Managing newly diagnosed thyroid cancer

Anna M. Sawka MD PhD, James D. Brierley MD, Shereen Ezzat MD, David P. Goldstein MD MSc

About 5600 Canadians[1] and more than 56 000 Americans[2] are estimated to have received a diagnosis of thyroid cancer in 2012, and both countries have seen recent dramatic increases in the incidence of the disease.[1,2] Cancer Care Ontario recently estimated the overall five-year survival rate for thyroid cancer to be 98%.[3] A similar rate of 97.5% was reported in the Surveillance Epidemiology and End Results (SEER) study (2002–2008).[4] In addition, the SEER investigators reported that the overall five-year survival rate among patients with disease confined to the thyroid was 99.9%, but that the rate was 97.1% for patients with regional disease (including involvement of regional lymph nodes) and 53.9% for those with distant metastatic disease,[4] with most thyroid cancer deaths occurring in patients aged 65 years or older.[4] Such data highlight the relatively low risk of dying of thyroid cancer, especially in younger patients.

The most common type of well-differentiated thyroid cancer, papillary thyroid cancer, is frequently diagnosed at an early stage.[5,6] For patients with papillary thyroid cancer localized to the thyroid who received definitive treatment, the 20-year cancer-specific survival rate reported by SEER investigators is 99% (95% confidence interval [CI] 93% to 100%).[7]

This review focuses on the primary management of well-differentiated thyroid cancer, specifically papillary thyroid cancer, and not other forms of thyroid cancer (e.g., medullary, poorly differentiated or anaplastic cancer). We examine the roles of surgery, radioactive iodine and thyroid hormone suppression in treating well-differentiated thyroid cancer across a spectrum of disease severity at initial diagnosis. Given the range of risk of disease recurrence in patients with diagnosed papillary thyroid cancer, stratifying therapeutic interventions according to risk level, with consideration of proof of efficacy for specific risk groups, is a rational approach to the development of a therapeutic framework. We outline several systems for classifying risk for papillary thyroid cancer, as well as a proposed primary therapeutic framework, applying the recently developed American Thyroid Association (ATA) Recurrence Risk Stratification System to primary treatment decision-making.[8]

Evidence-informed medical and surgical decision-making in the field of thyroid cancer is challenged by a paucity of randomized controlled trials examining the effect of interventions on risk of disease recurrence or related mortality. Most of the studies included in this review are retrospective analyses of observational data and thus subject to substantial methodologic limitations. Furthermore, given that disease-related death is a relatively infrequent event, it may not be a feasible outcome for the meaningful analysis of studies. Some of the challenges in this field are to prevent clinically significant disease persistence or recurrence, and to balance the potential benefits of therapies (and related evidence uncertainties) with potential complications and use of resources. The details of our literature review are shown in Box 1. A more detailed review of treatment controversies in the management of low-risk papillary thyroid cancer can be found elsewhere.[9]

How is disease-related risk of papillary thyroid cancer evaluated?

Clinicopathologic staging systems used in the stratification of risk of thyroid cancer are based on both clinical features and surgical histopathologic findings. Classic clinicopathologic staging systems, such as the American Joint Committee

Key points

- Total thyroidectomy is commonly recommended to treat papillary thyroid cancer, although less extensive surgery may be an option for the lowest-risk cases.
- For those with high-risk or complicated intermediate-risk thyroid cancer, adjuvant radioactive iodine treatment is commonly recommended; however, its use in low-risk cases is controversial.
- After definitive therapy for thyroid cancer, a target level of less than 0.1 mIU/L for thyroid-stimulating hormone suppression with chronic thyroid hormone treatment is recommended for patients at high risk of disease recurrence, including those with persistent disease.
- Less stringent suppression of thyroid-stimulating hormone is acceptable for patients at low risk of disease recurrence.

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Correspondence to:
Anna M. Sawka,
sawkaam@yahoo.com

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on Cancer/Union for International Cancer Control TNM (tumour site, lymph node involvement, metastasis) system[10,11] or MACIS (metastases, age, completeness of resection, invasiveness, and size of primary tumour),[12] have been shown to predict cause-specific survival in papillary thyroid cancer.[13]

Newer classification systems have been developed to predict the risk of disease recurrence, including the ATA system[8] and a modified system based on the European Thyroid Association (ETA) guidelines[14,15] (Table 1). Key features that are common to both systems include the identification of histologic characteristics suggestive of aggressive tumour behaviour (e.g., vascular or extrathyroidal invasion) and extent of disease (including metastases to lymph nodes or distant sites);[8,14,15] an important difference between the two is the exclusion of a tumour size criterion from the ATA system.

ATA risk classification

Tuttle and colleagues have reported that the ATA system accounted for 34% of the estimated variance in prediction of disease recurrence when applied retrospectively to data from 588 patients with thyroid cancer followed for a median of seven years.[16] Furthermore, the respective positive and negative predictive values of the system have been reported to be 39.2% and 90.6% by Castagna and colleagues in a retrospective analysis of data from 512 patients with differentiated thyroid cancer.[15] (In the same study,[15] the authors reported that a risk classification system based on the ETA guidelines had a positive predictive value of 38.4% and a negative predictive value of 91.3% for the outcome of disease recurrence.)

Tuttle and colleagues reported the rate of structural disease recurrence or persistence (i.e., positive results on imaging studies and/or biopsy) according to the ATA system as follows: 3% (4/136) for patients at low risk, 21% (61/291) for patients at intermediate risk and 68% (110/161) for patients at high risk, after a median follow-up of seven years.[16] In a retrospective study from Brazil, Vaisman and colleagues reported that the rate of disease persistence or recurrence (defined by structural evidence of disease or thyroglobulin increase) was 13% in patients at low risk, 36% in patients at intermediate risk and 68% in those at high risk (506 patients followed for a median of 10 years).[17] Furthermore, in a Memorial Sloan–Kettering Cancer Center study involving 289 patients who underwent hemithyroidectomy or total thyroidectomy but no radioactive iodine treatment, the risk of structural recurrence was 0.5% in low-risk patients and 9.3% in intermediate-risk patients (median follow-up of five years).[18] However, this relatively low risk of recurrence in patients who did not receive radioactive iodine may reflect a selection bias, with the exclusion of patients whose tumours had more worrisome histopathologic features.

An important limitation of the ATA risk classification system[8] is the wide clinical spectrum of lymph node disease that may be categorized as intermediate risk. Recently, the surgical affairs committee of the ATA described the risk of structural recurrence of nodal disease as dependent on the relative size (microscopic v. macroscopic/clinical) and number (> 5) of involved lymph nodes, as well as the presence of extranodal extension.[19]

Other prognostic markers

Some markers that are actively being studied for consideration in decision-making about treatment include serum thyroglobulin (a thyroid protein used as a surrogate marker for thyroid cancer after thyroidectomy, which may be stimulated [by thyroid hormone withdrawal or administration of recombinant human thyrotropin] or unstimulated [while on thyroid hormone treatment])[20,21] and molecular tumour biomarkers such as mutations in the *BRAF* gene.[22] However, a detailed look at such research is beyond the scope of this review.

Box 1: Evidence used in this review

We performed an electronic search of PubMed (no time limit) on Sept. 3, 2012, for the following medical subject headings and terms: radioactive iodine treatment, radioactive iodine remnant ablation, RAI treatment, RAI remnant ablation, I-131 treatment, I131 treatment, I-131 remnant ablation or I131 remnant ablation; thyroidectomy, lobectomy or hemithyroidectomy; lymph node dissection or neck dissection; TSH suppression, levothyroxine suppression, thyroxine replacement or thyroid replacement therapy. We applied the following filters: humans; clinical trial; comparative study; controlled clinical trial; evaluation studies; meta-analysis; practice guideline; randomized controlled trial; systematic reviews; validation studies; english; and adult ≥ 19 years. We also conducted a manual search of relevant cross-references for retrieved articles, personal records and recent issues of the journal *Thyroid*. We reviewed 1019 citations from our electronic search and about 250 full-text articles.

What primary surgery is favoured in the management of this disease?

Total thyroidectomy has been favoured over less-extensive surgeries in most patients with papillary thyroid cancer, particularly when the disease is not confined to a single intrathyroidal tumour less than 1 cm in diameter.[8,14] Papillary thyroid cancer can be multifocal, sometimes involving both lobes of the thyroid. One case series

reported that 44% (80/182) of resected contralateral lobes showed one or more tumour foci after initial hemithyroidectomy.[23] Multivariate analyses of prospectively collected observational data from the National Cancer Database in the United States have suggested that total thyroidectomy may offer a statistically significant advantage over hemithyroidectomy for patients with papillary thyroid cancer with a tumour diameter of 1 cm or more for the outcomes of disease recurrence (hazard ratio [HR] 1.15, 95% CI 1.02 to 1.30) and survival (HR 1.31, 95% CI 1.07 to 1.60) (n = 32 705).[24]

However, multivariate analyses from prospectively collected data from the SEER database (22 724 patients who had total thyroidectomy and 5964 patients who had hemithyroidectomy) have suggested that there may be no significant disease-specific or overall survival advantage of total thyroidectomy over hemithyroidectomy (HR 0.91, 95% CI 0.71 to 1.15 for disease-specific survival; HR 0.93, 95% CI 0.84 to 1.03 for overall survival).[25] Multivariate analyses of prospectively collected data from the National Thyroid Cancer Treatment Cooperative Study Group have suggested that overall, disease-specific and disease-free survival may not be significantly improved by total thyroidectomy compared with less-extensive surgery in low-risk patients (i.e., stages I and II).[26] Nevertheless, a significant overall survival benefit of more extensive surgery was seen in higher-risk patients (i.e., stages III and IV; relative risk [RR] of death 1.26, 95% CI 1.10 to 1.55, after surgery that was less extensive than near-total thyroidectomy).[26] Stages III and IV include people of any age with distant metastases, as well as those aged 45 years and older with primary tumours larger than 4 cm, macroscopic extrathyroidal invasion or cervical lymph node metastases.[26] This category would roughly correspond to ATA intermediate- and high-risk categories, and to the ATA low-risk category for older adults with large tumours (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.121742/-/DC1).

In a recent retrospective analysis involving a nationwide sample of inpatients in the United States, total thyroidectomy was reported to be associated with a higher risk of postoperative complications than hemithyroidectomy.[27] In that study, which included patients with malignant disease in addition to patients who underwent thyroidectomy for other conditions, multivariate analysis suggested that postoperative hypocalcemia was significantly more frequent in patients who had total thyroidectomy than in patients who underwent hemithyroidectomy (HR 2.80, 95% CI 2.00 to 3.92).[27] Moreover, lifelong treatment with thyroid hormone is universally required for patients after total thyroidectomy, but many patients who undergo hemithyroidectomy do not require hormone replacement.[28]

Some relevant factors that we consider in the surgical decision-making process for newly diagnosed thyroid cancer include the clinicopathologic features of the cancer (including the possible implication for subsequent adjuvant treatment with radioactive iodine), evidence of disease persistence after initial surgery (e.g., suspicious lesions in a contralateral remaining lobe after hemithyroidectomy or evidence of suspected unresected nodal metastases), patient comorbidities, individual risk factors for complications of surgery (e.g., pre-existing unilateral recurrent laryngeal nerve impairment), patient acceptability of life-long hormone replacement and patient preferences; the latter two factors are especially relevant in patients with low-risk disease.

Table 1: Recently developed risk stratification systems for the recurrence of differentiated thyroid cancer

Risk category	American Thyroid Association recurrence risk classification system[8]	Dichotomous recurrence risk classification system based on European Thyroid Association guidelines[14,15]
Low	Completely macroscopically resected thyroid carcinoma, with no worrisome histopathologic features,* which is restricted to the thyroid; no features of intermediate- or high-risk disease present	All cases that do not have features of high-risk disease
Intermediate	Completely macroscopically resected thyroid carcinoma, with some worrisome histopathologic features,* or cervical lymph node metastases	Not applicable
High	Extensive or persistent structural disease suggested by grossly incomplete removal, macroscopic invasion into adjacent neck tissue or distant metastases†	Primary tumour size ≥ 4 cm diameter, extrathyroidal extension, aggressive histologic variants or metastatic disease (lymph nodes or distant)

*These may include presence of extrathyroidal extension, vascular invasion or aggressive histologic variants (e.g., tall cell, columnar cell or dedifferentiated tumours).
†Patients with suspected persistent disease, based on substantially elevated blood thyroglobulin levels out of proportion to findings on radioisotope imaging, may be included in this category.

Total thyroidectomy is favoured in most patients with papillary thyroid cancer in an effort to reduce the risk of persistent and recurrent disease.[8] Considering less extensive surgical options may be reasonable for some patients with relatively small unilateral tumours who are at relatively low risk of disease-related morbidity or mortality if favoured by the patient and follow-up is feasible.

Lymph node dissection

Dissection of cervical lymph nodes that appear involved clinically or radiographically, as well as related compartment nodes, is ideal.[8,29–31] This aims to minimize the risk of clinically persistent structural disease in the neck. However, there is some controversy over the necessity and extent of resection of occult lymph node metastases in the central neck compartment.[8,32] In observational studies, the use of prophylactic ipsilateral[33,34] or bilateral[35] central neck dissection with total thyroidectomy has been associated with lower thyroglobulin measurements, compared with total thyroidectomy alone. In another study, the rate of detectability of simulated thyroglobulin measurements was not significantly affected by the use of prophylactic central neck dissection.[36] However, a recent meta-analysis suggested that the risk of recurrence of locoregional lymph node disease was not significantly reduced by prophylactic central neck dissection (risk difference [RD] –0.04, 95% CI –0.09 to 0.02, $I^2 = 0.79$, $n = 1641$).[37]

A pooled analysis of data from 2323 patients suggested that the risk of transient hypocalcemia was increased after total thyroidectomy and central neck dissection, compared with total thyroidectomy alone (RD 0.15, 95% CI 0.09 to 0.22, $I^2 = 0.67$]).[37] In other pooled analyses from the same systematic review, the risk of permanent hypocalcemia or recurrent laryngeal nerve injury (transient or persistent) was not significantly increased after total thyroidectomy with central neck dissection, compared with total thyroidectomy alone, although such events were relatively rare.[37]

In a recent retrospective study, multivariable analysis of data from 640 patients with papillary thyroid cancer followed for 10 years suggested that bilateral prophylactic central neck dissection was associated with reduced risk of locoregional recurrence (odds ratio [OR] 0.21, 95% CI 0.11 to 0.41), after adjustment for relevant prognostic factors and use of radioactive iodine.[38] Thus, currently, therapeutic central or lateral dissections of macroscopically involved cervical lymph nodes are generally indicated for patients with papillary thyroid cancer, but the role of routine prophylactic dissections for occult nodal disease in the central neck remains unclear.

What role can radioactive iodine or radiotherapy play after surgery?

Radioactive iodine therapy has been used for decades in the treatment of differentiated thyroid cancer, but its role in primary disease management after thyroidectomy is evolving, such that consideration of risk of disease-related morbidity or mortality, as well as evidence of treatment efficacy (according to risk level), have become important features in decision-making around treatment. There is little doubt that radioactive iodine treatment is indicated in patients with distant metastatic differentiated thyroid cancer with distant metastases, with a survival advantage reported in multiple respective observational studies,[26,39] particularly in patients with radioiodine-avid disease.[40]

Multivariate analyses of prospective data from the National Thyroid Cancer Treatment Cooperative Study Group have suggested that the use of postsurgical radioactive iodine treatment is associated with improved overall, disease-specific, and disease-free survival in higher-risk disease (i.e., stages III and IV) (overall survival RR 1.35, 95% CI 1.10 to 1.64; disease-specific survival RR 1.46, 95% CI 1.13 to 1.87; disease-free survival RR 1.32, 95% CI 1.02 to 1.68) (Appendix 1).[26] No significant overall survival advantage was seen in patients with stage I disease who were given radioactive iodine after a median follow-up of 5.3 years.[41]

Recent systematic reviews involving patients at low risk with differentiated thyroid cancer (defined mostly by TNM stage,[10,11] MACIS[12] or other staging systems predating the ATA[8] system), have suggested that radioactive iodine treatment in these patients is generally not associated with an improvement in disease-related survival in most relevant literature, but the effect on the risk of disease recurrence is inconsistent among studies.[42,43]

Radioactive iodine remnant ablation (i.e., radioactive iodine treatment in the absence of any known gross residual disease) was not associated with any significant advantage in survival or risk of recurrence in multivariate and propensity analyses of observational data from 1298 patients with well-differentiated thyroid cancer classified as at low risk in the ATA system (median follow-up 10.3 yr).[44] In this study, the authors reported that after stratification for propensity score using respective Cox univariate analyses, the HR for overall survival after radioactive iodine treatment was 0.75 (95% CI 0.40 to 1.38); the HR for disease-free survival was 1.11 (95% CI 0.73 to 1.70).[44] More informa-

tion on the treatment controversy associated with the use of radioactive iodine remnant ablation in low-risk papillary thyroid cancer is available in an in-depth review and summary of international clinical practice guideline recommendations.[9]

There has been some debate over the optimal dose activity of postsurgical radioactive iodine treatment, when used. However, two recent large, multicentre, randomized controlled trials predominantly involving patients with low-risk well-differentiated thyroid cancer, have suggested that a dose activity of 1110 MBq is not inferior to a dose activity of 3700 MBq in achieving successful thyroid remnant ablation (Appendix 2, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.121742/-/DC1).[45,46] Long-term outcome data are not yet available from those trials.

Postsurgical radioactive iodine treatment is most beneficial in patients at high risk of disease recurrence, and in some patients at intermediate risk, according to the ATA system. The long-term benefits in patients at low risk are not clearly established. The use of radioactive iodine should not be routinely mandated in patients with papillary thyroid cancer at low risk.

What is the role for long-term TSH suppression after surgery?

Treatment decision-making concerning the utility of long-term TSH suppression in the management of well-differentiated thyroid cancer after primary treatment includes considering factors such as risk of thyroid cancer–related morbidity or death, treatment efficacy according to risk group, and risks of the therapy itself.

Observational evidence suggests that the use of levothyroxine therapy to suppress TSH levels to 0.1 mIU/L or lower is associated with improved cause-specific survival in patients with advanced disease, including those with distant metastases.[26,40,47] However, in a single-centre, unblinded, randomized controlled trial involving patients with papillary thyroid cancer (most of whom were considered as having low- or intermediate-risk disease according to the ATA system), disease-free survival was not inferior when a strategy of levothyroxine dose titration aimed at keeping TSH within the normal range was used compared with a strategy aimed at keeping TSH levels below 0.01 mIU/L (HR 1.04, 95% CI 0.85 to 1.27, mean follow-up 6.9 yr) (Appendix 1).[48] Furthermore, in a retrospective analysis of observational data adjusted for risk factors, a median TSH in the low-normal range (median < 2 mIU/L) best predicted relapse-free survival in a mixed-risk population with differentiated thyroid cancer.[49]

Considering the potential adverse effects of TSH suppression in the context of disease status in addition to risk of recurrence or death is essential.[26] Older adult patients may be at particularly high risk for some potential adverse effects.[26] For example, in patients aged 60 years or older given thyroid hormone–suppressive therapy, the prevalence of atrial fibrillation was reported to be about 3 times the rate seen in age- and sex-adjusted published historical controls.[50] Data from the Study of Osteoporotic Fractures, a multicentre, prospective study involving women older than 65 years of age, has suggested that TSH measurements of 0.1 mIU/L or lower are associated with a threefold increased risk of hip fracture and a fourfold increased risk of vertebral fracture.[51] However, an important limitation of interpreting these data is that the study did not focus on patients with thyroid cancer. In a small cross-sectional study involving women postmenopause who had received treatment for thyroid cancer, bone mineral content was reduced and urinary hydroxyproline excretion was elevated (suggesting higher bone resorption) compared with age- and sex-matched controls.[52] Other potential adverse effects of TSH suppression are discussed elsewhere.[26]

In summary, TSH suppression (with a target TSH level < 0.1 mIU/L) is best reserved for patients in the high-risk category of the ATA system, including patients with recurrent or persistent structural disease. However, for most patients, especially those in the low-risk category with intermediate risk and no evidence of disease on reassessment, the dose of levothyroxine may be titrated to maintain TSH in the low normal range.

Conclusion

The management of papillary thyroid cancer continues to evolve, because of advances such as an understanding of the pathogenetic mechanisms of the disease,[53] improved clinical risk stratification and a growing number of randomized controlled trials of therapeutic interventions (Appendix 1). We have come to the understanding that using a "one size fits all" approach in the primary management of this disease is not appropriate. Instead, a personalized patient- and tumour-centric approach is needed, including an evaluation of the best available evidence of therapeutic efficacy according to risk group, potential treatment toxicities and, particularly when more than one reasonable treatment option exists, patient preference.

Considering the risk of recurrence in the management of papillary thyroid cancer is essential to minimize disease-related morbidity, recurrent

structural disease, death or therapeutic toxicity and related quality-of-life impairment. More research, ideally in the form of randomized controlled trials, is needed to evaluate the efficacy of interventions such as extent of surgery, radioactive iodine and thyroid hormone suppression in optimizing long-term outcomes.

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Affiliations: Division of Endocrinology (Sawka), Department of Medicine, University Health Network and University of Toronto; Department of Radiation Oncology (Brierley), University Health Network and University of Toronto; Endocrine Oncology Site Group (Ezzat), Princess Margaret Hospital; Department of Otolaryngology (Goldstein), University Health Network and University of Toronto, Ont.

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