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Post-treatment surveillance of thyroid cancer

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Abstract

An increased incidence of differentiated thyroid cancer (DTC) has resulted in an increased population of thyroid cancer survivors requiring ongoing disease surveillance. Our institution's risk-adapted surveillance strategy is based on a contemporary understanding of disease biology, guided by analysis of prognostic factors and balanced application of available surveillance modalities. The goal of this strategy is to detect recurrent disease early, identify patients who would benefit from further treatment and reduce over investigation of low risk patients. This article describes our center's risk-stratified approach to the postoperative surveillance of patients with differentiated thyroid cancer with reference to the recent 2015 American Thyroid Association management guidelines.

Keywords

thyroid neoplasm; surgery; epidemiology; cost-effectiveness; recurrence; survival

Introduction

Thyroid cancer has a low risk of disease-related mortality but significant risk of post-treatment disease persistence and recurrence although only a minority of this has clinical significance. In recent years, an increasing incidence of thyroid cancer around the world has been documented (1–3), a large proportion of which has been attributed to increased application and sensitivity of diagnostic imaging modalities. In the United States, the incidence of thyroid cancer has nearly tripled in the last 30 years, from 4.9 to 14.3 per 100,000 individuals (2), and this has largely been attributed to an increase in diagnosis of subclinical disease (4) with only a minority being attributed to a true increase in incidence of advanced disease (5). In 2009, 39% of all new thyroid cancer diagnoses were 1 cm or smaller, compared to 25% of cases 20 years ago (2). In contrast, mortality rates from thyroid cancer have been remarkably stable at 0.5 deaths per 100,000 (2). The combined effect of

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increased disease incidence, greater application and diagnostic sensitivity of tests for disease detection, and unchanged mortality has resulted in an increase in the pool of differentiated thyroid cancer survivors requiring follow up, the majority of whom will have a low risk of clinically significant disease recurrence. The estimated annual cost of thyroid cancer in the United States is projected by one study to increase from $1.4 billion in 2010 to $2.4 billion by 2019 by current practice standards (6). Similar trends are likely to be observed in other parts of the world. There is a clear need for optimizing surveillance, targeting the frequency, duration and modality of follow up investigations based on the risk of recurrence and death.

This review article will outline our approach to the postoperative surveillance of differentiated thyroid cancer where initial risk stratification, ongoing assessment of response to therapy and time from diagnosis guides follow-up regimes, by combining an understanding of the biology of the disease (response to initial therapy, likelihood of recurrence, common sites of recurrence, time to recurrence) with an improved understanding of the clinical utility of specific diagnostic tests. These postoperative surveillance strategies are in keeping with previous publications from our center (7–13) and the latest American Thyroid Association (ATA) guidelines (14).

Initial risk stratification

The process of staging and risk stratification is a vital component of thyroid cancer management and is based on categorization of patients based on established prognostic factors. As these factors are an indirect reflection of disease biology, risk-based categorizations of patients helps physician to select the most appropriate treatment and surveillance strategies.

Mortality Risk

Many risk stratification systems have been developed for patients with differentiated thyroid cancer. GAMES (grade, age, metastases, extrathyroidal extension, size) was described at our institution in the 1990s and is still used to predict cancer mortality. All recognize the importance of age and the presence of distant metastases. Additional primary tumor factors such as the presence of gross extrathyroidal extension (ETE) and aggressive histological features are further used to prognosticate disease outcomes. The impact of nodal metastases on survival was not considered an independent factor which had an impact on prognosis, but may have significance in older patients (5, 6). A recent large cohort of patients from the NCBD has suggested nodal disease is also associated with poorer overall survival in young patients (15). There are however several signification limitations to this study; disease specific survival outcomes and information on the quality and extent of neck dissection is notably not available, furthermore pathological review of slides were not performed.

The American Joint Committee on Cancer (AJCC) TNM staging system is internationally used to predict the risk of overall survival in cancer patients. Thyroid cancer is one of the few cancers in which patient age is an independent prognostic factor, and previous AJCC guidelines recommended a cut-off point at age >45 years for its adverse impact. However, ongoing research has led to a multi-institutional reappraisal of the age cut-off, and it is anticipated that the 8th edition will increase the cut off to age 55 (16). Staging of

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differentiated thyroid cancer in younger patients is based on the presence of distant disease; those without distant metastases are stage 1 and are upstaged to stage 2 in the presence of distant metastases. The staging system excludes categorization of young patient into the stage 3 and 4 groups, reflective of the excellent prognosis of such patients. For older patients, staging is based on tumor size, extent of gross extrathyroidal extension (ETE), and the presence of nodal and distant metastases. Several additional changes to the 8th edition of the TNM staging are expected to down stage a proportion of older patients. It is anticipated that disease localized to the thyroid gland measuring up to 4 cm without ETE will be categorized as stage 1. Patients with primary disease greater that 4cm, evidence of limited ETE into perithyroidal tissue or strap muscles, or regional nodal disease will be staged 2. Stage 3 is reserved for disease with extensive ETE to cervical viscera, including subcutaneous tissues, larynx, trachea, esophagus or recurrent laryngeal nerve (RLN). Local invasion of paravertebral fascia or carotid artery and distant disease are classified as stage 4.

Risk of recurrence (Table 1)

The overall goal of cancer therapy and surveillance is to prevent disease related death. Surveillance is performed with the intention to detect and provide appropriate treatment of recurrent disease and to decrease the risk of disease related mortality. Unlike most other solid cancers however, disease recurrence and mortality risk are not always concordant in thyroid cancer (17). Children with differentiated thyroid cancer are known to have very high recurrence risk, yet mortality rates are low. In contrast, older patients have higher recurrence rates that are associated with higher mortality rates. The difference in part is due to the more aggressive disease biology seen in older patients, reflected by decreased histopathologic differentiation, increased metabolic (PET-scan) positivity and decreased radioactive iodine (RAI) responsiveness among other factors.

With this in mind, the ATA risk stratification for recurrence is important guide to surveillance frequency and further treatment. Risk of recurrence is categorized into low, intermediate and high-risk groups as shown in Table 1. The low, intermediate and high-risk groups have recurrence risks of 5%, 20%, and 50% respectively (14). These variables are predominantly based on histopathological features and postoperative RAI findings where available. The 2009 edition has been validated, widely accepted, and shown to be a good predictor of disease recurrence (18–20). The new edition proposes more detailed stratification based on recent findings in the literature. In particular, the volume of nodal disease, the degree of tumor capsule and vascular invasion are associated with increased recurrence. Although the ATA risk grouping still has 3 categories, the proposed changes reflect a shift from a categorical to continuous risk grouping, allowing for more nuanced stratification. It is however important to note that these proposed changes have yet to be validated. The pertinent changes and related literature are discussed below.

ATA risk categories

Changes to the 2015 risk grouping

Nodal volume—Early studies suggested that regional lymph node (LN) metastases only impacted the survival of older patients with PTC (21–23). However, recent studies suggest

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that there may be some influence on recurrence in younger patients as well (24). Nodal disease has significant impact upon disease recurrence, and the recurrence risk can be further delineated by assessment of specific nodal factors such as number of nodes involved by metastasis, size of the metastatic nodes and presence or absence of extranodal extension. In the most recent edition of the ATA guidelines, patients with low volume nodal disease (<0.2mm and fewer than 5 involved nodes) are down staged to low-risk, akin to the risk profile of a patient with no evidence of nodal disease. This reflects the similar recurrence rates between patients undergoing a prophylactic central neck dissection and those who have the central neck compartment observed (25). In contrast, those with high volume nodal disease (greater than 3cm) have a recurrence rate closer to that associated with gross ETE or distant metastases. These changes are largely based on review of the literature which suggest that increasing metastatic nodal size, number and presence of extranodal spread are all associated with higher recurrence risk (26). Although the exact relationship between size, number and extranodal spread are incompletely delineated, number and involved LN size are useful markers of higher recurrence risk.

Histological subtypes—Our understanding of recurrence risk in individual differentiated thyroid cancer subtypes is also improved. Recent publications have highlighted that the extent of capsule and vascular invasion differentiate the follicular-patterned thyroid carcinomas including the rare follicular carcinomas (FTCs) and the much more common follicular variant of papillary thyroid carcinomas (FVPTCs) from benign follicular adenomas. Classical pathologic assessment aided by molecular analysis suggests that encapsulated FVPTC is biologically similar to the follicular thyroid tumors more so that the classical papillary-patterned tumors (classical PTC). For example, mutational profiling suggested that these two entities share RAS and many other mutations in contrast to PTCs (27). The overriding implication is that the malignancy profile of a significant proportion of PTCs is now gauged upon the presence or absence of capsular/vascular invasion rather than nuclear features, reclassifying a significant proportion of them as benign. As in other cancers, extensive vascular invasion is suggestive of aggressive disease biology. FTC with extensive vascular (≥4 foci) invasion is associated with high recurrence rates (28−30), in contrast to intrathyroidal FTC with minimal vascular invasion that has a clinically indolent disease course. Recently, a large multicenter series has shown encapsulated FVPTC have a benign clinical course similar to follicular adenoma (31). Renewed interest in vascular invasion as a potential indicator for distant metastases and associated RAI necessity has also developed in classical PTCs, although it is currently unclear whether vascular invasion is a truly independent driver of disease prognosis in this disease (32).

Micropapillary thyroid cancer—Micropapillary thyroid cancer is common, often incidental and of low aggressiveness. The significance of aggressive features of a papillary microcarcinoma was less certain. The presence of ETE is rare in papillary microcarcinomas, but has been observed with resultant adverse outcomes in some cases. Invasion of extrathyroidal central neck contents, regardless of tumor size is associated with poorer outcomes, especially in older patients (33) and patients with invasion of the posterior central neck contents (airway/esophagus).

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The three-tiered system of low, intermediate and high-risk recurrence categories are recognized as relatively arbitrary groups, as they are essentially an attempt at categorizing the progressive disease continuum that lies at the basis of the differentiated thyroid cancer spectrum. Nevertheless, risk categories help to convey risk profile, guide surveillance intensity and duration and need for further treatment.

Application of risk stratification

Histopathological reporting—The pathology report of the surgical specimen is preferably by a head and neck pathologist or one with special interest in thyroid cancer. At our institution, the characteristics of the thyroidectomy specimen include histological subtype, primary tumor, size, presence or absence and extent of ETE, quantification of capsule and vascular invasion (absent, 1, 2, 3 or ≤4 foci) (Table 2). The number of foci of vascular and capsule invasion is important to stratify FTC and FVPTC risk. For LN metastases, size of largest LN, size of largest metastatic focus, determination and quantification of extranodal spread, is reported for each involved LN as well as the total number of LNs resected.

Postoperative variables—An immediate postoperative RAI scan suggestive of uptake outside of the thyroid bed is suggestive of nodal disease and upstages patients to the intermediate group, due to the potential for residual nodal disease. Distant disease suggested by cross sectional imaging or fludeoxyglucose positron emission tomography (FDG-PET) uptake does not require tissue confirmation to upstage patients to high-risk of recurrence.

Surveillance modalities - Indications, frequency and duration

Historically, surveillance of differentiated thyroid cancer patients after surgery was life-long secondary to the belief that recurrence was common and estimated to be as high as 30% (17, 34). More recent literature suggests that recurrence rates are substantially less (20, 35–37). The current surveillance duration and intensity employed is personalized based on initial risk stratification and subsequent response to therapy.

Serum Thyroglobulin and anti-thyroglobulin antibodies

Serum thyroglobulin (Tg) levels are a quantitative reflection of remaining thyroid tissue; both normal and malignant cells. As such, serum Tg levels are useful to monitor patients with differentiated thyroid cancer after initial therapy. Tg values have the highest sensitivity and specificity for detection of recurrent disease after the patient has had a total thyroidectomy and RAI ablation. Select low and intermediate-risk group patients who have undetectable Tg after total thyroidectomy can often be managed safely without adjuvant RAI with no increase in risk of recurrence (38). In these patients serial Tg levels are similarly effective for surveillance. With a half-life of about 30 hours, serum Tg levels are expected to be very low after total thyroidectomy with (<1 to 2 ng/mL) or without RAI ablation (<5 ng/mL).

Serum Tg concentrations are further influenced and regulated by the degree of thyroid stimulating hormone (TSH) stimulation. Measurements of Tg can be *TSH suppressed* while

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patients remain on suppressive doses of thyroid hormone, or *TSH stimulated* after thyroid hormone withdrawal or administration of recombinant human TSH (rhTSH). Tg measurements are more sensitive for detection of recurrent disease following TSH stimulation, however clinically, we are trending away from TSH simulated Tg measurements for the majority of patients with low or intermediate-risk cancers. In our experience, the additional sensitivity obtained from a TSH stimulated Tg measurement compared to TSH suppressed measurement does not change management in most low and intermediate-risk patients. High-risk patients benefit from a baseline stimulated Tg measurement from which additional measurements can be compared should there be a clinical concern for recurrence. Minor fluctuations between measurements is common. However, a progressive increase in serum Tg concentrations strongly suggests recurrence and should lead to imaging tests to identify the site of recurrence.

Anti-thyroglobulin antibody (Anti-Tg Ab) are detectable in up to 20% of thyroid cancer patients (39). Tg values obtained in the presence of anti-Tg antibodies may not be clinically reliable. We routinely measure anti-Tg Ab with each measurement of serum Tg. As with Tg measurements, anti-TgAb are more reliable same when serially measured with should be measured in conjunction as the essay. Serum Tg and anti-Tg antibodies Anti-Tg anitbody can be used as a surrogate marker of disease recurrence. Tumor recurrence can be anticipated by a rise in Tg antibodies with or without a rise in serum Tg.

TSH suppression

Traditionally, almost all patients with thyroid cancer are given levothyroxine to suppress TSH levels below the normal range inducing a state of subclinical hyperthyroidism. The rationale for this approach stems from data showing that TSH stimulates thyroid cell proliferation, RAI uptake, and Tg production (6–13). In theory, removing this stimulus, inhibits growth of residual neoplastic tissue, (6, 7, 14).

However, increasing TSH suppression is associated with potential adverse cardiovascular and musculoskeletal effects. The extent of suppression should be balanced against the risk of recurrence and the risk of developing adverse cardiovascular and musculoskeletal effects. A recent publication demonstrated TSH suppression <0.4 mIU/L increased the risk of osteoporosis without changing the risk of tumor recurrence in ATA low and intermediate-risk thyroid cancer patients (10). Cardiovascular and musculoskeletal risk factors such as age, menopausal state, known atrial fibrillation, hypertension, diabetes, previous fractures and known osteopenia or osteoporosis should disease be considered in conjunction with risk of recurrence when determining the degree and duration of TSH suppression (Table 5). Generally patients at high-risk of developing adverse effects from suppression can have suppression stepped back to account for such risks.

Cervical ultrasonography

At our center, dedicated head and neck sonographers routinely evaluate the thyroid bed, central and lateral cervical nodal compartments in the surveillance of thyroid cancer patients. Synoptic reporting should detail nodule characteristics in the thyroid bed, central and lateral necks as well as any changes in the thyroid bed. An assessment of malignancy

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risk is additionally provided to communicate the level of suspicion for malignancy. Table 6 details features that are routinely reported on cervical US at our center.

For patients with complete tumor resection at the time of thyroidectomy, we perform annual screening neck ultrasounds. In our experience, more frequent screening in low and intermediate-risk patients are more likely to identify false-positive abnormalities rather than clinically significant disease (9). With the exception of patients with a suspect lesion threatening a vital structure such as the recurrent laryngeal nerve, additional imaging is rarely indicated. For higher risk patients, other imaging modalities between screening US provide information on disease progress (Table 6).

High-resolution neck US can detect nodules as small as 2–3 mm in diameter. Small nodal recurrence is often difficult to find intraoperatively due to scar tissue and likely has no relevance in the overall oncologic outcome and can often cause unnecessary physician and patient anxiety (11). Decision to biopsy of done with perform such small nodules should be careful consideration of the implications to management and long-term patient quality of life. Only nodules 8–10mm in size should be considered for biopsy Biopsy should be sent for cytology and Tg measurement from the needle washout fluid. Suspicious LNs less than 8–10mm can be followed without biopsy with consideration for FNA or intervention if there is growth or if the node threatens vital structures such as a functional recurrent laryngeal nerve. For patients with an excellent response to therapy with negative US and a low serum Tg, they can be followed primarily with clinical examination and Tg levels alone. While patients with elevated Tg levels, rising antiTg Ab or presence of structural abnormalities should continue to be followed with serial US, the benefit of prolonged routine use of neck US in patients with an excellent response to therapy is less certain.

Other imaging modalities

In our experience, nuclear medicine (RAI, FDG-PET) and cross sectional imaging (computer tomography (CT) magnetic resonance imaging (MRI)) is generally reserved for intermediate to high-risk patients or those with incomplete response to therapy and unexplained rising Tg level. For intermediate-risk patients we routinely perform whole body RAI scan at 18 months post initial therapy to screen for regional and distant structural disease. For the high-risk cohort, a routine CT of the neck and chest is performed at 12 and 24 months post initial therapy to monitor for regional and pulmonary disease. Additionally FDG-PET is generally performed at the same time to monitor for development of distant disease.

We have previously advocated for cost effective administration of routine surveillance for low-risk thyroid cancer patients (8). It is important to emphasize that those patients with structurally incomplete response and those with high-risk disease warrant careful imaging to monitor for disease recurrence. It is in these patients where early detection and timely treatment of recurrence can improve disease specific survival. In addition to yearly neck US, we perform on average 2.45 CT/MRI neck and chest and whole body FDG-PET scans for each ATA high-risk group patients in the first 36 months post initial treatment. Of these patients 13% develop a structural recurrence event. By comparison 0.49 CT, MRI or FDG-

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PET scans were ordered for each intermediate-risk patient with a recurrence rate of 8.7% in first 36 months (8)

Radioactive iodine scans—Low-risk and intermediate-risk patients with an excellent response to therapy (undetectable Tg with negative anti-Tg Ab and a negative cervical sonography) do not require routine diagnostic RAI scan during follow-up.

For higher risk patients, we generally perform RAI scan with low-dose 131-I for routine surveillance either following thyroid hormone withdrawal or rhTSH. Although isotope 123-I may be superior to 131-I for diagnostic purposes (40), it is associated with greater cost and a shorter half-life. At our center, the initial diagnostic scan done prior to ablation is done using 123-I (2 to 4 mCi), while other routine follow up scans are performed using 5 mCi of 131-I isotope.

Cross sectional imaging—Routine cross sectional imaging is predominately reserved for high-risk patients. We perform yearly CT neck and chest or MRI if there is a contraindication for CT imaging. Cross-sectional imaging of the neck and upper chest should also be considered in the setting of bulky nodal disease, for the assessment of potential visceral invasion (trachea, larynx, oesophagus or pharynx) or when neck and RAI findings are thought to inadequately explain high Tg levels (generally >10 ng/ mL) or rising Tg antibodies.

Cross sectional imaging of other organs including brain, abdomen and skeletal survey should be considered in high-risk DTC patients with unexplained elevation of serum Tg, rising anti Tg Ab or localized symptoms to those organs.

Fludeoxyglucose positron emission tomography—FDG-PET is more sensitive in patients with an aggressive histological subtype, particularly poorly differentiated, tall cell, and Hurthle cell thyroid cancer and thus are excellent for the detection of de-differentiated thyroid cancer metastases that no longer concentrate RAI. Initial PET screening for poorly differentiated thyroid cancer is warranted to identify and measure baseline volume of disease. FDG-PET is particularly useful in patients with a high pre-test probability of having aggressive/persistent/recurrent disease. These include high-risk patients with elevated Tg levels, suggestive of active disease and negative RAI scan. Such scenarios are concerning for of de-differentiation thyroid cancer. PET avidity may therefore also help to identify a subset of histologically (initially) well-differentiated thyroid cancers with increased metabolic activity suggestive of an increased potential for adverse behavior. For low-and intermediate-risk patients with known structural disease FDG-PET scans are generally not indicated, unless the above mentioned features are present or other factors suggest (the potential for) histopathological or metabolic dedifferentiation. We do not routinely stimulate TSH prior to obtaining FDG-PET scans, because its value has not been ascertained.

Initial surveillance based on risk stratification

A patients' risk of recurrence is stratified into low, intermediate or high-risk groups (Table 1). The initial surveillance regime based on the three-tiered risk stratification is outlined in

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Table 3 as per current recommendations by the ATA guidelines. All three-risk groups require surveillance with biannual suppressed Tg measurement and annual neck ultrasonography (US). Patients with no evidence of gross residual thyroid cancer either locally in the neck or at distant sites at the end of initial treatment are generally expected to have had a treatment response that results in very low disease specific mortality. The goal of surveillance in the first 2 years is therefore a balance of early recurrence detection and monitoring of indeterminate findings. A decision to treat suspicious abnormalities or confirmed disease should be balanced against the risk of iatrogenic complications as well as potential for subsequent recurrence. High-risk patients warrant additional 6 monthly neck US, cross-sectional imaging, FDG-PET scan, and diagnostic whole body scan. Diagnostic whole body scan is also indicated for intermediate-risk patient with low-level Tg values and indeterminate US, to determine the need for a second dose of RAI.

For patients with gross residual disease despite aggressive initial resection, or with distant metastases at presentation, additional therapy with RAI and/or external beam radiation therapy is likely required. Like other high-risk patients, intensive surveillance with RAI imaging, FDG-PET imaging, and cross-sectional imaging is required. In general, cross-sectional imaging at 6-month intervals is appropriate with additional FDG-PET scanning and RAI scanning, as indicated by the specific clinical symptoms and findings.

Ongoing risk stratification – Response to therapy (Table 4)

Following initial treatment, a patient's response to therapy can be classified into 4 categories; *excellent, biochemically incomplete, structurally incomplete* or *indeterminate*. This risk stratification system utilizes clinical data obtained during follow up to augment the initial estimates of recurrence risk Several modifications have been adopted since its initial description (20), however the four-tiered stratification scheme remain (14). Initial validation of this stratification was based on clinical outcomes after thyroidectomy with adjuvant RAI therapy. However, it has since been demonstrated effective also in patients undergoing lobectomy and total thyroidectomy without RAI therapy (41, 42).

Response to therapy is assessed at each clinical appointment during surveillance. Careful clinical assessment and review of serial Tg and antibody results, allows patients response to therapy to be measured. *Excellent* response refers to a patient with no evidence of disease on clinical exam and imaging and undetectable serum Tg measurements. *Biochemical incomplete* response refers to patients with no clinical or imaging evidence of disease but with an elevated or rising Tg or antiTg Ab level. *Structurally incomplete* response refers to the cohort of patients with evidence of disease in the thyroid bed, cervical nodal basin or at distant sites. Lastly, *indeterminate response* category is for patients with non-specific or borderline biochemical or structural findings. Often patient surveillance with serial Tg and imaging will allow them to be re-categorized into one of the above groups. Table 4 summarizes response to therapy definitions, expected outcomes and clinical implication of the categories.

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Long-term surveillance

Traditionally, thyroid cancer recurrence rates were quoted up to 30% based on reports in the literature from 30 to 40 years ago when patients presented with clinically detected primary or nodal disease (17, 34). Recurrences were also thought to occur later, becoming clinically evident 10–20 years after initial treatment. Increased application and sensitivity of diagnostic modalities has led to earlier detection of subclinical disease as well as recurrences. Nowadays thyroid cancer typically presents at an earlier stage, associated with substantially lower recurrence rates of between 3–10% (20, 35–37). Thyroid cancer surveillance was traditionally considered necessary for life. However, there is increasing evidence to suggest that this may not be necessary for the many low-risk patients with excellent response to therapy (7, 8, 36, 43).

After initial treatment, patients enter a of disease period surveillance. While clinical examination remains important, serial Tg, neck US and additional RAI and cross sectional imaging are applied routinely. Analysis of surveillance practice performed at our center, demonstrates a disproportionately high rate of investigations per recurrence detected in the ATA low-risk category. Routine follow up at our center is 6 monthly, non-stimulated Tg measurements and neck ultrasound 12 monthly for low-risk patients. If no abnormalities are detected within the first 24 months after surgery, patients are deemed to have had excellent response to therapy with very low-risk of recurrence and no additional surveillance is required (20, 44). For the small group of patients with biochemical or structural persistent disease, surveillance beyond 2 years is warranted to determine need for therapy (43). A cost-effectiveness analysis suggests that more intensive or prolonged surveillance is not justified in the low-risk patient category (8).

Surveillance of the intermediate-risk category of patients is similarly limited to 2 years in the absence of suspicious findings. Follow-up is similar to the low-risk group with the addition of a diagnostic RAI scan at 18 months to detect potential regional or distant disease. Routine cross-sectional imaging is limited to high-risk patients and those with raised Tg or abnormalities on neck US. US of the neck is accurate for the identification of lateral neck metastases. However, it is less useful in the central compartment due to the presence of air in the trachea which distorts the image. For high-risk patients and those that demonstrate rising Tg levels in the absence of demonstrable disease in the neck, contrast enhanced CT of the neck and chest is recommended. MRI is an alternative in patients where contrast enhanced CT is contraindicated. Surveillance RAI scans can be useful in select patients if further RAI therapy is warranted. FDG-PET may be considered in patients in whom there is a suspicion of dedifferentiated disease. Table 3 demonstrates our initial surveillance strategy. This surveillance regime is followed for the first 24 months, after which surveillance is adapted to the patients' response to therapy (45, 46).

In the longer term, we aim to titrate surveillance based on response to therapy. In general, ongoing surveillance past 2 years, for patients with excellent response to therapy is limited to 2 yearly Tg levels, and consideration of cervical US at 5 years. For patients with low but persistent Tg levels or non-specific US neck findings, we repeat serum Tg levels biannually and cervical US yearly for 5 years with no additional imaging modalities if Tg and cervical

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US are stable. For this cohort of patients we expect the Tg to continue to decrease over the ensuing years and potential indeterminate US findings to declare itself with time. For the concerning cohort of patients with structural incomplete response, we follow them with 6 monthly Tg levels, 6 monthly to yearly neck US depending on rate of progression, whole body RAI scan to confirm RAI avidity (marker of disease differentiation), yearly cross sectional CT or MRI for disease progression and baseline FDG-PET scan for the development of distant metastases. Several publications in recent years have similarly recognized a need to titrate duration of post thyroid cancer treatment surveillance (47), based on risk of recurrence and response to therapy (43).

Management of recurrent disease

Demonstration of small volume suspicious nodes on ultrasound can be problematic. In such patients, it is often preferable to follow the neck with serial ultrasounds. Evidence of disease progression or proximity to vital structures such as the recurrent laryngeal nerve, should instigate FNA with a view to revision a surgery. In the absence of such indications, period of observation with repeat US may improve clinical acumen. Demonstration of indolent disease may avoid the need for treatment while the development of additional suspicious nodal disease during observation will lead to a more comprehensive neck dissection that would have otherwise required multiple revision surgical procedures. For this reason, we advocate a period of observation for patients with small LNs. In this way patients can avoid unnecessary and multiple salvage neck operations.

Management of small, suspicious nodes confirmed as malignant on biopsy can be challenging. For LNs >10mm, in the previously undissected neck, a comprehensive neck dissection with preservation of uninvolved vital structures should be performed. In the previously dissected neck, a limited neck dissection may be sufficient in highly selected patients. Data from our department demonstrates outcomes are excellent after isolated cervical nodal recurrence or persistence. At 5 years, subsequent nodal and distant recurrence free survival are 89.2% and 93.7% respectively. RAI therapy alone for macroscopically recurrent nodal disease is generally not recommend. If amenable, surgical resection in combination with RAI therapy for palpable nodal disease is preferred.

Summary

The increased detection and treatment of differentiated thyroid cancer has been of great interest to the scientific community and the general public in recent years. The international trend towards increased early-stage disease is well documented (1–3) and has culminated in an increasing population of thyroid cancer survivors requiring ongoing disease surveillance. The majority of these patients will have very low-risk of disease. However a proportion will develop clinically significant recurrence requiring further treatment. There is an ongoing need for optimization of surveillance based on risk of recurrence and death.

We have outlined our center’s risk stratified approach to the postoperative surveillance of differentiated thyroid cancer and highlighted changes to the 2015 ATA guidelines. Intensity, frequency and duration of surveillance is based on an evolving understanding of disease biology, response to initial therapy, likely sites and timing of recurrence, as well as utility of

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specific serological and imaging modalities. Structured approaches to risk stratification at time of initial treatment and ongoing reassessment of response to therapy at subsequent follow-up tailors ongoing surveillance requirements to the individual patient.

It is important to emphasize that individual clinicians should tailor surveillance practice based on local circumstances, tailoring care based availability and access to subspecialty expertise. For the low-risk cohort of patients with an excellent response to therapy after 24 months, no additional surveillance is required (20, 44). Surveillance of intermediate-risk category with excellent response to therapy is similarly limited to 2 years in the absence of suspicious findings, with follow-up recommended to be similar as for the low-risk group with the exception of an added diagnostic RAI scan at 18 months to exclude potential regional or distant disease. For the small group of patients with biochemical or structural persistent disease, surveillance beyond 2 years is warranted to determine timing and need for therapy (43). We limit routine cross sectional imaging of the neck and chest to high-risk patients and those that demonstrate rising Tg levels in the absence of demonstrable disease in the neck. Surveillance RAI scans can be useful in select patients if further RAI therapy is warranted. We perform FDG-PET in patients whom there is suspicion of dedifferentiated disease. In the longer term, response we aim to titrate surveillance based on to therapy. These postoperative surveillance strategies are in keeping with previous publications from our center (7–13) and the latest American Thyroid Association (ATA) guidelines (14) which are ultimately based on the scientific literature.

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Table 1.

American Thyroid Association 2009 and 2015 initial risk stratification of differentiated thyroid cancer

2009 ATA guidelines		
Low-risk	**Intermediate-risk**	**High-risk**
No local or distant metastases	Microscopic perithyroidal invasion	Macroscopic tumor invasion
All macroscopic disease resected	Cervical LN metastases or ^{131}I uptake outside thyroid bed on post treatment scan, if done	Gross residual disease
No locoregional invasion	Aggressive histology	Distant metastases
No aggressive histology		
No vascular invasion		
No ^{131}I uptake outside thyroid bed on post treatment scan, if done		
Modifications from 2015 ATA guidelines		
Low-risk	**Intermediate-risk**	**High-risk**
Clinical N0 or ≤ 5 pathologic N1 micrometastastic (<0.2cm largest dimension)	*Papillary thyroid cancer with vascular invasion*	*Postoperative serum Tg suggestive of distant metastases*
Intrathyroidal encapsulated follicular variant of PTC	*Clinical N1 or >5 pathologic N1 All metastatic LNs <3 cm in largest dimension*	*Metastatic LN≥3 cm in largest dimension*
Intrathyroidal well differentiate follicular variant of PTC with capsular invasion and < 4 foci of vascular invasion	*Multifocal papillary microcarcinoma with ETE and BRAFV600E mutation (if known)*	*FTC with extensive vascular invasion (>4 foci of vascular invasion)*
Intrathyroidal PTC <1cm, uni or multifocal		

Italic – new modifications from the 2015 American thyroid Association management guidelines for differentiated thyroid cancer

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Table 2.

Synoptic histopathological reports for routine thyroidectomy specimens

For each thyroid lobe	For each foci of thyroid malignancy	For LN specimens	AJCC TNM Ed and summary
Number of foci of carcinoma	Tumor type and subtype	Number of LNs examined	pT
ETE; structures involved	Mitotic activity	Number of LNs with metastatic disease	pN
Surgical margins: involvement, location	Tumor necrosis	Size of largest LN involved by tumor	pM (if known)
Non neoplastic thyroid	Tumor location	Size of largest metastatic focus	
Parathyroid gland	Tumor size	Extranodal extension	
	Tumor encapsulation		
	Capsular invasion		
	Blood vessel invasion		

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Table 3.

Initial surveillance regime based on postoperative ATA risk stratification of differentiated thyroid cancer

	6 months	**12 months**	**18 months**	**24 months**
Thyroglobulin	All risk groups	All risk groups	All risk groups	All risk groups
Cervical ultrasonography	-	All risk groups	-	All risk groups
Diagnostic RAI scan	-	-	Intermediate-High-risk group	-
CT/MRI	-	High-risk group	-	High-risk group
PET scan	-	High-risk group	-	High-risk group

All- low, intermediate and high-risk

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Table 4.

Response the therapy; definition, clinical outcomes and management implications. (Based on 2015 the American Thyroid Association guidelines (14))

Category	Definitions	Clinical outcomes	Management implications
Excellent response	Negative imaging AND • stimulated Tg <1 ng/mL	1 –4% recurrence <1% DSD	Early decrease in intensity and frequency of follow up and TSH suppression
Biochemical incomplete response	Negative imaging AND • stimulated Tg >10ng/mL or • rising antiTg Ab	• 30% spontaneously resolve with time • 20% achieve NED after additional therapy • 20% develop structural disease <1% DSD	If stable or declining Tg, continued observation with ongoing TSH suppression Rising Tg and antiTg Ab, should prompt additional investigations
Structurally incomplete response	Structural or functional evidence of disease • any Tg level • any antiTg Ab	• 50–85% continue to have persistent disease despite additional therapy • DSD 11% in patients with locoregional metastases • DSD 50% with structural distant metastases	May require additional treatments or ongoing observation depending on factors including size, location, rate of growth, RAI avidity, FDG avidity, specific pathology of the lesion
Indeterminate response	• Non specific findings on imaging • Stimulated Tg detectable but <10ng/mL • AntiTg Ab stable or declining in the absence of structural or function disease	• 15–20% will have structural disease with follow up • The remainder will remain stable or resolve <1% DSD	Continue observation with appropriate serial imaging of non-specific changes and serum Tg monitoring. If non specific findings become suspicious over time, they can be further imaged or biopsied

AntiTg Ab – anti-thyroglobulin antibody, Tg – thyroglobulin, NED – no evidence of disease, DSD – disease specific death, RAI – radioactive iodine, FDG - fludeoxyglucose

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Table 5.

Preoperative risk for developing adverse effects from TSH suppression

	High-risk	Intermediate-risk	Low-risk
Atrial Fibrillation Risk	Clinical Heart Disease Age >75yo Comorbidities	Age >60yo HTN Thyrotoxic symptoms Cardiovascular risk Factors Diabetes	Age <60yo No comorbidities
Osteoporosis Risk	Osteoporosis Postmenopausal (>50yo) Prior radiotherapy	Perimenopausal women (40–50yo) Osteopenia Osteoporosis risk factors	Male Age <40 yo No comorbidities No osteoporosis risk factors

TSH – thyroid stimulating hormone

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Table 6.

Synoptic reporting of cervical ultrasonography in thyroid cancer (preoperative or surveillance)

Feature	Characteristic
Thyroid lobe *(thyroid bed if post resection)*	Size of left, right lobes, isthmus,
	Thyroid nodules; size, number, location
	Thyroid bed nodules; size, number, location
	Proximity to vital structures (cervical viscera, RLN)
Central and lateral nodal compartments	Location of LNs; neck level, laterality
	Characteristics of suspicious LNs, including size and number of LNs
	Proximity to vital structures (cervical viscera, RLN)
Comparison to previous scan	Characterize changes
Malignancy risk	High, intermediate, low-risk of malignancy, benign

LN – lymph nodes, RLN – recurrence laryngeal nerve