yet been published, but concerns have been raised over the high cost of new therapies compared with their potential level of benefit.

Chemotherapy for Recurrent Ovarian Cancer

Most women with ovarian cancer will achieve clinical remission following surgery and primary adjuvant chemotherapy. Unfortunately, the majority of patients eventually develop recurrent disease that is rarely curable. Patients who experience recurrence more than 6 months after completing a first-line chemotherapy regimen are considered to have “platinum-sensitive” ovarian cancer and have an excellent response rate when re-treated with platinum agents.

The optimal treatment of recurrent ovarian cancer is subject to ongoing debate and is affected by considerations of survival, toxicity, and quality of life. Prior studies indicate that patients with platinum-sensitive disease have a good response rate to re-treatment with platinum-based regimens. Two large RCTs compared the use of single-agent therapy with combination regimens for platinum-sensitive ovarian cancer. These studies identified a progression-free survival advantage for the combination regimens of gemcitabine plus carboplatin and paclitaxel plus platinum chemotherapy (as well as an overall survival advantage for paclitaxel plus platinum) compared with platinum alone, and the authors suggested that the combination regimens should be considered standard of care.

Based on these two studies, Havrilsky et al recently published a Markov state transition model that evaluated the optimal treatment strategy for patients with recurrent platinum-sensitive ovarian cancer. We determined that paclitaxel plus carboplatin has an ICER of $15,564 per additional progression-free year compared with single-agent carboplatin, while gemcitabine plus carboplatin has a less attractive ICER of $278,388 per additional progression-free year compared with paclitaxel plus carboplatin. Given that both carboplatin and paclitaxel are now available as generic drugs in the United States, their cost advantage is not surprising. We also evaluated neurologic and hematologic toxicities by incorporating these into a sensitivity analysis and varying the severity and costs associated with treatment. Over a reasonable range of utility (quality of life) scores, the paclitaxel/carboplatin regimen was still cost-effective compared with carboplatin alone, and gemcitabine plus carboplatin remained non-cost-effective. These results must be interpreted on an individual basis with the patient’s prior adverse event profile in mind. For example, it is unlikely that a patient with severe neurotoxicity due to prior taxane treatment would be re-treated with the same drug.

Recurrent ovarian cancer that occurs within 6 months of completing a first-line chemotherapy regimen has a poor prognosis, with cure being unlikely. Rocconi et al performed a cost-effectiveness analysis of treatment options for recurrent platinum-resistant ovarian cancer and concluded that only best supportive care (ie, no chemotherapy) was clearly cost-effective, while second-line monotherapy was possibly marginally cost-effective (ICER US $64,104 per year of life saved). Even without incorporation of toxicity rates and costs, the authors found that combination chemotherapy regimens were never cost-effective for platinum-resistant disease due to unfavorable ICERs.

Conclusions

While decisions surrounding the diagnosis and treatment of cancer are difficult and cost is not usually the most pressing concern of decision makers, the increasing burden of the rising cost of health care demands attention. As newer, higher-cost therapies become available, formal evaluation of the costs and benefits of these new treatments in comparison to existing and established strategies should be a high priority. Screening for ovarian cancer has yet to be proven effective in any population, and as such it has not been proven to be cost-effective. Women with ovarian cancer are at a high risk of recurrence and often receive multiple chemotherapy regimens. Cost-effectiveness studies to date support the use of IP chemotherapy under certain assumptions. Likewise, the use of multiagent chemotherapy regimens appears to be cost-effective for women with platinum-sensitive recurrence. For those with platinum-resistant disease, single-agent chemotherapy or even supportive care are the strategies of choice. Cost-effectiveness models offer a way to objectively examine management options and give perspective to difficult therapeutic decisions.

References


