INTRODUCTION

Differentiated thyroid carcinoma (DTC) accounts for the vast majority (90%) of thyroid cancers [1]. Of the differentiated cancers, papillary carcinoma comprises about 85% of cases compared to about 10% that have follicular histology, and 3% that are Hurthle cell or oxyphil tumors [2]. In the United States, approximately 37,200 new cases of thyroid cancer will be diagnosed in 2009 [3]. The yearly incidence has increased from 3.6 per 100,000 in 1973 to 8.7 per 100,000 in 2002, a 2.4-fold increase and this trend appears to be continuing. Almost the entire change to 8.7 per 100,000 in 2002, a 2.4-fold increase and this change consisted of cancers measuring 1 cm or smaller and 87% consisted of cancers measuring 2 cm or smaller [4]. This tumor shift may be due to the increasing use of neck ultrasonography. Certain histologic subtypes of papillary carcinoma have a worse prognosis related to vascular invasion, invasion into extrathyroidal tissues, extensive tumor necrosis and/or mitoses. Adequate surgery is the most important treatment variable influencing prognosis, while radioactive iodine treatment, TSH suppression, and external beam irradiation each play adjunctive roles in at least some patients. Numerous schemes have been developed in an effort to achieve more accurate risk factor stratification. Each of the schemes allows accurate identification of the majority (70-85%) of patients at low risk of mortality (T1-3, M0 patients), allowing the follow-up and management of these patients to be less intensive than the higher-risk minority (T4 and M1 patients), who may benefit from a more aggressive management strategy. Overall 5- and 20-year survival in the low-risk group was 100% and 99% respectively. However, the survival in the high-risk group dropped to almost 72% and 57% respectively.

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ROLE of PREOPERATIVE IMAGING and LABORATORY TESTS in PAPILLARY THYROID CARCINOMA

Papillary thyroid carcinoma involves cervical lymph nodes in 20-90% of patients, and may be present even when the primary tumor is small and intrathyroidal [7-14].
Preoperative neck US identifies suspicious cervical adenopathy in 20-31% of cases, potentially altering the surgical approach in as many as 20% of patients [15-18]. Preoperative neck US for the thyroid gland and cervical lymph nodes is recommended for all patients undergoing thyroidectomy for malignant cytologic findings on biopsy. US-guided FNA of sonographically suspicious lymph nodes should be performed to confirm malignancy if this would change management. Routine preoperative use of other imaging studies (CT Scan, MRI, PET) is not recommended.

Serum thyroglobuline (Tg) levels can be elevated in most thyroid diseases and are an insensitive and nonspecific test for thyroid cancer. There is limited evidence that high preoperative concentrations of serum Tg may predict a higher sensitivity for postoperative surveillance with serum Tg [19]. Evidence that this impacts patient management or outcomes is not yet available. Routine preoperative measurement of serum Tg is not recommended.

EXTENSION of THYROID SURGERY

The goals of thyroid surgery can include removal of the thyroid cancer, staging (Table I), and preparation for radioactive ablation and serum Tg monitoring. Surgical options to address the primary tumor should be limited to hemithyroidectomy with or without isthmusectomy, near-total thyroidectomy (removal of all grossly visible thyroid tissue, leaving only a small amount (< 1 g) of tissue adjacent to the recurrent laryngeal nerve near the ligament of Berry), and total thyroidectomy [20-27]. Subtotal thyroidectomy, leaving > 1 g of tissue with the posterior capsule on the uninvolved side, is an inappropriate operation for thyroid cancer [28]. Adequate surgery is the most important treatment variable influencing prognosis, while radioactive iodine treatment, TSH suppression, and external beam irradiation each play adjunctive roles in at least some patients [29-30].

Surgery for a biopsy suspicious for papillary carcinoma: Because of an increased risk for malignancy, near total or total thyroidectomy is indicated in patients with indeterminate nodules who have large tumors (> 4 cm), when marked atypia is seen on biopsy, when the biopsy reading is “suspicious for papillary carcinoma,” in patients with a family history of thyroid carcinoma, and in patients with a history of radiation exposure [31-35]. Thyroid lobectomy alone may be sufficient treatment in the other cases.

Surgery for a biopsy diagnostic for malignancy: Near-total or total thyroidectomy is recommended if the primary thyroid carcinoma is > 1 cm [36] + contralateral thyroid nodules or regional or distant metastases are present + the patient has a personal history of radiation therapy to the head and neck + or the patient has first-degree family history of PTC. Older age (> 45 years) may also be a criterion for recommending near-total or total thyroidectomy even with tumors < 1-1.5 cm, because of higher recurrence rates in this age group [20, 24-25, 37-38]. Increased extent of primary surgery may improve survival for high-risk patients [39-40] and low-risk patients [36]. Other studies have also shown that rates of recurrence are reduced by total or near-total thyroidectomy among low-risk patients [24, 41-42].

Thyroid lobectomy alone may be sufficient treatment for small (< 1 cm), low-risk, unifocal, intrathyroidal papillary carcinomas in the absence of prior head and neck irradiation or radiologically or clinically involved cervical nodal metastases [43].

<table>
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<td><strong>TNM CLASSIFICATION SYSTEM FOR DIFFERENTIATED THYROID CARCINOMA</strong></td>
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<td><strong>DEFINITION</strong></td>
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Completion thyroidectomy: Completion thyroidectomy may be necessary when the diagnosis of malignancy is made following lobectomy. Some patients with malignancy may require completion thyroidectomy to provide complete resection of multicentric disease [44], and to allow RAI therapy. Most studies of papillary cancer have observed a higher rate of cancer in the opposite lobe when multifocal (two or more foci), as opposed to unifocal, disease is present in the ipsilateral lobe [45-46]. The surgical risks of two-stage thyroidectomy (lobectomy followed by completion thyroidectomy) are similar to those of a near-total or total thyroidectomy [47].

Ablation of the remaining lobe with RAI has been used as an alternative to completion thyroidectomy [48]. It is unknown whether this approach results in similar long-term outcomes. Consequently, routine RAI in lieu of completion thyroidectomy is not recommended.

EXTENSION of LYMPH NODE DISSECTION

Regional lymph node metastases are present at the time of diagnosis in 20-90% of patients with papillary carcinoma [7-18]. Although PTC lymph node metastases are reported by some to have no clinically important effect on outcome in low-risk patients, a study database found that lymph node metastases, age > 45 years, distant metastasis, and large tumor size significantly predicted poor outcome on multivariate analysis [49]. All-cause survival at 14 years was 82% for PTC without lymph node and 79% with lymph node metastases (p < 0.05). Another recent registry study concluded that cervical lymph node metastases conferred an independent risk of decreased survival, but only in patients with follicular cancer and patients with papillary cancer over age 45 years [50].

The risk of regional recurrence is higher in patients with lymph node metastases, especially in those patients with multiple metastases and/or extracapsular nodal extension [51]. In many patients, lymph node metastases in the central compartment [52] do not appear abnormal preoperatively with imaging [17] or by inspection at the time of surgery. Central compartment dissection (therapeutic or prophylactic) can be achieved with low morbidity in experienced hands [53-57]. Although some lymph node metastases may be treated with RAI, several treatments may be necessary, depending upon the histology, size, and number of metastases [58].

Therapeutic central-compartment (level VI) neck dissection: for patients with clinically involved central or lateral neck lymph nodes should accompany total thyroidectomy to provide clearance of disease from the central neck. Bilateral central compartment node dissection may improve survival compared to historic controls and reduce risk for nodal recurrence [59]. In addition, selective unilateral paratracheal central compartment node dissection increases the proportion of patients who appear disease free with undetectable or low Tg levels six months after surgery [60]. Other studies of central compartment dissection have demonstrated higher morbidity, primarily recurrent laryngeal nerve injury and transient hypoparathyroidism, with no reduction in recurrence [61-62]. In another study, bilateral central compartment dissection demonstrated higher rates of transient hypoparathyroidism compared to selective (unilateral) dissection with no reduction in rates of undetectable or low Tg levels [63].

Prophylactic central-compartment neck dissection (ipsilateral or bilateral) may be performed in patients with papillary thyroid carcinoma with clinically uninvolved central neck lymph nodes, especially for advanced primary tumors (T3 or T4) [56-57].

Near-total or total thyroidectomy without prophylactic central neck dissection: may be appropriate for small (T1 or T2), noninvasive, clinically node-negative PTCs. These recommendations should be interpreted in light of available surgical expertise. For patients with small, noninvasive, apparently node-negative tumors, the balance of risk and benefit may favor simple near-total thyroidectomy with close intraoperative inspection of the central compartment with compartmental dissection only in the presence of obviously involved lymph nodes. This approach may increase the chance of future locoregional recurrence, but overall this approach may be safer in less experienced surgical hands.

Lymph nodes in the lateral neck (compartments II-V), level VII (anterior mediastinum), and rarely in Level I may also be involved by thyroid cancer [8, 64]. For those patients in whom nodal disease is evident clinically, on preoperative US and nodal FNA or Tg measurement, or at the time of surgery, surgical resection may reduce the risk of recurrence and possibly mortality [18, 65-66]. Functional compartmental en-bloc neck dissection is favored over isolated lymphadenectomy (“berry picking”) with limited data suggesting improved mortality [22, 67-70].

POSTOPERATIVE STAGING

Numerous schemes have been developed in an effort to achieve more accurate risk factor stratification, including CAEORTC, AGES, AMES, U of C, MACIS, OSU, MSKCC, and NTCTCS systems [20, 24, 39, 70-75]. These schemes take into account a number of factors identified as prognostic for outcome in multivariate analysis of retrospective studies, with the most predictive factors generally being regarded as the presence of distant metastases, the age of the patient, and the extent of the tumor. These and other risk factors are weighted differently among these systems according to their importance in predicting outcome, but no scheme has demonstrated clear superiority [73]. Each of the schemes allows accurate identification of the major (70-85%) of patients at low risk of mortality (T1-3, M0 patients), allowing the follow-up and management of these patients to be less intensive than the higher-risk minority
(T4 and M1 patients), who may benefit from a more aggressive management strategy [73-74]. For assessment of risk of recurrence, a three-level stratification can be used:

- **Low-risk patients** have the following characteristics:
  1) No local or distant metastases; 2) all macroscopic tumor has been resected; 3) there is no tumor invasion of loco-regional tissues or structures; 4) the tumor does not have aggressive histology (e.g., tall cell, insular, columnar cell carcinoma) or vascular invasion; and 5) if 131I is given, there is no 131I uptake outside the thyroid bed on the first posttreatment whole-body RAI scan [75-77].

- **Intermediate-risk patients** have any of the following:
  1) Microscopic invasion of tumor into the perithyroidal soft tissues at initial surgery; 2) cervical lymph node metastases or 131I uptake outside the thyroid bed on the whole-body RAI scan done after thyroid remnant ablation; or 3) tumor with aggressive histology or vascular invasion [78-82].

- **High-risk patients** have:
  1) Macroscopic tumor invasion, 2) incomplete tumor resection, 3) distant metastases, and possibly 4) thyroglobulinemia out of proportion to what is seen on the posttreatment scan [83].

**ROLE of POSTOPERATIVE RAI REMNANT ABLATION**

Depending on the risk stratification of the individual patient, the primary goal of the first dose of RAI after total thyroidectomy may be 1) remnant ablation, 2) adjuvant therapy (to decrease risk of recurrence and disease specific mortality by destroying suspected, but unproven metastatic disease), or 3) RAI therapy (to treat known persistent disease). Supporting the use of RAI as adjuvant therapy, a number of large, retrospective studies show a significant reduction in the rates of disease recurrence [24, 39-40, 70, 84] and cause-specific mortality [39-40, 84-85]. However, other similar studies show no such benefit, at least among the majority of patients with PTC who are at the lowest risk for mortality [2, 24, 42, 85-87]. In those studies that show benefit, the advantage appears to be restricted to patients with tumors > 1.5 cm, or with residual disease following surgery, while lower-risk patients do not show evidence for benefit [24, 39, 88]. There are recent data suggesting a benefit of RAI in patients with more aggressive histologies [89-90]. There are no prospective randomized trials that have addressed this question [37, 85, 91-93].

- **RAI ablation is recommended for all patients** with known distant metastases, gross extrathyroidal extension of the tumor regardless of tumor size, or primary tumor size > 4 cm even in the absence of other higher risk features.

- **RAI ablation is recommended for selected patients** with 1-4 cm thyroid cancers confined to the thyroid, who have documented lymph node metastases, or other higher risk features when the combination of age, tumor size, lymph node status, and individual histology predicts an intermediate to high risk of recurrence or death from thyroid cancer.

- **RAI ablation is not recommended for patients** with unifocal cancer < 1 cm without other higher risk features and for patients with multifocal cancer when all foci are < 1 cm in the absence of other higher risk features.

**Prognosis**

Overall five- and 20-year survival in the low-risk group was 100% and 99% respectively. However, the survival in the high-risk group drops to almost 72% and 57% respectively.

**CONCLUSION**

In PTC, adequate surgery is the most important treatment variable influencing prognosis. Near total or total thyroidectomy is recommended in the vast majority of cases. Thyroid lobectomy alone may be sufficient treatment for small (< 1 cm), low-risk, unifocal, intrathyroidal papillary carcinomas in the absence of prior head and neck irradiation or radiologically or clinically involved cervical nodal metastases. Therapeutic central-compartment (level VI) neck dissection for patients with clinically and or radiologically involved central or lateral neck lymph nodes should accompany total thyroidectomy to provide clearance of disease from the central neck. Prophylactic central-compartment neck dissection (ipsilateral or bilateral) may be performed in patients with papillary thyroid carcinoma with clinically uninvolved central neck lymph nodes, especially for advanced primary tumors (T3 or T4). For those patients in whom nodal disease in the lateral neck is evident clinically, on preoperative US and nodal FNA or Tg measurement, or at the time of surgery, surgical resection may reduce the risk of recurrence and possibly mortality. Postoperative RAI treatment is recommended in the majority of cases. RAI ablation is not recommended for patients with unifocal cancer < 1 cm without other higher risk features and for patients with multifocal cancer when all foci are < 1 cm in the absence other higher risk features. Overall five- and 20-year survival in the low-risk group was 100% and 99% respectively. However, the survival in the high-risk group drops to almost 72% and 57% respectively.

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