Approach to the Thyroid Cancer Patient with Extracervical Metastases

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Patients with distant, or extracervical, metastases from differentiated thyroid cancer require multimodality diagnostic, therapeutic, and monitoring approaches. Whereas cure is the initial goal, especially in those with small, radioiodine-avid pulmonary metastases, improved survival and management of symptoms become the primary objective in many patients with persistent disease, especially those with bone metastases. Levothyroxine therapy with suppression of serum TSH is a primary therapy in all patients with advanced differentiated thyroid cancer, and this therapy has been shown to improve overall survival and slow disease progression. Radioiodine is also an important systemic therapy for those patients with radioiodine-avid disease who respond to this targeted therapy. In this review, we compare standard fixed-dose radioiodine therapy *vs.* the dosimetric approach. Directed therapy such as external beam radiotherapy, surgery, and embolization is generally considered for large or painful lesions. Careful collaborations with multiple specialties through tumor boards or other mechanisms help to optimize complex management decisions in these patients with advanced thyroid cancer. Multimodality monitoring focused on the organ of interest such as pulmonary [computed tomography (CT)], bone (magnetic resonance imaging, CT, bone scan), and brain (CT, magnetic resonance imaging) metastases as well as general metastatic surveillance (bone scan, ^{18}F-fluorodeoxyglucose-positron emission tomography) aid decision making about careful monitoring *vs.* directed or systemic therapy. ^{18}F-fluorodeoxyglucose-positron emission tomography imaging has an additional role in patient prognosis and guiding directed therapy for fluorodeoxyglucose-avid lesions. Patients with asymptomatic, stable, radioiodine-resistant metastases may be carefully monitored for disease progression. Patients with symptomatic disease should receive directed therapy with the goal of symptom relief. Patients with progressive metastatic disease should be considered for clinical trials or targeted systemic therapy (sorafenib or sunitinib), although these agents are not Food and Drug Administration (FDA) approved for patients with thyroid cancer. The goals of therapy for patients with extracervical metastases should be to improve survival, relieve symptoms, and decrease the morbidity of disease progression and limit the morbidity associated with therapy. (*J Clin Endocrinol Metab* **95: 987–993, 2010**)

Thyroid cancer is the fifth most comm on cancer diagnosis in women, equal to non-Hodgkin lymphoma and melanoma, and approximately 300,000 patients in the United States are currently living with thyroid cancer

Abbreviations: AJCC, American Joint Committee on Cancer; ATA, American Thyroid Association; CT, computed tomography; EBRT, external beam radiotherapy; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; MTA, maximal tolerable activity; PET, positron emission tomography.

(1, 2). Most patients with thyroid cancer confined to the thyroid gland or cervical lymph node metastases do very well with standard therapy including surgery, long-term levothyroxine therapy, and radioiodine remnant ablation in selected individuals. Older patients (>45 yr old) with distant metastatic thyroid cancer are classified as stage IVC by the American Joint Committee on Cancer (AJCC) criteria (sixth edition). These patients have a much more limited 5-yr survival of approximately 30–40% (3, 4). There is good evidence that aggressive surgery, radioiodine therapy, and levothyroxine suppression therapy can improve the overall survival and disease-specific survival in this subgroup of patients (5). Unfortunately, many of these patients ultimately die from advanced disease and other therapeutic approaches are needed.

The Case

A 78-yr-old woman presented to her primary care physician with upper back pain. She had otherwise been in excellent health and was taking no medication. A spine radiograph revealed a lytic lesion at T3, and an MRI confirmed a 2.7 cm lesion that did not threaten the spinal cord. A biopsy was consistent with follicular thyroid carcinoma (FTC) and immunostaining was positive for thyrogloublin and TTF-1. She received external beam radiotherapy (EBRT) of 30 Gy over 10 fractions to the T3 lesion and underwent a thyroidectomy, which revealed a 2 cm FTC with tumor capsule invasion only. After withdrawal of thyroid hormone, she received 5.55 GBq (150 mCi) ^{131}I, and a post-therapy whole body scan revealed uptake in the thyroid bed region, right proximal humerus, right pelvis and 2 lesions in the left 4th rib.

Three months after the initial therapy, she was referred to the University of Colorado Cancer Center for further evaluation and treatment. Her upper back pain was improved, ECOG status was 0 and she had no new complaints. On 0.137 mg of levothyroxine, her TSH was 0.02 mU/L, free T4 was 1.67, thyroglobulin was 4575 ng/ml and antithyrogloublin antibody was <0.9 IU/ml.

This older woman has stage IVC FTC (T2N0M1) by AJCC criteria (1). She is at relatively high risk for disease-related mortality and progression, and her prognosis is guarded.

Clinical considerations

Staging criteria for thyroid cancer, which is a predictor of survival, are unique in that it is the only cancer that incorporates age into the common AJCC tumor node metastasis staging system. Patients younger than 45 yr old with extracervical, or distant, metastatic disease are classified as stage II by the AJCC. The prospectively developed staging system by the National Thyroid Cancer Treatment Cooperative Study Registry would classify these patients as stage III (3). Patients 45 yr old or older are stage IV in most staging systems (stage IVC in the AJCC sixth version). Patients with extracervical metastatic follicular thyroid carcinoma have a 50% survival of approximately 4 yr and a 5-yr disease-specific survival of approximately 35% (3). This estimate includes patients with pulmonary as well as osseous metastases. One large study that assessed the long-term outcome of 444 patients with distant metastases subdivided patients into those with pulmonary metastases and those with osseous metastases (6). Patients with lung metastases had a 63% 10-yr survival, whereas those with osseous metastases did much worse with only a 25% 10-yr survival. These data were confirmed in other studies (4, 7).

Tumor differentiation also appears to play a role in survival of patients with extracervical metastases. Those with distant metastases that concentrated radioiodine (more differentiated) had a 60% 10-yr survival, and the subset that did not achieve long-term remission still had a 30% 10-yr survival (6). Conversely, those patients with distant metastatic disease that was not radioiodine avid had a 10-yr survival limited to 10%. ^{18}F-fluorodeoxyglucose uptake measured by positron emission tomography (PET) imaging has emerged as an important diagnostic and prognostic tool in patients with advanced thyroid cancer. One study showed that patients with elevated serum thyroglobulin being evaluated for progressive or metastatic disease who had negative PET scan had a greater than 90% survival out to 7 yr, whereas patients with PET-positive disease had only a 40% 5-yr survival (8). Furthermore, a multivariate analysis confirmed that fluorodeoxyglucose (FDG) status and number of FDG-positive lesions significantly correlated with survival, supporting the value of this imaging modality as a prognostic tool in patients with metastatic thyroid cancer.

Pain is a common presenting symptom in patients with bone metastases (9). Other less common but clinically important presentations are pathological fracture and spinal cord compression (10).

Imaging modalities for extracervical metastases are divided into two basic categories: anatomic [computed tomography (CT), magnetic resonance imaging (MRI)] and functional imaging (radioiodine, FDG-PET, ^{99}Tc-diphosphonates, other radionuclides). Pulmonary metastases are best evaluated with thin-cut or spiral chest CT. Intravenous contrast is not needed to evaluate pulmonary parenchymal lesions but improves diagnostic accuracy when evaluating the mediastinum. Chest x-ray has a low sensitivity and limited utility in detecting early pulmonary metastases in most patients. Radioiodine (^{123}I and ^{131}I) imaging is particularly useful to identify radioiodine-avid pulmonary metastases of any size and determine whether

TABLE 1. Systemic therapies

Therapy	Advantages	Disadvantages
Levothyroxine (TSH suppression)	Improved overall survival Decreased recurrence rates	Bone loss Atrial dysrhythmias
Radioiodine	Original targeted therapy Relatively safe	Many metastases do not concentrate RAI Salivary gland damage Marrow suppression Secondary malignancies
Chemotherapy (doxorubicin/taxanes)	Doxorubicin is FDA approved Targets rapidly dividing tumors	Response rate is poor Toxicity
Clinical trials (targeted therapies) (clinicaltrials.gov, thyroid.org)	Promising new agents Relatively low toxicity profile	Not yet proven to be effective Current studies show low CR Travel to centers doing studies
Available targeted therapies (sorafenib, sunitinib)	Orally available agents Relatively low toxicity profile	Not approved for thyroid cancer Reimbursement issues Do not appear to be tumoricidal
Intravenous bisphosphonates	Reduces skeletal complications Improves bone pain	Limited evidence in thyroid cancer Osteonecrosis Renal insufficiency

RAI, Radioiodine; CR, complete response rate.

radioiodine therapy may be beneficial. FDG-PET imaging of pulmonary metastases is reserved for patients with high-risk features such as stage III or IV disease with elevated/rising serum thyroglobulin and negative radioiodine imaging. This modality is useful for prognostic value and identifying FDG-positive lesion for directed therapy (surgery, radiation). Lesions less than 5–8 mm may not be seen on FDG-PET imaging due to limited resolution of this modality.

Whole-body and bone MRI are particularly useful in patients with suspected bone metastases carrying a 91% diagnostic accuracy in multiple cancer types (11). CT imaging is another reasonable approach to evaluate bone destruction but may not have the same sensitivity as MRI, particularly in the axial spine. Plain radiographs can also detect bone destruction (thyroid cancer metastases are predominantly osteolytic) but are less sensitive than either CT or MRI.

Treatment considerations

Primary treatment considerations for patients with distant metastases from thyroid carcinoma include systemic therapy (TSH suppression with levothyroxine, radioiodine, consideration of clinical trials, and chemotherapy) or directed therapy (external beam radiotherapy, surgery, chemoembolization) for symptomatic or concerning lesions. Patients with metastatic thyroid carcinoma that is radioiodine resistant, but stable and asymptomatic, may be carefully monitored for disease progression with TSH suppression therapy alone (12).

Systemic therapy

Table 1 summarizes advantages and disadvantages of various systemic therapies for extracervical thyroid carcinoma.

The most fundamental systemic therapy in patients with metastatic differentiated thyroid cancer is levothyroxine therapy. Patients with stage III and IV have decreased recurrence rates and improved survival when TSH is chronically suppressed (13–15). This benefit of chronic TSH suppression (<0.1 mU/liter) needs to be weighed against the risks of atrial fibrillation and bone loss, especially in postmenopausal women.

Radioiodine remains the primary therapy for patients with metastatic thyroid carcinoma that is radioiodine avid. One study showed a significant survival benefit associated with radioiodine therapy in patients with osseous metastases that were further improved with higher cumulative doses (7). Other studies have shown an association between better survival and radioiodine uptake in distant bone metastases but not a specific association with radioiodine therapy (16, 17). Osseous metastases are rarely cured with radioiodine alone, but many patients can benefit from symptomatic improvement, partial tumor response, or disease stabilization. The primary and preferred patient preparation for radioiodine therapy is withdrawal of thyroid hormone for 3–6 wk and a low-iodine diet 1–2 wk before administration of radioiodine. Recombinant human TSH (TSH alpha, Thyrogen) may be considered as an alternative in those patients who cannot mount an adequate TSH response to thyroxine withdrawal or patients with significant medical or psychiatric conditions that may be severely exacerbated by hypothyroidism (18).

Treatment with radioiodine can be performed using an empirical dose (6) or dosimetric approach (19). Whole-body dosimetry, in which a patient is given a small dose

(1–3 mCi) of ^{131}I followed by daily blood and whole-body measurements for 4 d, is used to determine the maximal tolerable activity (MTA) that can be given to minimize toxicity to vulnerable organs (bone marrow or lungs in patients with lung metastases). Theoretical reasons to consider a personalized dosimetric approach include maximizing the amount of radiation delivered to tumors and identification of patients in whom the standard empirical dose may exceed the MTA for that patient. Recent studies have shown that the MTA decreases with age and that an empirical administered dose of 7.4 GBq (200 mCi) ^{131}I would exceed the MTA in 8–15% of patients younger than 70 yr old and 22–38% of patients older than 70 yr old, like our patient (20). A recent noncontrolled study attempted to examine whether dosimetric therapy could control metastatic disease in patients who failed empirical dose therapy (21). Fifteen percent of patients achieved complete remission and 32% achieved partial remission after dosimetry-based ^{131}I therapy in this group of 47 patients who failed empirical dose therapy, suggesting that the dosimetric approach may be superior to empirical fixed-dose therapy in this noncontrolled study. There remains, however, a paucity of data comparing effectiveness of dosimetry *vs.* empirical fixed-dose therapy. Currently the primary consideration for using a dosimetric approach is to limit toxicity of large empirical doses for patients with advanced disease, especially in older patients.

The ultimate goal of radioiodine therapy is to minimize toxicity to sensitive tissue (MTA) and maximize the therapeutic effect on targeted tumor tissue (lesion dosimetry) (22). Lesion dosimetry can help identify tumors that can be seen on imaging but may concentrate insufficient amounts of radioiodine to deliver an effective dose of radiation to the tumor. Recent studies have shown that the positron-emitting radioisotope ^{124}I as a PET imaging agent can be used to estimate MTA and lesion dosimetry (23, 24). ^{124}I is not yet widely available and is quite expensive, but this will likely be a very important imaging agent for patients with advanced thyroid cancer in the future.

Corticosteroids should be considered in patients undergoing radioiodine therapy for brain metastases, axial spine metastases that may threaten the spinal cord, or any bone metastases at high risk for pathological fracture. Dexamethasone 4–8 mg daily, or equivalent doses of other glucocorticoids, has been used with a steroid taper starting 5–7 d after administration of the ^{131}I (25).

Standard chemotherapy is of limited utility in patients with metastatic thyroid cancer and should be reserved for patients with rapidly progressive disease when other options (radioiodine, monitoring, clinical trials, directed therapy) are not available. Entry into clinical trials (clinicaltrials.gov, thyroid.org) should be considered for pa-

tients with progressive, radioiodine-resistant disease (26). Newer targeted agents, such as sorafenib or sunitinib, may be useful in patients with progressive metastatic disease, but there are currently no targeted agents FDA approved for advanced thyroid cancer (26, 27).

Intravenous bisphosphonates, primarily zoledronic acid or pamidronate, may help reduce skeletal complications in patients with osseous metastases. Most of the solid tumor evidence is in breast and prostate cancer, in which randomized, placebo-controlled trials show that bisphosphonates reduce skeletal morbidity including pain, time to progression, and pathological fractures (28). Bone marker-directed therapy, such as normalizing N-telopeptide levels, is currently under evaluation in randomized clinical trials. One small study showed that patients with painful osseous thyroid cancer metastases receiving monthly infusion of pamidronate had significant reduction in bone pain and improvement in quality of life, suggesting that observations in other solid tumors may be applicable to patients with metastatic thyroid cancer (29).

Directed therapy

Surgery can be considered for large, isolated metastases or unstable supportive bones such as femur, humerus, vertebrae, or tibia. The risk of potential fracture due to a bone metastasis can be assessed by extent of lytic lesion on plan films or CT scans, especially with respect to integrity of cortex and amount of bone involved. Consultation with orthopedic surgery is critical for assessing such lesions and offering options for stabilization, such as plates and/or nails, joint replacement, and/or resection. Less invasive techniques such as vertebroplasty (polymethylmethacrylate cement is injected percutaneously into the affected vertebral body), kyphoplasty (placing an inflatable bone tamp percutaneously into a collapsed vertebral body), and embolization may also be considered for tumor and pain control, but these will not provide stabilization of destroyed bone (10). Placement of rods to stabilize the spine after resection of involved vertebrae is also an option in appropriate patients. Embolization can be effective as a preoperative adjuvant therapy to reduce surgical blood loss in patients with large or very vascular metastases (30).

External beam radiotherapy (EBRT) is a useful modality for local pain or growth control of metastatic lesions that do not respond to radioiodine, particularly bone, central chest, and brain. If the intent is to control disease growth, 45–50 Gy are generally given in 1.8- to 2-Gy fractions, whereas palliation of symptoms can be achieved with 20 Gy in five fractions or 30 Gy in 10 fractions (31). Specific anatomic area and volume of tumor to be treated are taken into consideration. Systemic strontium 89 or samarium 153 can also play a role in patients with very wide-
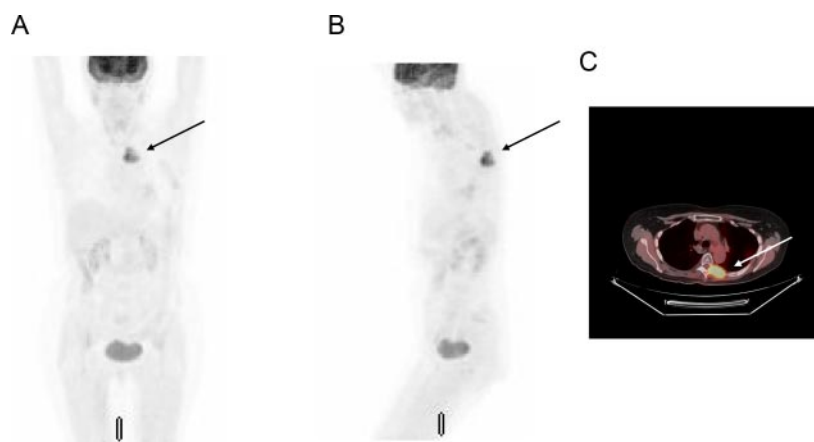
FIG. 1. ^{18}Fluorodeoxyglucose-PET scan. A majority of the FDG activity is seen in the thoracic spine at T3 (*arrow*). A, Anterior-posterior projection. B, Lateral projection. C, PET-CT fusion.

spread painful metastases because it will concentrate in the metastatic lesions and deliver radiotherapy to them. Myelosuppression can be a serious side effect, so blood counts must be monitored closely after treatment, and hematopoietic growth factors may offer benefit.

Guidelines

How do major guidelines assist us in management of our 78-yr-old patient with radioiodine-avid bone metastases?

The National Comprehensive Cancer Network practice guidelines in oncology version 1.2009 (www.nccn.org) recommend radioiodine treatment of bone metastases if radioiodine scan positive with consideration of dosimetry and/or EBRT. Clinicians should also consider bisphosphonate therapy and embolization of metastases. Surgical palliation should be considered for symptomatic lesions or asymptomatic lesions in weight-bearing extremities. Serum TSH should be suppressed less than 0.1 mU/liter in patients with known residual disease.

The American Thyroid Association (ATA) recently revised the thyroid cancer guidelines (12). The guidelines recommend the use of radioiodine in patients with radioiodine-avid metastatic disease, adding a new recommendation based on good evidence that empirical doses exceeding 200 mCi ^{131}I should be avoided in patients older than 70 yr of age.

The ATA guidelines have five recommendations specifically addressing patients with bone metastases. Considerations include risk for pathological fracture, risk for neurologic complications, presence of pain, and radioiodine avidity of the metastases.

Painful lesions should be managed by EBRT, radioiodine (if avid), periodic bisphosphonate infusions, or vertebroplasty/kyphoplasty. Asymptomatic, radioiodine-resistant lesions that do not threaten critical structures should be monitored on levothyroxine therapy. Finally, the ATA guidelines

recommend that skeletal metastases in which acute swelling (associated with elevated TSH or radioiodine) may produce fracture or neurological complications, EBRT, and concomitant use of glucocorticoids should be strongly considered.

The European consensus statement agrees that bone metastases should primarily be treated with a combination of surgery, EBRT, and radioiodine as outlined above (32).

Controversies and unanswered questions

Unfortunately, many unanswered questions remain for management of patients with extracervical metastases, especially those with osseous metastases. How often and for how long should patients with iodine-avid metastases be treated, especially because most patients will not be cured? Should a dosimetric approach be used in all or selected patients with distant metastases and, if only in selected patients, which ones? Which patients with bone metastases should receive iv bisphosphonates, how often, and for how long? Which patients with radioiodine-resistant metastases should be entered in clinical trials, especially those with osseous metastases that are not measurable by standard response evaluation criteria in solid tumors criteria?

Returning to the patient

Our 78-yr-old woman with metastatic follicular thyroid carcinoma underwent a staging PET-CT scan, which confirmed the multiple bone metastases seen on the post-therapy radioiodine scan. Many of these lesions had borderline FDG uptake (standardized uptake value 2–3), whereas the T3 lesion was FDG avid (standardized uptake value 10, Fig. 1). No pulmonary or soft tissue metastases were identified. A bone scan confirmed the lesions at T2-T5, T10, R humerus, L fourth rib, and sacrum. An MRI of the brain for evaluation of headaches was normal.

Nine months after her initial radioiodine therapy, she underwent repeat radioiodine therapy with 9.25 GBq (250 mCi) ^{131}I using a dosimetric approach (see *Treatment considerations* above) after withdrawal of thyroid hormone. Figure 2 demonstrates that many of her osseous metastases are radioiodine avid.

After discussion of risk and benefits, careful dental examination, and cleaning as well as documentation of normal serum creatinine, calcium, and repletion of vitamin D, she was begun on iv bisphosphonate (4 mg zoledronic acid monthly) to protect her from skeletal complications and potentially decrease formation of
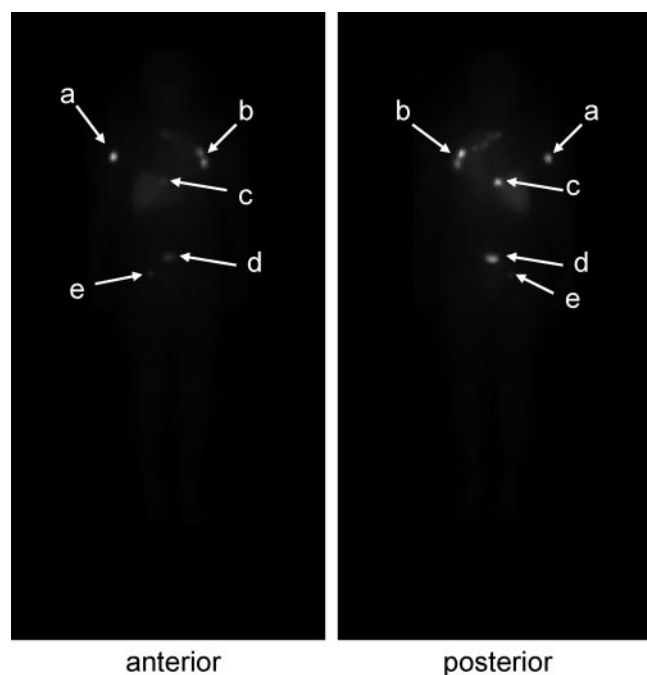
FIG. 2. Posttherapy radioiodine whole-body scan. Whole-body anterior and posterior images were acquired 12 d after oral therapy with 250 mCi ^{131}I. *Arrows* indicate areas of abnormal ^{131}I uptake. a, R humerus; b, L ribs; c, T10; d, sacrum; e, pelvis.

new bone metastases. TSH target was less than 0.1 mU/liter with a normal free T_4.

Six months later on 0.137 mg levothyroxine, her TSH was 0.07 mU/liter with a normal free T_4 and her serum thyroglobulin had decreased to 1222 ng/ml. A time course of her serum thyroglobulin tumor marker is shown in Fig. 3. She felt well and had no new symptoms. Spine MRI documented stable lesions with no cord involvement and bone scan showed no new lesions. Zoledronic acid was discontinued after six monthly infusions.
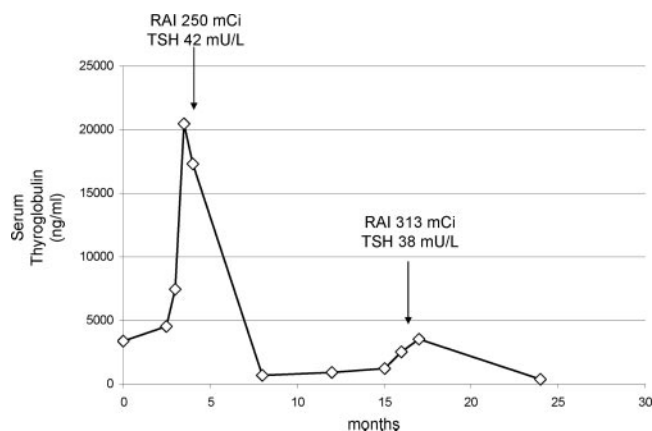
FIG. 3. Time course of serum thyroglobulin tumor marker. The time course on the x-axis is from her initial evaluation at the University of Colorado. All serum thyroglobulin levels are measured during suppressed TSH (<0.1 mU/liter) except for the two measurements during each dosimetry and treatment noted by the *arrows*. RAI, Radioiodine.

Ten months after her last radioiodine therapy, she was again prepared for radioiodine therapy by the dosimetric approach. The diagnostic whole-body scan documented persistent uptake of radioiodine in the osseous metastases and she was given 11.58 GBq (313 mCi) ^{131}I. Posttherapy scan confirmed the same lesions with no new lesions identified.

Six months later she was doing well, with complaints of moderate dry mouth only. On 0.137 mg levothyroxine, her TSH was 0.05 with a normal free T_4. Serum thyroglobulin was now 383 ng/ml (Fig. 3) and imaging documented stable osseous metastases with no new lesions.

Her plan is to monitor for symptoms and laboratory markers at 3-month intervals with imaging every 6 months over the next few years. No further therapy is planned unless there is evidence of progressive or symptomatic disease.

Conclusions

Patients with extracervical metastatic thyroid cancer present unique management challenges. Approaches to these patients may require monitoring and therapeutic tools not used in patients with typical localized disease. Radioiodine remains a mainstay of therapy in patients with radioiodine-avid metastatic disease, and this can be complemented with directed therapy such as EBRT, surgery, and embolization for large or painful lesions. Patients with progressive, radioiodine-resistant metastatic disease should be considered for entry into clinical trials, whereas patients with asymptomatic, stable metastatic disease may be monitored closely on levothyroxine suppression therapy. Newer targeted agents, such as sorafenib or sunitinib, may be useful in patients with progressive metastatic disease. There are currently no targeted agents approved by the FDA for advanced thyroid cancer. Osseous metastases in thyroid cancer are fortunately uncommon but when they occur result in increased morbidity and decreased survival. Patients with painful osseous metastases or those with impending fracture of weight-bearing bones may benefit from EBRT or surgical stabilization.

Acknowledgments

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