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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Background: Ultrasound and prophylactic dissections have facilitated identification of small-volume cervical lymph node (LN) metastases in patients with papillary thyroid carcinoma (PTC). Since most staging systems do not stratify risk based on size or number of LN metastases, even a single-microscopic LN 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 LN 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 LN metastases can be used to stratify the risk of recurrence in PTC.

Summary: In patients with pathological proven cervical LN metastases (pathological N1 disease; pN1), the median risk of loco-regional LN recurrence varies markedly by clinical staging, with recurrence rates for patients who are initially clinically N0 (clinical N0 disease; cN0) of 2% (range 0%–9%) versus rates of recurrence for patients who are initially clinically N-positive (clinical N1 disease; cN1) of 22% (range 10%–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%–32%) and possibly a 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 versus 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 Tumor, Nodal disease, and distant Metastasis 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 LN metastases in a patient >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 LN metastases (1–3). Likewise, identification of a single-microscopic LN metastasis moves a patient from low risk of recurrence (infrathyroidal papillary thyroid carcinoma [PTC], regardless of age or size) to intermediate risk of recurrence (N1 disease, microscopic extra-thyroidal 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 LNs (N1b) compared to central neck LNs (N1a), neither the AJCC nor the ATA risk system uses other characteristics of the LN metastases (e.g., size of metastatic LNs, number of metastatic LNs, presence of extranodal 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 LN metastases in many patients. Additionally, our ability to detect what was previously a subclinical disease has increased dramatically with the increased use of neck ultrasonography (US) 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” LN metastases (clinical N1 disease; cN1) includes any metastatic LN identified by palpation or imaging either before initial surgery or intraoperatively.

Upstaging based on the detection of microscopic locoregional 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 locoregional 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 apparent microscopic LN metastases (clinical N0 disease; cN0, pathologic N1 disease; 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 an 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 LN characteristics in patients with cervical LN metastases. Here we review and define the pathologic spectrum of cervical LN metastases in (PTC), and then attempt to determine if specific LN 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, PTC, nodal metastases, thyroid cancer staging, thyroid cancer risk groups, LN dissection, LN surgery, and 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 cN1 (clinically apparent nodes) as metastatic LNs identified by (i) physical examination, (ii) imaging, or (iii) intraoperative inspection (i.e., identified by the surgeon at surgery).

LN dissection prompted by identification of clinically apparent nodal disease (cN1) is classified as a prophylactic neck dissection. Conversely, dissection of a clinically uninvolved LN 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 LN was removed with either a prophylactic or therapeutic neck dissection, the identification of metastatic disease in a LN renders the patient as pathological N1 (pN1). If metastatic disease is not identified in any of the resected LNs, the patient was classified as having pathological N0 disease (pN0).

Pathologic spectrum of LN metastases in PTC

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

However, other characteristics in addition to the size of the largest LNs, such as the number of LNs and the presence of extranodal extension, also have been found to have prognostic significance (see next sections and Table 2) (8–20). Furthermore, other pathologic factors, including specific histologic subtype within the metastatic LN (as well as presence
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Table 1. Pathologic Spectrum of Lymph Node Metastases Based on Size

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node containing psammoma bodies without recognizable epithelium</td>
<td>Psammoma bodies within the lymph node or within subcapsular lymphatic sinuses</td>
</tr>
<tr>
<td>Lymph node containing tumor cells identified only with immunohistochemistry</td>
<td>Isolated cells or tiny clusters of cells measuring no more than 0.02 cm</td>
</tr>
<tr>
<td>Micrometastases</td>
<td>&gt;0.02 cm–&lt;0.2 cm.</td>
</tr>
<tr>
<td>Small nodal metastases</td>
<td>0.2 cm–&lt;1.0 cm</td>
</tr>
<tr>
<td>Intermediate-sized nodal metastases</td>
<td>1.0 cm–3.0 cm</td>
</tr>
<tr>
<td>Large nodal metastases</td>
<td>&gt;3.0 cm</td>
</tr>
</tbody>
</table>

of necrosis, mitotic index, and other molecular factors), may 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 LN metastases in PTC

Cervical LN metastases occur early and often in PTC. Extensive neck dissection coupled with meticulous pathologic examination reveals locoregional LN metastases in 12%–81% of patients with PTCs (21–33). Clinically apparent locoregional metastases are present in approximately 35% of patients with PTC at presentation, with higher rates possible in younger and older patients (10,12,14).

It is important to recognize that prophylactic neck dissections performed in patients with PTCs <1 cm in maximum diameter, referred to here and elsewhere as papillary thyroid microcarcinomas (PMCs), identify microscopic LN metastases in the central neck in 37% (34), 40% (35), 43% (17), 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 LNs 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) (34) and 0.47 ± 0.09 cm (36). Furthermore, in one study, the largest LN identified in the prophylactic central neck dissection was ≤0.5 cm in 66% of the cases and <1 cm in 95% of the patients (36). In a study by Noguchi et al., over 50% of the microscopically positive nodes had foci of disease of <0.3 cm (37).

Table 2. Risk Stratification Within the N1 Neck in Papillary Thyroid Cancers

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Locoregional recurrence</th>
<th>Patients with remnant ablation</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical N0 (cN0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Young patients, PMC excluded</td>
<td>0%</td>
<td>3%</td>
<td>Wada et al., 2008 (9)</td>
</tr>
<tr>
<td>PMC excluded</td>
<td>2%</td>
<td>91%</td>
<td>Bardet et al., 2008 (10)</td>
</tr>
<tr>
<td>PMC patients</td>
<td>2%</td>
<td>0%</td>
<td>Yamashita et al., 1997 (11)</td>
</tr>
<tr>
<td>All patients</td>
<td>6%</td>
<td>100%</td>
<td>Cranshaw and Carnaille, 2008 (12)</td>
</tr>
<tr>
<td>Older patients, PMC excluded</td>
<td>9%</td>
<td>3%</td>
<td>Wada et al., 2008 (9)</td>
</tr>
<tr>
<td>Clinical N1 (cN1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMC patients</td>
<td>10%</td>
<td>0%</td>
<td>Ito et al., 2004 (13)</td>
</tr>
<tr>
<td>All patients</td>
<td>13%</td>
<td>45%</td>
<td>Gemsenjager et al., 2003 (14)</td>
</tr>
<tr>
<td>PMC patients</td>
<td>14%</td>
<td>0%</td>
<td>Ito et al., 2009 (15)</td>
</tr>
<tr>
<td>PMC excluded</td>
<td>17%</td>
<td>0%</td>
<td>Wada et al., 2003 (8)</td>
</tr>
<tr>
<td>PMC patients</td>
<td>19%</td>
<td>91%</td>
<td>Bardet et al., 2008 (10)</td>
</tr>
<tr>
<td>PMC excluded</td>
<td>25%</td>
<td>3%</td>
<td>Ito et al., 2006 (16)</td>
</tr>
<tr>
<td>PMC excluded</td>
<td>25%</td>
<td>0%</td>
<td>Ito et al., 2005 (17)</td>
</tr>
<tr>
<td>Young patients, PMC excluded</td>
<td>28%</td>
<td>3%</td>
<td>Wada et al., 2008 (9)</td>
</tr>
<tr>
<td>All patients</td>
<td>30%</td>
<td>76%</td>
<td>Moreno et al., 2011 (18)</td>
</tr>
<tr>
<td>Older patients, PMC excluded</td>
<td>42%</td>
<td>3%</td>
<td>Wada et al., 2008 (9)</td>
</tr>
<tr>
<td>Pathological N1 (pN1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMC excluded</td>
<td>12%</td>
<td>0%</td>
<td>Ito et al., 2005 (17)</td>
</tr>
<tr>
<td>PMC excluded</td>
<td>13%</td>
<td>91%</td>
<td>Bardet et al., 2008 (10)</td>
</tr>
<tr>
<td>PMC excluded</td>
<td>12%</td>
<td>0%</td>
<td>Sugitani et al., 2004 (19)</td>
</tr>
<tr>
<td>All patients</td>
<td>14%</td>
<td>100%</td>
<td>Cranshaw and Carnaille, 2008 (12)</td>
</tr>
<tr>
<td>All patients</td>
<td>7%</td>
<td>45%</td>
<td>Gemsenjager et al., 2003 (14)</td>
</tr>
<tr>
<td>Specific pN1 descriptors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMC, no extranodal extension</td>
<td>2%</td>
<td>100%</td>
<td>Lebouleux et al., 2005 (20)</td>
</tr>
<tr>
<td>&lt;5 metastatic LNs</td>
<td>3%</td>
<td>100%</td>
<td>Lebouleux et al., 2005 (20)</td>
</tr>
<tr>
<td>1–3 LNs with ENE</td>
<td>4%</td>
<td>91%</td>
<td>Bardet et al., 2008 (10)</td>
</tr>
<tr>
<td>All metastatic LNs &lt;0.2cm</td>
<td>4%</td>
<td>100%</td>
<td>Lebouleux et al., 2005 (20)</td>
</tr>
<tr>
<td>6–10 metastatic LNs</td>
<td>5%</td>
<td>100%</td>
<td>Cranshaw and Carnaille, 2008 (12)</td>
</tr>
<tr>
<td>&lt;5 metastatic LNs</td>
<td>7%</td>
<td>100%</td>
<td>Lebouleux et al., 2005 (20)</td>
</tr>
<tr>
<td>Extranodal extension</td>
<td>8%</td>
<td>100%</td>
<td>Sugitani et al., 2004 (19)</td>
</tr>
<tr>
<td>&gt;5 metastatic LNs</td>
<td>15%</td>
<td>0%</td>
<td>Yamashita et al., 1997 (11)</td>
</tr>
<tr>
<td>&gt;10 metastatic LNs</td>
<td>19%</td>
<td>0%</td>
<td>Sugitani et al., 2004 (19)</td>
</tr>
<tr>
<td>Any metastatic LN &gt;1 cm</td>
<td>21%</td>
<td>100%</td>
<td>Lebouleux et al., 2005 (20)</td>
</tr>
<tr>
<td>&gt;3 metastatic LNs with ENE</td>
<td>32%</td>
<td>100%</td>
<td>Cranshaw and Carnaille, 2008 (12)</td>
</tr>
<tr>
<td>Any metastatic LN &gt;3 cm</td>
<td>32%</td>
<td>100%</td>
<td>Lebouleux et al., 2005 (20)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>27%</td>
<td>Sugitani et al., 2004 (19)</td>
</tr>
</tbody>
</table>

PMC, papillary microcarcinoma; ENE, histologically documented extranodal extension; LN, lymph node.
In addition to being small in size, the number of involved LNs 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) LNs removed (35). Therefore, while cervical LN metastases are quite common in the clinically N0 neck (even in PMCs), they are usually 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, locoregional recurrence rates in treated patients range from 2%–6% regardless of the extent of LN dissection and whether or not radioactive iodine (RAI) was given as adjuvant therapy after surgical resection (8,21,25,27,28,34,38–45). 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) (42,46) and 1.4% (n=230) (47). None of the patients followed with observation alone developed distant metastases or died of thyroid cancer over the follow-up period (46,47).

Recent work has also shown that patients with macroscopic PTC (primary tumor >1 cm) 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 (1,48). Therefore, it appears that both PMC and macroscopic PTC are often associated with subclinical microscopic LN 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 (49). Clinical stability of small-volume nodal disease appears to be the rule in the recurrent nodal setting as well. Rondeau et al. have recently shown the stability of untreated subcentimeter biopsy-proven nodal bed recurrence (50).

It is important to note that despite having a very high risk of harboring subclinical, microscopic locoregional disease, patients with PMC are considered low-risk patients (4,21,22). As such, they can potentially be managed with less than total thyroidectomy and do not require RAI ablation or prolonged thyroid stimulating hormone suppression (4).

**What are the characteristics of metastatic LNs associated with risk of recurrence?**

We reviewed the existing literature investigating what nodal characteristics relate to risk of nodal recurrence (8–20). As discussed below, we found that 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. This literature is summarized 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 cN1: palpable LN metastases**

Wada et al. (8) described the risk of nodal recurrence in a cohort of 259 patients with preoperatively 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 >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 (25% vs. 0% without palpable metastatic LNs) and old patients (42% vs. 9% without palpable metastatic LNs) (9). While the presence of palpable abnormal cervical LNs was associated with poorer disease-free survival, no significant impact was detected with regard to disease-specific survival.

Likewise, Ito et al. (46) 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 1055 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 cN0 (15). Very similar findings were reported by Genssenjager et al. (14) 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 (21,39), especially if lateral neck LNs are involved (16,22).

**Risk of recurrence in cN1: preoperative US detected LN metastases**

Since preoperative neck US is far more sensitive for the detection of abnormal lateral neck LNs than central neck LNs (51), studies examining the clinical implication of US detected abnormal LNs are primarily referring to US detected abnormalities in the lateral neck. In the series by Ito et al. (13) 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 LNs 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 LNs as detected preoperatively by US (p=0.0001). Abnormal LN detected in the central neck preoperatively were not associated with a decrease in disease-free survival compared to patients with pN0 neck status (52).
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In the subsequent series by Ito et al. (16), 560 patients with PTC > 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 preoperative US detected abnormal neck LNs (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 locoregional recurrence was 5% in patients with clinical N0 lateral necks (by neck US). However, the risk of recurrence increased to 30% in the patients that had clinical N1b disease defined by an abnormal preoperative lateral neck US (18). Furthermore, the presence of US detected abnormal lateral neck LNs (cN1) was associated with 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 US identification of central neck nodal disease was a robust age independent predictor of overall survival and nodal recurrence (53).

Bardet et al. (10) also noted that the risk of recurrence was significantly higher in patients with cN1 disease (detected by preoperative 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 (13,16), 91% of this cohort received RAI remnant ablation.

Therefore, it appears that abnormal lateral neck LNs detected on preoperative 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 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% (8–10,12). Interestingly, patients with clinically N0 necks who have microscopic cervical LN 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% (8–10,12).

Risk of recurrence in pN1: size of metastatic LNs

As is readily apparent in Table 2, the risk of recurrence in patients with pN1 can vary from as low as 3%–4% in patients with a small number of microscopic LN metastases to as high as 32% in patients with large-volume, bulky locoregional metastases.

Using the definition of LN micrometastases commonly used in breast cancer and other solid tumors (<0.2 cm), Cranshaw et al. (12) demonstrated that the risk of LN recurrence in patients with histologic proven micrometastases 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 >1cm treated with thyroidectomy and prophylactic central and lateral neck dissection without RAI ablation (55).

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 <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 >3 cm (27%) than in patients with pN1 disease <3 cm (11%) (19). Ito et al. also demonstrated that lateral neck LNs >3 cm in size was associated with poorer disease-free survival and cause-specific survival than in patients with small metastatic LNs or cN0 necks (15).

Risk of recurrence in pN1: number of metastatic LNs

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 >10 abnormal LNs (21%) than in patients with 6–10 LN metastases (7%) or <5 LN metastases (3%) (20). Similarly Ito et al. (16,52) demonstrated a significantly worse disease-free survival in patients with ≥10 LN metastases compared to patients with fewer LN metastases. Likewise, Sugitani demonstrated that the risk of recurrence was significantly higher in patients with ≥5 LN metastases (19%) that in those with <5 LN metastases (8%) (19). In a follow-up study of 621 patients with cN1b disease, the presence of >5 metastatic LNs was associated with a significantly worse disease-free survival than patients with <5 metastatic LNs (15).

Analyzing 9926 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 LNs, or the percentage of metastatic LNs removed was associated with overall survival in the N1 patients (n = 5288) (56). The impact of number or percent of LN metastases on the risk of recurrence was not evaluated.

Risk of recurrence in 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 (20). 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 extranodal extension, to 32% (6/19) if >3 metastatic LN demonstrated extra-nodal extension. Furthermore, Yamashita et al. (11) demonstrated that extra-nodal extension and LN size >1 cm (but not the simple presence of any LN metastasis) was associated with the development of distant metastases. In a subsequent series of 1743 patients with PMC (44) 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.
Table 3. Risk of Recurrence Based on the Characteristics of the Cervical Lymph Node Metastases

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Specific characteristic</th>
<th>Median</th>
<th>Range</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathological N1</td>
<td>Clinical N0</td>
<td>2%</td>
<td>0%–9%</td>
<td>Wada et al., 2008 (9); Bardet et al., 2008 (10); Cranshaw and Carnaille, 2008 (12)</td>
</tr>
<tr>
<td>&lt;5 metastatic nodes</td>
<td></td>
<td>4%</td>
<td>3%–8%</td>
<td>Sugitani et al., 2004 (19); Leboulleux et al., 2005 (20); Bardet et al., 2008 (10)</td>
</tr>
<tr>
<td>&gt;5 metastatic nodes</td>
<td></td>
<td>19%</td>
<td>7%–21%</td>
<td>Sugitani et al., 2004 (19); Leboulleux et al., 2005 (20)</td>
</tr>
<tr>
<td>Clinical N1</td>
<td></td>
<td>22%</td>
<td>10%–42%</td>
<td>Wada et al., 2003, 2008 (8,9); Ito et al., 2004, 2005, 2006, 2009 (13,15–17); Bardet et al., 2008 (10); Cranshaw and Carnaille, 2008 (12); Moreno et al., 2011 (18)</td>
</tr>
<tr>
<td>Clinical N1 with extranodal extension</td>
<td></td>
<td>24%</td>
<td>15%–32%</td>
<td>Leboulleux et al., 2005 (20), Yamashita et al., 1999 (44)</td>
</tr>
</tbody>
</table>

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 (15). Conversely, the Ito series of PTCs >1 cm (52) 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 LNs associated with disease specific mortality

Only a few of the published studies examined the impact of metastatic LN number or size on risk estimates for disease-specific survival. Yamashita et al. (11) found that extranodal extension, but not the size of the metastatic LN was associated with poorer overall survival. Similarly, Wada et al. (9) found no association between LN size and survival. In multivariate analysis, Sugitani et al. (19) identified an increased risk of disease-specific mortality in older patients with metastatic LNs >3 cm. Finally, an analysis of the SEER data demonstrated the risk of death increased as the proportion of removed LNs that contained metastatic foci increased (56). Therefore, it is difficult to determine at this time if the number or size of metastatic LNs 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 LNs identified at the time of initial treatment, as well as the presence of extranodal extension of the tumor. While not adequately studied, it is also possible that the specific histology of the tumor seen within the LN 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 LN, a spectrum of recurrence risk is seen ranging from approximately 4% in patients with cN0 necks to 34% in patients with large bulky locoregional metastases (see Tables 1 and 3). Not surprisingly, the risk of recurrence in microscopic pN1 disease (<1 cm, <3 involved LNs) is very similar to patients classified as clinical N0, since many of the cN0 patients have subclinical microscopic LN 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 lymph adenopathy.

Clinical implications of risk stratification based on specific LN characteristics

An improved understanding of the importance of specific LN 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.

1. In addition to reporting the location of cervical LN metastases (central neck vs. lateral neck locations), pathologists should describe the number of involved LNs, the size of the largest LN, and the presence/absence of extranodal extension. Consideration should also be given to reporting the specific histologic features of the LN metastases (e.g., specific histologic variant, presence of tumor necrosis/mitosis).
2. Staging systems designed to predict risk of recurrence should be modified to differentiate the risk of recurrence within the N1 neck based on specific LN characteristics. At a minimum, staging systems should differentiate lower risk N1 disease from higher risk N1 disease (See Table 4).
3. 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 LN 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.

4. 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 cN1 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 locoregional metastases. Therefore, a better understanding of the risk associated with specific LN characteristics in patients with locoregional 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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Disclosure Statement

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References


Leboulleux S, Rubino C, Baudin E, Caillou B, Hartl DM, Bidart JM, Tragagl JP, Schumberger 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.


50. Rondeau G, Fish S, Hann LE, Fagin JA, Tuttle RM Ultrasonographically detected small thyroid bed nodules identified after total thyroidectomy for differentiated thyroid cancer seldom show clinically significant structural progression. Thyroid 21:845–853.
52. Ito Y, Tomoda C, Uruno T, Takamura Y, Miya A, Kobayashi K, Matsuzuka F, Kuma K, Miyauchi A 2006 Minimal extrathyroidal extension does not affect the relapse-free survival of patients with papillary thyroid cancer measuring 4 cm or less over the age of 45 years. Surg Today 36:12–18.

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