Thyroid Cancer in Young Adults

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The incidence of thyroid cancer in young adults is rising. Differentiated carcinoma (ie, papillary, follicular, and their variants) and medullary thyroid carcinoma (MTC) represent the two most common subtypes, with differing etiologies, prognoses, and management strategies. Ultrasound (US)-guided fine needle aspiration (FNA) is the best initial test for evaluating a nodule or mass suspicious for malignancy. Tumor histology, in addition to radiographic findings and clinical presentation, guides surgical management, the need for adjuvant therapies, and the optimal approach to long-term follow-up. Radioactive iodine (RAI) is used to reduce recurrence and improve survival for differentiated thyroid carcinomas (DTCs). Emerging systemic therapies provide options for patients with progressive metastatic MTC or radio-resistant DTC. Overall, the prognosis for the most common thyroid malignancy, papillary thyroid carcinoma (PTC), is excellent. The treatment of young adult thyroid cancer patients occurs optimally as part of a multidisciplinary coordination of care.

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Thyroid carcinoma is the most common endocrine malignancy, with an estimated 37,340 new cases diagnosed in the United States during 2008. About 28% of these new thyroid cancers occur in the 20- to 40-year age group, and its incidence is rising by 5.6% per year in persons less than age 65, making it the fastest growing cancer diagnosis during the years 1996-2005. Differentiated thyroid carcinoma (DTC)—including papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), and their variants—is by far the most common type of thyroid malignancy in this age group, representing approximately 95% of thyroid cancers. Most of the remainder consists of medullary thyroid carcinoma (MTC). Anaplastic (undifferentiated) thyroid carcinomas (ATCs) have been reported but are extremely rare in the young adult population. Of cases diagnosed from 1988-2001, 96% of ATC diagnoses were made in patients >45 years of age. Given its rarity in 20- to 39-year-old patients, ATC will not be discussed in the current article, and the interested reader is referred to a recent review.

Using Surveillance, Epidemiology and End Results (SEER) data from 2001-2005, the annual incidence of thyroid carcinoma in patients aged 20-39 years ranged from 12 cases per million people per year in males aged 20-24 years to 201 cases per million per year in females aged 35-39 years (Figure 1). Thyroid carcinoma represents 5.9% to 11.5% of all malignancies diagnosed in this age group, with the 20- to 24-year-old age group having the highest percentage of thyroid cancers relative to all cancers. In 20- to 40-year-olds, it is five times more common in females, with the highest female: male ratio being 6.6:1 in 20- to 24-year-olds (Figure 1). Thyroid carcinoma represents 4% of all cancers in women, and it is the sixth most frequently diagnosed cancer in females; in women ages 20-29, it is the most common cancer site. At all ages, thyroid cancer in the United States is most prevalent among non-Hispanic whites and Asian/Pacific Islanders, and least common among African Americans.

Fortunately, the overall survival rate is excellent in patients with localized or locoregional disease (97%-100%), with only 1,590 estimated deaths from thyroid cancer expected in 2008. Overall 5-year survival rates are above 99% in individuals less than age 40 at diagnosis. The presence of distant metastases portends a worse survival (5-year survival, 56%), although younger patients have a better prognosis than older adults with a similar extent of disease presentation, reflecting a difference in clinical behavior that is not yet understood completely.
Although several prognostic staging systems have been described for thyroid cancer, specifically PTC, a thorough discussion of these is beyond the scope of the current review. The pathological tumor-node-metastasis (TNM) classification was adopted by the American Joint Committee on Cancer and the International Union Against Cancer Committee as the international reference staging system for thyroid cancer. By definition, however, the highest TNM stage for PTC or FTC that anyone less than age 45 can achieve is stage II, which is distinguished from stage I only by the presence of distant metastases. Therefore, the TNM staging system as an indicator of prognosis or the need for more aggressive up-front treatment is not as relevant in young adults with DTC. MTC is also staged according to the TNM classification, and ATC is always considered stage IV disease.

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Given the paucity of prospective research for this relatively rare disease with prolonged life expectancy, the majority of treatment approaches have been based on retrospective analyses and personal experience. Several multidisciplinary guidelines have been created to assist with clinical decision-making in the care of these patients, although the treatment approach should always be individualized for each patient, weighing the risks of therapy against the risks of morbidity and mortality from the underlying cancer.

**DIFFERENTIATED THYROID CARCINOMA**

**Epidemiology**

DTC accounts for the vast majority of cases in the 20- to 39-year age group, and of these cases PTC is the most common, representing about 85% of malignancies that arise from the thyroid. The highest incidence of DTC in the young adult group is in the 35- to 39-year-old age group. Similar to thyroid cancer in general, DTC is much more common in females and a clear increase in thyroid cancer cases has been recognized in the young adult population. DTC is among the most curable of malignancies, particularly if identified early and treated appropriately in a multidisciplinary setting. Cure rates are high and 5-year survival exceeds 99% in this age group. In some cases, DTC becomes a chronic condition, underscoring the frequently indolent nature of this disease and the importance of lifelong follow-up.

**Etiology**

DTC arises from the thyroid follicular epithelium. The diagnosis of PTC and FTC is based on unique histopathological features, and there are subtypes of each. These include follicular cell, tall cell, columnar cell, diffuse sclerosing, and encapsulated variants in PTC, and Hürthle-cell (oncocytic), clear cell, and insular (poorly differentiated) carcinoma in FTC. Certain tumor subtypes, such as the follicular and diffuse sclerosing variants of PTC, are more common in children and young adults as compared to older individuals.

The major risk factor for the development of PTC is radiation exposure to the head and neck, particularly in childhood. Most cases of radiation-induced PTC in the 21st century are due to therapeutic radiation to treat a prior malignancy. Although there are some conflicting data, it appears that cases of radiation-induced thyroid carcinoma are not significantly different in clinical behavior from sporadic non–radiation-induced tumors. Internal ionizing radiation, such as occurred with the large environmental exposure to radioactive iodine (RAI) from the Chernobyl nuclear accident in 1986, is another well-documented risk for the development of PTC. Fortunately, the doses of RAI used in the treatment of hyperthyroidism and routine diagnostic studies appear to be below the threshold needed for tumorigenesis. Iodine insufficiency is associated with an increased incidence of FTC and, as with many other cancers, obesity may be a risk factor as well.

Researchers are beginning to understand better the molecular and genetic basis of DTC, and it is recognized that activation of the RAS-RAF-MEK-ERK (mito-
The RET/PTC rearrangement produces a chimeric oncogene, resulting in a constitutively activated form of the RET receptor tyrosine kinase (normally not expressed in thyroid follicular cells), thereby promoting tumorigenesis. Mutations in BRAF (typically the V600E mutation) are the most common cause of PTC, occurring in 36%-83% of cases. PTCs that are positive for a BRAF mutation are also more clinically aggressive. A thorough discussion of other somatic events implicated in DTC tumorigenesis is beyond the scope of the current review, but other genes and gene products involved can include RAS (PTC and DTC), the TRK proto-oncogene (rearranged akin to RET, but found in a minority of PTCs), Pax8-PPARγ1 translocations (follicular adenomas and follicular thyroid carcinomas only), and PIK3CA (mostly FTC). Up to 5% of patients with PTC have a family history of the disease. Having a familial non-medullary thyroid carcinoma (FNMT) may portend a worse prognosis, given that these cases appear to have more aggressive disease and shorter disease-free intervals after initial treatment. Genetic anticipation also has been identified in such cases. As of yet, the genetic basis for FNMT has not been elucidated, although somatic mutations in RAS and BRAF have been identified in 52% of cases. Other genetic syndromes in which there is an increased risk of DTC include familial adenomatous polyposis (APC gene, Gardner syndrome), Cowden syndrome (PTEN gene), Werner syndrome (RECOIL2 gene), and the Carney complex (PRKAR1a gene). The PTC identified in familial adenomatous polyposis (FAP) is usually the rare cribriform (cribriform-morular) variant. If this subtype is identified, particularly in a young adult woman, a mutation in the APC gene and the subsequent risk for colonic neoplasia should be considered.

Diagnosis and Clinical Presentation

DTC usually presents as an asymptomatic neck mass, although occasionally the diagnosis may be made only after the discovery of distant metastases (Figure 2). Symptomatic thyroid cancers (ie, associated with hoarseness, dysphagia, or cough) are less common in young adults but, if present, should suggest a more aggressive clinical presentation. Uncommonly, thyroid carcinoma can arise ectopically in a thyroglossal duct remnant or cyst. Finally, although most patients are euthyroid at the time of diagnosis, rare cases of well-differentiated FTC can present with frank thyrotoxicosis.

There are some key differences in clinical behavior when comparing PTC and FTC. PTC is more likely to metastasize through lymphatic channels to regional neck lymph nodes, whereas hematogenous metastases, primarily to the lung, occur less frequently and typically only in the presence of significant locoregional metastatic disease. FTC, in contrast, is more prone to hematogenous metastases, predominantly affecting the lungs and bones; regional lymph node involvement is rare but can be seen with more aggressive subtypes of FTC. Furthermore, FTC is more likely to be multifocal and bilateral; FTC, in contrast, is usually a unifocal tumor.

In a patient presenting with a painless thyroid nodule or known thyroid cancer, the initial procedure should be a high-quality neck ultrasound (US) (together with fine needle aspiration [FNA] as indicated) by an experienced ultrasonographer, which assists greatly with surgical planning. US not only assesses completely the thyroid gland and facilitates the accuracy of FNA, but also it is useful to determine the extent of metastatic disease and allows performance of FNA of any metastatic lymphadenopathy in the central and lateral neck. Nuclear scintigraphy using RAI or technetium pertechnetate is not very useful in the initial evaluation of possible thyroid carcinoma, except in patients with a low thyroid-stimulating hormone (TSH) level who may have an autonomously functioning nodule or in those with an FNA diagnosis of “follicular neoplasm,” in whom nodule functionality may help to determine management. In DTC, tumor cells typically retain the ability to produce the thyroid-specific glycoprotein, thyroglobulin (TG). Once a diagnosis of DTC is established, a baseline serum TG level will be useful for follow-up and for the potential identification of a large metastatic disease burden. To assess for pulmonary metastases, a chest x-ray or chest computed tomography (CT) scan without contrast also should be considered at diagnosis, especially in those patients with significant locoregional disease, noting that many individuals with lung metastases may not have abnormalities visualized on plain radiographs. Finally, cross-sectional imaging of the neck (CT with contrast or magnetic resonance imaging [MRI], depending on local expertise) is recommended in those with significant metastatic neck lymphadenopathy, in order to better assess the extent of disease (specifically the superior mediastinum and central compartment, which are not well visualized via US). Although the use of iodinated contrast will delay subsequent RAI therapy, the information gained, which will allow for better surgical planning and oncologic outcomes, outweighs the risk of delaying RAI in the vast majority of cases.
Surgery

Surgery is the cornerstone of therapy for DTC, and in many cases is a curative intervention. For PTC, the initial procedure of choice is a total thyroidectomy (Table 1), which has been associated with lower recurrence rates and better survival compared to lobectomy alone, particularly for tumors greater than 1 cm in size. Lobectomy and isthmusectomy alone may suffice in the low-risk young adult patient with a small unifocal PTC (without evidence of lymphadenopathy or contralateral thyroid nodules), but such cases are rare. A central compartment (level VI) neck dissection should be performed for larger tumors or when metastatic central lymph nodes are identified at the time of surgery; a lateral neck dissection (selective neck dissection, including levels IIA-V) is performed when lateral neck metastatic lymphadenopathy is identified by imaging (US and/or CT) or is biopsy-proven. All lymph node dissections should be comprehensive and compartment-focused because the rates of recurrence are higher when “berry picking” alone is undertaken. Although total thyroidectomy and lymph node dissec-
<table>
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<tr>
<th>Tumor</th>
<th>Surgical Management of the Neck</th>
<th>Surgical Management of Parathyroid Glands That Are Devascularized/Removed</th>
</tr>
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</table>
| Papillary thyroid carcinoma   | - TT, consider prophylactic ipsilateral level VI ND in higher risk patients (tumor >1 cm, age > 45)  
- If clinical or radiographic evidence of level VI LN mets or large tumor size, perform level VI ND  
- If clinical or radiographic evidence of lateral LN mets, perform lateral neck dissection on that side | - Autograft in neck                                                                 |
| Follicular thyroid carcinoma  | - If known preoperatively (ie, distant mets), TT  
- If Hürthle cell carcinoma or poorly differentiated cancer, extent of ND as per PTC recommendations  
- If not known preoperatively (ie, follicular neoplasm), lobectomy followed by TT if tumor more than minimally invasive | - Autograft in neck                                                                 |
| Medullary thyroid carcinoma   |                                                                                                  | - Autograft in neck if RET mutation consistent with FMTC or MEN2B  
- Autograft in forearm for RET mutations consistent with MEN2A | - Autograft in neck if RET mutation consistent with FMTC or MEN2B  
- Autograft in forearm for RET mutations consistent with MEN2A |
| Prophylactic thyroidectomy in MEN2/FMTC | - TT if normal US and normal or minimally elevated calcitonin (<40-50 pg/mL)  
- Performance of level VI ND based on RET mutation, age of the patient, serum calcitonin level, and cervical US findings | - Autograft in neck if RET mutation consistent with FMTC or MEN2B  
- Autograft in forearm for RET mutations consistent with MEN2A | - Autograft in neck if RET mutation consistent with FMTC or MEN2B  
- Autograft in forearm for RET mutations consistent with MEN2A |
| Clinical MTC in MEN2/FMTC     | - TT plus level VI ND  
- Lateral neck dissection if clinical or radiographic evidence of lateral LN mets (consider bilateral prophylactic lateral neck dissections in MEN2B) | - Autograft in neck if RET mutation consistent with FMTC or MEN2B  
- Cryopreserve/autograft in forearm for RET mutations consistent with MEN2A | - Autograft in neck if RET mutation consistent with FMTC or MEN2B  
- Cryopreserve/autograft in forearm for RET mutations consistent with MEN2A |
| Sporadic MTC (no germline RET mutation) | - TT plus level VI ND  
- Lateral neck dissection if clinical or radiographic evidence of lateral LN mets | - Autograft in neck if RET mutation consistent with FMTC or MEN2B  
- Cryopreserve/autograft in forearm for RET mutations consistent with MEN2A | - Autograft in neck if RET mutation consistent with FMTC or MEN2B  
- Cryopreserve/autograft in forearm for RET mutations consistent with MEN2A |

Abbreviations: MEN, multiple endocrine neoplasia; FMTC, familial medullary thyroid cancer (MTC); TT, total thyroidectomy; ND, neck dissection; LN, lymph node; US, ultrasound; mets, metastases.
tions (particularly level VI) are associated with higher risks, such as hypoparathyroidism and recurrent laryngeal nerve injury.44 These risks should be lower and more likely to be transient when the initial surgery is performed by a surgeon with particular expertise in the management of thyroid cancer. Therefore, whenever possible, patients with thyroid cancer should be treated by a high-volume surgeon.45 Intraoperative monitoring of the recurrent laryngeal nerve (considered controversial by some) and routine auto-transplantation of devascularized parathyroid glands, particularly the at-risk inferior glands, help to minimize the risks associated with surgery.11

Since the characteristics of FTC (capsular and/or vascular invasion) cannot be made via FNA alone, a diagnosis of FTC is typically made only after pathologic review of a resected “follicular neoplasm” or “follicular lesion.” Although the prognosis of FTC may not be as dependent on the extent of the initial surgery (unlike PTC), a total thyroidectomy facilitates the use of RAI to ablate the normal thyroid remnant, which permits an increased sensitivity to detect disease recurrence, thus improving the outcome for patients with FTC.46 The lymph nodes should be managed similarly to PTC in poorly differentiated tumors and more aggressive variants such as Hürthle cell carcinoma.

Radioactive Iodine/External Beam Radiation Therapy

Although no prospective randomized controlled trials have been performed, RAI treatment to ablate the thyroid remnant and treat metastatic disease is believed to result in a lower recurrence rate and subsequent lower cancer-related mortality.47 This has been shown also in observational studies for young adults with small-volume metastatic disease.48 However, for the low-risk stage I individual, such as the young adult without distant metastases and without aggressive histology, the benefit of postoperative RAI is not as clear.49 Thus, the most recent guidelines by the American Thyroid Association recommend RAI only in stage I patients who are most likely to benefit, including those with multifocal disease, nodal metastases, extrathyroidal or vascular invasion, and/or more aggressive histologies.50 However, as with any treatment, the perceived benefits of RAI must be weighed against potential side effects of therapy (see below), particularly in young adults, who generally have an excellent prognosis.

Following total or completion thyroidectomy, the patient is typically rendered hypothyroid with plans to administer RAI therapy when the TSH level is above 30 μU/mL.17 A low-iodine diet is followed for 2 weeks prior to scanning and/or treatment with iodine 131 to facilitate RAI uptake by any remaining thyroid tissues. Recombinant TSH (rhTSH) was approved recently by the US Food and Drug Administration for RAI ablation of remnant thyroid tissue without evidence of metastatic disease, and many centers are currently using rhTSH-assisted RAI ablation in the majority of low-risk patients.50 Compared with thyroid hormone withdrawal (THW), rhTSH not only avoids hypothyroid symptoms, but it appears to limit radiation exposure to the blood and improves quality of life as compared with THW.51 At this time, the use of rhTSH should be reserved for low-risk patients, until further studies are performed and long-term outcomes assessed.

For the young adult, the dose of 131I is usually between 30-100 mCi for remnant ablation, depending on histopathological features, stimulated TG, and the diagnostic thyroid scan. Activities from 150-200 mCi are considered for patients with documented lymph node or pulmonary metastases; and doses of 200 mCi or more are administered for bony metastases. Instead of fixed doses of 131I, dosimetry studies can be used in select cases to estimate the appropriate dose of RAI that will limit whole-body retention to less than 80 mCi at 48 hours and blood exposure to less than 200 cGy.15 Patients who are most likely to benefit from dosimetry include those with diffuse and significant lung uptake on diagnostic scanning, and the elderly.52

External beam radiation therapy (EBRT) of the neck is not considered routinely in patients who are younger than 45 years of age, although the rare case of a pathologically unfavorable thyroid carcinoma with known residual neck disease may warrant such an aggressive approach. As with any cancer, radiation does play a role in palliation of distant metastases.53

Thyroid-Stimulating Hormone Suppression

Most DTCs continue to express functional TSH receptors, and there is an inverse relationship between expression of the TSH receptor and the degree of de-differentiation of the thyroid carcinoma.54 Because the trophic effects of TSH could accelerate recurrence and/or progression of TSH-dependent DTC, patients with PTC and FTC are treated with pharmacologic suppression of TSH. TSH suppression decreases the risk of disease recurrence, progression, and mortality.47,49,55,56 Therefore, in patients with DTC, thyroid hormone replacement is given at doses high enough to induce a subclinically hyperthyroid state, i.e., suppressed TSH values with normal T4 and T3 levels, and without signs or symptoms of thyrotoxicosis. Our current practice (similar to consensus guidelines)17 is to keep the TSH suppressed below 0.1 mU/L in patients at high risk for morbidity and mortality based on tumor pathology, tumor avidity for RAI, and stage of disease, and to keep the TSH minimally suppressed (between 0.1-0.5 mU/L) in low-risk patients (the vast majority of patients), noting that it is not unreasonable to keep the TSH low-normal in low-risk patients who have no evi-
idence of disease within the first year after initial therapy. Potential risks of long-term TSH suppression, including effects on the bones and heart, are minimal in the otherwise healthy 20- to 39-year age group.

**Clinical Follow-Up**

The patient with DTC is monitored initially every 6 months using physical examination, US in patients at risk for locoregional recurrence, and blood tests. TG serves as an excellent tumor marker, and it should become undetectable after successful therapy. Blood samples should be screened routinely for the presence of TG autoantibodies, which occur in up to 25% of thyroid cancer patients. In any individual with positive antibodies, the TG level cannot be interpreted due to assay interference and a likely false negative result. In these cases, the antibody titer can be followed, since many patients cured of their disease will ultimately reach undetectable levels, albeit several years after diagnosis.

A TSH-stimulated TG level after THW or rhTSH is typically obtained 12 months after initial treatment. Approximately 6% of patients with TG levels suppressed to <1 ng/mL will have a positive stimulated TG level, and this is the group that will most likely benefit from further testing. (Patients in whom the TG is detectable while on TSH suppressive therapy are very likely to have residual disease and therefore can be monitored for progression with a suppressed TG alone.) Eighty percent of patients with a rhTSH-stimulated TG value of >2 ng/mL will have disease identified within 5 years, although some patients with a positive test may ultimately have resolution of their minimally elevated stimulated TG. Therefore, there is some utility in repeating a stimulated TG in patients whose TG is negative on suppressive therapy but previously positive after THW or rhTSH, but it does not apply to patients in whom the stimulated and suppressed TG are undetectable, since these patients are likely cured. Many centers perform at least one follow-up thyroid scan, usually at the 12-month follow-up (6 months in very high-risk patients), although a concomitant thyroid scan (at the time of TSH stimulation) may not be necessary in low-risk patients who have had no evidence of disease. Regardless, there is little value in repeating additional thyroid scans once a negative scan has been documented, except perhaps to re-evaluate the patient who has evidence of serologic progression and a negative neck US.

If the TG is detectable, evaluation of the neck with US and, in select cases, cross-sectional imaging of the neck (CT or MRI) is important to localize resectable disease. Chest CT should be obtained to identify distant metastases. In the subset of patients with elevated serum TG levels and negative imaging studies (ie, negative diagnostic whole body RAI scan, neck imaging with US or CT, and chest CT), or with a level of TG that is out of proportion to the amount of disease identified, fluorodeoxyglucose positron emission tomography (FDG-PET)/CT fusion imaging can be helpful. Thyroid cancers that are iodine-avid are unlikely to be seen on FDG-PET imaging, whereas tumors with low iodine avidity tend to have higher glucose metabolism, and thus are seen on FDG-PET scans. This inverse relationship likely explains the finding that FDG-PET scans are significant prognostic indicators, with a positive scan predicting a high risk of cancer-associated mortality. The reported median sensitivity and specificity for FDG PET imaging are 77% and 78%, respectively.

If a patient is identified to have a local recurrence, surgery is the treatment of choice. If the recurrence is not amenable to surgical therapy or if distant metastases are identified, assessment and possible treatment with RAI is appropriate, assuming that the disease readily concentrates the isotope. Chemotherapy and/or targeted therapy may be required in patients who have progressive and/or life-threatening disease, despite maximized surgical and RAI therapies.

**Systemic Therapy**

For those patients with metastatic disease that is refractory to RAI, the treatment algorithm becomes less well-defined (Table 2). One difficulty has been the paucity of large clinical trials investigating new agents or salvage strategies. Traditional cytotoxic chemotherapy has been used for DTC, and the most commonly used agent has been doxorubicin, either as a sole agent or in combination with another drug such as cisplatin. However, the response to doxorubicin has not been exceptional, with response rates reported between 0% and 22%. Carboplatin and paclitaxel are sometimes given to patients with advanced thyroid cancer requiring systemic therapy, but this regimen has not been studied formally in this population. Thus, there is a definite need for new and better studied systemic therapies.

With the growing understanding of the molecular biology of DTC, there has been a significant amount of interest in the use of tyrosine kinase inhibitors (TKIs) for the treatment of refractory DTC. Some TKIs have demonstrated ability to inhibit more than one type of tyrosine kinase, which raises the possibility that such multilevel inhibition may increase the likelihood of tumor response. Motesanib (AMG-706, Amgen, Thousand Oaks, CA) is one such agent that targets vascular endothelial growth factor (VEGF) receptors 1-3, the platelet-derived growth factor (PDGF) receptor, and c-KIT. A phase I study using an oral dose of 125 mg daily found partial responses (PRs) in patients with DTC. A follow-up phase II study of 93 DTC cases demonstrated PRs in 14% of patients and stable disease (SD) in 67% of
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<tr>
<th>Drug and Reference</th>
<th>Clinical Phase</th>
<th>No. of Thyroid Carcinoma Patients</th>
<th>Patient Histology</th>
<th>Dose</th>
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<td>I</td>
<td>7</td>
<td>DTC and MTC</td>
<td>125 mg oral daily</td>
<td>PR in 2 DTC patients and 1 with MTC</td>
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<td>125 mg oral daily</td>
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<td>Pennell et al (2008)</td>
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<td>DTC and MTC</td>
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<td>58</td>
<td>DTC</td>
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<td>8% PR and 19% minor response</td>
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<td>Kober et al (2007)</td>
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<td>400-800 mg daily</td>
<td>CR and PR in 1 patient each</td>
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<td>1</td>
<td>MTC</td>
<td>400/200 mg daily + tipifarnib 200 mg twice daily</td>
<td>PR in one patient</td>
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<td>Salgia et al (2008)</td>
<td>I</td>
<td>13</td>
<td>MTC</td>
<td>Varied oral daily</td>
<td>PR in 3 patients and SD in 7 patients</td>
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</tbody>
</table>

Abbreviations: DTC, differentiated thyroid carcinoma; MTC, medullary thyroid carcinoma; PR, partial response; CR, complete response; SD, stable disease.
patients.71 Durable SD of at least 24 weeks was seen in 35% of patients.

Sorafenib (Nexavar, BAY 43-9006; Bayer HealthCare, Wayne, NJ, and Onyx Pharmaceuticals, Emeryville, CA) is another oral TKI with activity for VEGF receptors 2 and 3, RET, c-KIT, the PDGF receptor, and the serine kinase B-Raf. Thus far, there have been two phase II clinical trials studying the effects of sorafenib in all subtypes of thyroid cancer. The first published study included 30 patients with progressive thyroid cancer who were treated with sorafenib for a minimum of 16 weeks and a median of 27 weeks.72 Using RECIST (Response Evaluation Criteria in Solid Tumors), the PR rate was 23% and the rate of SD was 53%, giving an overall clinical benefit of 77%. Median progression-free survival (PFS) was 84 weeks. A clinical trial at Ohio State University73 enrolled a total of 36 assessable PTC patients, three (8%) of whom had a PR and seven (19%) of whom had a minor response, with a 23%-29% decrease in the target lesions. In both studies, significant declines (70%) in TG levels were observed during the course of treatment.

Axitinib (AG-013736; Pfizer, New York, NY) targets VEGF receptors 1, 2, and 3, c-KIT, and the PDGF receptor. A recent phase II study examined the response in 60 patients with advanced thyroid carcinoma using a dose of 5 mg twice per day.74 PRs were noted in 30% of patients and occurred independent of histologic subtype. SD of at least 16 weeks duration was found in 38% of patients. Median PFS was 18.1 months. Correlative studies indicated decreased soluble VEGF receptor 2 and 3 levels compared to KIT levels, which suggested a mechanism of action directed more toward VEGF.

Sunitinib (SU011248; Sutent; Pfizer) is an oral TKI targeting all of the VEGF receptors, c-KIT, FLT3, RET, and the PDGF receptor. There has been one report of sunitinib use in DTC.75 In that report, one patient had a metabolic PR, while the other patient had SD for 4 years. Currently, there are no published data on clinical trials using sunitinib for DTC or MTC, but phase II studies are ongoing.

MEDULLARY THYROID CARCINOMA

Epidemiology

MTC is a rare subtype of thyroid cancer that accounts for approximately 5% of all thyroid malignancies.4 The mean age at diagnosis is 50 years; only about one third of MTC cases occur in patients younger than 40 years of age.76 Incidence rates range from 0.6 cases per million per year in young adults ages 20-24 years to 1.5 cases per million per year in the 35- to 39-year-old age group.9 Unlike DTC, there is no clear gender predilection, with a female-to-male ratio of 1.6:1 in the young adult population.9 This may reflect the fact that a significant proportion of young adults diagnosed with MTC are likely to have a dominantly inherited genetic disease (see below). Five-year survival rates for MTC are lower than that for DTC, and generally range from 85%-95% in the young adult population.9 Many cases of MTC, when not diagnosed early, are incurable, yet they may demonstrate an indolent clinical course.

Etiology

MTC represents a malignancy arising from the parafollicular C cell, a cell of neural crest origin that migrates to the thyroid during embryogenesis and secretes the hormone calcitonin (CTN). At least 25% of MTC cases are familial (ie, secondary to a germline RET mutation), and the younger the patient is at the age of presentation, the more likely it is to be genetic.77 When a germline RET mutation is absent, the MTC is considered to be sporadic. Sporadic MTC is associated with a somatic RET mutation in up to 50% of cases. The M918T mutation is the most common, and such somatic mutations are associated with more aggressive disease and a worse outcome.78 In patients with sporadic MTC, only one thyroid lobe is involved, whereas in patients with heritable disease the MTC is usually bilateral, multicentric, located at the junction of the upper one third and lower two thirds of the thyroid lobes, and associated with C-cell hyperplasia, the initial stage in the development and progression of MTC.79

Young adults with hereditary MTC are afflicted with one of three hereditary tumor syndromes: multiple endocrine neoplasia type 2a (MEN2A) or type 2b (MEN2B), and familial MTC (FMTC). In addition to MTC, 50% of patients with MEN2A and MEN2B develop pheochromocytomas and up to 20% of MEN2A patients develop hyperparathyroidism.16 Other manifestations can include cutaneous lichen amyloidosis, PTC, and Hirschsprung’s disease.77 All patients with MEN2B develop a generalized ganglioneuromatosis, manifested most obviously by the presence of oral mucosal neuromas, and a characteristic facial appearance and Marfanoid body habitus. Patients with FMTC only manifest MTC, although this group also may have MEN2A that has not yet been recognized because of delayed penetrance of the pheochromocytoma and hyperparathyroidism phenotypes. MTC occurs virtually in all patients with these familial endocrinopathies, and it is the most common cause of death in affected individuals.

Hereditary MTC and its associated syndromes are caused by characteristic missense mutations in the RET proto-oncogene located on chromosome 10.80,82 RET encodes for a tyrosine kinase receptor and the germline mutations identified in MTC cause activation of intracellular signaling pathways in the absence of the endogenous ligand, glial cell line-derived neurotrophic factor (GDNF). There is a well-established genotype-phenotype correlation in hereditary MTC, and the spe-
cific mutation often predicts disease aggressiveness and the associated clinical phenotype.11,77

Diagnosis and Clinical Presentation

Similar to DTC, MTC usually presents as a firm, painless neck mass or as metastatic lymphadenopathy (Figure 2). However, with very high plasma CTN levels, diarrhea and/or flushing may be present. The initial approach to the evaluation of a young adult suspected to have MTC is similar to the assessment of PTC, including the use of US and FNA. One major difference, however, is that genetic testing for an activating mutation in the RET proto-oncogene (preferably with the assistance of a genetic counselor) should be performed in all young adults diagnosed with MTC.15 Preoperative measurement of CTN in patients with an established diagnosis of MTC or who have been identified to harbor a RET germline mutation is useful to document the baseline value and to help determine the extent of disease. In order to identify significant metastatic disease that may change the course of therapy, routine cross-sectional imaging of the neck, chest, and abdomen (with particular attention paid to the liver) is recommended in newly diagnosed patients who have extensive nodal metastases. Finally, until RET status is known, all patients with MTC should undergo biochemical screening for pheochromocytoma (plasma and/or urine metanephrines) to document that there is no concomitant pheochromocytoma, as is seen in 50% of patients with MEN2A and 2B.

Management

Surgery

By the time MTC becomes clinically apparent, it has usually spread to regional cervical lymph nodes.83 Therefore, any young adult diagnosed with MTC should have a total thyroidectomy with resection of lymph nodes in the central compartment (level VI) of the neck.11,15 Similar to PTC, if lateral nodal metastases are evident preoperatively, the lymph node dissection should be extended to levels II-V in a compartment-oriented approach.84 The correct operation and management of the parathyroid glands in young adults with a mutated RET allele is determined by the specific mutation present (Table 1). Resection of lymph nodes in the central zone of the neck is required in MEN2B patients but can be performed selectively in MEN2A and FMT patients undergoing prophylactic thyroidectomy, as long as the pre-operative evaluation is favorable (Table 1). Following surgery, MTC patients are started on thyroid hormone therapy to normalize their TSH levels.

External Beam Radiation Therapy

There have been no randomized controlled trials examining the role of adjuvant EBRT in MTC. Based on retrospective studies, EBRT is considered an adjunctive treatment for extensive neck or mediastinal disease, particularly in older patients at high risk for morbidity and mortality from locoregional relapse, or as palliative treatment for symptomatic metastatic bone disease.85-87 Recurrence-free rates for patients with microscopic residual disease, lymph node involvement, and/or extra-glandular invasion are 86% with adjuvant EBRT and 52% with surgery alone.85 However, local control is only 20%-25% for those patients with gross residual disease after surgery.85,86 Although recent reports have suggested more favorable locoregional control in such patients,87 Despite its possible benefits in the control of neck disease, EBRT has not been shown to increase overall survival.76,85 Therefore, the decision to treat a young adult with EBRT must consider the risk of local recurrence versus the risk of EBRT morbidity and the extent of distant metastasis, which are most likely to affect overall survival. Finally, unlike DTC, MTC is not iodine-avid and cannot be treated with RAI.

Clinical Follow-Up

MTC cells have great biosynthetic activity and secrete both CTN and carcinoembryonic antigen (CEA), which are excellent tumor markers for the disease. CTN, in particular, provides a high degree of diagnostic sensitivity, specifically in the long-term follow-up of MTC. Occasionally, MTC can lose its ability to produce CTN, which is usually indicative of a more aggressive tumor and hence a poorer prognosis. Following surgical therapy, CTN and CEA should be measured regularly, starting about 3 to 4 months after surgery, in order to remove the possibility that CTN synthesis is increased due to postoperative inflammatory effects or that CEA remains elevated due to its long half-life.77 The doubling time of CTN and CEA can be very useful in the follow-up of MTC, with a fast doubling time being associated with tumor progression and decreased survival.88,89

Patients with MTC are cured infrequently once the disease progresses beyond the thyroid gland, and an elevated postoperative CTN level almost always reflects residual disease. In these cases, patients may have microscopic disease (detectable only via tumor markers) and be asymptomatic for years; continued expectant surveillance with tumor marker and neck US monitoring is appropriate in this setting, since one is unlikely to find significant macroscopic disease if the CTN level is below 250 pg/mL.84 Most tumors ultimately do progress, and, in addition to locoregional recurrence, can metastasize distantly, most commonly to mediastinal lymph nodes, lung, liver, and/or bone. Recent reports have suggested that the most useful studies to identify disease sites include US of the neck, chest CT, liver MRI, bone scan, and MRI of the axial skeleton; 18F-FDG-PET scan appears to have limited
value in the follow up of MTC patients with elevated CTN levels.90 Because the hypervascular and often mi-
liary hepatic metastases may not be detected by con-
ventional CT or MRI, laparoscopy also has been recom-
mended by some centers to identify liver metastases
prior to repeat neck surgery.91 Finally, the lifelong
management of heritable MTC also includes appropri-
ate genetic counseling and at least annual screening for
the other endocrine manifestations of MEN2A and
MEN2B.

Systemic Therapy

Dacarbazine-based chemotherapeutic regimens have
been used in the systemic treatment of MTC and may
be effective in reducing tumor burden, but a survival
benefit has not been clearly demonstrated77 (Table 2).
Molecular therapies targeting tyrosine kinases have
piqued the interest of researchers, and multiple oral
TKIs have been studied in patients with refractory
MTC. Imatinib mesylate (STI571, Gleevec; Novartis,
Basel, Switzerland) was one of the first TKIs and was
tested originally in chronic myelogenous leukemia due
to its specific inhibition of the bcr-abl oncogene. How-
ever, imatinib also has activity against other tyrosine
kinases, such as the PDGF receptor and c-KIT. Two
phase II studies examining the use of imatinib for
MTC were completed recently. However, no objec-
tive responses were observed.92,93 Vandetanib (ZD
6474, Zactima; AstraZeneca, Wilmington, DE) is an oral
TKI that targets the VEGF-2 and 3 receptors, RET (in-
cluding the M918T RET mutation), and at higher con-
centrations, the epithelial growth factor (EGF) recep-
tor. A recently completed open-label phase II trial
investigated vandetanib activity in 30 MTC patients
using a dose of 300 mg daily.94 In early analysis, 20% of
patients had a PR and 30% of patients had SD. Also, 63%
of patients demonstrated a sustained drop in CTN lev-
els for at least 6 weeks. In a phase II trial of 91 patients
treated using a dose of 250 mg,95 only 2% had a confirmed PR,
but another 47% experienced SD for at least 24 weeks;
report of a PR with stabilization of disease for 8 months
in a patient with MTC using sorafenib with tipifarnib
(R115777, Zarnestra; Johnson & Johnson, Langhorne,
PA).98 Tipifarnib is an inhibitor of farnesyl transferase,
which is involved with RAS regulation. The rationale
for this combination is that both B-RAF and RAS are
members of the MAPK pathway, and thus some syner-
gism may be obtained. Sunitinib is currently being
studied in a phase II protocol, although one case report
has suggested efficacy in MTC.99 Finally, newer oral
TKIs are showing promise in the treatment of MTC.
XL-184 (Exelixis, San Francisco, CA) is an inhibitor of
VEGF receptors 1 and 2, c-MET, RET, c-KIT, FLT3, and
Tie-2. Preliminary results from a phase I study suggest
significant activity of this drug in MTC,100 and a phase
III study has been initiated recently.

REPRODUCTIVE ISSUES IN THE
YOUNG ADULT THYROID CANCER PATIENT

Thyroid Cancer and Pregnancy

Thyroid cancer is the second most common malign-
nancy during pregnancy, with a reported prevalence of
14 per 100,000 live births in a cohort from the United
States.101 When DTC is discovered during pregnancy,
definitive surgery usually can be postponed until the
postpartum period.102,103 Monitoring for rapid progress-
ion with physical examination, periodic neck ultra-
sound, and TG level is warranted. If surgery is nec-
essary because the tumor is exhibiting rapid growth, it
should be done in the second trimester due to the risks
of spontaneous abortion in the first trimester and pre-
term labor in the third trimester.103 Thyroidectomy
during pregnancy has not been associated with adverse
maternal or neonatal outcomes based on retrospective
cohort studies.104 However, ensuring intact parathyroid
function is vital since the calcium homeostasis of the
fetus relies on the maternal supply.105 RAI given at
diagnostic or therapeutic doses should be deferred
until the postpartum period and after breast feeding is
completed.

There is a theoretical concern of tumor growth for
patients with pre-existing disease who then become
pregnant, given the natural increase in thyroid volume
during pregnancy. Studies of patients with stable DTC
have not found significantly elevated TG levels or gross
disease progression after pregnancy, even in patients
with previously stable distant metastases.106,107 TSH
suppressive therapy should continue for pregnant pa-
tients with DTC and should be considered for those
with newly diagnosed, locally advanced PTC who are
delaying surgery until after delivery. Free T4 or total T4
levels should be at the upper range of normal for
pregnancy with a suppressed but detectable TSH
level.103 Thyroid hormone requirements are higher
during pregnancy, so patients already on therapy will
need at least a 25% increase in dosage when pregnancy is confirmed to maintain suppressive levels and to ensure adequate fetal supply.17,108

There are no specific guidelines or reports on management of MTC diagnosed during pregnancy. Since MTC often presents with more disease burden than DTC, and surgery is the primary therapeutic modality, surgery during the second trimester may be necessary. There is no role for TSH suppressive therapy in MTC, but the need for increased thyroid hormone replacement to ensure fetal supply for mothers with pre-existing post-surgical hypothyroidism still applies. Rarely, patients with MEN2A or 2B present during pregnancy due to peripartum hypertension or cardiac failure from a pheochromocytoma.109 Female patients with a history of MTC due to MEN2A or 2B should undergo screening for pheochromocytoma before or early in pregnancy.16 A genetic counselor should be available to guide the patient with a RET mutation regarding his or her risks of having a child with the same mutation, and to discuss options such as pre-implantation genetic screening, particularly in patients with MEN2B.

RAI and Fertility

When caring for young adults with thyroid cancer, providers should be prepared to address patients' concerns of future fertility. Systematic reviews of RAI effects on the gonadal system of men and women with DTC provide reassuring results.110,111 In men, there is elevation in FSH and LH concentrations and lower sperm counts and motility in the first 6 months after RAI, with normalization usually by 18 months, suggesting transient gonadal dysfunction. Higher cumulative doses of RAI (>350 mCi) appear to correlate with higher FSH levels and oligospermia. However, there is no evidence of increased rates of infertility. Nonetheless, the American Thyroid Association guidelines currently recommend offering pre-RAI sperm banking if cumulative RAI activities will exceed 400 mCi.17 It is not known how early after RAI treatment it is “safe” for men to father children. The European Thyroid Association112 suggests waiting for at least 4 months.

In women, FSH values are elevated at 6 months with normalization by 12 months.110 Between 12% and 51% of women experience new menstrual changes in the first year after RAI (with resolution by 12 months), and twice as many women enter menopause by age 51 years compared with controls. There appears to be no correlation with the dose of RAI, and no significantly increased risk of infertility, miscarriage, stillbirths, congenital defects, or cancers have been identified in offspring.115 Current recommendations state that pregnancy should be avoided for 6-12 months after receiving therapeutic RAI doses so that thyroid function can stabilize and remission of cancer can be verified.17,103 RAI should not be given to women who are breast feeding and should be deferred for at least 6 to 8 weeks after breast feeding cessation to decrease radiation exposure to breast tissue.17

LATE EFFECTS OF THYROID CANCER THERAPY

The young adult treated for DTC can usually anticipate excellent outcomes and long-term survival, and treatment is generally well tolerated with limited side effects. However, with the advent of increasingly aggressive therapies and the prospect of decades of survivorship, it is important to maintain an awareness of the potential early and late adverse events that may impact the patient’s quality of life.49,114,115

One of the unique aspects of DTC is the use of RAI in the evaluation and treatment of patients with this disease. Therapy with RAI is generally well tolerated and safe. Early and usually transient side effects of RAI include nausea, vomiting, diarrhea, sialadenitis, xerostomia, loss of taste and smell, thyroiditis (if a sizable thyroid remnant remains after surgery), and rarely bone marrow suppression (leukopenia and thrombocytopenia).116,117 Some of these early side effects may be minimized by asking patients to increase their oral hydration after therapy. Previous recommendations included sucking on a tart candy, such as a lemon drop, to decrease salivary gland damage. However, a recent study revealed that this practice, when initiated within 24 hours of RAI exposure, may actually increase the risk of salivary gland damage.118

There is growing understanding of the possible late effects of RAI, which include permanent damage to the salivary glands resulting in chronic xerostomia or salivary duct stones, excessive dental caries, reduced taste, pulmonary fibrosis (in those with diffuse pulmonary metastases), and the possibility of the development of other cancers (stomach, bladder, colon, salivary gland, breast, and leukemia) after very high cumulative doses of 131I.116,119,121 Therefore, caution should be exercised when giving multiple high doses of RAI to young adults, particularly in those patients whose disease is more indolent and may not require such aggressive therapy.

In the patient treated for DTC or MTC, surgical resection can be associated with potential late effects, including voice difficulties and hypoparathyroidism.122 If the recurrent laryngeal nerves or the external branches of the superior laryngeal nerve are damaged, patients may be hoarse following surgery and require additional surgical procedures to improve phonation.123 Patients who develop permanent hypoparathyroidism will require lifelong vitamin D and oral calcium preparations to maintain eucalcemia.

There has been concern about the adverse cardiac effects of long-term suppressive therapy for DTC. A few studies have shown increased left ventricular mass in-
dex (LVMi) in treated patients compared to controls, with resolution of the abnormalities with reduction in suppressive doses of L-thyroxine. The importance of this finding of demonstrable cardiac disease is unclear and other adverse cardiac effects have not been reported consistently. However, increased LVMi has been associated with left ventricular hypertrophy, which is an important risk factor for cardiovascular disease.

Many survivors of thyroid cancer express ongoing difficulty with problems that may impact quality of life. When compared to survivors of other cancers, thyroid cancer survivors were more likely to report memory problems, psychological issues, and migraine headaches. In another series, more than 50% of patients reported fatigue as a chronic complaint. Fatigue is frequently reported, even in those with normal or mildly suppressed TSH levels, and it is unclear how to intervene effectively. Studies combining L-thyroxine with tri-iodothyronine therapy have not shown clear benefit, but this may be considered in individual cases. Other reported problems include anxiety, insomnia, temperature sensitivity, skin changes, dryness, and pruritus.

CONCLUSION

The incidence of thyroid malignancies is increasing, and the last few years have seen an emergence of targeted systemic therapies for tumors not responding to surgery or RAI, in the case of DTC. For well-differentiated tumors, controversies remain concerning the extent of surgery, indications for adjunctive RAI in low-risk patients, modalities for long-term follow-up, and the degree and length of TSH suppression therapy. MTC in the young adult requires investigation of a hereditary syndrome. Fortunately, thyroid cancer in young adults can be cured or at least treated as a chronic disease in most cases. Therefore, management in this population requires additional consideration of long-term effects of therapy and reproductive issues. Coordination of care should be done by a multidisciplinary team with expertise in managing thyroid carcinoma.

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