A Risk-Adapted Approach to the Use of Radioactive Iodine and External Beam Radiation in the Treatment of Well-Differentiated Thyroid Cancer

R. Michael Tuttle, MD, Geneviève Rondeau, MD, and Nancy Y. Lee, MD

Background: Both radioactive iodine (RAI) and external beam radiation therapy (EBRT) offer important clinical benefits in properly selected patients with differentiated thyroid cancer. With the increased emphasis on a risk-adapted model for the management of thyroid cancer, it is important to identify which patients are most likely to benefit from radiation therapies given in the adjuvant setting and as treatment of gross residual disease.

Methods: This review compares the authors’ current management practices with the recommendations of published guidelines from both the National Comprehensive Cancer Network and the American Thyroid Association.

Results: Because of the lack of prospective randomized studies on either RAI or EBRT in differentiated thyroid cancer, recommendations must be based on retrospective cohort studies that vary in selection criteria, histologies, sample size, inclusion criteria, and follow-up.

Conclusions: RAI has an important adjuvant therapy and treatment function in properly selected patients. Likewise, EBRT is associated with increased locoregional control and palliative therapeutic effects in high-risk patients.

Introduction

While certainly not a new concept, a risk-adapted approach in the management of thyroid cancer has received renewed interest in the last 10 years. A risk-adapted approach tailors the extent and intensity of initial therapy according to individualized risk estimates of recurrence and mortality. As opposed to a “one size fits all” approach to thyroid cancer management, a risk-adapted approach relies on a more precise understanding of the clinicopathological factors that predict the risk of recurrence and/or mortality. In this approach, the risks and benefits of potential additional therapies are balanced against the specific risks of recurrence and mortality, as well as the response to therapy for individual patients. This risk-adapted approach is easily identified in the updated American Thyroid Association (ATA) guidelines, where the most important initial management recommendations are based on specific clinicopathologic risk factors rather than being a uniform recommendation for all thyroid cancer patients regardless of risk analysis. These include recommendations with regard to extent of initial surgery (recommendation 26), degree of initial thyroid-stimulating hormone (TSH) suppression (recommendation 40), indications for central neck dissection (recommendation 27), completion thyroidectomy (recommendation 29), radioactive iodine (RAI) remnant...
ablation (recommendation 37), and external beam radiation therapy (EBRT) (recommendation 41). Furthermore, the most important management issues with regard to the clinical follow-up of thyroid cancer patients are also based on the risk of recurrence and disease-specific mortality for individual patients. These issues range from the need for stimulated thyroglobulin (Tg) during follow-up (recommendation 45) to the role of diagnostic whole body scans (recommendations 46 and 47), neck ultrasoundography (recommendation 48), long-term TSH goals (recommendation 49), and additional therapies (recommendations 59 and 77). Similarly, the NCCN guidelines also provide recommendations based on risk of recurrence and disease-specific mortality regarding many of the most important management decisions. For example, individualized recommendations based on risk are provided for the degree of TSH suppression (THYR-A), extent of initial surgery (PAP-1), indications for completion thyroidectomy (PAP-2), indications for RAI ablation (PAP-3), administered activity of RAI (PAP-4), and the need for stimulated Tg, whole body scanning, and other cross-sectional imaging for detection of disease recurrence (PAP-5).

The most commonly used risk stratification systems, such as MACIS (metastases, age, completeness of resection, invasion, and size) and the TNM system of the American Joint Committee on Cancer (AJCC), were designed to predict disease-specific mortality rather than risk of recurrence. Therefore, the updated ATA guidelines recommend using a separate postoperative clinicopathologic staging system, in addition to the AJCC TNM system, to improve prognostication and to better tailor follow-up for differentiated thyroid cancer patients (recommendation 31).

It is our view that accurate risk estimates coupled with realistic expectations of the benefits and risks of proposed therapies allow the clinician and the patient to develop a treatment and follow-up plan designed to provide maximum benefit to high-risk patients while minimizing treatment-related side effects and unnecessary treatments in low-risk patients. To this end, we review a risk-adapted approach to the use of RAI and EBRT in the management of differentiated thyroid cancer in order to compare our current management practices with the current recommendations published by the ATA and the National Comprehensive Cancer Network (NCCN).

Potential Roles of Radiation Therapy (EBRT or RAI) in Thyroid Cancer

From an oncologic perspective, there are two major potential roles for radiation therapy in the management of differentiated thyroid cancer: adjuvant therapy for potential, residual microscopic disease remaining after appropriate surgical resection or as part of multimodality therapy for gross residual disease not amenable to definitive surgical resection (either as locoregional disease in the neck or distant metastases). In the adjuvant setting, the goals of radiation therapy are to reduce the risk of both locoregional and distant recurrence and to prolong overall survival. In addition, the ablation of any residual normal thyroid tissue with RAI may also facilitate initial staging (post-therapy RAI whole body scanning) and allow for more sensitive detection of recurrent disease (suppressed and TSH-stimulated Tg measurements) in properly selected patients. When used to treat gross residual disease, radiation therapy is seldom curative but can have significant palliative effects with regard to local invasive or compressive symptoms and pain control.

The Role of RAI in the Treatment of Differentiated Thyroid Cancer

**RAI as Adjuvant Therapy**

While the first dose of RAI administered after a total thyroidectomy has traditionally been referred to as **RAI remnant ablation**, we prefer to describe the primary function of this first dose as either **remnant ablation**, **adjuvant therapy** or **therapy of macroscopic disease**. **Remnant ablation** is used to define the clinical scenario in which the goal of therapy is simply to destroy the residual thyroid tissue in an effort to facilitate staging and follow-up. These patients are not thought to be at high risk for persistent micrometastatic disease and therefore are given the lowest administered activity that is likely to achieve ablation of the normal thyroid remnant (usually between 50 and 75 mCi). We use the term **adjuvant therapy** to refer to the first dose of RAI given in patients we consider to be at significant risk of having as yet undetected micrometastases. In these patients, administered activities between 100 and 150 mCi of RAI will not only facilitate initial staging and follow-up, but also provide a potentially tumoricidal dose of RAI that could result in lower recurrence rates and improved overall survival. Finally, the phrase **therapy of macroscopic disease** refers to those few patients with persistent macroscopic disease remaining after total thyroidectomy and appropriate lymph node dissection (either locoregional disease or distant metastases) in whom the primary goal of treatment is destruction of macroscopic disease. In these patients, higher administered activities of RAI may be warranted depending on the amount of residual normal tissue in the thyroid bed, the age of the patient, comorbid disease status, and the expectation that the tumor will be RAI-avid. Obviously, the distinction between the three RAI functions (ablative, adjuvant therapy, and therapy of macroscopic disease) is somewhat arbitrary and overlapping. However, we find that the use of these terms helps define the goals of initial therapy, thereby significantly impacting the recommended administered activity.

The data with regard to the impact of adjuvant RAI therapy on recurrence and overall survival are conflicting at best. Without randomized prospective clinical trials to address this issue, treatment recommendations are
largely based on several large retrospective clinical studies, each with its own associated strengths, weaknesses, and treatment biases. In most studies, low-risk patients seemed to gain little or no improvement in recurrence rates or overall survival from the routine use of RAI as adjuvant therapy. Conversely, most studies demonstrate benefit from RAI in patients with high risk of recurrence or death. In an effort to conceptualize the expected benefits of the first dose of RAI across the wide spectrum of thyroid cancer presentations, the updated ATA guidelines taskforce developed a table that provides the rationale for therapy as well as the strength of evidence either for or against the use of adjuvant RAI based on the TNM staging system (Table 1 and Table 2).

As can be seen from Table 1, routine use of RAI as adjuvant therapy is consistently associated with a decreased risk of recurrence and death only in those patients with high-risk disease (older patients with T3 lesions, any age with gross extrathyroidal extension, or the presence of distant metastases). With regard to decreasing the risk of recurrence, there is uniform agreement that small tumors confined to the thyroid (T1a, < 1 cm, N0) do not benefit from RAI ablation. However, for many of the TNM stages, data are “conflicting” with regard to whether or not a benefit can be expected in terms of decrease in recurrence from the use of RAI as adjuvant therapy. Because of conflicting data, it is impossible to provide a definitive recommendation either for or against the routine use of RAI in these subgroups. Therefore, clinical judgment is required to determine when the risk of recurrence is high enough to warrant adjuvant RAI therapy, in which support in the literature is best described as “conflicting.” Additional factors that could sway a decision toward RAI as adjuvant therapy in these groups with conflicting data could include other high-risk features such as more aggressive histologies (eg, follicular thyroid cancers with more than minimal capsular invasion, Hürthle cell thyroid cancers, tall cell variants, poorly differentiated histologies), the presence of vascular invasion, or the presence of significant microscopic extrathyroidal extension not appreciated as gross extrathyroidal extension intraoperatively.

While RAI has been safely used in the therapy of thyroid cancer for more than 50 years, it is not without side

<table>
<thead>
<tr>
<th>Factors</th>
<th>Description</th>
<th>Expected Benefit</th>
<th>May Facilitate Initial Staging and Follow-up</th>
<th>RAI Ablation Usually Recommended</th>
<th>Strength of Evidence**</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>1 cm or less, intrathyroidal</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>T1b</td>
<td>1 to 2 cm, intrathyroidal</td>
<td>No</td>
<td>Conflicting data*</td>
<td>Yes</td>
<td>Selective use*</td>
</tr>
<tr>
<td>T2</td>
<td>&gt; 2 to 4 cm, intrathyroidal</td>
<td>No</td>
<td>Conflicting data*</td>
<td>Yes</td>
<td>Selective use*</td>
</tr>
<tr>
<td>T3</td>
<td>&gt; 4 cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age &lt; 45 yrs</td>
<td>No</td>
<td>Conflicting data*</td>
<td>Yes</td>
<td>Yes</td>
<td>B</td>
</tr>
<tr>
<td>age ≥ 45 yrs</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>B</td>
</tr>
<tr>
<td>Any size, any age, minimal extrathyroidal extension</td>
<td>No</td>
<td>Inadequate data*</td>
<td>Yes</td>
<td>Selective use*</td>
<td>I</td>
</tr>
<tr>
<td>T4</td>
<td>Any size with gross extrathyroidal extension</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Nx, N0</td>
<td>No metastatic nodes documented</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>N1</td>
<td>age &lt; 45 yrs</td>
<td>No</td>
<td>Conflicting data*</td>
<td>Yes</td>
<td>Selective use*</td>
</tr>
<tr>
<td>age ≥ 45 yrs</td>
<td>No</td>
<td>Conflicting data*</td>
<td>Yes</td>
<td>Selective use*</td>
<td>C</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis present</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Because of either conflicting or inadequate data, we cannot recommend either for or against RAI ablation for this entire subgroup. However, selected patients within this subgroup with higher risk features may benefit from RAI ablation (see modifying factors in the text).

** See Table 2 on page 92 for a description of rankings.

effects. Multiple doses can be associated with a low but statistically significant increase risk of secondary malignancies.12,14 Transient effects on gonads, salivary glands, and bone marrow are well described.15,16 While most of the side effects resolve within weeks to months after RAI ablation, persistent dry mouth and salivary gland issues can continue in up to 5% of patients.15 Furthermore, a mild but statistically significant decline in white blood cell count and platelets is seen up to 1 year after routine RAI ablation.16 So while RAI is considered to be a safe therapy, it carries the potential for long-term side effects.

In an effort to summarize the data in Table 1 into clinical usable recommendations and to balance the risk/benefit ratio with regard to RAI ablation, the new ATA guidelines provide the following advice regarding the role of RAI ablation after total thyroidectomy (recommendation 32).4 It should be noted that the term ablation as used in the recommendations from the ATA broadly refers to all three functions of the first dose of RAI (remnant ablation, adjuvant therapy, and therapy of macroscopic disease).

• Radioiodine ablation is recommended for all patients with known distant metastases, gross extrathyroidal extension of the tumor regardless of tumor size, or primary tumor size greater than 4 cm even in the absence of other higher risk features.

• Radioiodine ablation is recommended for selected patients with 1 cm to 4 cm thyroid cancers confined to the thyroid and who have documented lymph node metastases or other higher risk features when the combination of age, tumor size, lymph node status, and individual histology predicts an intermediate to high risk of recurrence or death from thyroid cancer.

• Radioiodine ablation is not recommended for patients with unifocal cancer less than 1 cm without other higher risk features.

• Radioiodine ablation is not recommended for patients with multifocal cancers when all foci are less than 1 cm in the absence of other higher risk features.

While these bullet points provide strong recommendations for routine use of RAI ablation in high-risk patients and against RAI ablation in very low-risk patients, many of the patients we evaluate fall into the conflicting data category described in the second bullet. Therefore, the decision regarding the risks and benefits of routine use of RAI in these patients with intermediate risk of recurrence will continue to be controversial and must be made on an individual basis with each patient.

While the NCCN guidelines provide less specific detail with regard to indications for RAI ablation, they also use a risk-stratified approach to the use of RAI adjuvant therapy, recommending ablation/adjuvant therapy for individual patients based on risk of recurrence and risk of death. Consistent with the distinction between RAI ablation and RAI adjuvant therapy, the NCCN guidelines note that RAI ablation is not routinely required for patients with a postoperative Tg < 1 ng/mL and a negative

<table>
<thead>
<tr>
<th>Rating (Grade)</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Strongly recommends. The recommendation is based on good evidence that the service or intervention can improve important health outcomes. Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.</td>
</tr>
<tr>
<td>B</td>
<td>Recommends. The recommendation is based on fair evidence that the service or intervention can improve important health outcomes. The evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes.</td>
</tr>
<tr>
<td>C</td>
<td>Recommends. The recommendation is based on expert opinion.</td>
</tr>
<tr>
<td>D</td>
<td>Recommends against. The recommendation is based on expert opinion.</td>
</tr>
<tr>
<td>E</td>
<td>Recommends against. The recommendation is based on fair evidence that the service or intervention does not improve important health outcomes or harms outweigh benefits.</td>
</tr>
<tr>
<td>F</td>
<td>Strongly recommends against. The recommendation is based on good evidence that the service or intervention does not improve important health outcomes or harms outweigh benefits.</td>
</tr>
<tr>
<td>I</td>
<td>Recommends neither for nor against. The panel concludes that the evidence is insufficient to recommend for or against providing the service or intervention because evidence is lacking that the service or intervention improves important health outcomes, the evidence is of poor quality, or the evidence is conflicting. As a result, the balance of benefits and harms cannot be determined.</td>
</tr>
</tbody>
</table>

* The US Preventive Services Task Force revised its ranking system in 2007, and revisions of the thyroid cancer screening recommendations are in progress.

From the American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19(11):1167-1214. Courtesy of Mary Ann Liebert, Inc.
diagnostic whole body scan. The complete total thyroidectomy in these patients has rendered RAI ablation as an unnecessary therapy in the absence of other indications suggesting a high risk of persistent disease that may benefit from the adjuvant therapy function of RAI.

Therefore, a careful review of the data presented in Table 1 will at least allow us to provide reasonable estimates of the potential benefit for each patient with regard to risk of recurrence, risk of death, and facilitation of staging and follow-up. By balancing the potential benefit with the risk of side effects and the risk of disease recurrence or death, an individualized management plan can be developed.

**RAI as Therapy for Gross Residual Disease**

While RAI is commonly used to treat recurrent disease and distant metastases, excellent therapeutic results are usually limited to patients with small-volume RAI-avid disease. These are usually young patients with small-volume pulmonary metastatic deposits of well-differentiated thyroid cancer. In these patients, repeated doses of RAI at 6- to 18-month intervals (as long as the patient continues to have a clinically measurable response) are reasonable as the highest rates of disease remission are seen in these patients.

Macronodular RAI-avid pulmonary metastases and bone metastases should be treated with RAI if there is objective evidence of benefit following the previous therapy dose. Unfortunately, RAI is seldom curative in this setting and overall survival remains poor. Additionally, the presence of fluoro-2-deoxy-D-glucose (FDG)-avid metastases is a marker of resistance to RAI therapy and a poor prognostic sign.

Brain metastases are seldom RAI-avid and are therefore best treated with either surgical resection or EBRT.

RAI therapy is often considered for patients with cervical lymph node recurrence after initial therapy. In our experience, RAI is unlikely to destroy lymph node metastases greater than 1 cm, so surgery is the preferred treatment option in this setting. Subcentimeter metastatic lymph nodes are generally treated with additional RAI only if the lesional dosimetry is high enough to allow visualization of the metastatic lesions on a diagnostic RAI scan.

In addition to the side effects associated with RAI ablation, the use of RAI in the setting of gross residual disease has the potential to cause rapid growth or swelling of metastatic lesions (either secondary to the elevated TSH necessary for RAI therapy or as a consequence of the inflammation and edema that develops in the several days following effective RAI therapy). Therefore, metastatic deposits in areas in which swelling could be associated with significant neurovascular compromise (eg, metastases to the brain, spinal cord, near other major nerves or vasculature) should be treated with surgery or EBRT before proceeding with RAI therapy. Additionally, glucocorticoids are often used to minimize swelling during the period that the TSH is elevated and for 2 to 3 weeks after RAI therapy.

**Other Considerations Regarding RAI Therapy**

In the past, thyroid hormone withdrawal was required to allow for the TSH elevation necessary to enhance the uptake of RAI into the cells. More recently, the US Food and Drug Administration (FDA) approved recombinant human TSH (rhTSH, Thyrogen) for both diagnostic uses (diagnostic whole body scan and stimulated Tg determination) and adjuvant therapy uses (RAI remnant ablation in the absence of known distant metastases). Our approach to the method of preparation, the use of a low iodine diet for 7 to 10 days, and the selection of administered activity is consistent with that recommended in both the ATA and NCCN guidelines.

For routine remnant ablation in which the goal is to destroy the residual normal thyroid tissue to facilitate initial staging and follow-up, 50 to 75 mCi of iodine-131 is administered orally following rhTSH stimulation. When adjuvant therapy is planned, 100 to 150 mCi of iodine-131 is given following rhTSH stimulation. Post-therapy whole body scans are routinely performed 5 to 10 days after administration of the therapeutic dose.

Since rhTSH is not approved by the FDA as an adjunct to RAI therapy for distant metastases, most of these patients should still undergo traditional thyroid hormone withdrawal followed by RAI, with the administered activity determined either by whole body RAI clearance studies (dosimetry) or empirically determined activities ranging from 150 to 200 mCi depending on RAI avidity of the tumor, volume of the tumor, age of the patient, and cardiovascular-renal function status of the patient.

**The Role of EBRT in the Treatment of Differentiated Thyroid Cancer**

As with the use of RAI, the lack of prospective randomized clinical trials renders it nearly impossible to provide definitive recommendations with regard to the role of EBRT in the therapy of patients with differentiated thyroid cancer. Most published studies are retrospective analyses of small groups of patients with wide selection bias with regard to patient selection, EBRT technique, EBRT dosing, and irradiated volume. Furthermore, EBRT is usually used in combination with surgical resection and RAI therapy, making it difficult to define the specific benefit of EBRT alone. Most authors agree that EBRT is not required in young patients (under 45 years of age) with microscopic residual disease that is likely to be RAI-avid, but it probably improves locoregional control in the setting of non–RAI-avid, unresectable gross residual disease in patients of any age. However, considerable controversy exists regarding the role of EBRT in the management of microscopic residual disease remaining after...
appropriate surgical intervention in older patients. It is also important to balance the potential for significant EBRT and RAI-associated morbidities (such as mucositis, pharyngitis, xerostomia, thick saliva, skin fibrosis, tracheal stenosis, and esophageal stricture) with the potential benefit in terms of local control without an overall survival benefit.

**EBRT for Gross Locoregional Residual Disease**

EBRT does appear to improve locoregional control rates in high-risk patients who have gross residual non–RAI-avid disease remaining after attempted surgical resection. However, despite obtaining reasonable local control for several years, these high-risk patients often die of progressive distant metastatic disease.

Based on these findings, we consider EBRT to be an integral part of the therapy for most patients with gross disease remaining after attempted surgical resection. EBRT appears to be particularly important in older patients with poorly differentiated thyroid cancers that are likely to be both more aggressive and non–RAI-avid. These tumors tend to be positive on FDG positron emission tomography (PET). Using radiotherapy techniques such as intensity-modulated radiation therapy (IMRT), it is possible to deliver radiation doses as high as 70 Gy to the gross disease, in particular to the PET-avid disease, without exceeding the tolerance of surrounding critical structures. Postoperative EBRT is not usually indicated in the few young patients with an incomplete tumor resection as these tumors are usually still RAI-avid and can often be effectively treated with RAI. Therefore, EBRT in the management of gross residual disease in young patients is reserved for those few patients who have significant local progression after RAI therapy or the uncommon young patient with locally aggressive poorly differentiated thyroid cancer.

These recommendations are consistent with both the updated ATA thyroid cancer guidelines, which recommend that EBRT be considered in patients over 45 years of age with gross residual tumor in whom further surgery or RAI would likely be ineffective, and the NCCN guidelines, which recommend EBRT for gross residual disease if RAI is likely to be ineffective.

**EBRT as Palliative Therapy for Metastatic Lesions**

In addition to its role in the management of locoregional disease, EBRT is important in the palliation of individual metastatic lesions. EBRT has been successfully used to slow disease progression and provide dramatic pain relief in metastatic bone lesions. Brain metastases that cannot be resected can also be treated with EBRT. While lung metastases are not generally amenable to EBRT because of the size, number, and extent of malignant lesions, EBRT can be used to provide symptomatic relief of dominant pulmonary metastases causing either hemoptysis or local compressive symptoms on the airway, heart, or major vessels.

**EBRT as Adjuvant Therapy**

Because of local extension or locoregional metastases, it is often not possible to resect all microscopic thyroid cancer at the time of the initial surgery. For RAI-avid tumors, RAI is used as adjuvant therapy in an attempt to destroy this microscopic residual disease. However, high-risk patients with gross extrathyroidal extension apparent at the time of initial surgery with involvement of the trachea, larynx, great vessels, esophagus, or other major structures often have microscopic residual disease that is likely to develop an early recurrence and unlikely to respond to RAI. Several studies have demonstrated improved locoregional control when EBRT is used following complete resection of all visible disease (often in conjunction with RAI) in older patients demonstrating gross extrathyroidal extension at the time of initial surgical intervention. In our view, minor extrathyroidal extension into surrounding adipose tissue or skeletal muscle noted only on histological evaluation is not adequate justification for the use of EBRT in the absence of other high-risk features. Likewise, we do not believe that lymph node involvement, by itself, is an indication for EBRT since recurrences in cervical lymph nodes can effectively be treated with additional surgery in the future if they do not respond to RAI. In the setting of microscopic extrathyroidal extension and cervical lymph node involvement, we generally consider that the risks and side effect profile of EBRT outweigh the potential benefit of decreasing the risk of a locoregional recurrence that is likely to be adequately treated with additional surgery in the future if needed.

Therefore, we agree with the approach recommended by Brierley et al., the NCCN guidelines, and the ATA guidelines in which EBRT (in addition to surgical resection, RAI, and TSH suppression) is strongly considered for most older patients (> 45 to 50 years) who had a complete surgical resection of all visible non–RAI-avid tumor in the setting of gross extrathyroidal extension into surrounding major structures. This approach is particularly important in patients with poorly differentiated tumors that are unlikely to respond to RAI therapy. In the absence of other very high-risk features, we do not routinely recommend EBRT as adjuvant therapy for patients younger than 45 years of age, for patients with microscopic extrathyroidal extension noted only on histological examination, or for patients with locoregional lymph node involvement in the absence of other very high-risk features.

**Other Considerations Regarding EBRT**

Maximizing locoregional control is paramount in patients in whom EBRT is offered. Therefore, it is important to deliver the highest dose of radiation possible without causing injury to the surrounding normal tissues, eg, spinal cord. This is easily achieved with targeted radiation techniques such as IMRT. Furthermore, image-guided IMRT
(IG-IMRT, or commonly known as IGRT), can improve the precision of radiation delivery by capturing real-time positional films of the treatment volume during radiation delivery. Typically, when radiation is delivered in the postoperative setting, the target volume should include the preoperative tumor volume and the postoperative bed, paying attention to ensure coverage not only of the trachea-esophageal groove and neck to the level of the carina, but also of the anterior mediastinum. The doses typically range from 60 to 66 Gy. When resection is incomplete, the target volume is the same except that in regions of gross disease, the dose of radiation is increased to 70 Gy. PET scan obtained at the time of radiation planning can guide the appropriate dose levels to the target volume.

Conclusions
Risk stratification allows clinicians to select patients at high risk of recurrence and death from thyroid cancer. In addition, by risk stratifying with regard to the likelihood that our initial therapies are likely to be effective (surgical resection and RAI therapy), we can identify patients most likely to benefit from additional therapy with EBRT. In carefully selected high-risk patients, proper use of radiation therapy can improve locoregional control, decrease the risk of clinically significant recurrence, and perhaps even improve disease-specific survival. By carefully weighing the risk of recurrence and death with the potential benefits and risks of additional therapies, the clinician can develop an individualized, risk-adapted management and follow-up plan for patients with differentiated thyroid cancer.

References
9. Tuttle RM, Lopez N, Leboeuf R, et al. Radioactive iodine administered for thyroid remnant ablation following recombinant human thyroid stimulating hormone preparation also has an important adjuvant therapy function. Thyroid. 2010;20(3):257-263.