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ORIGINAL ARTICLE

Effect of skip metastasis to lateral neck lymph nodes on outcome of patients with papillary thyroid carcinoma

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Abstract

Context Lymph node metastasis (N1) is a prognostic factor for disease recurrence in papillary thyroid carcinoma (PTC) patients. Skip metastasis is defined as only lateral N1 with negative central lymph nodes (LNs).

Objective The aim of this study was to explore the outcome of PTC patients with skip N1.

Patients and design All patients who underwent a total thyroidectomy with ipsilateral central and lateral LN dissection for PTC from 1999 to 2019 in a high-volume endocrine surgery centre were included in this study.

Main outcome measure Demographic and outcomes—recurrence and disease-specific survival (DSS)—were compared between three groups: N1a (central N1 only), N1b-CL (central and lateral N1), and N1b-Skip (lateral N1 without central LN involvement).

Results During the study period, 3046 patients had surgery for PTC, including 1138 with N1 (37%, 860 women, mean age: 44.8 years) comprising 474 N1a (42%), 513 N1b-CL (45%), and 151 N1b-Skip (13%). The median follow-up was 74 months (range 12–216 months). The recurrence rate in the N1b-Skip group was 13% (20/151) and 10% (47/474) in the N1a group. This was significantly lower than that in the N1b-CL group (27%, 140/513) ($p < 0.0001$). DSS at 10 years was 99% for group N1a, 98% for the N1b-CL, and 99% in the N1b-Skip group.

Conclusion The recurrence rate of N1b-Skip patients was lower than that of N1b-CL patients and similar to that of N1a patients. This result could be used as an indication for the modality of radioiodine therapy, and for the pattern of follow-up procedures.

Keywords Lymph node dissection · Papillary thyroid carcinoma · Skip metastasis

Introduction

Lymph node (LN) involvement (central and lateral) is common in patients with papillary thyroid carcinoma (PTC) at the initial diagnosis or during follow-up [1].

Lateral neck node metastases (N1b) occur in 30–50% of cases [2] and have been related to a higher rate of local recurrence and distant metastases compared to those with central lymph nodes metastases [3–5]. LN involvement usually follows a stepwise dissemination, from thyroid tumour to central then lateral ipsilateral LN compartments, and later in the contralateral neck compartments and mediastinum. However, discontinuous lymphatic spread is quite common, and the lateral LN can be involved without central LN metastasis. These skip metastases could be explained by a complex lymphatic anatomy [3]. The frequency of skip metastasis in PTC is difficult to estimate, ranging from 0.6 to 37.5% [6–8] because of the various operative managements of PTC in reported case series. Many studies focused on the clinicopathological characteristics associated with skip metastasis, their patterns, and risk factors [9–13]. However, studies investigating the effect of skip metastases on prognosis are limited [14]. The purpose of the present study was to clarify the significance of skip metastasis on prognosis in N1 PTC patients when compared to PTC patients with LN

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involvement in the central compartment alone, or in both central and lateral compartments.

Patients and methods

All consecutive patients who underwent thyroidectomy with lymph node dissection (LND) for PTC in our department from 1999 to 2019 were included in this retrospective cohort study. Patients with incidental PTC that was discovered after thyroidectomy and patients with central compartment LND alone were excluded. A total of 3038 patients were identified, including 1180 N1 PTC patients. We excluded 42 patients who had no LN retrieved in the central compartment, leaving 1138 patients in the study (Fig. 1). Therapeutic LND was performed in patients with LN metastases that were confirmed cytologically before or during surgery using frozen-section analysis. For patients whose disease was classified as clinically node-negative (N0) before and/or during operation, a standardized prophylactic LND was done involving total thyroidectomy with central compartment (level VI) and ipsilateral lateral compartment (levels III and IV +—level II in case a carcinoma located in the upper third of the thyroid gland) LND. This is based on studies demonstrating that systematic LND reduces the risk of developing persistent or recurrent disease and facilitates the accurate staging of disease, which subsequently informs treatment and follow-up [15–17]. Laryngeal nerves were identified and parathyroid glands were preserved, except if they were macroscopically invaded.

Informed signed consent was obtained from each patient or subject after a full explanation of the purpose and nature of all procedures. As this is a retrospective study with no new data collection, in accordance with French recommendations, this study did not require ethical committee approval.

We compared three groups of patients: N1a (patients with the presence of metastasis in the central compartment, with no lateral compartment invasion), N1b-CL (patients with the presence of metastasis in the central and lateral compartment), and N1b-Skip (patients with metastasis only present in the lateral compartment).

We collected patient demographic data (age, sex, body mass index) and pathologic details including tumour size, multifocality and bilaterality, vascular invasion, tumour extracapsular extension, number of resected LNs, number of LN metastases (total, central, and lateral), size, and extranodal extension of positive LNs. We also calculated the LN ratio (LNR) by dividing the number of positive LNs by the total number of LNs removed.

Radioiodine ablation (RAI) was performed in all N1 patients. This treatment was administered for 1 month following the withdrawal of thyroid hormones or with the use of recombinant human thyrotropin (rh-TSH) in the low- or intermediate-risk patient groups. The radioactive iodine-131 (^{131}I) dose was either 1.1 or 3.7 GBq, depending on the aggressiveness of the PTC in the final pathology report.

All patients followed a standard follow-up schedule, which included physical examination, neck ultrasound imaging, and measurement of serum thyroglobulin (Tg) and Tg autoantibodies after stimulation by rh-TSH or under suppressive treatment, 6 months, 12 months, and every 3 years after the RAI procedure. After the 7-year follow-up, a periodic correspondence with patients or their referring physicians

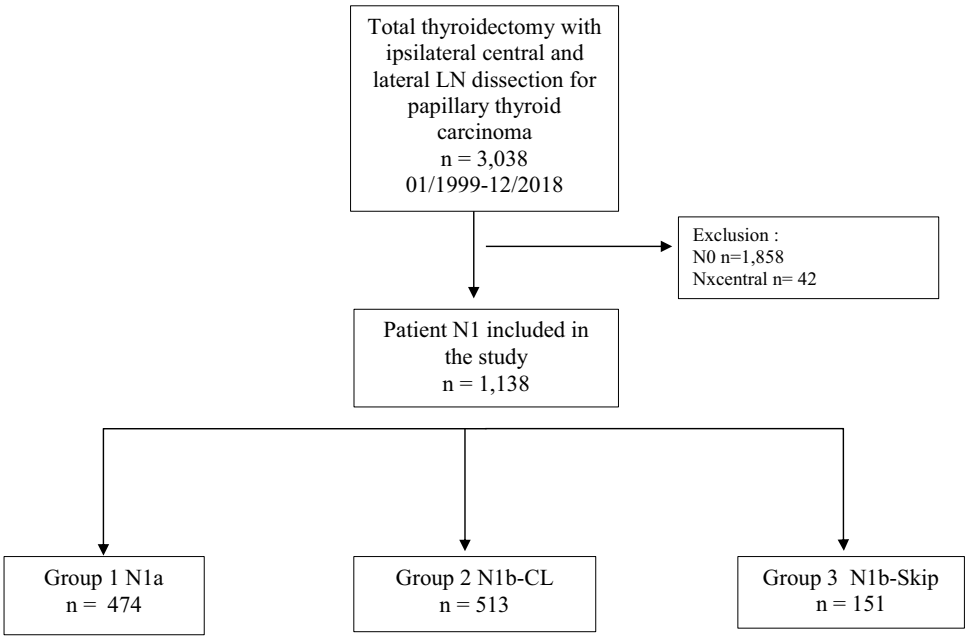

Fig. 1 Flow chart of patients included

was set up every 3 years. The locoregional recurrence was assessed using fine-needle aspiration biopsy of the LN or abnormal tissue in the thyroid bed. Recurrence was also indicated by the following biochemical evidence of disease: isolated and repeatedly elevated serum thyroglobulin levels (> 10 ng/mL after L-thyroxin withdrawal in the absence of interfering antibodies) [18].

Statistical analysis

Results are reported as the median (range) or mean ± standard deviation (SD). The primary outcome measure was the occurrence of a postoperative event (i.e., recurrence or persistence of disease). Clinicopathologic differences between the three groups were compared.

We used the *t*-test or Fisher exact test to compare the categorical variables of the clinicopathologic characteristics. The recurrence-free survival (RFS) and disease-specific survival (DSS) were estimated using the Kaplan–Meier method and the log rank test. A two-sided significance level of 0.05 was used for all statistical tests. Analyses were performed using SAS computer software (SAS Institute Inc, Cary, NC).

Results

Among the 1138 patients who met the inclusion criteria for the study (860 (76%) women, mean age: 44.8 years), there were 474 patients in the N1a group, 513 patients in the N1b-CL group, and 151 patients in the N1b-Skip group.

Table 1 summarizes the clinicopathological findings. Multifocality, bilaterality, and vascular invasion occurred more frequently in N1b-CL patients than in the other patient groups ($p < 0.001$). The number of tumour foci was

Table 1 Demographic, clinical, and pathological characteristics

	Group 1 N1a ***n*** **= 474**	**Group 2 N1b-CL** ***n*** **= 513**	**Group 3 N1b-Skip** ***n*** **= 151**	***p*** **value**
Sex Female	365 (77)	371 (72)	124 (82)	0.03
Age at diagnosis, years	44.8 (12.8–86.4)	42.5 (14.2–85.8)	45.6 (18.6–82.7)	0.1
BMI, kg/m^2	24.2 (16.4–48.8)	24.2 (17.6–45)	24.6 (15.9–47)	0.8
Prophylactic LND	401 (85)	189 (37)	98 (65)	< 0.001
Therapeutic LND	73 (15)	324 (63)	53 (35)	
T-TNM classification (8th edition) T1a	176 (37)	124 (24)	60 (40)	< 0.001
T1b	206 (43)	204 (40)	61 (40)	
T2	76 (16)	137 (27)	24 (16)	
T3/T4	16 (3)	48 (9)	6 (4)	
Tumour				
Multifocal	253 (53)	337 (66)	72 (48)	< 0.001
Bilateral	151 (32)	221 (43)	44 (29)	< 0.001
Number	2 (1–34)	2 (2–150)	1 (1–15)	< 0.001
Sum of the largest size of all foci, mm	16 (1–89)	25 (2–250)	16 (1–89)	< 0.001
Invasion				
Vascular	66 (14)	126 (25)	23 (15)	< 0.001
Capsular	74 (16)	57 (11)	17 (11)	0.09
Total LN removed	15 (3–77)	19 (4–94)	17 (4–60)	0.06
Central LN	6 (1–30)	6 (1–29)	5 (1–33)	0.14
Lateral LN	9 (1–63)	13 (1–54)	12 (1–36)	0.09
Total LN positive	2 (1–18)	7 (1–58)	1 (1–9)	< 0.001
Central LN +	2 (1–18)	3 (1–22)	0	
Lateral LN +	0	3 (1–23)	1 (1–9)	
Lateral LN ratio	0	0.22 (0.02–1)	0.16 (0.03–1)	< 0.001
Size of the largest positive LN, mm	3 (1–27)	11 (1–80)	4 (1–32)	< 0.001
Extranodal extension	100 (21)	260 (51)	24 (16)	< 0.001

Values are *n* (percentages) unless or median (i.q.r.)

BMI, body mass index; *LND*, lymph node dissection; *T-TNM*, tumour-tumour node metastases (8th staging system); *LN*, lymph node; *ratio*, number of metastatic LNs divided by the number of removed LNs

significantly higher in the N1b-CL group than in the other groups ($p < 0.001$).

The median number of resected LNs was similar between the three groups in the central and lateral compartments ($p = 0.06$). LN involvement was significantly more frequent in N1b-CL patients than in the other two groups ($p < 0.001$). The LNR of the lateral compartment, median size of the largest positive LN, and extranodal extension were significantly greater in N1b-CL patients than in the N1b-Skip and N1a groups ($p < 0.01$).

The median follow-up was 74 months (range 12–216 months) and 207/1138 (18%) patients experienced recurrence after the initial treatment (median time to recurrence: 19 months [range 3–324 months]). According to the three groups, 13.2% (20/151) of the N1b-Skip patients experienced recurrence; this was similar than the proportion of the N1a group that experienced recurrence (9.9%, 47/474; $p = 0.3$), but less than that of the N1b-CL group (27.3%, 140/513) ($p < 0.001$). The recurrence-free survival at 5 years was 95% for the N1a group, 91% in the N1b-Skip group, and 83% for the N1b-CL group ($p < 0.001$) (Fig. 2).

Local recurrence occurred in 176 patients (15%) of the cohort: 10% (15/151) N1b-Skip patients, compared to 23% (117/513) of N1b-CL and 9% (44/474) of N1a groups ($p < 0.001$). The same results were found for either prophylactic or therapeutic LND (Table 2).

Fifteen patients in the N1b-Skip group had local recurrence, exclusively in the lateral compartment. In the other patients, the lateral compartment was the most frequent site of recurrence, 30/44 (68%) of N1a patients and 84/117 (73%) of N1b-CL patients. Figure 3 shows the LN distribution of locoregional recurrence. One hundred and ten patients had a second surgery to remove local recurrence with a median time to reoperation of 17 months (range 3–60 months) for N1b-Skip, 11 months (3–180 months) for N1b-CL, and 13 months (3–124 months) for N1a patients ($p < 0.001$). The DSS rate at 10 years was 99% for the N1a group, 98% for the N1b-CL group, and 99% in the N1b-Skip group ($p = 0.7$).

Discussion

The incidence of skip metastasis in PTC patients varied, ranging from 0.6 to 37.5% [7, 8, 19]. However, the prognosis of skip metastasis is widely unknown since most studies had a limited number of patients and usually focused

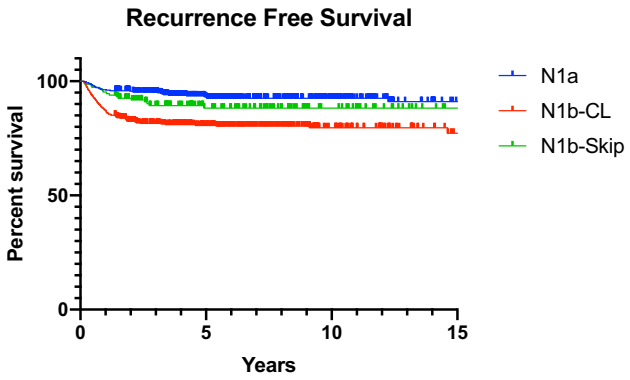

Fig. 2 Recurrence-free survival for patients with N1 PTC

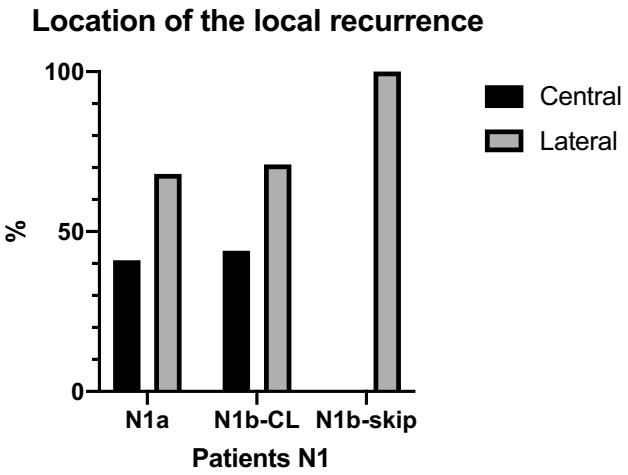

Fig. 3 Location of LN recurrence of the 3 groups

Table 2 Recurrence and death

	Group 1 N1a $n = 474$	Group 2 N1b-CL $n = 513$	Group 3 N1b-Skip $n = 151$	*p* value
Recurrence				
Local, *n* (%)	44 (9.3)	117 (22.8)	15 (9.9)	< 0.0001
Prophylactic LND	31/401 (7.7)	26/189 (13.8)	5/98 (5.1)	
Therapeutic LND	13/73 (17.8)	91/324 (28.1)	10/53 (18.9)	
Total, *n* (%)	47 (9.9)	140 (27.3)	20 (13.2)	< 0.0001
Prophylactic LND	34/401 (8.5)	34/189 (18)	7/98 (7.1)	
Therapeutic LND	13/73 (17.8)	106/324 (32.7)	13/53 (24.5)	
Death, *n* (%)	1 (0.2%)	5 (0.9%)	3 (1.9%)	

LND, lymph node dissection

on risk factors and not outcomes [10–12]. From our study, with a large number of patients and a standardized surgical procedure and follow-up, we found that patients with skip metastases demonstrate outcomes similar to patients with only central LN metastases, especially regarding local recurrences, and have a better prognosis than patients with central and lateral N1.

The definition of skip metastasis is important since an incomplete central LND could lead to a falsely high rate of skip N1. Zhao et al. [13] suggested that the status of central LN N1 is poorly described in most studies and might also contribute to the heterogeneity of incidence between studies. An increased number of false positive detections of skip metastases in PTC is associated with a decreased number of central LNs dissected [13]. In the present study, central lymph node dissection was adequate as the number of LNs removed from the central compartment was similar between the three groups of N1patients, with a rate of skip metastasis of 13% (151/1138).

It is now widely accepted that skip metastases are more frequent in PTC patients with a primary tumour in the upper portion of the lobe, if the tumour is 10 mm or less in maximum diameter, and if there is an invasion of the thyroid capsule [6–13, 20, 21]. Skip metastasis is more frequent in less aggressive PTCs such as microcarcinomas, which is consistent with our findings. This suggested that skip metastasis may be in the early stages of cancer. In our cohort, skip metastasis was not associated with the presence of lymphovascular invasion and extracapsular extension. The LNR of the lateral compartment, median size of the largest positive LN, and extranodal extension were significantly lower in the skip metastasis group than those in the N1b-CL group. To our knowledge, this is the first study to report that patients with skip metastasis had less aggressive LN ratio than other N1b patients.

The outcome of PTC patients according to their lymph node status is largely unknown.

In 2017, Lei et al. compared the survival rate of 39 patients with PTC with skip metastasis PTC patients and 411 other N1 PTC patients without skip metastasis. Their results showed no significant difference between the two groups for tumour-free survival [14]. However, these results were limited by the small sample size of the study and they enrolled all other N1 PTC patients without any distinction between central N1 alone or central and lateral N1 (N1a and N1b-CL, respectively in our study). In this study, it was difficult to compare prognosis between skip patients and non-skip patients since N1a and N1b-CL have different recurrence rates [5–14]. Another study with the same limitations (i.e., small sample size and no distinction between non-skip N1 patients) reported similar results [21] after comparing 72 skip metastasis patients with 675 N1b-CL patients. Only one recurrence in the skip metastasis group was reported (vs. 4% of the N1b-CL group). Tumour-free survival in the two groups was also compared, which showed no difference. Another concern is that, in this study, recurrence was defined as "local or regional disease requiring treatment 6 months after the initial standard operation," which is a limited definition of recurrence since it represents only persistent disease.

In our study, the median follow-up was over 6 years, with a recurrence rate in the N1b-Skip group of 13% (20/151), including 15 local recurrences with a median time to reoperation of 1 year. The skip metastasis group had a significantly better prognosis than patients with central and lateral LN invasion (N1b-CL) and a similar prognosis to patients with only central involvement (N1a). These results are consistent with the results of previous studies on lung cancer and colorectal cancer, which indicated that skip metastasis may have a positive impact on prognosis [22–24]. Further study of skip metastases in PTC is needed, but regarding our data, new classification of N1 diseases according to the involved LN stations could be proposed to better determine the prognosis of these patients.

Local recurrence occurred in 10% of N1b-Skip patients, exclusively in the lateral compartment. Management of these lateral recurrences is usually not challenging with a low complication rate. Treatment can be provided using a focused minimal access approach under local or general anaesthesia during an outpatient procedure [25–28].

This study has some limitations. It was a retrospective design and some data were lacking in the pathologic reports (e.g., location of the primary tumour, molecular markers). However, the aim of the present study was to investigate the outcome of patients with skip metastasis and not the risk factors of N1b-Skip. We believe that the large size of the cohort, standardized treatment, and unchanged follow-up over time overcome the retrospective nature of the study and the study provides useful information for the management of N1 PTC patients.

In addition, prophylactic lateral neck lymph node dissection is not done in most parts of the world because the benefit of prophylactic node dissection in the absence of evidence of nodal disease is controversial in patients with PTC. Since all of our patients had both a central and lateral neck dissection regardless of preoperative staging, this dataset is unique and can answer questions for the vast majority of surgeons who do not perform a prophylactic lateral neck dissection. This data could clarify the true frequency of skip metastasis to the lateral neck in patients without evidence of lateral neck disease on US.

Conclusion

We found that skip metastasis (N1b-Skip) is associated with a better recurrence rate than patients with central and lateral LN metastasis (N1b-CL) and a similar recurrence rate to

patients with only central metastasis (N1a). Local recurrence occurred in only 10% of N1b-Skip patients and exclusively in the lateral compartment, compared to 23% of the N1b-CL and 9% of the N1a groups. This result could be used as an indication for the modality of radioiodine therapy, and for the pattern of follow-up procedures.

Authors' contributions Jean Baptiste Bertin: study design—acquisition of data—analysis and interpretation of data—drafting of the manuscript. Camille Buffet: study design—critical revision of the manuscript. Laurence Leenhardt: study design—critical revision of the manuscript. Fabrice Menegaux: study design—analysis and interpretation of data—critical revision of the manuscript. Nathalie Chereau: study design—analysis and interpretation of data—critical revision of the manuscript.

Declarations

Conflict of interest The authors declare no competing interests.

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