Chapter 14
Follicular Thyroid Carcinoma with Pulmonary and Osseous Metastases

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Objectives

1. Discuss the appropriate screening modalities for osseous metastases in the setting of follicular thyroid carcinoma.
2. Discuss the role of biopsy in the evaluation of osseous metastases.
3. Discuss the role and efficacy of ^{131}I therapy in follicular thyroid carcinoma with osseous metastases.
4. Discuss the efficacy and side effects of intravenous bisphosphonates in the treatment of osseous metastases.
5. Discuss the role and efficacy of novel therapies (i.e., radiofrequency ablation, external beam radiation, and cryotherapy) in the treatment of osseous metastases.
6. Discuss the appropriate monitoring strategies for patients with follicular thyroid carcinoma and osseous metastases.

Case Presentation

A 72-year-old man underwent a total thyroidectomy in July 1989 for Hürthle cell thyroid carcinoma, which invaded lymphatic and venous channels at distant sites from the mass. A cervical lymph node also revealed metastatic involvement. He subsequently received iodine 131 (^{131}I) 168.7 mCi in August 1990, and a posttherapy whole-body scan was negative for distant metastases, although there was neck bed uptake. In November 1991, he received an additional 105 mCi 131–1 for Persistent thyroglobulin elevation. In December 1995, a left anterior cervical lymph node was palpated and a biopsy revealed Hürthle cell carcinoma. He underwent removal of this node and a third course of ablation radioiodine (208 mCi) therapy in January 1996. In 2000, on thyroid hormone suppression, his thyroglobulin was 22.3 ng/mL and thyroglobulin antibodies were negative. Following withdrawal of

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thyroid hormone, his thyroglobulin was 30.4 ng/mL and thyroid-stimulating hormone (TSH) was 63 uU/mL. A computed tomography (CT) scan of the neck and chest in June 2000 showed postsurgical changes in the left thorax related to a distant pulmonary operation for tuberculosis, but no masses or metastatic lesions were found. His past medical history is notable for tuberculosis as a teenager that required pulmonary surgery and osteoporosis. He has no allergies, and his medications include levothyroxine 150 μg daily, alendronate 70 mg once weekly, simvastatin 20 mg daily, aspirin 81 mg daily, and calcium carbonate 500 mg twice daily. He does not smoke or drink alcohol. He is retired and has no family history of thyroid disease.

On recent physical examination, blood pressure was 130/70 mm Hg, pulse 80/minute and regular, and respirations 18/minute. The thyroid scar was well healed and there were no palpable masses. The neck also had a well-healed scar in the left submandibular area without masses.

When the patient underwent a positron emission tomography (PET) scan in October 2000, two focal abnormalities highly suspicious for recurrent thyroid carcinoma were found. One focus was located in the left neck inferior to the angle of the mandible and the second was located in the superior mediastinal region involving the anterior aspect of one of the upper thoracic vertebral bodies. A magnetic resonance imaging (MRI) study of the neck and spine in November 2000 revealed an area (1.5×1.0 cm) of abnormal soft tissue to the left of the hyoid bone corresponding with the area of increased activity on the PET scan and a 1.0-cm focal lesion in the anterior and superior aspect of the T3 vertebral body most consistent with metastasis. A CT-guided biopsy of the neck mass in November 2000 detected Hürthle cell carcinoma, which was surgically resected in December 2000. The patient underwent ^{131}I dosimetry and was treated with 344 mCi of ^{131}I in March 2001. Posttherapy scanning demonstrated at least three foci of uptake in the chest compatible with metastatic disease.

In February 2002, a recombinant human TSH (rhTSH)-stimulated total body ^{131}I metastatic survey showed no evidence of abnormal ^{131}I uptake in the thyroid bed or neck. The previously noted abnormal foci of ^{131}I uptake in the lungs was no longer appreciated. The focal uptake in the midline of the lower chest/upper abdominal region was persistent, but less intense compared to prior studies.

In September 2002, his thyroglobulin rose from 50 to 98 ng/mL while on levothyroxine. The patient received 328 mCi 131-I using dosimetry, and posttherapy scanning demonstrated multiple metastases to the lung. A new left-sided cervical lymph node (1.4×1.0 cm) was seen on MRI in December 2002. The MRI continued to demonstrate a stable T3 vertebral body lesion, consistent with, but not specific for metastatic disease, without evidence of vertebral collapse. In an effort to achieve diagnostic certainty, the patient underwent a vertebral body biopsy that revealed metastatic Hürthle cell carcinoma. A whole-body bone scan was negative except for degenerative changes. The patient then received radiofrequency ablation of the T3 bony lesion. In light of the osseous metastasis, the patient was switched from alendronate 70 mg once weekly to zoledronic acid 4 mg intravenously every month.

In early 2004, the patient suffered an asymptomatic collapse of the T3 vertebral body without evidence of an enlarging mass or impingement of the spinal canal. A PET scan in February 2004 showed activity in the T3 vertebral body with a standardized uptake value (SUV) of 5.8 (SUV was 19.8 prior to radiofrequency ablation), a smaller focus in the posterior lung base, left mid-lung area of activity with an SUV of 3, and there was a focus in the abdominal area with an SUV of 2.7, but CT scans were unable to localize any specific abnormalities corresponding to the PET scan lesions. In July 2004, a repeat PET scan revealed interval worsening of the hypermetabolic focus of the T3 vertebra and a subtle new area of hypermetabolism in the T6 vertebra. These lesions were treated with cryoablation therapy. In January 2005, follow-up CT and MRI scans showed stability of his pulmonary and spine disease. Further imaging with CT and MRI in December 2005 and April 2006 showed stable disease except for the appearance of a new 1.0×2.0 cm nodule in the left lower lobe of the lung. An April 2006 ultrasound of his neck showed no evidence of disease.

How the Diagnosis Was Made

Thyroid nodules often present for clinical attention when noted by the patient, as a finding during routine physical examination, or as an incidental finding during a radiologic procedure. In recent years, the use of thyroid scintigraphy to assess thyroid nodules has become less common. Fine-needle aspiration (FNA) biopsy is now the accepted standard procedure performed in the diagnostic workup of thyroid nodules, and it is the most accurate method for selecting patients needing thyroid surgery [1]. High-resolution thyroid ultrasonography, which provides anatomic definition superior to thyroid scintigraphy, can be used to delineate the nodular makeup of the thyroid gland and can be used in conjunction with FNA to aid in performing the thyroid biopsy. Before proceeding with FNA biopsy, thyroid function should be assessed in all patients with thyroid nodules. If the serum TSH concentration is low, indicating overt or subclinical hyperthyroidism, the possibility that the nodule is "hot" or autonomous is increased and thyroid scintigraphy would be the logical next step. In those with a normal or high TSH, nodule evaluation with FNA biopsy should be the next step.

Fine-needle aspiration is a simple and safe procedure in which tissue samples are obtained for cytologic examination using small (23- to 27-gauge) needles. Often, adequate samples can be obtained in more than 90% of aspirations of solid nodules, although the success rate in degenerative nodules or cysts is lower. Ultrasound-guided FNA can be used for those nodules that are technically difficult to aspirate using palpation methods alone. The results of cytologic examination of samples obtained by FNA are usually reported as nondiagnostic, benign, suspicious or indeterminate, or malignant. It is important to realize that follicular and Hürthle-cell cancers cannot be distinguished cytologically from follicular and Hürthle-cell adenomas. As a result, approximately 15% to 20% of all biopsies are classified

as suspicious or indeterminate (or follicular neoplasm) [2]. Approximately 10% to 20% of all suspicious lesions that are surgically removed are ultimately found to be follicular carcinomas. FNA biopsy is a highly accurate procedure with false-negative rates ranging from 0% to 5% and false-positive results occurring in fewer than 5% of patients in experienced facilities.

Lessons Learned

How to Screen for Bone Metastases in Follicular Thyroid Carcinoma

Follicular thyroid cancer accounts for fewer than 15% of all differentiated thyroid cancers, but has an incidence of bone metastases of 7% to 20% [3]. The appearance of skeletal metastases is considered an ominous sign and often predicts a poor survival; mean survival has been estimated at 4 years. Detection of distant metastases may be difficult, and ^{131}I scanning has relatively poor sensitivity. X-rays and bone scintigraphy are often used in the evaluation of skeletal metastases. However, these imaging techniques detect disease only when more than 50% of bone has been destroyed, and there is no prospective study assessing their individual sensitivity and specificity in detecting osseous metastases from thyroid cancer [4]. Bone scintigraphy often detects skeletal metastases earlier than they appear on standard x-rays, but only if there is a significant osteoblastic component. Magnetic resonance imaging is superb for imaging the medullary component of bone and detailing the intraosseous and extraskeletal extent of disease. Computed tomography, on the other hand, is valuable in imaging for cortical erosion and subclinical fracture in osseous metastases. In practical terms, if a patient has pulmonary metastases or there is a clinical suspicion of osseous metastases, it seems prudent to consider obtaining a metastatic skeletal survey or a bone scan. However, once a bone lesion at a particular site is suspected, a directed MRI or CT scan is most appropriate to better define the lesion(s). An MRI or CT is particularly helpful in planning any surgical approaches to destructive skeletal metastases [4].

In a recent study [5], PET, whole-body scan with technetium-99m sestamibi (Tc-MIBI) and posttherapy ^{131}I imaging were compared under TSH stimulation for their ability to detect distant metastases. Only three of 19 patients had follicular thyroid cancer, but PET was found to be superior to Tc-MIBI body scan and posttherapy ^{131}I scan in the sensitivity of detecting distant spread. The 19 patients had 32 isolated lesions (10 lymph node, 15 lung, six bone, and one muscle) confirmed by histopathology or other imaging studies (x-ray, ultrasound, CT, MRI, and bone scan). PET detected 81.3%, MIBI 62.5%, and ^{131}I 68.8% of the total lesions. Lung metastases were detected in 73.3%, 46.7%, and 66.7% of cases, respectively. When it came to bone metastases, however, all imaging modalities were comparable, detecting about 83% of lesions.

Role of Biopsy in the Diagnosis of Bone Metastases

Even in situations where the primary carcinoma is known, it is often recommended to biopsy a metastatic lesion to bone, especially when the bone metastasis is the initial evidence of recurrence [6]. Biopsy is probably unwarranted in situations of multiple relapses when a previous biopsy has already proven there are osseous thyroid metastases. A needle biopsy is recommended for metastatic disease to the spine or pelvis. Once the biopsy specimen has been obtained, sections should be carefully examined to confirm the identity of the lesion and whether it represents a metastatic process. The osseous lesion should be examined cytologically by an experienced pathologist. Special stains for thyroid transcription factor 1 (TTF-1), thyroglobulin, as well as cytokeratin and calcitonin should be utilized. In addition, relevant supplementary stains, such as prostate-specific antigen (PSA), should be performed as clinically indicated.

Our approach is to recommend an osseous biopsy for the first such tumor even if a patient is known to have thyroid cancer, since it is still possible for another tumor to be present. However, when one bone biopsy has confirmed the origin of the tumor as thyroid, we do not necessarily recommend biopsy of each subsequent lesion except in special situations. It should also be noted that the cytologic characteristics of the osseous thyroid cancer metastases may not mimic those of the original thyroid cancer. That is, it is frequently difficult to determine the precise type of thyroid cancer (e.g., papillary, follicular, or Hürthle cell) from a bone biopsy, and the most important issue is determining the site of origin of the tumor.

Role and Efficacy of ^{131}I in Treating Pulmonary and Osseous Metastases

Prospective, randomized studies of ^{131}I in the treatment of lung and bone metastases from follicular thyroid carcinoma are lacking. Hürthle cell thyroid carcinoma is classified as a subtype of follicular thyroid cancer. Hürthle cell carcinoma is more aggressive than well-differentiated follicular cancer and it tends not to accumulate iodine as well—features that make Hürthle cell more difficult to treat with ^{131}I. The best available data regarding this topic come from retrospective studies. A recent retrospective analysis of 2200 patients with differentiated thyroid carcinoma identified 394 patients with lung or bone metastases [7]. Twenty-eight patients had well-differentiated follicular carcinoma, and 173 patients had less differentiated follicular carcinoma. Most patients underwent total thyroidectomy and received ablative therapy with ^{131}I. One third received postoperative external beam radiation therapy after surgery to the neck. Patients who had detectable lung or bone disease on posttherapy scanning received an additional 100 mCi of ^{131}I 3 months after a standard initial ablation dose of 100 mCi of ^{131}I. The same occurred for patients with a detectable thyroglobulin (Tg) during levothyroxine (LT_4) therapy or Tg >5 ng/mL off LT_4 therapy. Patients who had radiographically proven bone metastases also received

approximately 3000 rad of external beam radiation treatment to the affected region in association with ^{131}I therapy.

Patients with less differentiated follicular cancer had lower survival rates than those with well-differentiated papillary or follicular carcinoma. Positive ^{131}I uptake was associated with improved prognosis. The risk of death was greatest in those with macronodular pulmonary metastases or multiple bone metastases. Ten-year survival was 96% in those younger than 40 years old with normal chest x-rays and only 7% in those 40 years old and older with macronodular pulmonary or multiple bone metastases. Survival was 63% for all other patients. For those who had a complete response, survival was 96% at 5 years, 93% at 10 years, and 89% at 15 years. Without a complete response, survival was 37%, 14%, and 8%, respectively. Response to ^{131}I therapy was improved the earlier the disease was detected and treated. In addition to ^{131}I whole-body scans, Tg measurement is an important and sensitive marker for detecting metastatic disease. Although prolonged survival was not proven to be linked to ^{131}I treatment alone, those patients who survived more than 15 years after the detection of metastases had all been treated with ^{131}I alone or in combination with external beam radiation therapy if appropriate.

In the most recent report from the same group of investigators in the immediately preceding study mentioned above, researchers were able to distinguish survival rates among 444 patients with distant metastases from papillary and follicular thyroid carcinoma [8]. Among those who had radioiodine uptake, 20-year survival was 33% versus only 3% at 10 years for those without radioiodine uptake. Those who had lung metastases had 49% survival at 20 years, whereas those with bone metastases had 20-year survival of only 8%. For those with both lung and bone metastases, 20-year survival was 9%. Survival was not impacted if neck recurrences occurred or if metastases were discovered early or late in the course of a patient's care.

Efficacy of IV Bisphosphonates in Treatment of Bone Metastases

As just discussed, bone metastases from follicular thyroid cancer, particularly those that are less differentiated, respond poorly, if at all, to traditional treatment regimens that include ^{131}I. Since bone metastases destroy bone architecture through a local osteolytic process, some investigators have proposed using inhibitors of osteoclast activity (i.e., bisphosphonates) to slow or prevent the skeletal complications of osseous metastases. Although studies in thyroid cancer patients are quite limited, one protocol enrolled 10 patients with thyroid cancer and administered pamidronate 90 mg IV every month for 1 year [9]. Patients who received pamidronate reported significantly less bone pain by visual analogue scale, improved performance status, and a beneficial impact on quality of life. Only two of 10 patients demonstrated a partial radiographic response to therapy. Although the amount of narcotic pain medication used by patients did decline over time, the change was not statistically significant. A possible explanation for this discordant finding is that while the pain

score was lower at the end of the study, it had begun to rise again at 9 to 12 months of the study from its nadir at 3 months. Side effects, which can include fever, myalgias, and electrolyte abnormalities (mainly hypocalcemia), were mild and short-lived.

In a recent study, zoledronic acid (4 mg), a newer-generation bisphosphonate, was compared in a phase III randomized trial with pamidronate (90 mg) in breast cancer patients. Zoledronic acid significantly reduced the risk of developing a skeletal-related event (SRE), defined as a pathologic fracture, spinal cord compression, radiation therapy, or surgery to bone by an additional 20% versus 9% for pamidronate [10]. Furthermore, zoledronic acid was at least as effective as pamidronate in reducing the proportion of patients with one or more SRE and in delaying the onset of SREs. Moreover, a retrospective subset analysis of patients with one or more osteolytic lesion proved zoledronic acid more effective than pamidronate in reducing the risk and delaying the onset of SREs. Although there is no evidence to support improved survival rates, because this therapy is easy to administer and so well tolerated, it argues for the widespread adoption of these agents (with the evidence favoring zoledronic acid) in the management of those patients with bone metastases from thyroid cancer. In our center, because of the ease and rapidity of administration, as well as a growing body of literature demonstrating enhanced efficacy, we favor using zoledronic acid 4 mg intravenously on a monthly basis for 1 year followed by quarterly infusions indefinitely.

No discussion of bisphosphonates is complete without addressing the concern of osteonecrosis of the jaw (ONJ). The best review of this topic to date examined all case reports and case series of patients with bisphosphonate-associated ONJ published in Medline from 1966 to January 2006 [11]. Osteonecrosis of the jaw is a recently described side effect of bisphosphonate therapy. Patients with multiple myeloma and metastatic carcinoma to the skeleton who are receiving intravenous, nitrogen-containing bisphosphonates (e.g., pamidronate, zoledronic acid) are at greatest risk for ONJ (94% of published cases), but ONJ has been reported to occur with all of the available oral bisphosphonates as well (e.g., alendronate, risedronate, ibandronate). Eighty-five percent of affected patients have had multiple myeloma or metastatic breast cancer and 4% have had osteoporosis. The estimated prevalence of ONJ in patients with cancer is 6% to 10%, but the prevalence in those with osteoporosis is unknown. The mandible is more commonly affected than the maxilla (2:1 ratio), 60% of cases are preceded by a dental surgical procedure, and the remaining 40% related to infection or trauma. Oversuppression of bone turnover is thought to represent the predominant mechanism for the development of this condition, but there may be other contributing factors such as preexisting dental infection, radiation exposure to the jaw and a history of receiving chemotherapy. A recently issued recommendation calls for the eradication of all sites of potential jaw infection before bisphosphonate therapy is begun to lessen the need for subsequent dentoalveolar surgery. Conservative debridement of necrotic bone, pain control, infection management, use of antimicrobial oral rinses, and withdrawal of bisphosphonates are thought to be preferable to aggressive surgical measures for treating this condition.

Novel Modalities in the Treatment of Bone Metastases

Traditional therapy for differentiated thyroid cancer includes total thyroidectomy, removal of suspicious lymph nodes in the central compartment, and ^{131}I treatment. In cases of local or distant relapse, further surgery, ^{131}I, or external beam radiation therapy may be required. If none of those modalities is successful, novel treatments may be instituted to control the disease burden.

External beam radiation therapy (EBRT) is a significant component of the therapeutic options available to patients with skeletal metastases from thyroid cancer. The main objective of EBRT is to alleviate pain and neurologic complications from osseous disease. Although data on this subject as it specifically relates to thyroid cancer are lacking, it is thought that approximately 70% of patients experience pain relief with palliative EBRT [12]. Patients often report subjective improvement in their symptoms within 2 to 3 days, but some report improvement up to a month after therapy. EBRT must be tailored to the patient's life expectancy, anatomic site of the skeletal metastasis, and the size of area to be treated. EBRT is often implemented after surgical treatment of pathologic fractures or impending fractures to improve the patient's functional status. Finally, EBRT is undergoing investigation as to whether its integration with newer therapeutic modalities such as vertebroplasty and radiofrequency ablation may provide additional benefit to patients.

Radiofrequency ablation (RFA) and ethanol (EtOH) injection are relatively new, minimally invasive techniques that have been used as adjuvant therapy in other malignancies such as hepatocellular carcinoma or other malignancies that have metastasized to the liver. Radiofrequency ablation is thought to cause focal coagulative necrosis of diseased tissue in a specific region of interest. The role of these techniques in thyroid cancer is just beginning to be explored. Radiofrequency ablation has been found to reduce pain from thyroid cancer bone metastases, but data are lacking in terms of long-term resolution of disease at the treated sites.

One study recently evaluated the RFA and EtOH experience in local and focal distant metastases [13]. In this study, 16 patients underwent RFA treatment of biopsy-proven recurrent well-differentiated thyroid cancer in the neck. Under conscious sedation and local anesthesia and using ultrasound guidance, the radiofrequency (RF) electrode was connected to an RF generator and the lesions were treated with the maximum allowable current for approximately 2 to 12 minutes. The ultrasound-detected appearance of microbubbles and the achievement of a cytotoxic temperature of 50°C within the mass were accepted together as the end point of the treatment procedure.

Radiofrequency ablation works by inducing focal coagulative necrosis to eradicate small areas of tissue in a controlled fashion. Microbubbles occur from the local formation of water vapor as RF energy boils tissue within the treatment region and the temperature within the mass then achieves the cytotoxic threshold temperature of 50°C. Side effects of RFA included hoarseness (most likely thermal injury to the recurrent laryngeal nerve) and skin burns (most likely due to protrusion of the proximal portion of the electrode tip through the skin during the ablation procedure). Self-limited neck swelling and regional discomfort were reported in all 16 patients but resolved within 1 to 2 weeks.

Four patients underwent RFA for focal distant metastases. Three patients had solitary bone metastases and one patient had a solitary pulmonary metastasis. Radiofrequency ablation was performed in the same manner as described above. Six patients underwent EtOH ablation, under local anesthesia and with ultrasound guidance, of biopsy-proven recurrent thyroid cancer in the neck. EtOH is thought to induce tissue necrosis as a result of cellular dehydration and protein denaturation. Of the three patients treated with RFA for bone metastases, one presented at 1 year of follow-up with persistent disease. This individual was retreated with RFA and ^{131}I and subsequent ^{131}I whole-body scanning was negative. A second patient had persistent disease at the treated site and developed a new osseous metastasis. The third patient had biopsy-proven absence of disease at the treated site, and subsequent ^{131}I whole-body scans have been negative through 53 months of follow-up. The patient with the pulmonary metastasis had no evidence of uptake in the lung fields on follow-up ^{131}I whole-body scanning despite persistent uptake in the neck after multiple rounds of ^{131}I treatment.

This study suggests that RFA and EtOH can achieve resolution of solitary lymph node metastases from thyroid cancer in some patients. The data for bone metastases is less robust, with only one of the three treated patients showing a response at the focal distant site. RFA and EtOH have advantages and disadvantages. RFA produces a larger area of lesion destruction, and its energy delivered can be finely modulated. Therefore, RFA can be used to treat a larger region of interest than EtOH, but RFA may be more likely to cause local tissue injury from its thermal effect. Both of these techniques should be used carefully, especially when treating disease in the lateral aspect of the central compartment where the recurrent laryngeal nerve might be quite susceptible to the damaging treatment effect. This comment applies especially to ethanol injection, as extravasation can be extremely toxic to local tissues causing significant fibrosis. These techniques should only be used by experienced individuals.

The role of adjuvant EBRT in patients with locally advanced follicular thyroid cancer has been studied only retrospectively [14]. The efficacy of EBRT to the thyroid bed or to the upper cervical and superior mediastinal lymph nodes is uncertain, with some studies showing no benefit or even worse outcomes compared with those who did not receive EBRT; survival appears to be unchanged with EBRT. Of course, it is possible that only the more serious lesions were those chosen for treatment. However, some studies have shown improvements in local recurrence and disease-specific survival if EBRT was provided to those with papillary thyroid cancer but not to those with follicular thyroid cancer. Nonetheless, some centers offer EBRT to high-risk patients (age >45 years and resectable extrathyroidal disease) in conjunction with ^{131}I treatment. If EBRT is given, it is usually limited to the thyroid bed, but it can be tailored to the specific anatomic site of disease.

Newer techniques such as conformal radiotherapy intensity modulate radiation therapy (IMRT) can allow for more precise radiotherapy delivery to sites outside the thyroid bed, where more normal tissue can be spared and acute and late toxicity may be mitigated [15]. In those with solitary bone metastases for example, 50 Gy is usually given in several fractions over 4 weeks, but special caution must be taken to avoid delivering high doses (limited to 40 Gy) to the spinal cord. Side effects of EBRT include skin erythema, dry desquamation, and mucositis of the pharynx and

esophagus. Long-term sequelae include skin hyperpigmentation and esophageal and tracheal stenosis. In practical terms, patients receiving EBRT to the neck area almost invariably have some difficulty swallowing and neck pain during the last several weeks of therapy. We recommend EBRT to the neck for those patients with locally aggressive tumors, particularly those with residual disease invading the trachea.

Another adjuvant therapeutic modality for treating skeletal metastases is cryotherapy. Cryotherapy used to be performed by introducing liquid nitrogen into the tumor bed. Although this technique was somewhat successful, side effects included the formation of nitrogen emboli, bone fractures secondary to local necrosis of skeletal tissue, and damage to local neurovascular structures. More recently, cryotherapy has been performed using an argon-based system that allows for the controlled formation of ice around a metallic probe [16]. The technique is computer controlled and allows for the protection of surrounding structures. It is known that cell death occurs within 5 mm of the ice formed by the metallic probe if the temperature achieved is less than −40°C on two sequential cryotherapy cycles. In one study, 27 patients underwent argon therapy (14 patients had metastatic bone disease). No one suffered neurologic injury, and after 2 years only two of the surviving patients had a recurrence (none from the metastatic group). Additionally, there were no pathological fractures [16]. In light of these data, cryotherapy appears to be a useful addition to the therapeutic armamentarium available for the treatment of osseous metastases of thyroid carcinoma with minimal risk to local surrounding structures. Of course, definitive studies in this area are warranted.

Monitoring Strategies for Follicular Thyroid Carcinoma and Osseous Metastases

Diagnostic Tools for Follow-Up After Initial Treatment

Serum Tg Determination

Thyroglobulin is a specific and sensitive tumor marker for follow-up of patients with differentiated thyroid cancer. Serum Tg should be measured using a sensitive immunoradiometric assay (IRMA), but when using such methods, the presence of anti-Tg antibodies in the circulation may interfere with the assay, leading to false-negative serum Tg determination. Thus, the presence of anti-Tg antibodies must be ruled out by direct measurement of anti-Tg antibodies. Since Tg is produced by both normal and neoplastic thyroid cells and its production is under TSH control, serum TSH (and thyroglobulin antibodies) should always be measured at the time of Tg determination. After total thyroidectomy and radioiodine ablation, the Tg level should be undetectable (usually less than 0.2 ng/mL), and any detectable level should alert the clinician to the possibility of recurrence. In patients with a negative posttreatment ^{131}I whole-body scan (^{131}I WBS) other diagnostic imaging procedures (CT, MRI, or PET) should be performed to detect residual disease.

Management of Patients with Recurrent or Metastatic Disease

Remission can be obtained in about two thirds of patients with neck recurrence and in one third of those with distant metastases.

Lung Metastases

In the case of ^{131}I uptake, treatment consists of ^{131}I administration following prolonged withdrawal or rhTSH. A ^{131}I WBS performed about 4 to 10 days after administration of radioiodine in combination with Tg monitoring provides assessment of response to treatment. Although controversial, we also perform a pretherapy ^{123}I scan to detect areas of radioiodine uptake that were not known previously. There is no maximum limit for the cumulative ^{131}I activity that can be given to patients with persistent disease, but consideration should be given to the risks of xerostomia, increased lacrimation, neck pain, and bone marrow suppression.

Bone Metastases

Bone metastases should be treated by a combination of surgery, ^{131}I treatment if uptake is present in the metastases, and EBRT to eliminate the disease burden or in an effort to control it [3, 14, 17]. Other local treatment procedures such as the use of embolization or cement injection have been reported to be helpful in some patients.

Our Approach

Given the paucity of controlled prospective studies in thyroid cancer patients (especially with distant metastases), there is no single approach with widespread consensus. Our approach is generally as follows: total thyroidectomy, pretherapy radioiodine scan (with ^{123}I), and ^{131}I therapy for all patients with follicular thyroid cancer and for patients with papillary thyroid cancer who have lesions greater than 1 cm in size. For a select group of other patients, those with a family history of papillary thyroid cancer or tall-cell variant cancer, for example, we also recommend total thyroidectomy, 123-I scanning, and 131-I therapy. All patients who receive radioiodine therapy also have initial staging studies to include ultrasonography of the neck and CT of the chest without contrast. If there is no evidence of residual or recurrent disease, these patients will be followed with periodic lab tests and neck sonograms. Generally, the lab tests are performed every 4 to 6 months and our goal TSH is usually 0.1 μU/mL or less and serum thyroglobulin less than 0.2 ng/mL. The goal TSH depends on the status of the patient and those with potentially more aggressive disease or metastatic disease have a goal TSH of less than 0.01 μU/mL. Cardiac assessment is performed as appropriate, and bone mineral density is measured periodically.

Approximately 1 year after ^{131}I therapy, another TSH-stimulated radioiodine scan is performed in conjunction with measurement of a serum thyroglobulin level.

If there is no evidence of disease, then the patients are followed with lab tests and thyroid sonograms at 6-month intervals for about 5 years and then at yearly intervals, depending on the clinical context. A stimulated serum thyroglobulin level is obtained periodically, every 1 to 2 years for the first 5 years. At the end of 5 years, when there is no evidence of recurrent or residual disease, the frequency of these tests are decreased but are maintained for an indefinite period of time. In the course of follow-up, if a patient has known or suspected distant metastases or an inappropriately elevated serum thyroglobulin level, additional studies to include chest CT (without contrast), neck MRI, PET scans, and assessment for osseous metastases (e.g., bone scan or skeletal x-ray survey) are performed. If a specific lesion, for example in the bone, is suspected or identified, directed MRI or CT scans are performed and, as noted, a biopsy is considered.

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Multiple-Choice Questions

1. A 58-year-old man with a history of follicular thyroid cancer presents to his physician for routine follow-up. The patient underwent a total thyroidectomy 2 years ago and received an initial ablative dose of 122 mCi ^{131}I. His postoperative thyroglobulin (Tg) was 35 ng/mL (Tg antibody negative) and was undetectable on thyroid hormone withdrawal 1 year ago. The patient has been feeling well and has been taking levothyroxine 175 μg daily. His TSH is 0.089 μU/mL, and he asks you what additional tests need to be performed as part of his care. Which of the following would be the best recommendation for this patient?

   A. Positron emission tomography (PET) scan
   B. Computed tomography (CT) scan with contrast of neck and chest
   C. Plain radiograph (x-ray) of chest
   D. Thyroid hormone withdrawal with measurement of Tg and Tg antibodies
   E. Thyroid hormone withdrawal and administration of high dose ^{131}I therapy

   Answer: D. Explanation: Measurement of thyroglobulin (and thyroglobulin antibodies), either with thyroid hormone withdrawal or with recombinant human TSH administration, is the most sensitive means to detect residual well-differentiated thyroid cancer in a low-risk individual.

2. A 43-year-old woman was found to have follicular thyroid cancer 1 year ago. She underwent total thyroidectomy and received 100 mCi ^{131}I as an ablation dose at that time. She returns for follow-up now, feeling well. Her physical examination is unremarkable except for a well-healed thyroid scar without palpable masses. Her Tg level on suppressive doses of levothyroxine is 5.6 ng/mL. A thyroid ultrasound is normal. During recombinant human TSH stimulation, the patient's Tg level rises to 15.8 ng/mL, but her ^{131}I whole-body scan is negative. Which of the following is the best test to detect metastatic disease in this patient?

   A. Whole-body bone scan
   B. PET scan
   C. Thyroid hormone withdrawal followed by ^{131}I whole-body scan
   D. Sestamibi (MIBI) scan
   E. MRI of neck, chest, abdomen, and pelvis

Answer: B. Explanation: In a recent study, PET had the ability to detect more distant metastatic lesions than the other listed imaging modalities. PET, MIBI, and ^{131}I were equally sensitive in detecting bone metastases.

3. A 78-year-old man has a history of metastatic follicular thyroid carcinoma. He has been treated with total thyroidectomy and ^{131}I therapy on multiple occasions for detectable disease in the neck and chest. Despite this, the patient's Tg level has been rising steadily over the last 5 years and is now 43 ng/mL on levothyroxine suppression. He has begun to complain of lower back pain for several weeks, and on recent evaluation the patient was found to have a biopsy-proven skeletal metastasis of the L4 vertebra from thyroid cancer. He received EBRT but wants to know if there is anything else that can be done. Which of the following would you recommend?

   A. High-dose ^{131}I therapy
   B. Whole-body EBRT
   C. Intravenous zoledronic acid monthly for at least 1 year
   D. Intravenous pamidronate twice monthly for at least 1 year
   E. Intraosseous ethanol injection into lumbar spine

   Answer: C. Explanation: Intravenous zoledronic acid may reduce pain and skeletal-related events in patients with metastatic thyroid cancer to bone. Recent data suggest that zoledronic acid may be more effective than pamidronate, and it is more rapidly and easily administered in a clinical setting.