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ORIGINAL ARTICLE – ENDOCRINE TUMORS

Comprehensive Lateral Neck Dissection in Papillary Thyroid Carcinoma may Reduce Lateral Neck Recurrence Rates

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ABSTRACT

Objective. To Identify predictors of recurrent disease following lateral neck dissection (LND) for papillary thyroid carcinoma (PTC).

Methods. A retrospective review of patients who underwent first-time LND for PTC at our institution (2000–2015) was performed. Medical records were examined for biopsy or pathologically proven lateral neck recurrence. Differences between the groups with and without recurrence were compared. All LNDs were then classified in to two groups: "comprehensive" (CND), involving levels IIa-Vb at minimum, or "selective", labelling less extensive dissection (SND).

Results. Four hundred nine patients underwent 467 LNDs. Surveillance data were available for 317 patients who underwent 362 LNDs (mean age 45 ± 16; range 18–88). The median follow-up was 64 ± 48 months (range 3–197). Recurrence was detected in 71 lateral necks (20%). The total number of lymph nodes was greater in the group without recurrence compared to those with recurrence (23 vs. 19, $p = 0.02$). Among patient demographics, radioactive iodine treatment, primary tumor characteristics and characteristics of nodal metastases, only an older patient age (mean 50 vs. 43 years) was associated with lateral neck recurrence ($p < .01$). CND was performed in 102 lateral necks and SND in 143 necks. There were 12 recurrences recorded in the CND group (12%) vs. 31 in the SND group (22%, $p = .04$). The majority of recurrences (70%) involved levels included in the original dissection.

Conclusions. Younger patients, more extensive dissection and a higher total number of lymph nodes removed are associated with a lower incidence of lateral neck recurrence after LND for papillary thyroid carcinoma.

BACKGROUND

Lateral neck lymph node metastases are common in patients with papillary thyroid carcinoma (PTC). It is recognized that extensive lateral neck dissections (LNDs) may not be necessary, but the exact extent of the LND has been controversial. The Surgical Affairs Committee Statement of the American Thyroid Association recommends that LND performed for macroscopic differentiated thyroid cancer metastases should be the selective neck dissection of levels IIa, III, IV, and Vb.[1] Data supporting this approach can be found in studies reporting rates of nodal metastases within specific levels based on pathologic analysis of the specimens.[2–6] However, metastases encountered in these studies may be microscopic, and it is unclear whether these microscopic metastases would progress to clinically significant disease if not included in the dissection. It has been suggested that more extensive or aggressive lateral neck dissection carries a risk of morbidity and that less aggressive or less extensive lymphadenectomy from fewer compartments or levels may be appropriate.[7] Certain centers, including our institution, report performing LND involving fewer levels than IIa–Vb.[8–10] It is unclear whether less extensive resection would result in increased rates of lateral neck recurrence and if such dissection would be less morbid. A paucity of studies report the outcomes of such dissections and compare them with the outcomes of comprehensive dissection of levels IIa–Vb. The purpose of our study was to determine the risk

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factors for recurrence following LND for PTC and explore the association between the extent of dissection and lateral neck recurrence.

METHODS

A retrospective review of patients who underwent first-time LND for PTC at the Mayo Clinic between 2000 and 2015 was performed. Medical records were examined for the presence of ipsilateral lateral neck structural recurrence confirmed with cytology or pathology. Patients with and without recurrence were compared with regards to pathologic findings, demographic characteristics, and radioactive iodine treatment (RAI) to determine risk factors for recurrence.

Detailed standardized mapping of lateral neck lymph nodes (LN) is a routine component of neck ultrasound performed for thyroid cancer at our institution. Structured reports by attending radiologists are kept on record and were reviewed for the presence of lateral neck disease and its location both preoperatively and postoperatively. These reports also include schematic drawings detailing the involvement of different neck levels.[11]

All LNDs were classified into two groups: comprehensive (CND), involving levels IIa–Vb at minimum, or selective, labeling less extensive dissection (SND). The operations were performed by experienced, high-volume thyroid surgeons at the Mayo Clinic. The exact extent of dissection was considered to be known only when levels included in the dissection were clearly named in the operative note. No extrapolation or attempts to determine the extent based on the descriptions from the operative note were made. Recurrence rates were compared among patients who had different types of neck dissections. Preoperative ultrasounds were reviewed to determine proximal extent of LN metastases. Subgroups with no disease proximal to either level III or level IV were then analyzed to determine difference in recurrence rates for CND versus SND.

Statistical analysis was performed with JMP 13.0 (2016, SAS Institute Inc.). Lateral neck recurrence-free interval was correlated with the extent of surgery. Kaplan–Meier curves were constructed; log-rank test was used to analyze survival time data. Discrete variables were reported as frequencies (percentage) and continuous variables as mean ± SD. For analysis of categorical variables, Pearson's χ^2 or Fisher's exact test was used. Logistic regression analysis was used to assess the association between the risk of recurrence and continuous variables. A p value < 0.05 was used to determine statistical significance.

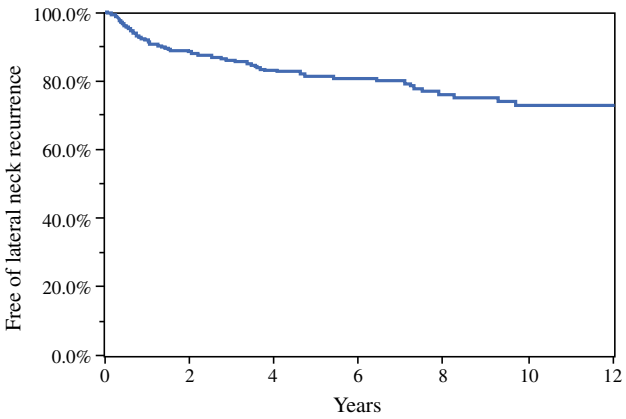

FIG. 1 Kaplan–Meier curve of lateral neck recurrence-free survival for the entire cohort

The study was approved by the Mayo Clinic Institutional Review Board, and a waiver of the requirement to obtain informed consent from the study subjects was approved considering the minimal risk of the study.

RESULTS

A total of 409 patients underwent 467 LNDs. Surveillance data were available for 317 patients who underwent 362 LNDs. There were 200 females and 117 males (mean age 45 ± 16 years; range 18–88). The median follow up was 64 ± 48 months (range 3–197).

Risk factors for lateral neck recurrence

Recurrence was detected in 71 lateral necks (20%). A Kaplan–Meier curve for the entire cohort is shown in Fig. 1; 81% of lateral necks were free of recurrence at 5 years. Characteristics of groups with and without lateral neck recurrence were compared (Table 1). Among patient demographics, primary tumor characteristics, and characteristics of nodal metastases, only older patient age (mean 50 vs. 43 years) was associated with lateral neck recurrence ($p < 0.01$). Patients with recurrence tended to be more likely to receive RAI before recurrence (65 (92%) vs. 241(83%), $p = 0.07$). Those with recurrence had fewer LNs harvested (19 vs. 23, $p = 0.02$). A receiver operating characteristic (ROC) curve was constructed, and optimal cutoff values to predict the absence of recurrence was greater than 32 harvested LNs (Fig. 2), and the area under the curve (AUC) was 0.58. A Scatterplot diagram of the number of LNs retrieved grouped according to the presence or absence of recurrence is shown in Fig. 3.

TABLE 1 Patient/tumor characteristics and lateral neck recurrence

	Recurred $N = 71$	No recurrence $N = 291$	p
Age (mean ± SD)	50 ± 17	43 ± 15	< 0.01
Gender (female, *n*, %)	46 (66%)	179 (61%)	0.5
RAI (*n*, %)	65 (92%)	241 (83%)	0.07
Total dose of RAI received until last follow-up or recurrence (mCi, mean ± SD)	130 ± 67	146 ± 117	0.3
Characteristics of nodal metastases and lateral neck recurrence			
Total number of LNs retrieved	19 ± 10	23 ± 13	0.02
Total number of metastatic LNs	4.8 ± 3	4.5 ± 4	0.5
Percentage of metastatic LNs	28 ± 18	23 ± 17	0.04
Largest metastasis (mean, mm)	26 ± 16	26 ± 14	0.9
Extranodal extension (*n*)	14 (20%)	47 (16%)	0.5
Primary tumor characteristics and lateral neck recurrence			
Aggressive histology (*n*)	6 (8%)	23 (8%)	0.9
Margin status (*n* +)	15 (21%)	57 (20%)	0.9
Multifocality (*n*)	38 (54%)	145 (50%)	0.7
Primary tumor diameter (mean, mm)	24 ± 13	24 ± 16	0.9
Extrathyroidal extension (*n*, %)	30 (42%)	105 (36%)	0.5

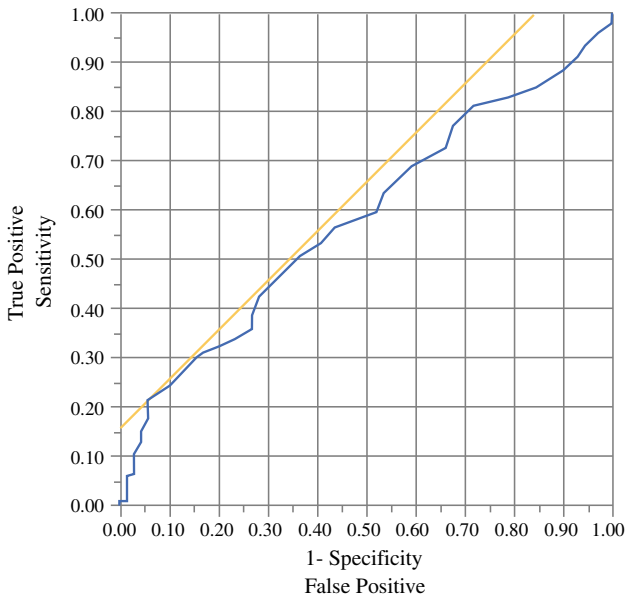

FIG. 2 ROC curve for total number of LNs harvested and freedom of lateral neck recurrence

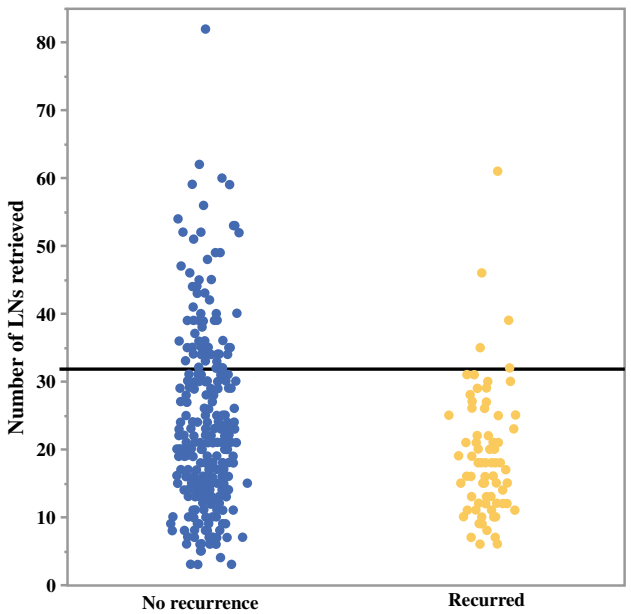

FIG. 3 Scatterplot diagram of individual lateral necks plotted against the number of lymph nodes retrieved. They were grouped according to the presence or absence of recurrence

Comprehensive compared with selective lateral neck dissection

Levels included in LND were clearly named for 245 LNDs, and the specific levels included in SND are further described in Table 2. CND was performed in 102 lateral necks and SND in 143 necks. Twelve recurrences were reported in the CND group (12%) versus 31 in the SND group (22%, $p = 0.04$). When dissection of levels IIa–Vb ($n = 102$) was compared with III–Vb dissection ($n = 103$), a similar difference in recurrence rates was found (CND, $n = 12$ (12%) versus SND, $n = 23$ (22%), $p = 0.04$). Comparison of groups according to the extent of dissection is further detailed in Table 3. Kaplan–Meier curves are shown in Fig. 4, and there was no difference in lateral neck

TABLE 2 Levels included in SND (n = 143)

Extent of dissection	No. of lateral necks	Recurrence (n, %)	No. of LNs removed (mean ± SD)	Positive LNs ratio
III-Vb	103 (72%)	23 (22%)	20 ± 10	0.21 ± 0.17
II, III, IV	13 (9%)	3 (23%)	19 ± 8	0.21 ± 0.16
III, IV	20 (14%)	5 (25%)	12 ± 6	0.28 ± 0.17
II, III	1 (1%)	0	17	0.06
IV, V	6 (4%)	0	15 ± 5	0.17 ± 0.06

TABLE 3 Differences between groups according to the extent of dissection (for patients who had the exact levels of dissection stated in operative note)

	CND n = 102	SND n = 143	p
Recurred (n, %)	12 (12%)	31 (22%)	0.04
LNs retrieved (n, mean ± SD)	28 ± 14	18 ± 10	< 0.01
Positive LNs (n, mean ± SD)	5.9 ± 4	3.3 ± 2	< 0.01
Positive LN ratio	0.23 ± 0.16	0.21 ± 0.17	0.3
Complications (n, %)	11 (11%)	7 (5%)	0.08
Marginal mandibular palsy/shoulder dysfunction	2 (2%)	0	0.09
	IIa-Vb n = 102	III-Vb n = 103	p
Recurred (n, %)	12 (12%)	23 (22%)	0.04
LNs retrieved (n, mean ± SD)	28 ± 14	20 ± 10	< 0.01
Positive LNs (n, mean ± SD)	5.9 ± 4	3.3 ± 2	< 0.01
Positive LN ratio	0.23 ± 0.16	0.21 ± 0.17	0.2
Complications (n, %)	11 (11%)	6 (6%)	0.2
Marginal mandibular palsy/shoulder dysfunction	2 (2%)	0	0.2

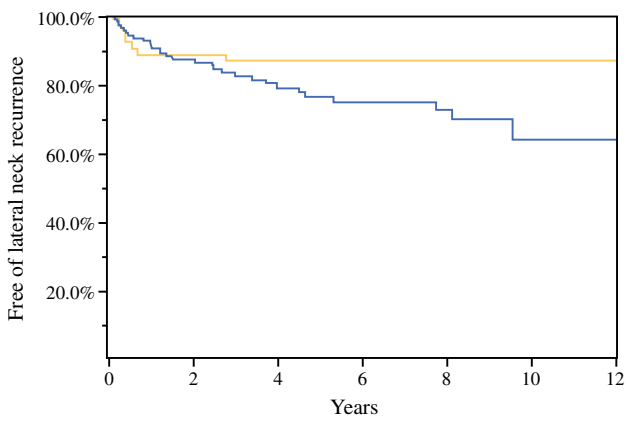

FIG. 4 Kaplan–Meier curve of lateral neck recurrence-free survival according to the extent of dissection: CND (yellow line) versus SND (blue line)

recurrence-free survival among the two groups (p = 0.09). Complications occurred after 11 LNDs in the CND group (11%) and after 7 LNDs in the SND group (5%, p = 0.08). Combined rates of shoulder dysfunction and marginal mandibular nerve-related complications were similar between the groups (CND n = 2, 2% vs. SND n = 0, p = 0.09).

Recurrence patterns

Among 71 lateral necks with recurrence from the entire cohort of LNDs (n = 362), the recurrence was detected in levels I (n = 2, 3%), II (n = 28, 39%), III (n = 26, 37%), IV (n = 27, 38%), and V (n = 8, 11%). For LNDs with clearly stated levels included in the dissection (n = 245), the recurrence was detected in 43 lateral necks in levels I (n = 1, 2%), II (n = 17, 40%) III (n = 16, 37%), IV (n = 14, 33%), and V (n = 6, 14%) with 30 recurrences (70%) involving levels included in the original dissection. Level II recurrence was detected in eight patients who had levels III–Vb dissected (8%) compared with six patients in the IIa–Vb group (6%, p = 0.6). Twenty-seven patients with lateral neck recurrence developed recurrence

elsewhere (48%) compared with 77 patients (30%) without lateral neck recurrence ($p = 0.01$). Distant disease was noted in 15 patients with lateral neck recurrence (26%) versus 11 patients without lateral neck recurrence (4%, $p < 0.01$). Central neck recurrence occurred in 26 patients with lateral neck recurrence (44%) versus 70 patients with no lateral neck recurrence demonstrated (28%, $p = 0.01$).

Correlation of preoperative ultrasound findings and the extent of dissection with recurrence risk

Preoperative ultrasound suggested no disease proximal to level III in 79 lateral necks in patients who underwent either selective dissection of levels III–Vb ($n = 49$, 48%) or CND ($n = 30$, 29%). Recurrences were detected in 2 lateral necks in the CND group (7%) and in 12 lateral necks in the SND group (24%, $p = 0.03$). In patients without nodal involvement proximal to level IV, recurrence was detected in 1 of 17 patients who underwent CND (6%) and in 10 of 53 patients who had SND of levels III–Vb (19%, $p = 0.2$).

DISCUSSION

Terms "comprehensive" and "selective" were used to describe different extents of LND for metastatic PTC. This distinction has been introduced in similar studies by McNamara et al. and Xu et al.[12, 13] However, according to classification of neck dissections suggested by the American Head and Neck Society and the American Academy of Otolaryngology–Head and Neck Surgery, all dissections described in this study should be labeled as "selective," because this classification does not define a "comprehensive" neck dissection.[14] While CND appears to represent dissections of levels IIa–Vb in all three studies, the extent of SND is more variable. McNamara et al. describe SND as dissection of levels III and IV routinely and dissection of level II if clinically suspicious nodes are found.[11] The main difference between CND and SND in the study by Xu et al. was in level Vb dissection technique.[12] In our study, the majority of SNDs included levels III, IV, and Vb (72%). Most of the remaining (28%) dissections involved either levels III and IV or dissection of levels II–IV. These patients were included together with SND of levels III–Vb only in the initial analysis. Because this is a heterogeneous group with different extents of dissection and a relatively small number of patients in each group, further detailed analysis focused on differences between CND and SND of levels III–Vb.

We found increased recurrence rates with less extensive dissection, even when SND encompassing levels III–Vb is compared with CND. It appears that dissection of levels IIa–Vb yields an average of eight LNs more and an additional one to two metastatic LNs, resulting in an absolute decrease in recurrence rate of 10%. Although it may be expected that recurrence in undissected level II in the III–Vb group would account for the difference, both groups (IIa–Vb and III–Vb) had similar level II recurrence rates (6% vs. 8%). Therefore, it appears that the association between the extent of dissection and recurrence risk is more complex. Our finding that the majority of recurrences have occurred within previously dissected neck levels was similar to the findings of Caron et al.[8] This may suggest that factors other than the extent of dissection, such as more aggressive biology, may play a major role in the development of recurrence. Alternatively, either incomplete dissection of these levels or discrepancies in determination of the anatomic boundaries by ultrasound and intraoperatively may explain this finding.

Albuja-Cruz et al. attempted to determine whether there is either a minimum acceptable or optimal number of LNs that should be harvested in LND for PTC, analogous to breast and colon cancer.[7] They were not able to demonstrate a significant association between the number of LNs removed and recurrence risk. In contrast to their study, we found an association between the number of LNs harvested and both the extent of dissection and the recurrence risk. While the association is statistically significant, ROC analysis demonstrates only a modest predictive value with AUC of 0.58, and the "cutoff" should be interpreted with caution. There are several potential explanations: (1) factors other than the extent of dissection may play a major role in recurrence risk; (2) LN counts can be influenced by individual patient anatomic variability and pathology lab processing of the specimen.

The concept of "freedom of recurrence" in the ipsilateral lateral neck (utilizing Kaplan–Meier curves) has been previously applied in two studies, and McNamara et al. found a difference according to the extent of dissection.[12, 13] We were unable to demonstrate a difference in our cohort, even though there appears to be a late separation of the curves. The CND curve appears to plateau while there is a steady decline in the SND group. Kaplan–Meier analysis of lateral neck recurrences for the entire cohort demonstrates slow but steady decline, in keeping with slow growth of metastatic PTC. It appears that leftover, initially clinically undetectable metastatic nodes, can progress to clinically significant metastases if followed for a prolonged period of time.

Reported rates of ipsilateral lateral neck recurrence after lateral neck dissection vary widely from 3 to 44%.[12, 15] As already noted by Chereau et al., this variability may be explained by differences in follow-up, quality of imaging, and different definitions of recurrence, as well as different thresholds for biopsy of suspicious LNs.[16] It should be

noted that our study spans a relatively long time period (16 years), and even suspicious LNs with the greatest diameter of 5 mm were biopsied.

Distant disease appears to be quite common among patients with lateral neck recurrence following LND occurring in 25% of patients with lateral neck recurrence compared with only 6% of patients without it. Lateral neck recurrence thus may be a herald of more aggressive disease, suggesting that such patients require particular attention during surveillance. Again, this suggests that factors other than the extent of dissection may play a role in the development of lateral neck recurrence. Therefore, we attempted to identify these risk factors. Prior literature identified multiple factors associated with either locoregional recurrence or, more specifically, lateral neck recurrence. These factors included nodal size, number of positive nodes, presence of extranodal extension, male gender, primary tumor size, and aggressive histology.[7, 16–19] However, the only significant factor in our cohort was patient age, because patients without recurrence were younger on average. This is in contrast to prior reports and may be the result of inconsistent reporting and recording of these characteristics during the long time period of this study. Finally, future studies focusing on molecular markers of the biology of thyroid cancer are needed, in the context of lateral neck recurrence and elsewhere.

One of the main arguments for less extensive selective neck dissection is the fear of increased morbidity associated with more extensive dissection, such as spinal accessory nerve injury. We were not able to support this presumption, because both overall complications and the rates of shoulder dysfunction were very similar between groups. Our rates are substantially lower than the rates reported in prospective studies.[20] This may be related to study design, because many associated lateral neck complications, such as shoulder dysfunctions and/marginal mandibular nerve-related complications, may be underreported and difficult to detect on a retrospective chart review, as noted by McNamara et al.[12] Furthermore, while the complications across the two approaches were not statistically significantly different, it appears that there were more complications associated with the CND (11% vs. 5%), and the events are relatively few, which could limit the ability to detect the difference.

Lastly, we sought to determine whether distribution of nodal metastases, mapped by preoperative ultrasound, can be used to tailor the extent of dissection. It appears that dissection should extend into level IIa when the ultrasound study suggests involvement of level III LNs. However, this is less clear when preoperative ultrasonography suggests that the disease does not involve LNs proximal to level IV, because there was no difference in the number of recurrences between CND and SND including levels III-Vb. It should be noted that the recurrence rate for SND was still 19% compared with only 6% in CND and that there were only 17 patients who underwent CND, suggesting potential loss of power when this subgroup is analyzed. Also, precise determination of the exact location of the metastatic node within particular neck level based on retrospective review of sonographic records may be prone to variability despite structured approach to LN mapping utilized at our institution.

Our study has multiple limitations, including its single-institution, retrospective design with associated selection bias. Retrospective determination of the exact level of dissection using operative notes over a prolonged period of time is difficult, and errors are possible.

CONCLUSIONS

Younger patients, more extensive dissection, and higher total number of lymph nodes removed were associated with a lower incidence of lateral neck recurrence after lateral neck dissection for papillary thyroid carcinoma.

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