New Treatments and Shifting Paradigms in Differentiated Thyroid Cancer Management

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Background: Although most thyroid cancer patients have an excellent prognosis, 10% of low-risk cancers and 25% of high-risk cancers recur, with mortality rates in excess of 50% at 3 years for aggressive thyroid cancer. Traditional paradigms including surgery, I\textsuperscript{131} ablation, and TSH suppression do not offer additional therapeutic options for cancers that fail these interventions. Risk stratification and outcomes data are shifting the treatment paradigms to favor more individualized therapies based on risk, and new treatment targets have been identified with promise to treat more aggressive thyroid cancer.

Methods: The authors review the recent literature and published guidelines on thyroid cancer and summarize changing management paradigms and treatments of thyroid cancer.

Results: Outcomes data and risk stratification have promoted changes to traditional paradigms. Total/near-total thyroidectomy improves outcomes in both recurrence and mortality. Central compartment lymph node dissection facilitates nodal status determination and likely improves outcomes, while low-risk patients with small tumors are not likely to benefit from I\textsuperscript{131} remnant ablation. Early-phase studies have demonstrated significant improvement in progression-free survival with multikinase inhibitors targeting MAPK and angiogenic pathways.

Conclusions: Risk stratification and outcomes data have modified treatment paradigms in thyroid cancer. Patients with progressive thyroid cancer that is no longer surgically resectable or iodine avid should be considered for treatment with multikinase inhibitors, preferably by enrollment in a therapeutic treatment trial.

Introduction

The rise in the incidence of thyroid cancer (2.4%) is the fastest in the United States, with annual cases exceeding 30,000 patients.\textsuperscript{1} Traditional paradigms have been the mainstay of treatment for thyroid cancer for most of the 20th century, with surgical resection followed by radioactive iodine (RAI) ablation and thyroid-stimulating hormone (TSH) suppression. Because thyroid cancer has a better prognosis than many other cancers have, and also because the mortality rates are relatively low, active investigation into new treatment paradigms has been limited.\textsuperscript{2} However, 10% of low-risk thyroid cancers and 25% of high-risk thyroid cancers recur, with mortality rates in excess of 50% for aggressive forms of thyroid cancer.\textsuperscript{3,5} Traditionally, recurrence or persistence of dis-
ease after thyroidectomy and RAI has led to additional treatment with $^{131}$I with successive decrease in efficacy, an increase in side effects of therapy, and the development of secondary radiation-influenced cancers.6,7 Risk stratification strategies and outcomes data have begun to shift the traditional paradigms of treatment, and the advent of new therapeutic strategies targeting key pathways in growth and survival of cancer cells has opened the opportunity for alternate therapies in treating thyroid cancer. By primarily targeting kinase or angiogenic pathways, the goals of new therapies are to limit progression, to stabilize disease rather than to “cure,” and to provide additional options for treating recurrence when iodine avidity wanes with successive treatments. This report discusses changing paradigms and highlights new targets and treatment trials in differentiated thyroid cancer.

The behavior of differentiated thyroid cancer can range from an indolent, clinically insignificant disease found incidentally to an aggressive pattern of locally invasive disease or distant metastases. Treatment planning should reflect our best estimate of risk of disease-related death and risk of recurrence. Unlike most cancers, differentiated thyroid cancer recurrence does not necessarily correlate with increased risk of mortality. This is particularly demonstrated in young patients who have higher rates of local recurrence but low mortality risk. Several clinical features enable initial risk stratification, including patient age, size of the primary tumor, histology, gross extrathyroidal extension, completeness of resection, involvement of the cervical lymph nodes, or distant metastasis.

**Risk Stratification**

Tuttle et al8 stratified risk of death into four categories: very low risk, low risk, intermediate risk, and high risk. High-risk features are age > 45 years, larger tumors (> 4 cm) or worrisome histology, incomplete resection, distant metastasis, and cervical lymph node metastasis. Low-risk features are young age, classical histology, smaller tumors, complete resection, no distant metastasis, and no cervical lymph node involvement (in patients < 45 years of age, lymph node involvement has not correlated with increase risk of death). Intermediate-risk disease includes young patients with classic papillary tumors > 4 cm, microscopic extrathyroidal disease, more aggressive histology or vascular invasion, or older patients with classic papillary histology with a size < 4 cm, or extrathyroidal extension, aggressive histology < 1 cm to 2 cm but with complete resection and without distant metastasis. Establishing a treatment plan with an emphasis on outcomes based on risk assessment has begun to shift the paradigms of treatment in differentiated thyroid cancer (Table 1).

**Table 1. — Risk of Death From Thyroid Cancer**

<table>
<thead>
<tr>
<th></th>
<th>Very Low Risk</th>
<th>Low Risk</th>
<th>Intermediate Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>&lt; 45 years</td>
<td>&lt; 45 years</td>
<td>Young patients (&lt; 45 years)</td>
<td>&gt; 45 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Classic PTC &gt; 4 cm</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Or vascular invasion</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Or extrathyroidal extension</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Or worrisome histology of any size‡</td>
<td></td>
</tr>
<tr>
<td>Primary tumor size</td>
<td>&lt; 1 cm</td>
<td>1–4 cm</td>
<td>Older patients (&gt; 45 years)</td>
<td>&gt; 4 cm classic PTC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Classic PTC &lt; 4 cm</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Or extrathyroidal extension</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Or worrisome histology &lt; 1–2 cm confined to the thyroid‡</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>Classic PTC, confined to the thyroid gland*</td>
<td>Classic PTC, confined to the thyroid gland*</td>
<td>Histology in conjunction with age as above</td>
<td>Worrisome histology &gt; 1–2 cm‡</td>
</tr>
<tr>
<td>Completeness of resection</td>
<td>Complete resection</td>
<td>Complete resection</td>
<td>Complete resection</td>
<td>Incomplete tumor resection</td>
</tr>
<tr>
<td>Lymph node involvement</td>
<td>None apparent</td>
<td>Present or absent†</td>
<td>Present or absent†</td>
<td>Present or absent†</td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>None apparent</td>
<td>None apparent</td>
<td>None apparent</td>
<td>Present</td>
</tr>
</tbody>
</table>

Only those patients meeting all criteria within the respective column would be classified as very low risk or low risk. Older patients with either incomplete tumor resection or presence of distant metastasis are considered high risk irrespective of tumor size and specific histology. Patients with a combination of risk factors (age, histology, and tumor size) crossing over between columns are classified as intermediate-risk patients. PTC = papillary thyroid cancer.

* Confined to the thyroid gland with no evidence of vascular invasion or extrathyroidal extension.
† Cervical lymph node metastases in older patients, but probably not in younger patients, may confer an increased risk of death from disease.
‡ Worrisome histologies include histologic subtypes of papillary thyroid cancer such as tall cell variant, columnar variant, insular variant, and poorly differentiated thyroid cancers.

A major determinant of risk involves the histologic subtype of thyroid cancer. Histopathologically, many variants exist for papillary thyroid carcinoma, some of which have been reported to behave more aggressively. As larger series have been studied, the only variant that seems to be clinically significant among differentiated thyroid carcinoma is the tall cell variant. Tall cell variant has been reported to represent between 5% and 10% of all cases. It was first described by Hawk and Hazard in 1976. This variant is more likely to present at an older age with associated high-risk features such as larger size, extrathyroidal extension, and distant metastasis. Con vincing data suggest more aggressive treatment as these tumors have a higher recurrence rate and mortality.

These tumors may also have a higher incidence of progression to more poorly differentiated subtypes like anaplastic (undifferentiated) carcinoma, which is among the most lethal of all human malignancies with a median survival in most series of approximately 3 months. Diagnosis of this important variant should be restricted to tumors with 50% or greater presence of the characteristic elongated cell where the height is at least three times the width.

Histopathologic features in all differentiated thyroid carcinomas that portend a higher recurrence rate and worse outcome have been well documented and include extrathyroidal extension and tumor size. Other features such as positive margins and multicentricity have also been implicated as predictors of a higher recurrence rate and overall poor outcome.

Surgical Treatment Options

Thyroid cancer is primarily a surgical disease. Except for low-risk cancer found incidentally on final pathology, most thyroid experts now advocate for total/near-total thyroidectomy as the procedure of choice. A total thyroidectomy facilitates adjuvant therapy using radioactive I ablation and provides a surrogate for evaluating completeness of surgical extirpation of cancer by post-operative measurement of thyroglobulin. Further, in a study by Bilimoria et al using National Cancer Data Base information, lobectomy alone resulted in a higher risk of recurrence and death in tumors > 1 cm compared to total/near-total thyroidectomy.

Although total/near-total thyroidectomy is now the standard approach for thyroid cancer, the extent of initial surgery remains debatable. In patients with papillary thyroid cancer, 20% to 50% have central (or level VI) lymph nodes involved at the time of initial presentation, even in low-risk patients. Traditionally, central lymph nodes were removed with clinically palpable disease, either preoperatively or at the time of thyroidectomy. In these cases, the common practice was to resect only the clinically involved nodes. Current evidence suggests that prophylactic central node dissection may improve outcomes, decreasing both recurrence rates and mortality.

Preoperative Ultrasound Evaluation

Although up to 20% of patients with lateral neck metastases “skip” the central compartment, most patients will have involvement of the central lymph nodes with lateral lymph node metastasis. Clinical staging alone is inaccurate as up to 90% of papillary thyroid cancers have micrometastatic involvement of these lymph nodes. Now recommended in all patients with malignant thyroid disease with a plan for thyroidectomy, a detailed ultrasound (US) evaluation of the cervical lymph nodes is an excellent staging study, identifying suspicious lymphadenopathy in 20% to 31%. US is primarily valuable in the lateral compartments. Shadowing of the intact thyroid lobes precludes detailed evaluation of the central neck except in cases of significantly bulky disease, and 50% of lymph node involvement is missed on preoperative US. If US evaluation identifies lymph nodes with features that suggest metastatic disease (eg, rounded contour and loss of fatty hilum, internal echogenicity or calcification, cystic change, or thickened capsule), US-guided fine needle aspiration for cytology is recommended. If cytologic evaluation confirms metastatic papillary thyroid cancer, a therapeutic dissection with clearance of the lymphatic compartment at the time of initial surgery should be performed. Recently, the use of needle washings for thyroglobulin after aspiration has been suggested to improve the yield of aspiration for detection of metastasis. While a preoperative, detailed US evaluation of the bilateral neck compartments potentially modifies the surgical approach in 20% of patients, the efficacy of US depends on the unique skill of the imager. Assessment by alternate imaging may be helpful in some cases, particularly with large, rapidly growing, or retrosternal disease. However, the sensitivity of PET, CT, or MRI to assess cervical lymph node disease is poor (30% to 40%) and is not recommended for routine evaluation.
Radioactive Iodine Ablation

The routine use of radioactive iodine (RAI) ablation using I\(^{131}\) for all papillary thyroid cancer has been standard for many decades. However, outcome data for this practice are limited. Recent publications suggest that local recurrence rates are not altered in low-risk patients by adjuvant treatment of I\(^{131}\), and a more selective use seems prudent. Selective use of RAI ablation based on risk of recurrence is an evolving strategy, and both histologic and molecular features contribute to this risk. Histologic evidence of tumor size (> 4 cm) or extension beyond the thyroid capsule (T3 lesions), aggressive variants of papillary thyroid cancer (tall cell, insular), age (> 45 years), and positive nodes for metastasis are factors that increase the risk of local recurrence. Conversely, T1N0 papillary cancers, particularly in patients < 45 years of age, are at low risk for recurrence, and interval evaluation with US of the thyroid bed and lateral lymph nodes, with measurement of thyroglobulin levels and TSH suppression, is likely adequate treatment for this group. RAI ablation is indicated for all patients with known distant metastases, gross extrathyroidal extension of tumor, and tumor size > 4 cm. It is also recommended for intermediate- or high-risk patients. RAI ablative treatment is not without side effects, including dry mouth, loss or change of taste, and risk of radiation induced cancers in higher doses.

The emerging technology of defining the molecular genomic patterns predictive of high risk for recurrence suggests that molecular testing will soon facilitate decisions on adjuvant treatments.

Thyroglobulin, a protein made only by thyroid cells, becomes a marker for persistence if postoperative levels are high or for recurrence when rising compared to the postoperative baseline value. Ideally, thyroglobulin should be measured at a minimum of 4 weeks after surgical resection to identify the “nadir” of thyroglobulin levels. Undetectable levels or levels < 1.0 ng/mL suggest optimal surgical resection of thyroid tissue and thyroid cancer cells. The “gold standard” of thyroid cancer treatment has been to eliminate all traces of thyroglobulin in an attempt to eradicate the disease, often leading to repeated doses of I\(^{131}\) for ablation. Recent data suggest that the persistence of detectable thyroglobulin in the serum does not readily correlate to progression or change in outcomes; therefore, treatment should be aligned more precisely with identifiable disease after initial ablation as adjuvant therapy in patients at higher risk for recurrence.

Disease Recurrence

Despite appropriate surgery, RAI ablation, and TSH suppression, disease recurs in some patients with papillary thyroid cancer. Recurrence is primarily in the neck, either local in the thyroid bed or within cervical lymph nodes. With US and thyroglobulin level surveillance, these recurrences are usually limited in size and are amenable to operative surgical resection. If the patient is relatively iodine naive (ie, one prior ablative dose or none), RAI ablation is indicated after best surgical resection. There is probably little utility in treating recurrences after multiple ablations or high levels of prior I\(^{131}\) exposure. In high-risk patients with histologically aggressive variants, particularly in cases of residual disease or close margins, postoperative external beam radiotherapy is likely helpful in limiting additional recurrences. However, this treatment comes with significant side effects and also makes additional surgical resection more complicated.

In few low-risk patients and in 25% of high-risk patients, unresectable local disease or distant metastases fail control with conventional therapy. Options for disease control are limited for these patients. Additional therapeutic options are necessary; and molecular targets have been identified with some success in stabilizing this aggressive form of thyroid cancer. Recent studies have shown that the mitogen-activated protein kinase (MAPK) pathway is active in growth and survival in differentiated thyroid cancer, and clinical trials have evaluated multikinase inhibitors of this pathway for treatment. Multikinase inhibitors are usually small molecule inhibitors of tyrosine kinases, which are partially selective of multiple pathways. The oncogenic roles of BRAF, RET, and RAS are prime targets, as are growth factor receptors that contribute to malignant growth, such as vascular endothelial growth factor receptor (VEGFR).

Targets in Thyroid Cancer

Several mutations are known to activate the MAPK pathway (Table 2). MAPK signaling is initiated by growth factor binding to receptor tyrosine kinases such as RET or NTRK. The receptors dimerize and the resultant activation is propagated by autophosphorylation of tyrosine residues in the intracellular domain. RAS is activated via adaptor proteins and begins a cascade of activation by binding BRAF, which phosphorylates MAPK/ERK kinase (MEK), which then activates extracellular signal-regulated kinase (ERK). When activated, ERK translocates to the nucleus.

Table 2. — Approximate Prevalence of Mutations in Thyroid Cancer

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<td>&gt; 95%</td>
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nucleus and regulates transcription of genes controlling proliferation and survival.42

In papillary thyroid cancer, point mutations in the BRAF and RAS genes constitutively activate the pathway. Activating BRAF mutations are the most common, found in 43% of papillary cancers.43,45 Nearly all of the mutations evaluated show a thymine to adenine transversion, which results in a valine to glutamate substitution at residue 600 (V600E).46-47 BRAF mutations are common in conventional and tall cell variants, but they are less common in follicular variants of papillary cancer and are not found in follicular thyroid cancer.45,48 Point mutations in RAS appear to occur in many neoplastic transformations involving thyroid follicular cells, both adenomas and carcinomas. RAS genes encode highly related G proteins (HRAS, KRAS, NRAS) and propagate signals arising from membrane receptors. Bound guanosine-5’-diphosphate (GDP) converts to guanosine-5’-triphosphate (GTP) with activation, which activates the MAPK pathway and the PI3K/AKT pathway. GTPase quickly inactivates RAS-GTP, but point mutations lead to increased affinity or inactive autacatalytic GTPase, resulting in permanent activation.39 The mutations occur in 10% to 20% of papillary cancer, most commonly the follicular variant, and with a low rate of lymph node metastasis.49-52 These mutations are also seen in 40% to 50% of follicular thyroid cancer49 and in 20% to 40% of follicular adenomas.53-55

Activation of the MAPK pathway also occurs with chromosomal translocations involving RET. Although RET is expressed in parafollicular cells, a rearrangement termed RET/PTC, a fusion of 3’ of the RET receptor tyrosine kinase gene and the 5’ portion of unrelated genes leads to activation of the MAPK cascade in 20% of papillary thyroid cancer.56-58 Multiple variations are reported, the most common being RET/PTC-1 and -3. These mutations occur with a higher incidence in cancers derived from radiation exposure (50% to 80%).59 Papillary thyroid cancers expressing RET/PTC mutations are typically classic on histology, present at younger ages, and have a high rate of lymph node metastasis.49,60

PAX8-PPAR gamma is another rearrangement in which a fusion of the PAX8 gene encoding a transcription factor and the peroxisome proliferator-activated receptor PPAR gamma gene occurs. PAX8 is a thyroid-specific paired-domain transcription factor, and there is strong expression of PPAR gamma, but the mechanism of transformation is not well understood.39 This mutation is seen in 30% to 40% of follicular thyroid cancer but less in the oncocytic variant (Hurthle cell). This mutation appears to be associated with younger age and small size, and it commonly exhibits vascular invasion. This mutation is harbored in 2% to 10% of follicular adenomas, although these lesions commonly have thick capsules and are described as preinvasive.61-65

Modulators of angiogenesis appear to have a role in progression of thyroid cancer as in other cancers. VEGF regulates endothelial cell proliferation and migration. Elevated levels have been demonstrated in thyroid cancer, and higher levels correlate with tumor size, nodal involvement, extrathyroidal invasion, and distant metastasis.66-69 These observations suggest that angiogenic pathways are targets for therapeutic intervention in thyroid cancer. Several other mutations that have been identified in poorly differentiated thyroid cancers include beta catenin,70 epidermal growth factor receptor (EGFR) overexpression, and p53,71,72 as well as RAS and BRAF. Each of these provides an opportunity for potential intervention in these aggressive cancers.

New Agents Under Investigation
Several agents have been studied in phase II trials, and phase III trials are enrolling for some treatments. Most of the agents target MAPK and antiangiogenic pathways (motesanib, sunitinib, sorafenib, and pazopanib), while others target specific pathways in some thyroid cancers such as gefitinib and erlotanib (anti-EGFR). The tyrosine kinase inhibitors are oral agents that can achieve nanomolar concentrations after oral dosing. Side effects are primarily hypertension, diarrhea, fatigue, and hand-foot syndrome sloughing, and they are reasonably well tolerated. Bone marrow suppression is possible, and monitoring is essential.

Motesanib (AMG-706) is a multikinase inhibitor targeting VEGFR, PDGFR, c-kit, and RET. In a phase II study of 93 patients with progressive, advanced, or metastatic differentiated thyroid cancer (67% papillary), the overall response rate was 14%, with 67% achieving stable disease, while 8% had progression of disease as best response. The median duration of durable response was estimated at 32 weeks. The median progression-free survival was 40 weeks, and 81% of patients had decreased thyroglobulin levels. Treatment was discontinued in 13% of patients due to adverse events, including 55% with grade 3 events. Two deaths were due to pulmonary hemorrhage in metastases in patients with progressive disease. This agent inhibits multiple signaling pathways, including angiogenic pathways, and suggests that targeting multiple pathways may improve outcomes.73

Sorafenib, a multitargeted kinase inhibitor, is active against BRAF, VEGFR, PDGFR, c-kit, and RET. This drug is approved for use in renal cell and hepatocellular carcinoma. In a phase II trial of 30 patients with differentiated or medullary thyroid cancer, a partial response rate was seen in 23% and stable disease in 53%, with a median progression-free survival of 79 weeks.74

Sunitinib is a multitargeted tyrosine kinase inhibitor against VEGFR, PDGFR, Flt3, c-kit, and RET. It is approved for treatment of renal cell carcinoma and imatinib-resistant gastrointestinal stromal tumors. This phase II study enrolled 43 patients, treated with 50 mg daily for 4 weeks, followed by a 2-week interval. In differentiated thyroid cancers, 13% achieved a partial response, while 68% had
stable disease. In medullary thyroid carcinoma, 83% had stable disease. Significant adverse events included neutropenia in 49% and thrombocytopenia in 16%.75

Pazopanib targets VEGFR-1, -2, -3, PDGFR-α and β, c-kit, and RET. Pazopanib is currently approved for the treatment of renal cell carcinoma, as a second-line agent. In a recent abstract, 19% of 32 patients with differentiated thyroid cancer patients achieved a partial response, and thyroglobulin levels were reduced by more than 50% in 11 of 16 patients. However, 23% required dose reduction for toxicity-related to hypertension, nausea/vomiting, diarrhea, anorexia, prolonged QT interval, and a hemorrhagic event.76

Axitinib, a relative selective inhibitor of VEGFR-1, -2, and -3, was used in 60 patients with any form of thyroid cancer. A partial response was seen in 30%, with stable disease of at least 16 weeks seen in an additional 38%. Side effects were similar to those of pazopanib: fatigue, diarrhea, nausea, anorexia, hypertension, and weight loss.77

Gefitinib and erlotinib target EGFR, a pathway activated in some differentiated and anaplastic carcinomas. In a study using gefitinib in 27 patients (41% papillary, 22% follicular, 19% anaplastic, and 15% medullary), there were no complete or partial responses, with 8 patients showing a small reduction in volume. The median progression-free survival was 4 months.78

Conclusions

For patients with thyroid cancer, multikinase inhibitors generally provide a limited initial partial reduction in tumor volume followed by a period of stable disease that creates an interval of control. Agents that also target antiangiogenic pathways appear to improve outcomes, but prolonged duration of control remains limited. With target therapies developed with rational approaches to disease progression in thyroid cancer, new treatments for advanced differentiated thyroid cancers are on the horizon. In patients with advanced disease who are no longer surgically resectable or iodine avid and in whom progression of disease is documented, consideration for a treatment trial using novel multikinase inhibitors is recommended.14 In the absence of an appropriate trial, consideration for off-label use of approved multikinase inhibitors should be included in the treatment paradigm as alternate therapies are currently lacking and the prognosis remains poor (Figure). Currently available medications sunitinib, sorafenib, and pazopanib have demonstrated some efficacy in phase II trials of thyroid cancer.

Differentiated thyroid cancer therapies and paradigms are shifting, with the development of new options for the treatment of advanced cancers. Adapting our treatments to reflect risk and outcomes will improve quality and hope in the care of differentiated thyroid cancer.


