Surgical Management of Cervical Lymph Nodes in Differentiated Thyroid Cancer

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Approximately 37,200 people are expected to be diagnosed with thyroid cancer in the United States this year.1 Prognosis largely depends on the degree of tumor differentiation. In contrast to anaplastic tumors, well-differentiated thyroid cancer (DTC), including papillary and follicular carcinomas and their subtypes, has an excellent prognosis.2 Although long-term survival can exceed 90%, regional lymph node metastases are common and contribute significantly to morbidity.2 Surgical management of cervical lymph nodes is integral to the comprehensive treatment of DTC. Unfortunately, data from large randomized clinical trials do not exist to aid in defining optimal surgical treatment. The choice of surgical strategy is thus founded on a thorough understanding of the behavior and significance of lymphatic metastases in DTC and guided by observational data.

BACKGROUND
Differentiated Thyroid Cancer Growth and Spread
The malignant behavior of well-differentiated thyroid cancer is characterized by varying degrees of local invasion, lymphatic infiltration, and hematogenous dissemination. Papillary thyroid cancers (PTCs) compose 77% of thyroid malignancies and demonstrate a strong propensity for regional nodal involvement.2 The most recent analysis of Surveillance, Epidemiology and End Results (SEER) data, including more than 33,000 patients with DTC, reports a 22% incidence of lymphatic involvement at initial operation in patients with PTC. Extrathyroidal extension was less common, involving 15% of patients, and distant metastases affected only 1% of patients at

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diagnosis. Other studies demonstrate lymphatic metastases in up to 50% of patients with DTC, depending on the timing of evaluation and diagnostic criteria.\cite{4-12}

In contrast to PTCs, follicular thyroid cancers (FTCs) are less common, with a low rate of lymphatic involvement but more frequent distant metastasis. According to SEER data, 10% of patients with FTC present with extrathyroidal spread, 3% with distant metastases, and only 2% with lymphatic involvement.\cite{3}

**Anatomy of Cervical Lymphatics**

The thyroid gland is seated amid a rich lymphatic network. The cervical lymph nodes are divided into levels I to VI and grouped into central and lateral compartments (Fig. 1).\cite{13} Level I nodes are submental and submandibular. Levels II to IV consist of the upper, mid-, and lower jugular nodes, respectively, with level V nodes lateral to the jugular groups in the posterior triangle. The pretracheal, paratracheal, and prelaryngeal (delphian) nodes compose level VI. Level VII lymph nodes are located in the superior mediastinum inferior to the sternal notch. Although not technically included in the cervical lymphatic system, the superior mediastinal group is another common site of DTC metastasis.\cite{14} Further subdivision of the levels I, II, and V nodes has been proposed based on significant anatomic landmarks. Ia refers to submental nodes whereas Ib nodes are submandibular. Level II is divided into superior (IIa) and inferior (IIb) nodes by the spinal accessory nerve, with IIb lateral to the nerve. Level Va is located superior to the level of the cricoid cartilage and Vb inferior. The spinal accessory nerve divides Va into inferior and superior sublevels.\cite{14} Grouping adjacent nodal levels together has practical application. Levels II to V compose the lateral or posterolateral compartment, whereas level VI is synonymous with the central or anterior compartment.\cite{14}

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**Fig. 1.** The designation of lymph node levels in the neck. (Reproduced from American Thyroid Association Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer [see comment]. Thyroid 2009;19[11]:1167–214; with permission.)
Patterns of Nodal Metastases

Several studies of cervical metastases in thyroid cancer suggest a general pattern of lymphatic spread from medial to lateral in the ipsilateral, then contralateral, neck. The incidence of nodal involvement is higher in the central compartment than the lateral compartment. Jugular lymph node metastases occur with greater frequency than do supraclavicular lymph node metastases, and involvement of submental or submandibular nodes is rare. Contralateral lymph node metastases greater than 1 cm have been described in 25% of patients with PTC. The majority of contralateral metastases are found in the central rather than lateral compartment.8 Mediastinal lymph node involvement is rare, occurring in only 5% of node-positive patients with PTC.15

Incidence and location of nodal metastasis is ideally studied in a representative cohort of patients with thyroid cancer who undergo complete bilateral modified radical neck dissection (MRND) regardless of clinical node status. Mirallie and colleagues8 examined 119 patients with PTC who underwent bilateral cervical neck dissection, excluding only node-negative patients with microcarcinomas less than 1 cm in diameter: 60.5% of patients were found to have cervical lymph node metastases. Of node-positive patients, 83% had central, 61% had midjugular, 36% had supraclavicular, and 28% had subdigastic involvement on the ipsilateral side. Contralateral involvement in the paratracheal nodes occurred in 35% of node-positive patients, with contralateral jugular metastases in less than 25%.8 DTC metastases are thus most common within the central compartment; they are also frequent in the ipsilateral jugular groups. Contralateral involvement is less likely but nonetheless affects a significant proportion of patients.

Although central and jugular involvement is common, several studies have suggested infrequent involvement of levels I, IIb, and V. A series of 52 patients with lateral metastases at initial diagnosis who underwent MRND identified lymph node metastases by neck level. Levels IIa, III, and VI were each involved in more than 70% of patients. Involvement of other levels was significantly less common: only 16.7% of patients had positive nodes at level IIb, 13% at Vai, and 3.7% at Vb and Ib; there was no involvement of Vas. Level Ia was not dissected. Involvement of Level Ib, IIb, or V was associated with multilevel disease in all cases.16 In contrast, another small series reported positive nodes above the spinal accessory nerve (level I or IIb) in 21% of 34 patients; nearly half of those had no involvement of level IIa.17

Many investigators have also described a relationship between the location of the cancer within the thyroid and the location of involved nodes. Quabain and coworkers9 prospectively studied a population of patients with DTC who underwent prophylactic MRND and were staged as pN0 by standard histopathology. Micrometastatic disease was identified by immunohistochemistry in 53% of the 80 patients enrolled, primarily occurring in those with tumors larger than 1 cm. Examination of the location of micrometastases indicated a tendency for upper-pole lesions to metastasize to more superior nodes, with isthmus and lower-pole lesions metastasizing to inferior nodes. Within the central compartment, all micrometastases occurred ipsilateral to the tumor unless the tumor was within the isthmus.

Despite the general pattern of medial to lateral spread, skip metastases—lateral compartment metastases without central compartment involvement—occur in a significant proportion of patients (Table 1). In the study by Quabain and coworkers,9 7% of patients with DTC micrometastases had lateral compartment involvement without evidence of central disease. In a prospective series of 52 patients with DTC and clinically positive lateral nodes who underwent MRND, 5 patients (9.6%) had no evidence of central compartment disease.11,16 Machens and colleagues19 examined
215 patients with thyroid cancer and lateral or mediastinal metastases and found skip metastasis in 19.7% of patients with PTC and 0 of 8 patients with FTC. A statistically significant inverse correlation was observed between the incidence of skip metastases and the number of positive lymph nodes. The presence of skip metastases was not significantly associated with tumor size or patient demographic characteristics.

**Risk Factors for Initial Nodal Metastases and Nodal Recurrence**

Several risk factors have been defined for nodal involvement in DTC (Table 2). At the time of initial treatment, patients with PTC and those younger than 45 years old are more likely to have lymph node metastases than their older counterparts or those with FTC. Patients with distant metastases are also more likely to harbor nodal metastases. Correlation between tumor size and lymph node metastases has been variably reported. Patients with tumors larger than 4 cm are 2 to 6 times more likely to have lymph node metastases present at operation than those with smaller tumors. In smaller tumors, the presence of lymph node metastases at initial operation correlated more strongly with vascular and soft tissue invasion than primary tumor size (<1 cm vs 1–2 cm). Locally invasive primary tumor and pronounced elevation in thyroglobulin levels have also been identified as possible risk factors. Patient and tumor characteristics associated specifically with mediastinal lymph node involvement include older age at diagnosis, poor tumor differentiation, more positive lymph nodes, and distant metastases.

Several risk factors are associated with regional lymph node recurrence in DTC. Male gender and extrathyroidal extension of the primary tumor have been implicated by several studies. Older age, larger tumor, and macroscopically involved nodes at initial surgery also are cited.

<table>
<thead>
<tr>
<th>Location of lymph node metastases at MRND in patients with DTC and positive lateral nodes&lt;sup&gt;a&lt;/sup&gt;</th>
<th>I</th>
<th>Ia</th>
<th>Ib</th>
<th>II</th>
<th>IIa</th>
<th>IIb</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>Vai</th>
<th>Vas</th>
<th>Vb</th>
<th>VI</th>
<th>Skip Mets&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pingpank&lt;sup&gt;17&lt;/sup&gt; (n = 44)</td>
<td>38</td>
<td>—</td>
<td>—</td>
<td>49</td>
<td>43</td>
<td>21</td>
<td>76</td>
<td>59</td>
<td>28</td>
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<td>—</td>
<td>—</td>
<td>—</td>
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</tr>
<tr>
<td>Roh&lt;sup&gt;16&lt;/sup&gt; (n = 52)</td>
<td>—</td>
<td>4</td>
<td>72</td>
<td>17</td>
<td>72</td>
<td>76</td>
<td>13</td>
<td>0</td>
<td>4</td>
<td>90</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yanir&lt;sup&gt;18&lt;/sup&gt; (n = 27)</td>
<td>—</td>
<td>—</td>
<td>54</td>
<td>—</td>
<td>68</td>
<td>57</td>
<td>20</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>95</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mirallie&lt;sup&gt;8&lt;/sup&gt; (n = 72)</td>
<td>—</td>
<td>—</td>
<td>28</td>
<td>—</td>
<td>61</td>
<td>61</td>
<td>36</td>
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<td>—</td>
<td>83</td>
<td>17</td>
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<tr>
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<td>4</td>
<td>39</td>
<td>59</td>
<td>19</td>
<td>68</td>
<td>64</td>
<td>31</td>
<td>13</td>
<td>0</td>
<td>4</td>
<td>88</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Values indicate the % of patients with positive lymph nodes at each level.

<sup>b</sup> Metastases to lateral nodes without evidence of central compartment involvement.

### Table 2

**Risk factors for lymph node metastases in DTC**

<table>
<thead>
<tr>
<th>At Presentation</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTC</td>
<td>Male &gt; female</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>Extrathyroidal extension</td>
</tr>
<tr>
<td>Age &lt;45 years</td>
<td>Age &gt;55 years</td>
</tr>
<tr>
<td>Large tumor</td>
<td>Large tumor</td>
</tr>
<tr>
<td>Extrathyroidal extension</td>
<td>Macroscopically positive</td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>Lymph nodes at initial operation</td>
</tr>
<tr>
<td>Elevated thyroglobulin</td>
<td></td>
</tr>
</tbody>
</table>

Fritze & Doherty
Ito and colleagues\textsuperscript{22} proposed a scoring system to stratify patients in terms of risk for lymph node recurrence, assigning 1 point each for

- Age older than 55 years
- Male gender
- Massive extrathyroid extension
- Tumor greater than 3 cm.

Patients with 0 points had a 10-year, lymph node disease-free survival of 98.4%. This declined in a stepwise fashion to 64.7% for patients with all 4 criteria.

**Detection and Diagnosis**

Regional metastases are routinely detected by physical examination and imaging studies. In the setting of a negative preoperative evaluation, unanticipated lymphatic metastases are also frequently discovered at thyroidectomy. Initial assessment for lymphadenopathy is by physical examination of the neck. The accuracy of this method varies with clinician experience and patient body habitus, but false-positive and -negative rates of 20% to 30% are reported.\textsuperscript{25} Clinician and patient factors also affect the accuracy of ultrasonography; however, ultrasound may detect cervical lymph node metastases in up to 34% of patients with a negative physical examination (Fig. 2).\textsuperscript{26} Reported sensitivities for ultrasound in diagnosis of lymphatic metastases in DTC are widely variable, ranging from 10% to 92%.\textsuperscript{26–31} Specificity, as confirmed by fine-needle aspiration (FNA), is high, with a reported range of 89% to 99%.\textsuperscript{26–31} The sensitivity of ultrasound is particularly limited in the central compartment due to the presence of the trachea and thyroid gland. In patients whose thyroid gland remains in place, the false-negative rate for ultrasound detection of central compartment lymph node metastases is 36%. This rate drops to 18% for patients whose thyroid gland is surgically absent.\textsuperscript{26} Positive or indeterminate findings on physical examination or imaging can be evaluated with FNA, particularly if the presence or absence of malignancy influences the choice of surgical procedure.\textsuperscript{32}

**SIGNIFICANCE OF LYMPH NODE METASTASES**

The impact of lymph node metastases on survival in DTC has yet to be unequivocally defined. Nonetheless, lymphatic involvement is well established as a predictor of locoregional recurrence and implicated as a harbinger of distant metastases.

![Ultrasound of the right neck showing a characteristic hypoechoic rounded lymph node metastasis from PTC. The carotid artery is denoted by the large arrowhead.](image-url)
Locoregional Recurrence

Lymph node metastasis is described as a risk factor for locoregional recurrence in several observational studies. A retrospective review of 700 patients with DTC demonstrated a relative risk of recurrence of 4.2 in patients with lymph node metastases as compared with those without. This difference existed independent of treatment and other tumor and patient factors. Similarly, McHenry and colleagues reported recurrence of DTC in 19% of patients with initially positive nodes and 2% in node-negative patients after thyroidectomy and MRND.

Similar results are reported in series of patients with PTC only. According to a retrospective study by Salvesen and colleagues, initial node-negative status in patients with PTC predicted recurrence-free survival with a hazard ratio (HR) of 3.6. Ninety percent of N0 patients were disease-free 10 years after resection compared with 65% of patients who presented with positive lymph nodes. Wada and colleagues compared the rates of recurrence and mortality in 231 patients who had PTC with and without palpable lymphadenopathy. All patients underwent thyroidectomy and MRND; only a small minority received radioactive iodine postoperatively. The overall HR for disease-free survival in patients without palpable lymphadenopathy compared to those with nodal disease detectable on physical examination was 14.9 by multivariate analysis. The effect of lateral involvement was stronger than that of central compartment disease.

There are fewer studies exclusively concerned with nodal metastases in FTCs. Two retrospective reviews examined the effect of initial node-positive status on subsequent recurrence after total thyroidectomy with central lymph node dissection (CLND) and radioactive iodine therapy. Of patients who were initially node positive, 80% developed recurrence whereas only 34% of node-negative patients developed recurrence. This difference remained statistically significant on multivariate analysis.

The effect of nodal involvement is more pronounced in certain subgroups of patients with DTC. A retrospective review of 342 patients with PTC revealed nodal status as a statistically significant predictor of recurrence and survival in patients with T1, T2, and T3 tumors but not in patients with T4 tumors. In a study of patients with small DTC less than 2 cm, 20-year disease-free survival was 71% in N0 patients versus 56% in initially node-positive patients (P = .02).

Distant Metastases

Nodal metastases have been identified as a predictor of systemic disease. In the series by McHenry and colleagues, 6% of patients with nodal involvement and 0.1% of patients without nodal involvement developed distant metastases. In another series stratified by tumor size, 0.7% of patients initially T1-T3N0 had distant metastases at diagnosis and 2.9% eventually developed distant spread. For T1-T3N1 patients, 8.5% had systemic involvement at diagnosis, and 15.1% later developed systemic disease. Reflexively, patients with metastatic disease are more likely to have lymphatic involvement. Analysis of 231 patients with PTC who underwent MRND revealed a significantly higher burden of positive regional lymph nodes, particularly lateral nodes, in patients with systemic metastases. These studies suggest that nodal involvement is reflective of more advanced or aggressive DTC.

Survival

Lymph node metastases have not traditionally been associated with mortality in DTC; however, recent evidence is accumulating to suggest decreased long-term survival in patients with lymphatic involvement. At least 6 case series have demonstrated no significant mortality risk associated with lymph node metastases in
In contrast, a large, population-based, nested case-control study of all patients diagnosed with DTC in Sweden over 30 years suggests that lymph node metastases are associated with increased mortality. In a multivariate analysis controlling for TNM stage, the odds ratio for DTC-related death was 1.9 in patients with lymphatic involvement compared with those without. Analysis of SEER data from more than 19,000 patients demonstrated a statistically significant survival difference in patients with DTC based on nodal status. The 14-year survival was 82% in node-negative patients versus 79% in node-positive patients. A more recent review of SEER data from more than 33,000 patients demonstrated no significant difference in all-cause mortality between patients with PTC younger than age 45 with and without positive lymph nodes. For patients age 45 and older with PTC, however, mortality was 46% greater in patients with lymphatic metastases compared with those without. Lymphatic metastases in patients with follicular cancers were significantly associated with increased mortality in patients older (HR 11.23) and younger (HR 2.86) than 45 years. A single institution series of 700 patients with DTC analyzing disease-specific mortality also reports a statistically significant risk ratio of 2.6 for patients with nodal metastases compared with those without. A study of papillary microcarcinomas <1 cm in size noted a statistically significant effect on survival for lateral but not central compartment lymph node metastases. Although a mortality risk is not uniformly identified in every series, high-quality observational data strongly suggest lower long-term survival rates in DTC patients with lymphatic metastases.

**Lymphatic Metastases and DTC Staging**

Historically, nodal status has been conspicuously absent from staging systems for DTC, primarily because of lack of data implicating nodal status as a negative prognostic indicator. Several such systems, including AGES, AMES, MACIS, and the European Organization for Research and Treatment of Cancer (EORTC) system, do not include an assessment of lymph node status, yet are useful predictors of survival. In 1987, the American Joint Committee on Cancer and International Union Against Cancer adopted a TNM classification for DTC with separate staging criteria for patients younger and older than 45 years (Table 3). For younger patients, stage is based entirely on the presence or absence of distant metastases. For older patients, nodal involvement equates to stage IIIb, with distant metastases stage IV. Several retrospective studies have demonstrated a correlation between TNM stage and mortality in thyroid cancer, with independent validation of the prognostic value of the regional lymph node or N classification.

**SURGICAL TREATMENT OF CERVICAL LYMPH NODES IN DTC**

Surgical treatment of cervical lymph nodes in DTC remains a subject of debate. There is widespread consensus that clinically involved cervical nodes should be resected when detected, provided that distant metastases do not preclude curative operation. Resection of involved cervical nodes is also appropriate in patients with M1 disease to prevent or treat aerodigestive compression by nodal metastases. In these circumstances, neck dissection is therapeutic. Prophylactic neck dissection also is proposed and variably practiced for patients without clinically evident lymph node involvement, preoperatively or at thyroidectomy. The optimal role of prophylactic dissection and the appropriate extent of neck dissection for DTC remain controversial.

**Techniques**

The superiority of systematic lymphadenectomy with removal of all lymphatic tissue in a particular level or compartment to berry-picking procedures has been repeatedly
### Table 3
#### Thyroid Cancer Staging

**Primary Tumor (T)**

Note: All categories may be subdivided: (a) solitary tumor, (b) multifocal tumor (the largest determines the classification).

<table>
<thead>
<tr>
<th>Stage (TX)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary T cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary T</td>
</tr>
<tr>
<td>T1</td>
<td>T &lt; 2 cm in greatest dimension limited to the thyroid</td>
</tr>
<tr>
<td>T2</td>
<td>T &gt; 2 cm but not &gt; 4 cm in greatest dimension limited to the thyroid</td>
</tr>
<tr>
<td>T3</td>
<td>T &gt; 4 cm in greatest dimension limited to the thyroid or any T with minimal extrathyroid ext (e.g., ext. to sternothyroid muscle or perithyroid soft tissues)</td>
</tr>
<tr>
<td>T4a</td>
<td>T of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve</td>
</tr>
<tr>
<td>T4b</td>
<td>T invades prevertebral fascia or encases carotid artery or mediastinal vessels</td>
</tr>
</tbody>
</table>

**Regional Lymph Nodes (N)**

Regional lymph nodes are the central compartment, lateral cervical, and upper mediastinal lymph nodes.

<table>
<thead>
<tr>
<th>Stage (NX)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed.</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis</td>
</tr>
<tr>
<td>N1a</td>
<td>Metastasis to Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)</td>
</tr>
<tr>
<td>N1b</td>
<td>Metastasis to unilateral, bilateral, or contralateral cervical or superior mediastinal lymph nodes</td>
</tr>
</tbody>
</table>

**Distant Metastasis (M)**

<table>
<thead>
<tr>
<th>Stage (MX)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

**STAGE GROUPING**

Separate stage groupings are recommended for papillary or follicular, medullary, and anaplastic (undifferentiated) carcinoma.

**Papillary or Follicular**

**UNDER 45 YEARS**

- **Stage I** Any T Any N M0
- **Stage II** Any T Any N M1

**Papillary or Follicular**

**45 YEARS AND OLDER**

- **Stage I** T1 N0 M0
- **Stage II** T2 N0 M0
- **Stage III** T3 N0 M0
  - T1 N1a M0
  - T2 N1a M0
  - T3 N1a M0
- **Stage IVA** T4a N0 M0
  - T4a N1a M0
demonstrated. Systematic lymphadenectomy is associated with lower rates of persist-ent and recurrent disease and possible survival benefit.6,17,21,43 For example, a recent single institution series studied patients with DTC referred for MRND after a berry-picking procedure in the lateral neck demonstrated metastasis. The rate of additional metastases discovered at formal neck dissection was 81%, suggesting that resecting only macroscopically involved nodes is likely to result in persistent nodal disease.17 Tisell and colleagues43 described a technique of surgical microdissection with en bloc resection of all lymphatic tissue within a compartment. Central compartment dissection was performed in all patients and lateral compartment dissection in patients with macroscopically positive lateral nodes. Mortality from thyroid cancer was 1.6% in his series compared with 8.6% in a series of historical controls who underwent node-picking procedures, despite a higher rate of radioactive iodine therapy in the control series. The superiority of systematic dissection was confirmed in a study demonstrating increased survival and decreased recurrence rates in those undergoing systematic compartment-oriented lymphadenectomy as opposed to other techniques.21

**Central Neck Dissection**

Central compartment cervical lymph nodes metastases are common, with a reported incidence of up to 50% in patients with PTC.44 Therapeutic central neck dissection..
prevents serious sequelae including compression or invasion of critical aerodigestive and neural structures. It also decreases the incidence of lymphatic recurrence, and may improve survival.\textsuperscript{5,21,43,45} Because of its clear benefits, therapeutic neck dissection is widely accepted. The role of prophylactic central neck dissection, however, remains controversial. As this practice has gained acceptance only recently, studies comparing thyroidectomy alone to thyroidectomy with CLND in patients with clinically negative node status have had short follow-up and differ in their conclusions. A decision of whether or not to perform prophylactic CLND for patients with DTC must be based on the anticipated risks and benefits of operation.

Unfortunately, central compartment involvement is inconsistently identified pre- and intraoperatively. Studies involving prophylactic central neck dissection report unanticipated central metastases in 38\% to 45\% of patients with PTC.\textsuperscript{44,46,47} Without prophylactic neck dissection, these metastases remain in situ as foci of persistent carcinoma. Prophylactic neck dissection thus results in more thorough clearance of disease in more than one-third of patients with PTC. As the frequency of lymphatic metastases in FTC is low, prophylactic dissection is not advocated for these patients.

Central neck dissection also is associated with lower thyroglobulin levels after thyroidectomy, neck dissection, and radioiodine ablation for PTC. Patients who underwent prophylactic central neck dissection were more likely to have undetectable thyroglobulin levels than those whose surgical treatment consisted of thyroidectomy alone.\textsuperscript{44} This confirms a more complete removal of thyroid tissue from the central neck in patients who underwent lymphadenectomy. The significance of undetectable thyroglobulin levels for survival or recurrence is unclear; however, low levels of thyroglobulin do facilitate surveillance for recurrent disease.

As the practice of prophylactic central neck dissection is recent, few studies directly address recurrence after this operation. One study reports no central node metastases in 28 patients at 5 years’ follow-up; however, this series is limited by small size and short duration.\textsuperscript{46} A retrospective review of patients without macroscopically positive lymph nodes noted no difference in recurrence rates at 10 years whether or not central neck dissection was performed.\textsuperscript{5} Therapeutic central neck dissection in patients with macroscopically positive central nodes is associated with decreased recurrence rates.\textsuperscript{5,45} Preventing nodal recurrence leads to fewer operations to resect involved nodes, which represents a significant reduction in the morbidity of DTC.

Although clearance of thyroid tissue and lymphatic metastases is improved by prophylactic central neck dissection, and recurrence rates may be reduced, the implications for survival are not clear. Several studies have failed to demonstrate a survival advantage but may be underpowered to detect small differences in mortality. In a study of nearly 1000 patients with DTC, 20-year survival was not influenced by surgical treatment with lymph node dissection versus thyroidectomy alone.\textsuperscript{48} Another retrospective analysis that identified nodal metastasis as a negative prognostic indicator failed to demonstrate a survival benefit to prophylactic neck dissection at 20-year follow-up.\textsuperscript{49}

When evaluating the additional morbidity of prophylactic CLND compared to thyroidectomy alone, it is imperative to also consider the risk of reoperation in the central compartment should the patient develop recurrence. The most frequent complications of thyroidectomy and neck dissection include temporary or permanent hypocalcemia due to hypoparathyroidism, temporary or permanent recurrent laryngeal nerve (RLN) palsy, and injury to the superior branch of the external laryngeal nerve. Rare complications include bleeding requiring reoperation, infection, chyle leak, tracheal injury, and pneumothorax.
For experienced surgeons performing total thyroidectomy, the accepted incidence of permanent RLN injury and permanent hypoparathyroidism is 1% to 2%, with rates less than 1% reported in large series.\(^{50,51}\) The reported incidence in case series ranges from 1% to 16% for permanent hypoparathyroidism and 1% to 9% for permanent RLN injury.\(^{5,38,44,47}\) A similar range of complication rates is reported for thyroidectomy with CLND, including therapeutic and prophylactic dissections (Table 4). Select series by experienced endocrine surgeons report rates of permanent nerve injury and hypoparathyroidism of 1% to 2% in patients undergoing thyroidectomy with CLND, indicating that central node dissection may be added to total thyroidectomy with little additional morbidity.\(^{38,44}\) One single-surgeon series of 300 patients with PTC undergoing total thyroidectomy alone, prophylactic unilateral CLND, or therapeutic bilateral CLND demonstrated a trend toward significantly increased rates of transient hypocalcemia with more extensive surgery. No difference in rates of permanent hypoparathyroidism or nerve injury were observed.\(^{52}\) In contrast, reoperation within the central neck has been repeatedly shown to carry higher morbidity than initial operation, particularly with respect to RLN injury.\(^{45,50,53,54}\) Prophylactic central neck dissection thus carries little additional morbidity compared with thyroidectomy alone but may decrease the rate of locally persistent or recurrent disease, thereby preventing the need for reoperation within the central compartment and its associated morbidity.

Bilateral and unilateral central compartment dissections have been proposed.\(^{55}\) Within the central compartment, ipsilateral metastases are more common than contralateral; however, contralateral involvement still occurs in 10% to 20% of individuals.\(^{8,56,57}\) Multifocal disease involving both thyroid lobes is often not discovered at the time of operation and is associated with increased incidence of bilateral central metastases.\(^{9}\) For patients with macroscopically positive lymph nodes, bilateral lymphadenectomy should be performed; however, high rates of athyroglobulinemia may be achieved with unilateral central compartment dissection in patients with macroscopically negative lymph nodes.\(^{44}\)

**Lateral Neck Dissection**

As with the central compartment, lateral compartment lymphadenectomy is indicated in the presence of clinically positive lymph nodes. Lateral lymphadenopathy detected on examination or imaging should be confirmed as metastatic thyroid cancer by FNA. For patients with DTC, MRND results in decreased local recurrence and fewer reoperative procedures than less extensive operations.\(^{5}\) For patients with macroscopically

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Frequency of complications after thyroidectomy with and without neck dissection (%)</th>
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<tr>
<td></td>
<td>Temporary Hypocalcemia</td>
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<tr>
<td>Thyroidectomy without CLND</td>
<td>4–16</td>
</tr>
<tr>
<td>Thyroidectomy with CLND</td>
<td>18–60</td>
</tr>
<tr>
<td>Reoperative CLND</td>
<td>0–13</td>
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</tbody>
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Both prophylactic and therapeutic CLND are included. Data from Refs.\(^{4,5,22,44,50,51,61,62}\)
positive lateral nodes, MRND is associated with statistically significant improvement in
disease-specific survival compared with thyroidectomy alone. 58

Several investigators have examined potential indications for MRND in the absence
of clinically positive lymph node disease. A series of 500 patients with DTC who under-
went thyroidectomy with or without CND or MRND demonstrated no difference in
lymphatic recurrence at 15 years in the absence of macroscopic nodal disease. 5
This was confirmed in a series consisting only of patients with FTC where no signifi-
cant difference in recurrence or mortality was detected based on MRND, even in
patients of more advanced stage. 36 Although not appropriate for all clinically node-
negative patients, ipsilateral MRND is advocated for patients with significant risk
factors for lateral metastasis. Confirmed risk factors include extrathyroidal extension,
older age, male gender, larger primary tumor size, and large metastatic burden within
the central compartment. For patients with these disease characteristics, MRND may
be beneficial. 28, 58, 59

Any potential benefits to MRND must be evaluated in the context of the procedure’s
morbidity. In one series of 1231 patients, 22 the overall complication rate for prophy-
lactic MRND was 24.1%. This included RLN injury, transient hypocalcemia and
permanent hypoparathyroidism, chyle leak, pneumothorax, Horner syndrome, and
injury to the phrenic, facial, and spinal accessory nerves. The lateral compartment is
not breached during thyroidectomy, so MRND performed at a separate operation
does not involve a previously operated field. Given the risk of complication at initial
operation and the lack of additional risk to MRND performed in a staged fashion after
thyroidectomy, dissection of the lateral compartment is routinely limited to patients
with FNA-proved lateral node metastases or obvious involvement at thyroidectomy.

The extent of lateral neck dissection necessary for regional control also is debated
but not prospectively evaluated. Several studies have demonstrated the low incidence
of metastases to levels IIb and V. 16 These observations suggest that dissection in these
areas may be low yield but confer increased risk of complication and higher morbidity.

Suprahyoid and Superior Mediastinal Dissection

Metastatic involvement of levels I and VII (superior mediastinal) lymph nodes is rare. In
a review of patients with lateral cervical metastases of PTC, less than 5% of patients
had suprahyoid involvement. 16 Similarly, approximately 5% of patients with PTC were
identified as having superior mediastinal metastases. 11, 15 Suprahyoid dissection is not
routinely included in lymph node dissections for DTC unless there is macroscopic
involvement of this compartment. When nodal metastases are identified, suprahyoid
dissection is associated with a low risk of complication and can be performed without
additional morbidity.

As is recommended for the other nodal groups, dissection of the superior medias-
tinal lymph nodes should be performed in the presence of gross nodal involvement.
This can often be accomplished via a standard cervical incision; however, sternotomy
may result in more complete clearance of nodal tissue. Some investigators advocate
for routine prophylactic superior mediastinal dissection in patients with PTC; however,
data indicating a survival or recurrence advantage are lacking.

GUIDELINES AND SUMMARY

In 2006, the American Thyroid Association Guidelines Taskforce published manage-
ment guidelines for patients with DTC. Recently revised guidelines recommend total
thyroidectomy with level VI neck dissection for patients with clinically involved central
or lateral lymph nodes. 60 For those patients with PTC who are clinically node negative,
particularly with larger primary tumors, unilateral or bilateral prophylactic central compartment dissection was deemed worthy of consideration but not specifically recommended. Therapeutic lateral neck dissection was recommended for patients with biopsy-proved lateral node involvement. No recommendations were included regarding prophylactic lateral neck dissection or the optimal extent of lateral dissection.32

In the absence of definitive level 1 data from a prospective, randomized controlled trial, the surgical management of cervical lymph node metastasis in DTC is based on observational data and knowledge of disease behavior and relevant anatomy. The decisions for a specific patient must be made with a clear understanding of the natural history of the disease, the likelihood that therapy can change that natural history, and the morbidity of the therapeutic options.

REFERENCES


