

Part IV
Thyroid Cancer

Introduction

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The cases in this section demonstrate multiple aspects concerning the approach to the diagnosis and treatment of thyroid nodules and thyroid cancer. These specific topics were chosen because of their frequency or their possible clinical relevance, especially when there is a controversy. In this entire area of thyroid nodules and thyroid cancer there are few controlled studies, and as a result any recommended approach has to be considered subjective to some degree. However, to the extent possible, these chapters have taken into account the appropriate and relevant literature and consensus recommendations. Nonetheless, there may be alternative approaches that are comparable, and clinicians should form their own opinions as to the proper approach in a patient they are seeing.

In Case 11, Drs. Ehrhardt and Bernet recommend a specific, detailed approach to patients with a thyroid nodule. They emphasize that the entire clinical context (history and physical examination) must be considered in conjunction with relevant sonogram and fine-needle aspiration. Certainly, the cornerstone of the approach hinges on the fine-needle aspiration, but this technique also has a false-negative rate of about 1% to 5%. A history of head and neck radiation and family history, for example, can influence the decision to recommend surgery, as can the size of the nodule and patient gender and age. Worrisome thyroid ultrasound characteristics for thyroid cancer include irregular borders, prominent intravascular flow, microcalcifications, and size >4 cm. However, the sensitivity of these radiologic findings is relatively low [1]. These authors review the various risk factors for thyroid cancer recurrence and discuss the controversial topic of micropapillary thyroid cancer [2]. Pellegriti et al [3] studied patients with tumors <1.5 cm and found that about 14% had persistent disease over about 4 years of monitoring.

Ehrhardt and Bernet also review clinical topics regarding the efficacy of iodine 131 (¹³¹I) therapy and of thyroid-stimulating hormone (TSH) suppression in decreasing tumor growth or progression. Although ¹³¹I therapy is considered the standard approach in many patients with differentiated thyroid cancer, there

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are surprisingly few controlled studies evaluating its efficacy. The authors review this topic and report a recent meta-analysis by Sawka et al [4] that concludes that radioactive iodine therapy is useful for most patients with differentiated thyroid cancer, although its benefit is less well demonstrated for low-risk patients. Moreover, they note that studies on this entire topic of ^{131}I therapy are inconsistent. In summary, Drs. Ehrhardt and Bernet have been able to take the common clinical entity of thyroid nodules, an area of sometimes conflicting or inadequate studies (e.g., differentiated thyroid cancer), and have been able to make relevant and appropriate clinical recommendations for physicians confronted with these patients.

In Case 12, Dr. Burch discusses the serious issue of papillary thyroid cancer that is metastatic to bone. I will comment on his case together with the case of Dr. Wexler (Case 14), who discusses follicular cancer that is metastatic to bone and lungs. There are some areas of mutual relevance to both cases. Both emphasize that the early diagnosis and treatment of metastatic thyroid cancer is important and that constant vigilance is appropriate. This translates to trying to identify patients who have a higher risk of developing or having distant metastases, such as patients who are older with larger tumors with more aggressive histology and clinical presentations. These patients in particular should be seen frequently and should have frequent laboratory studies such as serum thyroglobulin levels as well as periodic radiologic studies, to include sonogram of the neck, chest computed tomography (CT) without contrast, and ^{131}I scans (and in specific circumstances additional tests such as positron emission tomography [PET] scan and magnetic resonance imaging [MRI]). The frequency of these procedures depends on the individual patient characteristics. Our view is that every patient who has a sufficiently serious thyroid cancer to receive radioactive iodine should also have a neck sonogram perhaps every 6 months for several years as well as an initial chest CT without contrast and periodic radioactive iodine scans. The frequency of these studies and the duration of this relatively intense monitoring depend on the individual patient context, results, and findings. However, thyroid cancer patients should be monitored for an indefinite time period since recurrences can occur many years after the initial diagnosis and treatment. However, as an aside, I would expect that our modern radiologic techniques and serum thyroglobulin monitoring are capable of detecting thyroid cancer presence many years before it would have been detected by less sensitive techniques. As a result, the likelihood that a patient who has had completely negative studies for many years would suddenly develop recurrent disease must be low.

Burch and Wexler emphasize the importance of staining a biopsy of metastatic tumor for specific thyroid cancer markers (e.g., thyroglobulin and thyroid Transcription factor [TTF-1]) and of addressing this tumor in a multidisciplinary manner with consideration of surgical extirpation and directed radiotherapy. Recombinant human TSH (rhTSH)-assisted thyroid scans help avoid hypothyroidism due to levothyroxine withdrawal, and rhTSH-assisted radioactive iodine therapy also may be beneficial in terms of delivering radioactive iodine therapeutically. However, there are only a few relevant studies utilizing rhTSH in this manner [5]. In thyroid cancer patients, the Food and Drug Administration has recently approved rhTSH-assisted

radioactive iodine ablation of remnant thyroid tissue; the European Union had previously approved this use of rhTSH.

Both Burch and Wexler emphasize the potential utility of zoledronic acid infusions for the treatment of osseous metastatic lesions [6–8]. This approach is routinely utilized for many other cancer sites that metastasize to bone, but to date there are no specific controlled studies in patients with osseous metastases from thyroid cancer. It is believed that osseous metastases proliferate in a similar manner regardless of the original tumor, and that decreasing bone turnover will decrease future osseous events and will help treat the present osseous metastases. It seems prudent at the present time to adjunctively utilize zoledronic infusions for patients with metastatic thyroid cancer to the bone. However, the dose and duration of therapy can only be speculated upon. On the one hand, there is increasing evidence of the possible adverse event of osteonecrosis with the use of bisphosphonates (especially given intravenously) [9], but, on the other hand, its use seems to be of potential benefit in decreasing the growth of present osseous metastases and decreasing new bone events [6–8]. We have reached a compromise of recommending an infusion of zoledronic acid 4 mg per month for 12 months and then decreasing the frequency to every 3 months. Bone mineral density and specific radiologic studies of the osseous metastases (e.g., bone scan, MRI, or CT) as well as bone turnover markers are periodically assessed. Obviously, specific controlled studies in this area are needed.

Monitoring for the presence or development of osteonecrosis is also important. Zoledronic acid infusions should not be used in women of child bearing potential except in very select circumstances and with the patient's understanding and consent. Zoledronic acid is considered Pregnancy Category D in all trimesters. Studies in pregnant women have demonstrated a risk to the fetus; the potential benefits of therapy in a serious or life threatening circumstance must be considered against the possible benefits.

Burch and Wexler also discuss alternative adjunctive methods of addressing metastatic bone lesions. It appears that osseous metastases are more common in follicular cancer than papillary thyroid cancer and that Hürthle cell variant thyroid cancer also has a strong predilection for distant metastases. In addition to extirpation, ^{131}I therapy, and external radiotherapy, newer techniques such as radiofrequency ablation and cryoablation may be beneficial in selected patients [10, 11].

Although it is less common than differentiated thyroid cancer, medullary thyroid cancer has a higher rate of recurrence and progression [12]. In Case 13, Dr. Jonklaas discusses multiple aspects of medullary thyroid cancer, a very complex disease. Medullary thyroid cancer represents approximately 0.5% of all thyroid nodules, and it has become controversial whether to screen routine patients with a thyroid nodule with serum calcitonin levels [13]. Serum calcitonin levels may be slightly elevated due to nonspecific effects (e.g., Hashimoto's thyroiditis), and obviously such a false-negative elevation can lead to possibly unnecessary tests. On the other hand, a fine-needle aspiration does not seem to have a high sensitivity of detecting medullary thyroid cancer, which can be a devastating disease, especially when allowed to progress without thyroidectomy [13]. This dilemma is not resolved,

although it seems that in Europe there is more enthusiasm for routinely measuring serum calcitonin levels in patients with a thyroid nodule.

Medullary thyroid cancer has multiple aspects that require attention. Perhaps about 20% to 30% of all apparently “sporadic” cases of medullary thyroid cancer are actually previously unrecognized familial medullary thyroid cancer. Every patient diagnosed with medullary thyroid cancer should be considered for a total thyroidectomy with a central neck node dissection. Further, a complete diagnostic evaluation should be performed to assess for residual or persistent medullary thyroid cancer, to include CT scans of the entire body and perhaps a PET scan. Specific attention should be directed to the neck and upper chest to try to identify residual disease deposits. Serum calcitonin (and carcinoembryonic antigen [CEA]) monitoring is important. Every patient with medullary thyroid cancer should have a germline *ret* oncogene sequencing (usually white cells), and it is important that all the relevant exons be actually sequenced [12]. Laboratories that only attempt to identify and sequence specific areas that are considered most likely to harbor mutations should be avoided. Even when all of the relevant exons are entirely sequenced there is a chance of still missing a mutation, potentially either due to a technical or laboratory error or because the mutation is outside the known frequently sequenced exons. If there is a strong suspicion that the disease is familial, a new blood sample should be sent for sequencing, and if still negative, it would be appropriate to ask the laboratory supervisor for recommendations regarding additional exon sequencing. For example, at present, exon 8 is not routinely sequenced by most commercial laboratories [14, 15], but there are now identified mutations in this area. Jonklaas wisely recommends that even if the *ret* oncogene is negative, it is reasonable to periodically measure serum calcitonin levels and perform neck sonograms in family members depending on the individual case context.

Jonklaas also reviews the literature regarding genotype-phenotype correlations, and she makes specific recommendation regarding “prophylactic” thyroidectomy in family members who have the identical *ret* oncogene mutation as the index patient. She also discusses some of the clinically relevant ethical issues surrounding familial medullary thyroid cancer. Multiple ethical issues can arise including, as she presents, a mother with medullary thyroid cancer and a known *ret* oncogene mutation who does not want her children either tested for medullary thyroid cancer or to have clinically relevant studies (e.g., thyroid sonogram and serum calcitonin level). Unfortunately, outside of a thyroidectomy with central compartment dissection, there are no known specific systemic therapeutic options for patients with residual, recurrent, progressive, or metastatic medullary thyroid cancer. Some clinicians do recommend external radiotherapy to the neck area following thyroidectomy of a potentially aggressive medullary thyroid cancer or if known neck disease remains. Targeted specific molecular therapy may show promise in patients with aggressive or metastatic thyroid cancer [16–19].

Summarizing each of these four interesting chapter topics and discussions, specific long-term prospective controlled studies are needed to direct improved clinical care. Until such studies are performed, we will continue to make the best recommendations possible for these important clinical entities.

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