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

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ABSTRACT

Background: Ultrasound and prophylactic dissections have facilitated identification of small volume cervical lymph node metastases in patients with papillary thyroid carcinoma (PTC). Since most staging systems do not stratify risk based on size or number of lymph node (LN) metastases, even a single microscopic lymph node metastasis can upstage a patient with low risk papillary thyroid microcarcinoma (PMC) to an intermediate risk of recurrence in the American Thyroid Association (ATA) system and to an increased risk of death in the American Joint Committee on Cancer (AJCC) staging system (stage III if the metastatic node is in the central neck or stage IVa if the microscopic lymph node metastasis is identified in the lateral neck). Such "microscopic upstaging" may lead to potentially unnecessary or additional treatments and follow-up studies. The goal of this review is to determine if the literature supports the concept that specific characteristics (clinically apparent, size, number, and extranodal extension) of lymph node metastases can be used to stratify the risk of recurrence in PTC.

Summary: In patients with pathological proven cervical lymph node metastases (pN1), the median risk of loco-regional lymph node recurrence varies markedly by clinical staging, with recurrence rates for patients who are initially clinically N0 (cN0) of 2% (range 0-9%) vs. rates of recurrence for patients who are initially clinically N positive (cN1) of 22%, (range10-42%). Furthermore, the median risk of recurrence in pN1 patients varies markedly by the number of positive nodes, <5 nodes (4% [range 3-8%]) vs. >5 nodes (19%, [range 7-21%]). Additionally, the presence of extranodal extension was associated with a median risk of recurrence of 24% (range 15% to 32%) and possibly worse disease specific survival.

Conclusion: Our previous paradigm assigned the same magnitude of risk for all patients with N1 disease. However, small volume subclinical microscopic N1 disease clearly conveys a much

smaller risk of recurrence than large volume, macroscopic clinically apparent loco-regional metastases. Armed with this information clinicians will be better able to tailor initial treatment and follow-up recommendations. Implications of N1 stratification for PTC into small volume microscopic disease vs. clinically apparent macroscopic disease importantly relate to issues of prophylactic neck dissection utility, need for pathologic nodal size description and suggest potential modifications to the AJCC TNM and ATA risk recurrence staging systems.

INTRODUCTION

The American Joint Committee on Cancer (AJCC) utilizes summary staging from a combination of clinical (including preoperative physical exam, preoperative imaging and intraoperative assessment) and pathological data regarding extent of the primary *Tumor*, *Nodal* disease, and distant *Metastasis* (TNM). The summary TNM classification and subsequent staging is thought to reflect risk of death from disease and is used in counseling patients and treatment planning. In the AJCC TNM staging system, pathologic identification of a single microscopic cervical lymph node metastases in a patient more than 45 years of age with papillary thyroid microcarcinoma upstages the patient from stage I (T1N0Mx) to stage III (T1N1aMx) if the LN is identified in the central neck and to stage IVa (T1N1bMx) if the LN is identified in the lateral neck. In fact, several recent series have demonstrated that routine prophylactic central neck dissection results in upstaging of approximately one third of patients older than 45 years of age at diagnosis from AJCC stage I or II, to AJCC stage III simply based on the pathologic identification of small volume central neck lymph node metastases (1-3). Likewise, identification of a single microscopic LN metastasis moves a patient from low risk of recurrence (intrathyroidal PTC, regardless of age or size) to intermediate risk of recurrence (N1 disease, microscopic extrathyroidal extension, vascular invasion, or high grade histologies) in the American Thyroid Association (ATA) risk of recurrence system (4). While the AJCC system assigns an increased risk to metastatic disease for the lateral neck lymph nodes (N1b) compared to central neck lymph nodes (N1a), neither the AJCC or the ATA risk system uses other characteristics of the lymph node metastases (e.g. size of metastatic lymph nodes, number of metastatic lymph nodes, presence of extra-nodal extension) as further modifiers of risk of recurrence or death.

It appears that "microscopic upstaging" is becoming more frequent as both an increasing use of prophylactic central neck dissections and more meticulous examination of submitted surgical specimens by pathologists are identifying what were once subclinical lymph node metastases in many patients. Additionally, our ability to detect what was previously subclinical disease has increased dramatically with the increased use of neck ultrasonography and other high resolution cross sectional imaging in the initial evaluation and follow-up of thyroid cancer patients. It should be noted therefore, that the current definition of "clinically apparent" lymph node metastases (clinical N1 disease) includes any metastatic lymph node identified by palpation or imaging either prior to initial surgery or intra-operatively.

Upstaging based on the detection of microscopic loco-regional metastases often results in more aggressive treatment (1, 5) since the risk of persistent/recurrent disease is reported to be significantly higher in ATA intermediate risk (21%) than ATA low risk patients (3%) (6), and the risk of death in stage III and IV patients is significantly higher than in Stage I patients (7). While this upstaging may be rational in patients with extensive, large volume loco-regional nodal metastases, it appears to us that it is likely that the ATA and the AJCC TNM summary staging systems are significantly overestimating the risk of recurrence and disease specific mortality in patients with small volume, clinically inapparent microscopic LN metastases (cN0 pN1). This may lead to therapeutic interventions for patients with lower risk disease who are less likely to benefit from them.

Traditionally PTC nodal metastases have been associated with increased risk of recurrence with little influence on survival (except perhaps in older patients) and in fact nodal status is absent in a number of the traditional prognostic schema used for PTC including AMES (Age, Metastasis, Extent, Size), AGES (Age, Grade, Extent, Size), and MACIS (Metastasis, Age,

Completeness of surgery, Invasiveness, Size) (8). Since the majority of the important management recommendations in differentiated thyroid cancer are based on individualized estimates of the risk of recurrence and disease specific mortality (4), it is particularly important to determine if these risks are associated with the size, number or other histological lymph node characteristics in patients with cervical lymph node metastases. Here we review and define the pathologic spectrum of cervical lymph node metastases in (PTC) and then attempt to determine if specific lymph node characteristics (clinically apparent, size, number, and/or presence of extranodal extension) have an impact on the risk of recurrence.

The literature used as the basis for our review was obtained by a PubMed® search using the terms thyroid cancer, papillary thyroid carcinoma, nodal metastases, thyroid cancer staging, thyroid cancer risk groups, lymph node dissection, lymph node surgery, thyroid cancer recurrence. The majority of articles were from 2000 onward, excepting known important older articles which were selectively included.

Defining terminology

While "clinically apparent" nodal disease (clinical N1) describes a prognostically important subgroup of patients in the majority of publications, the definition of clinically apparent disease has changed over time and differs between studies. In this review, we follow the guidance of the AJCC TNM staging system which defines clinical N1 disease (clinically apparent nodes) as metastatic lymph nodes identified by (1) physical examination, (2) imaging or (3) intra-operative inspection (i.e. identified by the surgeon at surgery).

Lymph node dissection prompted by identification of clinically apparent nodal disease (cN1) is classified as a therapeutic neck dissection. Conversely, dissection of a clinically

uninvolved lymph node compartment (cN0: no clinically apparent nodal disease) is classified as a prophylactic neck dissection. Therefore, a neck dissection performed for obvious metastatic nodes discovered at the time of surgery would be classified as a therapeutic neck dissection. Regardless of whether a lymph node was removed with either a prophylactic or therapeutic neck dissection, the identification of metastatic disease in a lymph node renders the patient as pathological N1 (pN1). If metastatic disease is not identified in any of the resected lymph nodes, the patient was classified as having pathological N0 disease (pN0).

Pathologic spectrum of lymph node metastases in PTC

The pathologic size spectrum of loco-regional lymph node metastases from PTC ranges from detection of isolated psammoma bodies without associated recognizable thyroid epithelium to clinically palpable large (i.e. bulky) cervical lymph nodes (See Table 1). We arbitrarily divided nodal disease based on the size of the largest metastatic lymph node into (i) micrometastases (< 0.2 cm), (ii) small nodal metastases (0.2 to <1.0 cm), (iii) intermediate sized nodal metastases (1-3 cm) and (iv) large nodal metastases (> 3 cm). These size cut offs roughly correlate with how data is presented in existing peer reviewed literature and also have clinical applicability.

However, in addition to the size of the largest lymph nodes, other characteristics such as the number of lymph nodes, and the presence of extranodal extension also have been found to have prognostic significance (See next sections and Table 2). Furthermore, other pathologic factors including specific histologic subtype within the metastatic lymph node (as well as presence of necrosis, mitotic index and other molecular factors) may also provide useful information regarding differentiation status of the tumor with higher grade histologies, and/or the

presence of necrosis and mitosis suggesting that the tumor is becoming more poorly differentiated.

Clinical Spectrum of lymph node metastases in PTC

Cervical lymph node metastases occur early and often in PTC. Extensive neck dissection coupled with meticulous pathologic examination reveals locoregional lymph node metastases in 12-81% of patients with PTCs (9-21). Clinically apparent loco-regional metastases are present in approximately 35% of patients with PTC at presentation, with higher rates possible in younger and older patients (22-24).

It is important to recognize that prophylactic neck dissections performed in patients with PTCs less than 1 cm in maximum diameter, referred to here and elsewhere as papillary thyroid microcarcinomas (PMCs), identify microscopic lymph node metastases in the central neck in 37% (25), 40% (26), 43% (27), and 64% (8) of the cases. Furthermore, prophylactic lateral neck dissection can identify lateral neck metastases in as many as 45% of these patients with PMCs (8). Metastatic lymph nodes identified by prophylactic neck dissection are usually quite small with mean sizes reported as 0.35 +/- 0.24 cm (0.1-1.0 cm range) (26) and 0.47 +/- 0.09 cm (28). Furthermore, in one study the largest LN identified in the prophylactic central neck dissection was less than or equal to 0.5 cm in 66% of the cases and less than 1 cm in 95% of the patients (28). In a study by Noguchi *et al*., over 50% of the microscopically positive nodes had foci of disease of less than 0.3 cm (29). In addition to being small in size, the number of involved lymph nodes seen in patients undergoing prophylactic central neck dissection for PMCs is also rather small with one series reporting metastases in only a mean of 2.6 (+/- 3) out of a mean of 13 (+/- 5) lymph nodes removed (26). Therefore, while cervical lymph node metastases are quite

common in the clinically N0 neck (even in PMCs), they usually are very small in size and number.

Small volume microscopic LN metastases in PTC are often of little clinical significance. Even though small volume microscopic LN metastases appear to be present in up to 80% of patients diagnosed with PMC, loco-regional recurrence rates in treated patients range from 2-6% regardless of the extent of lymph node dissection and whether or not RAI was given as adjuvant therapy after surgical resection (8, 9, 13, 15, 16, 25, 30-37). Even in patients followed with observation alone after identification of biopsy proven PMC , the risk of developing clinically apparent LN metastases over a 5-10 year period was as low as 1% (n=340) (34, 38) and 1.4% (n= 230) (39). None of the patients followed with observation alone developed distant metastases or died of thyroid cancer over the follow up period (38, 39).

Recent work has also shown that patients with macroscopic PTC (primary tumor >1cm) also have rates of microscopic nodal disease in up to 62% of cN0 central neck compartments even though recurrence rates are only 1 to 6% if central neck dissection was not performed (1, 40). Therefore, it appears that both PMC and macroscopic PTC are often associated with subclinical microscopic lymph node metastases that usually do not progress and seldom become clinically relevant even if untreated.

It has been recognized for decades that while PTC small volume microscopic nodal disease exists commonly, it evolves into clinically recognizable significant disease in a very small minority of patients in whom it exists (41). Clinical stability of small volume nodal disease appears to be the rule in the recurrent nodal setting as well. Rondeau *et al*. have recently show the stability of untreated subcentimeter biopsy proven nodal bed recurrence (42).

It is important to note that despite having a very high risk of harboring subclinical, microscopic loco-regional disease, patients with PMC are considered low risk patients (4, 9, 10). As such they can potentially be managed with less than total thyroidectomy and do not require RAI ablation or prolonged TSH suppression (4).

What are the characteristics of metastatic lymph nodes associated with risk of recurrence?

We review the existing literature investigating what nodal characteristics relate to risk of nodal recurrence. As discussed below we find nodal size (microscopic/low volume vs. macroscopic/clinically apparent), number of positive nodes and presence of extranodal spread importantly relate to the main nodal prognostic parameter of recurrence and summarize this literature in Table 2 (discussed below). While it is not possible to use this type of literature review to assess the impact of RAI ablation on recurrence rates, for descriptive purposes we did include the percentage of patients within each cohort that received RAI remnant ablation as part of initial therapy.

Risk of recurrence in Clinical N1 Disease (cN1) - Palpable LN metastases

Wada et al. (8) described the risk of nodal recurrence in a cohort of 259 patients with pre-operatively diagnosed PMC. Fifty patients underwent prophylactic central neck dissection, 185 underwent prophylactic central and lateral neck dissection, and 24 patients with palpable nodal disease underwent therapeutic neck dissection. None received RAI. The risk of nodal recurrence over 5 years of follow up was significantly higher in patients with palpable abnormal cervical LN (4/24, 17%) than patients with prophylactic neck dissection (1/235, 0.43%). Interestingly,

the risk of nodal recurrence was nearly the same in those patients with PMC treated with thyroidectomy without prophylactic neck dissection (1/155, 0.65%).

Similarly, in a cohort of 231 patients with PTC greater than 1 cm treated with thyroidectomy, central neck and ipsilateral II-V lateral neck dissection (only 8 received RAI ablation), palpable cervical LN metastases were associated with a higher risk of recurrence in both young (28% vs. 0% without palpable metastatic LN's) and old patients (42% vs. 9% without palpable metastatic LN's) (43). While the presence of palpable abnormal cervical LN's was associated with poorer disease-free survival, no significant impact was detected with regard to disease-specific survival.

Likewise, Ito *et al*. (38) demonstrated that the presence of "clinically apparent lateral node metastases (N1b)" was associated with a significantly shorter disease-free survival than in patients with N1a or N0 disease in a cohort of 1,055 PMC patients followed for 10 years after thyroidectomy and lateral neck dissection without RAI ablation. In an additional cohort of 621 patients the risk of recurrence was again found to be significantly higher in patients with cN1b disease (14%) than in patients with clinical N0 disease. Very similar findings were reported by Gemsenjager *et al*. (22) in a cohort of 159 patients treated with total thyroidectomy and various types of neck dissection (some also received RAI ablation). In this cohort, a significantly higher rate of nodal recurrence was seen in clinically N1 necks (13% 5/39) than in either clinically N0 necks (2%, 2/88) or pathologically proven N0 necks (4%, 1/26)

Therefore, the presence of clinically apparent LN metastases at diagnosis increases the risk of recurrence (9, 31), especially if lateral neck LN are involved (10, 44).

Risk of recurrence in Clinical N1 Disease (cN1) -Pre-op US detected LN metastases

Since pre-operative neck US is far more sensitive for the detection of abnormal lateral neck LN's than central neck LN's (45), studies examining the clinical implication of US detected abnormal LN's are primarily referring to US detected abnormalities in the lateral neck.

In the series by Ito et al. (46) of 600 patients with PMC treated with thyroidectomy, and lateral neck dissection without RAI ablation, the risk of recurrent nodal disease was 0% in those with a pN0 neck, and only 2% in those with a pN1 neck (p=0.00074). However, patients that had abnormal lateral neck LN's detected by US (cN1b) had a 10 year LN recurrence-free survival of only 90% compared with 97% in patients that did not have abnormal lateral neck LN's as detected preoperatively by US (p=0.0001). Abnormal LNs detected in the central neck preoperatively were not associated with a decrease in disease-free survival compared to patient with pN0 neck status (47).

In the subsequent series by Ito et al. (44), 560 patients with PTC greater than 1 cm were treated with thyroidectomy and central and lateral neck dissection without RAI remnant ablation. The risk of recurrence was 25% (26/105) in patients with pre-op US detected abnormal neck LN's (cN1b) compared to a risk of recurrence of only 11.5% (30/261) in all patients with pathologically proven N1 (pN1) disease and 3% (6/194) in patients with pN0 disease (pathology proven N0).

In a series of 331 patients treated with total thyroidectomy and therapeutic lateral neck dissection (76% received RAI ablation), the risk of loco-regional recurrence was 5% in patients with clinical N0 lateral necks (by neck ultrasound). However, the risk of recurrence increased to 30% in the patients that had clinical N1b disease defined by an abnormal pre-operative lateral neck US (48). Furthermore, the presence of US detected abnormal lateral neck LN's (cN1) was associated with a significantly lower overall and disease-specific survival. A recent follow-up

study from the same group emphasized the prognostic importance of radiographically identified preoperative nodal disease. In a study of 331 patients preoperative ultrasonographic identification of central neck nodal disease was a robust age independent predictor of overall survival and nodal recurrence (49).

Bardet *et al*. (24) also noted that the risk of recurrence was significantly higher in patients with cN1 disease (detected by pre-operative US or palpation) (19%, 22/118) than in patients with microscopic LN metastases (4%, 3/76), N0 disease (2%, 4/190) or Nx necks (4%, 6/161). Unlike the Ito studies (44, 50), 91% of this cohort received RAI remnant ablation.

Therefore, it appears that abnormal lateral neck lymph nodes detected on pre-operative neck US convey a higher risk of recurrence than either clinical N0 necks or pathologically proven N1a disease, even when treated with therapeutic neck dissection and/or RAI ablation (See Table 2).

Risk of recurrence in Clinical N0 Disease (cN0)

As can be seen from Table 2, the average rate of recurrence for patients who are judged at presentation to be clinically N0 ranges from 0 to 9% with an average of 4% (8, 23, 24, 43). Interestingly, patients with clinically N0 necks who have microscopic cervical lymph node metastases identified only by prophylactic neck dissection (microscopic pN1) have a similar low risk of recurrence that ranges from 4 to 11.5% with an average of 6% (8, 23, 24, 46).

Risk of recurrence in Pathological N1 Disease (pN1): Size of metastatic lymph nodes

As is readily apparent in Table 2, the risk of recurrence in patients with pathological N1 disease (pN1) can vary from as low as 3-4% in patients with a small number of microscopic

lymph node metastases to as high as 32% in patients with large volume, bulky loco-regional metastases.

Using the definition of lymph node micro-metastases commonly used in breast cancer and other solid tumors (< 0.2cm), Cranshaw *et al*. (23) demonstrated that the risk of LN recurrence in patients with histologic proven micro metastases (N1) was significantly lower than the risk of recurrence in patients with larger pN1 disease (5% vs. 32%).

Ito *et al.* also demonstrated a significant impact of LN size on the risk of LN recurrence in a cohort of 626 patients with PTC greater than 1 cm treated with thyroidectomy and prophylactic central and lateral neck dissection without RAI ablation (51). The presence of LN metastases larger than 1.5 cm was associated with a significantly worse disease-free survival than patients with either N0 disease or patients with pN1 disease less than 1.5 cm. Similarly Sugitani et al. demonstrate that risk of recurrence in the 10 years following total thyroidectomy and neck dissection without RAI ablation was significantly worse in patients with pN1 disease with the largest metastatic LN greater than 3 cm (27%) than in patients with pN1 disease less than 3 cm (11%) (52). Ito *et al*. also demonstrated that lateral neck LN's greater than 3 cm in size was associated with poorer disease-free survival and cause-specific survival than in patients with small metastatic lymph nodes or cN0 necks (53).

Risk of recurrence in Pathological N1 Disease (pN1): Number of metastatic lymph nodes

The number of metastatic LNs detected is dependent on the extent of LN dissection and the intensity of pathologic evaluation. Regardless, several studies have found that the risk of recurrence is positively associated with a higher number of LN metastases at initial presentation. In a cohort of 148 patients with PTC who had pN1 disease or minor extrathyroidal extension

treated with total thyroidectomy, central neck dissection, ipsilateral level III/IV dissection and RAI remnant ablation, the 10 year risk of recurrence was significantly higher in patients with more than 10 abnormal LN's (21%) than in patients with 6-10 LN metastases (7%) or less than 5 LN metastases (3%) (54). Similarly Ito et al. (44, 47) demonstrated a significantly worse disease free survival in patients with greater than or equal to 10 LN metastases compared to patients with fewer LN metastases. Likewise, Sugitani demonstrated that the risk of recurrence was significantly higher in patients with more than 5 LN metastases (19%) that in those with fewer than 5 LN metastases (8%) (52). In a follow up study of 621 patients with cN1b disease, the presence of more than 5 metastatic LN's was associated with a significantly worse disease-free survival than patients with fewer than 5 metastatic LN's (53).

Analyzing 9,926 patients with differentiated thyroid cancer in the SEER (surveillance, epidemiology, and end results) data base (95% PTC, 55% N1, a median of 3 LN histologically examined), neither the absolute number of metastatic lymph nodes, or the percentage of metastatic LN's removed was associated with overall survival in the N1 patients (n= 5,288) (55). The impact of number or percent of LN metastases on the risk of recurrence was not evaluated.

Risk of recurrence in Pathological N1 Disease (pN1): Extranodal extension

In the series by Leboulleux et al., the presence of microscopic evidence of extranodal (or extracapsular) extension of the tumor outside the cervical LN metastases was indicative of a higher risk of recurrence (54). The risk of recurrence increased from 1% (1/72) in N1 patients without extra nodal extension, to 4% (1/23) if 1-3 metastatic LN showed extra-nodal extension, to 32% (6/19) if more than 3 metastatic LN demonstrated extra-nodal extension. Furthermore, Yamashita *et al*. (56) demonstrated that extra-nodal extension and LN size greater than 1 cm (but

not the simple presence of any LN metastasis) was associated with the development of distant metastases. In a subsequent series of 1,743 patients with PMC (36) evaluated by Yamashita *et al*, the overall risk of recurrence was 1.8%. The risk of recurrence was 14.5% (9/62) in those patients with extra-nodal extension compared to only 2.4% (3/122) for patients with N0 findings and 1.5% (2/140) for patients with N1 disease without extranodal extension.

Ito *et al*. demonstrated that gross extra-nodal extension (apparent at the time of surgical intervention) was associated with poorer disease-free survival and cause-specific survival than in patients with cN1b findings without extra-nodal extension (53). Conversely, the Ito series of PTCs greater than 1 cm (47) showed no increased risk of recurrence in the patients with extra-nodal extension (but was not analyzed by number of LN metastases with extra-nodal extension).

Characteristics of metastatic lymph nodes associated with disease specific mortality

Only a few of the published studies examined the impact of metastatic lymph node number or size on risk estimates for disease-specific survival. Yamashita *et al*. (56) found that extranodal extension, but not the size of the metastatic lymph node was associated with poorer overall survival. Similarly, Wada et al. (43) found no association between lymph node size and survival. In multivariate analysis, Sugitani et al. (52) identified an increased risk of disease-specific mortality in older patients with metastatic lymph nodes greater than 3 cm. Finally, an analysis of the SEER data demonstrated the risk of death increased as the proportion of removed lymph nodes that contained metastatic foci increased (55). Therefore, it is difficult to determine at this time if the number or size of metastatic lymph nodes will have independent prognostic importance for disease-specific survival in differentiated thyroid cancer.

Summary

Based on the evidence summarized in Table 2, it is readily apparent that risk of recurrence in patients with N1 neck status can vary widely depending on a variety of clinical factors that are primarily related to the size, number of metastatic LN's identified at the time of initial treatment as well as the presence of extra-nodal extension of the tumor. While not adequately studied, it is also possible that the specific histology of the tumor seen within the lymph node metastasis (e.g., tall cell variant, poorly differentiated, and tumor necrosis) may also have important prognostic significance. Further mutational analysis may in the future provide additional data with which to stratify nodal disease in PTC. The impact of these variables as independent predictors of disease-specific mortality remains to be defined.

Even when simply using the size of the largest metastatic lymph node, a spectrum of recurrence risk is seen ranging from approximately 4% in patients with cN0 necks to 34% in patients with large bulky loco-regional metastases (see Tables 1 and 3). Not surprisingly, the risk of recurrence in microscopic pN1 disease (less than 1 cm, fewer than 3 involved lymph nodes) is very similar to patients classified as clinical N0 since many of the cN0 patients have subclinical microscopic lymph node metastases that would only be apparent with prophylactic neck dissections. Clearly the risk of recurrence is substantially higher in patients with clinically apparent macroscopic metastatic cervical lymphadenopathy

Clinical implications of risk stratification based on specific lymph node characteristics

An improved understanding of the importance of specific lymph node characteristics on the risk of disease recurrence will have significant implications for pathologists, staging systems, and clinicians. Based on our review we make the following recommendations.

(i) In addition to reporting the location of cervical lymph node metastases (central neck vs. lateral neck locations), pathologists should describe the number of involved lymph nodes, the size of the largest lymph node and the presence/absence of extranodal extension. Consideration should also be given to reporting the specific histologic features of the lymph node metastases (e.g. specific histologic variant, presence of tumor necrosis/mitosis).

(ii) Staging systems designed to predict risk of recurrence should be modified to differentiate the risk of recurrence within the N1 neck based on specific lymph node characteristics. At a minimum, staging systems should differentiate lower risk N1 disease from higher risk N1 disease (See Table 4).

(iii) Staging systems designed to predict disease-specific survival, such as the AJCC TNM system, should be re-evaluated to ensure that the identification of small volume, microscopic lymph node metastases does not result in inappropriate upstaging of differentiated thyroid cancer patients. Until TNM summary nodal staging goes beyond N0, N1a, and N1b disease, clinicians may want to utilize both clinical (cN) and pathologic (pN) nodal staging in discussing risk of recurrence and possibly survival with patients and when considering extent of treatment.

(iv) Clinicians should base individualized treatment and follow-up recommendations on an improved understanding of risk stratification within the N1 neck by differentiating the relatively high risk of recurrence associated with clinical N1 disease from the rather low risk of recurrence associated with clinical N0, pathologic N1 disease.

In conclusion, accurate risk stratification in differentiated thyroid cancer requires a re-evaluation of our previous paradigm which assigned the same magnitude of risk for recurrence or death to all patients with N1 disease. Small volume subclinical N1 disease clearly conveys a much smaller risk of recurrence, and probably disease specific mortality, than large volume, clinically apparent loco-regional metastases. Therefore, a better understanding of the risk associated with specific lymph node characteristics in patients with loco-regional metastases will allow clinicians to better tailor initial treatment and follow-up recommendations for individual patients. Until TNM summary nodal staging goes beyond N0, N1a, and N1b disease, clinicians may want to utilize both clinical (cN) and pathologic (pN) nodal staging in discussing risk of recurrence and possibly survival with patients and when considering extent of treatment. For PTC all nodes are not the same.

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Table 1: Pathologic spectrum of lymph node metastases based on size

Descriptor	Size
Lymph node containing psammoma bodies without recognizable epithelium	Psammoma bodies within the lymph node or within subcapsular lymphatic sinuses
Lymph node containing tumor cells identified only with immunohistochemistry	Isolated cells or tiny clusters of cells measuring no more than 0.02 cm
Micrometastases	>0.02 cm – <0.2 cm.
Small nodal metastases	0.2 cm – <1.0 cm
Intermediate sized nodal metastases	1.0 cm to 3.0 cm
Large nodal metastases	> 3.0 cm

Table 2: Risk stratification within the N1 neck in papillary thyroid cancers

	Descriptor	Loco-regional Recurrence	Number of patients with remnant ablation	Source
Clinical N0 (cN0)	Young patients, PMC excluded	0%	3%	(43)
	PMC excluded	2%	91%	(24)
	PMC patients	2%	0%	(56)
	All patients	6%	100%	(23)
	Older Patients, PMC excluded	9%	3%	(43)
Clinical N1 (cN1)	PMC patients	10%	0%	(46)
	All patients	13%	45%	(22)
	All patients	14%	0%	(53)
	PMC patients	17%	0%	(8)
	PMC excluded	19%	91%	(24)
	PMC excluded	25%	1%	(44)
	PMC excluded	25%	0%	(27)
	Young patients, PMC excluded	28%	3%	(43)
	All patients	30%	76%	(48)
	Older patients, PMC excluded	42%	3%	(43)
Pathological N1 (pN1)	PMC excluded	12%	0%	(27)
	PMC excluded	13%	91%	(24)
	PMC excluded	12%	0%	(52)
	All patients	14%	100%	(23)
	All patients	7%	45%	(22)
Specific pN1 descriptors	PMC, no extranodal extension	2%	100%	(54)
	Fewer than 5 metastatic LN's	3%	100%	(54)
	pN1 but cN0	4%	91%	(24)
	1-3 LN's with ENE	4%	100%	(54)
	All metastatic LN's < 0.2cm	5%	100%	(23)
	6-10 metastatic LN's	7%	100%	(54)
	Fewer than 5 metastatic LN's	8%	100%	(52)
	Extranodal extension	15%	0%	(56)
	More than 5 metastatic LN's	19%	0%	(52)
	More than 10 metastatic LN's	21%	100%	(54)
	Any metastatic LN > 1 cm	32%	100%	(23)
	> 3 metastatic LN's with ENE	32%	100%	(54)
	Any metastatic LN > 3 cm	27%	0%	(52)

PMC = papillary microcarcinoma, ENE= histologically documented extra-nodal extension. LN = lymph node

Table 3. Risk of recurrence based on the characteristics of the cervical lymph node metastases.

Pathology	Specific Characteristic	Median	Range	Source
Pathological N1	**Clinical N0**	2%	0-9%	Wada 2008, Bardet 2008, Yamashita 2009, Cranshaw 2008
	< 5 metastatic nodes	4%	3-8%	Leboulleax 2005, Bardet 2008, Sugitani 2004
	> 5 metastatic nodes	19%	7-21%	Leboulleax 2005, Sugitani 2004
	Clinical N1	22%	10-42%	Ito 2004, Cranshaw 2008, Ito 2009, Wada 2003, Bardet 2008, Ito 2006, Ito 2005, Wada 2008, Moreno 2011, Wada 2008
	Clinical N1 with extranodal extension	24%	15-32%	Leboulleux 2005, Yamashita 2009

Table 4

Risk factors that modify standard N1 risk of recurrence estimates

Lower Risk N1 Disease (<5% risk of recurrence)	**Higher Risk N1 Disease (> 20% risk of recurrence)**
Clinically N0 Micrometastases, Small lymph node metastases 5 or fewer small lymph node metastases	Clinically detectable LN metastases (cN1) More than 5 metastatic lymph nodes Metastatic LN larger than 3 cm