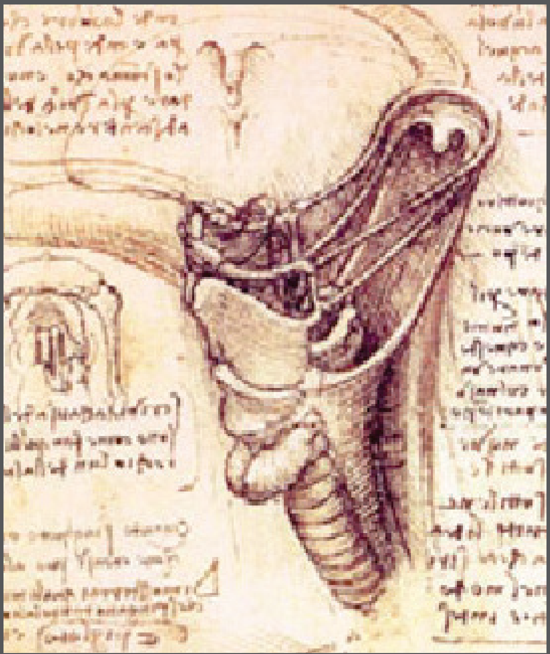
DIAGNOSTIC, PROGNOSTIC AND THERAPEUTIC IMPLICATIONS OF REGIONAL LYMPH NODE METASTASES IN DIFFERENTIATED THYROID CARCINOMA

Laura Y. Wang



Diagnostic, prognostic and therapeutic implications of regional lymph node metastases in differentiated thyroid carcinoma

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Research presented in this thesis has been performed on the Head and Neck Service of the Department of Surgery (Head: prof.dr. J.P. Shah), Memorial Sloan Kettering Cancer Center, New York, USA.

Cover: Da Vinci created the first depiction of the normal thyroid gland from his cadveric dissection in the 1500's. His remarkable drawings were not seen for over 200 hundred years before being rediscovered. They are currently on display in the Royal Library in England.

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Faculteit der Tandheelkunde

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Chapter 1

Introduction, aims and outlines

Introduction

Internationally, there were 567, 233 new cases of thyroid cancer diagnosed in 2018, 436, 344 of which were in women (76.9%) (1). In the USA, thyroid cancer is the most common endocrine malignancy and the fifth most common cancer in women with an estimated annual incidence of 56 870 cases. In the past 3 decades, the incidence of thyroid cancer has nearly tripled, from 4.9 to 14.3 per 100,000 individuals, with similar trends seen around the world (2-4). The increased incidence and stable mortality rate culminate in an increasing prevalence of thyroid cancer survivors in the population.

Metastases to regional cervical lymph nodes (LN) occur early and frequently in patients with differentiated thyroid cancer (DTC) (5). The prognostic significance of metastatic LNs has been debated and our understanding and management of patients with metastatic disease continues to evolve. Early studies reported that the presence of nodal disease was not prognostic of outcomes (6-8). However, later studies suggest that nodal disease is associated with poorer outcomes, particularly in older patients (8-10). Benefit of therapeutic neck dissection and improved outcomes are well established. However, the benefit of elective node dissection, the extent of regional lymph node dissection, the impact of microscopic disease in lymph nodes and timing of recurrent nodal disease management remain 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 lymph nodes to allow for improved prognostication (11-15).

Pattern of nodal spread

Like other primary malignancies of the head and neck, thyroid cancer follows a predictable 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 compartment levels 2-5, followed by contralateral spread (16-19). Skip metastases to the lateral LNs in the absence of central compartment disease has been reported in up to 20% of cases (20). Tumors involving the upper pole of the thyroid gland are more likely to drain into ipsilateral levels 2 and 3 lymph nodes(21). Involvement of lymph nodes in the submental or submandibular region (level 1) is rare.

Incidence and significance of nodal disease

The presence of nodal metastases at initial diagnosis in patients with thyroid cancer varies significantly between 20% - 90%. This variation is largely due to the method used to detect nodal disease. (22). Clinical examination can detect nodal metastases approximately 1cm or larger in diameter, while the use of high-resolution neck ultrasound 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 examination (23) compared to more recent series where nodal disease detection is primarily through the use of high resolution neck US, or CT scans or on detailed histopathological examination alone. Studies have also directly compared the outcomes of patients with clinical, sonographic and clinically occult but histopathologically detected nodal disease (12, 24). Both the direct and indirect comparisons demonstrate that patients with clinically palpable, bulky nodal disease have poorer outcomes compared to patients with microscopic disease detected only on histopathological analysis (25). 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 (26). However, increasing evidence suggests that nodal disease detected in this manner is of little prognostic impact with no impact on clinical outcomes (27). The prognostic significance of nodal metastases in papillary thyroid cancer (PTC), therefore is likely to be determined by the nodal disease characteristics.

The 8th edition of the AJCC staging system takes into account the location and presence of nodal disease in thyroid cancer and its impact on survival (**Table 1).** In 2009 the ATA risk stratification system considered all patients with nodal disease, whether clinically apparent or only microscopically identified disease, as intermediate-risk for recurrence and recommended adjuvant RAI therapy for all patients with any nodal metastases (**Table 2**). However, in the 2015 ATA risk stratification system, size (≤0.2cm) and number of LN metastases (≤5) are considered to be NOT important factors in recommending adjuvant therapy. This change was based upon increasing evidence that metastatic volume plays a role in prognosis (25). Although LN size and number have been the most extensively studied characteristics, other studies have suggested that the presence of extranodal spread (ENS) and the ratio of positive to total LN resected may also be important prognostic factors (12, 28). Evidence for the prognostic significance of nodal characteristics in PTC stems largely from retrospective reports on institutional cohorts. The findings for each LN characteristic will be discussed in this thesis with reference to the current literature.

Multiple studies have suggested that increasing size and number of involved LNs are associated with greater recurrence and poorer survival (11, 29-34). However, there is no clear consensus on the size and number threshold which is most prognostic of poorer outcome. The literature would suggest that LN size of 0.2cm and 5 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 for prognosis.

ENE is well recognized as an important marker of aggressive tumor biology in other cancers of the head and neck (35, 36) and is widely accepted as an indication for adjuvant chemoradiation in mucosal squamous cell carcinoma (37). However, its importance in the outcome of patients with thyroid cancer is less well established. 3

LN burden or ratio is defined as the number of metastatic LNs divided by the total number of LNs resected in a neck dissection. LN burden is dependent upon the extent and completeness 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 (38-41) including oral and cutaneous squamous cell carcinoma of the head and neck (42, 43). However, the prognostic impact of LN burden has not been well explored in thyroid cancer (28, 30).

Impact of nodal disease in staging and 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 of gross extrathyroidal extension (ETE). The prognostic significance of cervical lymph node metastases is however more controversial. Unlike most other solid cancers, metastatic spread to regional LNs in patients with differentiated carcinoma of the thyroid has been traditionally regarded as having no impact on prognosis. This may be because the majority of PTC patients with nodal disease are young and 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 AGES, MACIS and AMES from other centers (6, 8, 10). Variables such as multifocality, lymphovascular invasion, tumor capsule invasion, and extrathyroidal extension have been reported as predictors of nodal disease (44).

The 7th edition of the AJCC TNM staging system classified nodal status into N0, N1a (central neck node involvement, level VI only) and N1b (lateral neck node involvement and / or level VII disease). In the 8th edition of the AJCC staging system, level VII is included in N1a, and only lateral neck nodes are classified as N1b. This stratification differentiates nodal disease based on location of nodes within the neck. While nodal metastases occur more frequently in younger patients (22), they are generally not thought to be prognostic of survival. As such, all patients younger than 55 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 upon survival in older patients (45-48). The current AJCC 8th staging manual stages patients over 55 years of age with nodal disease as Stage II, present of ETE is Stage III and those with distant metastases are Stage IV (49)

The AJCC staging system stratifies patients into stages I to IV for overall survival. In contrast, the American Thyroid Association (ATA) stratifies patients into low, intermediate and high-risk groups for recurrence. The 2009 ATA risk stratification system had been validated and widely adopted into clinical use (**Table 1**) (50, 51). In the 2009 version of the ATA risk stratification, evidence of any cervical LN metastases upstaged patients from a low to intermediate-risk category and this typically leads to adjuvant radioactive iodine (RAI) administration. Recent data however, suggests that LN characteristics such as size, number, ratio, and the presence of extranodal extension (ENE) may all impact upon prognosis (11, 13, 15, 28, 30-33). 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 (25). 'Low risk N1' was defined as ≤5 positive LNs and measuring ≤0.2cm in maximum diameter. The definition of micrometastases (≤0.2cm) was based on data from breast cancer staging. The 2015 ATA risk stratification incorporates these modifications (52). Patients with low volume LN metastases measuring ≤0.2cm 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 (14). This may further call into question the need for prophylactic central neck dissection for the purpose of disease staging.

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 radiologically 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 (53). This contentious recommendation was subsequently modified, suggesting that prophylactic central compartment neck dissection may be performed in patients with thyroid carcinoma with only advanced primary tumors (T3 or T4) and those with lateral compartment nodal disease (52). 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 (54-56).

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 (57-59). 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 (60, 61). Advocates for prophylactic central neck dissection argue that this procedure provides more accurate assessment of nodal status. Prophylactic central neck dissection upstaged approximately

30% of patients 45 years and older which subsequently increased the need for adjuvant RAI therapy (62, 63). However, no data has demonstrated a survival benefit for patients with microscopic N1 disease.

Other centers including our own, perform a neck dissection only for clinically evident disease identified either on clinical examination or on preoperative imaging, typically US clinically negative neck or CT for patients with palpable disease. This practice is based on the philosophy that although microscopic nodal metastases may occur early and frequently, the majority of patients will have clinically indolent disease throughout their life. Resection can be associated with iatrogenic morbidity, while delayed nodal resection of clinically apparent disease remains safe and offers comparable prognosis (64). Increasingly, the literature, reports that low volume disease is not associated with poorer outcomes (14, 25). These findings further question the need for prophylactic staging central neck dissection in PTC.

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 is the most studied molecular marker in PTC. BRAF mutations, most commonly of V600E, activates 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 (65-71). Patients with recurrent or persistent PTC have a higher incidence of BRAF mutation (72). Based on these findings, some have advocated for the use of BRAF mutation status to guide extent of initial thyroidectomy and neck dissection (65, 73, 74). It is however important to emphasize that the identification of a molecular predictor of recurrence or mortality does not 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.

Aims

By having access to a high volume of thyroid cancer cases in a dedicated tertiary care academic institution with comprehensive electronic medical records, we decided to study the clinical spectrum of nodal disease in differentiated thyroid cancer with special emphasis on its diagnosis, extent of treatment, clinicopathologic characteristics and prognosis. Our aim was to study a large cohort of 3664 patients with differentiated thyroid cancer managed at a single tertiary care cancer center over a 25 year period from 1985 to 2010. All 3664 patients were previously untreated and diagnosed, treated and received follow up on the head and neck and endocrinology services at Memorial Sloan Kettering Cancer Center which has a long history and expertise in cancer care. Nodal disease in well differentiated thyroid cancer is common at presentation. The understanding of prognostic impact of nodal disease, however, is limited in thyroid cancer. Subsequently, the assessment, initial management, recurrence management and follow up of patients with nodal disease is varied and similarly controversial. We believe that our comprehensive characterization of nodal disease in differentiated thyroid cancer will contribute to a better understanding of the clinical implications of this common occurrence in thyroid cancer, which in turn will help to improve clinical guidelines for diagnosis and management of differentiated thyroid cancer.

Our main objective was to perform a comprehensive characterization of the spectrum of nodal disease in differentiated thyroid cancer. Our specific aims were to:

1. Correlate methods of preoperative nodal detection with clinical recurrence and survival outcomes.
2. Define the central and lateral compartment nodal disease features most prognostic of outcomes.
3. Describe patient outcomes following treatment of nodal metastases in well differentiated thyroid cancer.
4. Investigate efficient and cost effective surveillance strategies for thyroid cancer survivors.

Outline

Part I, Chapter 2 starts with a study to quantify the impact of preoperative ultrasound assessment of nodal status in patients with diagnosed thyroid cancer. At our institution we have in the past traditionally assessed the lateral neck by clinical examination alone and experienced a period of transition to a practice of preoperative US assessment of the neck. This unique period of transition provided patients of similar clinical features, similar surgical techniques, radioactive iodine use and follow up methods. This provided an ideal opportunity to investigate the utility and impact on outcomes of preoperative neck ultrasound by directly comparing patients who received preoperative neck US and those who were assessed with clinical examination alone. We describe changes in the preoperative assessment of nodal disease over time assessing the impact of clinical examination to the use of preoperative ultrasonography on the rates of lateral neck dissection, impact on response to therapy and disease recurrence.

In Part II we investigate central compartment nodal disease and its impact on clinical outcomes. In Chapter 3 we report that the routine use of adjuvant radioactive iodine following incidentally identified nodal disease in perithyroidal lymph nodes does not improve 5 year central compartment nodal recurrence free survival. Central compartment is comprised of level 6 and 7 denoting fibrofatty tissue above and below the sternal notch. In Chapter 4, we investigate patient outcomes associated with level 6 compared to level 7 disease. We demonstrate that level 7 disease does not confer worse DSS or RFS compared to patients with only level 6 disease. In Chapter 5, we analyze central compartment nodal metastases characteristics and demonstrate that the presence of extranodal extension (ENE) to be the most important prognostic factor for future neck recurrence.

Part III focuses on lateral compartment nodal metastases and its impact on outcomes. In Chapter 6 we report that the presence of lateral neck disease to be prognostic for the development of distant metastases in older by not younger patients. Chapter 7 investigates characteristics of lateral nodal metastases and report that the ratio of positive to total number of lateral nodes resected determine recurrence in all ages, while the presence of ENE is prognostic in older patients.

In Part IV, we study nodal recurrence patterns as well as subsequent outcomes. In Chapter 8, we report a detailed analyses of patients having a therapeutic lateral neck dissection to determine the impact of the type of neck dissection performed and the rate and pattern of disease recurrence. Chapter 9 reports our rate of clinically evident nodal recurrence and the subsequent treatment and outcomes after treatment of nodal recurrence. We find that patients who have appropriate surveillance and salvage treatment continue to enjoy excellent survival with subsequent 5 years disease free survival of 97.4%.

Part V looks at surveillance investigations aimed at detecting nodal recurrence for the ever increasing population of thyroid cancer survivors. Chapter 10 details the increased use of surveillance ultrasonography over the study period of 25 years. We report a 5.3 fold increase in the rate of post operative surveillance ultrasound in the ATA low risk category without a corresponding increase in the rate of disease detection. Chapter 11 follows on from this, investigating the cost effectiveness of current surveillance protocols. We highlight the relative cost effectiveness of present surveillance modalities across low, intermediate and high risk ATA categories. The cost of detecting a recurrence event in the low risk group was 6 and 7 times more than the detection of a recurrence in the high or intermediate risk group patient. Our findings suggest a need for improvements towards a risk-stratified, cost-effective surveillance approach.

Tables

Table 1 | AJCC TNM Thyroid cancer Nodal status comparison; 5^{th}, 6^{th}, 7^{th} and 8^{th} Editions

	5th Edition 1997	6th Edition 2002	7th Edition 2009	8^{th} Edition 2018
Regional Lymph Nodes	Cervical and upper mediastinal lymph node(s)	Central compartment, lateral cervical and upper mediastinal lymph node(s)	Central compartment, lateral cervical and superior mediastinal lymph node(s)	Central compartment, lateral cervical and superior mediastinal lymph node(s)
N0	No regional lymph node(s) metastases	No regional lymph node metastasis	No regional lymph node metastasis	No regional lymph node metastasis
N1a	Metastasis in ipsilateral cervical lymph node(s)	Metastasis to Level IV (pretracheal, paratracheal, and prelaryngeal / Delphian lymph node(s))	Metastases to Level VI (paratracheal and prelaryngeal/ Delphian lymph node(s))	Metastases to Level VI (paratracheal and prelaryngeal/Delphi an lymph node(s)) or superior mediastinal lymph node(s) (Level VII).
N1b	Metastasis in bilateral, midline or contralateral cervical or mediastinal lymph node(s).	Metastasis to unilateral, bilateral, or contralateral cervical or mediastinal lymph node(s).	Metastases to unilateral, bilateral or contralateral cervical (Levels I, II, III, IV, or V) or retropharyngeal or superior mediastinal lymph node(s) (Level VII).	Metastases to unilateral, bilateral or contralateral cervical (Levels I, II, III, IV, or V) or retropharyngeal lymph nodes.

Table 2 | American Thyroid Association Risk of Recurrence Classification changes between 2009 and 2015 (50)

	2009 Edition	2015 Edition
Low	No cervical lymph node or distant metastases No microscopic or macroscopic tumor invasion Tumor does not have aggressive histology (ie tall cell, insular, columnar cell carcinoma, Hurthle cell carcinoma, follicular)	PTC with all of the following • No local or distant metastases • All macroscopic tumor resected • No tumor invasion of loco regional tissues or structures • The tumor does not have aggressive histology (eg tall cell hobnail variant, columnar cell carcinoma • If I131 is given, there are no RAI avid metastatic foci outside the thyroid bed on the first post treatment whole body RAI scan • No vascular invasion • Clinical N0 or </= 5 pathological N1 micrometatases (<0.2cm in largest dimension) Intrathyroidal encapsulated follicular variant of PTC Intrathyroidal, well differentiated follicular thyroid cancer with capsular invasion and no or minimal (<4 foci) vascular invasion Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including BRAFV600E mutated (if known)
Intermediate	Microscopic tumor invasion Cervical Lymph node metastases or I^{131} uptake outside the thyroid bed on the post therapy scan Tumor with aggressive histology	Microscopic invasion of tumor into the perithyroidal soft tissues RAI-avid metastatic foci in the neck on the first posttreatment whole-body RAI scan Aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) Papillary thyroid cancer with vascular invasion Clinical N1 or >5 pathologic N1 with all involved lymph nodes <3cm in the largest dimension Multifocal papillary microcarcinoma with ETE and BRAF V600E (if known)

	2009 Edition	2015 Edition
High risk categories	Macroscopic tumor invasion Gross residual disease Distant metastases	Macroscopic invasion of tumor into the perithyroidal soft tissues (gross ETE) Incomplete tumor resection Distant metastases Postoperative serum thyroglobulin suggestive of distant metastases Pathologic N1 with any metastatic lymph node >/=3 cm in largest dimension Follicular thyroid cancer with extensive vascular invasion (> 4 foci of vascular invasion)

References

1. Globocan. World: New cancer diagnosis 2018 [Available from: https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf.
2. Davies L, Welch HG. Epidemiology of head and neck cancer in the United States. Otolaryngol Head Neck Surg. 2006;135(3):451-7.
3. Davies L, Welch H. Current thyroid cancer trends in the United States. JAMA Otolaryngol Head Neck Surg. 2014;140(4):317-22. doi: 10.1001/jamaoto.2014.1.
4. Aschebrook-Kilfoy B, Schechter RB, Shih YC, Kaplan EL, Chiu BC, Angelos P, et al. The clinical and economic burden of a sustained increase in thyroid cancer incidence. Cancer Epidemiol Biomarkers Prev. 2013;22(7):1252-9.
5. Crile G, Jr. The pattern of metastasis of carcinoma of the thyroid. Ann Surg. 1956;143(5):580-4; discussion, 4-7.
6. Shaha AR, Shah JP, Loree TR. Risk group stratification and prognostic factors in papillary carcinoma of thyroid. Ann Surg Oncol. 1996;3(6):534-8.
7. DeGroot LJ, Kaplan EL, McCormick M, Straus FH. Natural history, treatment, and course of papillary thyroid carcinoma. J Clin Endocrinol Metab. 1990;71(2):414-24.
8. Hay ID, Bergstralh EJ, Goellner JR, Ebersold JR, Grant CS. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. Surgery. 1993;114(6):1050-7; discussion 7-8.
9. Shaha AR, Loree TR, Shah JP. Intermediate-risk group for differentiated carcinoma of thyroid. Surgery. 1994;116(6):1036-40; discussion 40-1.
10. Cady B, Rossi R. An expanded view of risk-group definition in differentiated thyroid carcinoma. Surgery. 1988;104(6):947-53.
11. Sugitani I, Kasai N, Fujimoto Y, Yanagisawa A. A novel classification system for patients with PTC: addition of the new variables of large (3 cm or greater) nodal metastases and reclassification during the follow-up period. Surgery. 2004;135(2):139-48.
12. Ito Y, Fukushima M, Tomoda C, Inoue H, Kihara M, Higashiyama T, et al. Prognosis of patients with papillary thyroid carcinoma having clinically apparent metastasis to the lateral compartment. Endocr J. 2009;56(6):759-66.
13. Wang L, Palmer F, Nixon I, Thomas D, Shah J, Patel S, et al. Central lymph node characteristics predictive of outcome in patients with differentiated thyroid cancer. Thyroid. 2014;30(12):30.
14. Wang LY, Palmer FL, Migliacci JC, Nixon IJ, Shaha AR, Shah JP, et al. Role of RAI in the management of incidental N1a disease in papillary thyroid cancer. Clin Endocrinol (Oxf). 2015.
15. Wang LY, Palmer FL, Nixon IJ, Tuttle RM, Shah JP, Patel SG, et al. Lateral Neck Lymph Node Characteristics Prognostic of Outcome in Patients with Clinically Evident N1b Papillary Thyroid Cancer. Ann Surg Oncol. 2015;22(11):3530-6.
16. Goropoulos A, Karamoshos K, Christodoulou A, Ntitsias T, Paulou K, Samaras A, et al. Value of the cervical compartments in the surgical treatment of papillary thyroid carcinoma. World J Surg. 2004;28(12):1275-81.
17. Gimm O, Rath FW, Dralle H. Pattern of lymph node metastases in papillary thyroid carcinoma. Br J Surg. 1998;85(2):252-4.
18. Machens A, Hinze R, Thomusch O, Dralle H. Pattern of nodal metastasis for primary and reoperative thyroid cancer. World J Surg. 2002;26(1):22-8.
19. Mirallie E, Visset J, Sagan C, Hamy A, Le Bodic MF, Paineau J. Localization of cervical node metastasis of papillary thyroid carcinoma. World J Surg. 1999;23(9):970-3; discussion 3-4.
20. Machens A, Holzhausen HJ, Dralle H. Skip metastases in thyroid cancer leaping the central lymph node compartment. Arch Surg. 2004;139(1):43-5.
21. Fraser S, Zaidi N, Norlen O, Glover A, Kruijff S, Sywak M, et al. Incidence and Risk Factors for Occult Level 3 Lymph Node Metastases in Papillary Thyroid Cancer. Ann Surg Oncol. 2016;23(11):3587-92.
22. Grebe S, Hay I. Thyroid cancer nodal metastases: biologic significance and therapeutic considerations. Surg Oncol Clin N Am. 1996;5(1):43-63.
23. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. The American journal of medicine. 1994;97(5):418-28.
24. Ito Y, Tomoda C, Uruno T, Takamura Y, Miya A, Kobayashi K, et al. Ultrasonographically and anatomopathologically detectable node metastases in the lateral compartment as indicators of worse relapse-free survival in patients with papillary thyroid carcinoma. World J Surg. 2005;29(7):917-20.
25. Randolph G, Duh Q, Heller K, LiVolsi V, Mandel S, Steward D, et al. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. Thyroid. 2012;22(11):1144-52.

26. Edge SB, American Joint Committee on Cancer. AJCC cancer staging manual. 7th ed. New York: Springer; 2010. xiv, 648 p. p.
27. Moore KH, Thaler HT, Tan LK, Borgen PI, Cody HS, 3rd. Immunohistochemically detected tumor cells in the sentinel lymph nodes of patients with breast carcinoma: biologic metastasis or procedural artifact? Cancer. 2004;100(5):929-34.
28. Beal SH, Chen SL, Schneider PD, Martinez SR. An evaluation of lymph node yield and lymph node ratio in well-differentiated thyroid carcinoma. Am Surg. 2010;76(1):28-32.
29. Lang BH, Wong KP, Wan KY, Lo CY. Significance of metastatic lymph node ratio on stimulated thyroglobulin levels in papillary thyroid carcinoma after prophylactic unilateral central neck dissection. Ann Surg Oncol. 2012;19(4):1257-63.
30. Jeon MJ, Yoon JH, Han JM, Yim JH, Hong SJ, Song DE, et al. The prognostic value of the metastatic lymph node ratio and maximal metastatic tumor size in pathological N1a papillary thyroid carcinoma. Eur J Endocrinol. 2013;168(2):219-25.
31. Leboulleux S, Rubino C, Baudin E, Caillou B, Hartl DM, Bidart JM, et al. Prognostic factors for persistent or recurrent disease of papillary thyroid carcinoma with neck lymph node metastases and/or tumor extension beyond the thyroid capsule at initial diagnosis. J Clin Endocrinol Metab. 2005;90(10):5723-9.
32. Lee J, Song Y, Soh E. Prognostic Significance of the Number of Metastatic Lymph Nodes to Stratify the Risk of Recurrence. World J Surg. 2013;4:4.
33. Ito Y, Jikuzono T, Higashiyama T, Asahi S, Tomoda C, Takamura Y, et al. Clinical significance of lymph node metastasis of thyroid papillary carcinoma located in one lobe. World J Surg. 2006;30(10):1821-8.
34. Ito Y, Ichihara K, Masuoka H, Fukushima M, Inoue H, Kihara M, et al. Establishment of an intraoperative staging system (iStage) by improving UICC TNM classification system for papillary thyroid carcinoma. World J Surg. 2010;34(11):2570-80.
35. Carter R, Bliss J, Soo K, O'Brien C. Radical neck dissections for squamous carcinomas: pathological findings and their clinical implications with particular reference to transcapsular spread. Int J Radiat Oncol Biol Phys. 1987;13(6):825-32.
36. Johnson JT, Myers EN, Bedetti CD, Barnes EL, Schramm VL, Jr., Thearle PB. Cervical lymph node metastases. Incidence and implications of extracapsular carcinoma. Arch Otolaryngol. 1985;111(8):534-7.
37. Cooper J, Pajak T, Forastiere A, Jacobs J, Campbell B, Saxman S, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamouscell carcinoma of the head and neck. N Engl J Med. 2004;350(19):1937-44.
38. Marchet A, Mocellin S, Ambrosi A, Morgagni P, Garcea D, Marrelli D, et al. The ratio between metastatic and examined lymph nodes (N ratio) is an independent prognostic factor in gastric cancer regardless of the type of lymphadenectomy: results from an Italian multicentric study in 1853 patients. Ann Surg. 2007;245(4):543-52.
39. Dekker JW, Peeters KC, Putter H, Vahrmeijer AL, van de Velde CJ. Metastatic lymph node ratio in stage III rectal cancer; prognostic significance in addition to the 7th edition of the TNM classification. Eur J Surg Oncol. 2010;36(12):1180-6.
40. Berger A, Watson J, Ross E, Hoffman J. The metastatic/examined lymph node ratio is an important prognostic factor after pancreaticoduodenectomy for pancreatic adenocarcinoma. Am Surg. 2004;70(3):235-40; discussion 40.
41. Woodward WA, Vinh-Hung V, Ueno NT, Cheng YC, Royce M, Tai P, et al. Prognostic value of nodal ratios in node-positive breast cancer. J Clin Oncol. 2006;24(18):2910-6.
42. Gil Z, Carlson D, Boyle J, Kraus D, Shah J, Shaha A, et al. Lymph node density is a significant predictor of outcome in patients with oral cancer. Cancer. 2009;115(24):5700-10. doi: 10.1002/cncr.24631.
43. Mizrachi A, Hadar T, Rabinovics N, Shpitzer T, Guttman D, Feinmesser R, et al. Prognostic significance of nodal ratio in cutaneous squamous cell carcinoma of the head and neck. Eur Arch Otorhinolaryngol. 2013;270(2):647-53.
44. Blanchard C, Brient C, Volteau C, Sebag F, Roy M, Drui D, et al. Factors predictive of lymph node metastasis in the follicular variant of papillary thyroid carcinoma. Br J Surg. 2013;100(10):1312-7.
45. Harwood J, Clark OH, Dunphy JE. Significance of lymph node metastasis in differentiated thyroid cancer. Am J Surg. 1978;136(1):107-12.
46. Hughes CJ, Shaha AR, Shah JP, Loree TR. Impact of lymph node metastasis in differentiated carcinoma of the thyroid: a matched-pair analysis. Head Neck. 1996;18(2):127-32.
47. Nixon IJ, Wang LY, Palmer FL, Tuttle RM, Shaha AR, Shah JP, et al. The impact of nodal status on outcome in older patients with papillary thyroid cancer. Surgery. 2014;156(1):137-46.
48. Zaydfudim V, Feurer ID, Griffin MR, Phay JE. The impact of lymph node involvement on survival in patients with papillary and follicular thyroid carcinoma. Surgery. 2008;144(6):1070-7; discussion 7-8.

49. Tuttle RM, Haugen B, Perrier ND. Updated American Joint Committee on Cancer/Tumor-Node-Metastasis Staging System for Differentiated and Anaplastic Thyroid Cancer (Eighth Edition): What Changed and Why? Thyroid. 2017;27(6):751-6.
50. American Thyroid Association Guidelines Taskforce on Thyroid N, Differentiated Thyroid C, Cooper DS, Doherty GM, Haugen BR, Kloos RT, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2009;19(11):1167-214.
51. Pitoia F, Bueno F, Urciuoli C, Abelleira E, Cross G, Tuttle RM. Outcomes of patients with differentiated thyroid cancer risk-stratified according to the American thyroid association and Latin American thyroid society risk of recurrence classification systems. Thyroid. 2013;23(11):1401-7.
52. Haugen BRM, Alexander EK, Bible KC, Doherty G, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2015.
53. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2006;16(2):109-42.
54. British Thyroid Association (2007) Guidelines for the management of thyroid cancer, 2nd ed. http://wwwbritish-thyroid-associationorg/news/Docs/Thyroid_cancer_guidelines_2007pdf.
55. Pitoia F, Ward L, Wohllk N, Friguglietti C, Tomimori E, Gauna A, et al. Recommendations of the Latin American Thyroid Society on diagnosis and management of differentiated thyroid cancer. Arq Bras Endocrinol Metabol. 2009;53(7):884-7.
56. Network NCC. Thyroid Carcinoma. Ver 2.2015 2015 [Version 2.2015:[Available from: http://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf.
57. Gosnell JE, Sywak MS, Sidhu SB, Gough IR, Learoyd DL, Robinson BG, et al. New era: prophylactic surgery for patients with multiple endocrine neoplasia-2a. ANZ J Surg. 2006;76(7):586-90.
58. Eustatia-Rutten C, Corssmit E, Biermasz N, Pereira A, Romijn J, Smit J. Survival and death causes in differentiated thyroid carcinoma. J Clin Endocrinol Metab. 2006;91(1):313-9. Epub 2005 Nov 1.
59. Rosenbaum MA, McHenry CR. Central neck dissection for papillary thyroid cancer. Arch Otolaryngol Head Neck Surg. 2009;135(11):1092-7.
60. Lang BH, Lee GC, Ng CP, Wong KP, Wan KY, Lo CY. Evaluating the morbidity and efficacy of reoperative surgery in the central compartment for persistent/recurrent papillary thyroid carcinoma. World J Surg. 2013;37(12):2853-9.
61. Moreno MA, Edeiken-Monroe BS, Siegel ER, Sherman SI, Clayman GL. In papillary thyroid cancer, preoperative central neck ultrasound detects only macroscopic surgical disease, but negative findings predict excellent long-term regional control and survival. Thyroid. 2012;22(4):347-55.
62. Hughes DT, Haymart MR, Miller BS, Gauger PG, Doherty GM. The most commonly occurring papillary thyroid cancer in the United States is now a microcarcinoma in a patient older than 45 years. Thyroid. 2011;21(3):231-6.
63. Shindo M, Wu JC, Park EE, Tanzella F. The importance of central compartment elective lymph node excision in the staging and treatment of papillary thyroid cancer. Arch Otolaryngol Head Neck Surg. 2006;132(6):650-4.
64. Nixon IJ, Ganly I, Patel SG, Morris LG, Palmer FL, Thomas D, et al. Observation of clinically negative central compartment lymph nodes in papillary thyroid carcinoma. Surgery. 2013;154(6):1166-72; discussion 72-3.
65. Howell GM, Nikiforova MN, Carty SE, Armstrong MJ, Hodak SP, Stang MT, et al. BRAF V600E mutation independently predicts central compartment lymph node metastasis in patients with papillary thyroid cancer. Ann Surg Oncol. 2013;20(1):47-52.
66. Lang BH, Chai YJ, Cowling BJ, Min HS, Lee KE, Youn YK. Is BRAFV600E mutation a marker for central nodal metastasis in small papillary thyroid carcinoma? Endocr Relat Cancer. 2014;21(2):285-95.
67. Xing M, Alzahrani AS, Carson KA, Shong YK, Kim TY, Viola D, et al. Association between BRAF V600E mutation and recurrence of papillary thyroid cancer. J Clin Oncol. 2015;33(1):42-50.
68. Basolo F, Torregrossa L, Giannini R, Miccoli M, Lupi C, Sensi E, et al. Correlation between the BRAF V600E mutation and tumor invasiveness in papillary thyroid carcinomas smaller than 20 millimeters: analysis of 1060 cases. J Clin Endocrinol Metab. 2010;95(9):4197-205.
69. Elisei R, Viola D, Torregrossa L, Giannini R, Romei C, Ugolini C, et al. The BRAF(V600E) mutation is an independent, poor prognostic factor for the outcome of patients with low-risk intrathyroid papillary thyroid carcinoma: single-institution results from a large cohort study. J Clin Endocrinol Metab. 2012;97(12):4390-8.
70. Kebebew E, Weng J, Bauer J, Ranvier G, Clark OH, Duh QY, et al. The prevalence and prognostic value of BRAF mutation in thyroid cancer. Ann Surg. 2007;246(3):466-70; discussion 70-1.

71. Pak K, Suh S, Kim SJ, Kim IJ. Prognostic value of genetic mutations in thyroid cancer: a meta-analysis. Thyroid. 2015;25(1):63-70.
72. Tufano RP, Bishop J, Wu G. Reoperative central compartment dissection for patients with recurrent/persistent papillary thyroid cancer: efficacy, safety, and the association of the BRAF mutation. Laryngoscope. 2012;122(7):1634-40.
73. Xing M, Haugen BR, Schlumberger M. Progress in molecular-based management of differentiated thyroid cancer. Lancet. 2013;381(9871):1058-69.
74. Tufano RP, Teixeira GV, Bishop J, Carson KA, Xing M. BRAF mutation in papillary thyroid cancer and its value in tailoring initial treatment: a systematic review and meta-analysis. Medicine (Baltimore). 2012;91(5):274-86.

Part I

Diagnosis of Nodal Disease

Chapter 2

Preoperative Neck Ultrasound in Clinical Node Negative Differentiated Thyroid Cancer

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Abstract

Background

The impact of preoperative neck ultrasound (US) on management of the lateral neck in patients with differentiated thyroid cancer (DTC) is unclear. The objective of this study was to assess the impact of preoperative neck US on the rate of lateral neck dissection in clinical N0 neck and initial Response to Therapy.

Methods

An Institutional Review Board approved retrospective review of 890 patients that had thyroid surgery for DTC between 2009 and 2010 was performed at our institution. Patients with palpable neck disease, distant metastases, less than total thyroidectomy, no postoperative thyroglobulin (Tg) determinations, and positive Tg antibodies were excluded leaving 465 patients available for analysis. Patients were divided into those who had a preoperative neck US to evaluate lateral neck nodes (n=234) and those that did not (n=231). Patient and tumor characteristics were compared using the Chi square test. The primary endpoint was Response to Therapy, defined by postoperative US and Tg levels.

Results

There were no significant differences in age, histology, T stage, postoperative RAI dose, AJCC stage, ATA risk category or duration of follow up between the 2 groups. Patients with preoperative neck US were more likely to have lateral neck dissection (LND) compared to patients without preoperative neck US (n=31 (13.2%) vs. n=2 (0.9%); $p<0.001$). Preoperative neck US resulted in better RTT ($p= 0.005$); more likely to be no evidence of disease (NED), less likely to have biochemical or structural incomplete response or return for delayed neck dissection. Preoperative US group also resulted in fewer recurrences; 10 patients from the no preoperative US group returned to operating room compared to 2 patients (4.3% vs. 0.9%, $p = 0.018$) that had a preoperative neck US.

Conclusion

Preoperative neck US detects more lateral neck disease, leading to an increase in LND with subsequent improvement in Response to Therapy and fewer return to OR for regional recurrence management.

Differentiated thyroid cancer (DTC) is increasing in prevalence. In patients over 45 years of age, metastasis to the regional lymphatic system is a potent indicator of the biological behavior and the distant metastatic potential of the disease. As such, adequate evaluation of the lateral neck is essential for better determining the nuances of an individual's disease progression. Furthermore, a comprehensive understanding of preoperative disease status is important because it can be informative for selecting appropriate therapeutic interventions.

The American Thyroid Association (ATA) recommends the routine use of US to assess the lateral neck for metastatic lymph nodes in patients with DTC (1). This is based upon evidence from several studies that have found that patients with US detectable neck metastasis have a significantly worse outcome than those with no metastases (2) or microscopic metastases detected only on histopathology (3). Others have demonstrated that US increases the detection of nodal disease compared to physical examination alone (4). Although these studies may demonstrate the usefulness of preoperative neck US in the diagnosis of lymph node metastasis, it is still controversial, if and how much preoperative neck US can improve prognosis.

At our institution, we have traditionally assessed the lateral neck by clinical examination alone and have recently transitioned to a practice of preoperative US assessment. Early adopters within our institution practice preoperative US assessment of the neck while later adopters relied on clinical assessment of the neck over the study period. This unique period of transition provided patients of similar clinical features, similar surgical techniques, radioactive iodine (RAI) use and follow up methods. This graduated change in practice therefore gave us an ideal opportunity to investigate the utility and impact on outcome of preoperative neck US by directly comparing patients who receive a preoperative neck US and those who do not. Our objective was to determine the impact of preoperative neck US on the patient's initial Response to Therapy, postoperative use of RAI and need for additional neck surgery.

Patients and Methods

Following Institutional Review Board approval, 890 consecutive surgical patients with DTC, operated on within our institution between January first 2009 and December 31st 2010, were reviewed from our hospital database. Patients were excluded if they had surgery outside of MSKCC, had clinically palpable neck disease or missing neck examination findings. The primary endpoints was Response to Therapy. Response to Therapy was developed to determine patients' likelihood of disease recurrence based on response to treatment as measured by serum thyroglobulin levels and regional imaging studies. To allow for this, patients with less than total thyroidectomy, distant metastases at presentation, no follow up thyroglobulin (Tg) or Tg antibody were also excluded. This left 465 patients for analysis (**Figure 1**).

Patient, tumor and treatment characteristics were recorded. Patient characteristics included age and gender. Tumor characteristics recorded included tumor histology, primary tumor size, presence of extrathyroid extension or vascular invasion, number and site of lymph nodes resected. All patients had total thyroidectomy. At our institution, we do not carry out prophylactic central neck dissection (CND)or lateral neck dissection (LND) in patients with a clinically N0 neck. Assessment of the lateral neck is performed by palpation at preoperative clinical visit or by preoperative US. Assessment of the central compartment for all patients is intraoperative palpation of the central compartment lymph nodes at the time of thyroidectomy. If no palpable nodes were present in the central compartment, then elective CND is not performed. If nodes are palpable and confirmed to have cancer on frozen section, then a central compartment neck dissection is carried out. N0 stage was defined if nodes were removed and found to be benign on pathology (pN0) or if no nodes were suspicious on palpation during surgery and therefore not removed (Nx). We have recently published our data on management of the clinically negative neck (5) reporting that N0/Nx have similar outcomes. Others have also demonstrated that Nx have very low incidence of recurrent/persistent disease, comparable to N0 groups.

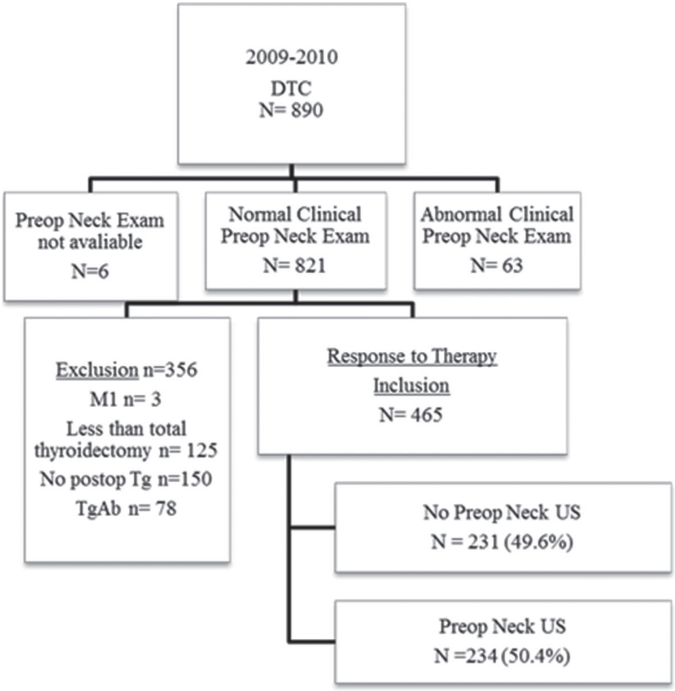


Figure 1 | Inclusion Criteria

Postoperative treatment details recorded were use of RAI I^{131}. Postoperative thyroid stimulating hormone (TSH) suppression is practiced for all patients, aiming for a level of between 0.1–0.5 mcUnits/ml. All patients had follow up with Tg and postoperative ultrasound. Survival outcome was classified using the AJCC stagingsystem and recurrence risk classified using the ATA risk group stratification.

The primary end point was initial Response to Therapy. Response to Therapy was defined as no evidence of disease (NED), biochemical persistent disease or structural persistent disease, as per previously published risk of recurrence stratification (6). Patients were considered to be NED if they had a suppressed serum Tg < 1 ng/mL, no detectable Tg antibodies, and no structural evidence of disease on ultrasound assessment. Patients with persistent disease were further classified as having either biochemical evidence of disease (elevated Tg values alone without structural correlate) or structural evidence of disease (elevated Tg values with structural correlate on ultrasound)

The presence of local or regional structural disease recurrence following treatment was based on cytological or histopathological confirmation of structurally identifiable disease. The median follow-up for the entire patient cohort was 29 months (range 1–52 months).

Patient, tumor and treatment variables were compared within groups using Pearson's chi squared test. A p value less than 0.05 was considered significant. Statistical analysis was carried out using JMP statistical package (SAS Institute Inc. SAS Campus Drive, Cary, NC 27513) and SPSS (IBM Company Headquarters, 233 S. Wacker Drive, 11th Floor, Chicago, Illinois 60606).

Results

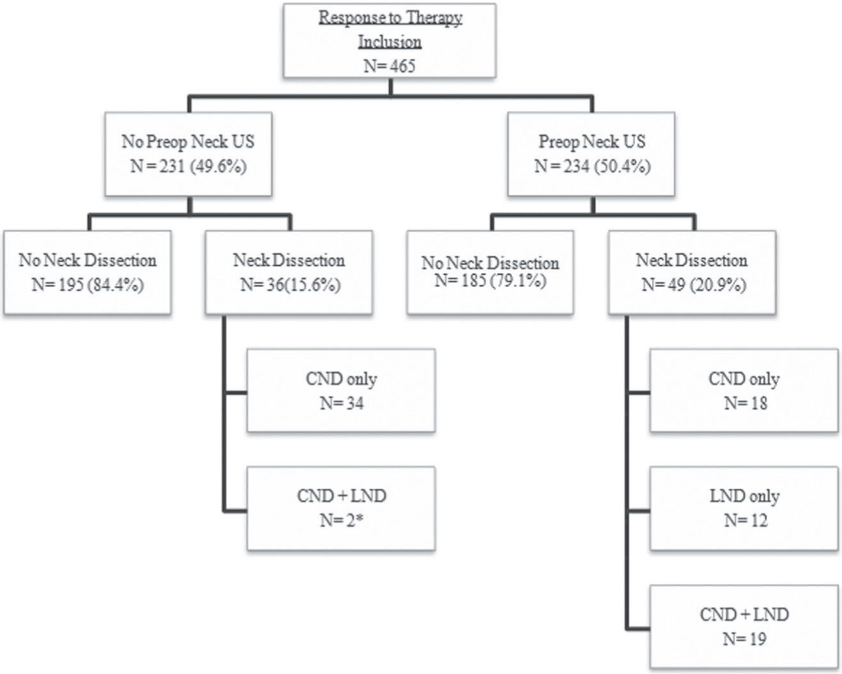
The median age of the cohort was 48.7 years (range14–84 years) and 337 were female (72.4%). Two hundred and thirty four patients (50.4%) had a preoperative ultrasound evaluation of cervical neck lymph nodes and 231 patients (49.6%) did not. Patient demographics stratified by preoperative neck US status are shown in Table 1. There were no significant differences in age, histology, T stage, postoperative RAI dose, AJCC stage, ATA risk category or duration of follow up between the 2 groups. The N1a and N1b patients were more likely to have T3T4 tumors as one would expect. There was no difference in the histologic subtypes between patients who were N0/ Nx, N1a and N1b.

Table 1 | Comparison of Patients with and without Preoperative Neck US

		No Preop US		Preop US		
		n	(%) or Mean +/-SD	n	(%) or Mean +/-SD	*p value*
Age	<45yo	100	43.3	83	35.5	*0.084*
	≥45 yo	131	56.7	151	64.5	
Gender	Female	181	78.4	156	66.7	***0.005***
	Male	50	21.6	78	33.3	
Histology	Papillary	215	93.1	224	95.7	*0.096*
	Follicular	9	3.9	2	0.9	
	Hurthle Cell	7	3.0	8	3.4	
T Stage	T1	114	49.4	117	50.0	*0.536*
	T2	31	13.4	41	17.5	
	T3	70	30.3	60	25.6	
	T4	16	6.9	16	6.9	
N Stage	pN0/Nx	168	72.7	171	73.1	***0.000***
	pN1a	59	25.5	34	14.5	
	pN1b	4	1.7	29	12.4	
Neck Dissection	CND only	34	14.7	18	7.7	***0.000***
	LND only	0	0.0	12	5.1	
	CND and LND	2	0.9	19	8.1	
	No ND	195	84.4	185	79.1	
Side Adjusted LNs removed	Mean Positive LNs/CND	36	3.8+/-3.4	38	4.2+/-4.2	*0.637*
	Mean Total LN/CND	36	9.9+/-5.0	38	10.8+/-6.8	*0.526*
	Mean Positive LNs/LND	2	2.5+/-3.5	31	2.5+/-2.4	0.988
	Mean Total LN/LND	2	32.0+/-21.2	31	25.8+/-16.4	*0.752*
RAI Therapy	Yes	99	42.9	70	29.9	***0.004***
	No	132	57.1	164	70.1	
RAI Dose (mCi)	Mean +/- SD	98	121 +/-41	69	119+/-34	*0.713*
AJCC Stage	I	153	66.2	153	65.4	*0.227*
	II	15	6.5	17	7.3	
	III	49	21.2	39	16.7	
	IV	14	6.1	25	10.7	
ATA Risk Category	Low	94	40.7	113	48.3	*0.240*
	Intermediate	121	52.4	105	44.9	
	High	16	6.9	16	6.9	
Lowest Tg (within 6 months postop)	(mean+/-SD)	231	0.602 +/-2.64	234	0.094 +/-0.334	***0.004***
Response to Therapy	NED	205	88.7	226	96.6	***0.005***
	Biochemical incomplete	13	5.6	4	1.7	
	Structural incomplete	13	5.6	4	1.7	
Neck Dissection for persistent or recurrent disease	Yes	10	4.3	2	0.9	***0.018***
	No	221	95.7	232	99.1	
FU (months)	Mean +/- SD Range	231	31 +/-13 004–57	234	30+/-13 007–54	*0.352*

Rate of neck dissection

Management of the neck stratified by preoperative US is shown in **Figure 2**. Patients with and without preoperative neck US did not differ in the rate of CND (15.8% ((18 +19)/234) vs. 15.6% (36/231) respectively). In contrast, the use of preoperative neck US significantly impacted on the operative management of the lateral neck. Patients with a preoperative neck US were more likely to have a LND compared to those without (13.2% ((12+19)/ 234) vs. 0.9% (2/231), *P < .001).*



CND – Central neck dissection
LND – Lateral neck dissection
*CND and LND – patient 1 had preoperative left RLN paralysis, left neck disease on CT neck. Patient 2 had abnormal intraoperative right level 2, 3 nodes

Figure 2 | Surgical Neck Management in patients with and without Preoperative Neck US

A detailed flowchart showing the management of the lateral neck is shown in **Figure 3**. Of the 234 patients who had preoperative neck US, 48 patients had abnormal lateral compartment nodes detected. Of these, 31 patients underwent LND. Of the 17 patients that did not have LND: 8 patients had benign fine needle biopsy, 6 patients had the 'abnormal' lymph node sampled intraoperatively and found to be benign on frozen section, 1 patient had known Hodgkin's lymphoma, 1 had metastatic prostate cancer and 1 patient had a preoperative decision for RAI over neck dissection. No patient with a normal preoperative lateral neck on US had LND. Of the 31 patients who had lateral ND, preoperative FNA was performed in 17 patients; 16 of which were malignant, 1 was benign. The remaining 14 patients did not have a preoperative FNA as the findings on US were deemed suspicious enough to warrant ND. Nine of these 14 patients had lateral neck metastases on final histopathological evaluation.

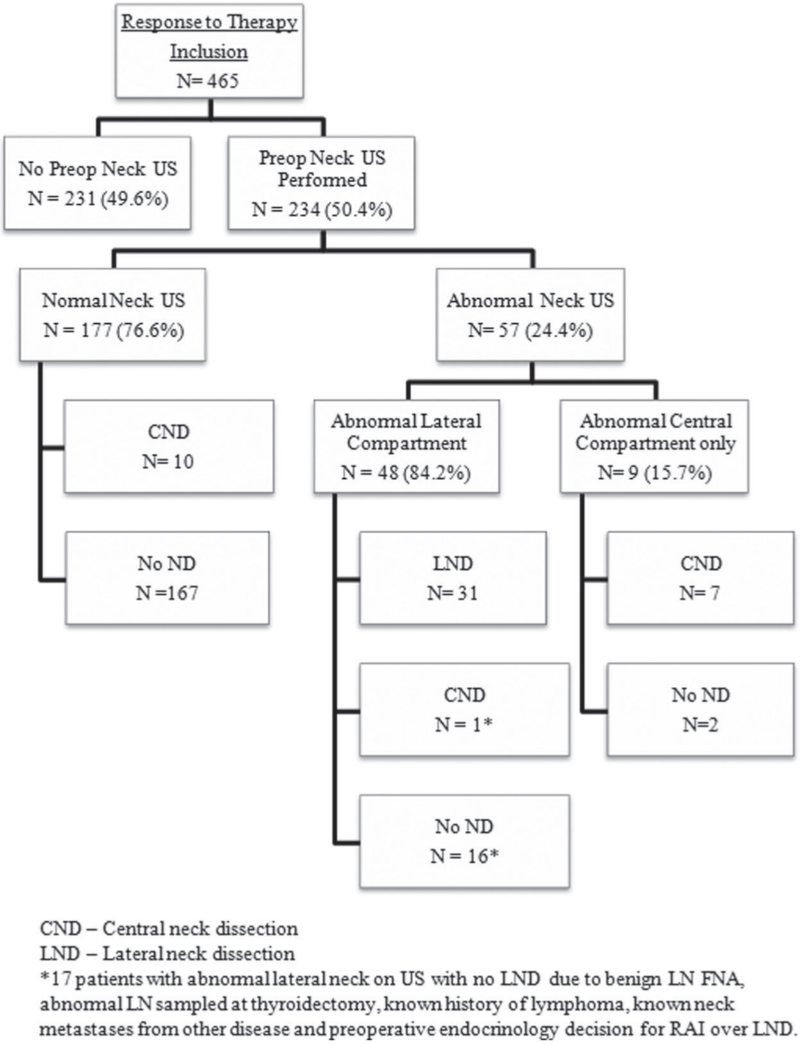


Figure 3 | Lateral Neck Management based on Preoperative Neck US result

Nodal Disease and Quality of Neck Dissection

The quality of neck dissection (defined by the mean number of nodes resected per neck dissection) was similar in both groups. The mean number of side adjusted positive nodal disease in the central and lateral compartments did not differ in patients with and without a preoperative neck ultrasound *(P* = .637, *P* **=** .988 respectively). Twenty-seven patients had false negative preoperative US. Most these (n = 25) were in level 6 of the central neck (N1a), 1 was in level 7 of the central neck (N1b) and 1 patient had a borderline lateral LN sampled intraoperatively .

RAI therapy

Patients without a preoperative neck US were more likely to receive postoperative RAI therapy compared to patients who had a preoperative neck US (*P* = *.004*). In patients that received RAI, the mean RAI administered activity did not differ between the two groups (*P* = *.713*).

Response to initial therapy

Response to Therapy was significantly better in patients with a preoperative neck US (Table 1). Two hundred and twenty six patients (*96.6%*) with a preoperative neck US were classified as NED within 18 months compared to 205 patients (88.7%) without a preoperative neck US (*P* = *.005)*. Biochemical and structural persistence were also lower in the group with preoperative US (1.7% vs. 5.6%, 1.7 vs. 5.6% respectively).

Neck Dissection for Recurrent or Persistent disease

In addition to better Response to Therapy, patients who had preoperative US were significantly less likely to have a subsequent lateral neck dissection for recurrent or persistent disease. **Figure 4** shows details of 12 patients who required neck dissection. Ten patients from the no preoperative US group returned to operating room compared to 2 patients (4.3% vs. 0.9%, *P* = *.018)* that had a preoperative neck US. Overall median follow up for this group was 38 months. No patient with a normal preoperative neck US required a neck dissection following treatment for recurrent or persistent disease.

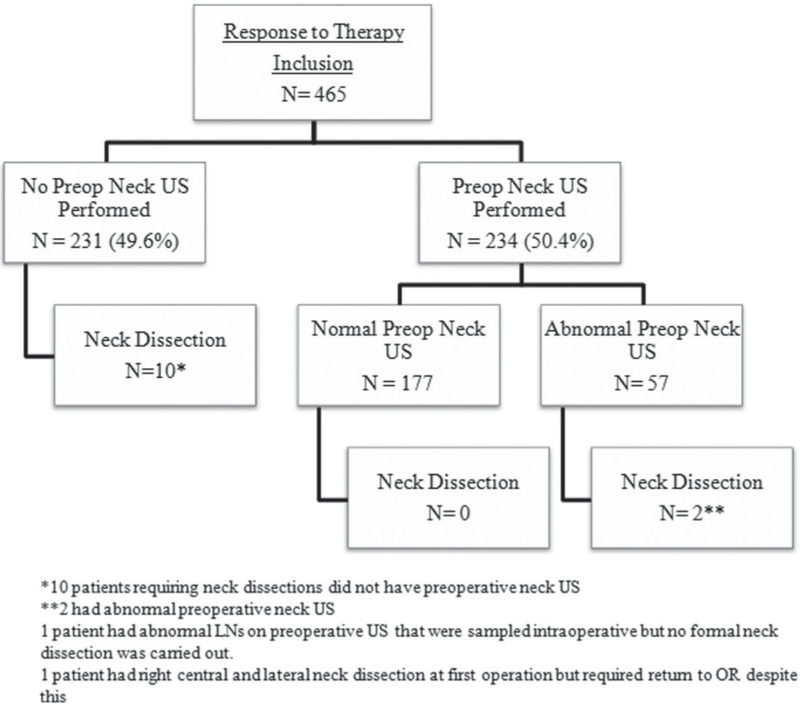


Figure 4 | Lateral neck dissection for recurrent or persistent disease

Discussion

Occult metastases in patients with DTC are common occurring in 20%–90% of patients (7, 8). Despite this high frequency, occult central or lateral metastases have no effect on outcome and are largely thought to be indolent disease (3). However, lateral compartment location and macrometastases (nodes > 1cm in size) are thought to confer worse prognosis, especially in older patients (9,10). This is reflected in the AJCC staging system where patients over 45 years of age are stage III if they have central neck disease and stage IV if they have lateral neck disease. It is therefore important to carefully assess the lateral neck by clinical examination supplemented with imaging in patients with DTC.

In the assessment of neck nodes, it has been shown that preoperative neck ultrasound has improved sensitivity compared to preoperative physical examination for the diagnosis of nodal disease. Kouvaraki et al demonstrated that preoperative neck US detected LN metastases in neck compartments believed to be uninvolved by physical examination in 21% of patients undergoing primary thyroid surgery (11) and the detection of preoperative US cervical lymph nodes potentially alters the surgical management in up to 30% of patients (11,12). Furthermore, diagnosis of positive regional lymph nodes has been associated with poorer outcomes, particularly in older patients (2, 3). As a result of these studies, the ATA recommends preoperative neck US to assess the lateral neck compartment lymph nodes for all patients undergoing thyroidectomy for thyroid cancer (1). However, it should be noted that the use of US in the assessment of the central neck lymph nodes is much less sensitive (13). In the present study, the overall sensitivity and specificity of US assessment of both lateral and central neck nodes was 57% and 88% respectively. The reduced sensitivity was largely due to the failure to detect positive nodes in the central neck. Twenty-seven patients had false negative preoperative US. Most these (n = 25) were in level 6 of the central neck (N1a), 1 was in level 7 of the central neck (N1b) and 1 patient had a borderline lateral LN sampled intraoperatively (N1b). This further illustrates the limitations of preop US in assessing the central compartment neck nodes.

Sonographic features suggestive of abnormal metastatic lymph nodes include loss of the fatty hilus, a rounded rather than oval shape, hypoechogenicity, cystic change, calcifications, and peripheral vascularity. However, no single feature is adequately sensitive for detection of lymph nodes with metastatic thyroid cancer (14, 15). US has been shown to be superior to other imaging modalities such as computer tomography (CT), magnetic resonance imaging (MRI), (MRI) and positron emission tomography (PET) for the detection of cervical lymph node metastases where sensitivities range between 30%-40% (16). US examination also has the additional benefit of being easily combined with fine needle aspirate biopsy (FNAB). US with FNAB is a more accurate method for assessment of neck node status. A Dutch study of 120 patients found the specificity of combined US and FNAB results was significantly higher than US alone; 92.9% compared with 60.0% (17). Our institution increasingly utilizes FNAB cytological confirmation of sonographically suspicious cervical lymph nodes to guide the extent of neck dissection. While the utility of US in regional LN diagnosis has been established, how preoperative neck US changes prognosis is still unclear.

At our institution, we have traditionally assessed the lateral neck by clinical examination and have only recently employed US assessment in selected patients. In the years 2009 to 2010 approximately 50% of our patients did not have preoperative lateral neck node assessment prior to surgery. This therefore gave us an ideal and unique opportunity to investigate the ATA recommendations with regards to the utility and efficacy of preoperative neck US. By directly comparing patients who had and those that did not have preoperative neck US we were able to directly compare response to therapy between groups and also directly compare subsequent later neck dissection rates for persistent or recurrent neck disease. This study also gave us an opportunity to compare the therapeutic outcome, with reference to disease specific and recurrence free survival, as well as the frequency of neck dissection in each group.

In our cohort, suspicious cervical LNs were identified in 24.4% of patients with normal clinical neck exams on preoperative US, a finding consistent with the literature; preoperative US identifies suspicious cervical lymph nodes in 20%–31% of cases (2, 18, 19). One of the major findings of our study was that patients with a preoperative neck US had a higher rate of lateral neck dissection (13.2% vs. 0.9%, *$P < .001$)* and a significantly better Response to Therapy than patients without preoperative US *($P = .005$)*. In addition, patients who had preoperative neck US were less likely to return to the OR for recurrent or persistent disease (0.9% vs. 4.3%, *P* = *.018*). Another important finding from our study was that those who did not have a preoperative neck US were more likely to receive postoperative RAI (42.9 vs. 29.9%, *P* = *.004*). Patients without a preoperative lateral neck node assessment by US were more likely to have an elevated Tg following total thyroidectomy and this likely led to the initiation of adjuvant RAI. This is supported by the finding that patients with a preoperative neck US have a significantly lower postoperative Tg value (0.094 ug/ml +/-0.334) compared to patients without preoperative US (0.602 ug/ml +/- 2.64) (*P* = *.004*). These 3 observations (improved Response to Therapy, reduced rate of subsequent neck dissection for persistent or recurrent neck disease and reduced RAI usage) support the recommendation that preoperative assessment of the lateral neck detects impalpable lateral neck disease thereby identifying select patients who will benefit from subsequent lateral neck dissection.

These results therefore provide some justification for the use of preoperative ultrasound. However, one could also argue that the use of preoperative ultrasound results in many patients being overtreated with some patients having lateral neck dissections unnecessarily. While preoperative US decreases return to OR for persistent or recurrent disease, it is not clear if early detection and surgical intervention results in improved survival. When we compare the DSS of our preoperative US cohort vs the no preoperative US cohort, the 3 year DSS are identical at 100% for both groups. Longer follow up of both groups is required to better define the impact of this improved Response to Therapy on survival. It is possible that early detection results in no improvement in survival compared to a management strategy of only carrying out a lateral neck dissection when nodes become clinically palpable. In addition, early detection by preoperative US may result in some patients having a neck dissection unnecessarily. For example, in our study, neck dissection was performed initially in 13.2% of preoperative US patients (31/234). In the no preoperative US cohort, 2 patients required neck dissection initially but a further 10 required a neck dissection later on making an overall neck dissection rate of 5.2% (12/231). This suggests that over 50% of the preoperative US patients may have underwent LND for potentially indolent disease.

Therefore one can argue that both management strategies (1. preoperative US and early detection of nodes with early LND and 2. no preoperative US with salvage LND when clinically palpable nodes become apparent) are equally effective in terms of survival. The early detection strategy has the potential advantage in terms of patient counseling; as these patients can be reassured after the first Tg blood measurement and postoperative US assessment that they have a negligible risk of recurrence and can thus have less intense follow up. The same cannot be said for the late detection strategy (no preoperative US cohort) as we do not know which of these patients will recur and therefore all patients in this cohort require long term follow up. The benefit of the late detection strategy means that all LND will be performed for clinically detectable disease, rather than for subclinicial disease.

In conclusion, our study demonstrates that the use of preoperative neck node assessment by US facilitates a more complete surgical resection to the regional lymph nodes in patients with DTC. This results in improved Response to Therapy, reduces adjuvant RAI treatments and reduces regional recurrence rates. Such a policy is beneficial for patient counseling, limits subsequent follow up tests and allows for early patient discharge. However, although this policy results in improved Response to Therapy, it remains unclear if there is any impact on survival.

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References

1. **Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, Mazzaferri EL, McIver B, Pacini F, Schlumberger M, Sherman SI, Steward DL, Tuttle RM.** Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2009;19:1167–1214.
2. **Moreno M, Agarwal G, de Luna R, Siegel E, Sherman S, Edeiken-Monroe B, Clayman G.** Preoperative lateral neck ultrasonography as a long-term outcome predictor in papillary thyroid cancer. *Arch Otolaryngol Head Neck Surg*. 2011;137:157–162. doi: 110.1001/archoto. 2010.1254.
3. **Ito Y, Tomoda C, Uruno T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Kuma K, Miyauchi A.** Ultrasonographically and anatomopathologically detectable node metastases in the lateral compartment as indicators of worse relapse-free survival in patients with papillary thyroid carcinoma. *World J Surg*. 2005;29:917–920.
4. **Kouvaraki M, Shapiro S, Fornage B, Edeiken-Monro B, Sherman S, Vassilopoulou-Sellin R, Lee J, Evans D.** Role of preoperative ultrasonography in the surgical management of patients with thyroid cancer. *Surgery*. 2003;134:946–954; discussion 954–945.
5. **Nixon I, Ganly I, Patel S, Morris L, Palmer F, Thomas D, Tuttle R, Shah J, Shaha A.** Observation of clinically negative central compartment lymph nodes in papillary thyroid carcinoma. *Surgery*. 2013;154:1166–1172; discussion 1172–1163. doi: 1110.1016/j.surg. 2013.1104.1035.
6. **Tuttle RM, Tala H, Shah J, Leboeuf R, Ghossein R, Gonen M, Brokhin M, Omry G, Fagin JA, Shaha A.** Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. *Thyroid*. 2010;20:1341–1349.
7. **Qubain S, Nakano S, Baba M, Takao S, Aikou T.** Distribution of lymph node micrometastasis in pN0 well-differentiated thyroid carcinoma. *Surgery*. 2002;131:249–256.
8. **Arturi F, Russo D, Giuffrida D, Ippolito A, Perrotti N, Vigneri R, Filetti S.** Early diagnosis by genetic analysis of differentiated thyroid cancer metastases in small lymph nodes. *J Clin Endocrinol Metab*. 1997;82:1638–1641.
9. **Hughes CJ, Shaha AR, Shah JP, Loree TR.** Impact of lymph node metastasisindifferentiated carcinomaofthe thyroid:amatched-pair analysis. *Head Neck*. 1996;18:127–132.
10. **Sugitani I, Kasai N, Fujimoto Y, Yanagisawa A.** A novel classification system for patients with PTC: addition of the new variables of large (3 cm or greater) nodal metastases and reclassification during the follow-up period. *Surgery*. 2004;135:139–148.
11. **Kouvaraki MA, Shapiro SE, Fornage BD, Edeiken-Monro BS, Sherman SI, Vassilopoulou-Sellin R, Lee JE, Evans DB.** Role of preoperative ultrasonography in the surgical management of patients with thyroid cancer. *Surgery* 2003;134:946–954; discussion 954–945.
12. **Stulak JM, Grant CS, Farley DR, Thompson GB, van Heerden JA, Hay ID, Reading CC, Charboneau JW.** Value of preoperative ultrasonography in the surgical management of initial and reoperative papillary thyroid cancer. *Arch Surg* 2006;141:489–494; discussion 494–486.
13. **Lesnik D, Cunnane M, Zurakowski D, Acar G, Ecevit C, Mace A, Kamani D, Randolph G.** Papillary thyroid carcinoma nodal surgery directed by a preoperative radiographic map utilizing CT scan and ultrasound in all primary and reoperative patients. *Head Neck*. 2014;36:191–202. doi: 110.1002/hed. 23277. Epub 22013 Apr 23272.
14. **Leboulleux S, Girard E, Rose M, Travagli J, Sabbah N, Caillou B, Hartl D, Lassau N, Baudin E, Schlumberger M.** Ultrasound criteria of malignancy for cervical lymph nodes in patients followed up for differentiated thyroid cancer. *J Clin Endocrinol Metab*. 2007;92:3590–3594. Epub 2007 Jul 3593.
15. **Kuna S, Bracic I, Tesic V, Kuna K, Herceg G, Dodig D.** Ultrasonographic differentiation of benign from malignant neck lymphadenopathy in thyroid cancer. *J Ultrasound Med*. 2006;25:1531–1537;quiz 1538–1540.
16. **Jeong H, Baek C, Son Y, Choi J, Kim H, Ko Y, Chung J, Baek H.** Integrated 18F-FDG PET/CT for the initial evaluation of cervical node level of patients with papillary thyroid carcinoma: comparison with ultrasound and contrast-enhanced CT. *Clin Endocrinol (Oxf)*. 2006;65:402–407.
17. **Baatenburg de Jong R, Rongen R, Lameris J, Harthoorn M, Verwoerd C, Knegt P.** Metastatic neck disease. Palpation vs ultrasound examination. *Arch Otolaryngol Head Neck Surg*. 1989;115:689–690.

18. **Solorzano C, Carneiro D, Ramirez M, Lee T, Irvin Gr.** Surgeonperformed ultrasound in the management of thyroid malignancy. *Am Surg*. 2004;70:576–580; discussion 580–572.

19. **Shimamoto K, Satake H, Sawaki A, Ishigaki T, Funahashi H, Imai T.** Preoperative staging of thyroid papillary carcinoma with ultrasonography. *Eur J Radiol*. 1998;29:4–10.

Part II

Prognostic Features of Central Compartment Nodal Disease

Chapter 3

Level 7 Disease Does Not Confer Worse Outcome Than Level 6 Disease in Differentiated Thyroid Cancer

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Abstract

Background

Level 7 nodal disease increases patients from N1a to N1b in the American Joint Committee on Cancer (AJCC) TNM classification of differentiated thyroid cancers (DTCs). This results in upstaging of patients older than 45 years of age from stage III to IV. Our objective was to determine if patients with level 7 disease had poorer outcome in comparison to patients with isolated level 6 disease.

Methods

A total of 599 patients with DTC limited to the central neck (level 6 and 7) were identified from an institutional database. Patients with N1b disease due to lateral compartment (level 1–5) involvement or M1 disease were excluded. Fifty-seven patients had positive level 7 disease, and 542 patients had nodal disease limited to level 6. Disease-specific survival (DSS) and recurrence-free survival (RFS) were calculated for each group.

Results

Median age was 41 years (range 12–91) and follow-up was 61 months (range 1–330). There were no disease-specific deaths at 5 years. Among patients with level 6 disease at presentation, there were 42 nodal recurrences, and among patients with level 7 disease, there were two recurrences. There were no differences in overall RFS between patients with level 6 or 7 disease (5-year RFS 90.7 vs. 98.2 %, respectively; $p = 0.096$).

Conclusions

Our results suggest that N1b disease due to level 7 disease does not confer worse DSS or RFS compared with patients with level 6 disease only. Classifying all central neck disease (levels 6 and 7) into the N1a category, and reserving the N1b classification only for patients with lateral neck disease may be more reflective of prognosis.

Patients with differentiated thyroid cancer (DTC) with metastatic disease to the level 6 neck compartment, without level 7 or lateral neck disease, are classified as N1a according to the American Joint Committee on Cancer (AJCC) 7th edition TNM staging system.[1] The addition of positive lymph nodes (LNs) in level 7 or in the lateral neck (levels 1–5) increases that same patient's nodal status to N1b. In patients older than 45 years of age, the addition of level 7 nodal disease or lateral neck disease will upstage their overall AJCC TNM classification from stage III to IV. This results in a decrease in 5-year relative survival of patients from 90 % for stage III disease to 50 % for stage IV disease.[1] There is good evidence reporting poorer outcomes in patients with N1b disease due to lateral neck disease (level 1–5).[2–5] However, to our knowledge, there is no data to suggest that level 7 (superior mediastinal) disease, in the absence of lateral neck disease, confers poorer survival or recurrence prognosis in comparison to level 6 disease. Rather, the recommendation to upstage patients to N1b status based on positive level 7 disease is based on expert opinion. Our objective was therefore to determine if patients with central compartment level 7 disease have poorer outcomes in comparison to patients with only level 6 disease.

Methods

Following approval by the Institutional Review Board, the records of 3,664 consecutive patients treated with surgery for DTC at the Memorial Sloan Kettering Cancer Center (MSKCC) between 1986 and 2010 were identified from our institutional database. All patients without nodal disease (N0/NX), with lateral nodal disease (level 1–5), and with M1 disease were excluded. Five hundred and ninety-nine patients with histologically confirmed nodal metastases limited to only the central neck (level 6 and 7) were included for analysis. Fifty-seven patients had positive LNs in level 7 (with or without level 6 disease), and 542 patients had nodal disease limited to level 6. Patient selection for superior mediastinal compartment dissection was based on surgeon judgment.

We performed a retrospective review of patient demographics, surgical details, tumor features, treatment factors, and patient outcomes for the 599 inclusion patients. Histopathological details reviewed included tumor histology, size, presence of extrathyroidal extension, and location of metastatic LNs. Pathologists would report the location of LNs based on surgeon-labeling of specimens. As this was a retrospective study, extent of central neck dissection and specimen labeling was surgeon-dependent. Pathology reports describing LN location as 'central neck' were considered to be level 6 (not level 7). Those explicitly described as 'level 6' or 'level 7' on pathology reports were considered level 6 and 7, respectively. Postoperative treatment details were recorded for all patients, including the use of radioactive iodine (RAI) or external radiotherapy.

The primary outcomes of this study were overall recurrence-free survival (RFS), nodal RFS, and disease-specific survival (DSS). Local recurrence in the thyroid bed and regional recurrences in the neck LNs were determined by clinical examination supplemented with imaging and fine-needle aspiration. Distant recurrence was determined by imaging studies, including RAI uptake scans, computer tomography scans, positron emission tomography scans, or cytological and histopathological evidence where available. Serum thyroglobulin was routinely used to identify recurrence from the year 2000 onwards. Follow-up ultrasound of the neck and thyroid bed was employed to detect locoregional recurrence from 2005 onwards, and both have become standard practice and now influence further investigation of patients within this cohort.

Disease-specific outcomes were calculated using the date of last follow-up with the treating surgeon or endocrinologist at MSKCC. Details of death were determined from the social security death index and hospital records where available. All patients who had evidence of active structural disease at the time of last follow-up and who died during follow-up were considered to have died of disease. The median follow-up for the entire patient cohort was 61 months (range 1–330), and outcomes were therefore calculated at 5 years.

Statistical analysis was carried out using SPSS, version 21 (IBM Corporation, Armonk, NY, USA). Variables were compared within groups using Pearson's χ^2 test. Recurrence and survival outcomes were analyzed using the Kaplan–Meier method. A *p* value less than 0.05 was considered significant.

Results

The median age of this cohort was 41 years (range 11–91). In patients in whom the largest central LN diameter could be determined from the pathology report, 94.4 % (*n* = 419) had a central LN diameter measuring ≥0.2 cm, and less than 0.2 cm in 5.6 % (*n* = 25).

The demographics of the two patient groups are shown in Table 1. Patient, tumor, and treatment characteristics were similar between the level 6 and level 7 cohorts in terms of sex (*p* = 0.956), age (*p* = 0.547), extent of thyroid surgery (*p* = 0.053), histology (*p* = 0.586) and T stage (*p* = 0.144). Level 7 disease was associated with a higher rate of extrathyroidal extension (*p* = 0.018), and patients with level 7 disease were more likely to receive RAI therapy (*p* = 0.006).

TABLE 1 | Comparison of patient, tumor and treatment, by group: level 6 vs. level 7 nodal metastases

	Level 6		**Level 7**		***p* value**
	n	**%**	***n***	**%**	
Sex					
Female	388	71.6	41	71.9	0.956
Male	154	28.4	16	28.1	
Age, years					
<45	320	59.0	36	63.2	0.547
≥45	222	41.0	21	36.8	
Thyroid surgery					
Less than total[a]	65	12.0	2	3.5	0.053
Total thyroid	477	88.0	55	96.5	
Histology					
Follicular	5	0.9	0	0.0	0.586
Hurthle	5	0.9	0	0.0	
Papillary	532	98.2	57	100.0	
ETE					
None	272	50.2	19	33.3	**0.018**
Micro	185	34.1	22	38.6	
Macro	85	15.7	16	28.1	
T stage					
T1	189	34.9	13	22.8	0.144
T2	66	12.2	5	8.8	
T3	248	45.8	35	61.4	
T4	39	7.2	4	7.0	
Adjuvant RAI					
No	171	31.5	8	14.0	**0.006**
Yes	371	68.5	49	86.0	

Bold values indicate statistically significant $p < 0.05$

ETE extrathyroidal extension, *RAI* radioactive iodine

[a] Less than total—isthmusectomy, lobectomy, subtotal thyroidectomy

There were no disease-specific deaths (DSD) in level 6 or 7 patients at 5 years. Overall, nine patients developed distant metastases, five of whom were dead of disease at last follow-up (Table 2). Among patients with level 6 disease at presentation, there were 42 regional recurrences—10 in the central compartment only, 29 in the lateral compartment only, and 3 in both compartments. Among patients with level 7 disease at presentation, there were two recurrences, both of which were in the lateral neck. There was no significant difference in the 5-year RFS between patients with level 6 disease and those with level 7 disease (90.7 vs. 98.2 %, respectively; $p = 0.096$). There was no significant difference in nodal RFS between patients with level 6 and 7 disease (91.4 vs. 98.2 %, respectively; $p = 0.167$) (Fig. 1).

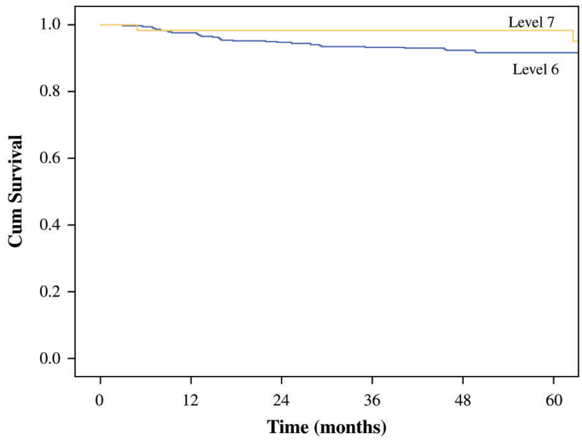

FIG. 1 | Nodal recurrence-free survival by level 6 and level 7 nodal disease

Table 2 | Characteristics of nine patients who developed distant recurrence

	Sex	Age at surgery (years)	Tumor size (cm)	Nodal level	ETE	T stage	Neck recur	Distant recur (month)	Last status	FU (month)
1	M	27.9	4	6	Macro	T3	No	14.5	AWD	153.7
2	F	38.9	1.1	6	None	T1b	No	11.1	AWD	162.9
3	M	44.8	7.5	6	Micro	T3	No	49.8	DSD	69.6
4	M	55.9	4	6	None	T2	Lateral	133.7	DSD	144.6
5	F	56.2	5	6	Macro	T4a	No	126.6	DSD	155.5
6	M	59.4	4.5	6	Macro	T4a	No	66.7	AWD	69.2
7	M	65.1	3	6	Macro	T4a	No	79.0	DSD	90.1
8	M	69.3	1.2	6	Macro	T4a	Central	75.5	AWD	132.8
9	F	72.4	2	6	Macro	T4a	Lateral	135.0	DSD	142.6

M Male, *F* Female, *Ete* Extrathyroidal Extension, *Awd* Alive With Disease, *Dsd* Disease-Specific Death, *Fu* Follow-Up

Discussion

The objective of our study was to determine if patients with DTC and metastatic disease to level 7 of the neck had poorer outcome compared with those with metastatic disease confined to level 6 alone. Level 7 is defined superiorly by the sternal notch, inferiorly by the innominate vessels, and laterally by the carotid arteries, in direct continuity with the level 6 compartment. Our data provides evidence that suggests that patients with level 7 disease do not have poorer outcome in terms of survival (100 vs. 100 %) or overall recurrence (90.7 vs. 98.2 %, $p = 0.096$) at 5 years. This would suggest that upstaging level 7 disease to N1b stage may not be justified. Furthermore, it suggests that prognosis based on location of nodal disease may be better defined by stratifying into central compartment disease (level 6 and 7) and lateral compartment disease (level 1–5) only.

Traditional risk stratification systems in DTC (GAMES/MACIS/AMES) uniformly recognize the importance of age and the presence of distant metastases in outcome. Nodal metastases has traditionally not been considered to be an independent prognostic factor of survival.[6–8] Over the years, the AJCC TNM classification system has gone through a variety of changes. The changes in nodal (N) status between the 5th edition in 1997, the 6th edition in 2002, and the 7th and latest edition in 2009 are highlighted in Table 3. Interestingly, the 5th edition of the AJCC manual did not consider those with level 6 (first echelon pretracheal, paratracheal, prelaryngeal or Delphian) LNs to be prognostically significant.[9] N1a status described patients with ipsilateral cervical LN metastasis, and N1b status described patients with bilateral, midline, or contralateral node disease. It was in the AJCC 6th edition in 2002 that regional nodal disease was changed to the current understanding of central and lateral compartments. N1a status was allocated to LN metastases in level 6, and N1b status allocated to metastases in any lateral neck compartment but also the superior mediastinal compartment LNs.[10] These recommendations suggest that level 7 or superior mediastinal disease carried poorer prognosis when compared with level 6 disease. However, it is important to note that these recommendations were based on expert opinion at the time and not on any published literature on this topic. The 7th and latest edition in 2009 clarified the wording of N1b disease and included retropharyngeal LN metastasis as a component of N1b disease. No other changes were made to the N0 or N1a categories.[1]

Table 3 | AJCC TNM thyroid cancer nodal status comparison: 5th, 6th and 7th editions[1,9,10]

	5th edition, 1997	6th edition, 2002	7th edition, 2009
Regional lymph nodes	Cervical and upper mediastinal lymph node(s)	Central compartment, lateral cervical and upper mediastinal lymph node(s)	Central compartment, lateral cervical and superior mediastinal lymph node(s)
N0	No regional lymph node(s) metastases	No regional lymph node metastasis	No regional lymph node metastasis
N1a	Metastasis in ipsilateral cervical lymph node(s)	Metastasis to level IV [pretracheal, paratracheal, and prelaryngeal/ Delphian lymph node(s)]	Metastases to level VI [paratracheal and prelaryngeal/Delphian lymph node(s)]
N1b	Metastasis in bilateral, midline, or contralateral cervical or mediastinal lymph node(s)	Metastasis to unilateral, bilateral, or contralateral cervical or mediastinal lymph node(s)	Metastases to unilateral, bilateral, or contralateral cervical (levels I, II, III, IV, or V), or retropharyngeal or superior mediastinal lymph node(s) [level VII]

The AJCC TNM staging system for DTC now recognizes the impact of nodal disease, categorizing patients over 45 years of age as stage IV if they have a greater extent of nodal disease (N1b) and stage III if they have less extensive nodal disease (N1a). Recent literature increasingly highlights the prognostic importance of LN characteristics in DTC.[11–15] Patients with N1b disease may either have metastases to the lateral neck or have metastases to level 7 (superior mediastinum) of the neck. Although there is good evidence reporting poorer outcome if patients have N1b disease due to lateral neck disease,[2,3,16] to our knowledge there is no data to suggest that level 7, superior mediastinal disease, in the absence of lateral neck disease, confers poorer survival or recurrence prognosis. In our study, we provide strong evidence that suggests that patients with level 7 disease do not have poorer outcome in terms of survival or overall recurrence, suggesting that upstaging level 7 disease to N1b stage may not be justified (Table 3).

However, it is important to realize that our study has several limitations which require discussion. Our study was retrospective and therefore we cannot fully account for physician treatment selection bias, both in the selection for level 7 neck dissection and subsequent adjuvant RAI therapy. Level 7 dissection is not routinely recommended with level 6 dissections by the American Thyroid Association guidelines,[17] nor other international guidelines.[18–20]

Therefore, the decision to dissect level 7 was determined by the individual surgeon based on the degree of suspicion of disease in that compartment as well as risks associated with dissection. For example, if the surgeon was concerned about the functional status of the recurrent laryngeal nerve following dissection of level 6, they may not risk further injury by dissecting level 7. Similarly, if the surgeon considered dissection of level 7 to be high risk due to the presence of prominent veins, dilated innominate artery, or high riding brachiocephalic vein, then level 7 dissection may have been avoided. Additionally, if palpable disease is noted in level 6 but not in level 7, the surgeon may also have decided not to perform a superior mediastinal dissection on the presumption that non-palpable disease in level 7 was not clinically important.

A further limitation of our study was the potential for misclassification of LN level. It is possible that some surgeons dissected both level 6 and level 7 but that the specimen was then labeled as central compartment. This would result in some level 7 LNs being misclassified as level 6. If nodal disease in level 7 represents poorer outcome, then this would negatively bias the outcome of our level 6 cohort. On the other hand, specimens distinctly labeled as level 7 LNs were considered as such. Thus, recurrence outcomes for level 7 are therefore accurate.

Conclusions

Our results suggest that level 7 nodes do not carry a poorer outcome in patients with DTC; however, our results should be interpreted with some caution due to potential selection bias and misclassification effects. The issue of selection bias and misclassification can be addressed with a prospective trial in which all patients undergoing a central neck dissection have both levels 6 and 7 dissected, and all neck dissection specimens be divided in the operating room into level 6 and 7 by the operating surgeon so that correct level-specific pathology can be produced. We would encourage any other large institution with such systematic data to analyze their data and publish their results so that this important topic can be adequately addressed. If our results are validated by other datasets, the current AJCC staging system may need to be adjusted to classify all patients with central neck disease as N1a, and for the N1b category to be reserved for positive lateral neck disease alone.

DISCLOSURE Laura Y. Wang, Frank L. Palmer, Dorothy Thomas, Iain J. Nixon, R. Michael Tuttle, Jatin P. Shah, Snehal G. Patel, Ashok R. Shaha, and Ian Ganly have no commercial associations or potential conflicts of interests to declare.

References

1. Sobin L, Gospodarowicz M, Wittekind C. International Union Against Cancer (UICC) TNM classification of malignant tumors. 7th ed. New York: Wiley-Blackwell; 2009. New York: Springer
2. Ito Y, Tomoda C, Uruno T, Takamura Y, Miya A, Kobayashi K, et al. Ultrasonographically and anatomopathologically detectable node metastases in the lateral compartment as indicators of worse relapse-free survival in patients with papillary thyroid carcinoma. *World J Surg*. 2005;29:917-920
3. de Meer SG, Dauwan M, de Keizer B, Valk GD, Borel Rinkes IH, Vriens MR. Not the number but the location of lymph nodes matters for recurrence rate and disease-free survival in patients with differentiated thyroid cancer. *World J Surg*. 2012;36:1262-1267
4. Ito Y, Miyauchi A. Lateral lymph node dissection guided by preoperative and intraoperative findings in differentiated thyroid carcinoma. *World J Surg*. 2008;32:729-739.
5. Ito Y, Miyauchi A, Jikuzono T, Higashiyama T, Takamura Y, Miya A, et al. Risk factors contributing to a poor prognosis of papillary thyroid carcinoma: validity of UICC/AJCC TNM classification and stage grouping. *World J Surg*. 2007;31:838-848.
6. DeGroot LJ, Kaplan EL, McCormick M, Straus FH. Natural history, treatment, and course of papillary thyroid carcinoma. *J Clin Endocrinol Metab*. 1990;71:414-424
7. Hay ID, Bergstralh EJ, Goellner JR, Ebersold JR, Grant CS. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. *Surgery*. 1993;114:1050-1057; discussion 1057-1058
8. Grebe SK, Hay ID. Thyroid cancer nodal metastases: biologic significance and therapeutic considerations. *Surg Oncol Clin N Am*. 1996;5:43-63
9. Sobin L, Wittekind C. UICC: TNM classification of malignant tumors. 5th ed. New York: Wiley, 1997.
10. Sobin L, Wittekind C. International Union Against Cancer (UICC) TNM classification of malignant tumors. 6th ed. New York: Wiley-Liss; 2002:78
11. Gimm O, Rath FW, Dralle H. Pattern of lymph node metastases in papillary thyroid carcinoma. *Br J Surg*. 1998;85:252-254
12. Scheumann GF, Gimm O, Wegener G, Hundeshagen H, Dralle H. Prognostic significance and surgical management of locoregional lymph node metastases in papillary thyroid cancer. *World J Surg*. 1994;18:559-567; discussion 567-558
13. Ito Y, Jikuzono T, Higashiyama T, Asahi S, Tomoda C, Takamura Y, et al. Clinical significance of lymph node metastasis of thyroid papillary carcinoma located in one lobe. *World J Surg*. 2006;30:1821-1828
14. Randolph G, Duh Q, Heller K, LiVolsi V, Mandel S, Steward D, et al. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. *Thyroid*. 2012;22:1144-1152.
15. Sugitani I, Kasai N, Fujimoto Y, Yanagisawa A. A novel classification system for patients with PTC: addition of the new variables of large (3 cm or greater) nodal metastases and reclassification during the follow-up period. *Surgery*. 2004;135:139-148
16. Takada H, Kikumori T, Imai T, Sawaki M, Shibata A, Kiuchi T. Patterns of lymph node metastases in papillary thyroid carcinoma: results from consecutive bilateral cervical lymph node dissection. *World J Surg*. 2011;35:1560-1566
17. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid*. 2009;19:1167-1214
18. British Thyroid Association. Guidelines for the management of thyroid cancer. 2nd ed. 2007. http://www.british-thyroid-association.org/news/Docs/Thyroid_cancer_guidelines_2007.pdf
19. Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JW, Wiersinga W. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. *Eur J Endocrinol*. 2006;154:787-803
20. Takami H, Ito Y, Okamoto T, Yoshida A. Therapeutic strategy for differentiated thyroid carcinoma in Japan based on a newly established guideline managed by Japanese Society of Thyroid Surgeons and Japanese Association of Endocrine Surgeons. *World J Surg*. 2011;35:111-121

Chapter 4

Central Neck Failures in Patients with Papillary Thyroid Cancer and Incidentally Discovered Level 6 Lymph Nodes

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Abstract

Background

Following total thyroidectomy (TT) for papillary thyroid cancer (PTC), pathological assessment can occasionally reveal incidental perithyroidal lymph nodes (LNs) with occult metastases. These cN0pN1a patients often receive radioactive iodine (RAI) therapy for this indication alone. The aim of this study was to determine the central compartment nodal recurrence-free survival in patients treated without RAI compared to those who received RAI treatment.

Methods

An institutional database of 3664 previously untreated patients with differentiated thyroid cancer operated between 1986 and 2010 was reviewed. A total of 232 pT1-3 patients managed with TT and no neck dissection were subsequently found to have incidental level 6 LNs on pathology. Patients with other indications for RAI, such as extrathyroidal extension and close or positive margins, were excluded. One hundred and four patients remained for analysis. Kaplan–Meier method was used to determine central neck LN recurrence-free survival (RFS).

Results

The median age of the cohort was 40 years (range 17–83). The median follow-up was 53 months (range 1–211). The median number of positive LNs removed and maximum LN diameter were 1 (range 1–8) and 5 mm (range 1–16 mm), respectively. A total of 67 (64%) patients had adjuvant RAI and 37 (36%) did not. Patients with vascular invasion ($P = 0{\cdot}01$), LNs >2 mm ($P = 0{\cdot}07$) and >2 positive nodes ($P = 0{\cdot}06$) were more likely to be selected for adjuvant RAI therapy. Patients without RAI therapy had similar 5-year central neck LN RFS compared to those treated with RAI: 96·2% *vs* 94·6%, respectively ($P = 0{\cdot}92$).

Conclusion

There is no difference in the 5-year central compartment nodal recurrence-free survival in patients treated without RAI compared to those who received RAI treatment.

Introduction

Following total thyroidectomy for papillary thyroid cancer (PTC), pathological assessment can occasionally reveal incidental perithyroidal lymph nodes (LNs) with occult metastases. In the absence of prospective evidence, subsequent management of these patients is largely dependent on personal preferences and institutional practices.[1] Although management guidelines do not specifically address this clinical scenario, clinical N0 but pathological N1a patients often receive radioactive iodine (RAI) therapy, in the absence of other indications for RAI. This practice was, in part, justified by the 2009 American Thyroid Association (ATA) risk stratification of differentiated thyroid cancer.[2] These clinical N0, pathological N1a patients were classified as intermediate risk of recurrence as a result of microscopic nodal disease. In the anticipated 2015 ATA guidelines, the low-risk category will be expanded to incorporate patients with ≤5 pathological N1 micrometastases that measure <0·2 cm in dimension. The aim of this study was to determine the central compartment nodal recurrence-free survival in patients treated without RAI compared to those who received RAI treatment.

Methods

Following approval by the Institutional Review Board, the records of 3664 consecutive patients treated surgically for differentiated thyroid cancer between 1986 and 2010 were identified from an institutional database. Patients with non-PTC, less than total thyroidectomy, neck dissection of the central or lateral neck, and those presenting with distant metastases were excluded. This left 248 patients with PTC managed with total thyroidectomy and no planned neck dissection that had incidental level 6 LNs on pathology. Patients with other indications for adjuvant RAI therapy, such as the presence of extrathyroidal extension (ETE) and close or positive margins, were then excluded. This left 104 patients for analysis. A flow chart showing the patients selected for analysis is shown in Fig. 1.

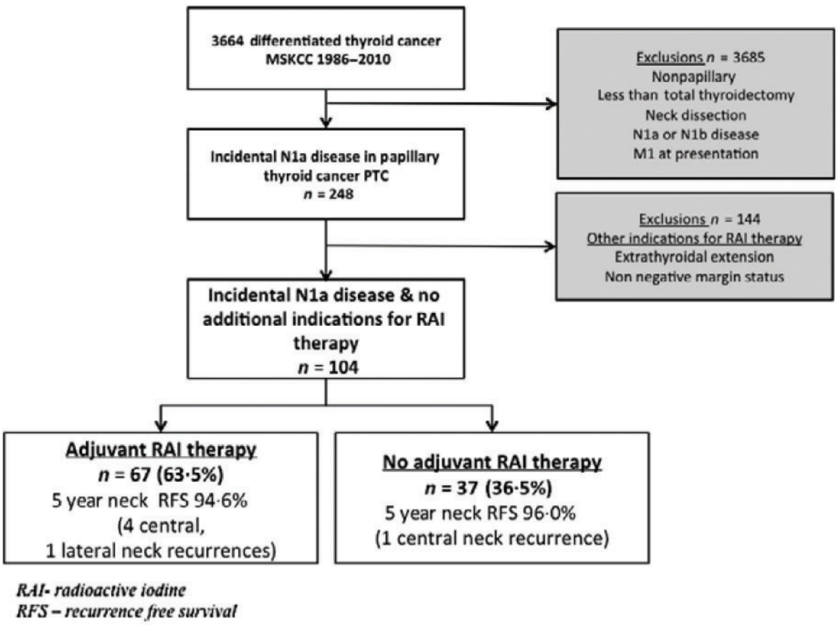

Figure 1 | Flow chart of inclusion patients.

At our institution, neck dissections are only carried out for clinically confirmed lymph node metastases, or if suspicious LNs are found on clinical examination, on preoperative imaging or during surgery. Intra-operative LN biopsies for frozen section are performed based on surgeon preference. If no LNs are suspected to contain metastases, then thyroidectomy alone is performed. We do not practise elective central compartment node dissection. Therefore, all included patients had either incidental occult LN metastases detected on pathological examination of perithyroidal tissue, which was included with the thyroidectomy specimen or positive LNs found on permanent sectioning after a negative frozen section biopsy.

Patient demographic information, surgical details and histopathological details including number of positive LNs, size of largest positive LN and the presence of LN extracapsular spread (ECS) were recorded. LN diameter was defined as the diameter of the largest LN containing a focus of metastatic thyroid cancer. The presence of ECS was defined as tumour extension beyond the LN capsule. As this study includes patients with pathology reports from 1986 through 2010, all LN features were not reported in patients from the earlier years. Analysis of LN characteristics was limited to patients with available pathology details. Size cut-off of micrometastatic positive LNs was based on other studies in the literature[3,4] Details of postoperative adjuvant RAI therapy were recorded, and patients were then stratified into 2 groups: those who received RAI and those who did not. Postoperative serum thyroglobulin (Tg) levels were taken as the lowest Tg level prior to adjuvant RAI therapy or within 1 year of surgery if no RAI was administered. Tg measurements for patients with raised Tg antibodies within the same time period were excluded from analysis. Since 1999, Tg values have been measured using the Dynotest-TgS immunoradiometric assay (Brahms, Inc., Berlin, Germany; functional sensitivity 0·6 µg/l normalized to Certified Reference Material 457).[5]

The primary outcome of interest was central compartment nodal recurrence-free survival (RFS). LN recurrences were determined by clinical examination supplemented with imaging and fine-needle aspiration. Patients with biochemical recurrences alone, defined by elevated thyroglobulin (Tg) levels, were not considered to be sufficient measures for nodal recurrence outcome. Outcomes data were calculated at 5 years. Statistical analysis was carried out using SPSS (version 21, IBM Corporation, Armonk, NY, USA). Pearson's chi-squared test was used to compare variables between the RAI and no RAI groups. Survival outcomes were analysed using the Kaplan–Meier method. Univariate analysis was carried out by the log-rank test. A P value $<0·05$ was considered significant.

Results

The median age of the cohort was 40 years (range 17–83). The median follow-up was 53·4 months (range 1–211). The median number of positive LNs identified was 1 (range 1–8). The median LN diameter was 5 mm (range 1–16 mm). Sixty-seven (74%) patients received adjuvant RAI and 37 (34%) patients had no RAI. Table 1 shows patient, tumour and treatment characteristics for the RAI and no RAI groups. Those with vascular invasion ($P = 0·01$), LNs >2 mm ($P = 0·07$) and >2 positive nodes ($P = 0·06$) were more likely to be selected for adjuvant RAI therapy. There were no statistically significant differences in terms of age, primary tumour size ($P = 0·23$), multicentricity ($P = 0·67$), LN extracapsular spread ($P = 0·37$) or postoperative Tg measurements ($P = 0·22$). Central neck recurrence occurred in 5 patients: 4 patients in the RAI group and 1 patient in the no RAI group. Fig. 2 demonstrates the Kaplan–Meier plot for central neck nodal recurrence for patients who received adjuvant RAI therapy and those who did not. Patients with and without RAI therapy had similar 5-year central neck LN RFS of 94·6% and 96·2%, respectively ($P = 0·92$).

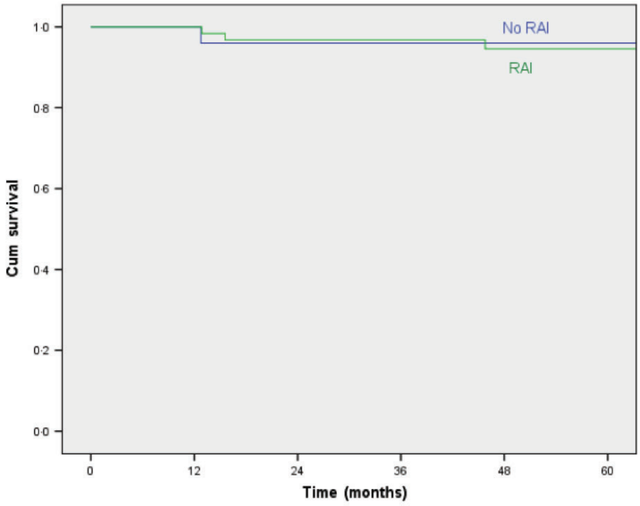

Figure 2 | Kaplan Meier plot for Central neck recurrence-free survival in patients with incidental pN1aM0 managed with and without adjuvant RAI therapy.

Table 1 | Comparison of patient demographics with and without RAI ablation

	No Adjuvant RAI		Adjuvant RAI		
	n **= 37**	**%**	***n*** **= 67**	**%**	***P*** **value**
Gender					
Female	31	83·8%	44	65·7%	**0·05**
Male	6	16·2%	23	34·3%	
Age					
<45 years	26	70·3%	41	61·2%	0·36
≥45 years	11	29·7%	26	38·8%	
Size					
≤2 cm	30	81·1%	50	74·6%	0·23
≤4 cm	7	18·9%	12	17·9%	
>4 cm	0	0·0%	5	7·5%	
T Stage					
T1a	13	35·1%	21	31·3%	0·41
T1b	17	45·9%	29	43·3%	
T2	7	18·9%	12	17·9%	
T3	0	0·0%	5	7·5%	
Multifocality					
No	16	43·2%	26	38·8%	0·66
Yes	21	56·8%	41	61·2%	
Vascular Invasion					
Absent	35	94·6%	48	73·8%	**0·01**
Present	2	5·4%	17	26·2%	
ECS					
Absent	27	90·0%	41	95·3%	0·37
Present	3	10·0%	2	4·7%	
LN size					
≤0·2 cm	8	33·3%	7	14·9%	0·07
>0·2 cm	16	66·7%	40	85·1%	

	No Adjuvant RAI		Adjuvant RAI		
	***n* = 37**	**%**	***n* = 67**	**%**	***P* value**
No. of Positive LNs					
1	25	67·6%	33	49·3%	0·07
>1	12	32·4%	34	50·7%	
2	32	86·5%	47	70·1%	0·06
>2	5	13·5%	20	29·9%	
Postsurgery Tg level					
≤1 lg/l	23	95·8%	45	86·5%	0·22
>1 lg/l	1	4·2%	7	13·5%	

RAI – radioactive iodine, ECS – extracapsular spread, LN – lymph node, Tg – thyroglobulin.
Bold text represents statistically significant findings.

Discussion

After total thyroidectomy for PTC, histopathological examination occasionally detects unexpected microscopic LN metastases in the perithyroidal tissue. Physicians are faced with a clinical dilemma of whether or not to treat these patients with adjuvant RAI therapy. Patients with pathologically confirmed central compartment LN metastases were previously considered to be ATA intermediate risk of recurrence, and as such, many clinicians administer adjuvant RAI therapy to destroy suspected nodal metastases with the intention of reducing risk of recurrence in these patients.[2] The new 2015 ATA management guidelines are anticipated to recognize that this upstaging of patients with micrometastatic nodal disease is likely unwarranted. The new expanded criteria for ATA low-risk category will include patients with micrometastases in the central compartment. The management and outcomes of patients with occult, perithyroidal LN metastases, however, has not been studied. In this study, we analysed the outcomes of patients with T1-3 PTC tumours with incidentally discovered level 6 lymph nodes. We report that selected patients, without any adverse features in the primary tumour and with incidental nodal disease <2 mm, can be safely managed without adjuvant RAI.

Numerous publications have described LN characteristics such as size and number of lymph nodes to be predictive of recurrence.[6,7] The American Thyroid Association recently published a detailed systematic review quantifying thyroid cancer nodal volume and its relationship to prognosis. It was observed that recurrence rates in PTC have varied greatly, between 0% and 42%, depending on size of primary tumour as well as the volume of nodal disease.[4] The literature has reported on a wide range of metastatic LN sizes between 0·2 cm and 3 cm, to be associated with greater recurrence rates.[6,8] Publications from our institution suggest that LN extracapsular spread may also be prognostic.[9] As the prognostic impact of central LN characteristics is elucidated, N1a disease should no longer be considered a homogeneous entity requiring RAI therapy in all circumstances.

The question of whether or not incidentally found central neck LNs require further adjuvant RAI has not been studied. In our series, 64% of patients with incidental N1a disease were determined to be at risk for recurrence and therefore received adjuvant RAI therapy following surgery. Patients with vascular invasion were significantly more likely to receive postoperative RAI therapy compared to those without vascular invasion (P = 0·01). Although the presence of vascular invasion has been associated with increased risk of disease recurrence,[10] there are inadequate data to determine whether RAI ablation has benefits after adjusting for tumour size and patient age.[2] Nevertheless, at our institution, the presence of vascular invasion was associated with greater rates of RAI therapy administration.

RAI therapy is not without adverse effects; consideration must be given to the balance of minimizing iatrogenic harm versus preventing cancer morbidity. Uptake outside the thyroid gland results in salivary and lacrimal dysfunction which results in a significant, deleterious impact on patients quality of life[11] as well as a small but significant increase in the rate of secondary malignancy at high doses.[12,13] Clinical indications for adjuvant RAI therapy are frequently based on limited data, and guidelines often leave decisions to clinician discretion.[2] Although management recommendations should ideally be based on prospective randomized studies, in the absence of such studies, the analysis presented here is a very useful adjunct to physician judgment in the management of PTC patients with incidentally discovered, low-volume central compartment nodal disease.

It is important to point out the limitations of our study. This is a retrospectively conducted study with inherent patient- and physician-related selection bias relating to the administration of RAI therapy. However, at Memorial Sloan Kettering Cancer Center, we have a large experience in managing patients with thyroid cancer with a multidisciplinary team approach. Therefore, selection bias will be limited due to this extensive experience. Another limitation is the small sample size, which can limit a rigorous statistical analysis. However, our database of 3664 patients is one of the largest single institution cohorts reported. It is highly probable that the pathological details reported in our analysis are not recorded in many other institutional data sets. We would encourage other institutions with detailed synoptic reporting on pathology, to analyse their data and verify the results presented here. Lastly, one may argue that follow-up was limited, thereby underestimating the true risk of recurrence. However, the previous literature now reports that recurrence is most likely in the first 2–3 years following treatment.[14] Therefore, with a follow-up of 53 months, the majority of recurrences would have occurred in our patient cohort.

Our data therefore provide further evidence for the 2015 ATA risk stratification system which is anticipated to categorize patients with low-volume central neck disease as low risk. We report that in selected PTC patients with incidental central compartment nodal disease, there is no difference in the 5-year central compartment nodal recurrence-free survival in patients treated without RAI compared to those who received RAI treatment.

References

1. Haymart, M.R., Banerjee, M., Stewart, A.K. *et al.* (2011) Use of radioactive iodine for thyroid cancer. *JAMA,* **306**, 721–728.
2. Cooper, D.S., Doherty, G.M., Haugen, B.R. *et al.* (2009) Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid,* **19**, 1167–1214.
3. Cranshaw, I.M. & Carnaille, B. (2008) Micrometastases in thyroid cancer. An important finding? *Surgical Oncology,* **17**, 253–258.
4. Randolph, G., Duh, Q., Heller, K. *et al.* (2012) The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. *Thyroid*, **22**, 1144–1152.
5. Persoon, A.C., Links, T.P., Wilde, J. et al. (2006) Thyroglobulin (Tg) recovery testing with quantitative Tg antibody measurement for determining interference in serum Tg assays in differentiated thyroid carcinoma. *Clinical Chemistry*, **52**, 1196–1199.
6. Sugitani, I., Kasai, N., Fujimoto, Y. et al. (2004) A novel classification system for patients with PTC: addition of the new variables of large (3 cm or greater) nodal metastases and reclassification during the follow-up period. *Surgery*, **135**, 139–148.
7. Ito, Y., Jikuzono, T., Higashiyama, T. et al. (2006) Clinical significance of lymph node metastasis of thyroid papillary carcinoma located in one lobe. *World Journal of Surgery*, **30**, 1821–1828.
8. Jeon, M., Yoon, J., Han, J. *et al.* (2013) The prognostic value of the metastatic lymph node ratio and maximal metastatic tumor size in pathological N1a papillary thyroid carcinoma. *European Journal of Endocrinology*, **168**, 219–225.
9. Wang, L., Palmer, F., Nixon, I. *et al.* (2014) Central lymph node characteristics predictive of outcome in patients with differentiated thyroid cancer. *Thyroid*, **30**, 30.
10. Akslen, L. & LiVolsi, V. (2000) Prognostic significance of histologic grading compared with subclassification of papillary thyroid carcinoma. *Cancer*, **88**, 1902–1908.
11. Almeida, J.P., Sanabria, A.E., Lima, E.N. *et al.* (2011) Late side effects of radioactive iodine on salivary gland function in patients with thyroid cancer. *Head and Neck*, **33**, 686–690.
12. Iyer, N., Morris, L., Tuttle, R. *et al.* (2011) Rising incidence of second cancers in patients with low-risk (T1N0) thyroid cancer who receive radioactive iodine therapy. *Cancer*, **117**, 4439–4446.
13. Sawka, A.M., Thabane, L., Parlea, L. et al. (2009) Second primary malignancy risk after radioactive iodine treatment for thyroid cancer: a systematic review and meta-analysis. *Thyroid*, **19**, 451–457.
14. Young, S., Harari, A., Smooke-Praw, S. *et al.* (2013) Effect of re-operation on outcomes in papillary thyroid cancer. *Surgery* **154**, 1354–1361; discussion 1361-1352.

Chapter 5

Characteristics of Lymph Nodes Predictive of Outcome in the Central Neck

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Abstract

Background

The aim of our study was to determine central compartment lymph node (LN) characteristics predictive of outcomes in patients with differentiated thyroid cancer (DTC) and pathologically confirmed positive central LNs, in the absence of lateral neck disease or distant metastases at presentation.

Methods

An institutional database of 3664 previously untreated patients with DTC operated between 1986 and 2010 was reviewed. Six hundred patients with central compartment nodal disease on histopathology were identified. Patient demographics, number of positive LNs, size of largest LN, and presence of extranodal spread (ENS) were recorded for each patient. Variables predictive of recurrence-free survival (RFS) were identified using the Kaplan–Meier method. Univariate analysis was carried out by the log-rank test and multivariable analysis was carried out using cox proportional hazard model.

Results

The median age of the cohort was 41 years (range 12–91 years). The median follow-up was 61 months (range 1–330 months). Neck recurrence occurred in 43 patients. Recurrence occurred in the central neck in 11 patients, lateral neck in 27 patients, and both compartments in five patients. Factors predictive of neck RFS on univariate analysis were higher T stage ($p = 0.007$), increased number of positive LNs, increased LN diameter, and presence of ENS ($p = 0.001$). Multivariable analysis of LN characteristics showed that the only statistically significant predictor of neck recurrence was the presence of ENS. Neck RFS at five years for patients with and without ENS was 84.7% and 94.5% respectively ($p = 0.001$).

Conclusion

The LN feature most predictive of neck recurrence appears to be the presence of ENS in the positive central neck.

Introduction

Metastases to the central compartment lymph nodes (LNs; levels 6 and 7) in patients with differentiated thyroid cancer (DTC) are common. In the majority of patients, these LNs are subclinical micrometastases of uncertain prognostic significance. In the majority of cases, the presence of micrometastases represents indolent disease. Because of this, the presence of cervical nodal metastases was not considered to be associated with survival and thus was not included in traditional scoring systems such as GAMES, MACIS, and AMES (1–3). However, some studies have reported that cervical LNs measuring > 1.5 cm (4) or >3 cm (5) are prognostic. Other studies have suggested that the number of pathologically positive LNs is prognostic (6,7). Reflective of these data on the prognostic significance of positive nodal disease, the AJCC staging system now upstages patients with N1a disease to stage III in patients >45 years of age.

The aim of our study was to explore this topic further by determining central compartment LN characteristics predictive of recurrence outcomes in patients with DTC and pathologically confirmed positive central LNs. Size, number of positive nodes, and the presence of extranodal spread (ENS) were analyzed in a large data set of patients treated at a single institution.

Methods

Following approval by the Institutional Review Board, the records of 3664 consecutive patients treated surgically for DTC between 1986 and 2010 were identified from an institutional database. Six hundred pN1a patients on histopathology were identified for review. Patients who were treated at an outside facility prior to referral, had disease confined to the thyroid gland, had evidence of lateral compartment nodal disease, presented with distant metastasis, or were discovered to have distant metastases on postoperative RAI scan (within six months) were excluded from analysis. At our institution, we do not routinely carry out prophylactic central neck dissections but only dissect the central neck whenever nodes are found on palpation, on preoperative imaging, or during surgery. Therefore, the 600 pathologically confirmed patients with central compartment disease consist of patients having a central neck dissection for macroscopic LNs on clinical or radiologic examination. In addition, we also included patients with occult metastases found in perithyroidal LNs included in the thyroidectomy specimen, and included nodes found to be positive on node sampling.

Patient demographic information, surgical details, and histopathological details, including number of positive central LNs, size of largest positive LN, and presence of ENS, were recorded. LN diameter was defined as the diameter of the largest LN containing a focus of metastatic thyroid cancer. The presence of ENS was defined as tumor extension beyond the LN capsule. Details of postoperative use of radioactive iodine (RAI) therapy were recorded and postoperative thyrotropin (TSH) suppression was initiated based on individual risk of recurrence.

As this study includes patients with pathology reports from 1986 to 2010, LN features were not reported in all patients. Figure 1 shows the LN data available for analysis. To maximize statistical power, patients with one or more missing LN feature were censored for the analysis of that LN variable. To ensure there was no selection bias between patients with all LN features reported and patients with one or more missing LN features, Pearson's chi square test was performed comparing these two groups. No difference in sex, age, T stage, or histology was found (data not shown).

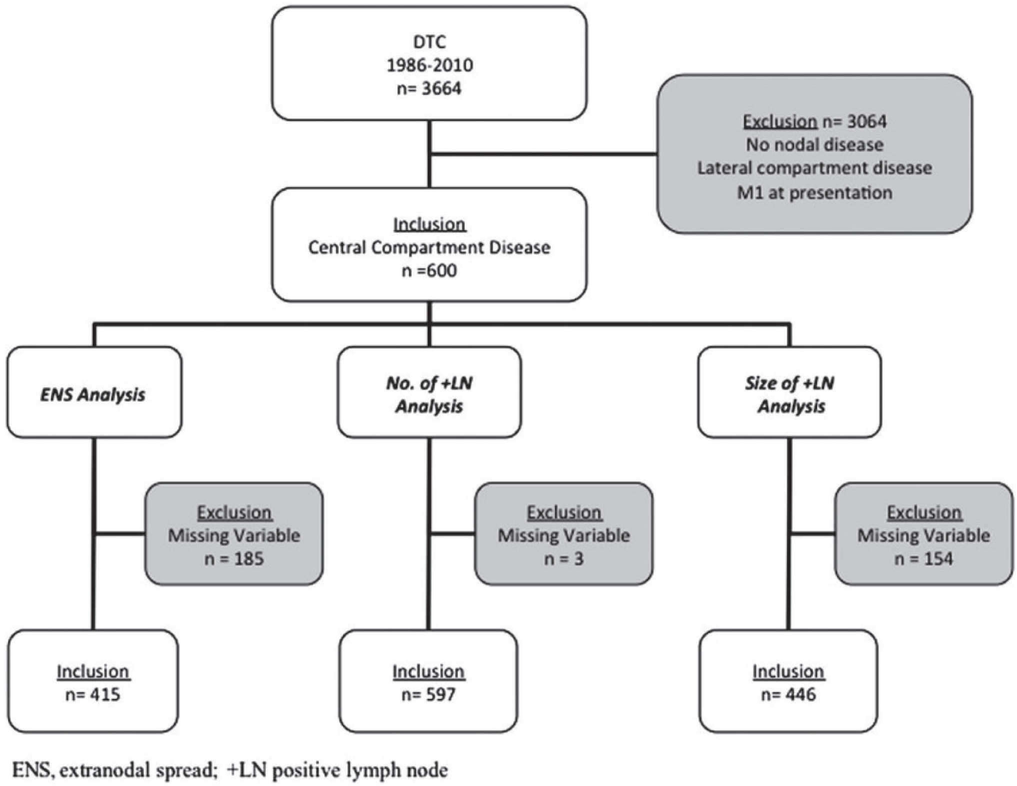

Figure 1 | Inclusion criteria.

The primary outcome of interest was nodal recurrence-free survival (RFS). Neck LN recurrences were determined by clinical examination supplemented with imaging and fine-needle aspiration. Patients with biochemical recurrences defined by elevated thyroglobulin levels were not considered to be robust endpoints to measure nodal recurrence outcome. Prior to 2000, postoperative serum thyroglobulin (Tg) was not used to detect recurrence. The use of serum Tg measurements and serial ultrasounds has become standard practice at our institution since 2005, and now influence the further investigation of patients in this cohort. The median follow-up for the cohort was 61 months (range 1–330). Outcome data were therefore calculated at five years.

Statistical analysis was carried out using SPSS Statistics for Windows v21 (IBM Corp., Armonk, NY). Categorical cutoffs for size and number of positive LNs were based on frequently used cutoff from the literature as well as by receiver operating characteristic (ROC) curves. ROC curves were plotted for all LN number and size cut-points. The value at which sensitivity and specificity was maximized for nodal RFS was also selected for analysis. Pearson's chi-square test was used to compare variables within groups. Survival outcomes were analyzed using the Kaplan–Meier method. Univariable analysis was carried out by the log-rank test, and multivariable analysis was carried out using the Cox proportional hazard model. A p-value < 0.05 was considered significant.

Results

The median age of the cohort was 41 years (range 12–91 years). The median time to regional nodal recurrence was 50.5 months (range 1–330 months). Nodal recurrence occurred in 43 patients. Recurrence occurred in the central neck in 11 patients, lateral neck in 27 patients, and both compartments in five patients. Distant recurrence developed in 10 patients, and disease-specific death occurred in five patients.

Predictors of neck RFS on univariable analysis

Factors predictive for neck RFS were increasing LN diameter and the presence of ENS (Table 1). Although T stage was predictive ($p = 0.007$), sex, age, histology, and postoperative RAI administration were not predictive.

LN diameter (n = 446). Patients with central LN micrometastases of ≤0.2 cm had similar five-year neck RFS compared to patients with LNs > 0.2 cm (93.6% vs. 92.6%; p = 0.603). At a LN cutoff of 0.75 cm, determined by ROC analysis, patients with LN ≤0.75 cm had a small but statistically significant superior five-year neck RFS (96.8% vs. 90.2%; p = 0.040). Similarly, patients with a LN diameter ≤1 cm and ≤2 cm had superior five-year neck RFS compared to patients with LNs > 1 cm and > 2 cm respectively (Table 1).

Table 1 | Regional Lymph Node Recurrence-Free Survival

	n	**No. events**	**5 year neck RFS**	***p*-Value**
Sex				
Female	430	27	93.0%	0.216
Male	170	16	90.5%	
Age				
< 45 years	357	26	92.4%	0.882
≥ 45 years	243	17	92.3%	
T stage				
T1	202	9	94.4%	**0.007**
T2	70	2	98.1%	
T3	283	24	91.3%	
T4	45	8	81.8%	
Histology				
Follicular	5	0	100.0%	0.815
Hürthle	4	0	100.0%	
Papillary	591	43	92.2%	
Nodal stage				
N1a	543	41	91.6%	0.179
N1b	57	2	98.2%	
Max diameter of largest node				
≤ 0.2 cm	48	2	93.6%	0.603
> 0.2 cm	398	24	92.6%	
≤ 0.75 cm	247	9	96.1%	**0.007**
> 0.75 cm	199	21	88.6%	
< 1 cm	299	13	95.3%	**0.006**
≥ 1 cm	147	17	87.5%	
≤ 2 cm	431	27	93.3%	**0.042**
> 2 cm	15	3	75.8%	
Number of positive nodes				
≤ 3	423	24	94.1%	**0.043**
>3	174	19	88.2%	
≤ 5	495	31	93.5%	0.070
> 5	102	12	87.6%	
≤ 8	543	33	93.5%	**0.001**
> 8	54	10	80.7%	

	n	No. events	5 year neck RFS	*p*-Value
ENS				
None	318	15	94.5%	**0.001**
Micro/macro	97	15	84.7%	
ATA risk category				
Low	*NA*	*NA*	*NA*	
Intermediate	488	31	92.7%	0.243
High	112	12	90.8%	
Adjuvant RAI				
No	180	7	97.2%	0.121
Yes	420	36	90.8%	

Bold indicates significant values.

RFS, recurrence-free survival; RAI, radioactive iodine.

Number of positive LNs (*n*=597). Comparison of five-year neck RFS for patients with three or fewer and more than three positive LNs (94.1% vs. 88.2%, $p = 0.043$), five or fewer and more than five positive LNs (93.5% vs. 87.6%; $p = 0.070$) as well eight or fewer and more than eight positive LN patients (93.5% vs. 80.7%;$p = 0.001$; Table 1) showed a general trend toward poorer neck RFS with increasing number of positive central LNs. A cutoff of eight or fewer positive LN was determined by ROC analysis.

ENS (*n*=415). A total of 23.4% of patients with N1a disease had evidence of ENS reported on histopathology. Patients with ENS had a significantly poorer five-year neck RFS survival compared to patients without ENS (84.7% vs. 94.5%; $p = 0.001$; Table 1 and Fig. 2). When stratified by age > 45 and < 45 years, the presence of ENS remained significant in both age cohorts ($p = 0.044$ and $p = 0.005$ respectively).

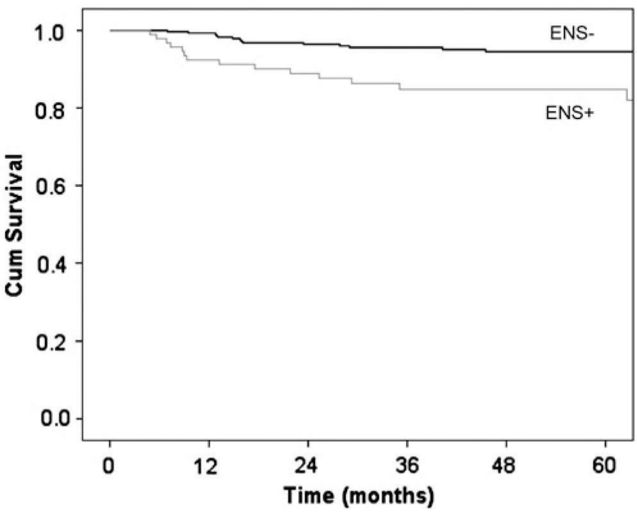

Figure 2 | Neck recurrence-free survival in patients with and without extranodal spread.

Predictors of neck RFS on multivariable analysis

A total of 354 patients had all LN variables (maximal LN diameter, number of positive LNs, and ENS) available for analysis and were therefore included in the multivariable analysis of significant LN characteristics predictive for neck recurrence. We were limited to three variables for multivariable analysis due to the limited number of neck recurrences. Table 2 shows nine models of multivariable analysis of LN variables, including all combinations of LN diameters (<0.75 cm/≥0.75 cam, < 1 cm/≥1 cm, and < 2 cm/≥2 cm), number of positive LNs (three or fewer/more than three, five or fewer/more than five, eight or fewer/more than eight) and presence of ENS. In all nine models, the presence of ENS was independently predictive for neck RFS.

When we controlled for T stage, ENS remained a significant predictor for neck recurrence conferring a hazard ratio of 3.1 ([confidence interval (CI) 1.491–6.515], $p = 0.003$).

Table 2 | Multivariable Model of Central Lymph Node Features

		CI		
	HR	**Lower**	**Upper**	***p*-Value**
Model 1				
Largest LN 0.75 cm	—	—	—	0.075
>3 positive LNs	—	—	—	0.860
LN ENS	2.997	1.238	7.257	**0.015**
Model 2				
Largest LN 0.75 cm	—	—	—	0.092
>5 positive LNs	—	—	—	0.490
LN ENS	2.738	1.092	6.863	**0.032**
Model 3				
Largest LN 0.75 cm	—	—	—	0.117
>8 positive LNs	—	—	—	0.116
LN ENS	2.520	1.021	6.221	**0.045**
Model 4				
Largest LN 1 cm	—	—	—	0.292
>3 positive LNs	—	—	—	0.668
LN ENS	3.121	1.241	7.849	**0.016**
Model 5				
Largest LN 1 cm	—	—	—	0.329
>5 positive LNs	—	—	—	0.352
LN ENS	2.816	1.087	7.298	**0.033**
Model 6				
Largest LN 1 cm	—	—	—	0.406
>8 positive LNs	—	—	—	0.080
LN ENS	2.619	1.029	6.663	**0.043**
Model 7				
Largest LN 2 cm	—	—	—	0.185
>3 positive LNs	—	—	—	0.714
LN ENS	3.430	1.409	8.349	**0.007**
Model 8				
Largest LN 2 cm	—	—	—	0.224
>5 positive LNs	—	—	—	0.378
LN ENS	3.066	1.213	7.754	**0.018**
Model 9				
Largest LN 2 cm	—	—	—	0.309
>8 positive LNs	—	—	—	0.088
LN ENS	2.809	1.129	6.986	**0.026**

Bold indicates significant values.

CI, confidence interval; LN, lymph node; ENS, extranodal spread.

Distant recurrence and disease-specific survival

No central compartment LN features were predictive of distant RFS or disease-specific survival (DSS) on univariable analysis.

Discussion

Metastases to the central compartment LNs (levels 6 and 7) in patients with DTC are common. In the majority of patients, these are subclinical micrometastases, and the prognostic significance of them is very controversial. Recent data suggest that the size and number of positive LNs are prognostic (4–8). The American Thyroid Association recently published a detailed systematic review quantifying thyroid cancer nodal volume and its relationship to prognosis. In this review, it was recommended that patients be classified into "lower and higher risk N1" categories based on volume of nodal disease (9). The definition of micrometastases being ≤ 0.2 cm was based on data from breast cancer staging. No recommendation at the time was made for stratification of patients with evidence of ENS. To explore this controversial subject further, we sought to analyze our own results using a data set of 600 patients with central compartment nodal disease. We analyzed size of LNs, number of positive nodes, and the presence of ENS using this data set, and report that all three characteristics are significant. However, it is the presence of ENS that appears to be the most prognostic in the central compartment.

With regards to the size of the metastatic LN, several studies have reported larger LN size and metastatic foci diameter to be prognostic in DTC. Ito *et al.* have published several studies on the prognostic implications of central neck metastatic LN size in papillary thyroid cancer (4,10). That group reported on 626 patients with papillary thyroid cancer > 1 cm undergoing prophylactic central neck dissection with or without lateral neck dissection. On multivariable analysis, in addition to other predictors, central LN features associated with a significantly worse RFS were LN diameter > 1.5 cm and more than 10 positive LNs (4). In a similar study by Sugitani *et al.*, patients with papillary thyroid cancer > 1 cm with central and/or lateral neck disease were examined. Multivariable analysis suggested that LN metastases > 3 cm were predictive of DSS and RFS in patients aged 50 years or older but not in younger patients (5). In a case control study by Yamashita *et al.*, large LN deposits >1 cm in size as well as ENS were significantly higher in the metastatic group on univariable analysis. LN size, however, was not significant on multivariable analysis when controlling for other LN variables. A more recent study reported central LN metastases of > 0.2 cm to be prognostic of recurrence. However, presence of ENS was not controlled for in this study (8). Data from this current study suggest that increasing size of positive central compartment LNs is associated with a trend toward poorer RFS: 96.1% for those with LNs ≤ 0.75 cm in contrast to 75.8% for patients with LN > 2 cm (Table 1). However, at no size was LN diameter independently predictive of nodal recurrence when controlling for presence of ENS (Table 2).

Many international groups have also reported on the prognostic significance of increasing number and ratio of positive LNs in DTC. The cutoffs considered to be prognostic have differed significantly between groups from more than two positive LNs in the central or lateral compartment (6) to more than five LNs in younger but not older patients (5). Others have found > 10 LNs in the central or lateral compartment (7) and > 10 LNs in the central compartment alone (4) to be prognostic of recurrence when adjusting for the presence of ENS. In our own study, we explored various cutoffs for the number of central LNs that were predictive of recurrence. We did not find a clear cutoff for the number of positive LNs. For this reason, systematic multivariable analysis for three or fewer or more than three LNs, five or fewer or more than five LNs as well as eight or fewer or more than eight LNs, adjusting for LN diameter and presence of ENS, was performed (Table 2). Whilst an increasing number of positive central LNs increases risk of recurrence on univariable analysis (Table 1), this risk would seem to be secondary to its association with ENS rather than an independent predictor.

With regards to ENS, many studies have shown ENS to be an important predictor of outcome in other head and neck cancers (11,12), and it is widely accepted as an indication for additional adjuvant therapy in squamous cell carcinoma (13). However, there are few studies on the impact of ENS on outcome in patients with thyroid cancer. Earlier studies were unable to detect an association between ENS and outcome, possibly due to the small sample size (14). However, several recent international groups have observed ENS to be prognostic of outcome (7,15–17). More recently, a review of 111 PTC patients with total thyroidectomy and positive central LN metastases by Lee *et al.* suggested that the rate of ENS in PTC patients was higher with younger age, large tumor size, and increased number of central neck LN metastasis. However, due to the short follow-up period in this study, the impact on outcome could not be determined (18).

The extent of ENS on prognosis has also been investigated. Several Japanese groups have demonstrated poorer outcomes in patients with evidence of macroscopic ENS (17,19) in central or lateral neck LNs. Macroscopic ENS was defined as LN invasion of cervical organs, vessels, or nerves that required partial or full excision. The same group investigated the role of ENS in central compartment LNs and found no association between ENS and outcome (4). Other studies have reported microscopic ENS alone is predictive of RFS and DSS outcome (20,21). Yamashita *et al.* performed a matched pair analysis of 50 patients with distant metastatic DTC disease with 50 control patients without distant disease, together with histological review of pathology slides. Univariable analyses demonstrated that among other tumor and patient factors, LN deposits > 1 cm and presence of microscopic ENS were significantly higher in the distant metastatic group. However, on multivariable analyses, ENS was the only statistically significant LN predictor of outcome (20).

It is important to note that our study has several limitations. Due to its retrospective nature, our study is susceptible to all the limitations associated with such studies. First, our institutional policy is to perform neck dissections only in patients with palpable or ultrasound evidence of cervical neck metastases. It is therefore possible that some N1a patients included in this study had subclinical lateral neck disease not detected at the time of preoperative work-up. Lateral neck recurrence events in this cohort may therefore represent persistent disease rather than recurrent disease and thus neck recurrence events may have been overestimated. Nevertheless, the impact of microscopic disease on outcome has not been demonstrated. A second limitation is that the quality and detail of histopathology reporting of both the primary tumor and the LN features has improved significantly in the modern era. Of the 600 patients, only 354 (59.0%) patients had all three LN features (size of largest LN, number of positive LNs, and presence of ENS) available for analysis. Our multivariable analysis is therefore based upon this smaller number of patients.

In conclusion, in patients with positive central compartment nodes, we have found LN diameter, number of LN metastasis, and LN ENS to be predictive for neck recurrence. We report that the strongest predictor appears to be the presence of ENS. Management guidelines may consider these data when recommending adjuvant therapy for patients with differentiated thyroid cancer. However, further studies on larger data sets with complete synoptic reporting of all of these LN characteristics is required to support the impact that ENS has on outcome definitively.

Author Disclosure Statement

The authors have no commercial associations or potential conflicts of interests to declare.

References

1. DeGroot LJ, Kaplan EL, McCormick M, Straus FH 1990 Natural history, treatment, and course of papillary thyroid carcinoma. J Clin Endocrinol Metab **71**:414–424.
2. Hay ID, Bergstralh EJ, Goellner JR, Ebersold JR, Grant CS 1993 Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. Surgery **114**:1050–1057; discussion 1057–1058.
3. Grebe SK, Hay ID 1996 Thyroid cancer nodal metastases: biologic significance and therapeutic considerations. Surg Oncol Clin N Am **5**:43–63.
4. Ito Y, Jikuzono T, Higashiyama T, Asahi S, Tomoda C, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Kuma K, Miyauchi A 2006 Clinical significance of lymph node metastasis of thyroid papillary carcinoma located in one lobe. World J Surg **30**:1821–1828.
5. Sugitani I, Kasai N, Fujimoto Y, Yanagisawa A 2004 A novel classification system for patients with PTC: addition of the new variables of large (3 cm or greater) nodal metastases and reclassification during the follow-up period. Surgery **135**:139–148.
6. Lee J, Song Y, Soh E 2013 Prognostic significance of the number of metastatic lymph nodes to stratify the risk of recurrence. World J Surg **4**:4.
7. Leboulleux S, Rubino C, Baudin E, Caillou B, Hartl DM, Bidart JM, Travagli JP, Schlumberger M 2005 Prognostic factors for persistent or recurrent disease of papillary thyroid carcinoma with neck lymph node metastases and/or tumor extension beyond the thyroid capsule at initial diagnosis. J Clin Endocrinol Metab **90**:5723–5729.
8. Jeon M, Yoon J, Han J, Yim J, Hong S, Song D, Ryu J, Kim T, Shong Y, Kim W 2013 The prognostic value of the metastatic lymph node ratio and maximal metastatic tumor size in pathological N1a papillary thyroid carcinoma. Eur J Endocrinol **168**:219–225.
9. Randolph G, Duh Q, Heller K, LiVolsi V, Mandel S, Steward D, Tufano R, Tuttle R 2012 The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. Thyroid **22**:1144–1152.
10. Ito Y, Tomoda C, Uruno T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Kuma K, Miyauchi A 2006 Clinical significance of metastasis to the central compartment from papillary microcarcinoma of the thyroid. World J Surg **30**:91–99.
11. Carter R, Bliss J, Soo K, O'Brien C 1987 Radical neck dissections for squamous carcinomas: pathological findings and their clinical implications with particular reference to transcapsular spread. Int J Radiat Oncol Biol Phys **13**:825–832.
12. Johnson J, Myers E, Bedetti C, Barnes E, Schramm VJ, Thearle P 1985 Cervical lymph node metastases. Incidence and implications of extracapsular carcinoma. Arch Otolaryngol **111**:534–537.
13. Cooper J, Pajak T, Forastiere A, Jacobs J, Campbell B, Saxman S, Kish J, Kim H, Cmelak A, Rotman M, Machtay M, Ensley J, Chao K, Schultz C, Lee N, Fu K 2004 Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med **350**:1937–1944.
14. Spires J, Robbins K, Luna M, Byers R 1989 Metastatic papillary carcinoma of the thyroid: the significance of extranodal extension. Head Neck **11**:242–246.
15. Ricarte-Filho J, Ganly I, Rivera M, Katabi N, Fu W, Shaha A, Tuttle RM, Fagin JA, Ghossein R 2012 Papillary thyroid carcinomas with cervical lymph node metastases can be stratified into clinically relevant prognostic categories using oncogenic BRAF, the number of nodal metastases, and extra-nodal extension. Thyroid **22**:575–584.
16. Lango M, Flieder D, Arrangoiz R, Veloski C, Yu J, Li T, Burtness B, Mehra R, Galloway T, Ridge J 2013 Extranodal extension of metastatic papillary thyroid carcinoma: correlation with biochemical endpoints, nodal persistence, and systemic disease progression. Thyroid **23**:1099–1105.
17. Ito Y, Fukushima M, Tomoda C, Inoue H, Kihara M, Higashiyama T, Uruno T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Miyauchi A 2009 Prognosis of patients with papillary thyroid carcinoma having clinically apparent metastasis to the lateral compartment. Endocr J **56**:759–766.
18. Lee Y, Lim Y, Lee J, Wang S, Kim I, Son S, Shin D, Lee B 2013 Nodal status of central lymph nodes as a negative prognostic factor for papillary thyroid carcinoma. J Surg Oncol **107**:777–782.
19. Asanuma K, Kusama R, Maruyama M, Fujimori M, Amano J 2001 Macroscopic extranodal invasion is a risk factor for tumor recurrence in papillary thyroid cancer. Cancer Lett **164**:85–89.

20. Yamashita H, Noguchi S, Murakami N, Kawamoto H, Watanabe S 1997 Extracapsular invasion of lymph node metastasis is an indicator of distant metastasis and poor prognosis in patients with thyroid papillary carcinoma. Cancer **80**:2268–2272.

21. Yamashita H, Noguchi S, Murakami N, Toda M, Uchino S, Watanabe S, Kawamoto H 1999 Extracapsular invasion of lymph node metastasis. A good indicator of disease recurrence and poor prognosis in patients with thyroid microcarcinoma. Cancer **86**:842–849.

Part III

Prognostic Features of Lateral Compartment Nodal Disease

Chapter 6

Characteristics of Lymph Nodes Predictive of Outcome in the Lateral Neck

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Abstract

Purpose

To identify lateral lymph node (LN) characteristics predictive of outcome in papillary thyroid cancer patients with clinically evident nodal disease.

Methods

A total of 438 patients with lateral neck metastases from papillary thyroid cancer were identified from an institutional database of 3,664 differentiated thyroid cancers. The number of positive LNs, size of the largest LN, number of positive LNs to total number of LNs removed (LN burden), and presence of extranodal spread (ENS) were recorded. Cutoffs for continuous variables were determined by receiver operating characteristic curves. LN variables predictive of recurrence free survival and disease-specific survival (DSS) were identified by the Kaplan–Meier method and the Cox proportional hazard model.

Results

The median age was 41 years (range 5–86 years). The median follow-up was 65 months (range 1–332 months). Fifty-nine patients developed disease recurrence; these were local in five, regional in 40, and distant in 30 patients. Fifteen patients died of disease. Receiver operating characteristic cutoffs were >10 positive LNs and a LN burden >17 %. No lateral LN characteristics were predictive of DSS. In patients <45 years old, univariate predictors of recurrence were >10 positive nodes ($p = 0.049$) and LN burden >17 % ($p < 0.001$). In patients ≥45 years old, >10 positive nodes, LN burden >17 %, and presence of ENS were predictive of recurrence ($p = 0.019$, $p = 0.019$, and $p = 0.029$, respectively).

Conclusions

LN burden >17 % (1 positive LN in 6 LNs removed) in the lateral neck is predictive for recurrence in patients of all ages, whereas ENS is also prognostic for recurrence in older patients.

Previously published retrospective studies have suggested that regional lymph node (LN) metastases do not affect survival in patients with papillary thyroid cancer (PTC).[1–3] As such, prognostic scoring systems such as GAMES from our institution, as well as MACIS and AMES, based on multivariate analyses, did not find nodal disease to be a predictor of outcome.[1–3] However, more recent literature shows that nodal disease is important, particularly in patients over 45 years of age; this is now reflected in the American Joint Committee on Cancer (AJCC) staging system for thyroid cancer.[4] In patients aged ≥45 years, N1a status is considered stage III disease, and N1b status is considered stage IV disease. This staging system, however, considers only the location of the metastatic nodes and does not take into consideration other characteristics of the metastatic nodes. Several recent publications have suggested that increasing number, size, and ratio of positive LNs in the neck predicts poorer outcome in patients with PTC.[5–10] The objective of this study was to define which lateral LN characteristics have prognostic significance in patients with clinical or radiologic evidence of metastatic LNs in the lateral neck.

Methods

After receipt of approval by the institutional review board, the records of 3,664 consecutive patients treated surgically for PTC between 1986 and 2010 were identified from an institutional database. Of these, 438 patients had pathologic confirmation of palpable or radiologic ally demonstrated lateral neck metastases after a therapeutic neck dissection. Patients who were treated at an outside facility before referral, who did not have pN1b disease, who presented with distant metastasis, or who were discovered to have distant metastasis on postoperative radioactive iodine (RAI) scan (within 6 months) were excluded from analysis. Figure 1 demonstrates the inclusion cohort. Our institutional policy is not to perform prophylactic neck dissections. Therefore, these patients had macroscopic LNs either on clinical or radiologic examination.

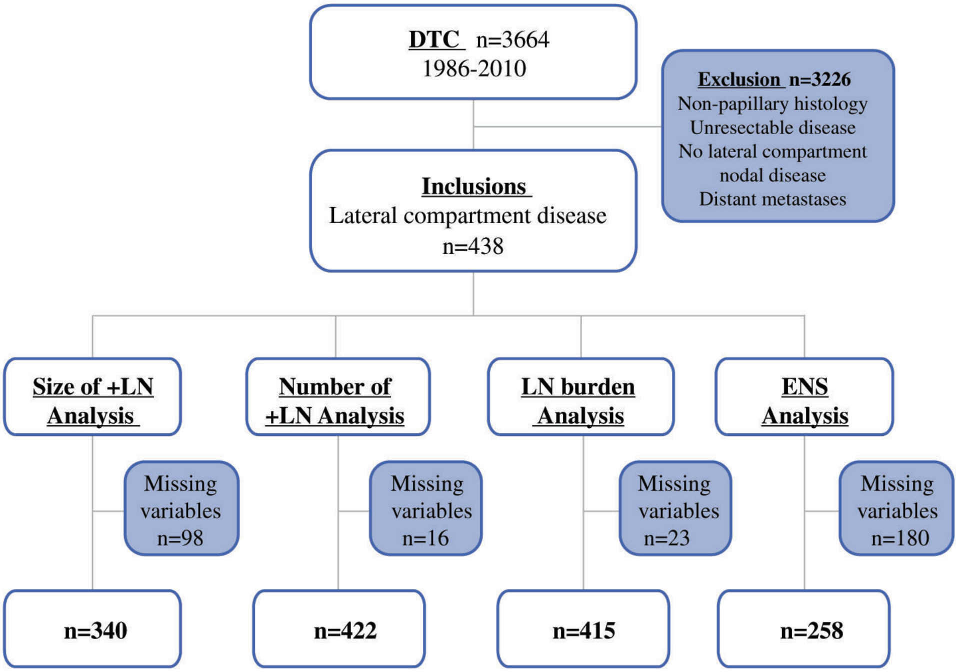

Figure 1 | Flowchart indicating study inclusion and exclusion criteria

Patient demographic information, surgical details, and histopathologic details, including number of positive lateral LNs, total number of LNs removed, size of largest LN, and presence of extranodal spread (ENS), were recorded. Details of postoperative use of RAI were recorded. Postoperative thyroid-stimulating hormone suppression was practiced according to recurrence risk for all patients.

Because this study spans patients with pathology reports between 1986 through 2010, the desired LN features were not reported in some patients from earlier years. Figure 1 shows the LN data available for analysis. Patients with one or more missing LN features were censored for the analysis of that LN variable.

Disease outcomes of interest were disease-specific survival (DSS) and recurrence-free survival (RFS). DSS was calculated using the date of last follow-up with a Memorial Sloan Kettering Cancer Center physician from the thyroid cancer multidisciplinary team. Details of death were determined from the Social Security Death Index and hospital records. All patients who had evidence of structural disease at the time of last follow-up and died during follow-up were considered to have died of disease. Local and regional recurrences were determined by clinical examination supplemented with imaging and fine-needle aspiration. Distant recurrence was determined by imaging studies including ultrasound, RAI scan, computer tomography, and positron emission tomography scan. Confirmation of disease by cytology and histopathology were recorded when available. Before 2000, postoperative serum thyroglobulin was not routinely used to detect recurrence. Serum thyroglobulin measurements and serial ultrasounds have become standard practice at our institution since 2005, and they now influence the further investigation of patients in this cohort. The median follow-up for the cohort was 65 months (range 1–332 months). Outcomes data were therefore calculated at 5 years.

Statistical analysis was carried out by SPSS software, version 21 (IBM, Armonk, NY). To determine categorical cutoffs for LN size, number, and burden of metastatic LNs that were predictive of DSS and RFS, we used cutoff values previously reported in the literature as being significant. In addition, we also plotted receiver operating curves for number of positive LNs as well as LN burden (LN burden was defined as the percentage of positive LN out of total number LNs resected) from the lateral compartment. Values were chosen to maximize sensitivity and specificity for RFS and DSS. Survival outcomes were analyzed by the Kaplan–Meier method. Univariate analysis was carried out by the log rank test, and hazard ratios were calculated by the Cox proportional hazard model. A p value of <0.05 was considered significant.

Results

The median age was 41 years (range 5–86 years). A total of 188 patients (43 %) were ≥45 years old at the time of diagnosis. Extent of lateral neck dissection was determined by a combination of surgeon preference and patient risk profile. Of the 438 patients, the majority of the cohort (71 %) underwent an ipsilateral comprehensive neck dissection including at least levels 2, 3, 4, and 5. Twenty percent of patients had an ipsilateral selective neck dissection of neck levels at highest risk of harboring disease, and a further 9 % received bilateral neck dissection. An average of 33 LNs were removed per patient.

The majority (79 %) of this cohort received adjuvant RAI therapy within 6 months of thyroidectomy surgery. The median dose received was 150 mCi (range 29–478 mCi). Fifty-nine patients (13.5 %) had recurrent disease; this was local in 5, regional in 40, and distant in 30 patients (Supplementary Fig. 1). Receiver operating characteristic analysis showed that cutoffs that maximized sensitivity and specificity were number of positive nodes of >10 and a LN burden >17 %.

LN Characteristics Prognostic of DSS

A total of 15 patients died of disease. All but one patient was aged <45 years at the time of diagnosis. As such, predictors of DSS were limited to only patients ≥45 years of age. No LN characteristics—size, number, burden, or presence of ENS—were predictive of DSS (Supplementary Table 1).

Table 1| LN characteristics predictors of 5-year recurrence-free survival in patients <45 years of age

Characteristic	5 year RFS (%)	*p*	HR (95 % CI)	*p*
No. of positive LNs				
≤5 nodes	92.0		–	–
>5 nodes	87.1	0.46	1.3 (0.6–2.6)	0.46
≤6 nodes	91.8		–	–
>6 nodes	86.1	0.26	1.5 (0.7–3.1)	0.27
≤10 nodes	91.7		–	–
>10 nodes	81.1	0.05	2.2 (1.0–4.8)	0.05
Largest LN size (cm)				
≤1	94.1		–	–
>1	89.4	0.54	0.7 (0.2–2.1)	0.54
≤2	93.3		–	–
>2	87.1	0.68	1.19 (0.5–2.7)	0.68
≤3	93.0		–	–
>3	79.4	0.22	1.7 (0.7–4.2)	0.22
LN burden (%)				
≤17	99.1		–	–
>17	81.2	<0.001	4.8 (2.0–11.9)	0.001
Extranodal spread				
None	91.1		–	–
Yes	92.7	0.99	1.0 (0.3–3.3)	0.99

LN lymph node, *HR* hazard ratio, *CI* confidence interval

LN Characteristics Predictive of RFS

Factors predictive of RFS in patients <45 years of age are shown in Table 1. Number of positive nodes >10 (5-year RFS 81.0 vs. 91.7 %, $p = 0.05$) and a LN burden >17 % (5-year RFS 81.2 vs. 99.1 %, $p < 0.001$) were predictive of recurrence on Kaplan–Meier analysis (Fig. 2a, b). Increasing LN size was associated with poorer RFS, but this was not statistically significant (5-year RFS 79.4 vs. 93.0 %, $p = 0.20$ for size >3 cm). LN ENS was not predictive of recurrence (Fig. 2c). Using the Cox proportional hazard model, we found that patients with >10 positive nodes were 2.2 times more likely to experience recurrence. Patients with a LN burden >17 % were 4.8 times more likely to experience recurrence compared to patients with a ≤17 % LN burden ($p < 0.001$).

Table 2 shows factors predictive of recurrence in patients ≥45 years of age. Number of positive nodes >10 (5-year RFS 71.8 vs. 87.3 %, $p = 0.02$) and a LN burden >17 % (5-year RFS 77.7 vs. 90.5 %, $p = 0.02$) were also predictive of recurrence (Fig. 3a, b). Patients with >10 positive nodes were 3.1 times more likely to experience recurrence ($p = 0.03$). Patients with a LN burden >17 % were 2.7 times more likely to experience recurrence compared to patients with <17 % LN burden ($p = 0.02$). Increasing LN size was not significant. In addition, the presence of ENS was also significant in the older patients (5-year RFS 79.5 vs. 93.0 % $p = 0.03$) (Fig. 3c). Patients with ENS were 3.4 times more likely to experience recurrence compared to patients with no ENS ($p = 0.04$).

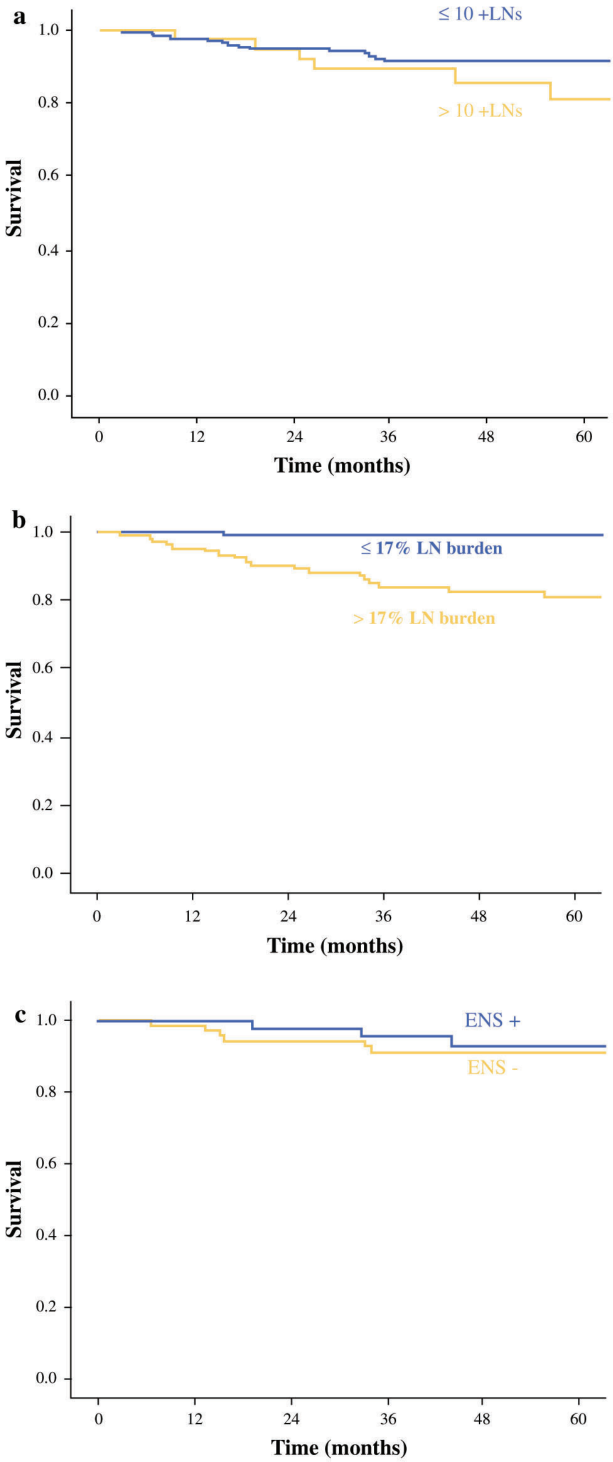

Figure 2 | Kaplan–Meier graph for RFS for patients <45 years old based on **a** number of positive LNs ($p = 0.05$), **b** LN burden ($p < 0.001$), and **c** ENS ($p = 0.99$)

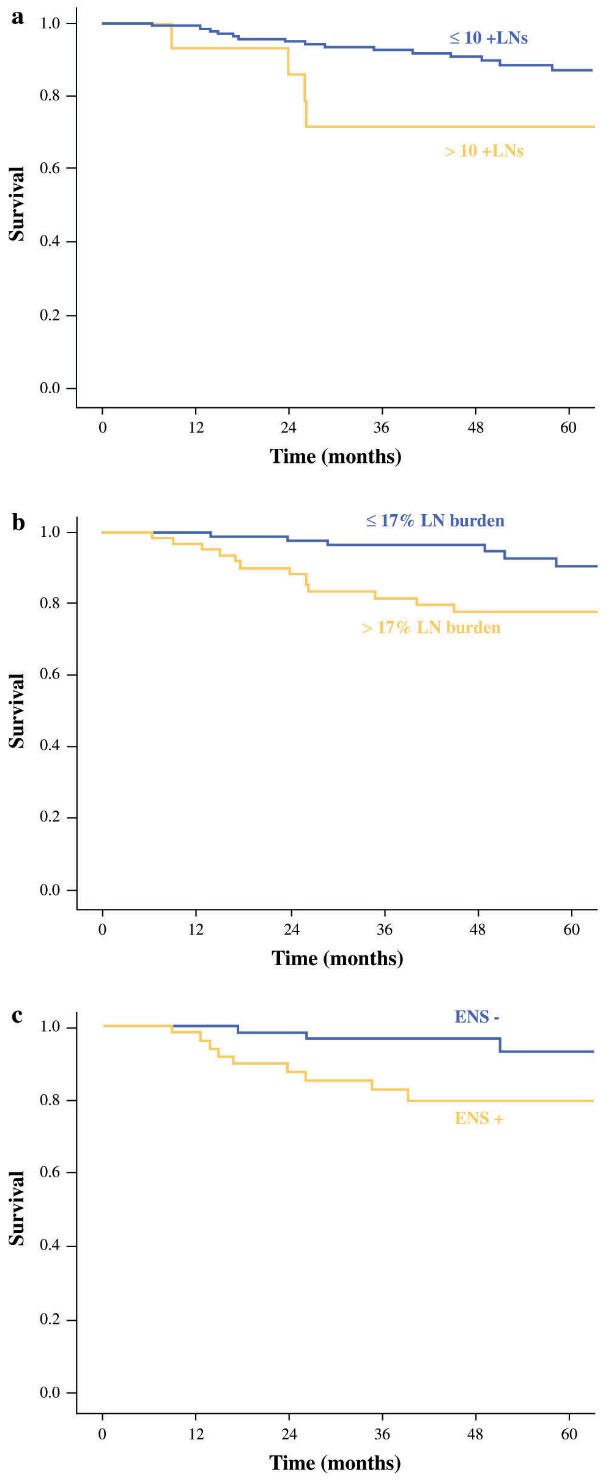

Figure 3 | Kaplan–Meier graph for RFS for patients ≥45 years old based on **a** number of positive LNs ($p = 0.02$), **b** LN burden ($p = 0.02$), and **c** ENS ($p = 0.03$)

Table 2 | LN characteristics predictors of 5-year RFS in patients ≥45 years of age

Characteristic	5 year RFS (%)	*p*	HR (95 % CI)	*p*
No. of positive LNs				
≤5 nodes	87.7		–	–
>5 nodes	81.2	0.16	1.81 (0.8–4.2)	0.17
≤6 nodes	87.5		–	–
>6 nodes	80.8	0.19	1.77 (0.7–4.2)	0.20
≤10 nodes	87.4		–	–
>10 nodes	71.8	0.02	3.10 (1.5–8.4)	0.03
Largest LN size (cm)				
≤1	80.0		–	–
>1	86.5	0.84	1.2 (0.2–9.2)	0.84
≤2	88.3		–	–
>2	84.6	0.72	1.2 (0.5–2.8)	0.72
≤3	87.1		–	–
>3	83.1	0.75	0.8 (0.3–2.5)	0.75
LN burden (%)				
≤17	90.5		–	–
>17	77.7	0.02	2.70 (1.1–6.4)	0.02
Extranodal spread				
None	93.0		–	–
Yes	74.2	0.03	3.38 (1.1–10.7)	0.04

LN lymph node, *RFS* recurrence-free survival, *HR* hazard ratio, *CI* confidence interval

A total of 30 patients (6.8 %) developed distant metastases, 21 of whom were ≥45 years old at the time of initial diagnosis. Univariate predictors of distant recurrence were >10 positive lateral neck LNs (5-year distant RFS 87.2 vs. 94.5 %, $p = 0.01$) and LN burden >17 % (5-year distant RFS 89.8 vs. 96.4 %, $p = 0.01$). Presence of ENS was associated with a poorer distant RFS, but this was not statistically significant (5-year distant RFS 96.0 vs. 92.6 %, $p = 0.08$).

Discussion

Metastatic disease in the lateral compartment LNs of the neck in patients with PTC is known to be predictive of poorer outcomes, particularly in older PTC patients, and as such, it is recognized by the current edition of the AJCC staging manual.[4,11] Recent data suggest that in addition to LN location, LN characteristics such as maximal size, number, ratio, and ENS are also prognostic.[5–10] Age at diagnosis is uniquely critical in the staging of differentiated thyroid cancer, and in this series of 438 PTC patients with lateral neck disease, we report LN characteristics that are predictive of outcome in two age cohorts of patients, those <45 years old and those ≥45 years old. In both age groups, both number of positive LNs >10 and LN burden >17 % (which equated to 1 positive node per 6 removed) were predictive for recurrence. In addition, the presence of ENS was predictive of recurrence in patients ≥45 years old. Size of LNs did not appear to be predictive in our cohort of patients.

Many studies have reported the size of the metastatic lateral neck LN to be prognostic in PTC. Studies have suggested that LN metastases >3 cm are associated with poorer prognosis.[9,12] In a study of LN characteristics by Ito et al., N1b patients with metastatic nodes >3 cm were found to have a significantly poorer RFS compared to N1a patients.[12] In a study of both central and lateral LNs by Sugitani et al., it was found that LN metastases >3 cm were predictive of DSS in patients aged ≥50 years but not in patients aged <50 years at the time of diagnosis.[9] These results suggest that the size of lateral neck LN is likely to be prognostic in PTC, particularly in older patients. In the present study, no discrete size cutoff was statistically associated with poorer prognosis in either age cohort. However, the data suggest that larger LN metastases are associated with poorer RFS; patients with LNs measuring <1 cm had a 5-year RFS of 91.2 % compared to those with LN >3 cm, who had a 5-year RFS of just 80.9 %.

Several groups have also investigated the prognostic impact of the number of positive lateral compartment LNs. Studies have reported a wide range of LNs considered to be prognostic, ranging from 2 to >10 positive LNs, when looking at the number of LNs within the central and lateral compartments.[7,8] When focusing only on LN metastases within the lateral compartment, Ito et al. reported that >5 positive lateral neck LNs affected RFS.[12] Moreno et al. similarly focused on the lateral neck LNs features and observed that the number of abnormal neck compartments on ultrasound, as an indirect marker of the number of positive LNs, correlated with the risk of regional recurrence.[13] In our own cohort, receiver operating characteristic analysis suggested that 10 positive nodes was the cutoff that maximized sensitivity and specificity. Indeed, >10 nodes was predictive of recurrence. Interestingly, the previously reported cutoffs of >5 positive nodes was not prognostic in our series.

LN burden is defined as the number of metastatic LNs divided by the total number of LNs resected, expressed as a percentage. Because LN burden is the percentage of positive to total LNs resected, the two are closely correlated. However, LN burden additionally takes into consideration the extent of surgical resection as well as the extent and aggressiveness of disease. LN burden has been found to be a significant predictor of outcome in other cancers, including oral and cutaneous squamous cell carcinoma of the head and neck.[14–19] Within the thyroid cancer literature, the prognostic impact of lateral LN burden has not been well explored. Several publications have previously investigated the significance of LN burden in the central compartment alone and within the central and lateral compartments combined. Beal et al. analyzed data from the Surveillance, Epidemiology, and End Results database to identify 9,926 patients with primary, well-differentiated, M0 thyroid cancer.[20] Increasing LN burden was associated with decreased survival on multivariate analysis in all primary thyroidectomy patients. Others have observed central compartment LN burden to be predictive of postoperative thyroglobulin levels as well as recurrence.[5,6] Our study specifically focuses on the prognostic significance of lateral compartment LN characteristics. Our data show that younger patients with LN burden >17 % were 4.8 times ($p < 0.001$) and older patients 2.7 times ($p < 0.02$) more likely to develop disease recurrence.

With regard to ENS, we have noted that ENS was the LN characteristic most prognostic of nodal recurrence within the central neck compartment.[21] In the current study on lateral neck LN metastases, we observed that ENS is predictive of RFS specifically in patients ≥45 years of age. ENS was similarly distributed between the older (41.3 %) and younger (39.4 %) cohorts ($p = 0.755$). However, in older patients, the presence of lateral nodal ENS was associated with higher T4 disease ($p < 0.001$) as well as ATA high-risk category ($p < 0.001$) (data not shown). Lee et al. similarly found ENS to be associated with large tumor size.[22] Others have reported similar findings; Ito et al. concluded that the presence of lateral compartment ENS was independently prognostic of DSS in patients aged ≥55 years.[12] ENS is a known indicator of aggressive tumor biology in other head and neck cancers.[23,24] Its importance in relation to older age is a unique finding and requires further research.

Some limitations of this study warrant discussion. This is a retrospectively conducted study and therefore susceptible to limitations associated with such studies. First, our institutional policy is to perform lateral neck dissection only for patients with clinical or radiologic evidence of neck disease. This cohort therefore does not include subclinical disease. However, it can be argued that it is the higher-risk, clinically evident N1b patients who are of most relevance. Second, the extent of lateral neck dissection is surgeon dependent, and the identification of LN characteristics is pathologist dependent. Both of these physician factors may bias the reported LN characteristics. Last, only 224 (51.1 %) of our patients had all LN features available on histopathology for data collection and analysis. This could limit our analysis. To ensure there was no selection bias by excluding patients without all characteristics, we compared the clinical and tumor characteristics of patients with variables reported and those without. For LN size, number, and ENS, we found no significant differences in terms of age, T stage, adjuvant therapy, or duration of follow-up between groups with these variables reported and not reported (data not shown). Nevertheless, it would be desirable to have complete data on all these LN variables on all patients. As such, future studies with larger sample size and complete synoptic reporting are required to validate our findings.

In summary, our data suggest that the presence of LN burden >17 % is predictive for overall recurrence and development of distant metastases in both patient age cohorts, <45 and ≥45 years of age. In patients ≥45 years, the presence of ENS is also predictive of recurrence.

DISCLOSURE The authors declare no conflict of interest.

References

1. Shaha AR, Loree TR, Shah JP. Intermediate-risk group for differentiated carcinoma of thyroid. *Surgery*. 1994;116:1036–40.
2. Hay ID, Bergstralh EJ, Goellner JR, Ebersold JR, Grant CS. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. *Surgery*. 1993;114:1050–7.
3. Cady B, Rossi R. An expanded view of risk-group definition in differentiated thyroid carcinoma. *Surgery*. 1988;104:947–53.
4. Sobin LH, Gospodarowicz MK, Wittekind CW. TNM classification of malignant tumours. 7th ed. New York: Wiley-Blackwell; 2009.
5. Lang BHH, Wong KP, Wan KY, Lo CY. Significance of metastatic lymph node ratio on stimulated thyroglobulin levels in papillary thyroid carcinoma after prophylactic unilateral central neck dissection. *Ann Surg Oncol*. 2012;19:1257–63.
6. Jeon M, Yoon J, Han J, et al. The prognostic value of the metastatic lymph node ratio and maximal metastatic tumor size in pathological N1a papillary thyroid carcinoma. *Eur J Endocrinol*. 2013;168:219–25.
7. Leboulleux S, Rubino C, Baudin E, et al. Prognostic factors for persistent or recurrent disease of papillary thyroid carcinoma with neck lymph node metastases and/or tumor extension beyond the thyroid capsule at initial diagnosis. *J Clin Endocrinol Metab*. 2005;90:5723–9.
8. Lee J, Song Y, Soh E. Prognostic significance of the number of metastatic lymph nodes to stratify the risk of recurrence. *World J Surg*. 2013;4:4.
9. Sugitani I, Kasai N, Fujimoto Y, Yanagisawa A. A novel classification system for patients with PTC: addition of the new variables of large (3 cm or greater) nodal metastases and reclassification during the follow-up period. *Surgery*. 2004;135:139–48.
10. Ito Y, Jikuzono T, Higashiyama T, et al. Clinical significance of lymph node metastasis of thyroid papillary carcinoma located in one lobe. *World J Surg*. 2006;30:1821–8.
11. Nixon I, Wang L, Palmer F, et al. The impact of nodal status on outcome in older patients with papillary thyroid cancer. *Surgery*. 2014;156:137–46.
12. Ito Y, Fukushima M, Tomoda C, et al. Prognosis of patients with papillary thyroid carcinoma having clinically apparent metastasis to the lateral compartment. *Endocr J*. 2009;56:759–66.
13. Moreno MA, Agarwal G, de Luna R, et al. Preoperative lateral neck ultrasonography as a long-term outcome predictor in papillary thyroid cancer. *Arch Otolaryngol Head Neck Surg*. 2011;137:157–62.
14. Marchet A, Mocellin S, Ambrosi A, et al. The ratio between metastatic and examined lymph nodes (N ratio) is an independent prognostic factor in gastric cancer regardless of the type of lymphadenectomy: results from an Italian multicentric study in 1853 patients. *Ann Surg*. 2007;245:543–52.
15. Dekker J, Peeters K, Putter H, Vahrmeijer A, van de Velde C. Metastatic lymph node ratio in stage III rectal cancer; prognostic significance in addition to the 7th edition of the TNM classification. *Eur J Surg Oncol*. 2010;36:1180–6.
16. Berger A, Watson J, Ross E, Hoffman J. The metastatic/examined lymph node ratio is an important prognostic factor after pancreaticoduodenectomy for pancreatic adenocarcinoma. *Am Surg*. 2004;70:235–40.
17. Woodward W, Vinh-Hung V, Ueno N, et al. Prognostic value of nodal ratios in node-positive breast cancer. *J Clin Oncol*. 2006;24:2910–6.
18. Gil Z, Carlson D, Boyle J, et al. Lymph node density is a significant predictor of outcome in patients with oral cancer. *Cancer*. 2009;115:5700–10.
19. Mizrachi A, Hadar T, Rabinovics N, et al. Prognostic significance of nodal ratio in cutaneous squamous cell carcinoma of the head and neck. *Eur Arch Otorhinolaryngol*. 2013;270:647–53.
20. Beal S, Chen S, Schneider P, Martinez S. An evaluation of lymph node yield and lymph node ratio in well-differentiated thyroid carcinoma. *Am Surg*. 2010;76:28–32.
21. Wang L, Palmer F, Nixon I, et al. Central lymph node characteristics predictive of outcome in patients with differentiated thyroid cancer. *Thyroid*. 2014;30:30.
22. Lee Y, Lim Y, Lee J, et al. Nodal status of central lymph nodes as a negative prognostic factor for papillary thyroid carcinoma. *J Surg Oncol*. 2013;107:777–82.
23. Carter R, Bliss J, Soo K, O'Brien C. Radical neck dissections for squamous carcinomas: pathological findings and their clinical implications with particular reference to transcapsular spread. *Int J Radiat Oncol Biol Phys*. 1987;13:825–32.
24. Johnson J, Myers E, Bedetti C, Barnes E, Schramm VJ, Thearle P. Cervical lymph node metastases. Incidence and implications of extracapsular carcinoma. *Arch Otolaryngol*. 1985;111:534–7.

Chapter 7

The Impact of Nodal Stage on Outcome in Older Patients with Papillary Thyroid Cancer

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Abstract

Background

The impact of clinically or radiologically detected nodal metastases on survival inpatients with papillary thyroid cancer (PTC) is controversial but seems more important and relevant in older patients. The objective of this study was to determine the impact of clinically or radiologically detected nodal metastases on outcome in patients 45 years of age or older.

Methods

Retrospective analysis of 834 patients 45 years or older who underwent operation for PTC between 1986 and 2005.

Results

With a median follow up of 77 months, the 5 year disease-specific survival (DSS) and recurrence-free survival (RFS) were 99% and 94%, respectively. Patients with clinically N+ nodes with pathologic confirmation were stratified into pN0/Nx, pN1a, and pN1b, respectively. Five-year DSS was 100%, 100%, and 91% for pN0/Nx, pN1a, and pN1b disease; $P < .001$. Patients with pN1b disease had poorer distant RFS compared with pN0/Nx and pN1a patients (84%, 99%, and 99%; $P < .001$). The presence of pN1b disease was an independent predictor of worse DSS and distant RFS on multivariate analysis, conferring a 10-fold increased risk of distant metastases and death. All cause-specific deaths were due to distant metastases.

Conclusion

Older patients with PTC and N1b disease at presentation have poorer DSS compared with patients with pN0/Nx or N1a disease. The cause of death in these patients is due to distant metastases rather than locoregional recurrence. (Surgery 2014;156:137-46.)

Many risk-stratification systems (GAMES[1]/MACIS[2]/AMES[3]) have been developed for patients with papillary thyroid cancer (PTC). All recognize the importance of age and the presence of distant metastases. Primary tumor factors, such as size, the presence of extra thyroid extension, and aggressive histologic features, also are recognized, but the presence of nodal metastases generally are not. The impact of nodal metastases on survival is thus not considered an independent factor impacting on prognosis, although nodal metatstases often appear to have prognostic importance in older patients.[4,5] This recognition of nodal status is now reflected in the current tumor-node-metatstasis (TNM) staging system categorizing patients older than 45 years of age as stage IV if they have N1b disease and stage III if they have N1a disease. We have previously published matched pair analysis data demonstrating that older patients presenting with lateral neck disease had a decreased 20-year survival compared with patients with no nodal disease,[4] but these findings did not reach clinical importance.[4] The objective of this current study was to analyze the impact of clinically evident neck metastases on outcome in patients 45 years of age or older in a larger and more recent cohort of patients.

Patients and Methods

After approval by the institutional review board, records of 834 consecutive patients who were 45 years or older at the time of operation for PTC between 1986 and 2005 were identified from our institutional database. All patients were treated by 1 of 14 surgeons in our institution with an interest and training in thyroid surgery. We excluded patients who underwent initial treatment elsewhere before referral and those presenting with evidence of distant metastasis at presentation or on postoperative radioactive iodine (RAI) scan within 6 months.

Data collected included patient demographics and operative details, including the presence of gross extrathyroid extension. Histopathologic details recorded included tumor histology, primary tumor size, presence of extra-thyroid extension, and presence of metastatic lymph nodes. TNM/Union for International Cancer Control was defined as recommended by the American Joint Committee on Cancer Staging Manual 2010.[6] N status was defined as pN0 if nodes were removed and found to be benign on pathology or if no nodes were suspicious on palpation during operation and, therefore, not removed (Nx). pN1a was defined as pathologically positive metastatic nodes removed from the central compartment (level VI), and pN1b was defined as pathologically positive metastatic nodes removed from the lateral neck (Levels I–V) or from the superior mediastinum (Level VII). Postoperative treatment details recorded were use of RAI or external radiotherapy.

On the basis of clinical and histopathologic features, cases were classified into low-, intermediate-, and high-risk groups for death based on the previously published Memorial Sloan Kettering Cancer Center risk-stratification system.[1] Low-risk patients are younger than 45 years and have low risk disease (T1/2 M0), high-risk patients are ≥45 years with high risk disease (T3/4 or M+), and intermediate-risk patients comprise older patients with low-risk disease or younger patients with high-risk disease.

Patients were also assigned a risk according to the system published by the American Thyroid Association.[7] This system considers patients at low risk of recurrence if the patient is considered disease-free and without evidence of extra thyroid extension after initial therapy, at intermediate risk if regional metastases are detected or if there is microscopic extra thyroid extension or aggressive pathology, and high risk if patients have gross extra thyroid extension, incomplete tumor excision, or distant metastases.

In the cohort of patients from 1986 to 2005, preoperative ultrasonography was not used routinely for the assessment of the central and lateral compartment lymph nodes. The assessment of the lateral neck nodes was based on preoperative clinical examination and, if enlarged, ultrasonography or other imaging studies such as computed tomography were carried out in some patients. Assessment of the central compartment for all patients was intraoperative by palpation of the central compartment lymph nodes at the time of thyroidectomy. If no palpable nodes were present in the central compartment, then central compartment neck dissection was not done. If nodes were palpable, then a therapeutic, compartment-oriented neck dissection was preformed. In the cases of a central neck dissection, nodal tissue was cleared from carotid to carotid and from the level of the hyoid to the innominate vein. In lateral nodal disease, levels II-V were dissected with preservation of the internal jugular vein, accessory nerve, and sternomastoid muscle where possible. Postoperative suppression of thyroid-stimulating hormone was practiced for all patients based on risk, aiming for a level of between 0.1 and 0.5 μU/mL.

Outcomes data included local, regional, and distant recurrence as well as details of death. Local and regional recurrences were determined by clinical examination supplemented with imaging and fine-needle aspiration if recurrence was suspected. Locoregional recurrence was only recorded if proven with cytologic or histologic evidence. Local recurrence was defined as recurrence within the operated thyroid bed. Regional recurrence was defined as recurrence within the regional lymph nodes. Distant recurrence was determined by imaging studies including radioiodine uptake scans, computed tomography, positron emission tomography, or cytological and histopathologic evidence where available. From 1985 to 2000, serum thyroglobulin was not routinely used to detect recurrence. Similarly, annual ultrasonography was not used uniformly as a tool for detection of recurrent disease during the majority of the study period. Both the use of thyroglobulin monitoring and serial ultrasonography have become standard practice within our institution, however, since 2005 and now influence the further investigation of patients within this cohort.

Disease-specific survival (DSS) was calculated using the date of last follow up with the treating surgeon or endocrinologist at Memorial Sloan Kettering Cancer Center. Details of death were determined from death certificates and hospital records where available. All patients who had evidence of active structural disease at the time of last follow-up and died during follow up were considered to have died of disease. The median follow-up for the entire patient cohort was 77 months (range, 1–320 months). Outcomes data were therefore calculated at 5 years.

Statistical analysis was performed using the JMP statistical package (SAS Institute Inc, Cary, NC) and SPSS (IBM Company Headquarters, Chicago, IL). Variables were compared within groups using the Pearson's χ^2 test. Survival outcomes were analyzed using the Kaplan-Meier method. Univariate analysis was carried out by the log rank test and multivariate analysis by Cox proportional hazards method.

Results

The median age of the cohort was 57 years (range, 45–91 years), and 589 were female (71%). A total of 421 patients were pT1 (50%), 109 pT2 (13%), 231 pT3 (28%), and 72 (9%) pT4. Two hundred sixty-six patients were pT1a, and 155 were pT1b. Six hundred and five patients (73%) were pN0/Nx, 229 (27%) were pN1 (99 pN1a and 130 pN1b). The demographics of the overall cohort were stratified by pN status are shown in Table I. The presence of pN1 disease was significantly associated with male sex, larger tumors and the presence of extra thyroid extension. Three hundred seventy-three patients (45%) received RAI; 99 of 130 N1b (76%), 76 of 99 N1a (77%), and 198 of 605 N0/Nx patients (33%).

Table I | Comparison of group by pN stage

	Total (%),* n = *834	***pN0/Nx (%),* n = *605***	***pN1a (%),* n = *99***	***pN1b (%),* n = *130***	**P *value***
Sex					
Female	589 (71)	461 (76)	65 (66)	63 (48)	<.001
Male	245 (29)	144 (24)	34 (34)	67 (52)	
Tumor size, cm					
<4	764 (92)	566 (94)	88 (89)	110 (87)	.013
≥4	66 (8)	38 (6)	11 (11)	17 (13)	
ETE					
No gross ETE	719 (86)	558 (92)	67 (68)	94 (72)	<.001
Gross ETE	115 (14)	47 (8)	32 (32)	36 (28)	
pT status					
pT1	421 (50)	364 (60)	21 (21)	36 (28)	<.001
pT1a	266 (32)	229 (38)	11 (11)	26 (20)	
pT1b	155 (18)	135 (22)	10 (10)	10 (8)	
pT2	108 (13)	90 (15)	12 (12)	6 (5)	
pT3	231 (28)	129 (21)	46 (47)	56 (43)	
pT4	72 (8)	21 (4)	20 (20)	31 (24)	
pT4a	69 (8)	20 (3)	19 (19)	30 (23)	
pT4b	1 (1)	1 (1)	1 (1)	1 (1)	
AJCC stage[10]					
I	364 (44)	364 (60)	0 (0)	0 (0)	<.001
II	90 (11)	90 (15)	0 (0)	0 (0)	
III	208 (25)	129 (21)	79 (80)	0 (0)	
IV	171 (20)	21 (4)	20 (20)	130 (100)	
IVa	167 (20)	20 (3)	19 (19)	128 (99)	
IVb	1 (<1)	1 (1)	1 (1)	1 (1)	
GAMES risk group[1]					
Low	0 (0)	0 (0)	0 (0)	0 (0)	<.001
Int	537 (64)	456 (75)	35 (35)	46 (35)	
High	297 (36)	149 (25)	64 (65)	84 (65)	
ATA risk group[13]					
Low	451 (54)	451 (75)	0 (0)	0 (0)	<.001
Intermediate	267 (32)	106 (17)	67 (68)	94 (72)	
High	116 (14)	48 (8)	32 (32)	36 (28)	

AJCC, American Joint Committee on Cancer; *ATA*, American Thyroid Association; *ETE*, extrathyroid extension.

Survival

The median follow-up of the cohort was 77 months (range, 1–320 months). Five hundred ninety-five patients (71%) had a minimum of 5 years' follow-up, and 207 (25%) had at least 10 years of follow-up. The 5 year DSS was 99%. There were 20 disease-specific deaths. When stratified by N status, 5-year DSS was 100%, 100%, and 91% for pN0/Nx, N1a, and N1b disease, respectively, $P < .001$ (Table II, Fig 1). Factors predictive of DSS on univariate and multivariate analysis are shown in Table II. Tumor size, extrathyroid extension (ETE), nodal status, pT status, and overall AJCC stage were predictive for worse outcome. The low number of disease-specific deaths in our cohort limited the number of variables we could include in our multivariate models. Not surprisingly, analysis showed gross ETE was independently predictive of poorer survival, conferring a 4-fold risk of death. Our data also demonstrated that the presence of pN1b disease was independently predictive of poorer survival, conferring a greater than 10fold risk of death. The DSS for N1b at 5 years was 91% compared with a DSS of 100% for pN0/ Nx and N1a patients. ($P < .001$). Thus, in our cohort all patients dying with disease presented with N1b disease at presentation.

Table II | Factors predictive of DSS

	5-yr DSS	*Univariate* **P** *value*	*Multivariate*		
			HR	**95% *CI***	**P *value***
Sex					
Female	99%	.062			
Male	98%				
Tumor size, cm					
≤4	99%	<.001*			
>4	92%				
ETE					
No gross ETE	99%	<.001*	Referent		
Gross ETE	93%		4.264	1.727–10.562	.002*
Nodal status					
pN0/Nx	100%	<.001*	Referent		
pN1a	100%				
N1b	91%		10.195	3.607–28.814	<.001*
pT1	99.7%	<.001*			
pT1a	99.5%				
pT1b	100%				
pT status					
pT2	100%				
pT3	98%				
pT4	91%				
pT4a	90%				
pT4b	100%				
AJCC stage[10]					
I	100%	<.001*			
II	100%				
III	100%				
IV	93%				
IVa	93%				
IVb	100%				

*Statistically significant.

CI, Confidence interval; *DSS*, disease-specific survival; *ETE*, extrathyroid extension; *HR*, hazard ratio.

Recurrence

Local. Only three patients in our cohort developed local recurrence. All patients had excellent local recurrence-free survival (RFS) irrespective of nodal status at presentation (100%, 99%, and 99%, $P < .001$ for pN0/Nx, N1a, and N1b, respectively Fig 2). Only 14 patients in our cohort received postoperative radiotherapy to the neck; 6 of 130 N1b, 4 of 99 N1a, and 4 of 605 N0/Nx patients. Therefore, excellent local control was not related to the use of postoperative radiotherapy.

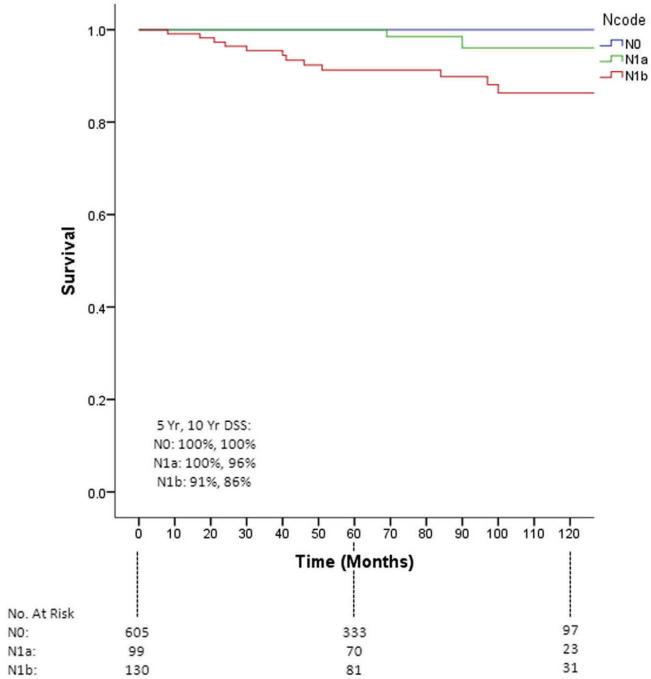

Figure 1| DFS stratified by N stage.

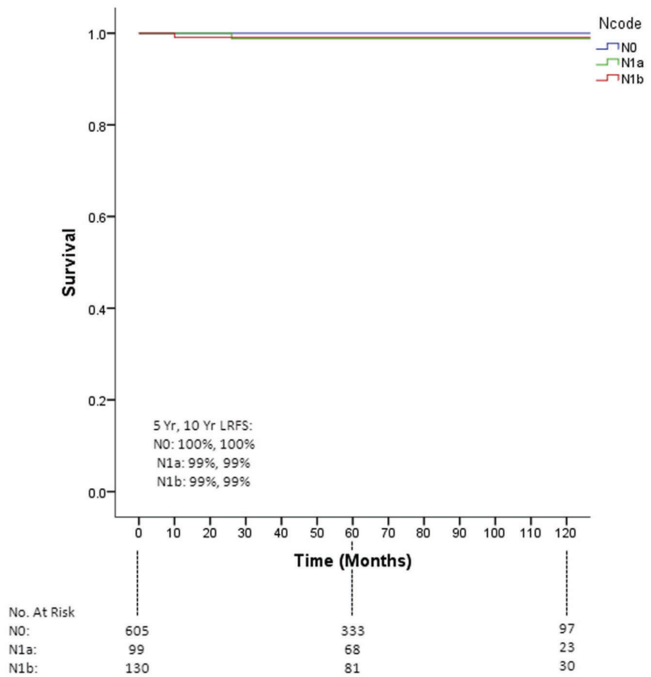

Figure 2 | Local RFS stratified by N stage.

Regional

Table III shows 5-year regional RFS. In our cohort, 35 patients developed regional recurrences. The regional RFS stratified by N status showed patients with N1b disease had a decreased incidence of regional RFS compared with pN0/Nx patients (99%, 93%, and 90%, *P* < .001 for pN0/ Nx, pN1a and pN1b; Fig 3). Multivariate analysis of gross ETE and pN status showed that both were independent predictors of regional recurrence conferring a 4.5x and 4.2x risk of recurrence.

Table III | 5-year regional RFS

	5-year regional RFS	Univariate *P* value	Multivariate		
			HR	95% CI	*P* value
Sex					
Female	97%	.014*			
Male	95%				
Tumor size, cm					
≤4	97%	.199			
>4	94%				
ETE					
No gross ETE	98%	<.001*	Referent		
Gross ETE	88%		4.481	2.228–9.013	.002*
pT status					
pT1	99%	<.001*			
pT1a	99%				
pT1b	98%				
pT2	100%				
pT3	94%				
pT4	84%				
pT4a	93%				
pT4b	100%				
N status					
pN0/Nx	99%	<.001*	Referent		
N1a	93%		2.523	0.981–6.494	.055
N1b	90%		4.160	1.865–9.278	<.001*

*Statistically significant.

CI, Confidence interval; *ETE*, extrathyroid extension; *HR*, hazard ratio; *RFS*, recurrence-free survival.

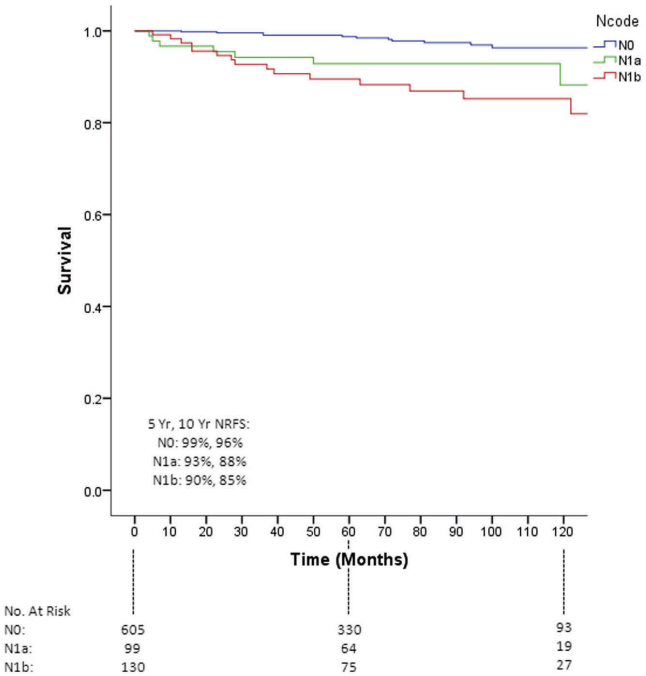

Figure 3 | Regional RFS stratified by N stage.

Distant

The 5-year distant RFS for our cohort is shown in Table IV. There were 32 distant recurrences identified more than 6 months after initial therapy. The distant RFS stratified by N status showed patients with N1b disease had a decreased incidence of distant RFS compared with pN0/Nx patients (99%, 99%, and 84%, $P < .001$ for pN0/Nx, pN1a, and pN1b; Fig 4). Multivariate analysis of ETE and pN status showed that both were independent predictors of distant recurrence. Gross ETE conferred a 3.6x risk of distant recurrence. In comparison with pN0/Nx, N1b conferred a 10.5x risk of distant recurrence.

Table IV | 5-year distant recurrence-free survival

	5-year distant RFS	Univariate *P* value	HR	Multivariate 95% CI	*P* value
Sex					
Female	98%	.003*			
Male	94%				
Tumor size, cm					
≤4	98%	<.001*			
>4	87%				
ETE					
No gross ETE	98%	<.001*	Referent		
Gross ETE	90%		3.619	1.765–7.418	<.001*
pT status					
pT1	99%	<.001*			
pT1a	99.5%				
pT1b	97%				
pT2	100%				
pT3	95%				

	5-year distant RFS	Univariate *P* value	HR	Multivariate 95% CI	*P* value
pT4	88%				
pT4a	87%				
pT4b	100%				
N Status					
pN0/Nx	99%	<.001*	Referent		
N1a	99%		3.506	1.097–11.205	.034*
N1b	84%		10.481	4.091–26.852	<.001*

*Statistically significant.

CI, Confidence interval; *ETE*, extrathyroid extension; *HR*, hazard ratio; *RFS*, recurrence-free survival.

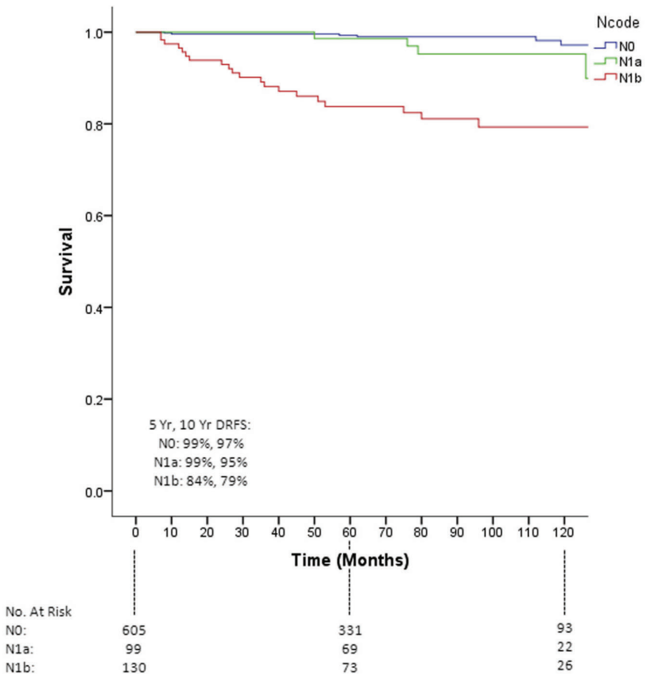

Figure 4 | Distant RFS (DRFS) stratified by N stage.

Cause of death

There were 20 disease-specific deaths. Of these patients, 12 had pulmonary metastasis alone, 2 had extrapulmonary distant metastases alone, and 6 had distant metastases with locoregional recurrence at the time of death. All 20 patients had N1b disease at presentation. No patients died of uncontrolled locoregional recurrence. Thus, all disease-specific deaths were associated with distant metastases.

Discussion

Nodal disease is not considered as a prognostic factor in many of the major prognostic scoring systems (eg, GAMES[1]/MACIS[2]/AMES[3]) designed to predict the risk of death in patients with PTC. Some published risk stratifications, including work from the Ohio State University[8] and the National Treatment Co-opertation Study Registry Group,[9] however, do recognize lymph node status as a predictive factor. The current TNM staging system does categorize patients older than 45 years of age as stage IV if they have N1b disease and stage III if they have N1a disease. Although the impact of nodal metastases on outcome has been debated in younger patients, its impact in older patients is becoming clearer. As a greater number of older patients are seen presenting with PTC, understanding factors that predict outcome in this group is more important than ever.

The overall impact of nodal metastases on survival in PTC is controversial. Early work suggested that the presence of regional metastases was in fact protective.[10,11] However, as our understanding of the disease evolved, clinicians came to recognize that this may have been related to the greater rates of metastatic lymph nodes in younger patients. The difference in impact of nodal disease in older patients was demonstrated in earlier work from our institution4 and in work from Japan.[12] This finding was again observed when Zaydfudim et al[13] analyzed outcomes from the Surveillance, Epidemiology, and End Results database in 2008 and is reflected in the current AJCC staging system.[6] Our findings reported in the present study further corroborate that patients older than 45 year of age presenting with lateral neck disease at presentation have poorer DSS at 5 years compared with patients with no lateral neck disease (99% vs 100%; $P < .001$). Interestingly, patients with central compartment nodal metastases had no adverse impact on DSS.

The impact of nodal disease on recurrence has been well documented. Factors including the number of metastatic lymph nodes, their size, and the presence of extra nodal extension have all been reported to predict recurrence.[7,14,15] When neck dissection specimens are analyzed, those patients with lateral nodal metastases (pN1b) and those with multiple positive nodes have been shown to be at greater risk of recurrence.[16-19] This information can be used, not only to identify those at greater risk but also to identify patients with small volume nodal disease who are at very low risk for recurrence.[20] This is particularly true when prophylactic nodal dissection is performed, as recognized by the American Thyroid Association in 2012.[21]

Consistent with published literature, our results show that nodal disease is related to more aggressive features of the primary tumor, including size and ETE. When analyzed in a multivariate model, the presence of lateral neck disease (pN1b) was found to be an independent predictor of regional and distant recurrence. Those patients without evidence of nodal metastases (pN0/Nx) had a regional and distant RFS of 99% and 99% compared with 90% and 84% at 5 years for those with lateral neck metastases (pN1b). Although central compartment nodal metastases did not impact on DSS in our study, it did decrease the regional RFS to 93%, compared with 99% for patients who were N0/Nx.

In contrast to other groups, our results also confirm the impact of nodal status on survival. When analyzed in a multivariate model, the presence of lateral neck disease (pN1b) was also found to be the most powerful independent predictor of DSS, conferring a greater than 10-fold risk of death. These results confirm our previously published findings[4] that the presence of clinically evident nodal metastases in older patients impacts not only recurrence but also survival. These older patients with advanced loco-regional disease should be considered high risk and treated accordingly.

As an institution, our departmental policy is not to perform prophylactic central or lateral neck dissections. Therefore, the nodes excised in this current study represent only clinically or radiologically apparent metastases. When we examine the 605 patients who did not have clinically apparent metastases (pN0/Nx), these patients all had excellent outcomes. Therefore, the concept that additional neck surgery performed prophylactically to identify occult disease would improve either survival (5-year DSS 100%) or recurrence (5-year RFS 98%) is questionable. This finding is in keeping with findings from analysis of the Surveillance, Epidemiology, and End Results database, which confirm that even in patients considered N0, potential nodal under staging is inconsequential to survival in PTC.[22]

One of the major findings of our study was that despite the advanced loco-regional disease of these patients at presentation, the cause of death was not uncontrolled loco-regional disease. All of our disease-specific deaths were attributable to distant metastases. Thus, the presence of N1b disease in older patients represents a surrogate indicator for future distant metastases and poorer survival. It is likely that patients with N1b disease who die of disease will have neoplasms with a different genomic profile compared with those who do not die. Hence, future research should be directed toward studying the genomic landscape of these patients. These studies may result in the identification of new targets for therapy for patients with N1b disease at risk of death.

Another important finding from our study is that the DSS and distant RFS of N1a patients are similar to those of the pN0/Nx patients (DSS of pN0/Nx and N1a are both 100% at 5 years; distant RFS for pN0/Nx and N1a are both 99% at 5 years). This finding is in significant contrast to the DSS and Distant RFS for N1b patients which are 91% and 84% respectively.

As a result of these findings, it is clear that older patients with lateral neck disease should be treated aggressively. This approach involves total thyroidectomy, comprehensive neck dissection, and postoperative RAI in most cases. In contrast, however, those patients who have no evidence of lateral neck metastases are at very low risk. No such patient died during follow-up in our study, and recurrence rates in pN0/Nx patients was rare. In these low-risk cases, a less aggressive approach is called for. Although therapeutic central neck dissection is indicated for those with apparent central neck disease, elective neck dissection is not recommended. In addition with such low rates of recurrence and death, clinicians should consider carefully the potential for benefit from adjuvant RAI.

Like all retrospective studies, our data have limitations. The use of ultrasonography and serial Tg monitoring has only become routine practice in the last decade. Many of the patients included in this dataset were managed before this time and as such were followed with clinical examination. For this reason, the clinically occult nodal disease at presentation or during follow-up may have been overlooked. Current practice within our institution has evolved, and now preoperative ultrasonography is routine in all patients who present with PTC. Cross-sectional imaging is used in those patients who have bulky nodal metastases. Whether there is any clinical significance in finding microscopic disease is unclear. Certainly no patients considered pN0/ Nx within our reported cohort died of disease during follow-up, and only 2% had suffered recurrence at 5 years, so it is unlikely that more intense investigation would have resulted in improved outcomes.

In conclusion, our results show that those patients with PTC who are 45 years of age or older with N1b disease at presentation have poorer DSS and distant RFS compared with patients with pN0/ Nx or N1a disease. The cause of death in these patients is attributable to distant rather than locoregional recurrence. N1b is a strong independent predictor of distant metastases and DSS, conferring a greater than 10-fold risk for distant metastases and death.

References

1. Shaha AR, Shah JP, Loree TR. Risk group stratification and prognostic factors in papillary car cinoma of thyroid. Ann Surg Oncol 1996;3:534-8.
2. Hay ID, Bergstralh EJ, Goellner JR, Ebersold JR, Grant CS. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. Surgery 1993;114:1050-7; discussion 1057-8.
3. Cady B, Rossi R. An expanded view of risk-group definition in differentiated thyroid carcinoma. Surgery 1988;104:947-53.
4. Hughes CJ, Shaha AR, Shah JP, Loree TR. Impact of lymph node metastasis in differentiated carcinoma of the thyroid: a matched-pair analysis. Head Neck 1996;18:127-32.
5. Harwood J, Clark OH, Dunphy JE. Significance of lymph node metastasis in differentiated thyroid cancer. Am J Surg 1978;136:107-12.
6. Edge SB, American Joint Committee on Cancer. AJCC cancer staging manual. 7th ed. New York: Springer; 2010. xiv, 648 p.
7. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.
8. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 1994;97:418-28.
9. Sherman SI, Brierley JD, Sperling M, Ain KB, Bigos ST, Cooper DS, et al. Prospective multicenter study of thyrois] carcinoma treatment: initial analysis of staging and outcome. National Thyroid Cancer Treatment Cooperative Study Registry Group. Cancer 1998;83:1012-21.
10. Cady B, Sedgwick CE, Meissner WA, Bookwalter JR, Romagosa V, Werber J. Changing clinical, pathologic, therapeutic, and survival patterns in differentiated thyroid carcinoma. Ann Surg 1976;184:541-53.
11. Hirabayashi RN, Lindsays. Carcinoma of the thyroid gland: a statistical study of 390 patients. J Clin Endocrinol Metab 1961;21:1596-610.
12. Sugitani I, Kasai N, Fujimoto Y, Yanagisawa A. A novel classification system for patients with PTC: addition of the new variables of large (3 cm or greater) nodal metastases and re-classification during the follow-up period. Surgery 2004;135:139-48.
13. Zaydfudim V, Feurer ID, Griffin MR, Phay JE. The impact of lymph node involvement on survival in patients with papillary and follicular thyroid carcinoma. Surgery 2008;144:1070-7; discussion 1077-8.
14. Leboulleux S, Rubino C, Baudin E, Caillou B, Hartl DM, Bidart JM, et al. Prognostic factors for persistent or recurrent disease of papillary thyroid carcinoma with neck lymph node metastases and/or tumor extension beyond the thyroid capsule at initial diagnosis. J Clin Endocrinol Metab 2005;90:5723-9.
15. Ito Y, Fukushima M, Tomoda C, Inoue H, Kihara M, Higashiyama T, et al. Prognosis of patients with papillary thyroid carcinoma having clinically apparent metastasis to the lateral compartment. Endocr J 2009;56:759-66.
16. de Meer SG, Dauwan M, de Keizer B, Valk GD, Borel Rinkes IH, Vriens MR. Not the number but the location of lymph nodes matters for recurrence rate and disease-free survival in patients with differentiated thyroid cancer. World J Surg 2012;36:1262-7.
17. Takada H, Kikumori T, Imai T, Sawaki M, Shibata A, Kiuchi T. Patterns of lymph node metastases in papillary thyroid carcinoma: results from consecutive bilateral cervical lymph node dissection. World J Surg 2011;35:1560-6.
18. Lang BH-H, Wong KP, Wan KY, Lo C-Y. Significance of metastatic lymph node ratio on stimulated thyroglobulin levels in papillary thyroid carcinoma after prophylactic unilateral central neck dissection. Ann Surg Oncol 2012;19:1257-63.
19. O'Neill CJ, Coorough N, Lee JC, Clements J, Delbridge LW, Sippel R, et al. Disease outcomes and nodal recurrence in patients with papillary thyroid cancer and lateral neck nodal metastases. ANZ J Surg 2014;84:240-4.
20. Ricarte-Filho J, Ganly I, Rivera M, Katabi N, Fu W, Shaha A, et al. Papillary thyroid carcinomas with cervical lymph node metastases can be stratified into clinically relevant prognostic categories using oncogenic BRAF, the number of nodal metastases, and extra-nodal extension. Thyroid 2012;22:575-84.
21. Randolph G, Duh QY, Heller KS, Livolsi VA, Mandel SJ, Steward D, et al. The Prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. Thyroid 2012;22:1144-52.
22. Beal SH, Chen SL, Schneider PD, Martinez SR. An evaluation of lymph node yield and lymph node ratio in well-differentiated thyroid carcinoma. Am Surg 2010;76:28-32.

Part IV

Outcomes Following Nodal Disease

Chapter 8

Pattern of Neck Recurrence Following Lateral Neck Dissection for Cervical Metastases in Papillary Thyroid Cancer

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Abstract

Background

The objective of this study was to determine the rate and pattern of nodal recurrence in patients who underwent a therapeutic, lateral neck dissection (LND) for papillary thyroid cancer (PTC) with clinically evident cervical metastases and to determine if there was any correlation between the extent of initial dissection and the rate and pattern of neck recurrence.

Methods

A total of 3,664 patients with PTC treated between 1986 and 2010 at Memorial Sloan Kettering Cancer Center were identified from our institutional database. Tumor factors, patient demographics, extent of initial LND, and adjuvant therapy were recorded. Patterns of recurrent lateral neck metastases by level involvement were recorded and outcomes calculated using the Kaplan-Meier method.

Results

A total of 484 patients had an LND for cervical metastases; 364 (75%) had a comprehensive LND (CLND) and 120 (25%) had a selective neck dissection (SND). The median duration of follow-up was 63.5 months. As expected, patients with CLND had a greater number of nodes removed as well as a greater number of positive nodes ($P < .001$). There was no difference in overall lateral neck recurrence-free status (CLND 94.4% vs SND 89.4%, $P = .158$), but in the dissected neck, the ipsilateral lateral neck recurrence-free status was superior in the CLND patients (97.7% vs 89.4%, $P < .001$).

Conclusion

Patients with clinically evident neck metastases from PTC managed by CLND have lesser rates of recurrence in the dissected neck compared with patients managed by SND. SND should only be done in highly selected cases with small volume disease. (Surgery 2016;159:1565-71.)

In patients with well-differentiated papillary thyroid cancer (PTC), metastases to the cervical lymph nodes are common. The majority of these are clinically occult, metastatic nodes, which are thought to be of no prognostic significance in the majority of patients.[1,2] In contrast, clinically evident neck metastases, especially in the lateral neck, are of greater clinical importance, because these patients are at increased risk of additional regional nodes and distant disease. This is especially true in patients >45 years of age.[3,4] In patients with clinically evident lateral neck disease, optimum management of the lateral neck is, therefore, of great importance.

There has been much debate in the literature as to the extent of dissection of the lateral neck nodes when clinically evident neck metastases are present. The most commonly involved levels of the lateral neck with metastases are levels III and IV.[5] These levels are included in all lateral neck dissections (LNDs) carried out for metastatic PTC. Nodal metastases to level I occur rarely, and therefore, dissection of this level is generally not indicated.[6] In contrast, metastases to level II and level V are not infrequent. Operations that have been recommended range from a modified radical neck dissection type 3, removing lymph nodes in levels II–V, to the super-selective nodal dissections, which remove only the compartments demonstrating gross nodal disease. There is no published evidence that one procedure is better than another, although it is well known that "berry-picking" procedures are associated with a greater incidence of regional recurrence.[7]

The decision on the extent of neck dissection is based on volume of disease and levels involved as well as surgeon and patient preference. At our institution, patients with gross lateral neck nodal disease are managed with a comprehensive lateral dissection of lymph nodes from levels II–V. Rarely, patients with lesser volume disease localized to levels III or IV may be managed with a selective neck dissection (SND). The objectives of our study were to answer 3 questions. First, which patients are selected to have comprehensive LND (CLND) versus SND? Second, what is the neck recurrence rate and pattern of nodal recurrence in patients who have had CLND and SND? Lastly, do patients who undergo CLND have less recurrence in the ipsilateral neck compared with those who have an SND?

METHODS

After Institutional Review Board approval, patients who had a therapeutic LND were identified from an institutional database of 3,664 patients with thyroid cancer treated between 1986 and 2010 at Memorial Sloan Kettering Cancer Center. Patients who had nonpapillary histology, M1 disease at presentation, and those who were considered to have unresectable disease were excluded, leaving 484 patients available for analysis. LND was categorized into comprehensive (CLND), which includes levels II–V, and selective (SND), which removes only the nodal basins with macroscopic disease with or without the addition of other at-risk levels. In CLND for thyroid cancer, we remove levels II–V preserving the sternocleidomastoid muscle, internal jugular vein, and accessory nerve. In level II, level IIA is dissected. Level IIB is dissected if there are suspicious lymph nodes in level IIA. In level V, only level VB (infra-accessory nerve) is dissected; it has been reported widely that metastases to level VA are rare.[8] In SND, we dissect levels III and IV routinely but will dissect level II if clinically suspicious nodes are found at operation. The neck dissections were done in conjunction with thyroidectomy. The incision used for both SND and CLND were skin crease incisions in the mid neck extending laterally. The incision used for CLND extends more posteriorly to the level of the trapezius muscle. Both incisions follow natural skin creases (Fig 1).

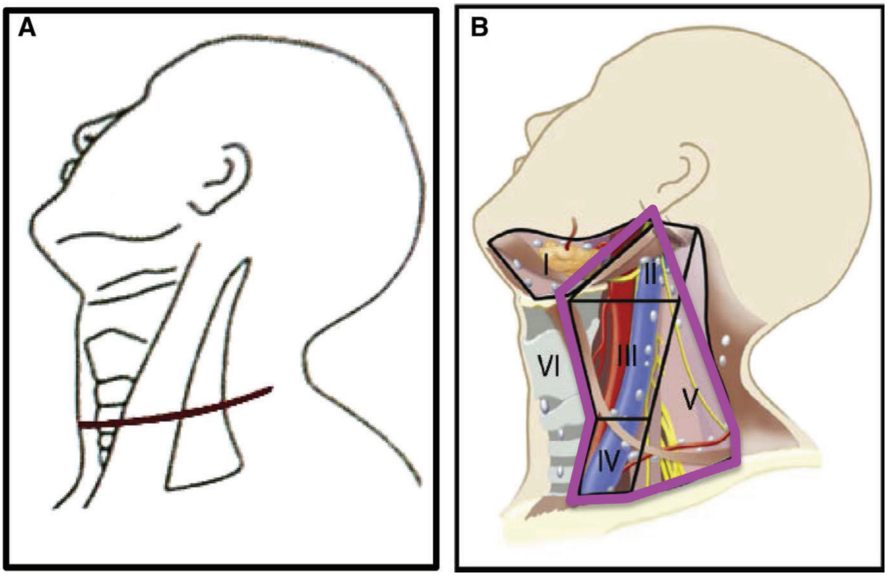

Figure 1 | Skin incision (*A*) and levels dissected (*B*) in CLND for thyroid cancer. (Color version of figure is available online.)

Data collected included patient demographics and operative details such as the extent of thyroidectomy and the extent of LND. Histopathologic details recorded included pathologic T stage, N stage, and presence of extracapsular extension. TNM/International Union Against Cancer stage as defined in the American Joint Committee on Cancer Staging Manual 2010 was used.[9] N status was defined as pN0 if nodes were removed and found to be benign on pathology. pN1a was defined as pathologically positive metastatic nodes removed from the central compartment (level VI), and pN1b was defined as pathologically positive metastatic nodes removed from the lateral neck (levels I–V) or from superior mediastinum (level VII). The postoperative treatment details recorded were use of radioactive iodine (RAI) or external beam radiotherapy.

The neck was staged by clinical examination supplemented with imaging and cytology. Preoperative ultrasonography (US) is effective for identifying metastatic nodes in the lateral neck. Since the year 2000, the sensitivity of this imaging modality has improved considerably, and we have increased our use of the modality. In addition, in patients with bulky neck disease, we supplement our examination with preoperative contrast-enhanced computed tomography (CT).

The number and level of positive lymph nodes in the neck dissection specimen were recorded from pathology reports. In patients who had neck recurrence, the patterns of recurrent lateral neck metastases by level involvement were recorded. Recurrence was detected by physical examination, radiologic imaging (I-131 whole body uptake scan, US, CT, and positron emission tomography), and/or measurements of serum thyroglobulin. Fine-needle aspiration biopsy of metastatic nodes was performed to confirm recurrent thyroid cancer in all patients with regional recurrence. The time from the initial thyroidectomy and neck dissection until a documented recurrence and subsequent treatment was determined for all patients.

Statistical analysis was carried out using SPSS (version 21, IBM Corporation, Armonk, NY). Clinical and pathologic variables were compared between CLND and SND groups using the χ^2 analysis. Recurrence outcomes were analyzed using the Kaplan-Meier method. The overall lateral neck recurrence-free probability (Overall LNRFP) and the ipsilateral dissected neck recurrence free probability (Ipsilateral LNRFP) was determined for the CLND and SND groups using the Kaplan-Meier method and compared using the log-rank test.

Results

Of the 484 patients, 281 (58%) patients were female, and 203 (42%) were male; 275 (56.8%) were >45 years old; 432 (89.3%) patients underwent total thyroidectomy; 364 (75%) patients had a CLND; and 120 (25%) patients had an SND (Fig 2).

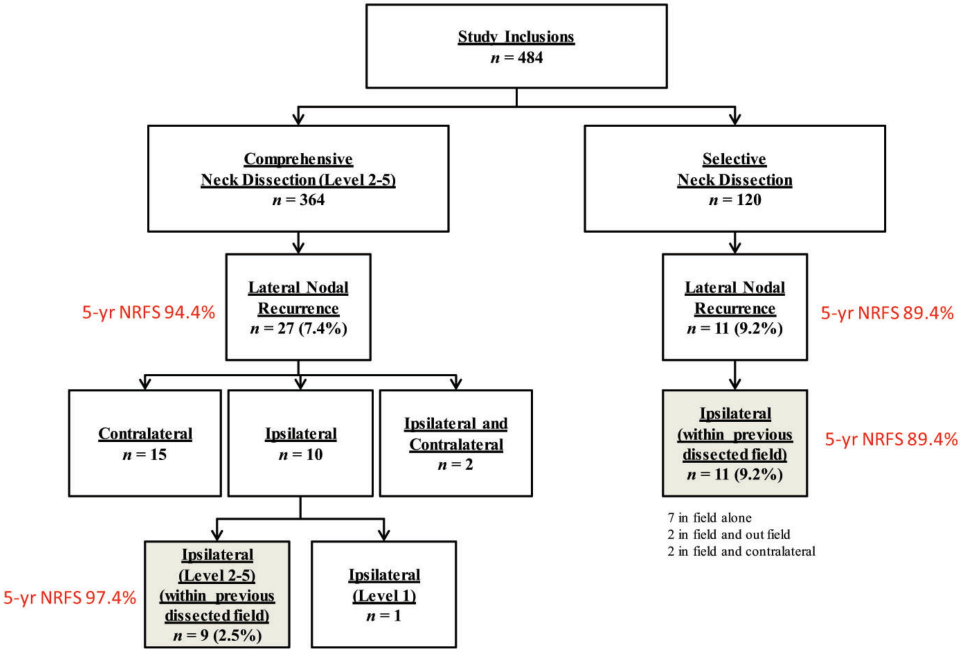

Figure 2 | Flowchart showing pattern of recurrence and recurrence rates in CLND and SND patients. *NRFS*, Nodal recurrence free survival.

Comparison of clinical and pathologic characteristics of CLND and SND patients

The 2 groups were similar with respect to age, sex, and initial thyroidectomy performed (Table). There was no difference between the 2 groups regarding adjuvant RAI administration or postoperative radiation therapy ($P > .3$ each). With regard to tumor characteristics, there was no difference between the 2 groups for pT stage; 222 patients in the CLND group (62%) had T3 or T4 tumors versus 73 (62%) patients in the SND group ($P = .34$). As expected, the CLND group had more advanced nodal disease with 96% of patients having pN1b disease versus 78% in the SND group ($P = .002$). The CLND group had a greater number of nodes removed in the specimen as well as a greater number of positive nodes (ie, Nodal burden) than the SND group did ($P < .001$).

Table | Comparison of patient, tumor, and treatment characteristics in patients managed with CLND and SND

	All patients		CLND patients		SND patients		
Variable	*n*	%	*n*	%	*n*	%	*P* value
Age (y)							
≤45	275	56.8	214	58.8	61	50.8	.127
>45	209	43.2	150	41.2	59	49.2	
Sex							
Female	281	58.1	209	57.4	72	60.0	.619
Male	203	41.9	155	42.6	48	40.0	

Variable	All patients *n*	All patients %	CLND patients *n*	CLND patients %	SND patients *n*	SND patients %	*P* value
Operation							
Less than total thyroid	52	10.7	42	11.5	10	8.3	.325
Total thyroidectomy	432	89.3	322	88.5	110	91.7	
T stage							
pT1	146	30.4	114	31.6	32	26.9	.335
pT2	39	8.1	25	6.9	14	11.8	
pT3	228	47.5	176	48.8	52	43.7	
pT4	67	14.0	46	12.7	21	17.6	
N stage							
pN0	23	4.8	11	3.0	12	10.0	.002
pN1a	20	4.1	5	1.4	15	12.5	
pN1b	441	91.1	348	95.6	93	77.5	
ECS							
No	154	59.7	120	58.5	34	64.2	.458
Yes	104	40.3	85	41.5	19	35.8	
PORT							
No	475	98.1	356	97.8	119	99.2	.463
Yes	9	1.9	8	2.2	1	0.8	
RAI							
No	120	24.8	86	23.6	34	28.3	.3
Yes	364	75.2	278	76.4	86	71.7	
Variable	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	***P* value**
Number of positive nodes	5.2	5.3	5.7	5.4	3.6	4.5	<.001
Total number of nodes	32.2	19.4	35.2	19.4	22.1	15.6	<.001
Duration of follow-up	91	73.9	94.3	73.1	81.1	75.6	.098

CLND, Comprehensive lateral neck dissection; *ECS*, extracapsular extension; *PORT*, postoperative radiation therapy; *SND*, selective neck dissection; *RAI*, radioactive iodine.

Overall neck recurrence rate and pattern of nodal recurrence in patients who had CLND and SND

The median duration of follow-up was 63.5 months. Overall, 38 (8.0%) patients developed a lateral neck recurrence: 27 of 364 (7.4%) in the CLND group and 11 of 120 (9.2%) in the SND group (Fig 2). In CLND patients, 9 recurrences occurred in the ipsilateral dissected neck (9 of 364 = 2.5%), 1 in ipsilateral level 1 (0.2%), 15 (4.1%) in the contralateral neck, and 2 (0.5%) in both ipsilateral and contralateral neck. In SND patients, all recurrences (11 of 120 = 9.2%) were in the ipsilateral dissected neck. Seven patients recurred within the previously dissected nodal levels only. Two patients recurred within the previous dissected nodal levels as well as in ipsilateral levels that had not been dissected previously. Two patients recurred in both the ipsilateral (dissected and undissected neck levels) and contralateral neck. Kaplan-Meier analysis demonstrated no difference in overall LNRFP between the 2 groups (CLND 94.4% vs 89.4%; *P* = .158) (Fig 3).

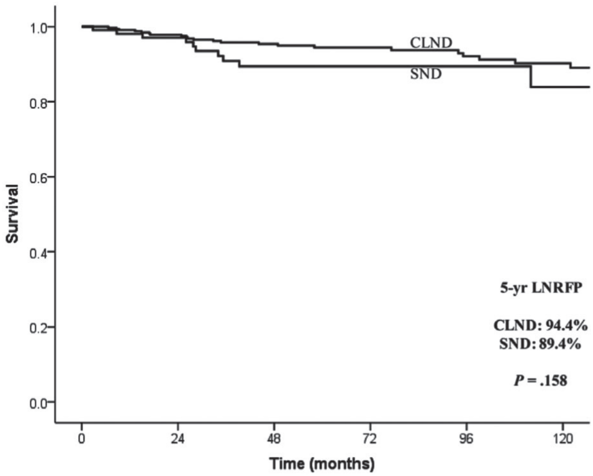

Figure 3 | Kaplan-Meier plot showing the 5-year overall lateral neck recurrence-free probability (ipsilateral and contralateral) in CLND and SND patients.

Ipsilateral (dissected neck field) LNRFP for CLND and SND groups

Although there was no difference in overall neck recurrence rates, patients who underwent SND were more likely to recur in the ipsilateral dissected neck compared with the CLND patients (Fig 2 shaded boxes: 9.2% vs 3%; $P = .001$). Kaplan-Meier analysis demonstrated a difference in ipsilateral (dissected neck) LNRFP between the 2 groups (CLND 97.7% vs 89.4%; $P < .001$) (Fig 4).

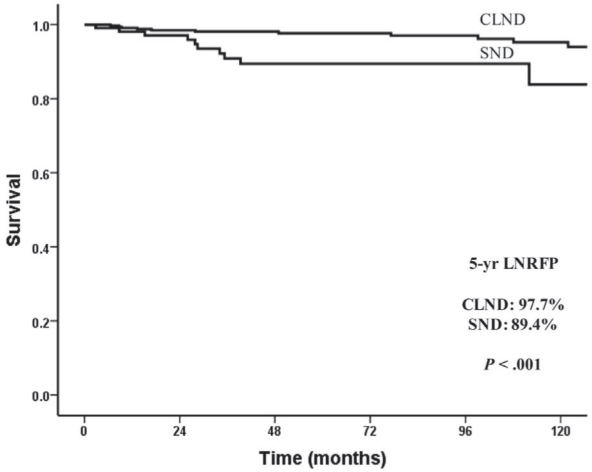

Figure 4 | Kaplan-Meier plot showing the 5-year ipsilateral (dissected neck field), lateral neck, recurrence-free probability in CLND and SND patients.

Complications associated with neck dissection for CLND and SND

Complications associated with neck dissection, ie, chyle leak, hematoma, shoulder dysfunction, and hypoglossal nerve or marginal mandibular nerve injury, are shown in the Supplementary Figure. Shoulder dysfunction complications were more frequent in patients having CLND ($P = .019$); however, these were temporary in duration, and only 1 patient had long-term shoulder dysfunction. There were no differences in the rate of chyle leak, hematoma, and hypoglossal or marginal mandibular nerve injury between groups.

Discussion

Clinically evident lateral neck disease in patients with differentiated thyroid cancer is clinically important because these patients are at increased risk of developing additional regional and distant disease. This possibility is especially true in patients who are >45 years of age. A recent report from our institution demonstrated that patients with PTC who are ≥45 years old with N1b disease at presentation have poorer, disease-specific survival as well as distant recurrence-free survival compared with patients who have pN0/Nx or N1a disease.[4] Optimum management of the lateral neck is, therefore, of great importance, especially in the older patient. Because there has been much debate as to the extent of dissection of the lateral neck in patients with clinically evident lateral neck disease, we sought to answer 3 questions. First, which patients are selected to have a CLND versus an SND? Second, what is the neck recurrence rate and pattern of nodal recurrence in patients who had CLND and SND? Finally, do patients who undergo CLND have less recurrence in the ipsilateral neck compared with those who have an SND?

Our data support our practice of offering CLND to patients with more extensive and bulky nodal disease (Table) with more N1b disease. Those patients with a lesser volume of neck disease and disease limited to 1 or 2 levels were chosen to have a more selective approach. With regard to question 2, we found that in these highly selected patients who had a limited neck dissection, all recurrences were within the previously dissected neck levels (2 patients also had contralateral neck recurrence). This finding was in contrast to patients managed by CLND, where more than half of the patients developed contralateral neck recurrence, which would be consistent with the CLND cohort's more advanced neck disease, including metastasized neck nodes and a greater volume and number of levels compared with patients with SND. For question 3, we report that the overall neck recurrence rates between the 2 groups were similar. It is important, however, to observe that control in the ipsilateral dissected neck was superior in the CLND patients compared with the SND patients, despite the fact that the CLND patients had a greater volume of neck disease; this finding would be consistent with the greater efficacy of a CLND compared to an SND.

In our series, there were 27 recurrences in the CLND patients (7.4%) and 11 recurrences in the SND patients (9.2%), with an overall recurrence rate of 38 (7.8%). Published data analyzing specific disease outcomes in patients with PTC who undergo therapeutic LNDs at the time of primary thyroidectomy are limited. The literature suggests recurrence that develops in the cervical lymph nodes ranges from 5.4–13% after the initial thyroidectomy.[10] A study by O'Neill et al[11] demonstrated a 13% neck nodal recurrence rate after total thyroidectomy, central neck dissection, and compartment-oriented nodal dissection of involved lateral lymph node compartments ($n = 116$). Nine of their 15 recurrences occurred within the previously dissected ipsilateral lateral neck, and 3 patients recurred in the contralateral neck, totaling a lateral neck recurrence rate of 10.3%.

Kim et al[12] reviewed 126 patients who underwent therapeutic LND with total thyroidectomy and bilateral central neck dissection concomitantly for PTC at the National Cancer Center in Korea. Recurrence occurred in 22 patients (17.5%), with 1 patient (0.8%) dying of brain metastasis. Excluding 2 of those recurrences who recurred with distant disease only and another 4 patients who recurred in the central neck only, they had 16 lateral neck recurrences (including contralateral lateral neck recurrences) for a lateral neck recurrence rate of 12.7%; 12 patients recurred in the previously dissected ipsilateral lateral neck. Lastly, Forest et al[13] reported an 11.8% recurrence rate in 34 patients who underwent central and LND with the initial management of their PTC.

Although our data suggest that the ipsilateral neck recurrence rate is less in patients who had CLND (3%) compared with SND (9%), one may argue that the rates of recurrence for SND are still acceptable and may potentially avoid any complications that may occur from a more comprehensive neck dissection. It is widely accepted that complications, such as chyle leak, hematoma, and shoulder dysfunction resulting from damage either to the accessory nerve or to the nerve supply to the posterior triangle neck musculature, are more common after CLND.[14–18] In our own series, we did not observe any statistically significant differences in complication rates for chyle leak, hematoma, and hypoglossal or marginal nerve injury. Shoulder dysfunction complications were more frequent in patients undergoing a CLND ($P = .019$), but shoulder dysfunctions were temporary in duration, and only 1 patient had long-term shoulder dysfunction.

We do, however, acknowledge that a retrospective chart review for functional complications in shoulder movement is highly prone to underreporting. It is important to note that we were only able to achieve a recurrence rate of 9% in SND patients by being highly selective and only carrying out this operation in patients with small volume lymph nodes limited to 1 or 2 neck levels. One would expect recurrence rates to be greater if SND was done in multilevel bulky neck nodes scenarios.

As is the nature of retrospective studies, our data have limitations associated with retrospective data collection. Collected data are dependent on the accuracy of chart review as well as pathology review. It is well recognized that the nodal yield reported by pathologists can vary widely between pathologists and is highly dependent on the investment of time and detail to which neck dissection specimens are scrutinized. Our institution has many years of experience in the management of thyroid cancer, and as such, the variation of nodal yield from pathologic analysis is limited by such quality control. Second, one can never fully account for the selection bias that takes place in the decision to carry out an LND and the extent of such a dissection, but our philosophy of treatment has remained uniform; patients with bulky lateral neck disease tend to have more comprehensive neck dissection.

We were stringent in choosing patients for SND, limiting our selection to patients with low volume of disease restricted to 1 or 2 neck levels. As well as selection bias, we recognize that there is also possible misclassification bias within our own data set. For example, some surgeons may remove part of level V, such as the anterior portion, yet these dissections may be labeled as an SND of levels II–IV. In addition, some surgeons may remove level V incompletely through a medial approach and code this as a CLND (levels II–V).

Furthermore, our data may underestimate the extent of neck recurrence. Regular US and serial monitoring of serum thyroglobulin has only become routine practice in the last decade. Many of the patients included in this data set were managed before this time and as such were followed with clinical examination alone. For this reason, small, nonpalpable recurrent neck disease may not have been identified in those early years, which would lead to an underestimation of the rate of subclinical neck recurrence that we are reporting.

In conclusion, despite having more aggressive disease, patients with clinically evident lateral neck disease in PTC managed by CLND have comparable overall rates of neck recurrence to patients with SND. Importantly, we report less rates of ipsilateral dissected neck recurrence in the CLND cohort compared with patients managed by SND (3% vs 9%, $P < .05$) in keeping with the more comprehensive nature of these types of neck dissection. As such, we recommend that SND should be reserved only for highly selected patients who have low volume disease localized to 1 or 2 specific nodal compartments.

Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.surg.2016.02.005.

References

1. Randolph GW, Duh Q, Heller KS, LiVolsi VA, Mandel SJ, Steward DL, et al. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. Thyroid 2012;22:1144-52.
2. Bozec A, Dassonville O, Chamorey E, Poissonnet G, Sudaka A, Peyrottes I, et al. Clinical impact of cervical lymph node involvement and central neck dissection in patients with papillary thyroid cancer: a retrospective analysis of 368 cases. Eur Arch Otorhinolaryngol 2011;268:1205-12.
3. Hughes CJ, Shaha AR, Shah JP, Loree TR. Impact of lymph node metastasis in differentiated carcinoma of the thyroid: a matched-pair analysis. Head Neck 1996;18:127-32.
4. Nixon IJ, Wang LY, Palmer FL, Tuttle RM, Shaha AR, Shah JP, et al. The impact of nodal status on outcome in older patients with papillary thyroid cancer. Surgery 2014;156:137-46.
5. Machens A, Hinze R, Thomusch O, Dralle H. Patterns of nodal metastasis for primary and reoperative thyroid cancer. World J Surg 2002;26:22-8.
6. Kupferman ME, Patterson M, Mandel SJ, Livolsi V, Weber RS. Patterns of lateral neck metastasis in papillary thyroid cancer. Arch Otolarnygol Head Neck Surg 2004;130:857-60.
7. Caron NR, Clark OH. Papillary thyroid cancer: surgical management of lymph node metastases. Curr Treat Options Oncol 2005;6:311-22.
8. Khafif A, Medina JE, Robbins KT, Silver CE, Weber RS, Rinaldo A, et al. Level V in therapeutic neck dissections for papillary thyroid carcinoma. Head Neck 2013;35:605-7.
9. Edge S, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A. AJCC cancer staging manual. 7th ed. New York: Springer-Verlag; 2010.
10. Grant CS, Hay ID, Gough IR, Bergstralh EJ, Goellner JR, McConahey WM. Local recurrence in papillary thyroid carcinoma: is extent of surgical resection important? Surgery 1988;104:954-62.
11. O'Neill CJ, Coorough N, Lee JC, Clements J, Delbridge LW, Sippel R, et al. Disease outcomes and nodal recurrence in patients with papillary thyroid cancer and lateral neck nodal metastases. ANZ J Surg 2014;84:240-4.
12. Kim SJ, Park SY, Lee YJ, Lee EK, Kim SK, Kim TH, et al. Risk factors for recurrence after therapeutic lateral neck dissection for primary papillary thyroid cancer. Ann Surg Oncol 2014;21:1884-90.
13. Forest VI, Clark JR, Ebrahimi A, Cho EA, Sneddon L, Gao K, et al. Central compartment dissection in thyroid papillary carcinoma. Ann Surg 2011;253:123-30.
14. Kupferman ME, Patterson DM, Mandel SJ, LiVolsi V, Weber RS. Safety of modified radical neck dissection for differentiated thyroid carcinoma. Laryngoscope 2004;114:403-6.
15. Terrell JE, Welsh DE, Bradford CR, Chepeha DB, Esclamado RM, Hogikyan ND, et al. Pain, quality of life, and spinal accessory nerve status after neck dissection. Laryngoscope 2000;110:620-6.
16. Inoue H, Nibu K, Saito M, Otsuki N, Ishida H, Onitsuka T, et al. Quality of life after neck dissection. Arch Otolaryngol Head Neck Surg 2006;132:662-6.
17. van Wilgen CP, Dijkstra PU, van der Laan BF, Plukker JT, Roodenburg JL. Shoulder complaints after neck dissection; is the spinal accessory nerve involved? Br J Oral Maxillofac Surg 2003;41:7-11.
18. Cappiello J, Piazza C, Giudice M, De Maria G, Nicolai P. Shoulder disability after different selective neck dissections (levels II-IV versus levels II-V): a comparative study. Laryngoscope 2005;115:259-63.

Chapter 9

Management and Outcome of Clinically Evident Neck Recurrence in Patients with Papillary Thyroid Cancer

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Abstract

Background

The aim of this study was to report our incidence of clinically evident neck recurrence, salvage neck management and subsequent outcomes in patients with papillary thyroid cancer. This is important to know so that patients with thyroid cancer can be properly counselled about the implications of recurrent disease and subsequent outcome.

Methods

An institutional database of 3664 patients with thyroid cancer operated between 1986 and 2010 was reviewed. Patients with nonpapillary histology and gross residual disease and those with distant metastases at presentation or distant metastases prior to nodal recurrence were excluded from the study. Of these, 99 (3.0%) patients developed clinically evident nodal recurrence. Details of recurrence and subsequent therapy were recorded for each patient. Subsequent disease-specific survival (sDSS), distant recurrence-free survival (sDRFS) and nodal recurrence-free survival (sNRFS) were determined from the date of first nodal recurrence using the Kaplan-Meier method.

Results

Of the 99 patients, 59% were female and 41% male. The median age was 41 years (range 5-91). The majority of patients had pT3/4 primary tumours (63%) and were pN+ (78%) at initial presentation. The median time to clinically evident nodal recurrence was 28 months (range: 3-264). Nodal recurrence occurred in the central neck in 15 (15%) patients, lateral neck in 74 (75%) patients and both in 10 (10%) patients. After salvage treatment, the 5-year sDSS was 97.4% from time of nodal recurrence. The 5-year sDRFS and sNRFS were 89.2% and 93.7%, respectively.

Conclusion

In our series, isolated clinically evident nodal recurrence occurred in 3.0% of patients. Such patients are successfully salvaged with surgery and adjuvant therapy with sDSS of 97.4% at 5 years.

Keywords

lymph nodes, neck recurrence, outcomes, papillary thyroid cancer, survival

Introduction

There is great controversy about the true incidence of recurrence in papillary thyroid cancer (PTC). Long-term overall PTC recurrence rates are commonly referenced at 30%.[1,2] However, recurrence rates vary widely depending on the extent of primary disease and on the method of recurrence measurement.[3,4] Recurrence rates are greater if one includes subcentimetre nodes identified on high-resolution ultrasound with elevated thyroglobulin measurements. Recurrence due to clinically evident nodal recurrence which requires further surgery is less common. The majority of regional recurrences manifest within the first few years after initial therapy.[5] Of those who develop regional nodal recurrence, few patients ultimately succumb to their disease. Although prognostic factors of PTC have been extensively investigated, patient outcomes after clinically evident nodal recurrence remain unclear. The objectives of our study were twofold: firstly, to report the incidence of clinically evident nodal recurrence in a large cohort of previously untreated patients managed at a single tertiary care institution and secondly, to describe the subsequent treatment of these patients and report the long-term outcomes after salvage treatment.

Methods

Following institutional review board approval, the records of 3664 consecutive patients treated with primary thyroid surgery for differentiated thyroid cancer at Memorial Sloan Kettering Cancer Center (MSKCC) between 1986 and 2010 were reviewed. Patients with nonpapillary histology and gross residual disease and those with distant metastases at presentation or distant metastases prior to nodal recurrence were excluded from the study, leaving 3344 cases. Of these, 99 (3.0%) patients with PTC developed clinically evident nodal recurrence which required further treatment. All patients had biopsy-proven neck recurrence prior to further treatment. Patients with subclinical recurrence, defined as subcentimetre nodules in the central or lateral neck with or without an elevated thyroglobulin level, were not included in this study.

Patient demographics and primary surgical and histopathological details were recorded. Details of all adjuvant radioactive iodine (RAI) treatments or radiotherapy (RT) were also recorded. Clinically evident nodal recurrence was identified by clinical examination and imaging studies with ultrasound (US) or CT scan and was confirmed with cytology or histopathology.

Disease outcomes included subsequent disease-specific survival (sDSS), subsequent distant recurrence-free survival (sDRFS) and subsequent nodal recurrence-free survival (sNRFS). These outcomes were calculated from the date of first nodal recurrence. sDSS was calculated using the date of last follow-up with an MSKCC physician from the thyroid cancer multidisciplinary team. Details of death were determined from the social security death index and hospital records. Biochemical disease in the absence of imaging disease was not considered sufficient evidence of tumour recurrence. Imaging studies to detect recurrence included US, diagnostic RAI, computer tomography and positron emission tomography scans. Patients with evidence of structural disease at the time of last follow-up and died during follow-up were considered to have had disease-specific death.

Statistical analysis was carried out using SPSS (version 21, IBM Corporation, Armonk, NY, USA). Variables were compared within groups using Pearson's chi-squared test. Survival outcomes were analysed using the Kaplan-Meier method. Outcomes data were calculated at 5 years.

Results

Initial patient, disease and management characteristics

Of 3364 patients, 99 (3.0%) patients developed clinically evident nodal recurrence. Table 1 shows the patient, primary disease and initial treatment characteristics of the patients that developed nodal recurrence. Of the 99 patients, 59% were female. The median age of the cohort was 41 years (range: 5-91) at time of initial PTC diagnosis. The majority of patients had locally advanced disease (63% T3 or T4 disease) and presented with nodal disease in 78% (42% N1a and 35% N1b disease). At the time of primary surgery, 85 (86%) patients underwent total thyroidectomy and 14 (14%) less than total thyroidectomy. Central neck dissection was performed in 25 (25%), lateral neck dissection in nine (9%), both in 24 (24%) and not performed in 41 (41%) patients. Adjuvant RAI was administered to 74 (75%) patients.

Table 1 | Initial patient, treatment and tumour characteristics

	n=99	%
Gender		
Female	58	38.6
Male	41	41.4
Age		
<45 y	58	38.6
≥45 y	41	41.4
Thyroid surgery		
Less than total	14	14.1
Total thyroidectomy	85	85.9
Neck dissection		
None	41	41.4
Central compartment	25	25.3
Lateral compartment	9	9.1
Central & lateral	24	24.2
pT stage		
T1	26	26.3
T2	10	10.1
T3	47	47.5
T4	16	16.2
pN stage		
N0/X	22	22.2
N1a	42	42.4
N1b	35	35.4
AJCC stage		
Stage 1	59	59.6
Stage 2	1	1.0
Stage 3	14	14.1
Stage 4	25	25.3
ATA risk group		
Low	6	6.1
Intermediate	69	69.7
High	24	24.2
Adjuvant RAI		
No	25	25.3
Yes	74	74.7

Range of RAI dose was 60.5–268 mCi.

RAI, radioactive iodine.

Nodal recurrence location and treatment

Nodal recurrence details are summarized in Table 2. The median time to clinically evident nodal recurrence was 28 months (range: 3-264). The median follow-up from the time of nodal recurrence was 50 months (range: 1-330). Nodal recurrence occurred in the central neck compartment alone in 15 (15%) patients, lateral neck compartment only in 74 (75%) patients and both neck compartments in 10 (10%) patients.

Table 2 | Nodal recurrence characteristics

	n=99	%
Time to nodal recurrence (mo)		
Median	27.8	-
Range	3-264	-
Site of nodal recurrence		
Central compartment	15	15.2
Lateral compartment	74	74.7
Central and lateral	10	10.1
Recurrence management		
Surgery only	65	65.7
Surgery and RAI	22	22.2
RAI only	6	6.1
RT	4	4.0
Observation only	2	2.0

RAI, radioactive iodine; RT, radiotherapy.

The majority of patient were treated either with surgery alone (65 of 99, 66%) or surgery with adjuvant therapy (22 of 99, 22%). Ten patients (10%) were treated without surgery (RAI and/or external beam radiation therapy [EBRT]), and two (2.0%) patients were observed without treatment.

Outcomes after nodal recurrence

Subsequent disease-specific survival

The 5-year sDSS was 97.4% from time of nodal recurrence (Figure 1A). A total of four patients died of disease during follow-up. All four patients died after developing lung metastases, and one patient also developed brain metastases (Table 3).

Table 3 | Details of patients who died following neck recurrence

Age/Gender	Stage	ATA risk category	Primary RAI	Site of NR	NR treatment	Overall survival (mo)	Cause of death
64.4 F	T3N1b	High	Yes	Central, lateral	RT	30.2	Lung metastases
70.9 F	T1bN1b	Intermediate	Yes	Lateral	Surgery & RAI	135.5	Lung metastases
55.9 M	T4aN1a	High	No	Lateral	Surgery	144.6	Lung metastases
72.4 F	T4aN1a	High	Yes	Lateral	Surgery	142.6	Lung metastases
91.3 M	T4aN1a	High	No	Lateral	Surgery	49.7	Other
85.3 F	T4aNX	High	No	Lateral	Surg & RAI	102.3	Other

Six patient deaths; four disease-specific deaths and two deaths due to other causes.

RAI, radioactive iodine treatment; NR, nodal recurrence.

Subsequent distant recurrence

Eight patients (8.0%) went on to develop distant disease at a median of 85 months (range: 5-130) from time of nodal recurrence. Five patients developed isolated lung metastases, one patient had lung and brain metastases, one had lung and bone metastases, and one patient developed isolated bone metastases. The 5-year sDRFS was 89.2% (Figure 1B).

Subsequent nodal recurrence

Twelve of the 99 patients went on to develop a further episode of nodal recurrence at a median of 118 months (range 76-300) from the time of initial nodal recurrence. At 5 years, the sNRFS was 93.7% (Figure 1C).

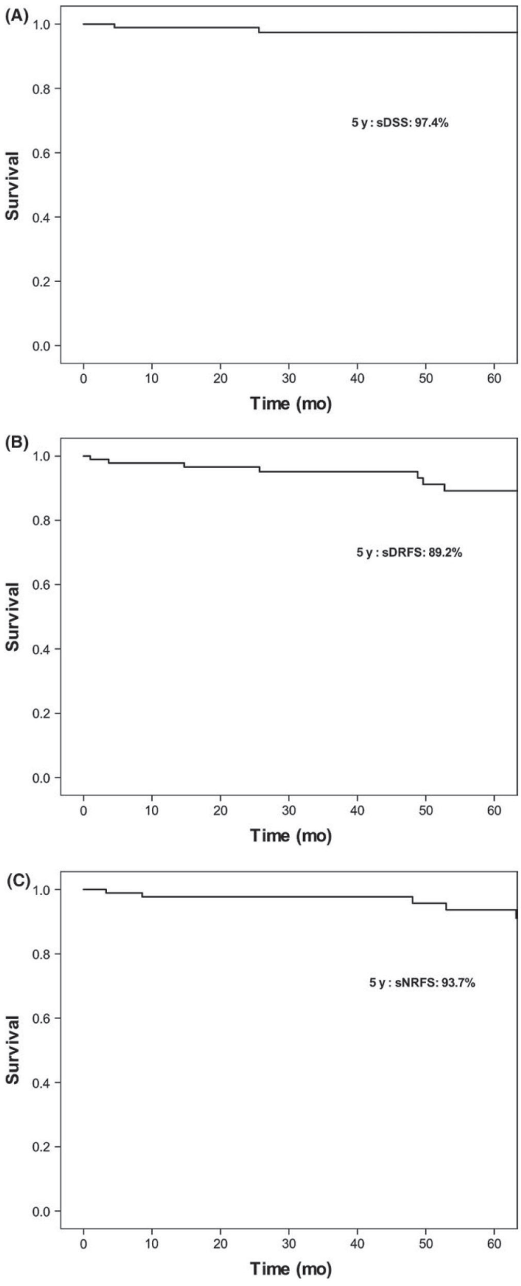

Figure 1 | (A) Five-year subsequent disease-specific survival following salvage neck management. (B) Five-year subsequent distant recurrence-free survival following salvage neck management. (C) Five-year subsequent neck recurrence-free survival following salvage neck management

Discussion

In our experience, the incidence of clinically evident nodal recurrence after initial surgery for patients with well-differentiated PTC was 3%. The majority of patients can be salvaged such that the 5-year subsequent DSS is 97.4%.

Our low rate of clinically evident nodal recurrence merits a detailed discussion. The literature generally reports on combined local and regional recurrence-free survival, with limited breakdown of recurrence sites by thyroid bed and regional lymph node (LN) recurrence. Traditionally, the recurrence figure of 30% by Mazzarferri et al.[1,2] is commonly quoted. In this study, two-thirds of the recurrences were locoregional. However, subsequent publications have reported much lower figures. Durante et el reported 1.4% locoregional recurrence rate in 1020 patients with PTC,[6] and Ito et al.[7] reported 7% reoperation rate in the central neck compartment in a series of 5969 patients with PTC, while Coburn et al.[8] reported 9.4% regional LN recurrence in 382 patients with differentiated thyroid cancer. Yim et al. reported 10.0% locoregional recurrence rate in a series of 1357 patients with PTC, and Shen et al. published central neck recurrence rate of 11.6% and lateral neck recurrence rate of 21.7%. In a recent review by Randolph et al.,[3] locoregional recurrence rates in PTC ranged widely between 0% and 42% based on the size of primary tumour and volume of initial LN metastases. This review suggested the range of recurrence figures was determined by the variety of inclusion criteria and outcomes reported in these studies. Locoregional recurrence rate of 24% was reported with 40 years of follow-up by the Mazzaferri series.[2] This is in contrast to the low recurrence rate of 3.0% that we report in our study. One explanation for the high rate reported by Mazzaferri could be the longer follow-up period that the Mazzaferri cohort underwent. However, given that approximately 84% of neck reoperations occur within the first 2 years of primary surgery, additional follow-up beyond the first 5 years is unlikely to dramatically impact nodal recurrence rates. Of note, data collection from the Mazzarferri series started in the 1960s, on military personnel and their families under the care of military general surgeons. These surgeons were not specialty trained, and the technique of carrying out subtotal thyroidectomy was readily accepted at that time. These two factors are associated with higher recurrence and mortality rates.[9]

With the introduction of high-resolution ultrasound and the use of serum thyroglobulin, it is now possible to detect subclinical recurrent disease in the neck due to small subcentimetre nodes. We did not include these patients in our study, and therefore, it is likely that we have underestimated the true recurrence rate in our patient cohort. However, it is now recognized that the majority of these patients do not require any treatment as the majority of subclinical disease remains indolent.[10,11] The decision to operate in patients with subclinical disease has to be weighed against the possible complications which may result from such surgery.[10,11] It is also possible that some of the patients in our cohort may represent persistent disease rather than recurrence as there were several patients who developed disease within 3 months of initial therapy. In these patients, it is likely that subclinical disease was present initially and this became clinically and radiologically evident on the post-treatment ultrasound scan. This would tend to overestimate the recurrence rate.

In our series, the majority of nodal recurrences were managed surgically with or without additional RAI therapy. Occasionally, in earlier years, the management of nodal recurrence was with nonsurgical modalities alone. The majority of patients were successfully salvaged with a subsequent survival at 5 years of 97.4%. This compares favourably with reports from the literature. In a series of 329 PTC patients with initial central nodal recurrence, Ito el al reported DSS of 95% at 5 years.[7] Other institutional publications have reported death due to disease ranging between 0% and 16% of patients after locoregional recurrence.[2,12-14] In a study of DSS after salvage neck reoperation in PTC, conducted through the Californian Cancer Registry, DSS was found to be approximately 90% at 5 years.[5] Our 5-year disease-specific death rate of 3.6% is within the lower end of the reported range presented in the literature. Therefore, we can conclude that despite nodal recurrence, the 5-year subsequent survival in these patients remains very high at 97.4%.

Few publications in the literature report subsequent nodal or distant recurrence outcomes after initial nodal recurrence. Those that do tend to report subsequent locoregional and distant failure rates in term of a percentage figure, making comparisons difficult as each series is associated with a different length of follow-up. For example, subsequent locoregional failure was reported in 9.6% patients by Yim et al. and in 18.2% of patients by Onkendi et al.[12,13] In this current series, only 12 (12.1%) patients went on to develop a second episode of clinically evident nodal failure after treatment of their initial nodal recurrence, corresponding to a 5-year sNRFS of 93.7%.

Distant recurrence-free survival after the development of nodal disease is also infrequently reported in the literature. Yim et al.[13] reported five of 83 (6.0%) patients subsequently developed distant disease after treatment for nodal recurrence. This is comparable to the subsequent distant failure rate of eight (8.1%) patients and 5-year sDRFS of 89.2% observed in this present study.

Our study has some limitations that require discussion. Firstly, this is a retrospective cohort with patients managed at a single institution over a 25-year period. As such, we cannot account for changes in follow-up management practices over this time. In particular, postoperative neck ultrasound and thyroglobulin measurements were not routine prior to 2000-2005. Prior to this time, recurrence was determined on clinical examination and then confirmed by fine-needle aspirate. It is therefore probable that we may have misclassified patients as being free of disease in patients not assessed by US or thyroglobulin (Tg), and this would have resulted in an underestimation of nodal disease recurrence. Although serum Tg is a more sensitive marker of differentiated PTC disease,[4,13-18] its use in determining indication and success of nodal recurrence treatment can be problematic. The use of biochemical determinants of persistent or recurrent disease can lead to additional surveillance and intervention along with its associated morbidity. This is particularly of concern for the many patients who are already at very low risk from their disease. In this regard, one can argue that the use of structural disease is a more clinically meaningful measure of outcome.

Another limitation of our cohort is the relatively short follow-up period. There may be patients with nodal recurrence who are lost to follow-up. This would artificially improve our NRFS. However, as the majority of nodal recurrence in PTC occur within the first 2-3 years of diagnosis,[5] we do not expect the true nodal recurrence rate to be significantly higher than 3.0% with longer follow-up. Outcomes after nodal recurrence are reported here with a median follow-up of 50 months. It may be likely that with additional follow-up, DSS and sDFRS may decrease. However, as nodal recurrence events tend to occur early, we expect that sNRFS would remain the same with additional follow-up.

In conclusion, in this series of patients with PTC, clinically evident nodal recurrence occurred in 3.0% of patients. Salvage management is mainly surgical with or without additional RAI therapy. Patients continue to experience excellent outcomes after nodal disease recurrence, with a subsequent 5-year DSS of 97.4%.

Conflict of Interest

The authors have no disclosures.

References

1. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med*. 1994;97:418-428.
2. Mazzaferri EL, Kloos RT. Clinical review 128: Current approaches to primary therapy for papillary and follicular thyroid cancer. *J Clin Endocrinol Metab*. 2001;86:1447-1463.
3. Randolph G, Duh Q, Heller K, et al. The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension. *Thyroid*. 2012;22:1144-1152.
4. Steward DL. Update in utility of secondary node dissection for papillary thyroid cancer. *J Clin Endocrinol Metab*. 2012;97:3393-3398.
5. Young S, Harari A, Smooke-Praw S, Ituarte P, Yeh M. Effect of reoperation on outcomes in papillary thyroid cancer. *Surgery*. 2013;154:1354-1361; discussion 1361-1352.
6. Durante C, Montesano T, Torlontano M, Attard M, Monzani F, Tumino S. Papillary thyroid cancer: time course of recurrences during postsurgery surveillance. *J Clin Endocrinol Metab*. 2013;98:636-642.
7. Ito Y, Higashiyama T, Takamura Y, Kobayashi K, Miya A, Miyauchi A. Prognosis of patients with papillary thyroid carcinoma showing postoperative recurrence to the central neck. *World J Surg*. 2011;35:767-772.
8. Coburn M, Teates D, Wanebo H. Recurrent thyroid cancer. Role of surgery versus radioactive iodine (I131). *Ann Surg*. 1994;219:587-593; discussion 593-585.
9. Duren M, Yavuz N, Bukey Y, et al. Impact of initial surgical treatment on survival of patients with differentiated thyroid cancer: experience of an endocrine surgery center in an iodine-deficient region. *World J Surg*. 2000;24:1290-1294.
10. Tufano RP, Clayman G, Heller KS, et al. Management of recurrent/persistent nodal disease in patients with differentiated thyroid cancer: a critical review of the risks and benefits of surgical intervention versus active surveillance. *Thyroid*. 2014;25:15-27.
11. Urken ML, Milas M, Randolph GW, et al. Tuttle M 2015 A review of the management of recurrent and persistent metastatic lymph nodes in well differentiated thyroid cancer: a multifactorial decision making guide created for the Thyroid Cancer Care Collaborative. *Head Neck*. 2015;37:605-614.
12. Onkendi EO, McKenzie TJ, Richards ML, et al. Reoperative experience with papillary thyroid cancer. *World J Surg*. 2014;38:645-652.
13. Yim JH, Kim WB, Kim EY, et al. The outcomes of first reoperation for locoregionally recurrent/persistent papillary thyroid carcinoma in patients who initially underwent total thyroidectomy and remnant ablation. *J Clin Endocrinol Metab*. 2011;96:2049-2056.
14. Al-Saif O, Farrar WB, Bloomston M, Porter K, Ringel MD, Kloos RT. Long-term efficacy of lymph node reoperation for persistent papillary thyroid cancer. *J Clin Endocrinol Metab*. 2010;95:2187-2194.
15. Clayman GL, Agarwal G, Edeiken BS, Waguespack SG, Roberts DB, Sherman SI. Long-term outcome of comprehensive central compartment dissection in patients with recurrent/persistent papillary thyroid carcinoma. *Thyroid*. 2011;21:1309-1316.
16. Rubello D, Salvatori M, Ardito G, et al. Iodine-131 radio-guided surgery in differentiated thyroid cancer: outcome on 31 patients and review of the literature. *Biomed Pharmacother*. 2007;61:477-481.
17. Schuff KG, Weber SM, Givi B, Samuels MH, Andersen PE, Cohen JI. Efficacy of nodal dissection for treatment of persistent/recurrent papillary thyroid cancer. *Laryngoscope*. 2008;118:768-775.
18. Shah MD, Harris LD, Nassif RG, Kim D, Eski S, Freeman JL. Efficacy and safety of central compartment neck dissection for recurrent thyroid carcinoma. *Arch Otolaryngol Head Neck Surg*. 2012;138:33-37.

Part V

Surveillance for Nodal Recurrence

Chapter 10

Effectiveness of Routine Ultrasonographic Surveillance of Patients with Low-Risk Papillary Carcinoma of the Thyroid

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Abstract

Background

Over the last 15 years, there has been a change in clinical practice for the detection of recurrence in all patients with papillary thyroid cancer (PTC). In the past, recurrence was detected by clinical examination supplemented with fine-needle aspiration cytology; however, routine neck ultrasonography (US) and measurements of serum thyroglobulin were introduced for follow-up in 2000 and are now used widely for recurrence surveillance. The aim of this study was to describe the effectiveness of this changing trend in the use of routine surveillance ultrasonography for the detection of recurrence in low-risk PTC at a single institution.

Methods

Patients undergoing total thyroidectomy for PTC between January 2000 and December 2010 were identified from an institutional database. Of these, 752 (43.1%) were categorized as low risk by the risk stratification of the American Thyroid Association and included for analysis. The number of US examinations per patient per year of follow-up was then determined. The number of recurrences and deaths from disease was recorded similarly.

Results

The median age was 48 years (range, 16–83) and the median follow-up was 34 months (range, 1–148). Between 2003 and 2012, the number of US examinations per patient-year of follow-up increased by 5.3-fold. Over the same time period, 3 structural recurrences (clinically evident neck masses or nodes) were detected with no disease-related deaths.

Conclusion

At our institution, the annual rate of neck US examination increased by 5.3-fold per low-risk PTC patients between 2003 and 2012. Despite this increase, only 3 structural recurrences were detected. The routine use of neck US for surveillance of low-risk PTC patients requires review. (Surgery 2016;159:1390-5.)

Over the last 15 years, there has been a progressive change in the methods employed to detect locoregional recurrence in patients with papillary thyroid cancer (PTC). Detection of locoregional recurrence in the past was by clinical examination supplemented with fine-needle aspiration cytology (FNAC). Now, neck ultrasonography (US) and postoperative measurements of thyroglobulin (Tg) are the mainstay of postoperative surveillance for recurrence.

In the 2006 edition of the management guidelines of the American Thyroid Association (ATA), surveillance US of the neck was recommended every 6 months in the first year and then annually for ≥3–5 years, depending on the patient risk for recurrent disease.[1] This recommendation was based on evidence that suggested that neck US was more sensitive than clinical examination and serum Tg levels alone.[2-5] In the updated 2009 edition, the recommended frequency and duration of surveillance neck US was relaxed to "1 or 2" US examinations in the first postoperative year and then periodically, depending on patient risk.[6] The change in the recommended frequency of surveillance was in part due to the high rate of unwarranted FNAC of minute, subclinical disease as a result of increased neck imaging. In the current 2015 ATA guidelines, recommendations concerning surveillance neck US recommendations remain unchanged with much of surveillance management based on clinician discretion.

The focus of this study was to analyze the impact of the frequency of surveillance neck US in ATA low-risk patients over the past decade and to correlate surveillance practices with detection of recurrence over the same time period. With the rapid increase in low-risk PTC over the past 15 years, optimizing follow-up management in this low-risk category will have substantial clinical and economic benefits.

Methods

After approval by our institutional review board, we identified 1,746 consecutive patients with differentiated thyroid cancer operated on within our institution between 2000 and 2010 from an established institutional database. Patient, tumor, and treatment characteristics were reviewed to categorize patients based on ATA risk stratification (Table I).[6] Patients with nonpapillary histology or ATA intermediate-/high-risk categories were excluded from analysis. Patients with another cancer diagnosis at any time and those treated outside of the head and neck surgical service were also excluded, because this may influence choice of postoperative imaging modality and frequency. After this approach, 752 ATA low-risk PTC patients were available for analysis.

Table I | American Thyroid Association 2009 risk categories for papillary thyroid cancer

Low risk	Intermediate risk	High risk
No local or distant metastases	Microscopic perithyroidal invasion	Macroscopic tumor invasion
All macroscopic disease resected	Cervical lymph node metastases or ^{131}I uptake outside thyroid bed on posttreatment 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		

Follow-up duration was calculated from the date of thyroidectomy to the date last seen by a physician within the thyroid cancer multidisciplinary team at Memorial Sloan Kettering Cancer Center (MSKCC). All follow-up surveillance data were captured between 2003 and 2012. In 2003, we instituted a policy of annual postoperative US surveillance. We therefore elected to analyze the outcomes related to US after the initiation of our US surveillance program in 2003. The annual surveillance US rate relative to outcomes are therefore analyzed for 2003 through to 2012.

The number of thyroid cancer patients under surveillance and the number of surveillance US was recorded for each calendar year with adjustments for a partial year of follow-up (ie, 6 months of follow-up surveillance for the calendar year equates to 0.5 patients). Similarly, the number of neck US performed per calendar year was also recorded. The total number of neck US performed was divided by the total number of patients under surveillance to calculate the average number of surveillance US per patient for each calendar year between 2003 and 2012. All US examinations included in this study were performed within the MSKCC radiology department by head and neck sonographers, not the head and neck surgeons.

Over the past 5 years, we have progressively used preoperative US examinations to assess the lymph nodes in the central and lateral compartment. We published our data recently on our institution's use of preoperative neck US.[7] Assessment of the central compartment for all patients is by intraoperative palpation of the lymph nodes in the central compartment at the time of thyroidectomy. Prophylactic neck dissections are not performed in patients with a clinically N0 neck. Assessment of the lateral neck is performed by palpation at preoperative clinical visit or by preoperative US examination.

Surveillance practices have evolved at our center over recent years. For low risk patients, routine radioactive iodine scans are no longer performed. There is increasing preference for routine, non-stimulated, serum Tg levels and high-resolution US of the thyroid bed and cervical lymph nodes. Current surveillance practices at our institution are shown in Table II.[8]

Locoregional recurrence outcomes were determined by clinical examination supplemented with US or other imaging and FNAC confirmation. Only patients with a recurrence with structural abnormality (enlarged lymph node or mass) confirmed by cytology were considered to have recurrence. Only patients with nodules in the thyroid bed or lateral neck of >1 cm were considered for FNAC. Patients with biochemical recurrence, defined by increased serum levels of Tg, without cytologic or histopathologic confirmation, were not considered sufficient endpoints of disease outcome.

Table II | Postoperative surveillance strategy based on American Thyroid Association risk stratification of papillary thyroid cancer

	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; *RIA*, radioactive iodine.

Results

The median age was 48 years (range, 16–83), and the median follow-up was 34 months (range, 1–148). Fig 1 shows the progressive increase in surgical volume in low-risk PTC patients over time. Low-risk PTC increased from 15 patients in 2000 to 142 patients in 2010, corresponding to a 9.5-fold increase in annual incidence over a decade.

The number of patients with low-risk PTC under surveillance, corresponding number of surveillance US performed, and the recurrence events by calendar year are shown are Table III; 1,115 surveillance neck US were performed on this cohort of low-risk patients between 2003 and 2012. In 2003, 11 neck US were performed for 69 patients under surveillance, or 0.16 US per patient. By 2012, there were 247 US performed for 290 patients being followed, or 0.85 per patient. These changes represent a 5.3-fold increase in the number of surveillance US examinations per patient (Fig 2). Over this time period, adjuvant radioactive iodine therapy for patients with low-risk PTC decreased over the 10-year period from 40% in 2000 to 8.5% in 2010 ($P < .001$; Supplementary Table, available at http://dx.doi.org/10.1016/j.surg.2015.11.018).

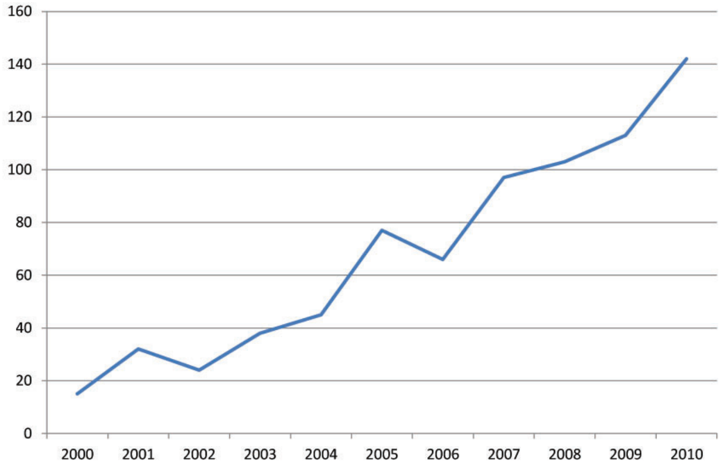

Figure 1 | Number of patients with low-risk papillary thyroid cancer requiring operative management by year.

Table III | Number of patients with low-risk papillary thyroid cancer under surveillance and corresponding number of surveillance US performed by calendar year

ATA Low-risk	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
No of patients followed	69.4	102.4	138.8	179.7	225.8	282.0	347.3	413.8	416.9*	290.2*
No of surveillance US	11	17	27	31	68	104	142	210	258*	247*
No of US per patient	0.16	0.17	0.19	0.17	0.30	0.37	0.41	0.51	0.62	0.85
Recurrence	0	0	0	0	1	0	0	1	1	0

*Only includes patients and US for patients with papillary thyroid cancer between 2000 and 2010.

ATA, American Thyroid Association; *US*, ultrasonography.

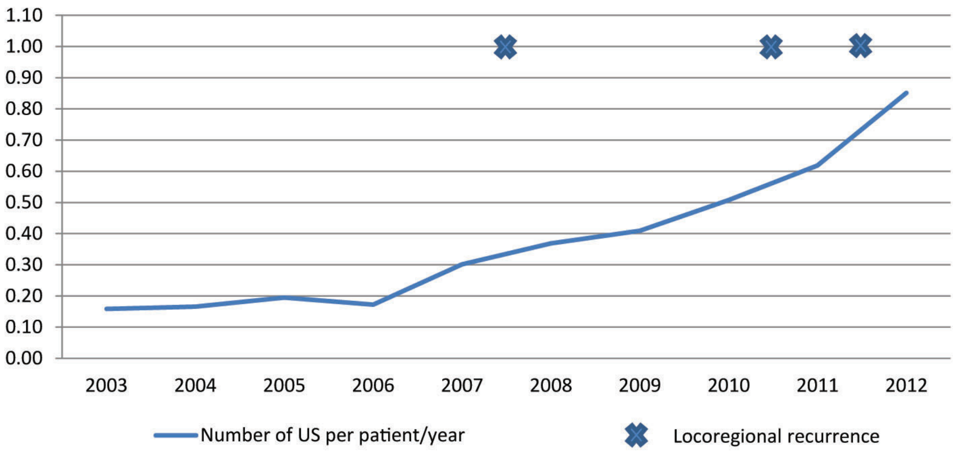

Figure 2 | Number of locoregional structural recurrences and number of surveillance neck ultrasonographies (US) per patient per year of follow-up.

Over the same time period, 3 structural recurrences (0.4%) were detected. All 3 recurrences were detected with routine neck surveillance US. Two patients were found to have thyroid bed nodules confirmed on FNAC and were treated with therapeutic radioactive iodine dose. One patient had an enlarged lateral neck lymph node and was treated with lateral neck dissection. All 3 patients had no evidence of disease at last follow-up, and there were no disease-related deaths in the cohort.

Discussion

Over the last 15 years, there has been a change in the management of thyroid cancer with increased emphasis on a systematic care plan and institution of management guidelines.[1] Traditionally, locoregional recurrences were detected by clinical palpation of the neck supplemented with FNAC when necessary. High-resolution neck US and serum measurements of Tg are now recommended and used in routine surveillance.[6] In this study, we analyzed the impact of this change in the use of surveillance US examinations in patients with low-risk PTC at our institution and correlated these changes with locoregional recurrences over the same time period.

The average number of surveillance US examinations performed on each patient increased from 0.16 to 0.85 during the study period, corresponding with a >5-fold increase over the decade. During this still short follow-up period for PTC, only 3 locoregional recurrences (0.4%) were detected, and there were no disease-specific death events. These data question what is appropriate follow-up of low-risk PTC. Is routine performance of follow-up US always necessary or cost effective in patients with low-risk PTC? If so, how frequently should this be done and for what duration? More controversially, is surveillance of patients with low-risk PTC necessary at all, given the extremely low rates of recurrence? Although we cannot resolve all these issues based on a single institutions experience and still somewhat limited follow-up, the data herein should promote a discussion regarding the clinical and economic aspects of care in patients with low-risk PTC.

Historically, surveillance of PTC patients after surgery was life-long secondary to the belief that recurrence was common and estimated to be as high as 30%. These outcomes reported by Mazzaferri et al,[9,10] however, were based on patients treated 30–40 years ago. More recent literature suggests that recurrence rates are substantially less.[11-14] Patients with low-risk PTC have an excellent recurrence-free survival of in excess of 97%.[11,12] Durante et al[12] followed 312 consecutive patients with T1aN0M0 classic PTC and with a median follow-up of 6.7 years; there were no structural disease recurrences and no disease-specific deaths. The authors demonstrated that, in a well-selected cohort of patients with very low-risk PTC, outcomes are excellent irrespective of surveillance. Our data along with the recent literature demonstrates clearly that recurrence rates for patients with low-risk PTC are very low. Given this fact, it seems that follow-up imaging should be tailored to the risk of recurrence.

The ATA now categorizes patients with PTC into low, intermediate, and high risk for recurrence and recognizes that follow-up imaging should be tailored to this risk. The ATA guidelines recommend currently neck US 6–12 months postoperatively and then periodically, depending on the risk of recurrent disease and Tg status.[6] Survey results from thyroid cancer clinicians in the United States by Haymart et al,[15] however, demonstrated wide variation in all aspects of long-term management of patients with thyroid cancer. Of the 534 endocrine and nuclear medicine physicians surveyed, 45.4% would routinely follow American Joint Committee on Cancer stage I patients with PTC with an undetectable serum Tg level with surveillance US examinations.[15] Limited research, the ready availability of portable US machines, and the clinician concern over missing disease recurrence are likely reasons for the increased use of surveillance US over the past decade.

The rationale for surveillance US in PTC is based on the fact that neck US is more sensitive than clinical examination or other modalities of disease follow-up.[2,3] Neck US can detect cervical nodal disease as small as 2–3 mm in diameter. Such small nodal recurrence is often difficult to find even intraoperatively in scar tissue and likely has no relevance in the overall oncologic outcome. The use of neck US would be justified if the development of clinically meaningful recurrence was a frequent event; however, the recurrence events in our series have remained remarkably stable with a total of only 3 (0.4%) recurrence events.

Neck US is viewed generally as a safe, low-cost imaging modality with greater sensitivity than clinical examination alone. One may argue that there is no harm associated with routine US surveillance. Also it is important to acknowledge that results of US are known to be highly user dependent and frequently cannot distinguish thyroid bed recurrences from benign nodules.[16,17] In the postoperative setting, indeterminate or false-positive readings on US examination can lead to unnecessary FNAC and additional investigations. Such investigations are associated with additional cost and complications and can lead to unnecessary anxiety for the physician and the patient.[18] Any iatrogenic harm associated with low-risk PTC is difficult to justify, when recurrence rates in ATA low-risk patients are only 3%, and disease-specific mortality is zero. The incidence of PTC is increasing in the United States and worldwide, and the majority of increases are owing to low-risk, and often subclinical, disease.[19-21] Although physicians generally view US as a low-cost imaging modality, from a societal perspective, the cumulative cost of routine US surveillance in all patients with low-risk PTC is substantial and will only continue to increase if not addressed.

It is important to note that our study has several limitations. Owing to its retrospective nature, our study is susceptible to all the limitations associated with such studies. First, many patients are followed ultimately by their local endocrinologist; it is not possible to know how many of these patients also underwent additional surveillance US. Our study therefore, underestimates the true rate of increase in US examinations. Similarly, it may also underestimate the "true" risk of recurrent disease in patients who were followed elsewhere and did not return to our institution when recurrence developed. Second, we report a very low rate of structural recurrence. One may argue that due to the surgical expertise of our high-volume center and the inherent bias of a tertiary referral center, these findings are not generalizable. It is important to emphasize that surgical and medical expertise has remained unchanged at our institution over the study period, yet the rate of surveillance US has increased with no corresponding change in structural recurrence. Nevertheless, we would recommend that similar studies should be repeated at other institutions to establish the generalizability of our findings.

In conclusion, we report a 5.3-fold increase in the use of surveillance neck US for patients with low-risk PTC over a decade. This increase in US surveillance has not resulted in increased detection of structural recurrence events nor improved the already excellent outcomes of this low-risk cohort. The results presented in this study question the benefit and justification of routine and frequent surveillance US in patients with low-risk PTC. We acknowledge that patients with an increased Tg level in the absence of structural abnormality should continue to be followed with serial US; however, the routine use of US in patients with undetectable Tg level seems difficult to justify. In the context of the increasing incidence of low-risk PTC in the United States and worldwide, the clinical and economic implications of routine US surveillance will become more substantial with time if follow-up US use is not rationalized.

Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.surg.2015.11.018.

References

1. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2006;16:109-42.
2. Kouvaraki M, Shapiro S, Fornage B, Edeiken-Monro B, Sherman S, Vassilopoulou-Sellin R, et al. Role of preoperative ultrasonography in the surgical management of patients with thyroid cancer. Surgery 2003;134:946-54; discussion 54–5.
3. Torlontano M, Crocetti U, Augello G, D'Aloiso L, Bonfitto N, Varraso A, et al. Comparative evaluation of recombinant human thyrotropin-stimulated thyroglobulin levels, 131I whole-body scintigraphy, and neck ultrasonography in the follow-up of patients with papillary thyroid microcarcinoma who have not undergone radioiodine therapy. J Clin Endocrinol Metab 2006;91:60-3.
4. Pacini F, Molinaro E, Castagna M, Agate L, Elisei R, Ceccarelli C, et al. Recombinant human thyrotropin-stimulated serum thyroglobulin combined with neck ultrasonography has the highest sensitivity in monitoring differentiated thyroid carcinoma. J Clin Endocrinol Metab 2003;88:3668-73.
5. Bachelot A, Cailleux A, Klain M, Baudin E, Ricard M, Bellon N, et al. Relationship between tumor burden and serum thyroglobulin level in patients with papillary and follicular thyroid carcinoma. Thyroid 2002;12:707-11.
6. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.
7. Wang L, Palmer F, Thomas D, Shaha A, Shah J, Patel S, et al. Preoperative neck ultrasound in clinical node negative differentiated thyroid cancer. J Clin Endocrinol Metab 2014;99:3686-93.
8. Momesso DP, Tuttle RM. Update on differentiated thyroid cancer staging. Endocrinol Metab Clin North Am 2014;43:401-21.
9. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 1994;97:418-28.
10. Mazzaferri EL, Kloos RT. Clinical review 128: current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metab 2001;86:1447-63.
11. Tuttle RM, Tala H, Shah J, Leboeuf R, Ghossein R, Gonen M, et al. Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. Thyroid 2010;20:1341-9.
12. Durante C, Attard M, Torlontano M, Ronga G, Monzani F, Costante G, et al. Identification and optimal postsurgical follow-up of patients with very low-risk papillary thyroid microcarcinomas. J Clin Endocrinol Metab 2010;95:4882-8.
13. Durante C, Montesano T, Torlontano M, Attard M, Monzani F, Tumino S. Papillary thyroid cancer: time course of recurrences during postsurgery surveillance. J Clin Endocrinol Metab 2013;98:636-42.
14. Ito Y, Higashiyama T, Takamura Y, Kobayashi K, Miya A, Miyauchi A. Prognosis of patients with papillary thyroid carcinoma showing postoperative recurrence to the central neck. World J Surg 2011;35:767-72.
15. Haymart MR, Banerjee M, Yang D, Stewart AK, Sisson JC, Koenig RJ, et al. Variation in the management of thyroid cancer. J Clin Endocrinol Metab 2013;98:2001-8.
16. Rondeau G, Fish S, Hann L, Fagin J, Tuttle R. Ultrasonographically detected small thyroid bed nodules identified after total thyroidectomy for differentiated thyroid cancer seldom show clinically significant structural progression. Thyroid 2011;21:845-53.
17. Shin J, Han B, Ko E, Kang S. Sonographic findings in the surgical bed after thyroidectomy: comparison of recurrent tumors and nonrecurrent lesions. J Ultrasound Med 2007;26:1359-66.
18. Robenshtok E, Fish S, Bach A, Dominguez J, Shaha A, Tuttle R. Suspicious cervical lymph nodes detected after thyroidectomy for papillary thyroid cancer usually remain stable over years in properly selected patients. J Clin Endocrinol Metab 2012;97:2706-13.
19. Davies L, Welch HG. Epidemiology of head and neck cancer in the United States. Otolaryngol Head Neck Surg 2006;135:451-7.
20. Davies L, Welch H. Current thyroid cancer trends in the United States. JAMA Otolaryngol Head Neck Surg 2014;140:317-22.
21. Hughes DT, Haymart MR, Miller BS, Gauger PG, Doherty GM. The most commonly occurring papillary thyroid cancer in the United States is now a microcarcinoma in a patient older than 45 years. Thyroid 2011;21:231-6.

Chapter 11

Cost Effectiveness Analysis of Thyroid Cancer Surveillance by ATA Risk-Category

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Abstract

Background

The recent overdiagnosis of subclinical, low-risk papillary thyroid cancer (PTC) coincides with a growing national interest in cost-effective health care practices. The aim of this study was to measure the relative cost-effectiveness of disease surveillance of low-risk PTC patients versus intermediate- and high-risk patients in accordance with American Thyroid Association risk categories.

Methods

Two thousand nine hundred thirty-two patients who underwent thyroidectomy for differentiated thyroid cancer between 2000 and 2010 were identified from the institutional database; 1845 patients were excluded because they had non-PTC cancer, underwent less than total thyroidectomy, had a secondary cancer, or had <36 months of follow-up. In total, 1087 were included for analysis. The numbers of postoperative blood tests, imaging scans and biopsies, clinician office visits, and recurrence events were recorded for the first 36 months of follow-up. Costs of surveillance were determined with the Physician Fee Schedule and Clinical Lab Fee Schedule of the Centers for Medicare and Medicaid Services.

Results

The median age was 44 years (range, 7-83 years). In the first 36 months after thyroidectomy, there were 3, 44, and 22 recurrences (0.8%, 7.8%, and 13.4%) in the low-, intermediate-, and high-risk categories, respectively. The cost of surveillance for each recurrence detected was US $147,819, US $22,434, and US $20,680, respectively.

Conclusions

The cost to detect a recurrence in a low-risk patient is more than 6 and 7 times greater than the cost for intermediate- and high-risk PTC patients. It is difficult to justify this allocation of resources to the surveillance of low-risk patients. Surveillance strategies for the low-risk group should, therefore, be restructured.

Keywords

cost-effectiveness analysis, epidemiology, recurrence, thyroid neoplasm, ultrasonography.

Introduction

The increasing incidence of thyroid cancer in the United States and many parts of the world has been well documented in recent years.[1-3] 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. This is largely due to an increase in the diagnosis of subclinical disease arising largely from increased sensitivity and frequency of ultrasound use.[4] Despite this increase in thyroid cancer incidence, mortality rates have been remarkably stable at 0.5 deaths per 100,000.[1] The combined effect of this increased diagnosis of low-risk disease, increased sensitivity of tools for disease surveillance, and stable disease mortality is a dramatic increase in the pool of papillary thyroid cancer (PTC) survivors in need of disease surveillance. Limited attention has been directed toward the clinical and financial implications for surveillance these thyroid cancer survivors.[5] Which is especially important at a time of growing national interest in cost-effective health care. It is against this backdrop that we sought to analyze our institution's surveillance practice for PTC patients. Our aim was to measure the relative cost-effectiveness of disease surveillance on the basis of American Thyroid Association (ATA) risk categories.

Materials and Methods

Following approval by the Institutional Review Board, records of Two thousand nine hundred thirty-two patients who underwent thyroidectomy for differentiated thyroid cancer between January 2000 and December 2010 at Memorial Sloan Kettering Cancer Center were reviewed. Only surveillance within 36 months of primary total thyroidectomy was included for analysis. The choice for the 3-year time frame was 2-fold. First, the literature suggests that the majority of recurrences in PTC occur within the first 2 to 3 years after the diagnosis.[6] Second, the costs associated with surveillance for thyroid cancer are mostly incurred immediately after surgery. Unless the recurrence event developed within 3 years of surgery, all patients completed 3 years of follow-up. One thousand eight hundred forty-five patients were excluded from the analysis for one or more of the following indications. One hundred two patients (5.5%) were excluded for having nonpapillary histology, 487 patients (26.2%) were excluded for having a secondary cancer diagnosis, 65 patients (3.5%) were excluded because of surgical management outside of the head and neck department, 483 (26.4%) were excluded for less than total thyroidectomy, and 704 patients (38.2%) without a recurrence event and less than 36 months of follow-up were excluded. This left 1087 patients available for analysis. The inclusion cohort was stratified into low, intermediate, and high recurrence risk categories as per the ATA classification system[7] (Table 1).

Table 1 | American Thyroid Association Risk Categories, 2009 Edition

Low Risk	Intermediate Risk	High Risk
No local or distant metastases	Microscopic perithyroidal invasion	Macroscopic tumor invasion
All macroscopic disease resected	Cervical lymph node metastases or ^{131}I uptake outside thyroid bed on posttreatment 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 posttreatment scan, if done		

The number of postoperative serum thyroglobulin (Tg) tests, Tg antibody tests, imaging studies (including ultrasound, computer tomography, magnetic resonance imaging, positron emission tomography, and fine-needle aspiration biopsy), and office visits for thyroid cancer were recorded in the first 36 months of follow-up by retrospective chart review (Fig. 1). Disease recurrence events were similarly recorded.

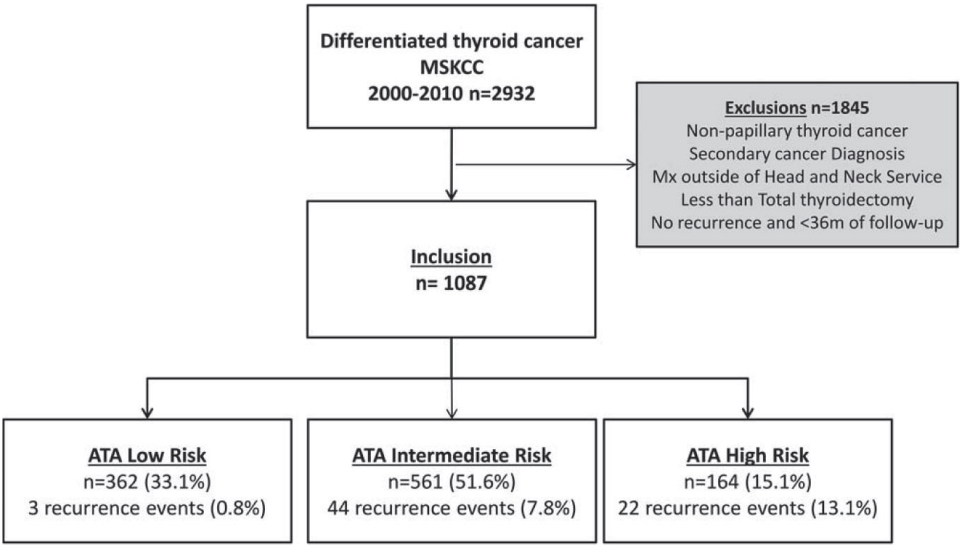


Figure 1 | Inclusion cohort. ATA indicates American Thyroid Association; MSKCC, Memorial Sloan Kettering Cancer Center; Mx, management.

Costs of surveillance were determined with the fee schedules of the Centers for Medicare and Medicaid Services (CMS). For services involving a physician (ie, radiologic or nonlaboratory tests/procedures), the 2014 Medicare National Payment Amount nonfacility reimbursement rates were obtained from the CMS Physician Fee Schedule Search Web site through the entry of the appropriate Current Procedural Terminology/Healthcare Common Procedure Coding System code.[8] Current Procedural Terminology codes are a trademark of the American Medical Association; they correspond to Medicare's Healthcare Common Procedure Coding System level I codes. The dollar amount includes the "26" professional component and the technical component. For laboratory services, the 2014 CMS Clinical Lab Fee Schedule was used to determine midpoint reimbursement fees.[9]

The total cost of surveillance for each ATA risk category was calculated by the summation of the cost of each surveillance investigation for each patient within the risk category. The cost of surveillance for an average patient was calculated by the division of the total cost by the number of patients under surveillance in each risk group. The benefit of disease surveillance was measured by the detection of recurrence events in each ATA risk category. The cost to detect 1 recurrence event was calculated by the division of the cost of surveillance for all patients by the number of recurrence events in each respective risk category.

The calculated ratios of cost per recurrence were dependent in this analysis on actual clinical data of events gathered from this cohort. Therefore, a deterministic sensitivity analysis was performed to analyze the robustness of these results. In the first sensitivity analysis, we varied the rate of recurrences by a factor of 3 in all risk groups and determined the cost per recurrence. We chose a factor of 3 because this approximates higher published rates of recurrence based on 2009 ATA risk stratification.[10,11] For the second sensitivity analysis, we varied the rate of testing. Specifically, we varied the rate of ultrasonography by a factor of 3 in all risk groups and determined the cost per recurrence. We only to vary chose ultrasound rates because our observed rates of 1 to 2 ultrasounds per patient in a 3-year period might realistically be as high as 6 at some institutions (every 6 months as suggested as a maximum in the 2009 ATA guidelines). We did not vary the number of other tests because 1) it seems unlikely that patients would get several factors more or less of Tg or radioactive iodine scans than our observed group, for example and 2) there are no guidelines or published higher or lower rates of these other tests and procedures.

Results

The median age was 44 years (range, 7-83 years). Three-hundred sixty-two patients (33.3%) were low-risk, 561 (51.6%) were intermediate-risk, and 164 (15.1%) were high-risk according to the ATA. The rates of recurrence in the low-, intermediate-, and high-risk groups were 0.8% (n 5 3), 7.8% (n 5 44), and 13.4% (n 5 22), respectively.

Surveillance Cost per Patient

Table 2 presents the Medicare cost associations with thyroid cancer surveillance as per the CMS reimbursement schedules.[8,9] The number of surveillance office visits with Memorial Sloan Kettering clinicians and the number of serum Tg, Tg antibody, and imaging scans performed in the first 36 months of surveillance at our institution are shown in Table 3 and Figure 2. The overall Medicare reimbursement cost of surveillance was US $443,456 for low-risk patients, US $987,080 for intermediate-risk patients, and US $454,961 for all high-risk patients (ATA categories). For patients in the low-, intermediate-, and high-risk categories, the Medicare reimbursement cost of surveillance was US $1225, US $1760, and US $2774 respectively. The relative cost of surveillance for an individual patient with an intermediate risk of recurrence was 1.4 times the cost of surveillance for a low-risk patient. For a patient with a high risk of recurrence, the surveillance cost was 2.3 times greater than that for a low-risk patient.

Table 2 | Cost per Surveillance Modality

	Cost (US $)	CPT/HCPCS Code	Source
Office visit	73.08	99213	CMS Physician Fee Schedule
Tg test	29.61	84432	CMS Clinical Lab Fee Schedule
Tg Ab test	29.32	86800	CMS Clinical Lab Fee Schedule
Neck ultrasound	123.59	76536	CMS Physician Fee Schedule
FNA of neck	295.89	—[a]	CMS Physician Fee Schedule
RAI scan	319.54	78018	CMS Physician Fee Schedule
CT scan	247.89	70491	CMS Physician Fee Schedule
MRI scan	510.47	70543	CMS Physician Fee Schedule
PET scan	693.51	—[b]	CMS Physician Fee Schedule

Abbreviations: Ab, antibody; CMS, Centers for Medicare and Medicaid Services; CPT, Current Procedural Terminology; CT, computed tomography; FNA, fine-needle aspirate; HCPCS, Healthcare Common Procedure Coding System; MRI, magnetic resonance imaging; PET, positron emission tomography; RAI, radioactive iodine; Tg, thyroglobulin

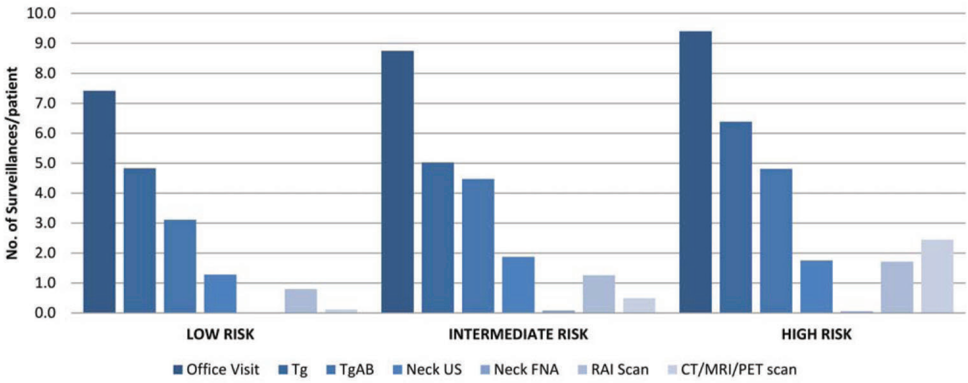
[a] Multiple codes are billed when this study is performed: initial for adequacy ($146.87, code 88173); first determination ($54.45, code 88172); and special stains, first group ($94.57, code 88312).

[b] Multiple codes are billed when this study is performed: PET component ($124.31, code 78815), CT chest ($241.80, code 71260); and CT abdomen/ pelvis ($327.40, code 74177)

Table 3 | First 3 Years of Surveillance for Patients With Papillary Thyroid Cancer Undergoing Operations Between 2000 and 2010

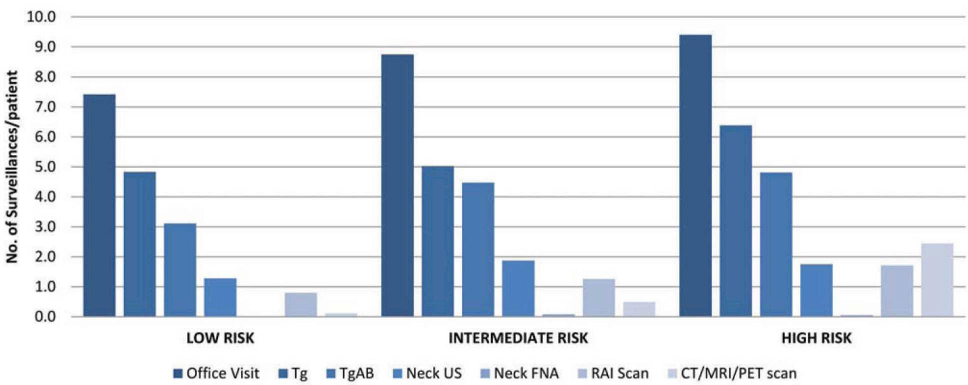
			Surveillance Investigations in 36 mo, (per risk category)							Surveillance Cost (US $)		
ATA Risk Category	**Patients, No. (%)**	**Recurrences, No. (%)**	**Office Visit**	**Tg**	**Tg Ab**	**Neck US**	**Neck FNA**	**RAI Scan**	**CT/MRI/ PET Scan**	**Overall Cost**	**Cost per Patient**	**Cost per Recurrence**
Low	362 (33.3)	3 (0.8)	2686 (7.4)	1748 (4.8)	1127 (3.1)	462 (1.3)	7 (0.02)	288 (0.80)	39 (0.11)	443,456	1225	147,819
Intermediate	561 (51.6)	44 (7.8)	4907 (8.7)	2817 (5.0)	2509 (4.5)	1050 (1.9)	43 (0.08)	706 (1.26)	275 (0.49)	987,080	1760	22,434
High	164 (15.1)	22 (13.4)	1542 (9.4)	1047 (6.4)	789 (4.8)	287 (1.8)	8 (0.05)	281 (1.71)	401 (2.45)	454,961	2774	20,680
Total	1087	69	9135	5612	4425	1799	58	1275	715	1,885,497	1735	27,326

Abbreviations: Ab, antibody; ATA, American Thyroid Association; CT, computed tomography; FNA, fine-needle aspirate; MRI, magnetic resonance imaging; PET, positron emission tomography; RAI, radioactive iodine; Tg, thyroglobulin; US, ultrasound.



ATA Risk category	No. of patients	Surveillance per patient						
		Office Visit	Tg	TgAB	Thyroid US	Neck FNA	RAI Scan	CT/MRI/ PET scan
Low-risk	362	7.4	4.8	3.1	1.3	0.0	0.8	0.1
Intermediate-risk	561	8.7	5.0	4.5	1.9	0.1	1.3	0.5
High-risk	164	9.4	6.4	4.8	1.8	0.0	1.7	2.4

Figure 2 | Surveillance by ATA risk category in the first 3 years after thyroidectomy. Ab indicates antibody; ATA, American Thyroid Association; CT, computed tomography; FNA, fine-needle aspirate; MRI, magnetic resonance imaging; PET, positron emission tomography; RAI, radioactive iodine; Tg, thyroglobulin; US, ultrasound.



ATA Risk category	No. of patients	Surveillance per patient						
		Office Visit	Tg	TgAB	Thyroid US	Neck FNA	RAI Scan	CT/MRI/ PET scan
Low-risk	362	7.4	4.8	3.1	1.3	0.0	0.8	0.1
Intermediate-risk	561	8.7	5.0	4.5	1.9	0.1	1.3	0.5
High-risk	164	9.4	6.4	4.8	1.8	0.0	1.7	2.4

Figure 3 | Surveillance ATA risk category in the first 3 years after thyroidectomy. Ab indicates antibody; ATA, American Thyroid Association; CT, computed tomography; FNA, fine-needle aspirate; MRI, magnetic resonance imaging; PET, positron emission tomography; RAI, radioactive iodine; Tg, thyroglobulin; US, ultrasound.

Table 4 | Sensitivity Analysis 1: 3 Times the Number of Recurrences

			Surveillance Investigations in 36 mo, Total (per risk category)							Surveillance Cost (US $)		
ATA Risk Category	**Patients, No. (%)**	**Recurrences, No. (%)**	**Office Visit**	**Tg**	**Tg Ab**	**Neck US**	**Neck FNA**	**RAI Scan**	**CT/MRI/ PET Scan**	**Overall Cost**	**Cost per Patient**	**Cost per Recurrence**
Low	362 (33.3)	9 (2.5)	2686 (7.4)	1748 (4.8)	1127 (3.1)	462 (1.3)	7 (0.02)	288 (0.80)	39 (0.11)	443,456	1225	49,272
Intermediate	561 (51.6)	132 (23.5)	4907 (8.7)	2817 (5.0)	2509 (4.5)	1050 (1.9)	43 (0.08)	706 (1.26)	275 (0.49)	987,080	1760	7,477
High	164 (15.1)	66 (40.2)	1542 (9.4)	1047 (6.4)	789 (4.8)	287 (1.8)	8 (0.05)	281 (1.71)	401 (2.45)	454,961	2774	6,893
Total	1087	207	9135	5612	4425	1799	58	1275	715	1,885,497	1735	9108

Abbreviations: Ab, antibody; ATA, American Thyroid Association; CT, computed tomography; FNA, fine-needle aspirate; MRI, magnetic resonance imaging; PET, positron emission tomography; RAI, radioactive iodine; Tg, thyroglobulin; US, ultrasound.

Table 5 | Sensitivity Analysis 2: 3 Times the Number of Neck Ultrasounds

			Surveillance Investigations in 36 mo, Total (per risk category)							Surveillance Cost (US $)		
ATA Risk Category	**Patients, No. (%)**	**Recurrences, No. (%)**	**Office Visit**	**Tg**	**Tg Ab**	**Neck US**	**Neck FNA**	**RAI Scan**	**CT/MRI/ PET Scan**	**Overall Cost**	**Cost per Patient**	**Cost per Recurrence**
Low	362 (33.3)	3 (0.8)	2686 (7.4)	1748 (4.8)	1127 (3.1)	1386 (3.8)	7 (0.02)	288 (0.80)	39 (0.11)	557,653	1540	185,884
Intermediate	561 (51.6)	44 (7.8)	4907 (8.7)	2817 (5.0)	2509 (4.5)	3150 (5.6)	43 (0.08)	706 (1.26)	275 (0.49)	1,246,619	2222	28,332
High	164 (15.1)	22 (13.4)	1542 (9.4)	1047 (6.4)	789 (4.8)	861 (5.3)	8 (0.05)	281 (1.71)	401 (2.45)	525,902	3206	23,904
Total	1087	69	9135	5612	4425	5397	58	1275	715	2,330,174	2143	35,306

Abbreviations: Ab, antibody; ATA, American Thyroid Association; CT, computed tomography; FNA, fine-needle aspirate; MRI, magnetic resonance imaging; PET, positron emission tomography; RAI, radioactive iodine; Tg, thyroglobulin; US, ultrasound.

Surveillance Cost to Detect 1 Recurrence

Next, we calculated the cost of surveillance for each recurrence detected. At 3 years, there were 3, 44, and 22 recurrences in the low-, intermediate-, and high-risk categories, respectively; these values corresponded to recurrence rates of 0.8%, 7.8%, and 13.4% at 3 years. The cost of surveillance to detect 1 recurrence event was greatest for the low-risk cohort at US $147,819. The cost of recurrence detection for the intermediate- and high-risk categories was similar at US $22,434 and US $20,680, respectively (Table 3 and Fig. 3). The cost to detect 1 recurrence event in the low-risk category was 6.6 and 7.1 times greater than the cost in the intermediate- and high-risk categories.

Sensitivity Analyses

Sensitivity analyses were performed to determine the effect on the cost per recurrence if the rates of recurrence and the rates of testing were different from what was observed in our cohort. If the rates of recurrence were 3 times higher (ie, 2.5%, 24%, and 40%), the magnitude difference between the 3 groups would be the same, but the cost to detect a recurrence would be $49,272 in the low-risk group (Table 4). If the rates of ultrasound use were 3 times higher for all groups (3.8%, 5.6%, and 5.3%), the magnitude difference between the low-risk group and the intermediate- and high-risk groups would again be the same, but costs would increase to $185,884 per recurrence for low-risk patients versus $28,332 for intermediate-risk patients and $23,904 for high-risk patients (Table 5).

Discussion

Thyroid cancer detection is continuing to rise with an increasing shift toward low-risk PTC in the United States. These trends coincide with a growing national interest in cost-effective health care practices. The aim of our study was to analyze the cost-effectiveness of PTC surveillance in the first 3 years after surgery for low-risk patients versus intermediate- and high-risk patients according to ATA categories. To our knowledge, this is the first study to investigate the cost-effectiveness of posttreatment PTC disease surveillance. As anticipated, we found that the relative cost of the surveillance of higher risk patients to be greater than that of lower risk patients. The surveillance cost of intermediate- and high-risk PTC patients was 1.4 and 2.3 times greater than the surveillance cost of a low-risk patient. More importantly, the cost to detect 1 recurrence event in the low-risk category was 7 times greater than that for the high-risk category (low risk, US $147,819; high-risk, US $20,680). Changing the frequency of recurrence or the frequency of testing in sensitivity analyses led to different dollar amounts but did not eliminate the magnitude of the differences between the groups. Because of the epidemic proportional rise in the incidence of low-risk thyroid cancer, it is important to question this allocation of health resources to the surveillance of low-risk PTC patients after initial treatment.

What Are Current Management Recommendations?

The ATA management guideline recommendations for surveillance are based on a patient's risk of disease recurrence. The 2009 and 2015 editions of the ATA guidelines recommend surveillance neck sonography 6 to 12 months after the operation and then periodically according to the patient's risk of recurrent disease and Tg status.[7] Much of the recommended long-term surveillance regimen is left to the individual physician's interpretation and discretion. This is reflected in the wide variation in long-term thyroid cancer management strategies in a survey conducted among United States–based thyroid cancer clinicians. Of the 534 United States–based endocrine and nuclear medicine physicians surveyed, more than 45% reported that they would routinely follow American Joint Committee on Cancer stage I patients with an undetectable serum

Tg level with surveillance ultrasound.12 However, despite management guidelines suggesting risk-stratified surveillance, there is significant variation in the surveillance strategies being performed.

Why It Is Important to Address Low-Risk PTC Surveillance Practices?

The estimated annual cost of thyroid cancer to the US health care system is expected to increase from $1.4 billion in 2010 to $2.4 billion in 2019 with current practice standards.[5] The incidence of thyroid cancer increased nearly 3-fold between 1975 and 2009, and almost all of this was due to an increase in PTC. Furthermore, this increase is dominated by low-risk PTC cases, many of which are papillary microcarcinomas. In 2009, 39% of all new thyroid cancer diagnoses were 1 cm or smaller, whereas only 25% of cases were 20 years ago.[1] Because of these well-documented epidemiological trends of increasing low-risk PTC in conjunction with stable disease mortality, the reservoir of thyroid cancer survivors in the community will continue to increase at an exponential rate. Medical resources associated with disease surveillance for these thyroid cancer survivors will further increase. A recent Surveillance, Epidemiology, and End Results Medicare database study demonstrated a trend toward increased use of postdiagnostic imaging modalities across all risk categories over recent decades.[13] Although thyroid cancer is a disease with a relatively low clinical recurrence and death burden, the economic burden of the disease is not insignificant and continues to grow. A review of surveillance practices to improve cost-effectiveness in low-risk PTC could significantly curb the rising costs of thyroid cancer management.

The increase in low-risk thyroid cancer is occurring during a time of increasing concern over health care spending. In 2012, US national health expenditures were estimated at $2.8 trillion, or 18% of the gross domestic product, the highest of any developed country. Cancer care accounted for an estimated $124.6 billion in medical care.[14] It is anticipated that by 2022, national health spending will account for nearly one-fifth of the US economy.[15] The escalation in health care costs is a growing burden on society and poses a great challenge to all aspects of government and medicine. As physicians, we have a responsibility to recognize the significance of the situation, encourage open discussion and research, and move toward more sustainable and cost-effective care.

What Is the Physician's Role and Position on Cost-Effective Practices?

In general, most physicians are aware of the costs of health care. However, studies suggest that physicians often hold more conflicted views about the implementation of cost-effective health care delivery. In a cross-sectional survey mailed to more than 3800 US physicians (response rate, 65%), it was found that most physicians agreed that "trying to contain costs is the responsibility of every physician" and that "doctors need to take a more prominent role in limiting use of unnecessary tests." The same group of physicians disagreed with the statement that they "should sometimes deny beneficial but costly services to certain patients because resources should go to other patients that need them more."[16] Similar inconsistencies are demonstrated in a survey of US and Canadian oncologists. When directly asked how much benefit a new drug would need to provide to justify its cost and warrant its use, the majority of oncologists agreed that less than $100,000 per life-year gained would be worthwhile therapy. However, when this was rephrased in the context of a hypothetical patient case, the oncologists endorsed a cost as high as $250,000 per life-year gained.[17] This inconsistency is likely a reflection of the tension between the fundamental principles of beneficence and nonmaleficence (to individual patients) and justice (to society as a whole). When this is applied to PTC surveillance, the low cost-effectiveness of surveillance in low-risk PTC patients suggests that as a subspecialty we have tipped too far toward beneficence for the individual, low-risk patient and away from concerns about justice for non–low-risk patients.

What Evidence Is There for Surveillance of Low-Risk Patients?

Commonly, the thyroid cancer recurrence rate is quoted at 30%. This outcome was reported by Mazzaferri et al[18,19] for patients treated 30 to 40 years ago, most of whom had clinically palpable primary or nodal disease at the time of presentation. Our subspecialty's vigilance for surveillance in PTC is still deeply influenced by the outcomes of Mazzaferri et al's publications of thyroid cancer outcomes. Many recent publications have demonstrated substantially lower recurrence rates of 3% to 10%.[10,20-22] Durante et al[20] followed 312 consecutive stage T1aN0M0 patients with classic PTC, and with a median follow-up of 6.7 years, the group reported no structural disease recurrence events and no disease-specific deaths.[20] Our data, along with the recent literature, clearly demonstrate that recurrence rates for low-risk PTC are very low. Several publications in recent years have similarly recognized a need for reduced PTC surveillance[23] based on the risk of recurrence.[24] The challenge now is to recalibrate surveillance regimes to reflect modern recurrence outcomes for more cost-effective surveillance practices.

Limitations

It is important to note that our study has several limitations. Because of its single-institution and retrospective nature, our study is susceptible to a selection bias due to physician management and the large number of patients excluded from the analysis. We report the results from an institution with a high volume of thyroid cancer and decades of experience in the management of PTC. Our experience is characterized by a very low structural recurrence rate. This is a limitation of the study, and consequently, our results may not be translatable to the wider community. The threshold for instigating surveillance investigations is also likely to be different between centers. Physicians at our center have previously advocated for a higher threshold before biopsy of suspicious ultrasound findings.[25] This would also influence the cost-effectiveness of surveillance practices if our findings were applied to other centers. Second, surveillance practices evolved during the inclusion period. Current surveillance practices are presented in Table 6.[26] The cost-effectiveness data presented are, therefore, averaged for 2000 to 2010. A prospectively conducted, multi-institution study would better ensure uniformity of the patient cohort as well as subsequent management.

Table 6 | Postoperative Surveillance Strategy Based on the American Thyroid Association Risk Category

	6 mo	12 mo	18 mo	24 mo
Thyroglobulin	All	All	All	All
Neck ultrasound	—	All	—	All
Diagnostic RAI scan	—	—	Intermediate/high risk	—
CT/MRI	—	High risk	—	High risk
PET scan	—	High risk	—	High risk

Abbreviations: All, low, intermediate, and high risk; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; RAI, radioactive iodine.

The cost to detect a recurrence in a low-risk patient is more than 7 times greater than the cost for a high-risk papillary thyroid cancer patient. It is difficult to justify this allocation of resources, and surveillance strategies for the low-risk group should be reviewed.

Other limitations are related to the degree to which we might be underestimating the true cost of surveillance practices. For example, some patients had additional surveillance investigations performed outside Memorial Sloan Kettering Cancer Center, often for personal or logistic reasons. It is not possible to know how many patients or which additional surveillance investigations were performed. In addition, the data used for costs are from CMS reimbursement schedules, and those costs may be below the costs and charges for patients with private insurance. Finally, we have not accounted for the costs and harms of surveillance practices, which are hard to measure in dollars (eg, days of work missed and harm from needle biopsy or contrast imaging). Ultimately, the question of whether or not our data can be extrapolated to the general population should be explored by an analysis of the incidence of disease recurrence and surveillance practices at other high-volume thyroid surgery centers.

In summary, we have demonstrated that the Medicare reimbursement cost to detect a recurrence event in a low-risk patient (ATA category) is more than 6 times greater than the cost to detect a recurrence event in a high-or intermediate-risk patient at US $147,819. We acknowledge, of course, that this dollar amount could not possibly be representative of the costs of surveillance nationally. Regardless, our findings raise important questions regarding the allocation of health care resources and the ways in which surveillance of low-risk PTC patients should be tailored to maximize effectiveness. Currently, in this cohort, we believe that the cost of surveillance for PTC patients is unjustifiably greater for low-risk patients. In light of the continued rise in the incidence of low-risk PTC, surveillance costs will continue to increase. We cannot comprehensively resolve this issue on the basis of a single institution's experience. We, therefore, encourage other centers to review the cost-effectiveness of their surveillance practices for their own low-risk PTC patients. We hope to promote discussion on appropriate PTC surveillance practices that reflect contemporary recurrence rates so that we can improve the cost-effectiveness of thyroid cancer management.

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Conflict of Interest Disclosures

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References

1. Davies L, Welch H. Current thyroid cancer trends in the United States. *JAMA Otolaryngol Head Neck Surg.* 2014;140:317-322.
2. Davies L, Welch HG. Thyroid cancer survival in the United States: observational data from 1973 to 2005. *Arch Otolaryngol Head Neck Surg.* 2010;136:440-444.
3. Blomberg M, Feldt-Rasmussen U, Andersen KK, Kjaer SK. Thyroid cancer in Denmark 1943-2008, before and after iodine supplementation. *Int J Cancer.* 2012;131:2360-2366.
4. Wang L, Palmer F, Thomas D, et al. Preoperative neck ultrasound in clinical node negative differentiated thyroid cancer. *J Clin Endocrinol Metab.* 2014;99:3686-3693.
5. Aschebrook-Kilfoy B, Schechter RB, Shih YC, et al. The clinical and economic burden of a sustained increase in thyroid cancer incidence. *Cancer Epidemiol Biomarkers Prev.* 2013;22:1252-1259.
6. Young S, Harari A, Smooke-Praw S, Ituarte P, Yeh M. Effect of reoperation on outcomes in papillary thyroid cancer. *Surgery.* 2013;154:1354-1361.
7. Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid.* 2009;19:1167-1214.
8. Centers for Medicare and Medicaid Services. Physician Fee Schedule Search. http://www.cms.gov/apps/physician-fee-schedule/search/search-criteria.aspx. Accessed November 1, 2014.
9. Centers for Medicare and Medicaid Services. Clinical Lab Fee Schedule. http://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/clinlab.html. Accessed November 1, 2014.
10. Tuttle RM, Tala H, Shah J, et al. Estimating risk of recurrence in differentiated thyroid cancer after total thyroidectomy and radioactive iodine remnant ablation: using response to therapy variables to modify the initial risk estimates predicted by the new American Thyroid Association staging system. *Thyroid*. 2010;20:1341-1349.
11. Pitoia F, Bueno F, Urciuoli C, Abelleira E, Cross G, Tuttle RM. Outcomes of patients with differentiated thyroid cancer risk-stratified according to the American Thyroid Association and Latin American Thyroid Society risk of recurrence classification systems. *Thyroid*. 2013;23:1401-1407.
12. Haymart MR, Banerjee M, Yang D, et al. Variation in the management of thyroid cancer. *J Clin Endocrinol Metab.* 2013;98:2001-2008.
13. Wiebel JL, Banerjee M, Muenz DG, Worden FP, Haymart MR. Trends in imaging after diagnosis of thyroid cancer. *Cancer.* 2015;121:1387-1394.
14. National Cancer Institute. Cancer trends progress report—2011/2012 update. http://progressreport.cancer.gov/sites/default/files/archive/report2011.pdf. Accessed June 2015.
15. Centers for Medicare and Medicaid Services. National health expenditure projections 2012-2022. http://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/National-HealthExpendData/downloads/proj2012.pdf. Accessed November 15, 2014.
16. Tilburt JC, Wynia MK, Sheeler RD, et al. Views of US physicians about controlling health care costs. *JAMA*. 2013;310:380-388.
17. Ubel PA, Berry SR, Nadler E, et al. In a survey, marked inconsistency in how oncologists judged value of high-cost cancer drugs in relation to gains in survival. *Health Aff (Millwood).* 2012;31:709-717.
18. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. *Am J Med.* 1994;97:418-428.
19. Mazzaferri EL, Kloos RT. Clinical review 128: current approaches to primary therapy for papillary and follicular thyroid cancer. *J Clin Endocrinol Metab.* 2001;86:1447-1463.
20. Durante C, Attard M, Torlontano M, et al. Identification and optimal postsurgical follow-up of patients with very low-risk papillary thyroid microcarcinomas. *J Clin Endocrinol Metab.* 2010;95:4882-4888.
21. Durante C, Montesano T, Torlontano M, Attard M, Monzani F, Tumino S. Papillary thyroid cancer: time course of recurrences during postsurgery surveillance. *J Clin Endocrinol Metab.* 2013;98:636-642.
22. Ito Y, Higashiyama T, Takamura Y, Kobayashi K, Miya A, Miyauchi A. Prognosis of patients with papillary thyroid carcinoma showing postoperative recurrence to the central neck. *World J Surg.* 2011;35:767-772.
23. Wu JX, Beni CE, Zanocco KA, Sturgeon C, Yeh MW. Cost-effectiveness of long-term every three-year versus annual postoperative surveillance for low-risk papillary thyroid cancer. *Thyroid*. 2015;25:797-803.
24. Durante C, Costante G, Filetti S. Differentiated thyroid carcinoma: defining new paradigms for the post-operative management. *Endocr Relat Cancer.* 2013;20:R141-R154.

25. Rondeau G, Fish S, Hann LE, Fagin JA, Tuttle RM. Ultrasono-graphically detected small thyroid bed nodules identified after total thyroidectomy for differentiated thyroid cancer seldom show clinically significant structural progression. *Thyroid*. 2011;21:845-853.

26. Momesso DP, Tuttle RM. Update on differentiated thyroid cancer staging. *Endocrinol Metab Clin North Am*. 2014;43:401-421.

Chapter 12

Discussions, Conclusions and Future Directions

Dicussion

Our main objective was to perform a comprehensive characterization of the spectrum of nodal disease in well differentiated thyroid cancer. The studies presented in this thesis show that well differentiated thyroid cancer is common with excellent survival outcomes in a great majority of patients. Between 1986-2010, 3664 patients were diagnosed and treated with well differentiated thyroid cancer in the Head and Neck service, while 39 patients were diagnosed with poorly differentiated thyroid cancer and 95 patients with anaplastic thyroid cancer. The cohort of previously untreated, well differentiated thyroid cancers comprised of 73% females, with PTC accounting for 93.8% of histologies (Table 1). Patients with T1 disease accounted for 51.2%, central neck disease in the absence of lateral neck disease was identified in 15.0% of patients and an additional 15.3% of patients had lateral neck disease at the time of diagnosis. 2% of patients had distant disease at the time of diagnosis. The overall disease specific survival was excellent at 98.6% at 5 years and 96.2% at 10 years (Table 2).

CHAPTER 2: Preoperative Neck Ultrasound in Clinical Node Negative Differentiated Thyroid Cancer

The initial diagnosis of well differentiated thyroid cancer, was typically established through physical examination, imaging with US and FNA confirmation. Work up included a thorough physical examination complemented with an ultrasound to evaluate the extent of primary tumor and any nodal disease in the central compartment. The most frequent site of spread is to the regional cervical lymph nodes. Over the past decade, increased availability and sensitivity of ultrasound has permitted the detection of subclinical disease which would have been previously undiagnosed with physical examination alone. Previous studies have shown US to be more sensitive than clinical examination alone (1). This is particularly true when assessing the lateral compartment of cervical lymph nodes, as this compartment is free from the distorting effects of air in the trachea. A direct comparison of the extent of neck dissection and treatment outcomes following the use of preoperative neck ultrasound had not been evaluated until our publication. Consistent with the literature, 24% of patients with negative clinical examination of the neck were found to have suspicious lymph nodes on ultrasound. We carried out a direct comparison of patients with and without preoperative neck ultrasound and demonstrated that preoperative neck ultrasound increased the rate of initial lateral neck dissection from 0.9% to 13.2%. The preoperative ultrasound cohort undergoing neck dissection had lower postoperative unstimulated Tg levels (0.09ug/ml vs. 0.6 ug/ml, p=0.004), reduced need for adjuvant RAI therapy (30% vs. 43%, p= 0.004), and reduced rate of salvage neck dissections (0.9% vs. 4.3%, *p =0.018*) (2). We conclude that preoperative use of ultrasound identifies patients who may benefit from upfront lateral neck dissection affording the patient a more comprehensive initial clearance of disease.

CHAPTER 3: Level 7 Disease Does Not Confer Worse Outcome Than Level 6 Disease in Differentiated Thyroid Cancer

The central compartment is important in thyroid cancer as it is the first echelon of nodal spread. This nodal compartment encompasses the fibrofatty tissue between the two carotid arteries laterally, hyoid bone, superiorly and innominate artery inferiorly. It also contains the thyroid gland as well as the parathyroid glands, recurrent and superior laryngeal nerves. The central compartment is further divided into an upper (level 6) and a lower (level 7), also termed the anterior mediastinal nodes. The junction between these two levels is demarcated by the level of the sternal notch. On cross sectional imaging, the sternal notch is a definite bony landmark. However, in the operating room with the patient lying supine, the demarcation of the sternal notch is highly variable based largely on the degree of cervical extension. At the time of publication, of our study presence of level VII disease, upstaged it to N1b status according to the 7th edition of the AJCC staging system. In older patients this resulted in upstaging from stage III to stage IV disease. However, this recommendation for the upstaging level VII disease was based on expert recommendation. Data from our publication demonstrated that overall recurrence free survival and disease specific survival for patients with level VI vs. level VII nodal disease were statistically comparable. (3). Our data contributed to the revision of the nodal staging for level VII to N1a in the AJCC 8th edition in 2017, where all lymph nodes in the central compartment (Level VI and level VII) are now grouped together in the N1a category.

CHAPTER 4: Central Neck Failure in Patients with Papillary Thyroid Cancer and Incidentally Discovered Level 6 Lymph Nodes

Cancer is characterized by its ability to spread to adjacent structures, to regional lymphatics and to distant sites. As the central compartment lymph nodes are the most common site of initial spread, patients with central compartment nodal metastases may be considered to have more aggressive disease, with higher risk of recurrence. As such, clinicians administer adjuvant RAI therapy, often for a concern of residual nodal metastases in order to reduce the risk of recurrence in these patients. When routine histopathological examination of thyroidectomy specimens detects unexpected microscopic LN metastases in perithyroidal lymph nodes adjacent to the thyroid gland, physicians are faced with a clinical decision on whether to reoperate, and complete a central compartment node dissection, treat these patients with RAI or to observe. The management and outcomes of patients with incidentally found occult, perithyroidal LN metastases in thyroidectomy specimen, however has not been studied. Commonly used management guidelines do not specifically address this scenario. In such circumstances clinicians often offer patients additional treatment for concern of undertreatment with an increased risk of recurrence in the central neck compartment. We identified a subset of patients with well differentiated, encapsulated thyroid tumors who underwent only a total thyroidectomy, and no formal neck dissection and were found to have incidental perithyroidal (central compartment) lymph node metastases on routine histopathological evaluation of the thyroid gland. The characteristics of these central nodal metastases and further treatment were further scrutinized. The median number of positive central lymph nodes removed was 1 (range 1-8), the median size of disease containing lymph node removed was 5mm (1-16mm). No patients returned to the OR for immediate completion central neck dissection, 64% received adjuvant RAI therapy and 34% were only on surveillance/observation. The 5 year central neck recurrence free survival was 96% in the RAI treated cohort vs. 95% in the observation group (*$p = 0.92$*). We report that in selected patients with low risk features such as lymph nodes < 2mm, fewer involved nodes, encapsulated primary disease without lymphovascular invasion may be observed safely without additional surgery or adjuvant RAI (4). Our observations provided support to the 2015 recommendations of the ATA to downstage intermediate risk patients (according to 2009 recommendations), to low risk group if they have less than 5 lymph nodes and less than 2 mm metastatic deposits.

CHAPTER 5: Characteristics of Lymph Nodes Predictive of Outcome in the Central Neck

Routine histopathological evaluation is increasingly more rigorous. Finer histopathological sections, comprehensive review of all specimen slides, synoptic reporting and dedicated pathologists with thyroid focus have led to greater detail and accuracy of thyroid cancer histopathological reports in recent years. Details such as size of metastatic deposit in the lymph nodes, number of involved lymph nodes, total number of resected lymph nodes, and presence of extranodal extension (ENE) are now routinely reported in the synoptic pathology reports as recommended by the College of American Pathologists (CAP). With this new documentation, we can conclude that nodal disease occurs across a continuous spectrum rather than a binary categorization of patients based on presence and absence of nodal disease. At the time of our publication, AJCC stratified nodal disease based on presence (N0 or N+) and location (N1a or N1b), while the ATA grouped all patients with nodal disease in to intermediate or high risk group. To assess the importance of these nodal characteristics we first studied patients with central neck disease in the absence of lateral and distant metastases to identify which central nodal characteristics were most prognostic in determining patient outcomes. It was unclear which central nodal characteristics were most prognostic of outcome, or how such nodal characteristics prognosticate in younger and older patients. In our study we found increasing nodal size, number of nodal metastases and presence of ENE were predictive for neck recurrence. In the central compartment, the strongest independent predictor of nodal recurrence was the presence of ENE. Twenty three percent (23%) of N1a patients had ENE seen on pathology review. Patients with ENE had significantly poorer 5 year nodal RFS (recurrence free survival) of 85% compared to 95% in those without ENE (*p=0.001*). While patients with evidence of central nodal disease and ENE on pathology have a slightly increased risk of nodal recurrence, these patients can be reassured that they are not at increased risk of distant recurrence or death compared to other N1a patients without ENE (5).

CHAPTER 6: Characteristics of Lymph Nodes Predictive of Outcome in the Lateral Neck

We then carried out an analysis of patients with lateral compartment or N1b disease. In addition to analyzing metastatic nodal size, number and ENE, we additionally analyzed our data to determine impact of LN burden (ratio of positive to total LNs removed), which has been reported to be prognostic in other head and cancers (6, 7). We found that the most significant lateral neck nodal characteristic to predict recurrence is nodal burden >17% (or presence of greater than 1 positive LN per 6 removed) in both younger and older patients, conferring a 5 year recurrence free survival of 78% compared to 91% in those with a nodal burden of <17% (*p=0.02*). In the older cohort, the presence of LN ENE also appears important conferring a recurrence free survival of 80% vs 93% at 5 years (*p = 0.03*), in the younger patients and a trend toward poorer distant RFS although in our cohort this did not reach statistical significance (8).

CHAPTER 7: The Impact of Nodal Stage on Outcome in Older Patients with Papillary Thyroid Cancer

Continuing our analysis of patients with lateral nodal disease, we noted that patients who die of disease are usually older patients and tend to develop distant disease prior to their demise. In our next analysis we focused on the older cohort to quantify the magnitude of risk associated with lateral neck disease. We stratified these patients into N0, pathological N1a, and N1b cohorts. The 5 year DSS was 100% for both N0 and pN1a groups while the 5 years DSS for the N1b cohort was significantly lower at 91% *(p = 0.001)*. Patients with pN1b disease similarly had poorer distant RFS compared with pN0/Nx and pN1a patients (84% vs. 99%, *p=0 .001*). The presence of lateral neck disease in older patients was an independent predictor of worse DSS and distant RFS on multivariate analysis, conferring a 10-fold increased risk of distant metastases and death (9).

CHAPTER 8: Pattern of Neck Recurrence Following Lateral Neck Dissection for Cervical Metastases in Papillary Thyroid Cancer

Much of the prognosis of patients with thyroid cancer is dependent on tumor biology. Treatment options offered by clinicians are often secondary. Management of clinically apparent nodal disease in well differentiated thyroid cancer is first and foremost with surgical resection. The extent of lateral neck dissection offered to thyroid cancer patients however varies between clinicians since the optimal extent of dissection is unclear. We therefore went on to compare patients with clinically detectable nodal disease managed by comprehensive lateral neck dissection and those who had a more selective neck dissection. We found that patients undergoing comprehensive lateral neck dissection (level IIa, III, IV, Vb) have comparable rates of neck recurrence compared to patients managed by selective lateral neck dissection (level III, IV, +/-Va). However, the pattern of nodal recurrence is different between the two cohorts of different extents of neck dissection performed. When assessing the rate of recurrence in the ipsilateral operated neck, rates of recurrence at 5 years were significantly lower in the comprehensive neck dissection group (98% vs. 89%, *p = 0.001*). Our data suggests that ipsilateral neck control is improved with a comprehensive initial nodal clearance. We conclude that a comprehensive neck dissection provides the best neck control in patients with lateral neck disease and should be the treatment of choice in patients with clinically or radiologically demonstrated nodal disease. However, selective neck dissection may be considered in patients who have very low volume disease. (10).

CHAPTER 9: Management and Outcome of Clinically Evident Neck Recurrence in Patients with Papillary Thyroid Cancer

Disease recurrence in thyroid cancer occurs most frequently in the neck. Overall recurrence rates in differentiated thyroid cancer are reported to be as high as 30% (11). The most common site of recurrence is in the cervical LNs. However, relatively little is known about recurrence characteristics and outcomes after nodal recurrence. Therefore, next, we went on to assess the outcomes of patients who developed a neck node recurrence. We report an overall nodal recurrence rate of 3% with a median follow up of 62 months in our series. Of the patients that developed a neck recurrence, the majority had advanced stage primary tumor (T3/4) (63%) and 78% had nodal disease at presentation. Nodal recurrence was most common in the lateral neck (74%) followed by the central neck (15%) and both compartments in 10%. These recurrences were treated with surgery alone in 66%, surgery and RAI in 22% and non surgical (RAI or EBRT) in 10%. Reassuringly, the overall 5 year DSS after salvage surgery for nodal recurrence remained excellent at 97% (12).

CHAPTER 10: Effectiveness of Routine Ultrasonographic Surveillance of Patients with Low-Risk Papillary Carcinoma of the Thyroid

Just as preoperative nodal assessment now routinely includes sonographic evaluation, postoperative surveillance for thyroid cancer recurrence also includes routine assessment of the neck for local and regional disease recurrence. As a result, the use of postoperative US surveillance has increased exponentially in recent years. In light of the increasing incidence of differentiated thyroid cancer, particularly in the low-risk category, we went on to measure the cost effectiveness of routine neck ultrasound in the low risk cohort. Between 2000 and 2010, 752 low risk differentiated thyroid cancer patients were surgically managed. With a median follow up of 34 months, the relative number of surveillance ultrasounds increased, from 11 ultrasounds for a total of 69 patients, to 247 ultrasounds in 290 patients under surveillance. This correlates to a 5.3 fold increase in incidence of US with only a total of 3 recurrences detected in the 10 years period. Our study suggested that the increased use of neck sonography for the detection of recurrence is not cost effective and may not be warranted in the low risk cohort (13).

CHAPTER 11: Cost Effectiveness Analysis of Thyroid Cancer Surveillance by ATA Risk-Category

In light of increasing awareness of the cost of healthcare, and continued increase in thyroid cancer diagnoses, we next analyzed the cost of thyroid cancer surveillance with respect to each recurrence event within ATA low, intermediate and high-risk categories. We hypothesized that risk-stratified surveillance is not only safe but also cost-effective. Based on Medicare reimbursements and ATA surveillance recommendations, we calculated the cost to detect one recurrence event in the low risk group was US$147 000, compared to US$22 000 for intermediate risk group and US$21 000 for the ATA high-risk cohort. These estimates are conservative but our analysis highlights the cost of surveillance is at least 7x greater in the low risk cohort. We anticipate the costs associated with thyroid cancer surveillance will continue to increase with the increased diagnoses of low risk thyroid cancer (14). We therefore suggest that the routine use of neck US to detect recurrence in patients with low risk thyroid cancer may not be justifiable.

Conclusions

This thesis is a comprehensive characterization of the clinicopathologic characteristics of a uniform cohort of well differentiated thyroid cancer patients. The cohort of 3664 well differentiated thyroid cancer patients spans the full spectrum of disease severity treated over a 25year period from 1985 to 2010. All of these patients were diagnosed, treated and followed at a single academic tertiary care cancer center, MSKCC.

Developments in technology have resulted in improved ability to detect disease. High resolution computer tomography, ultrasonography and nuclear imaging are common place. Measurements of serum thyroglobulin allow for sensitive detection of potential clinically occult disease. Histopathology slides are reviewed with greater detail and with synoptic reporting. These technological advances have altered the detail with which we can scrutinize patients for evidence of the extent of disease at the time of initial diagnosis, within the surgical specimen and in the surveillance period. Over the same time period, there has been a well-documented global increase in the diagnosis of patients with low risk well differentiated thyroid cancer in particular, the majority of which have been attributed to increased (over) diagnosis. There has also been an increased awareness of cost effective healthcare delivery in the USA. In this thesis, we address the implications of these technological advances in the treatment of well differentiated thyroid cancer patients. We highlight that an increased ability to detect disease does not equate to improvement in patient outcome. The increased ability to detect disease at all timepoints of care, has lead clinicians to face a range of diagnostic, treatment and surveillance dilemmas. Throughout this thesis we analyze how to use this increased ability to detect disease to achieve improved patient outcomes, with consideration of economically effective healthcare delivery.

In Part I we demonstrate that preoperative neck ultrasonography has resulted in increased performance of lateral neck dissections and reduced need for salvage neck dissections in DTC. Analyses in Part II and III, with increased detail of histopathological review of nodal specimens reveal that nodal disease is a heterogeneous cohort associated with varying prognostic implications. Furthermore, patients with low volume nodal disease require an individualized management strategy, not always necessitating adjuvant radioactive iodine therapy. We demonstrate that lymph node characteristics, particularly ENE and lymph node burden are predictors of nodal recurrence at all age groups and distant recurrence in the older age group. Part IV described the pattern of nodal recurrence after lateral neck dissection followed by data showing significantly improved nodal recurrence rates in a modern cohort of differentiated thyroid cancer patients. In Part V, we address the need for risk-stratified and cost-effective surveillance approaches to DTC patients in the context of increasing differentiated thyroid cancer diagnosis around the world.

From our study we can make the following conclusions: some of which have influenced revisions into the 2015 ATA guidelines and 8th edition of the AJCC staging for thyroid cancer:

- Routine preoperative ultrasound assessment of the cervical nodal basins identifies patients who benefit from a therapeutic lateral neck dissection leading to an improvement in recurrence free outcomes.
- Patients with level 7 disease in the anterior mediastinum have comparable outcomes to patients with level 6 disease. The AJCC 8th edition staging system no longer upstages patients to N1b with the presence of level 7 disease.
- Select patients with otherwise favorable primary tumor characteristics and low volume central lymph node metastases may be safely observed without the need for radioactive iodine. The 2015 American Thyroid Association guidelines, now allows for patients with low volume disease (<5 positive central

lymph nodes, smaller than 0.2cm in diameter) to be classified as low risk with the option of avoiding RAI if no high risk primary tumor characteristics are present.

- Pathological lymph node characteristics such as increasing size, number, ratio, and presence of ENE negatively impact on prognosis across a continuum. However these nuances for the extent of nodal disease are not yet fully captured in AJCC staging and ATA risk stratification systems.
- Within the central compartment, nodal metastases with ENE are more prognostic of future nodal recurrence than lymph node size or number in both the older and younger age groups.
- Within the lateral compartment, a high ratio of positive to total lymph nodes resected and presence of ENE are both prognostic of future lateral compartment recurrences in older patients. In younger patients, the ratio of positive to total number of lymph nodes resected also prognosticate for future nodal recurrence.
- Clinically or radiologically evident lateral neck disease warrants therapeutic neck dissection. The extent of therapeutic dissection varies between a selective versus comprehensive lateral neck dissection. The rate of ipsilateral neck recurrence is significantly lower in patients who have a comprehensive neck dissection. Selective neck dissections should only be done in patients with very low volume neck disease confined to 1 or 2 neck levels.
- The most common site of disease recurrence after initial surgery is within the cervical lymph nodes. With appropriate work up and salvage surgery, patient outcomes after nodal recurrence remain excellent with subsequent 5 year disease free survival in excess of 97%.
- Postoperative surveillance neck ultrasound has been routine in the follow up of patients with thyroid cancer including the low risk cohort. Over a period of 10 years, sonography rates in the low risk category have increased 5.3 fold at our center. This led to a total of 3 structural recurrences detected in 752 patients. The relative cost of surveillance in the low risk categories were 6 and 7 times greater than the intermediate and high risk cohorts. Improved cost effective surveillance regimes may be warranted in select low risk patients.

Table 1 | Patient and tumor characteristics

		Total (n= 3664; 100.0%)
Gender	Female Male	2668 (72.8) 996 (27.2)
Age (years) Median (range)	< 45 ≥ 45 < 55 ≥ 55	47 (4-94) 1672 (45.6) 1992 (54.4) 2485 (67.8) 1179 (32.2)
Histology	Follicular Carcinoma Hurthle Cell Carcinoma Papillary Carcinoma	129 (3.5) 99 (2.7) 3436 (93.8)
T Stage	T1 T2 T3 T4	1874 (51.2) 546 (14.9) 1086 (29.6) 158 (4.3)
N Stage	N0 N1a N1b	2555 (69.7) 550 (15.0) 559 (15.3)
M Stage	M0 M1	3592 (98.0) 72 (2.0)
AJCC 7th Stage	Stage I Stage II Stage III Stage Iva Unknown	2539 (69.3) 235 (6.4) 565 (15.4) 322 (8.8) 3 (0.1)
Postoperative RAI	No Yes	2119 (57.8) 1545 (42.2)
Median Follow-up months (range)		55 (0-332)

RAI – radioactive iodine

Table 2 | Overall outcomes

	5-year	**10-year**
Overall survival	94.3%	86.2%
Disease specific survival	98.6%	96.2%
Local regional recurrence free probability	99.5%	98.8%
Regional recurrence free probability	96.6%	94.3%
Distant recurrence free probability	98.1%	96.3%

Future Directions

Contemporary thyroid cancer management is largely based on histopathological features, age and stage at presentation, response to therapy measured by serial thyroglobulin levels and imaging modalities. There is increasing understanding and emphasis on the genomic characteristics of thyroid cancer. However, at this time its role has remained in the realm of thyroid cancer diagnosis. While driver mutations causing PTC are now identifiable in 96.5% of all PTCs (15), no mutation or combination of mutations are currently considered indicators to increase the extent of surgical dissection, or increase the use of adjuvant therapy.

While targeted therapies have now largely replaced cytotoxic chemotherapy agents, their role remains limited to the management of patients with RAI refractory disease and patients with distant metastases (16). Although these targeted therapies have improved overall survival for patients with advanced disease, there are as yet no approved agents for use in patients with high-risk locoregional disease. It can be anticipated that the number of approved targeted therapies for thyroid cancer will likely 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 of papillary carcinomas and and follicular cancers (15). Further improved characterization of the relationship between genomic profiles and tumor behavior may 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 the time of diagnosis have significantly poorer outcomes. Previous publications from our center, demonstrate that in older patients in the N1b group, development of distant disease is a surrogate marker for disease specific death (9). We are working towards 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.

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. As new molecular markers and targeted therapies become available, it will be increasingly crucial for ongoing dialogue 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.

References

1. Kouvaraki MA, Lee JE, Shapiro SE, Sherman SI, Evans DB. Preventable reoperations for persistent and recurrent papillary thyroid carcinoma. Surgery. 2004;136(6):1183-91.
2. Wang L, Palmer F, Thomas D, Shaha A, Shah J, Patel S, et al. Preoperative neck ultrasound in clinical node negative differentiated thyroid cancer. J Clin Endocrinol Metab. 2014;99(10):3686-93.
3. Wang L, Palmer F, Thomas D, Nixon I, Tuttle R, Shah J, et al. Level 7 Disease Does Not Confer Worse Outcome than Level 6 Disease in Differentiated Thyroid Cancer. Ann Surg Oncol. 2014;5:5.
4. Wang LY, Palmer FL, Migliacci JC, Nixon IJ, Shaha AR, Shah JP, et al. Role of RAI in the management of incidental N1a disease in papillary thyroid cancer. Clin Endocrinol (Oxf). 2015.
5. Wang L, Palmer F, Nixon I, Thomas D, Shah J, Patel S, et al. Central lymph node characteristics predictive of outcome in patients with differentiated thyroid cancer. Thyroid. 2014;30(12):30.
6. Mizrachi A, Hadar T, Rabinovics N, Shpitzer T, Guttman D, Feinmesser R, et al. Prognostic significance of nodal ratio in cutaneous squamous cell carcinoma of the head and neck. Eur Arch Otorhinolaryngol. 2013;270(2):647-53.
7. Gil Z, Carlson D, Boyle J, Kraus D, Shah J, Shaha A, et al. Lymph node density is a significant predictor of outcome in patients with oral cancer. Cancer. 2009;115(24):5700-10. doi: 10.1002/cncr.24631.
8. Wang LY, Palmer FL, Nixon IJ, Tuttle RM, Shah JP, Patel SG, et al. Lateral Neck Lymph Node Characteristics Prognostic of Outcome in Patients with Clinically Evident N1b Papillary Thyroid Cancer. Ann Surg Oncol. 2015;22(11):3530-6.
9. Nixon IJ, Wang LY, Palmer FL, Tuttle RM, Shaha AR, Shah JP, et al. The impact of nodal status on outcome in older patients with papillary thyroid cancer. Surgery. 2014;156(1):137-46.
10. McNamara WF, Wang LY, Palmer FL, Nixon IJ, Shah JP, Patel SG, et al. Pattern of neck recurrence after lateral neck dissection for cervical metastases in papillary thyroid cancer. Surgery. 2016.
11. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. The American journal of medicine. 1994;97(5):418-28.
12. Wang LY, Migliacci JC, Tuttle RM, Shaha AR, Shah JP, Patel SG, et al. Management and outcome of clinically evident neck recurrence in patients with papillary thyroid cancer. 2017;87(5):566-71.
13. Wang LY, Roman BR, Palmer FL, Tuttle RM, Shaha AR, Shah JP, et al. Effectiveness of routine ultrasonographic surveillance of patients with low-risk papillary carcinoma of the thyroid. Surgery. 2015.
14. Wang LY, Roman BR, Migliacci JC, Palmer FL, Tuttle RM, Shaha AR, et al. Cost-effectiveness analysis of papillary thyroid cancer surveillance. Cancer. 2015.
15. Network CGAR. Integrated genomic characterization of papillary thyroid carcinoma. Cell. 2014; 159(3):676-90.
16. Brose MS, Cabanillas ME, Cohen EE, Wirth LJ, Riehl T, Yue H, et al. Vemurafenib in patients with BRAF(V600E)-positive metastatic or unresectable papillary thyroid cancer refractory to radioactive iodine: a non-randomised, multicentre, open-label, phase 2 trial. Lancet Oncol. 2016;17(9):1272-82.

Chapter 13

Summary

Samenvatting

SUMMARY

In the past three decades, the incidence of thyroid cancer has nearly tripled, from 4.9 to 14.3 per 100,000 individuals, making thyroid cancer one of the fastest increasing cancers in the United States. Similar trends are seen in many parts of the world. The majority of newly diagnosed cases are small, low-risk papillary cancers and the overall mortality has remained stable for this disease at approximately 0.5 deaths per 100,000 individuals. These observations suggest the incidence reflects increased detection of occult subclinical disease due to increased screening, rather than a true increased occurrence of thyroid cancer. Over the same time period, clinical management of thyroid carcinoma has evolved from a 'one-size fits-all' management approach to one that is based on risk-stratification; tailoring treatment to the risk of recurrence and death. This shift in management philosophy has arisen in part due to better understanding of primary tumor characteristics and its impact on prognosis. The impact of lymph node metastases however remains less well defined. Management of regional lymph nodes varies depending on individual or institutional philosophies and is supported by limited data. The diagnostic, prognostic and therapeutic implications of regional lymph node metastases in differentiated thyroid carcinoma (DTC) warrants further investigations and is the topic of this thesis.

Chapter 1 describes changes in the preoperative assessment of nodal disease over time and its impact on recurrence. Traditionally, clinical palpation was used to detect nodal disease. However, the increasing use of imaging now detects subclinical disease which would have been previously undiagnosed. Recurrence rates in patients with and without preoperative neck ultrasound are directly compared. We demonstrated that preoperative neck ultrasound increases rate of initial lateral neck dissection and reduces need for re-operative salvage neck dissections.

Chapter 2 outlines improvements in our understanding of central compartment nodal disease on recurrence. The 7th ed AJCC nodal staging considered nodal disease in level 6 to be N1a disease while disease below the sternal notch was level 7 and upstaged to N1b. We compared patients with level 6 only disease to patients with level 7 disease and demonstrated comparable outcomes, suggesting that level 7 should be considered N1a status. Since our publication, AJCC 8th edition now appropriately stages level 7 disease as stage N1a. In this chapter we also studied the recurrence rates in patient with low volume central nodal disease. Patients with pathologically confirmed central compartment lymph node metastases are considered to be at a higher risk of recurrence and as such, many clinicians administer adjuvant radioactive iodine (RAI) therapy with the intention of reducing risk of nodal recurrence in these patients. Analysis of our dataset suggests that highly selected papillary thyroid cancer patients with incidental central compartment nodes smaller than 5mm and with no other adverse features in the primary tumor may be safely managed without additional surgery or adjuvant RAI. In addition, we found that in patients with positive central compartment nodes, lymph node diameter, number of lymph node metastasis and lymph node extracapsular spread to be predictive for neck recurrence. With the strongest predictor of nodal recurrence to be the presence of lymph node extracapsular spread.

Chapter 3 focuses on characteristics of lateral compartment nodal metastases and its impact on outcomes. We found that the strongest lateral neck nodal characteristic predictive for recurrence is lymph node burden >17% (presence of greater than 1 positive lymph node per 6 removed) in both patients <45 and ≥45 years of age. In patients ≥45 years of age, the presence of nodal extracapsular spread is also important. Furthermore, our findings indicate that older patients with clinically apparent lateral neck disease are at higher risk of disease related death compared to those without. The cause of death in these older N1b patients is due to distant metastases rather than locoregional recurrence.

Chapter 4 goes on to describe nodal recurrence patterns and subsequent outcomes in these patients in two publications. We report that patients with clinically detectable nodal disease managed by comprehensive lateral neck dissection have lower rates of ipsilateral neck recurrence compared to patients managed by selective lateral neck dissection. We recommend that selective dissection should be reserved for select patients with low volume disease localized to specific neck levels.. Overall recurrence rates in DTC are reported to be as high as 30% in literature. In our series, we report clinically evident nodal recurrence occurs in 3.0% of patients. Such patients are successfully salvaged with surgery and adjuvant therapy with excellent subsequent disease specific survival of 97.4% at 5 years.

The last chapter 5, outlines changes in postoperative recurrence surveillance and proposes improvements towards a risk-stratified, cost-effective surveillance approach. We report postoperative ultrasound use has increased exponentially in recent years across all risk categories. At Memorial Sloan Kettering Cancer Center, the annual rate of neck ultrasonographies increased 5.3-fold per low-risk PTC patients between 2003 and 2012. 1115 ultrasounds were performed during this time to detect a total of 3 recurrence events. In context of increasing incidence of low risk differentiated thyroid cancer, intensive postoperative surveillance needs to be justified in terms of benefit to health outcomes. We analyzed the cost of thyroid cancer surveillance with respect to each recurrence event within ATA low, intermediate and high-risk categories. The cost to detect a recurrence in a low-risk patient is more than 7x greater than the cost in a high-risk papillary thyroid cancer patient. It is difficult to justify this allocation of resources and surveillance strategies in the low risk group should be reviewed.

The evidence presented in this thesis demonstrates that nodal disease is nuanced, occurring across a continuum. The understanding of nodal prognostic features will allow more accurate risk stratification, subsequent individualized management and tailored long-term surveillance. Risk-stratification is central to quality of patient-care and also vital to delivery of cost-effective healthcare in the context of rapidly rising incidence of low-risk thyroid cancer.

SAMENVATTING

In de afgelopen 3 decennia is de incidentie van schildklierkanker bijna verdrievoudigd, van 4.9 naar 14.3 per 100.000 personen, waardoor het een van de snelst groeiende vormen van kanker in de Verenigde Staten is. Vergelijkbare trends zijn te zien in vele andere delen van de wereld. Een groeiende proportie van nieuw-gediagnosticeerde gevallen zijn kleine, vaak niet palpabele, papillaire carcinomen met een minimaal mortaliteitsrisico. De sterfte aan deze ziekte is cumulatief ook stabiel gebleven met ongeveer 0,5 sterfgevallen per 100.000 personen. Deze observaties suggereren dat de verhoogde incidentie een toegenomen detectie van occulte subklinische ziekten weerspiegeld, als gevolg van betere en/of toegenomen screening, in plaats van een reële toename van het aantal gevallen van schildklierkanker. In dezelfde periode is de klinische behandeling van schildkliercarcinoom geëvolueerd van een ‹one-size fits-all› benadering naar een aanpak die gebaseerd is op risicostratificatie ofwel het afstemmen van de behandeling op het risico van recidief en overlijden. Deze verschuiving in de behandelingsstrategie is mede ontstaan aan de hand van een groeiend begrip van de primaire tumorkarakteristieken en de invloed daarvan op de prognose. De prognostische kenmerken van lymfekliermetastasen zijn echter minder goed gedefinieerd. De behandeling van regionale lymfeklieren varieert afhankelijk van individuele of institutionele opvattingen en wordt slechts ondersteund door beperkte data. De diagnostische, prognostische en therapeutische implicaties van regionale lymfekliermetastasen bij goed gedifferentieerd schildkliercarcinoom rechtvaardigen verder onderzoek en vormen het onderwerp van dit proefschrift

In hoofdstuk 1 worden de temporele veranderingen beschreven met betrekking tot de preoperatieve beoordeling van halslymfeklieren. Traditioneel vormde klinische palpatie de basis van de diagnostiek. Het toenemende gebruik van beeldvorming heeft echter de identificatie van subklinische metastasen mogelijk gemaakt, die voorheen niet gediagnosticeerd werden. Vergelijking van de recidiefpercentages van patiënten met en zonder preoperatieve echografie van de hals toont aan dat preoperatieve echografie van de hals het aantal index laterale halslymfeklierdissecties verhoogt en de noodzaak van heroperaties vermindert.

Hoofdstuk 2 schetst verbeteringen in ons begrip van halslymfekliermetastasen in het centrale compartiment van de hals. Volgens de zevende editie van de AJCC stadiering werden lymfekliermetastasen in niveau 6 als N1a ziekte geduid, terwijl metastasen onder het niveau van de bovenrand van het sternum (Level 7) gestadiëerd werden als N1b. Wij vergeleken patiënten met Level 6 metastasen en patiënten met level 7 metastasen wat vergelijkbare uitkomsten laat zien. Dit suggereert dat lymfekliermetastasen in level 7 als N1a status moet worden beschouwd. Sinds de publicatie van ons artikel over dit onderwerp, wordt in de 8^{e} editie van de AJCC een lymfekliermetastase in level 7 voortaan gestadiëerd als N1a.

Patiënten met pathologisch bevestigde lymfekliermetastasen in het centrale compartiment hebben een hoger risico op recidief en veel clinici behandelen dit postoperatief met radioactief jodium (RAI) om het risico op recidief te verminderen. Analyse van onze database suggereert dat een selecte groep patiënten met papillair schildklier carcinoom met lymfeklieren (<5mm) in het centrale compartiment, zonder slechte prognostische kenmerken van de primaire tumor, het veilig zonder extra chirurgie of adjuvante RAI kunnen stellen. Naast de grootte van lymfklier metastasen, suggereert ons onderzoek ook dat het aantal positieve lymfekliermetastasen en extracapsulaire groei voorspellend zijn voor een recidief in de hals. Van deze factoren blijkt extracapsulaire groei het meest voorspellend.

Hoofdstuk 3 richt zich op kenmerken van lymfekliermetastasen in de laterale hals en de invloed daarvan op het klinisch beloop. Ons onderzoek suggereert dat de proportionele metastaselast en extracapsulaire groei belangrijke prognostische factoren zijn. In patiënten jonger dan 45 jaar is metastaselast > 17%

(meer dan 1 positieve lymfeklier per zes verwijderde lymfeklieren) de belangrijkste prognostische factor, terwijl in patiënten ouder dan 45 jaar metastaselast >17% en extracapsulaire groei de prognose bepalen. Voorts toont ons onderzoek aan dat oudere patiënten met klinisch aantoonbare laterale halslymfekliermetastasen een hoger risico lopen op sterfte aan schildklierkanker dan patiënten zonder lymfekliermetastasen, in tegenstelling tot jongere patiënten. De primaire doodsoorzaak bij deze oudere N1b patiënten wordt bepaald door afstandsmetastasen maar niet door locoregionaal recidief

In hoofdstuk 4 wordt het recidiveringspatroon van lymfekliermetastasen in de laterale hals na chirurgische behandeling beschreven. Na een volledige laterale halsklierdissectie ontwikkelen patiënten minder recidieven in de ipsilaterale hals dan patiënten die een selectieve laterale halsklierdissectie hebben ondergaan. Wij adviseren om selectieve dissecties te reserveren voor geselecteerde patiënten met laag volume ziekte gelokaliseerd in een specifiek level. In de literatuur wordt een overall recidief percentage van ca 30% beschreven na laterale halsklierdissectie voor het papillair schildklier carcinoom. In onze serie wordt een klinisch recidiefpercentage van 3,0% geconstateerd. Zulke patiënten hebben na heroperatie plus adjuvante therapie een uitstekende ziekte specifieke overleving van 97,4% na 5 jaar.

Het laatste hoofdstuk 5 schetst de veranderingen in de postoperatieve follow-up en stelt voor de planning daarvan te ontwerpen aan de hand van risico en kosteneffectiviteitscriteria. De echografische follow-up wordt beschreven voor verschillende risicogroepen. De toepassing van postoperatieve echografische follow-up is de laatste jaren voor alle risicocategorieën exponentieel toegenomen. In het Memorial Sloan-Kettering Cancer Center is het jaarlijkse aantal echo's van de hals tussen 2003 en 2012 met een factor 5,3 toegenomen voor laag-risico papillair schildkliercarcinoom patiënten. Er weren 1115 echo's uitgevoerd om slechts 3 recidieven te ontdekken. In de context van de toenemende incidentie van het goed-gedifferentieerde laag risico schildkliercarcinoom moet intensieve postoperatieve surveillance worden gerechtvaardigd. De kosten voor het opsporen van een recidief bij een patiënt met een laag risico zijn meer dan 7x hoger dan de kosten bij een patiënt met een hoog risico op papillair schildkliercarcinoom. Het is daarom moeilijk om toewijzing van middelen te rechtvaardigen. Surveillance strategieën in de groep met een laag risico moeten daarom worden herzien.

Het in dit proefschrift beschreven onderzoek illustreert dat de benadering van lymfekliermetastasen van goed gedifferentieerd schildkliercarcinoom genuanceerd is en zich beweegt op een continuüm. Het begrip van prognostische lymfeklier kenmerken maakt een nauwkeuriger risico analyse met daaropvolgend een geïndividualiseerde behandeling en lange termijn surveillance mogelijk. Een individuele risico analyse is cruciaal voor de kwaliteit van de patiëntenzorg en is ook van vitaal belang voor een kosteneffectieve gezondheidszorg in het licht van een snel toenemend aantal laag risico schildklier carcinoom patiënten.

Chapter 14

Appendices

Authors, Affilications and Contributions
Curriculum Vitae
Portfolio
Acknowledgments

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CURRICULUM VITAE

KEY QUALIFICATIONS

- Fellow of the Royal Australasian College of Surgeons (FRACS), General Surgery, 2018
- Masters Degree, Level 7 nodal disease in papillary thyroid cancer, University of Sydney, 2013
- Bachelor of Medicine, Bachelor of Surgery (MBBS), Bachelor of Science (Med) University of New South Wales, 2008

CAREER HISTORY

- Head and Neck Surgeon, Academic position, Nepean Hospital, Sydney, Current
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- Microvascular Fellowship, Plastics Reconstructive Service, Memorial Sloan Kettering Cancer Centre, New York, 2020
- Head and Neck Clinical Fellowship, Head & Neck Service, Memorial Sloan Kettering Cancer Centre, New York, 2019
- Registrar 3-5, Royal Australasian College of Surgeons trainee, 2015-18
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- Intern & Resident, Prince of Wales Hospital, 2009-10

INVITED SPEAKER

1. Dynamic risk stratification in thyroid cancer surveillance, Asian Society of Endocrine Surgeons Annual Meeting, Melbourne, Australia, 2020
2. Role of neck dissection in Medullary thyroid cancer, Annual post graduate endocrine course, Melbourne, Australia, 2020

COURSES COMPLETED

- Cadaveric perforator course, University of Pennsylvania, Philadelphia, 2019
- Microsurgery course, Columbia University, New York, 2019
- Neck Ultrasonography course, American Head and Neck Society, Austin, 2018
- American Head and Neck Society cadaver training course for Robotic surgery, Atlanta, 2018
- Current Concepts in Head and Neck Surgery and Oncology, MD Anderson, University of Toronto, Memorial Sloan Kettering, Toronto, 2018
- Transoral endoscopic laser microsurgery course, New York, 2018
- Thyroid and Parathyroid Surgery Course for Residents and Fellows, American Head and Neck Society, Boston, 2015
- Surgery of the Thyroid and Parathyroid Glands Course, Harvard Medical School, Boston, 2014

- Current Concepts in Head and Neck Surgery and Oncology, MD Anderson, University of Toronto, Memorial Sloan Kettering, New York, 2013
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- American Thyroid Association, Trainee's grant, 2013

ADDITIONAL INFORMATION

- Speaks English and Mandarin
- Would like to play the piano again someday
- Loves good food and would like to get better at cooking
- Daughter to loving parents Xiao Wen and Jian
- Mother to one small child Hudson, named after my time in NYC
- Wife to Tooraj, my biggest fan

PORTFOLIO

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PRIMARY AUTHOR PUBLICATIONS

1. Wang LY, Ganly I. Post-treatment surveillance of thyroid cancer. Eur J Surg Oncol. 2018
2. Wang LY, Migliacci JC, Tuttle RM, Shaha AR, Shah JP, Patel SG, Ganly I. Management and outcome of clinically evident neck recurrence in patients with papillary thyroid cancer. Clinical Endocrinology. 2017
3. Wang LY, Nixon IJ, Palmer FL, Thomas D, Tuttle RM, Shaha AR, Patel SG, Shah JP, Ganly I. Surgical Management of Locally Advanced Differentiated Thyroid Cancer. Surgery. 2016
4. Wang LY, Ganly I. Nodal metastases in Papillary thyroid cancer- prognostic implications and management. Future Oncology. 2016
5. Wang LY, Palmer FL, Nixon IJ, Tuttle RM, Shaha AR, Shah JP, Patel SG, Ganly I Outcomes of patients with papillary thyroid cancer after clinical cervical node recurrence. Clinical Endocrinology. 2015
6. Wang LY, Roman BR, Palmer FL, Tuttle RM, Shaha AR, Shah JP, Patel SG, Ganly I. Effectiveness of routine ultrasounds in surveillance of low risk patients with papillary carcinoma of the thyroid. Surgery. 2015
7. Wang LY, Roman BR, Palmer FL, Tuttle RM, Shaha AR, Shah JP, Patel SG, Ganly I. Cost-effectiveness analysis of papillary thyroid cancer surveillance. Cancer. 2015
8. Wang LY, Ghossein R, Palmer FL, Nixon IJ, Tuttle RM, Shaha AR, Shah JP, Patel SG, Ganly I. Microscopic Positive Margins in differentiated thyroid cancer is not an independent predictor of local failure. Thyroid. 2015
9. Wang LY, Palmer FL, Migliacci JC, Nixon IJ, Shaha AR, Shah JP, Tuttle RM, Patel SG, Ganly I. Role of RAI in the management of incidental N1a disease in papillary thyroid cancer. Clinical Endocrinology. 2015
10. Wang LY, Palmer FL, Nixon IJ, Tuttle RM, Shah JP, Patel SG, Shaha AR, Ganly I. Lateral Neck Lymph Node Characteristics Prognostic of Outcome in Patients with Clinically Evident N1b Papillary Thyroid Cancer, Annals of Surgical Oncology, 2015
11. Wang LY, Ganly I. Oral Cancer and the Microbiome, Clinics of North America, 2014
12. Wang LY, Smith AW, Palmer FL, Tuttle RM, Mahrous A, Patel SG, Ganly I, Fagin JA, Boucai L. TSH Suppression increases the risk of osteoporosis without decreasing recurrence in non -high risk patients with differentiated thyroid carcinoma, Thyroid, 2014
13. Wang LY, Palmer FL, Thomas D, Shaha AR, Shah JP, Patel SG, Tuttle RM, Ganly I. Preoperative neck ultrasound in clinical node negative differentiated thyroid cancer, Journal of Clinical Endocrinology and Metabolism, 2014
14. Wang LY, Nixon IJ, Palmer FL, Thomas D, Tuttle RM, Shaha AR, Patel SG, Shah JP, Ganly I. Comparable outcomes for patients with pT1a and pT1b differentiated thyroid cancer: is there a need for change in the AJCC classification system? Surgery, 2014
15. Wang LY, Palmer FL, Nixon IJ, Thomas D, Shah JP, Patel SG, Tuttle RM, Shaha AR, Ganly, I. Central lymph node characteristics predictive of outcome in patients with differentiated thyroid cancer, Thyroid, 2014

16. Wang LY, Palmer FL, Nixon IJ, Thomas D, Patel SG, Shaha AR, Shah JP, Tuttle RM, Ganly I. Multiorgan distant metastases confer worse disease specific survival in differentiated thyroid cancer, Thyroid, 2014

17. Wang LY, Palmer FL, Thomas D, Nixon IJ, Tuttle RM, Patel SG, Shaha AR, Shah JP, Ganly I. Level 7 disease does not confer worse outcome than Level 6 disease in differentiated thyroid cancer, Annals of Surgical Oncology, 2014

18. Wang LY, Versnick MA, Gill AJ, Lee JC, Sidhu SB, Sywak MS, Delbridge LW. Level VII is an Important Component of Central Neck Dissection in Papillary Thyroid Cancer. Annals of Surgical Oncology, 2013

COAUTHOR PUBLICATIONS

19. George Kokosis, Joshua Vorstenbosch, Arianna Lombardi, Meghana G Shamsunder, Babak Mehrara, Geoffrey E Hespe, Laura Wang, Cameron W Brennan, Ian Ganly, Evan Matros. Use of the Omental Free Flap for Treatment of Chronic Anterior Skull Base Infections. Plast Reconstr Surg Glob Open, 2020

20. Wu JX, Hanson M, Lohia S, Li H, Wang L, Shaha AR, Ganly I. Prospective anatomical study to determine the site of insertion of recurrent laryngeal nerve into the larynx. Clin Otolaryngol. 2020

21. Harries V, Wang LY, McGill M, Xu B, Tuttle RM, Wong RJ, Shaha AR, Shah JP, Ghossein R, Patel SG, Ganly I. Should multifocality be an indication for completion thyroidectomy in papillary thyroid carcinoma? Surgery 2019

22. Sood A, Wykes J, Roshan D, Wang LY, McGuinness J, Fowler A, Ebrahimi A. A critical analysis of the prognostic performance of the 8th edition American Joint Committee on Cancer staging for metastatic cutaneous squamous cell carcinoma of the head and neck. Head Neck. 2019

23. Sood A, Wykes J, Roshan D, Wang LY, McGuinness J, Forstner D, Fowler A, Lee M, Kernohan M, Ngo Q, Estall V, Ebrahimi A. Number of nodal metastases and prognosis in metastatic cutaneous squamous cell carcinoma of the head and neck. ANZ J Surg. 2019

24. Shaha AR, Migliacci JC, Nixon IJ, Wang LY, Wong RJ, Morris LGT, Patel SG, Shah JP, Tuttle RM, Ganly I. Stage migration with the new American Joint Committee on Cancer (AJCC) staging system (8th edition) for differentiated thyroid cancer. Surgery. 2019

25. Tran B, Roshan D, Abraham E, Wang L, Garibotto N, Wykes J, Campbell P, Ebrahimi A, An Analysis of The American Joint Committee on Cancer 8th Edition T Staging System for Papillary Thyroid Carcinoma, Journal of Clinical Endocrinology and Metabolism, 2018

26. Tran B, Roshan D, Abraham E, Wang L, Garibotto N, Wykes J, Campbell P, Ebrahimi A. The Prognostic Impact of Tumor Size in Papillary Thyroid Carcinoma is Modified by Age. Thyroid. 2018

27. Shaha MA, Wang LY, Migliacci JC, Palmer FL, Nixon IJ, Tuttle RM, Shaha AR, Shah JP, Patel SG, Ganly I. Previous External Beam Radiation Treatment Exposure Does Not Confer Worse Outcome for Patients with Differentiated Thyroid Cancer. Thyroid, 2017

28. Xu B, Ibrahimpasic T, Wang LY, Sabra M, Migliacci JC, Tuttle RM, Ganly I, Ghossein R. Clinico-Pathologic Features of Fatal Non-Anaplastic Follicular Cell-Derived Thyroid Carcinomas. Thyroid 2016

29. McNamara WF, Wang LY, Palmer FL, Nixon IJ, Shah JP, Patel SG, Ganly I. Pattern of Neck Recurrence Following Lateral Neck Dissection for Cervical Metastases in Papillary Thyroid Cancer. Surgery 2016

30. Nixon IJ, Wang LY, Migliaci JC, Eskander AE, Campbell MJ, Anassis A, Morris L, Vaisman F, Corbo R, Momesso D, Vaisman M, Carvalho A, Nason RW, Kuk D, Wreesmann V, Morris L, Palmer FL, Ganly I, Patel SG, Singh B, Tuttle RM, Shaha AR, Gönen M, Pathak AK, Shen WT, Sywak M, Kowalski L, Freeman JJ, Perrier N, Shah

JP. An International Multi-Institutional Validation of Age 55 Years as a Cut-off for Risk Stratification in the AJCC/UICC Staging System for Well Differentiated Thyroid Cancer. Thyroid 2016

31. Ganly I, Nixon IJ, Wang LY, Palmer FL, Migliacci, JC, Aniss A, Sywak M, Eskander A, Freeman J, Campbell M, Shen W, Vaisman F, Momesso D, Corbo R, Vaisman M, Shaha AR, Tuttle RM, Shah JP, Patel SG. Survival from differentiated thyroid cancer. Whats age got to do with it? Thyroid, 2015
32. Nixon IJ, Wang LY, Ganly I, Patel SG, Morris L, Migliacci JC, Tuttle RM, Shah JP, Shaha AR. Fate of the observed central neck in papillary thyroid cancer. British Journal of Surgery 2016
33. Xu B, Wang L, Tuttle RM, Ganly I, Ghossein R. Prognostic impact of extent of vascular invasion in low-grade encapsulated follicular cell-derived thyroid carcinomas: a clinicopathologic study of 278 cases. Human Pathol, 2015
34. Ho AS, Davies L, Nixon IJ, Palmer FL, Wang LY, Patel SG, Ganly I, Wong RJ, Tuttle RM, Morris LG. Increasing diagnosis of subclinical thyroid cancers leads to spurious improvements in survival rates. Cancer, 2015
35. Ganly, I, Wang L, Tuttle RM, Ghossein R. Invasion rather than nuclear features correlates with outcome in encapsulated follicular tumors: further evidence for the reclassification of the encapsulated papillary thyroid carcinoma follicular variant. Human Pathol, 2015
36. Nixon IJ, Wang LY, Palmer FL, Tuttle RM, Shaha AR, Shah JP, Patel SG, Ganly I. The Impact of Nodal Stage on Outcome in Older Patients with Papillary Thyroid Cancer, Surgery, 2014

BOOK CHAPTERS

Wang LY, Ganly I, Randolph G. Sataloff's Comprehensive Textbook of Otolaryngology, Surgical management of multinodular goitre, 2015

PODIUM PRESENTATIONS

1. A Classification System and Reconstructive Algorithm for Reconstruction of Defect of the Oral Cavity and Oropharynx: A 25 Year Experience with 179 Free Flaps American Society of Reconstructive Microsurgery, Orlando Florida, 2020
2. Breaking barriers to research and academic surgery – SET trainees' perspective, Academic Surgery Meeting, Adelaide, 2016
3. Multifocality is not an independent predictor of recurrence in papillary thyroid cancer, Australian Scientific Congress, Perth, 2015
4. Cost benefit of surveillance of low risk papillary thyroid cancer, American Head and Neck Society, Boston, 2015
5. Should incidental multifocality be an indication for completion thyroidectomy? Australian Society of Otolaryngology and Head and Neck Surgery, Sydney, 2015
6. Importance of central compartment extranodal spread in differentiated thyroid cancer, New York Thyroid Club, New York, 2014
7. Lymph node characteristics predictive of outcome in patients with thyroid cancer having a lateral neck dissection, International Federation of Head and Neck Oncologic Societies, New York, 2014
8. Outcomes of patients with papillary thyroid cancer after isolated neck recurrence, International Federation of Head and Neck Oncologic Societies, New York, 2014

9. Central lymph node characteristics predictive of outcome in patients with differentiated thyroid cancer, International Federation of Head and Neck Oncologic Societies, New York, 2014
10. Microscopic positive Margins in differentiated thyroid cancer is not an independent predictor of local failure, Australian Scientific Congress, Singapore, 2014
11. Comparable outcomes for patients with pT1a and pT1b differentiated thyroid cancer: is there a need for change in the AJCC classification system? American Endocrine Surgeons Society, Boston, 2014
12. TSH Suppression increases the risk of osteoporosis without decreasing recurrence in non -high risk patients with differentiated thyroid carcinoma, American Thyroid Association, Puerto Rico, 2013
13. The Impact of Nodal Stage on Outcome in Older Patients with Papillary Thyroid Cancer, World Thyroid Congress, Toronto, 2013
14. Is there benefit in Level VII Central Neck Dissection in Papillary Thyroid Cancer? Australian Scientific Congress, Kuala Lumpur, 2012
15. Transoral Salivary Gland Resection, Australian Society Otolaryngology Head and Neck Surgery, Melbourne, 2011
16. RIFalgia, Annual Hunter Surgical Association Meeting, Hunter Valley, 2011

POSTER PRESENTATIONS

17. The surgical management of intracranial metastasis in Thyroid Cancer. American Head and Neck Society, Austin, 2018
18. Increasing incidence of young oral tongue cancer. Australia and New Zealand Head and Neck Society meeting, Brisbane, 2017
19. Multifocality is not an independent predictor of recurrence in papillary thyroid cancer, American Thyroid Association, San Diego, 2014
20. Is routine use of ultrasonography justifiable in the management of patients with low risk papillary carcinoma of the thyroid? American Thyroid Association, San Diego, 2014
21. Central neck failure in patients with papillary thyroid cancer and incidentally discovered level 6 lymph nodes, American Thyroid Association, San Diego, 2014
22. Should incidental multifocality be an indication for completion thyroidectomy? American Thyroid Association, San Diego, 2014
23. Previous radiotherapy exposure does not confer worse outcome for patients with differentiated thyroid cancer, International Federation of Head and Neck Oncologic Societies, New York, 2014
24. Multiorgan distant metastases confer worse disease specific survival in differentiated thyroid cancer, International Federation of Head and Neck Oncologic Societies, New York, 2014
25. Level 7 disease does not confer worse outcome than Level 6 disease in differentiated thyroid cancer, American Endocrine Surgeons Association, Boston, 2014
26. Preoperative Neck Ultrasound in Clinically Node Negative Well Differentiated Thyroid Cancers improves Response to Therapy, American Thyroid Association, San Juan, 2013
27. Level VII in a Component of Central Neck Dissection in Papillary Thyroid Cancer American Association of Endocrine Surgeons, Iowa City, 2012

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