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Therapeutic lateral neck dissection in well-differentiated thyroid cancer: Analysis on factors predicting distribution of positive nodes and prognosis

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Abstract

Background: Neck dissection is considered the treatment of choice in patients with lateral neck metastases from well-differentiated thyroid cancer.

Methods: A multicenter, retrospective review of patients who underwent therapeutic lateral neck dissection for well-differentiated thyroid carcinoma was carried out.

Results: The study included a total of 405 lateral neck dissections performed in 352 patients; 197 women (56%) and 155 men (44%). When considering ipsilateral neck metastases, levels IIa, IIb, III, IV, Va, Vb, and V (not otherwise specified) were involved in 42%, 6%, 73%, 67%, 11%, 31%, and 35% of cases, respectively. Five-year and 10-year overall survival (OS) were 93% and 81%, respectively. Age >55 years, pathologic T (pT)4 category, tumor diameter >4 cm, aggressive variants of well-differentiated thyroid carcinoma, endovascular invasion, and number of positive nodes >5 turned out to be the most important prognostic factors.

Conclusion: Neck dissection is a valid treatment option in the presence of neck metastasis from well-differentiated thyroid carcinoma. Levels IIa, III, IV, and Vb should always be removed.

KEYWORDS

lateral neck metastases, neck dissection, neck levels, survival, well-differentiated thyroid cancer

1 | INTRODUCTION

Well-differentiated thyroid cancer has a high and well-known propensity to spread to lymph nodes in the neck, in both the central and lateral compartments.[1] The pattern of regional spread is often predictable and determined by the site of the primary tumor. Lymphatic drainage of lesions located in the upper pole of the gland follows the lymphatic vessels around the superior thyroid veins with consequent involvement of lymph nodes in level II, with possible sparing of level VI; conversely, tumors arising in the middle and lower portion of the thyroid gland tend to involve the central compartment first and then the lateral neck (levels III and IV) through the lymphatic vessels running along the middle and lower thyroid veins, respectively.[1] It has been demonstrated that the higher the number of involved nodes in the

central compartment, the higher the possibility to have lateral neck involvement.[2]

Although the pattern of lymphatic spread is well known, the impact of nodal metastases on survival is still a controversial issue,[3] even though some recent investigations have concluded that patients with N-positive disease seem to have a worse prognosis.[4-6] The relatively good prognosis of patients with well-differentiated thyroid carcinoma, the unclear prognostic value of nodal disease,[7] and the possible complications related to neck dissection (neural damage, shoulder syndrome, chyle leak, and hemorrhage)[3,8] are all factors that contribute to the lack of clear indications for management of the N-positive neck. The neck levels to be removed in neck dissection for well-differentiated thyroid carcinoma is one of the most debated issues; particular emphasis has been placed on levels I and V and sublevel IIb,[9] namely those with a lower metastatic rate and whose dissection is associated with important complications and sequelae.[10] Therefore, we performed a retrospective, multicenter study in the attempt to better define the ideal management of the lateral neck in well-differentiated thyroid carcinoma, analyzing the distribution of metastatic nodes in each level, possible predictors of involvement, rate of complications of neck dissection, and impact of nodal disease on survival.

2 | MATERIALS AND METHODS

A retrospective observational cohort study was designed to analyze patients who underwent therapeutic lateral neck dissection for well-differentiated thyroid carcinoma (as primary treatment or salvage procedure). Data between 1994 and 2015 were retrieved from 3 different tertiary referral institutions (University of Brescia, Arcispedale "S. Maria Nuova," and Istituto Nazionale dei Tumori "Regina Elena") and analyzed in a dedicated database. Preoperative fine-needle aspiration cytology was obtained in all cases to confirm the imaging or clinical suspect of nodal involvement. In selected cases with discrepancy between imaging and cytologic profile, thyroglobulin (Tg) assay on fine-needle aspirates washing was performed. All patients were treated with curative intent and were followed for at least 12 months. Neck dissection was considered ipsilateral or contralateral in relation to the site of the primary tumor; in the presence of multifocal disease, the side of the larger neoplastic nodule was arbitrarily defined as ipsilateral. Follow-up policy comprised a combination of clinical evaluation, Tg testing, neck ultrasound, iodine-131 (^{131}I) whole-body scan, and positron emission tomography/CT in selected cases. Postoperative Tg monitoring included both thyroid stimulating hormone (TSH)-stimulated at the time of initial ^{131}I treatment (either by thyroid hormone withdraw or recombinant human TSH administration) and basal TSH-unstimulated levels during follow-up.

TABLE 1 The neck dissection quality of life questionnaire (Giordano et al[11] 2012): each question is scored from 1 (worst) to 5 (best)

Question	Score
Are you bothered by neck or shoulder stiffness?	1–5
Are you bothered by constriction of your neck?	1–5
Are you bothered by neck or shoulder pain?	1–5
Are you bothered by numbness of your neck?	1–5
Do you think your shoulder has dropped?	1–5
Have you been limited in your ability to reach above for objects because of your shoulder or neck?	1–5
Are you bothered by the appearance of your neck?	1–5
Total	7–35

The presence of anti-Tg antibodies was assessed with each serum Tg level determination. Biochemical remission was defined as a Tg level of <1.0 ng/mL (either stimulated or unstimulated) in the absence of anti-Tg antibodies. Threshold for anti-Tg antibodies positivity was set at 4 ng/mL.

Subjective evaluation after lateral neck dissection was assessed using the neck dissection quality of life questionnaire (Table 1).[11] A score from 7 to 35 was obtained in relation to 7 questions concerning neck and shoulder function, pain, and aesthetic appearance. Each question was scored from 1 (worst) to 5 (best).

Primary endpoints of the study were defined as: evaluation of the prevalence of lateral neck metastases in each level or sublevel and the assessment of the correlation between predetermined risk factors, involvement of different levels, and survival.

Furthermore, secondary endpoints were: analysis of 5-year and 10-year overall survival (OS), locoregional control, disease-specific survival (DSS), distant metastases-free survival, and evaluation of type and prevalence of complications.

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and the principles of Good Clinical Practice. The study protocol was approved by the respective local ethics committees (Protocol Number: NP 1974).

2.1 | Surgical technique

Surgical technique was slightly modified over the years in terms of skin incision and levels to be removed. At the beginning, indeed, a classic "apron-flap" incision was the procedure of choice, whereas in the following years a horizontal incision carried along a skin crease and prolonging the thyroidectomy incision has been adopted. Moreover, at the beginning of our experience, levels IIa, III, and IV were removed in all cases and IIb in a vast majority, whereas level

V was included only in selected cases (ie, preoperative evidence of level V involvement and relevant metastatic burden at levels II-IV). More recently, also considering the division of level V in 2 sublevels (Va and Vb), it was considered more appropriate to also remove sublevel Vb. Level I and sublevel Va were removed only if involved or whenever a massive nodal metastatic burden was encountered at level II and at levels II-IV, respectively. All surgical specimens were intraoperatively divided by the first surgeon and labeled for histopathologic evaluation.

2.2 | Statistical analysis

Statistical analysis was carried out using STATA 13 software (StataCorp. 2013 release 13; Stata Statistical Software, College Station, TX). Comparisons between categorical variables were performed with Pearson's chi-square or Fisher's exact tests. Continuous variables were compared with the Wilcoxon-Mann-Whitney test. The OS, DSS, locoregional control, and distant metastases-free survival were evaluated by the Kaplan-Meier product limit estimate. Specific survival was calculated in treated patients who were alive or died of disease by excluding patients lost to follow-up or who died of concurrent diseases. Comparisons between survival curves were carried out with the log-rank test. For patient survival evaluation, the entry time point was the date of neck dissection, whereas the final time point was the date of death or date of last follow-up for patients alive at the end of the study (censored observations). The final time point for locoregional control was the date of the first local, regional, or locoregional recurrence (patients who died without any recurrences were considered as censored). The final time point for distant metastases-free survival was the date of presentation of metastases (patients who died without metastases were considered as censored).

3 | RESULTS

The study included a total of 405 lateral neck dissections performed in 352 patients (53 bilateral neck dissections): 197 women (56%) and 155 men (44%), with a mean age of 43.1 years (range 18-84 years). In 286 patients (81.2%), neck dissection was performed concomitantly to total thyroidectomy and central compartment neck dissection, whereas in 16 patients (4.5%) only total thyroidectomy and lateral neck dissection were carried out. In the remaining 50 patients (14.2%), neck dissection was a salvage procedure, in 32 patients (9.1%) after total thyroidectomy alone, and in 18 patients (5.1%) after total thyroidectomy and central compartment neck dissection. Tumor histology was papillary carcinoma in 246 patients (69.9%), papillary follicular-variant in 54 (15.3%), tall cell in 16 (4.6%), papillary sclerosing variant in 13 (3.7%), mixed papillary - follicular in 8 (2.3%), papillary with poorly differentiated areas in 6 (1.7%), Hürthle cell in 5 (1.4%), and follicular in 4 (1.1%). Overall, aggressive histologic variants (ie, tall cell, Hürthle cell, sclerosing variant, and poorly differentiated areas) were identified in 40 patients (11.4%). Distribution of pathologic (p)T classification was as follows: 78 pT1 (22.1%), 9 pT2 (2.6%), 10 pT3a (2.8%), 190 pT3b (54.0%), and 56 pT4a (15.9%) according to the TNM Classification of Malignant Tumors (8th edition Union for International Cancer Control).[12] In 13 patients (3.7%), it was not possible to retrieve data on staging of the primary tumors.

TABLE 2 Prevalence of nodal metastases in dissected lateral neck levels

Level	Ipsilateral (%)	Contralateral (%)
I	3/14 (21)	1/3 (33)
IIa	148/352 (42)	21/47 (45)
IIb	18/305 (6)	4/45 (9)
III	257/352 (73)	35/54 (65)
IV	236/352 (67)	33/54 (61)
Va	7/62 (11)	0/8 (0)
Vb	42/135 (31)	6/23 (26)
V (not specified)	48/136 (35)	2/13 (15)

Among the 286 patients who received total thyroidectomy concomitantly with central and lateral neck dissection, 209 (73%) had metastases at level VI ipsilateral to the primary lesion; contralateral central compartment involvement was found in 85 of 187 patients (45.5%). Among the 50 patients who underwent salvage lateral neck dissection, ipsilateral and contralateral central compartment neck dissection was performed in 26 cases (52%) and 7 cases (14%), respectively, and metastases were found in 14 patients (28%) and 2 patients (4%), respectively.

The mean number of total nodes removed in lateral neck specimens was 37 (range 18-95; median 35) when levels from II to V were dissected and 28 (range 19-91; median 26) when level V was not included in the specimen. The mean number of positive nodes was 5 (range 1-32). Involvement of each dissected level or sublevel is summarized in Table 2. In particular, when considering ipsilateral neck metastases, levels IIb, Va, Vb, and V (when division in sublevels was not performed) were involved in 5.9% (18/305), 11.3% (7/62), 31.1% (42/135), and 35% (48/136) of cases, respectively.[12] Extracapsular extension in metastatic nodes was not analyzed in consideration of the fact that, in the early part of the cohort, the histopathologic report did not consistently specify this feature.

TABLE 3 Summary of significant variables affecting survival as assessed by univariate analysis

Variables	Age >55 y	pT4 classification	Tumor diameter >4 cm	Aggressive histologic variant	Endovascular invasion	No. of positive nodes >5
OS	$P < .001$	$P < .001$	$P = .041$	$P = .007$	...	...
DSS	$P < .001$	$P = .003$	$P = .048$	$P = .047$	...	...
Locoregional control	$P = .003$	$P = .002$	$P < .001$	...	...	...
Distant metastases-free survival	$P = .002$	$P = .028$	$P < .001$	...	$P = .027$	$P = .048$

Abbreviations: DSS, disease-specific survival; OS, overall survival.

Fifty-two patients (15%) developed postoperative complications: shoulder syndrome (ie, shoulder disability due to spinal accessory nerve damage, with consequent denervation and atrophy of the trapezius muscle) was the most frequent (N = 27; 7.8%), followed by chyle leak (N = 9; 3%), and hematoma (N = 9; 3%). A total of 121 patients (34%) were evaluated with the neck dissection quality of life questionnaire.[11] The mean value was 29.1. In particular, 110 patients (81%) had a score ranging from 22 to 35, 23 (17%) from 16 to 25, and 3 (2%) from 7 to 15.

Considering radioactive iodine therapy, patients underwent a mean of 2 treatments after thyroidectomy (range 1-11). Mean administered activity was 12.987 GBq (range 1.11-86.58) before neck dissection and 8.325 GBq (range 0-77.7) after neck dissection.

Mean follow-up time was 73 months (range 12-255 months). At the last follow up, 264 patients showed no evidence of disease at clinical and radiologic evaluation, 25 were lost to follow-up, 25 were alive with disease, 23 died of other causes, and 14 died of disease. Considering patients with no evidence of disease, Tg levels were <1.0 ng/mL in 234 patients (66%), 49 of whom (21%) had positive anti-Tg antibodies. Among the 30 patients without evidence of macroscopic disease and Tg >1 ng/mL, the median Tg value was 3.5 ng/mL (range 1.1-85.5 ng/mL), with only 3 patients exceeding 10 ng/mL.

Different patient-related and tumor-related variables were considered to evaluate their impact on the risk of involvement at level V (Va, Vb, or not specified) or sublevel IIb: age (≤55 vs >55 years), T classification (T1-T3 vs T4a), tumor diameter (≤4 cm vs >4 cm), involvement of levels IIa, III, and IV, tumor endovascular or lymphatic invasion, and aggressive histologic variant. The pT4 tumors, level IV involvement, and lesions >4 cm turned out to be associated with the presence of metastases at level V ($P = .001$, $P < .001$, and $P = .046$, respectively). Similarly, pT4 tumors and sublevel IIa involvement (even when considering a single metastasis) was related with the presence of sublevel IIb metastases ($P = .045$ and $P = .029$, respectively). Analyzing the distribution of positive nodes, the mean number was 6.4 (range 1-19) and 4.5 (range 1-32) in patients with T4a and T1-T3 lesions, respectively ($P < .001$); moreover, the mean number of neck levels involved was 2.5 and 2.0, respectively ($P = .005$). Considering tumor diameter, the number of positive nodes was 7.3 (range 1-32) and 4.6 (range 1-23) in T >4 cm and T <4 cm, respectively ($P = .003$); the mean number of neck levels involved was 2.7 and 2.0, respectively ($P = .02$).

Five-year and 10-year OS for the entire cohort was 92.5% and 80.6%, respectively. Five-year and 10-year DSS was 97.2% and 93.6%, respectively. Five-year and 10-year locoregional control was 88.6%, and 80%, respectively. Finally, 5-year and 10-year distant metastases-free survival was 86.3% and 82.7%, respectively.

Age (≤55 vs >55 years), T classification (pT1-3 vs pT4), tumor diameter (≤4 vs >4 cm), endovascular and lymphatic invasion, aggressive histologic variant, nodal burden (≤17% vs >17%),[13] number of positive nodes at final histopathology (≤5 vs >5), and lymph node maximum diameter were analyzed to evaluate their impact on survival. Significant variables are summarized in Table 3 (Figures 1–4). Notably, no significant difference in terms of risk of regional recurrence was found in patients who underwent neck dissection including, or not, level Va or IIb. The significant variables in multivariate analysis (and their respective hazard ratio) are summarized in Table 4.

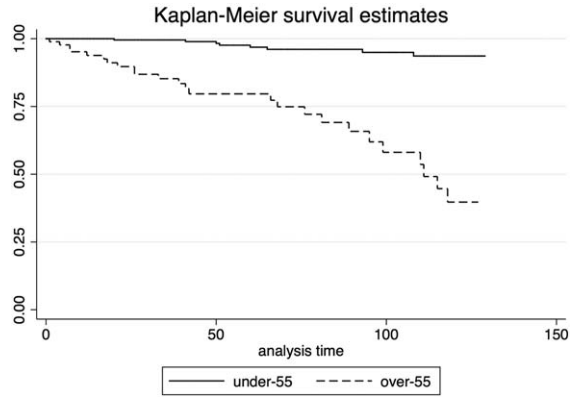

FIGURE 1 Overall survival curves according to age of patients (≤55 years vs >55 years)

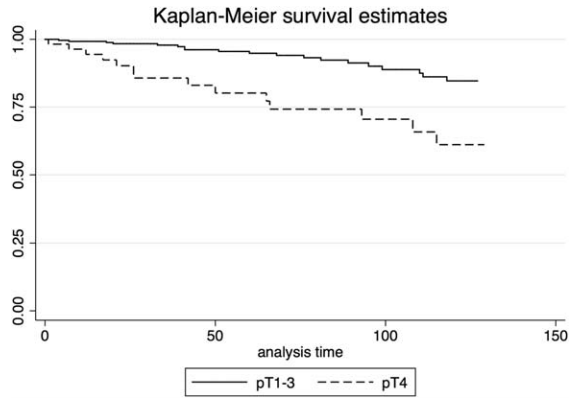

FIGURE 2 Overall survival curves according to pathologic T (pT) classification (T1-T3 vs T4)

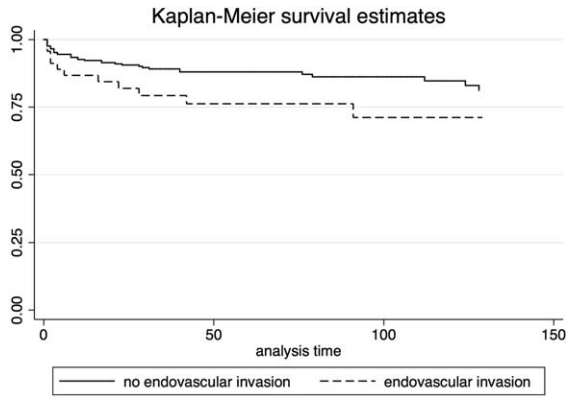

FIGURE 4 Distant metastases-free survival curves according to the presence or absence of endovascular invasion

Assessing disease recurrence, 26 patients (7%) developed recurrent disease in the central compartment: treatment was surgical excision only in 19 cases, radioactive iodine therapy in 5, and palliative treatment with subsequent tracheotomy in 2. A total of 33 patients (9.3%) developed a lateral neck recurrence during the follow-up period, 17 in the ipsilateral neck and 16 in the contralateral neck. Distribution of these patients is detailed in Table 5. Furthermore, 50 patients (14.2%) developed distant metastases: 35 to the lungs, 8 to the bone, and 7 to multiple metastases. Ipsilateral neck recurrence was associated with central compartment involvement in 2 patients (12%), and with distant metastases in 8 patients (47%). Similarly, contralateral neck recurrence was associated with central compartment relapse and distant metastases in 3 patients (19%) and 6 patients (37%), respectively (Table 5).

4 | DISCUSSION

The present study confirmed low rates of involvement of sublevels IIb and Va (6% and 11%, respectively), whereas sublevel Vb harbored metastatic nodes in a nonnegligible percentage of patients (31%). Risk factors for level IIb involvement were pT4 category and level IIa positivity; similarly, the risk of positive nodes at level V was higher in the presence of pT4 tumors, tumor diameter >4 cm, and level IV metastases. Considering survival, although it is possible to observe good results in terms of OS (92.5% and 80.6% at 5-years and 10-years, respectively), some specific risk factors were associated with a higher risk of death and/or recurrence: age over 55 years, pT4 category, tumor >4 cm in diameter, and aggressive histologic variants. Conversely, endovascular invasion and high number of nodal metastases (>5) were associated only with a higher risk of distant metastases. Finally, we confirmed the acceptable rate of complications of neck dissection (15%), with 81% of patients having a normal or near-normal score at functional evaluation.

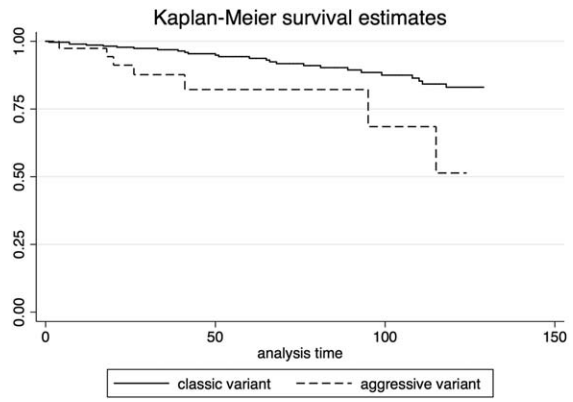

FIGURE 3 Overall survival curves according to histology (nonaggressive variants vs aggressive variants)

To date, the role of nodal metastases in well-differentiated thyroid carcinoma is still not well defined.[8] For a long time, indeed, regional spreading has been considered as a factor carrying "per se" a higher risk of recurrence without a significant impact on survival.[7] However, 2 different Surveillance, Epidemiology, and End Results database evaluations showed that nodal involvement was one of the factors independently affecting survival[4] and that nodal metastases could carry an increased risk of death, even though only in patients with follicular thyroid cancer or with papillary thyroid cancer and older than 45 years.[5] More recently, patients younger than 45 years with nodal metastases showed a limited but significant increase in the risk of death compared with patients of the same age without nodal involvement.[6] For these reasons, in the Union for International Cancer Control/American Joint Committee on Cancer TNM classification, lateral neck involvement is associated with a higher N classification (N1b), and these patients are included in the intermediate and high-risk groups in the American Thyroid Association and European Thyroid Association risk stratification.[14,15]

According to statements in the latter, adequate management of lateral neck nodal metastases seems to be of paramount importance to optimize outcomes in terms of risk of

TABLE 4 Summary of significant variables affecting survival in multivariate analysis

	Variables	Hazard ratio	*P* value
OS	Age >55 y	13.5	< .001
	pT4 classification	3.5	.001
DSS	Age >55 y	52.6	< .001
	pT4 classification	5.1	.016
Locoregional control	Age >55 y	2.5	.004
	pT4 classification	2.2	.017
	tumor diameter >4 cm	2.5	.006
Distant metastases-free survival	Age >55 y	2.2	.009
	tumor diameter >4 cm	2.9	.001

Abbreviations: DSS, disease-specific survival; OS, overall survival.

recurrence, survival, and quality of life. In most guidelines, lateral neck dissection is indicated for patients with biopsy-proven metastatic lateral cervical lymphadenopathy, by compartmental excision, because the practice of "berry picking" has been shown to have a much higher recurrence rate.[16-19] However, there is inconsistency in the literature regarding predictors of level involvement in metastatic well-differentiated thyroid carcinoma and, consequently, lateral neck levels to be included in the specimen. The American Thyroid Association consensus review on the rationale of lateral neck dissection in well-differentiated thyroid carcinoma recommends the routine dissection of levels IIa, III, IV, and Vb in the presence of single or multiple positive nodes. Similarly, the Triological Society Best Practice guidelines recommend a selective neck dissection targeting levels IIa through Vb, with inclusion of levels IIb and Va only when involved by the disease at preoperative diagnostic workup.[20] Apart from the risk of involvement of each level and sublevel and the capability of imaging techniques in detecting subclinical disease,[21-23] the morbidity of the surgical procedure is essential in selecting the most appropriate neck dissection. Indeed, the rationale behind possible sparing of sublevels IIb and Va is based, on one hand, on the low prevalence of involvement and, on the other, on the course of XI cranial nerve: dissection of these sublevels implies a high risk of damage to the spinal accessory nerve, potentially leading to upper limb and shoulder functional issues. This has been confirmed by Dijkstra et al[24] who demonstrated that the type of neck dissection was directly related to postoperative shoulder pain and functionality, and by Cappiello et al[25] who showed that clearance of the posterior neck triangle increased shoulder morbidity. Moreover, Celik et al[26] stated that, according to their experience, preserving sublevel IIb during selective neck dissection "decreases trauma to the accessory nerve and improves functional results" with optimal outcomes in all 30 patients included in their analysis. Apart from the functional consequence on the shoulder, the skin incision required in neck dissection may have a significant impact on quality of life even in terms of aesthetic results.[11] In order to minimize the possible aesthetic drawbacks, in the last few years, we progressively adopted a modified skin incision that horizontally lengthens the incision required in a thyroidectomy, thus lacking the vertical portion of a classic "apron-flap" incision. This transverse incision, carried along a skin crease, even if it makes dissection of the sublevel IIb more difficult, is undoubtedly associated with a much better long-term aesthetic outcome because it is less visible and may be completely hidden by the patient (see Figure 5).

Analyzing the pattern of nodal spreading of well-differentiated thyroid carcinoma, Eskander et al[27] reviewed

TABLE 5 Distribution of lateral neck recurrences

	Percentage of recurrences	Percentage in previously undissected levels/necks	Percentage of association with distant metastases (*P* value)
Ipsilateral neck	5	22[a]	47 ($P < .001$)
Contralateral neck	5	44[b]	37 ($P = .009$)

[a]Two patients in whom level V was previously dissected without specifying sublevel "a" or "b" that later developed recurrence at level Va.
[b]Percentage in previously undissected necks.

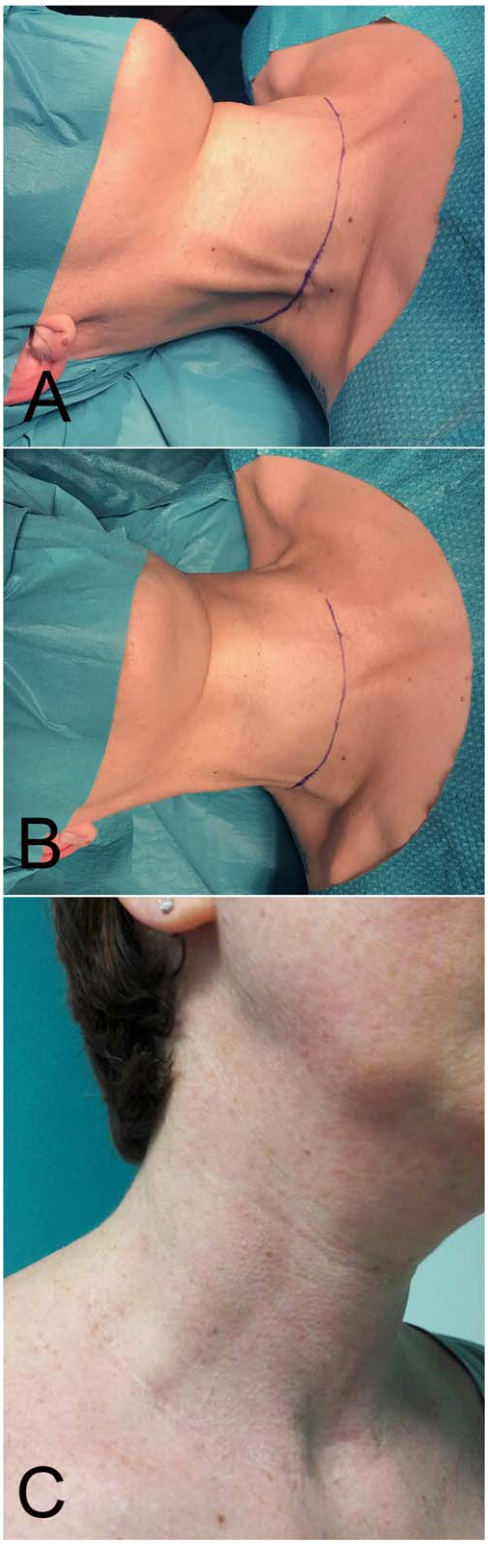

FIGURE 5 A and B, intraoperative view showing the horizontal cervical incision used for total thyroidectomy with ipsilateral neck dissection. C, Long-term aesthetic result of the previously mentioned cervical incision (different patient) [Color figure can be viewed at wileyonlinelibrary.com]

all the pertinent literature up to 2011 (a total of 1145 patients and 1298 neck dissections) and reported an overall rate of metastases of 53.1%, 15.5%, 70.5%, 66.3%, 7.9%, and 21.5% at levels IIa, IIb, III, IV, Va, and Vb, respectively. Nine of 18 studies distinguished between sublevel "a" and "b" while analyzing level II,[9,28-35] and only 3 studies considered level V sublevels separately.[9,29,36] Therefore, it was possible to confirm the general suggestion of a selective neck dissection including levels from II to V, with preservation of level I,[37] whereas the indications on the specific need for inclusion of sublevels IIb and Va was lacking. Vayisoglu and Ozcan[38] reviewed the recent literature in order to evaluate the rate of involvement of sublevel IIb in papillary thyroid cancer, finding values ranging from 2.1% to 61.5%; however, considering the same studies[9,29-32,34,36,39-41] and extrapolating the cumulative involvement of level IIb, the actual rate is 14.3%, which is comparable with our result. Similarly, Farrag et al[9] found sublevel IIb and Va metastases in 8.5% and 0% of cases, respectively; moreover, all patients with metastases at sublevel IIb had grossly positive nodes at sublevel IIa. Based on these results, it was suggested to remove sublevel IIb in case of positive nodes at sublevel IIa.[9,30,32,36,39] It is worth remembering that Merdad et al,[10] conversely, prefer to remove sublevel IIb in all cases due to the fact that subdivision of level II in sublevels may be arbitrary, especially in the presence of metastatic nodes. When considering sublevel Va, conversely, the rates of involvement range between 0 and 13%,[9,29,36] which is consistent with the value of 11% found in our study. On the other hand, published data concerning level Vb suggests a much higher rate of involvement, with a cumulative value of 21.5%.[27] However, this result is burdened by a poor statistical significance due to its low number of evaluations, because distinction between sublevels Va and Vb was performed in only 3 studies (137 patients).[9,29,36]

Our series show results that are comparable to those of the meta-analysis performed by Eskander et al,[27] with similar rates of metastases at levels IIa, III, and IV, slightly higher rates of involvement at sublevels Vb (31% vs 21.5%) and Va (11% vs 7.9%), and lower rates of sublevel IIb (6% vs 15.5%) involvement. In this view, the rate of nodal disease at level V, also confirmed by other reports,[22,23,42] seems to be mainly related to the presence of sublevel Vb involvement.[9] Therefore, we concur with authors who advocate inclusion of sublevel Vb in all neck dissections, regardless of the extension of the disease.[3,20,27] Conversely, sublevel IIb should be dissected only when involved or in the presence of advanced T classification and sublevel IIa metastases. Finally, sublevel Va is so rarely involved that it should be removed only in the presence of clinically evident disease.

Similar to sublevel IIb and Vb involvement, our results also reinforce the concept that specific clinical factors, namely pT4a classification and T diameter >4 cm, may predict the peculiar distribution of positive lymph nodes in the neck; the number of positive nodes and involved levels, indeed, were significantly higher than in patients with T1-T3 and T <4 cm lesions, respectively.

As confirmed by our experience, lateral neck dissection is an effective treatment for well-differentiated thyroid carcinoma with lateral neck metastases, both at presentation and in the recurrent setting. Our survival outcomes are comparable with those obtained by the analysis of large-scale databases, such as the Surveillance, Epidemiology, and End Results (79% at 14 years),[4] showing a 10-year OS of 80.6%, and reaching 93.6% when considering 10-year DSS. Prognostic factors confirmed what has been previously reported in the literature: age >55 years and locally advanced disease (tumor diameter >4 cm, and pT4 classification) are the most important risk factors in patients with lateral neck metastases.[6] Comparing our results with those recently analyzed by Wang et al,[43] we can confirm the impact of lymph nodal burden >17% even on DSS, with no significant influence of the number of positive lymph nodes (>10) and lymph node maximum diameter (>3 cm). Furthermore, none of these variables reached statistical significance when assessing the risk of recurrence. Interestingly, our report also validates previous data showing a higher rate of distant metastases in patients with tumoral endovascular invasion.[44-46]

Lateral neck dissection for N1b well-differentiated thyroid carcinoma can be considered an effective treatment, with low rates of regional recurrence (9%), optimal long-term survival outcomes, and an acceptable incidence of complications. The prevalence of sublevel Vb involvement should dictate its removal in all cases, especially in patients with a high T classification and primary lesions >4 cm, whereas a more conservative approach may be adopted in the management of sublevel IIb, and especially Va. Survival rates of patients treated by neck dissection are excellent and the detrimental prognostic role played by age >55 years, tumor diameter >4 cm, advanced T classification, and aggressive histologic variants was confirmed.

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DISCLOSURE STATEMENT

The authors declare that there is no actual or potential conflict of interest regarding the publication of this article.

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REFERENCES

[1] Dralle H, Machens A. Surgical management of the lateral neck compartment for metastatic thyroid cancer. *Curr Opin Oncol.* 2013;25(1):20–26.

[2] Machens A, Hauptmann S, Dralle H. Lymph node dissection in the lateral neck for completion in central node-positive papillary thyroid cancer. *Surgery.* 2009;145(2):176–181.

[3] Stack BC Jr, Ferris RL, Goldenberg D, et al. American Thyroid Association consensus review and statement regarding the anatomy, terminology, and rationale for lateral neck dissection in differentiated thyroid cancer. *Thyroid.* 2012;22(5):501–508.

[4] Podnos YD, Smith D, Wagman LD, Ellenhorn JD. The implication of lymph node metastasis on survival in patients with well-differentiated thyroid cancer. *Am Surg.* 2005;71(9):731–734.

[5] Zaydfudim V, Feurer ID, Griffin MR, Phay JE. The impact of lymph node involvement on survival in patients with papillary and follicular thyroid carcinoma. *Surgery.* 2008;144(6):1070–1077; discussion 1077-1078.

[6] Adam MA, Pura J, Goffredo P, et al. Presence and number of lymph node metastases are associated with compromised survival for patients younger than age 45 years with papillary thyroid cancer. *J Clin Oncol.* 2015;33(21):2370–2375.

[7] Hay ID. Papillary thyroid carcinoma. *Endocrinol Metab Clin North Am.* 1990;19(3):545–576.

[8] Madenci AL, Caragacianu D, Boeckmann JO, Stack BC Jr, Shin JJ. Lateral neck dissection for well-differentiated thyroid carcinoma: a systematic review. *Laryngoscope.* 2014;124(7):1724–1734.

[9] Farrag T, Lin F, Brownlee N, Kim M, Sheth S, Tufano RP. Is routine dissection of level II-B and V-A necessary in patients with papillary thyroid cancer undergoing lateral neck dissection for FNA-confirmed metastases in other levels. *World J Surg.* 2009;33(8):1680–1683.

[10] Merdad M, Eskander A, Kroeker T, Freeman JL. Predictors of level II and Vb neck disease in metastatic papillary thyroid cancer. *Arch Otolaryngol Head Neck Surg.* 2012;138(11):1030–1033.

[11] Giordano L, Sarandria D, Fabiano B, Del Carro U, Bussi M. Shoulder function after selective and superselective neck dissections: clinical and functional outcomes. *Acta Otorhinolaryngol Ital.* 2012;32(6):376–379.

[12] Brierley JD, Gospodarowicz MK, Wittekind C, eds. *TNM Classification of Malignant Tumours*, *Eighth Edition*. Hoboken, NJ: John Wiley & Sons, Inc.; 2017.

[13] Wang LY, Palmer FL, Nixon IJ, et al. Lateral neck lymph node characteristics prognostic of outcome in patients with clinically evident N1b papillary thyroid cancer. *Ann Surg Oncol.* 2015;22(11):3530–3536.

[14] Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid.* 2016;26(1):1–133.

[15] Pacini F, Schlumberger M, Dralle H, et al. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. *Eur J Endocrinol.* 2006;154(6):787–803.

[16] Wang TS, Dubner S, Sznyter LA, Heller KS. Incidence of metastatic well-differentiated thyroid cancer in cervical lymph nodes. *Arch Otolaryngol Head Neck Surg.* 2004;130(1):110–113.

[17] Kupferman ME, Patterson M, Mandel SJ, LiVolsi V, Weber RS. Patterns of lateral neck metastasis in papillary thyroid carcinoma. *Arch Otolaryngol Head Neck Surg.* 2004;130(7):857–860.

[18] Kupferman ME, Patterson DM, Mandel SJ, LiVolsi V, Weber RS. Safety of modified radical neck dissection for differentiated thyroid carcinoma. *Laryngoscope.* 2004;114(3):403–406.

[19] Goropoulos A, Karamoshos K, Christodoulou A, et al. Value of the cervical compartments in the surgical treatment of papillary thyroid carcinoma. *World J Surg.* 2004;28(12):1275–1281.

[20] Hasney CP, Amedee RG. What is the appropriate extent of lateral neck dissection in the treatment of metastatic well-differentiated thyroid carcinoma? *Laryngoscope.* 2010;120(9):1716–1717.

[21] Khafif A, Ben-Yosef R, Kesler A, et al. The sensitivity of preoperative scanning in regional recurrence of papillary thyroid cancer. *Otolaryngol Head Neck Surg.* 2007;137(3):412–415.

[22] Kupferman ME, Weinstock YE, Santillan AA, et al. Predictors of level V metastasis in well-differentiated thyroid cancer. *Head Neck.* 2008;30(11):1469–1474.

[23] Shim MJ, Roh JL, Gong G, et al. Preoperative detection and predictors of level V lymph node metastasis in patients with papillary thyroid carcinoma. *Br J Surg.* 2013;100(4):497–503.

[24] Dijkstra PU, van Wilgen PC, Buijs RP, et al. Incidence of shoulder pain after neck dissection: a clinical explorative study for risk factors. *Head Neck.* 2001;23(11):947–953.

[25] Cappiello J, Piazza C, Giudice M, De Maria G, Nicolai P. Shoulder disability after different selective neck dissections (levels II-IV versus levels II-V): a comparative study. *Laryngoscope.* 2005;115(2):259–263.

[26] Celik B, Coskun H, Kumas FF, et al. Accessory nerve function after level 2b-preserving selective neck dissection. *Head Neck.* 2009;31(11):1496–1501.

[27] Eskander A, Merdad M, Freeman JL, Witterick IJ. Pattern of spread to the lateral neck in metastatic well-differentiated thyroid cancer: a systematic review and meta-analysis. *Thyroid.* 2013;23(5):583–592.

[28] Ahn JE, Lee JH, Yi JS, et al. Diagnostic accuracy of CT and ultrasonography for evaluating metastatic cervical lymph nodes in patients with thyroid cancer. *World J Surg.* 2008;32(7):1552–1558.

[29] King JM, Corbitt C, Miller FR. Management of lateral cervical metastases in papillary thyroid cancer: patterns of lymph node distribution. *Ear Nose Throat J.* 2011;90(8):386–389.

[30] Koo BS, Yoon YH, Kim JM, Choi EC, Lim YC. Predictive factors of level IIb lymph node metastasis in patients with papillary thyroid carcinoma. *Ann Surg Oncol.* 2009;16(5):1344–1347.

[31] Pingpank JF Jr, Sasson AR, Hanlon AL, Friedman CD, Ridge JA. Tumor above the spinal accessory nerve in papillary thyroid cancer that involves lateral neck nodes: a common occurrence. *Arch Otolaryngol Head Neck Surg.* 2002;128(11):1275–1278.

[32] Lee J, Sung TY, Nam KH, Chung WY, Soh EY, Park CS. Is level IIb lymph node dissection always necessary in N1b papillary thyroid carcinoma patients? *World J Surg.* 2008;32(5):716–721.

[33] Sivanandan R, Soo KC. Pattern of cervical lymph node metastases from papillary carcinoma of the thyroid. *Br J Surg.* 2001;88(9):1241–1244.

[34] Yanir Y, Doweck I. Regional metastases in well-differentiated thyroid carcinoma: pattern of spread. *Laryngoscope.* 2008;118(3):433–436.

[35] Yuce I, Cagli S, Bayram A, Karasu F, Guney E. Regional metastatic pattern of papillary thyroid carcinoma. *Eur Arch Otorhinolaryngol.* 2010;267(3):437–441.

[36] Roh JL, Kim JM, Park CI. Lateral cervical lymph node metastases from papillary thyroid carcinoma: pattern of nodal metastases and optimal strategy for neck dissection. *Ann Surg Oncol.* 2008;15(4):1177–1182.

[37] Caron NR, Tan YY, Ogilvie JB, et al. Selective modified radical neck dissection for papillary thyroid cancer-is level I, II and V dissection always necessary? *World J Surg.* 2006;30(5):833–840.

[38] Vayisoglu Y, Ozcan C. Involvement of level IIb lymph node metastasis and dissection in thyroid cancer. *Gland Surg.* 2013;2(4):180–185.

[39] Lee BJ, Wang SG, Lee JC, Son SM, Kim IJ, Kim YK. Level IIb lymph node metastasis in neck dissection for papillary thyroid carcinoma. *Arch Otolaryngol Head Neck Surg.* 2007;133(10):1028–1030.

[40] Vayisoglu Y, Ozcan C, Turkmenoglu O, et al. Level IIb lymph node metastasis in thyroid papillary carcinoma. *Eur Arch Otorhinolaryngol.* 2010;267(7):1117–1121.

[41] Kim YS. Patterns and predictive factors of lateral lymph node metastasis in papillary thyroid microcarcinoma. *Otolaryngol Head Neck Surg.* 2012;147(1):15–19.

[42] Zhang XJ, Liu D, Xu DB, Mu YQ, Chen WK. Should level V be included in lateral neck dissection in treating papillary thyroid carcinoma? *World J Surg Oncol.* 2013;11:304.

[43] Wang TS, Cheung K, Farrokhyar F, Roman SA, Sosa JA. A meta-analysis of the effect of prophylactic central compartment neck dissection on locoregional recurrence rates in patients with papillary thyroid cancer. *Ann Surg Oncol.* 2013;20(11):3477–3483.

[44] Gardner RE, Tuttle RM, Burman KD, et al. Prognostic importance of vascular invasion in papillary thyroid carcinoma. *Arch Otolaryngol Head Neck Surg.* 2000;126(3):309–312.

[45] Falvo L, Catania A, D'Andrea V, Marzullo A, Giustiniani MC, De Antoni E. Prognostic importance of histologic vascular invasion in papillary thyroid carcinoma. *Ann Surg.* 2005;241(4):640–646.

[46] Wreesmann VB, Nixon IJ, Rivera M, et al. Prognostic value of vascular invasion in well-differentiated papillary thyroid carcinoma. *Thyroid.* 2015;25(5):503–508.

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