Long-term Results of Observation vs Prophylactic Selective Level VI Neck Dissection for Papillary Thyroid Carcinoma at a Cancer Center

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**IMPORTANCE** The indication for prophylactic central neck dissection in papillary thyroid cancer (PTC) is controversial.

**OBJECTIVE** To compare long-term results of observation vs prophylactic selective level VI neck dissection for PTC.

**DESIGN, SETTING, AND PARTICIPANTS** We performed a retrospective cohort study of 812 patients with PTC who were treated from January 1, 1996, through January 1, 2007, at the Department of Head and Neck Surgery and Otorhinolaryngology of A. C. Camargo Cancer Center. A group of 580 consecutive patients with previously untreated PTCs and without lymph node metastasis were eligible for the study. We collected and analyzed retrospective data from February 1, 2012, through August 31, 2013.

**INTERVENTIONS** One hundred two patients (group A) underwent total thyroidectomy with elective central neck dissection; 478 patients (group B) underwent total thyroidectomy alone.

**MAIN OUTCOMES AND MEASURES** Absence of difference in rates of locoregional control and rates of major complications in group A.

**RESULTS** In group A, the rate of occult metastatic disease was 67.2%. Patients in group A exhibited higher rates of temporary hypocalcemia (46.1% vs 32.2%; \( P = .004 \)) and permanent hypoparathyroidism (11.8% vs 2.3%; \( P < .001 \)). We also found a significantly higher incidence of temporary (11.8% vs 6.1%; \( P = .04 \)) and permanent (5.9% vs 1.5%; \( P = .02 \)) recurrent laryngeal nerve dysfunction in group A. The overall recurrence rate at level VI was 1.9%.

**CONCLUSIONS AND RELEVANCE** Although the risk for occult lymph node metastasis reached 67.2% in a selected group of patients, elective central neck dissection for patients with PTC increased the risk for complications and did not contribute to a decrease in local recurrence rates.
Papillary carcinoma corresponds to more than 80% of malignant tumors of the thyroid gland. Despite the excellent prognosis associated with this carcinoma, as many as 30% of patients undergoing total thyroidectomy will develop recurrences, most often in the cervical lymph nodes. Lymph node metastases are common, occurring in 20% to 90% of patients. These metastases are located most often in the central compartment and are associated with a higher risk for recurrence. However, for a long time, nodal metastases were not identified among prognostic factors in patients with well-differentiated thyroid carcinomas. Recently, several studies have reported an association between lymph node metastasis and shorter survival, in particular in patients older than 45 years.

Central compartment lymph node levels of the neck (level VI) are considered the first step for lymph node metastasis in papillary thyroid carcinoma (PTC) and include the pretracheal, paratracheal, and delphian lymph nodes. A consensus exists that metastasis, as diagnosed by clinical or imaging examination, demands central compartment dissection. However, the role of prophylactic level VI dissection is a matter of debate. In theory, the advantages of routine lymph node dissection include better results of disease staging (pathologic stage); reduction of the risk for recurrence; reduction of the risk for complications associated with reoperation at level VI; a higher rate of patients with low serum levels of thyroglobulin and antithyroglobulin antibodies, which facilitate the tracking; and potentially improved rates of overall survival. Conversely, the disadvantages are related to the potential complications, especially hypoparathyroidism and recurrent laryngeal nerve injury. The present study aims to evaluate the effectiveness of selective indication for prophylactic level VI lymph node dissection in patients with PTC.

Methods

This retrospective cohort study was approved by the Ethics Committee on Research of the A. C. Camargo Cancer Center (agreement 1207/09). From January 1, 1996, through January 1, 2007, 812 patients with thyroid carcinoma were treated at the Department of Head and Neck Surgery and Otorhinolaryngology of A. C. Camargo Cancer Center. Patients eligible for this study included those with PTC that was histologically confirmed (classic or variants) of any T stage (including micro-papillary tumors) and no evidence of lymph node metastases as diagnosed by preoperative imaging or intraoperative findings (cN0). We included those patients who underwent completion thyroidectomy after the initial hemithyroidectomy. Patients undergoing therapeutic lymph node dissection beyond the central compartment were excluded. Based on information from patient medical records, we divided patients into group A, consisting of those who underwent total thyroidectomy associated with elective level VI lymph node dissection (unilateral or bilateral), and group B, including patients who underwent total thyroidectomy alone.

Most operations were performed by third- to fifth-year residents under the direct supervision of an experienced head and neck surgeon. Total thyroidectomy was established as the criterion standard treatment, especially in PTCs larger than 1.0 cm. Elective dissection of the central compartment with total thyroidectomy was not performed routinely but according to the surgeon’s discretion, especially in tumors larger than 2.0 cm or in the presence of extrathyroidal extension. Lymphadenectomy was performed according to the standardized technique, which consisted of dissection and isolation of the recurrent laryngeal nerve from the cricothyroid membrane to the sternal notch and from the common carotid artery (lateral limit) to the trachea (medial limit). In the inferior direction, dissection could extend to the level of the innominate artery (level VII). In this procedure, the paratracheal, pretracheal, and delphian lymph nodes were removed. Autotransplant of parathyroid glands was performed if the surgical team deemed it necessary.

Postoperative laryngoscopy was performed within 30 days and repeated when necessary. The rates of recurrent laryngeal nerve dysfunction (temporary or permanent) were compared between the 2 groups. Calcium levels were measured during the first 24 hours and 1 week after surgery, and measurement was repeated if necessary. Supplementation of calcium and calcitriol was instituted only in patients with clinical (symptomatic) and/or hypocalcemia confirmed by laboratory test results and defined by a serum total calcium level of less than 8.0 mg/dL or an ionized calcium level of less than 1.0 mg/dL (to convert to millimoles per liter, multiply by 0.25). Hyoparathyroidism was considered to be established when the patient needed replacement of calcium and calcitriol 6 months after surgery. We recorded all information concerning patients who had a hematoma that required surgical intervention and all postoperative infections (defined by the need for antibiotic therapy).

Whole-body scintigraphy was performed approximately 4 weeks after surgery and in patients with indications for radiiodine ablation therapy. We also performed scintigraphy after ablation therapy. Scintigraphy was repeated in cases with suspected recurrence during follow-up. Basal serum levels of thyroglobulin and antithyroglobulin antibodies were recorded during follow-up and at least every 6 months. The measurement of stimulated thyroglobulin levels became routine at the 1-year follow-up for patients treated near the end of the study period.

Data were collected from February 1, 2012, through January 31, 2013, and analyzed from February 1 through August 31, 2013. We used a frequency distribution to describe categorical variables and used measures of central tendency and variability for numerical or continuous variables. The χ² test assessed the association between categorical variables and study groups (performance of level VI lymph node dissection). When at least 1 expected frequency was less than 5 in 2 × 2 tables, we used the Fisher exact test. When the normality of the data was not identified, we applied the Mann-Whitney test to compare the numerical variables. We adopted the significance level of 5% for all statistical tests and used commercially available software (Intercooled STATA, version 7.0; Stata Corporation) to perform the statistical analysis.
Results

From January 1, 1996, through January 1, 2007, 812 patients underwent surgical treatment for PTC at A. C. Camargo Cancer Center. Of these patients, 580 met the established selection criteria. One hundred two patients underwent total thyroidectomy and elective lymph node dissection of the central compartment (group A). In 23 of these 102 patients (22.5%), the lymph node dissection of the central compartment was bilateral. Total thyroidectomy alone was performed in 478 patients (group B).

The characteristics of the patients and tumors were different between groups. Although patients in group A were younger (mean age, 41.2 vs 45.2 years; \( P = .004 \)) and had larger tumors (mean tumor size, 14.8 vs 10.2 mm; \( P < .001 \)) and more frequent lymphatic and/or vascular invasion (10.8% vs 3.1%; \( P = .004 \)) than those in group B. In our analysis of patients in group A, no differences in permanent hypoparathyroidism were found between bilateral paratracheal elective neck dissection (3 of 23 patients [13%]) compared with patients who underwent unilateral dissection (9 of 79 patients [11%]). We found a significantly higher incidence of temporary (11.8% vs 6.1%; \( P = .04 \)) and permanent (5.9% vs 1.5%; \( P = .02 \)) recurrent laryngeal nerve dysfunction in group A (Table 2).

Ablative radiiodine treatment was performed in 270 patients, with a mean dose of 133.6 (range, 30-400) mCi (to convert to millibecquerels, multiply by 3.7 × 10^10). All patients treated with iodine I 131 in this study underwent a single ablation. More patients in group A underwent this adjuvant treatment (56.9% vs 44.4%; \( P = .03 \)), and the doses were higher in group A (mean, 151.1 vs 129.3 mCi; \( P = .01 \)). In the Figure, the results were stratified between those who underwent radiiodine ablation and those who did not and the profile of recurrence in the respective groups. This analysis did not find any statistically significant differences between groups.

The proportion of cases with elevated thyroglobulin antibody levels during follow-up was equivalent in both groups (9.5% vs 7.7%; \( P = .58 \)). The number of patients with basal serum thyroglobulin levels less than 1.0 ng/mL (to convert to micrograms per liter, multiply by 1.0), measured at 6 months postoperatively, was also comparable (97.8% vs 96.6%; \( P = .75 \)). The percentage of patients with serum levels of stimulated thyroglobulin (using endogenous thyrotropin) less than 1.0 mg/L, measured 1 year after surgery, was similar in both groups (51.5% vs 48.6%; \( P = .82 \)).

After a mean follow-up of 69.7 months, no PTC-related deaths occurred. Recurrences were documented in 11 of the

Table 1. Characteristics of Patients and Tumors

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment Group*</th>
<th>Group A (n = 102)</th>
<th>Group B (n = 478)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (range)</td>
<td></td>
<td>41.2 (13-75)</td>
<td>45.2 (17-84)</td>
<td>.004b</td>
</tr>
<tr>
<td>( \geq 45 )</td>
<td></td>
<td>35 (34.3)</td>
<td>231 (48.3)</td>
<td>.01c</td>
</tr>
<tr>
<td>(&lt; 45 )</td>
<td></td>
<td>67 (65.7)</td>
<td>247 (51.7)</td>
<td>.37</td>
</tr>
<tr>
<td>Distribution by sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>87</td>
<td>423</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>15</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Tumor size, mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (range)</td>
<td></td>
<td>14.8 (4-40)</td>
<td>10.2 (1-125)</td>
<td>&lt;.001b</td>
</tr>
<tr>
<td>( pT1a )</td>
<td></td>
<td>38 (37.3)</td>
<td>290 (60.7)</td>
<td>.03</td>
</tr>
<tr>
<td>( pT3-pT4a )</td>
<td></td>
<td>19 (18.6)</td>
<td>73 (15.3)</td>
<td>.03</td>
</tr>
<tr>
<td>Adverse histologic variant</td>
<td></td>
<td>8 (7.8)</td>
<td>20 (4.2)</td>
<td>.12</td>
</tr>
<tr>
<td>Multifocality</td>
<td></td>
<td>35 (34.3)</td>
<td>136 (28.5)</td>
<td>.24</td>
</tr>
<tr>
<td>Bilaterality</td>
<td></td>
<td>23 (22.5)</td>
<td>78 (16.3)</td>
<td>.19</td>
</tr>
<tr>
<td>Positive margins</td>
<td></td>
<td>13 (12.7)</td>
<td>47 (9.8)</td>
<td>.38</td>
</tr>
<tr>
<td>Extracapsular extension, extranodal</td>
<td></td>
<td>35 (34.3)</td>
<td>118 (24.7)</td>
<td>.045</td>
</tr>
<tr>
<td>Extrathyroidal extension</td>
<td></td>
<td>20 (19.6)</td>
<td>74 (15.5)</td>
<td>.31</td>
</tr>
<tr>
<td>Associated thyroiditis</td>
<td></td>
<td>45 (44.1)</td>
<td>174 (36.4)</td>
<td>.14</td>
</tr>
<tr>
<td>Lymphatic and/or vascular invasion</td>
<td></td>
<td>11 (10.8)</td>
<td>15 (3.1)</td>
<td>.002c</td>
</tr>
<tr>
<td>Mean follow-up time, mo</td>
<td></td>
<td>80.2</td>
<td>67.4</td>
<td>&lt;.001b</td>
</tr>
</tbody>
</table>

Abbreviation: p, pathologic.

*Group A included patients who underwent total thyroidectomy with elective central neck dissection (level VI); group B, patients who underwent total thyroidectomy only. Unless otherwise indicated, data are expressed as number (percentage) of patients.

b Calculated using the Mann-Whitney test.

c Calculated using the Fisher exact test.
580 patients (1.9%), including 4 (3.9%) in group A and 7 (1.5%) in group B. In 10 of these 11 cases, relapse occurred in cervical lymph nodes, and 9 cases were detected by means of ultrasonography. The observed pattern of recurrence differed between groups. All 4 cases of recurrence observed in group A occurred exclusively in the lateral chains of the neck. In group B, 2 of the 7 cases of relapse occurred in the central compartment of the neck. In addition, 4 cases occurred in the lateral chains of the neck and 1 case occurred as a distant metastasis.

**Discussion**

The central compartment of the neck (level VI) is bounded superiorly by the hyoid bone, inferiorly by the superior border of the sternal manubrium, and laterally by the common carotid arteries. This compartment consists of the parathyroid and the pretracheal, paratracheal, and delphian lymph nodes. The compartment continues inferiorly to the superior mediastinum (level VII) and to the level of the innominate artery. Elective lymph node dissection of the central compartment of the neck in patients with PTC is defined as a complete excision of the level VI lymph nodes in patients without evidence of regional metastasis after clinical and preoperative ultrasonography beyond the intraoperative evaluation. Lymph node metastases of PTC can be diagnosed in rare cases by clinical examination or preoperative ultrasonography. Most metastases are diagnosed during surgical exploration and are treated using a therapeutic indication for lymph node dissection. In such cases, lymph node dissection is associated with lower recurrence rates and better survival rates. However, the role of elective lymph node dissection of the central compartment remains a controversial topic.

Surgeons who advocate elective lymph node dissection of the central compartment argue that nodal metastases are present in as many as 90% of surgical specimens and are indicative of a worse prognosis. In the present study, positive lymph nodes were identified in the pathologic examination of the specimen (pN1a) in 67.2% of patients in group A. Regional metastases are believed to be associated with a higher risk for recurrence according to published data, with poor survival. Moreover, preoperative ultrasonographic evaluation and intraoperative central compartment exploration have demonstrated low sensitivity in detecting lymph node metastases.

Despite the growing interest in prophylactic lymph node dissection of the central compartment, a routine indication remains questionable owing to the lack of demonstrated benefit in terms of reduced rates of tumor recurrence and mortality. Zetoune et al examined 1264 patients, and results of a meta-analysis showed no significant decrease in the rate of local recurrence after prophylactic lymph node dissection of the central compartment. No randomized prospective studies have analyzed the impact of prophylactic lymph node dissection on mortality and survival.

<table>
<thead>
<tr>
<th>Complication</th>
<th>Group A (n = 102)</th>
<th>Group B (n = 478)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative hemorrhage</td>
<td>0</td>
<td>8 (1.7)</td>
<td>.36</td>
</tr>
<tr>
<td>Postoperative infection</td>
<td>4 (3.9)</td>
<td>19 (4.0)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Patients with ≥1 parathyroid gland removed</td>
<td>36 (35.3)</td>
<td>64 (13.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Temporary hypocalcemia</td>
<td>47 (46.1)</td>
<td>154 (32.2)</td>
<td>.004</td>
</tr>
<tr>
<td>Permanent hypoparathyroidism</td>
<td>12 (11.8)</td>
<td>11 (2.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Temporary dysfunction of the recurrent laryngeal nerve</td>
<td>12 (11.8)</td>
<td>29 (6.1)</td>
<td>.04</td>
</tr>
<tr>
<td>Permanent dysfunction of the recurrent laryngeal nerve</td>
<td>6 (5.9)</td>
<td>7 (1.5)</td>
<td>.02</td>
</tr>
</tbody>
</table>

* Group A included patients who underwent total thyroidectomy with elective central neck dissection (level VI); group B, patients who underwent total thyroidectomy only.

† Indicates serum calcium level less than 8 mg/dL (to convert to millimoles per liter, multiply by 0.25).

§ Defined as supplementation of calcium and/or calcitriol after 6 postoperative months.

**Table 2. Distribution of Postoperative Complications**

**Figure. Stratified Results According to Radioiodine Ablation Therapy and Recurrence**

Group A included patients who underwent total thyroidectomy with elective central neck dissection (level VI); group B, patients who underwent total thyroidectomy only. This analysis found no statistically significant differences between groups.
Selective Level VI Neck Dissection for Papillary Thyroid Carcinoma

Original Investigation Research

Selective Level VI Neck Dissection for Papillary Thyroid Carcinoma

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spective randomized clinical study to evaluate the clinical advantages and disadvantages of prophylactic central neck dissection. Their results showed a similar oncologic outcome between groups, but the main disadvantage was a higher prevalence of permanent hypoparathyroidism. Therefore, based on these findings, a careful evaluation is essential to avoid the risks associated with elective lymph node dissection of the central compartment and should be based not on the risk for occult metastases but on the risk for lymph node recurrence. Perhaps the best strategy is to restrict the central neck dissection to a high-risk population because no difference regarding the recurrence in the central compartment was found. Most likely, this question can be addressed only with more patients and by taking into account the molecular profile of the studied tumors. Owing to the low number of recurrences in the central compartment, risk factors for recurrence could not be identified.

The central compartment lymphadenectomy was performed according to standard technique and aimed to promote a comprehensive lymphatic clearance and minimize the potential risk for complications. The mean number of lymph nodes removed was 6.8, whereas 67.2% of patients exhibited metastases as detected by results of a routine histopathologic evaluation. The dissection was performed with direct visualization of the laryngeal nerves, avoiding excessive manipulation and use of electrocautery along its entire route. Palestini et al reported a higher rate of temporary dysfunction of the recurrent laryngeal nerve in patients undergoing total thyroidectomy and bilateral lymph node dissection (1.4% vs 5.4%; \( P < .05 \)). The central compartment lymph node dissection may compromise the irrigation of the parathyroid glands, particularly the inferior glands. Therefore, the dissection must be meticulous, with delicate handling of recurrent laryngeal nerve and parathyroid glands and preservation of their blood supply. The autotransplant must be performed whenever necessary. Most operations in our study were performed by third- through fifth-year residents under the direct supervision of an experienced head and neck surgeon. Although reports in the literature associate the risk for postoperative complications with the experience level of the surgeon, the safety of thyroidectomy is not in doubt when performed at resident training centers under supervision. Present study showed significant differences concerning the rates of complications (not exclusively hypoparathyroidism but also recurrent laryngeal nerve dysfunction) between the 2 groups. These findings are probably correlated with recent (within the past 10 years) changes in the staff team: some team surgeons performed procedures associated with greater manipulation of the central compartment structures (recurrent laryngeal nerve and parathyroid). Furthermore, not all physicians adopted reimplantation of the parathyroid as routine care.

Despite the high risk for regional metastases, papillary carcinoma remains a disease with an excellent prognosis. Even with the finding of micrometastases in 61% of cases, several authors have reported very low rates of recurrence in patients undergoing elective lymph node dissection of the central compartment (0%-0.43%) and in those undergoing isolated thyroidectomy (0%-0.65%). After a mean follow-up of 69.7 months, we observed no deaths related to the disease, and only 11 of 580 patients (1.9%) developed tumor recurrence; most of these recurrences (10 of 11) were in the neck. We must highlight the possibility that selection bias (specifically, the disproportionate numbers of patients with T1a tumors in the group that did not undergo neck dissection) might play a role in this sample.

Conclusions

The evidence-based guidelines from the National Comprehensive Cancer Network do not support the routine use of lymph node dissection of the central compartment in patients treated for PTC. In its latest review, the American Thyroid Association recommends dissection selectively in patients with tumors larger than 4.0 cm or with extrathyroidal extension. Although the present study has a number of limitations, such as the retrospective nature and the bias of the therapeutic decision of each surgeon, our results support these guidelines and do not confirm the need for elective dissection in most cases. Therefore, a good assessment with preoperative ultrasonography is highly recommended, especially in patients at low risk, to ensure that gross disease is not left behind. The real impact of elective lymph node dissection of the central compartment in the management of PTC must be evaluated by a randomized prospective study with patients at higher risk for lymph node recurrence.
Selective Level VI Neck Dissection for Papillary Thyroid Carcinoma


Shen WT, Ogawa L, Ruan D, Shi H, Duh QY, Clark OH. Central neck lymph node dissection for papillary thyroid cancer: the reliability of surgeon judgment in predicting which patients will benefit. Surgery. 2010;148(2):398-403.


Selective Level VI Neck Dissection for Papillary Thyroid Carcinoma


