REVIEW

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Nodal metastases in thyroid cancer: prognostic implications and management

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The significance of cervical lymph node metastases in differentiated thyroid cancer has been controversial and continues to evolve. Current staging systems consider nodal metastases to confer a poorer prognosis, particularly in older patients. Increasingly, the literature suggests that characteristics of the metastatic lymph nodes such as size and number are also prognostic. There is a growing trend toward less aggressive treatment of low-volume nodal disease. The aim of this review is to summarize the current literature and discuss prognostic and management implications of lymph node metastases in differentiated thyroid cancer.

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Metastases to regional cervical lymph nodes (LNs) occur early and frequently in patients with differentiated thyroid cancer (DTC) [1]. The prognostic significance of metastatic LNs has been debated and our understanding and management of patients with metastatic disease continues to evolve. Early publications suggested that the presence of nodal disease was not prognostic of outcomes. However, later series suggested that nodal disease is associated with poorer outcomes, particularly in older patients [2–4]. Improved outcomes following therapeutic neck dissection are well established. However, the role of routine prophylactic neck dissection is more controversial. Since the advent of high-resolution ultrasonography and detailed histopathological analysis, contemporary series have further stratified nodal disease by characteristics such as size and number of LNs to allow for improved prognostication [5–9]. The aim of this review is to summarize the current approach to the assessment, management and surveillance of cervical LNs in patients with DTC with a focus on papillary thyroid cancer (PTC).

KEYWORDS

• lymph nodes • neck • neck dissection • outcomes
• prognosis • radioactive iodine • recurrence
• survival • thyroid cancer

Prognostic significance of nodal metastases in thyroid cancer

• Pattern of nodal spread

Like other primary malignancies of the head and neck, thyroid cancer follows a consistent pattern of spread in the cervical LNs. The central compartment, level 6 and 7, is the first echelon of involvement followed by spread to the lateral compartments levels 2–5, followed by the contralateral side [10–13]. Involvement of LNs in the submental or submandibular region (level 1) is rare. Skip metastases to the lateral LNs in the absence of central compartment disease has been reported in up to 20% of cases [14].

• Importance of nodal disease in current staging & risk stratification systems

The unique prognostic importance of age is well established in thyroid cancer. Other important prognostic factors include the presence of distant metastases, histological subtype and the presence

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of gross extrathyroidal extension. The significance of cervical LN metastases is however more controversial. Unlike most other solid cancers, metastatic spread to regional LNs has been traditionally regarded as having no impact on prognosis. This may be because the majority of PTC patients with nodal disease harbor subclinical micrometastases that are often indolent in nature. For this reason, the presence of nodal disease has not been included in traditional scoring systems including GAMES, from our institution, and MACIS and AMES from other centers [3–4,15]. Variables such as multifocality, lymphovascular invasion, absence of tumor capsule and extrathyroidal extension have been reported as predictors of nodal disease [16].

Currently, the 7th edition of the AJCC TNM staging system classifies nodal status into N0, N1a (central neck node involvement) and N1b (lateral neck node involvement). This stratification differentiates nodal disease based on location within the neck. While nodal metastases occur more frequently in younger patients [17], they are generally not thought to be prognostic of survival. As such, all patients younger than 45 years of age with no evidence of distant metastases are stage I regardless of nodal status (N0/N1a/N1b). In contrast, nodal disease has been shown to impact survival in older patients [18–21]. Patients over 45 years of age with central compartment nodal disease (N1a) are stage III and those with lateral compartment disease (N1b) are stage IV [22].

The AJCC staging system stratifies patients into stages I to IV based on overall survival. By contrast, recurrence risk is classified by the American Thyroid Association (ATA) risk categorization system into low-, intermediate- and high-risk groups. The 2009 ATA risk stratification system has been validated and widely adopted into clinical use (Box 1) [23,24]. Evidence of cervical LN metastases upstages patients from a low- to intermediate-risk category and this typically leads to adjuvant radioactive iodine (RAI) administration. Recent data suggest that LN characteristics such as size, number, ratio and the presence of extranodal spread (ENS) may all impact prognosis [5,7,9,25–29]. A detailed systematic review was published by the ATA, quantifying the relationships between nodal volume and its relationship to prognosis in thyroid cancer. It was recommended that patients be classified into ‘lower and higher risk N1’ categories based on number and size of nodal disease [30]. ‘Low-risk N1’ was defined as ≤ 5 positive LNs

and measuring ≤ 0.2 cm in maximum diameter. The definition of micrometastases ≤ 0.2 cm was based on data from breast cancer staging. The 2015 ATA risk stratification incorporates these modifications [31]. Patients with low-volume LN metastases measuring ≤ 0.2 cm and ≤ 5 involved LNs will be considered in the same low-risk category as N0 patients. The clinical implications of this modification are significant because it allows patients with low-volume nodal disease, of questionable significance, to be downstaged and potentially managed without adjuvant RAI therapy [8]. This may further call into question the need for prophylactic central neck dissection for the purpose of disease staging.

Internationally, thyroid associations vary in their recommendations for the management of patients with nodal disease. Table 1 shows a summary of the recommendations from select international thyroid associations. The British Thyroid Association (BTA) risk stratification largely mirrors that of the ATA [32]. However, the European Thyroid Association (ETA) and Latin American Thyroid Society (LATS) consider all patients with N1 disease to be high risk warranting postoperative RAI therapy [33,34]. The Japanese Society of Thyroid Surgeons (JSTS) and Japanese Association of Endocrine Surgeons (JAES) recommend routine prophylactic central neck dissection, in part due the limited access to RAI therapy [35].

• Rate & significance of nodal disease

Rates of nodal metastases vary significantly between 20 and 90%. This variation is largely due to the method used to detect nodal disease [17]. Clinical examination can detect nodal metastases approximately 1 cm in diameter, while the use of high-resolution neck ultrasound (US) can detect smaller subcentimeter LNs. Detailed histopathological examination can increase the sensitivity of tumor detection down to a fraction of a millimeter. Depending on the method of diagnosis, the prognostic significance of nodal disease similarly varies. This has been indirectly demonstrated from outcomes of patients from earlier series where nodal disease detection was predominantly through clinical palpation [36] compared with more recent series where nodal disease detection is primarily through the use of high-resolution neck US or on detailed histopathological examination alone. Studies have also directly compared the outcomes of patients with clinical, sonographic and histopathological

detected nodal disease [6,37]. Both the direct and indirect comparisons demonstrate that patients with clinically palpable disease have poorer outcomes compared with patients with disease detected only on histopathological analysis. More recently, molecular techniques have been employed in the histopathological analysis of nodal disease, allowing for the detection of isolated tumor cells in regional LNs [22]. However, increasing evidence suggests that nodal disease detected in this manner is of little prognostic impact [38]. The prognostic significance of nodal metastases in PTC, therefore is likely to be determined by the nodal disease characteristics.

• Controversy over management of nodal disease

It is well established that clinically palpable nodal disease is associated with adverse prognosis in PTC and as such therapeutic neck dissection is routinely performed in such patients. The practice of elective or prophylactic central neck dissection in patients without clinically palpable or radiological detected LNs is more controversial.

The 2006 edition of the American Thyroid Association guidelines, suggested that routine central compartment (level 6) neck dissection should be considered for patients with DTC [39]. This contentious recommendation was subsequently modified, suggesting that prophylactic central compartment neck dissection may be performed in patients with thyroid carcinoma for advanced primary tumors (T3 or T4) and those with lateral compartment disease [31]. Around the world, the majority of thyroid cancer guidelines, similarly do not recommend routine prophylactic central neck dissections. Rather, the guidelines allow for clinician judgment based upon surgeon experience and patient risk [34,40–41].

Proponents of prophylactic central neck dissection have demonstrated that prophylactic neck dissection may reduce postoperative serum thyroglobulin (Tg) levels and improve short-term recurrence rates [42–44]. However, there remains little evidence to suggest that microscopic disease, not visible on preoperative imaging or intraoperative palpation, is associated with poorer outcomes. Furthermore, there is little evidence to suggest that the resection of such microscopic disease in prophylactic central neck dissection improves overall survival [45,46]. Advocates for prophylactic central neck dissection argue that this procedure provides more

Box 1. American Thyroid Association 2009 risk stratification.

Low risk

- No local or distant metastases
- All macroscopic disease resected
- No locoregional invasion
- No aggressive histology
- No vascular invasion
- No ¹³¹I uptake outside thyroid bed on post-treatment scan, if done

Intermediate risk

- Microscopic perithyroidal invasion
- Cervical lymph node metastases or ¹³¹I uptake outside thyroid bed on post-treatment scan, if done
- Aggressive histology

High risk

- Macroscopic tumor invasion
- Gross residual disease
- Distant metastases

accurate assessment of nodal status. Prophylactic central neck dissection upstages approximately 30% of patients 45 years and older which subsequently increases the need for adjuvant RAI therapy [47,48]. However, in the absence of data demonstrating survival benefit for patients with microscopic N1 disease, routine neck dissection and adjuvant RAI therapy, with their associated complications, would appear to be unjustified.

The practice in our department is to perform a neck dissection only for clinically evident disease identified either on clinical examination or on preoperative imaging. This practice is based on the philosophy that although nodal metastases may occur early and frequently, the majority of patients will have clinically indolent disease throughout their life. Resection of such indolent disease can be associated with iatrogenic morbidity, both from surgery as well as from RAI. Furthermore, with appropriate surveillance, delayed resection of nodal disease once it becomes clinically evident is safe [49]. Increasingly, the literature, including publications from our department, reports that microscopic or low-volume disease is not associated with poorer outcomes [8,30]. These findings further question the need for prophylactic staging central neck dissection in PTC.

• Prognostic nodal characteristics not in staging systems

As stated earlier, the current 7th edition of the AJCC staging system takes into account the

Table 1. Summary of recommendations across select international thyroid associations.

International association	Prophylactic central neck dissection	Prophylactic lateral neck dissection	Adjuvant RAI therapy
ATA (2009)	Consider for T3/4	Not recommended	Aggressive histology, extrathyroidal extension, any nodal or distant disease
BTA (2014)	Consider for age ≥45 years, multifocal, >4 cm, extrathyroidal extension, adverse histology	Consider for advanced central compartment disease	Consider for multifocal, T >1 cm, extrathyroidal extension, lymph node metastases
ETA (2006)	Not recommended	Not recommended	Indicated for distant metastases, R2 margin, nodal disease, T3/4, extrathyroidal extension Consider for T >1 cm, adverse histology
LATS (2009)	Consider for T3/4	Not recommended	Indicated for >45 years of age with T3 and T4, nodal or distant disease, extrathyroidal extension aggressive histology Consider for T >1 cm
JSTS/JAES (2010)	Routinely recommended	To be considered	Limited access due to legal restrictions

ATA: American Thyroid Association; BTA: British Thyroid Association; ETA: European Thyroid Association; JSTS/JAES: Japanese Society of Thyroid Surgeons, Japanese Association of Endocrine Surgeons; LATS: Latin American Thyroid Society.

location and presence of nodal disease in thyroid cancer. The 2009 ATA risk stratification system considers all patients with nodal disease, whether clinically apparent or microscopic only disease, as intermediate risk for recurrence and recommend adjuvant RAI therapy. The new 2015 ATA risk stratification system now considers size (≤0.2 cm) and number of LN metastases (≤5) to be important. This has been based upon increasing evidence that metastatic volume plays a role in prognosis. Although LN size and number have been the most extensively studied characteristics, other studies have suggested that the presence of ENS and the ratio of positive to total LN resected may also be important prognostic factors [6,27]. Evidence for the prognostic significance of nodal characteristics in PTC stems largely from retrospective institutional cohorts. The findings for each LN characteristic will be discussed below with reference to current literature.

Size & number

Multiple studies have suggested that increasing size and number of involved LNs are associated with greater recurrence and poorer survival [5,25,26,28,29,50,51]. However, there is no clear consensus on the size and number threshold which is most prognostic of poorer outcome. Due to the single institution, retrospective nature of many of these studies, inclusion criteria have been heterogeneous. With regards to LN size, 1.5 cm has been proposed as an independent predictor of recurrence, while others have suggested LN size of 3 cm or more is prognostic

for poorer survival in older but not younger patients [5,26]. It is apparent that increasing LN size is important. However, no cutoff is definitive and therefore size may not be the most prognostic LN feature [7,52]. When considering the number of positive LNs, significant cutoffs have similarly varied in the literature. Greater than 2 through ten positive LNs in the lateral or both neck compartments, have been suggested as markers of poorer outcome [5,25,26,28]. For patients with N1b disease, data from our institution suggest that the presence of more than ten LNs in the lateral neck maximized sensitivity and specificity for predicting poorer outcomes [9]. The literature would suggest that LN size of 0.2 cm and five LNs is a conservative cutoff for ATA low-risk nodal disease. Nevertheless, this is an important step acknowledging the heterogeneity of nodal disease and the characteristics of nodal disease that may be important to prognosis.

Extranodal spread

ENS is well recognized as an important marker of aggressive tumor biology in other cancers of the head and neck [53,54] and is widely accepted as an indication for adjuvant chemoradiation in squamous cell carcinoma [55]. However, its importance in the outcome of patients with thyroid cancer is less well established. Earlier studies were unable to detect an association between ENS and outcome, possibly due to small sample size [56]. However, recent groups have reported ENS to predict a poorer outcome [6,25,51,57–59]. Data from our center suggest that ENS is the

most important LN characteristic predictive of recurrence in patients with central compartment disease (Figure 1). This characteristic may also be important in older patients with lateral compartment disease [7,9]. Interestingly, the presence of lateral compartment ENS appears less prognostic in younger patients. Until further data confirm its utility, it has not been included in the new ATA risk stratification system.

LN burden

LN burden or ratio is defined as the number of metastatic LNs divided by the total number of LNs resected. LN burden is dependent upon the extent of surgical resection and is also influenced by the extent of pathological scrutiny. The concept of LN burden or ratio has been studied in other cancers [60–63] including oral and cutaneous squamous cell carcinoma of the head and neck [64,65]. However, the prognostic impact of LN burden has not been well explored in thyroid cancer [27,29]. Our recent publications suggest that LN burden of more than one positive LN in six LNs resected is likely to be important in

N1b patients and more prognostic in younger patients (Figure 2) [9]. However, further studies are required to verify its clinical utility.

• Role of molecular markers in nodal disease

In recent years, *BRAF* mutations, *RAS* mutations and *RET-PTC* rearrangements have been identified as the main driver events in thyroid cancer. *BRAF* mutations occur in approximately 60% of patients with PTC and are the most studied molecular marker in PTC. *BRAF* mutations, most commonly of V600E, constitutively activate the *BRAF* kinase in the MAPK pathway thereby promoting cell-proliferation. Its presence is diagnostic of thyroid cancer. Some studies suggest it may be associated with adverse disease characteristics and advanced disease stages [66–72]. Patients with recurrent or persistent PTC have a higher incidence of *BRAF* mutation [73]. Based on these findings, some have advocated for the use of *BRAF* mutation status to guide extent of initial thyroidectomy and neck dissection [66,74–75]. It is, however, important to emphasize that the identification of a molecular predictor of recurrence or mortality does not

Figure 1. Kaplan–Meier plots for nodal recurrence-free survival in differentiated thyroid cancer patients with central compartment nodal disease with and without presence of extranodal spread.

ENS: Extranodal spread; NRFS: Nodal recurrence-free survival.

Figure 2. Kaplan–Meier plots for recurrence-free survival in patients with lateral lymph node burden of $>17\%$ (one positive lymph nodes in six lymph nodes removed).

LN: Lymph node; RFS: Recurrence-free survival.

equate to improved outcomes with more aggressive therapy; prospective studies are required to confirm therapeutic benefit. At present, mutational status does not routinely impact management guidelines nor risk stratification systems. Further studies are required to demonstrate if *BRAF*-positive patients will experience therapeutic benefit from more aggressive treatment.

MSKCC management philosophy of nodal disease in thyroid cancer

• Nodal disease assessment

Traditionally at our institution, the presence of nodal disease is determined by clinical examination alone. However, with increasing sensitivity and widespread availability of ultrasonography, we have transitioned to a practice of preoperative US for the detection of neck metastases [76]. Studies have correlated nodal appearance on ultrasonography with pathological findings. Cystic and hypoechoic LNs, hyperechoic punctuations, LN wider than tall, size >7 mm in the smallest axis, loss of fatty hilum, presence of microcalcifications are suggestive of malignancy [31]. **Table 2** outlines characteristics that should be reported in all

routine preoperative US of the neck for performed for patients diagnosed with thyroid cancer.

The literature demonstrates that US increases the detection of nodal disease compared with physical examination alone [77], and that patients with US detectable neck metastases have a significantly higher recurrence rate than those with no metastases or microscopic metastases [37,78]. We have recently reported that preoperative US of the lateral compartment can lead to improved response to therapy, reduced need for adjuvant RAI treatment as well as reduced regional recurrence [76].

Ultrasound assessment of central compartment neck LNs in level 6 and 7, is less sensitive due to the presence of air in the trachea and the bone of the sternum and clavicles [79]. Assessment of the central compartment for all patients is therefore supplemented with intraoperative palpation of the central compartment at the time of thyroidectomy.

• Surgical management

It has been our department's practice to perform compartment based, therapeutic neck dissection

when clinically evident LNs are present. Central neck compartment is assessed through careful intraoperative palpation. If any suspicious LNs are identified then frozen section is done. If positive, a central neck dissection is then carried out. We have previously demonstrated that in properly selected patients, observation of the clinically negative central neck, as determined by physical examination and ultrasonography, is safe with a very low structural recurrence rate of 0.4%. In addition, delayed neck dissection in these patients still results in excellent outcomes [49].

The extent of the lateral compartment neck dissection (selective or comprehensive) is based upon the volume of involved nodes and individual patient risk. Unpublished data from our institution demonstrates that selective lateral neck dissection is suitable for highly selected low-risk patients with low-volume nodal disease confined to 1 or 2 LN levels. We found comprehensive lateral neck dissection is associated with lower ipsilateral recurrence rates in patients with higher nodal volume or risk of recurrence. Thus the extent of lateral neck dissection is assessed on an individual basis.

• Adjuvant RAI therapy

There is good evidence supporting adjuvant RAI therapy in patients with locally advanced and distant disease. However, its benefit in the treatment of nodal disease is less certain [23]. Although RAI therapy is generally considered safe, its use, especially in high doses, is not without adverse effects. RAI uptake outside the thyroid gland can result in salivary and lacrimal gland dysfunction and have a deleterious

impact on quality of life [80]. In addition, there is a small but significant increase in the rate of second malignancies, particularly hematological malignancies [81,82]. In the absence of definitive guidelines, much of the clinical decision is made by treating physicians. A multidisciplinary team discussion should balance the risk of cancer recurrence against the risk of iatrogenic harm from RAI. Patient selection for RAI therapy is based on clinical factors such as age and gender, tumor variables such as extrathyroidal extension and histology subtype as well as postoperative serum thyroglobulin (Tg) levels [83]. Importantly, we do not consider the presence of nodal disease as an absolute indication for adjuvant RAI therapy. We rely on further risk stratification of nodal characteristics such as size, number, extent of neck dissection and presence of ENS. In our experience, select patients with otherwise favorable primary tumor characteristics and low-volume central LN metastases can be safely observed without the need for additional RAI [8]. We would advocate other clinicians to consider N1 patients as a heterogeneous group, warranting individualized RAI therapy.

There is increasing awareness that high doses of RAI do not result in an increased cancer risk reduction. The 2009 ATA guidelines recommended an ablative dose of between 30 and 100 mCi for patients with ATA low risk cancer and 100–200 mCi for patients with residual microscopic disease or if an aggressive histologic variant of DTC was present. Since then, several studies have compared clinical outcomes following various adjuvant RAI doses. These suggest little improvement in clinical outcome for patients with increasing doses of RAI in ATA

Table 2. The following characteristics should be reported in routine preoperative ultrasound of the neck for performed for patients diagnosed with thyroid cancer.

Feature	Description
Thyroid nodule	Nodule characteristics Location/s; left, right lobes, isthmus Proximity to vital structures (trachea, recurrent laryngeal nerve)
Thyroid gland	Size of left, right lobes and isthmus Presence of simple cysts, multinodular goiter
Central compartment	Location/s; pretracheal, paratracheal, prelaryngeal, laterality Characteristics of suspicious LNs, including size and number of LNs Proximity to vital structures
Lateral compartment	Location/s; neck level, laterality Characteristics of suspicious LNs, including size and number of LNs Proximity to vital structures
Summary/recommendation	High, intermediate, low risk of malignancy, benign

LN: Lymph node.

intermediate and high-risk patients [84,85]. A lower ablative dose of 30 mCi and adjuvant dose of up to 150 mCi is recommended in the new edition of the ATA guidelines [31].

• Postoperative surveillance of nodal disease

After initial treatment, patients enter a period of disease surveillance. While clinical examination remains important, more sensitive methods have been increasingly used to detect small volume disease. In recent years, serial Tg, neck US and additional RAI and cross sectional imaging have become routine in the surveillance of many thyroid cancer patients, across all risk categories. Analysis of surveillance practice performed at our center, demonstrates a disproportionately high rate of investigations per recurrence detected in the ATA low-risk category (Figure 3). Routine surveillance at our center has evolved to one of 6 monthly, nonstimulated Tg measurements and USs of the neck 12 monthly for low-risk patients (Table 3). 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 [86,87]. For the small group of patients with biochemical or structural persistent disease, surveillance beyond 2 years is warranted to determine need for therapy [88]. Cost-effectiveness analysis of our centers' practice demonstrates that more intensive or prolonged surveillance is not justified particularly in the low-risk patient category [89].

Surveillance of intermediate-risk category is similarly limited to 2 years in the absence of suspicious findings. Follow-up is as for the

low-risk group with the option of a diagnostic RAI scan at 18 months to detect regional or distant disease. Cross sectional imaging is warranted in 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. In high-risk patients and in those that demonstrate rising Tg levels in the absence of demonstrable disease in the neck, contrast-enhanced computer tomography (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. Positron emission scans may be considered in patients in whom there is suspicion of dedifferentiated disease. Table 3 demonstrates our present surveillance strategy. This surveillance regime is followed for the first 24 months, after which surveillance is reduced and is based on the patients' response to therapy [90,91].

• Management of recurrent nodal disease

Demonstration of small volume suspicious nodes on US can be problematic. In such patients, it is often preferable to follow the neck with serial USs. Evidence of disease progression or proximity to vital structures such as the recurrent laryngeal nerve, should instigate FNA with a view to revision surgery. In the absence of such indications, a period of observation with repeat US may improve clinical acumen. Demonstration of indolent disease may avoid the need for revision dissection while the development of additional suspicious nodal disease during observation

Figure 3. Number of surveillance investigations required to detect one recurrence event stratified by the American Thyroid Association risk categories (2009 edition).

CT: Computed tomography; RAI: Radioactive iodine; Tg: Thyroglobulin; TgAB: Thyroglobulin antibody; US: Ultrasound.

Table 3. Postoperative surveillance strategy based on American Thyroid Association risk category.

Investigation	6 months	12 months	18 months	24 months
Thyroglobulin	All	All	All	All
Ultrasound neck	–	All	–	All
Diagnostic RAI scan	–	–	Intermediate/high risk	–
CT/MRI	–	High risk	–	High risk
PET scan	–	High risk	–	High risk

All low, intermediate and high risk.
CT: Computed tomography; RAI: Radioactive iodine.
Data taken from [90].

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 identified on US and confirmed on biopsy can be challenging. For LNs >10 mm, in the previously undissected neck, a comprehensive neck dissection with preservation of uninvolved

vital structures should be done. In the previously dissected neck, a limited neck dissection may be sufficient in highly selected patients. Unpublished 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.

Future perspective

Contemporary thyroid cancer management is largely based on histopathology,

Figure 4. Kaplan–Meier plots for distant recurrence-free survival in papillary thyroid cancer patients 45 years or older with N0/x, N1a and N1b disease at presentation at 5 years.

DRFS: Distant recurrence-free survival.

stage at presentation and response to therapy, with increasing emphasis on the genomic characteristics of cancer.

Thyroid cancer is associated with a high frequency of point mutations in the *BRAF* and *RAS* genes as well as fusions involving the *RET* tyrosine kinase gene. The Cancer Genome Atlas Research Network has recently published an integrated genomic characterization of a large cohort of PTC. Driver mutations causing PTC are now identifiable in 96.5% of all PTCs [92]. While targeted therapies have now largely replaced chemotherapy agents, their role remains limited to the management of patients with RAI refractory disease and patients with distant metastases [93]. Although these targeted therapies have improved overall survival for patients with advanced disease, there are as yet no agents suitable for use in patients with high-risk locoregional disease. It can be anticipated that the number of approved targeted therapies for thyroid cancer will increase in the coming decade with our increased understanding of the genomics of thyroid cancer.

The mutational classification of thyroid tumors tends to correspond well to conventional histopathological subtypes; with *BRAF*-like tumors corresponding to PTC and *RAS*-like tumors corresponding to follicular variants and follicular tumors [92]. Further improved

characterization of the relationship between genomic profiles and tumor behavior will allow identification of patients likely to develop progressive disease. These patients may benefit from early administration of targeted therapies prior to disease recurrence.

The subgroup of older patients with evidence of lateral compartment (N1b) disease at time of diagnosis have significantly poorer outcomes (Figure 4). Previous publications from our center demonstrate that in this older patients N1b group, development of distant disease is a surrogate marker for disease specific death [20]. We are currently working toward identifying mutational markers associated with the development of distant metastases in this high-risk patient population. Using targeted next generation sequencing we hope to identify the mutations, which drive the distant metastases phenotype. This may allow the early identification and treatment of such high-risk patients, and ultimately aim for development of new, targeted therapy. As new molecular markers and targeted therapies become available, it will be increasingly crucial for ongoing dialog between members of the treating multidisciplinary team. Ultimately, discussion is required between the surgeon, patient, endocrinologist, medical oncologist and/or radiation oncologist, in making precise individual treatment decisions.

EXECUTIVE SUMMARY

- Pathological lymph node (LN) characteristics such as size, number, ratio and presence of extranodal spread may all impact prognosis.
- The practice in our department is to perform therapeutic neck dissections only for clinically evident disease either on preoperative examination or imaging.
- Select patients with otherwise favorable primary tumor characteristics and low-volume central LN metastases may be safely observed without the need for radioactive iodine.
- Postoperative surveillance at our center has evolved to one of 6 monthly, nonstimulated thyroglobulin measurements and ultrasounds of the neck 12 monthly for low-risk patients.
- Routine surveillance for low-risk patients with excellent response to therapy beyond 24 months is not required.
- During follow-up surveillance, demonstration of small volume suspicious nodes on ultrasound can be problematic. We advocate a period of observation for select patients with small LNs and low-risk primary disease. In this way, patients can avoid unnecessary or multiple salvage neck operations.
- In recent years, there has been increasing knowledge on the genomic characteristics of thyroid cancer. However at present these characteristics do not impact routine management.
- Targeted therapies have improved overall survival for patients with advanced disease. However, there are presently no agents suitable for use in patients with high-risk locoregional disease.
- Future identification of genetic alterations that drive the distant metastases phenotype may allow the early identification and treatment of high-risk patients, and ultimately identify pathways suitable for new, targeted therapy.

Conclusion

The significance of cervical LN metastases in differentiated thyroid cancer has been controversial and continues to evolve over time. Management comprises accurate staging by clinical examination and preoperative imaging, appropriate surgery to the primary and neck, selective use of RAI and surveillance based upon risk of recurrence. Patients with clinically evident LN metastases are best served by therapeutic neck dissection and the selective use of RAI. The literature supports the concept that prognosis worsens with increasing LN size, number and presence of extracapsular spread, particularly in older patients. Until recently, the American Thyroid Association guidelines have advocated for adjuvant radioactive iodine therapy for all patients with nodal disease. The new 2015 guidelines recognize that patients

with low-volume nodal disease and otherwise favorable primary tumor characteristics may not require RAI. Therefore a more personalized risk adapted management strategy in patients with cervical LN metastases has been developed. The increasing knowledge of genomics in thyroid cancer may play an evolving role in the management of LNs in DTC.

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