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ORIGINAL SCIENTIFIC REPORT

Occult Contralateral Lateral Lymph Node Metastases in Unilateral N1b Papillary Thyroid Carcinoma

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Abstract

Objective Therapeutic lateral neck dissection (ND) is recommended for N1b papillary thyroid carcinoma (PTC), while prophylactic contralateral lateral ND is not. Given the paucity of data, we investigated the frequency of and risk factors for occult lymph node metastases (LNM) in the contralateral lateral neck for N1b patients.

Patients and methods This is a retrospective study conducted at a cancer center. Inclusion criteria were: unilateral PTC and ipsilateral lateral LNM confirmed by fine-needle aspiration biopsy. Patients with contralateral lateral LNM or bilateral tumor on ultrasound were excluded. All patients were treated with total thyroidectomy, bilateral central ND, ipsilateral therapeutic lateral ND and prophylactic contralateral ND of levels III–IV, followed by radioactive iodine.

Results Sixty-three patients met the inclusion criteria. Occult contralateral lateral LNM were found in 23/63 patients (36.5%) who had more LNM in ispilateral ($p = .01$) and contralateral level VI ($p < .0001$), more frequent microscopic tumor in the contralateral lobe ($p = .017$) and a trend toward being at high risk ($p = .06$). Using receiver operating characteristic analysis, a cutoff of >4 LNM in ipsilateral level VI optimized sensitivity and specificity for predicting contralateral lateral LNM, with a sensitivity of 74%, specificity of 65%, positive predictive value of 55% and negative predictive value of 81%. Neck recurrence occurred in 14%, with only 1 patient recurring only in the contralateral lateral neck (1.5%).

Conclusion Occult LNM in the contralateral lateral neck was found in 36.5% of patients. Five or more ipsilateral central LNM may aid in predicting contralateral lateral LNM, and high-risk patients may be more at risk. The clinical benefit of prophylactic contralateral lateral ND remains doubtful, however.

Introduction

Therapeutic lateral neck dissection (ND) is currently recommended for N1b papillary thyroid carcinoma (PTC), while prophylactic lateral ND is not currently advocated due to the lack of evidence of its clinical utility [1].

Patients with extensive nodal disease often present with clinically evident bilateral lateral neck node metastases, even with a unilateral thyroid tumor. In unilateral N1b patients without evidence of contralateral lymph node metastases (LNM) on ultrasound, our practice has been to systematically perform prophylactic contralateral ND of

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levels III and IV, but without data regarding the frequency of or risk factors for occult LNM in the contralateral lateral neck for these patients. The aim of this study was to evaluate our practice, to determine the incidence of occult LNM in the contralateral lateral neck in unilateral N1b patients and to analyze risk factors associated with occult LNM.

Patients and methods

We retrospectively reviewed files of patients treated in a comprehensive cancer center from 1997 to 2016 for N1b PTC with no previous surgery. Inclusion criteria were patients with only unilateral PTC confirmed by ultrasound and fine-needle aspiration biopsy and ipsilateral lateral LNM with or without uni- or bilateral central LNM. All patients underwent preoperative ultrasound, and patients with contralateral lateral LNM or obvious locally invasive cancer, bilateral, isthmus or pyramidal lobe PTC at diagnosis were excluded. Multifocal unilateral PTC were allowed.

All patients were treated with total thyroidectomy, bilateral central neck dissection, ipsilateral lateral neck dissection of levels II, III and IV and prophylactic contralateral neck dissection of levels III–IV [2, 3], followed by radioactive iodine (Fig. 1).

We recorded the following data: tumor size, multifocality, bilaterality, microscopic extrathyroidal extension, vascular invasion, location in the superior pole, number of central LNM ipsilaterally and contralaterally, number, size and presence of extranodal spread of ipsilateral LNM in each compartment and of contralateral lateral LNM in levels III–IV (taken together), American Thyroid Association risk group and response to therapy (Table 1) [1, 4]. These characteristics were analyzed in patients with and without occult contralateral lateral LNM, using the SPSS software (version 5.0) and nonparametric statistical tests (Mann–Whitney and Fisher's exact test) with a significance level of .05.

Risk factors that may be ascertained preoperatively or intraoperatively with frozen section analysis (gender, age, tumor size, superior pole, number of central LNM, size and extranodal extension of lateral LNM) were particularly analyzed in order to find factors enabling surgeons to preoperatively predict the presence of occult contralateral lateral LNM.

Results

Sixty-three patients (34 females and 29 males, average age 37 years, range 11–84, median 32 years) met the inclusion criteria. Patient, tumor and lymph node characteristics are shown in Table 1. In the ipsilateral lateral neck, patients had an average of 4 ± 3 LNM (range 1–18). LNM size ranged from 9 to 90 mm (average 30 mm), and 34% of patients had LNM measuring 3 cm or more.

Occult contralateral lateral LNM were found in 23/63 patients (36.5%), with an average of 3 ± 3 LNM (range 1–17). All were <10 mm in the largest dimension. Extranodal spread was found in at least one LNM in the prophylactic contralateral lateral neck dissection specimen in 11/23 cases (48%).

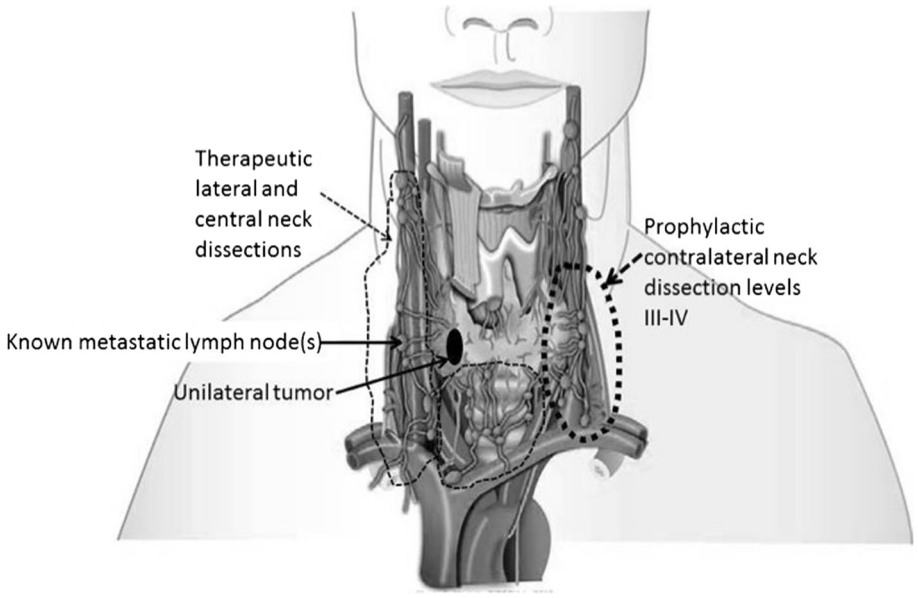

Fig. 1 Schematic representation of the unilateral tumor, unilateral lateral metastatic lymph nodes and the therapeutic and prophylactic neck dissections performed

Table 1 Characteristics of the study group and comparison (nonparametric statistical tests) between patients with occult contralateral lymph node metastases and those without

Characteristic	Entire cohort	Occult contralateral LNM+	Occult contralateral LNM-	*p* value
Number of patients	63	23 (37%)	40 (63%)	
Age (min–max)	37 (11–84)	33 (11–82)	39 (12–84)	.17
Male sex	29/63 (46%)	11/23 (49%)	18/40 (45%)	>.99
Primary tumor size, mean ± std dev (median)	22 ± 15 (20)	22 ± 18 (18)	22 ± 13 (20)	.69
T stage (TNM 8th edition)	T1a: 12	T1a: 5	T1a: 7	.94
	T1b: 24	T1b: 9	T1b: 15	
	T2: 17	T2: 6	T2: 11	
	T3a: 5	T3a: 1	T3a: 4	
	T4a: 5	T4a: 2	T4a: 3	
Aggressive pathology *n* (%)	9/63 (14%)	4/23 (17%)	5/40 (13%)	.7
Multifocality	45/63 (71%)	19/23 (83%)	26/40 (65%)	.15
Bilateral tumor	33/63 (52%)	17/23 (74%)	16/40 (40%)	.0175
Extrathyroidal extension (microscopic)	38/63 (60%)	11/23 (49%)	27/40 (68%)	
Vascular invasion	36/61	17/23	19/49	.1
Superior pole tumor	42/63	17/23	25/40	.5
Ipsilateral lateral neck: number of LNM (avg ± std dev)	4.2 ± 3	5.0 ± 3	3.7 ± 3	.15
Ipsilateral lateral neck: size of the largest LNM (mm)	30 ± 17	34 ± 17	27 ± 17	.17
Ipsilateral lateral neck LNM > 30 mm	16/63	9/16	7/16	.07
Ipsilateral lateral neck: extranodal spread present	46/63 (73%)	18/23 (78%)	28/40 (70%)	.56
Ipsilateral level VI: number of LNM	4.9 ± 4	6.7 ± 4.7	3.9 ± 3.7	.011
Level VI: extranodal spread present	34/63 (54%)	16/23 (69%)	18/40 (45%)	.07
Contralateral level VI: number of LNM	2.3 ± 3.3	4.7 ± 4.2	1.1 ± 1.7	<.0001
Total number of LNM (avg ± std dev, min–max)	12.2 ± 9.2 (1–45)	18.8 ± 10.6 (2–45)	8.5 ± 5.5 (1–25)	<.0001
ATA high risk	25/63 (40%)	13/23 (57%)	12/40 (30%)	.06
ATA intermediate risk	38/63 (60%)	10/23 (43%)	28/40 (70%)	.06
Total activity RAI (GBq) (avg ± std dev, min–max)	4.9 ± 2.7 (1.1–18.5)	5.9 ± 3.6 (3.7–18.5)	4.3 ± 1.9 (1.1–11.1)	.022
Excellent response *n* (%)	39/63 (62%)	10/23 (43%)	29/40 (73%)	.08

LNM lymph node metastases, *Avg* ± SD: average ± standard deviation, TNM AJCC 8th edition (REF) *ATA* American Thyroid Association risk levels (REF Haugen), *RAI* radioactive iodine

Patients with occult contralateral lateral LNM had significantly more metastatic nodes in the central compartment ispilateral to the tumor ($p = .011$) and contralateral to the tumor ($p < .001$) and had a higher total number of metastatic nodes ($p < .0001$), as well as microscopic PTC in the contralateral thyroid lobe (only seen on pathology, and not on preoperative ultrasound) more frequently ($p = .017$) (Table 1). There was a trend toward more patients with occult contralateral lateral neck metastases in the high-risk group and more patients without occult metastases in the intermediate-risk group ($p = .06$).

Using receiver operating characteristic analysis, the area under the curve for the association of occult contralateral lateral LNM with the number of ipsilateral central LNM was .6. For all of the other risk factors, the area under the curve was <.5. A cutoff of 5 or more metastatic nodes in ipsilateral level VI optimized sensitivity and specificity for predicting contralateral lateral nodal metastases, with a sensitivity of 74%, specificity of 65%, positive predictive value of 55% and a negative predictive value of 81% for an overall accuracy of 68%. The other factors evaluated in Table 1, with, in addition, the palpable nature of the ipsilateral metastatic nodes, were not significantly different between the two groups.

All patients received radioactive iodine at least once, with a cumulative activity ranging from 1.1 to 18.5 GBq (average 4.9 GBq, median 3.7 GBq), with a higher average total activity delivered to patients with contralateral LNM ($p = .022$, Mann–Whitney test).

Follow-up ranged from 1 month (1 patient lost to follow-up 1 month after radioactive iodine therapy) to 19 years (average follow-up 46 months, median 39 months). The rate of structural recurrent/persistent disease in the neck after the first surgery and administration of radioactive iodine was 14% (9/63 patients, 3 in the high-risk category and 6 in the intermediate-risk category), all addressed with reoperation. Of the 9 patients who had structural recurrent/persistent neck disease after the first treatment, 5 had no contralateral LNM in the prophylactic neck dissection specimen, while 4 had contralateral lateral LNM (1, 2, 4 and 5 positive nodes, respectively). Of the 5 patients with no contralateral LNM in the specimen, one recurred in the bilateral lateral neck, 3 recurred in the ipsilateral lateral neck and one in an ipsilateral retropharyngeal node. Of the 4 patients with contralateral LNM in the prophylactic neck dissection specimen, one patient recurred in the contralateral lateral neck only (1.5%), 2 recurred bilaterally in the lateral neck, and one recurred in an ipsilateral retropharyngeal node. The presence of contralateral LNM was thus not related to persistent/recurrent disease in the neck in these patients. A total of 4/63 patients had recurrence in the contralateral lateral neck (6.3%).

Four further patients had lung metastases with no regional recurrence. One patient had radioiodine refractory lung metastases and was the only one to die from disease over the follow-up period. Of the 4 patients with lung metastases, 3 had harbored contralateral lateral LNM (1, 2 and 5 metastatic nodes, respectively).

At the last follow-up, response to therapy was excellent in 39 cases (62%), biologically incomplete in 6 cases (9.5%), structurally incomplete in 6 cases (9.5%, of which 4 also had lung metastases, with one death) and indeterminate in 12 cases (19%). A trend to more excellent results (73% versus 43%) was found for patients in the group without occult contralateral lateral metastases ($p = .08$).

Discussion

There is actually little data regarding the frequency of occult contralateral node metastases in patients with N1b PTC. In our referral center, few patients actually fit the stringent criteria of no previous surgery, only a unilateral tumor and only unilateral lateral LNM with no contralateral lateral LNM on preoperative ultrasound: the majority of our patients had had previous surgery and were referred to our center for completion surgery or for neck recurrence.

We were surprised to find contralateral lateral LNM in 36.5% of patients, despite negative preoperative ultrasound findings in the contralateral lateral neck. We looked particularly at risk factors that could be identified preoperatively, in order to select patients that may have a higher risk of occult contralateral LNM and may possibly benefit from a prophylactic contralateral neck dissection.

Age, gender, primary tumor size, extrathyroidal extension and the size of the largest lateral LNM did not differ between patients with and without occult contralateral lateral LNM. A higher total number of lymph node metastases, a risk factor for neck recurrence [5, 6, 7], was seen in patients with contralateral LNM. We also found a higher number of central LNM in patients with occult contralateral LNM, particularly in the contralateral central neck. As a means of predicting occult contralateral LNM preoperatively or intraoperatively, we found that the presence of five or more metastatic nodes in the ipsilateral central neck had the best predictive value. Preoperative ultrasound findings or intraoperative frozen section analysis of ipsilateral central ND finding five or more LNM could thus guide surgeons to perform a prophylactic contralateral lateral ND.

The number of patients with an ipsilateral lateral LNM > 30 mm [6, 8, 9] was not significantly different between patients with or without occult contralateral LNM ($p = .07$), nor was the presence of extranodal spread in the contralateral nodes [1, 5] ($p = .07$), but a slight trend was noted. Due to the retrospective nature of our study, however, the total number of LNM with extranodal spread was not available for all of the patients, and we were only able to note when extracapsular spread was present in at least 1 LNM. The total number of retrieved nodes was also not reported for the earlier patients in our study, so the lymph node ratio could not be calculated with precision. All of the patients were surgically treated by the surgeons at our institution using the same technique for comprehensive compartment-oriented neck dissection, however, and no lymph node "picking" or more limited resections were performed at initial surgery, so that the neck dissections could be considered comparable at least in technique and extent.

Patients with contralateral LNM received a higher cumulative dose of radioactive iodine than patients without contralateral LNM, most probably due to the fact that these patients had a tendency to be high-risk patients, with globally more LNM than patients without contralateral LNM.

Our rate of excellent response of 62% is comparable to the study of N1b patients by Hughes et al. [10] who reported a 68% excellent response rate. They also reported an 18% recurrence rate, comparable to the 14% rate in our series. In other studies of N1b patients, reported neck recurrence rates vary from 8% to up to 42% [1, 11, 12, 13], the rate depending on the above-noted primary tumor and lymph node-related risk factors (tumor and lymph node size, tumor extrathyroidal extension, number of LNM and number with extranodal extension).

Our study aimed at investigating the frequency of occult contralateral lateral LNM in this context, but the prognostic impact of a prophylactic lateral ND remains unclear. Unfortunately, we did not have a control group of patients without prophylactic contralateral neck dissection, so we could not compare recurrence rates in the contralateral lateral neck. Few published studies have specifically analyzed the location of neck recurrences in PTC, so it is in fact difficult to evaluate the incidence of contralateral lateral neck recurrence and the potential impact of prophylactic contralateral lateral neck dissection. However, one very large retrospective study by Ito et al. [14] analyzed outcomes for 744 patients initially staged N1b. All of the patients underwent a therapeutic ipsilateral lateral neck dissection and a central compartment neck dissection, with no postoperative radioactive iodine. The authors found a 7% recurrence rate in the contralateral lateral neck. The statistically significant risk factors for contralateral lateral nodal recurrence were primary tumor size >4 cm and extrathyroidal extension (microscopic or macroscopic), with a 13% rate of contralateral lateral neck recurrence for patients with both of these tumor characteristics.

In the study by McNamarra et al. [12] retrospectively reviewing 484 N1b patients, without prophylactic contralateral lateral ND, the rate of contralateral lateral neck recurrence was 4.6%. For Chereau et al. [13] who retrospectively reviewed the outcomes of 320 patients, the rate of recurrence in the contralateral lateral neck was 3.8% (12/320).

Finally, in the study of Keum et al., whose inclusion criteria most closely resembled ours, out of 65 patients with unilateral thyroid tumors and unilateral N1b disease undergoing only therapeutic ipsilateral and central ND, recurrence in the undissected contralateral lateral neck was found only in two patients (3%) [15].

It would thus seem that the low rate of contralateral lateral neck recurrence in these studies, comparable to our rate of 6%, does not justify systematically performing a prophylactic contralateral lateral neck dissection, despite our finding of occult contralateral lateral metastases in 36.5% of patients.

It is well known that occult central compartment lymph node metastases are frequent in N0 papillary thyroid carcinoma, but the clinical benefit of prophylactic neck dissection for low-risk patients has not been proven, and prophylactic neck dissection is not currently recommended in routine [1]. One hypothesis is that these micrometastases are indolent and do not progress to clinically detectable disease, even without radioactive iodine therapy. The low rate of contralateral recurrence in unilateral N1b patients may also be related to this indolent nature, but also to the radioactive iodine typically administered to these intermediate- to high-risk patients. A slightly higher reported rate of contralateral lateral recurrence in the Japanese study as compared to other studies could then be hypothetically related to the lack of adjuvant treatment, but no direct comparisons have been performed. And even without radioactive iodine, the reported contralateral lateral recurrence rate is lower than the rate of occult LNM that we found.

Thus, only a little over one third of these patients will harbor micrometastases in the contralateral lateral neck, and the rate of contralateral lateral neck recurrences seems to be low even in the absence of prophylactic contralateral lateral neck dissection. These results have led us to conclude that a prophylactic contralateral lateral ND is not useful in patients with unilateral tumors and unilateral N1b disease with normal contralateral lateral neck ultrasound, and we have discontinued this practice. The French Society of Otolaryngology Head and Neck Surgery still recommends performing prophylactic contralateral lateral ND in patients with an ipsilateral metastatic node more than 3 cm in diameter [16.] This factor was not significant in the present study ($p = .07$), but this may be due to the small number of patients with a lack of statistical power. There are other limitations to our study as well: its retrospective nature spanning over several years, the lack of a control nondissected group, a short mean follow-up of 4 years, all precluding more detailed statistical analysis such as multivariate analysis or meaningful Kaplan–Meier analysis.

Conclusion

This study suggests that occult LNM in the contralateral lateral neck is not an infrequent occurrence. Occult lateral metastases tended to be more frequent in high-risk patients and in patients with a high number of central LNM. Five or more ipsilateral central LNM best predicted the risk of contralateral lateral LNM. This characteristic may aid in selecting patients with occult lateral LNM for prophylactic lateral ND (compartments IV and III), but this does not imply that a prophylactic contralateral neck dissection improves outcomes in these patients, given the low rate of contralateral lateral neck recurrence without prophylactic ND reported in other retrospective studies.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest.

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