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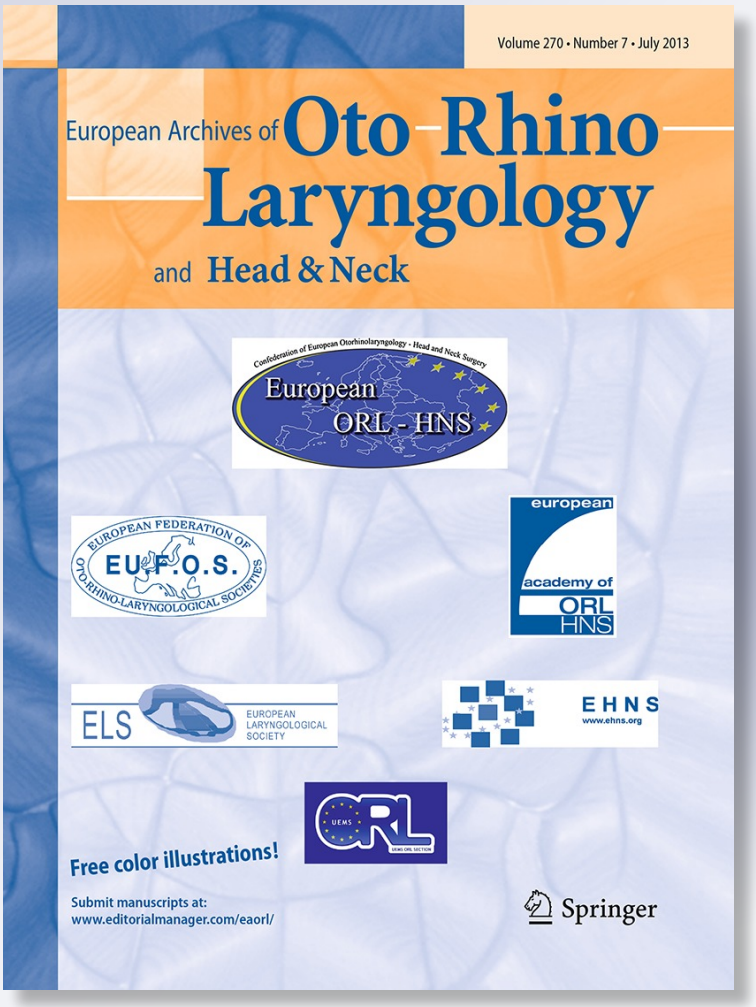

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HEAD AND NECK

Predictive factors for lateral occult lymph node metastasis in papillary thyroid carcinoma

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Abstract Management of lateral no necks in papillary thyroid carcinoma (PTC) is very controversial. The aim of this study was to find predictive factors of lateral neck involvement in N0 PTC to help the clinician in his decision to treat the lateral compartment. We retrospectively analysed 173 patients who underwent thyroidectomy and lateral prophylactic neck dissection for PTC >10 mm. Predictive factors for occult lateral lymph node metastasis including sex, age, tumour size, multifocality and bilaterality, tumour extracapsular spread, vascular invasion and presence of a tumour capsule were examined by multivariate analysis. There were three independent predictive factors for occult lateral lymph node metastases in multivariate analysis: tumour extracapsular spread ($p < 0.0001$), vascular invasion ($p < 0.001$) and age <45 years ($p < 0.027$). When none of these factors was present, the risk of occult metastases was <5 %. The risk increased up to 56 % when at least two of these factors were present. These findings suggest that, in patients older than 45 years with neither tumour extracapsular spread nor vascular invasion on histopathological examination, occult lymph node metastases are very uncommon. In that case further discussion regarding the risks and benefits of lateral nodal dissection may be warranted.

Keywords Thyroid carcinoma · Papillary carcinoma · Lymph node · Predictive factors · Neck dissection

Introduction

The prognosis of papillary thyroid carcinoma (PTC) is excellent, with a 10-year survival rate ranging from 85 to 99 % [1]. Numerous studies report initial lymph node involvement in 30–90 % of patients [2–4]. When lymph node metastases are clinically or echographically evident, most authors recommend therapeutic neck dissection (ND) to improve locoregional control and survival [5–8]. The management of N0 necks is more controversial and raises many questions such as: who may benefit from ND? Which ND should be performed? When should central or lateral ND be performed? At present, the consequences of ND in terms of locoregional control and survival have not yet been clearly established.

Many methods have been proposed to manage N0 lateral necks including: a wait-and-see policy, sentinel node biopsy, selective ND and modified radical neck dissection (MRND) [9, 10]. As several pathological predictive factors for high recurrence risk have been identified, it would be better to delay ND until a complete histopathological analysis of the thyroid gland has been performed.

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Thus, to identify predictive factors for occult lateral lymph node metastasis (OLLNM) in PTC in order to support the decision to carry out ND and improve the selection of patients who may benefit from it is important. The purpose of this study was to examine the incidence of OLLNM in patients with PTC and to determine the predictive factors for metastasis.

Materials and methods

The medical records of 631 patients who underwent surgery for thyroid carcinoma at our institution between January 1974 and December 2006 were reviewed. Inclusion criteria included patients with a histopathological diagnosis of previously untreated PTC >10 mm in size, who underwent a lateral neck dissection, and had no evidence of node involvement on clinical examination and ultrasound imaging (after 1985). Other histological types (follicular, lymphoma, anaplastic, etc.), clinically positive necks (N+), exclusive central ND or incomplete files were systematically excluded ($n = 458$).

A total of 173 patients were enrolled in this study (Table 1): 135 women (75 %) and 38 men (25 %), with a mean age of 39.9 ± 14.3 years. Total thyroidectomy was the standard procedure (Table 1). Ipsilateral MRND including levels II, III, IV and V with or without level I was routinely performed if the lesion was located in one lobe. Bilateral MRND was performed if the lesion was located in the isthmus or in both lobes. ND was called "selective" if less than level II to V ND was performed. The spinal accessory nerve, internal jugular vein and sternocleidomastoid muscle were systematically preserved. All patients underwent level VI (central compartment) per-operative exploration. In the case of suspicious central node involvement, a full dissection of level VI was performed: all fat and fascias between the trachea and common carotid artery were removed after the systematic identification of the inferior laryngeal nerve (paratracheal ND). An additional pretracheal and pericricoid ND were also performed. Due to the large number of surgeons employed during the study period (1974–2006), other surgical treatments were occasionally performed including lobectomy, systematic prophylactic central and lateral ND, selective lateral ND, lateral ND with level Ib dissection, or exclusive central ND. Only patients who underwent a lateral ND were included in the study. All neck levels were marked and sent for pathologic examination. Histopathological examination was based on several sections with conventional haematoxylin–eosin staining.

A review of the clinical records and pathology reports was conducted to determine the prevalence of lateral lymph node metastases, and data regarding age, sex, tumour size, multifocality and bilaterality, vascular invasion, absence of a tumour capsule and tumour extracapsular spread (TECS) were collected. TECS was evaluated by the pathologist as extrathyroid spread of the tumour on microscopic examination. Fine needle aspiration cytology was not systematically

Table 1 Patients characteristics

	Patients $n = 173$ (%)
Sex	
Male	38 (22)
Female	135 (78)
Age	
Mean (years)	39.9 ± 14.3
<45	109 (63)
≥45	64 (37)
Tumour size[a]	
Mean (mm)	20.10 ± 11.88
≤20 mm	106 (66)
>20 mm	54 (34)
Plurifocality	
Present	55 (32)
Absent	118 (68)
Bilaterality	
Present	35 (20)
Absent	138 (80)
TECS	
Present	18 (10)
Absent	155 (90)
Vascular invasion	
Present	36 (21)
Absent	137 (79)
Tumour capsule[b]	
Present	102 (70)
Absent	44 (30)
Surgical procedures	
Total thyroidectomy	167 (97)
Lobectomy	6 (3)
Neck dissections	
Unilateral	155 (97)
Bilateral	18 (3)
Neck dissections[c]	ND $n = 191$ (%)
Central and lateral ND	42 (22)
Central exp. and lateral ND	121 (63)
Selective lateral ND	26 (14)
Unknown lateral	2 (1)

[a] In 160 patients

[b] In 146 patients

[c] According to the number of neck dissections

performed in our institution at the time of the study and was not considered for the analysis. The presence of central lymph nodes was not introduced in statistical analysis as it was considered that our management of central neck compartment without systematic neck dissection induced an intolerable bias. Indeed, a central neck dissection was performed only in case of intraoperative clinically suspicious lymph node, leading to possible underestimation of occult central lymph node metastasis. This is the reason why the data were not introduced in the statistical analysis.

Based on previous studies, age 45 years was used as a cut-off for univariate and multivariate analyses [11, 12]. Tumour size was divided into two groups (≤20, >20 mm).

Statistical analysis

Univariate analysis was carried out using the χ^2 test and Fischer's exact test if needed. The Student's t test and Mann–Whitney test were used for parametric and non-parametric testing of quantitative variables, respectively. Multiple logistic regression analysis was used to identify independent factors correlated with OLLNM for significant or near significant variables in univariate analysis. Statistical significance was defined for $p < 0.05$.

Results

The incidence of OLLNM was 20 % (34/173 patients) (Table 2). Mean tumour size was 20.10 ± 11.88 mm. One-hundred and six patients had lesions <20 mm. Plurifocality and bilaterality of the tumour were observed in 32 and 20 % of patients, respectively ($n = 55$ and $n = 35$). TECS was observed in 10 % ($n = 18$) and vascular invasion in 21 % ($n = 36$). 70 % of the tumours were delimited by a capsule ($n = 102$).

In univariate analysis, five factors were significantly related to node involvement: TECS ($p < 0.0001$), vascular invasion ($p < 0.0001$), absence of a tumour capsule ($p = 0.001$), bilaterality of the tumour ($p = 0.015$) and plurifocality of the tumour ($p = 0.011$). No significant difference in node involvement was found for the following three factors: age <45 years ($p = 0.070$), tumour size ($p = 0.144$) and sex ($p = 0.479$).

The relative risks for OLLNM were calculated independently for each factor and are shown in Table 3. Multivariate analysis revealed three independent factors to be predictive of increased OLLNM: TECS ($p < 0.0001$), presence of vascular invasion ($p = 0.001$) and age <45 years ($p = 0.027$). The probability of OLLNM was then calculated according to the number of risk factors present in each of the 173 patients, using the three independent factors identified by the multivariate analysis (Table 4). When none or one of the three predictive factors was present, the probability of OLLNM was 4.4 %. When two or more factors were present, the probability increased to 56.3 %.

Table 2 Relationship between clinical and histological features of occult lateral lymph node metastasis

	Total $n = 173$	pN+ $n = 34$	Row % 19.7 %	p value
Sex				
Male	38	9	23.7	0.479
Female	135	25	18.5	
Age				
<45	109	26	23.9	0.070
≥45	64	8	12.5	
Tumour size[a]				
≤20 mm	106	25	23.6	0.144
>20 mm	54	7	13.0	
Plurifocality				0.011
Present	55	17	30.9	
Absent	118	17	14.4	
Bilaterality				0.015
Present	35	12	34.3	
Absent	138	22	15.9	
TECS				<0.0001
Present	18	11	61.1	
Absent	155	23	14.8	
Vascular invasion				<0.0001
Present	36	15	41.7	
Absent	137	19	13.9	
Tumour capsule[b]				0.001
Present	102	13	12.7	
Absent	44	16	36.4	

[a] In 160 patients

[b] In 146 patients

Table 3 Multivariate analysis for the identification of prognostic factors for occult lateral lymph node metastasis

	Odds ratio	95 % CI	p value
TECS	10.1	(3.2–31.6)	<0.0001
Age <45 years	3.1	(1.1–8.4)	0.027
Vascular invasion	5.0	(2.0–12.4)	0.001

Discussion

Management of the N0 neck in PTC is controversial, mainly because the role of OLLNM as a predictive factor for locoregional control and survival is unclear. Management of the central compartment is more consensual and

Table 4 Risk of occult lateral lymph node metastasis according to number of predictive factors

Number of predictive factors[a]	N−	N+	Probability of node involvement (binomial 95 % CI)
0	43	2	4.4 % (0.5–15.2)
1	82	14	14.6 % (8.2–23.3)
≥2	14	18	56.3 % (37.7–73.6)

[a] Only predictive factors from the multivariate model

many authors recommend prophylactic central ND because of improved staging and reduced morbidity in cases of second look [13, 14]. Prophylactic lateral ND is more controversial because its relation to locoregional control and survival has not been demonstrated. Moreover, the predictive factors for high recurrence risk reported to date are mainly histopathological, thus, a decision to carry out ND would be better made after a more complete analysis. The majority of reports on predictive factors associated with a high risk of node metastasis have included clinically N+ necks and do not address the issue of lateral lymph nodes.

This study is the second study to focus on lateral N0 necks in PTC, and was made possible due to our management of N0 lateral necks [15]. This management is historical and has been performed in our department from 1974 to 2006. Since 2006, prophylactic lateral ND is no longer performed in our department, in accordance with international guidelines [16].

Nevertheless, our previous policy, still widely performed by Japanese surgeons but not recommended outside Japan, allowed us to collect important information on OLLNM after prophylactic ND: we found OLLNM in 20 % of patients. In the multivariate analysis, there were three independent predictive factors for increased OLLNM: TECS ($p < 0.0001$), vascular invasion ($p = 0.001$) and age <45 years ($p = 0.027$). When none of these factors was present, the risk of OLLNM was <5 %. The likelihood of OLLNM increased to 56.4 % when at least two of these factors were present. Unfortunately, vascular invasion and TECS are difficult to evaluate accurately on frozen sections and, as for numerous other prognostic factors, the factors identified in the current study should be evaluated further in a complete histopathological study. This could support the clinician's decision to avoid unnecessary lateral ND in patients without predictive risk factors.

As most surgeons do not practice prophylactic lateral lymphadenectomy, the incidence of OLLNM has not been widely reported in the medical literature. According to our data, 20 % of N0 patients with PTC have OLLNM, which is in accordance with other French study in papillary carcinoma by Bardet et al. [10] and close from another French study from Vergez et al. [17] who found 31 % of OLLNM. In contrast, Asian and American studies show a higher rate of OLLNM. Wada et al. [9] reported OLLNM in 61 % of their patients with papillary microcarcinoma, while Ito et al. [18] found lateral OLLNM in 64 % of 1,321 patients with papillary carcinoma and Lim et al. [15] reported OLLNM in 55 % of 62 N0 PTC. According to Attie et al. [19], the rate varied from 21 to 69 %. This wide variation between studies highlights the difficulty in identifying clear data in thyroid pathologies. However, it is obvious that thyroid carcinoma varies in different geographical areas, not only with regard to genetic changes in the tumour tissue (*ras*-, *gsp*-, *p53*- and *p21*-mutations) but also clinically (e.g. rate of regional and distal spread and disease course) [20].

In our study, patients >45 years had a lower risk of OLLNM. Numerous authors have also noticed that younger patients are more likely to have LNM than older subjects [6, 14, 21]. Paradoxically, age >45 years is a commonly reported negative predictive factor for recurrence and survival [12, 22]. Two explanations for this could be the relatively weak power of LNM involvement as a predictive factor or more aggressive LNM in older patients.

TECS was a strong predictive factor in our study. This factor also had the highest predictive value in the studies of Mirallié et al. [23] and Lee et al. [24]. McHenry et al. [25] reported that the frequency of node involvement was five times greater with extrathyroid disease, and the rate doubled for Henry et al. [26] when the perithyroid capsule was involved. Lim et al. [15] did not find any role of TECS in N0 PTC but their study included a small number of patients.

In the present study, OLLNM was also significantly associated with lymph vessel and vein invasion in multivariate analysis. In gastrointestinal and breast cancer, vascular invasion is also associated with the high incidence of locoregional lymph node metastasis [27, 28]. Only a few studies have been carried out regarding problems related to vascular invasion in thyroid carcinoma, but there appears to be a trend towards more distant metastases and lymph node recurrence when vascular invasion is present [29, 30].

The presence of a tumour capsule has received far less attention than TECS, age or vascular invasion. The presence of a fibrous capsule surrounding the tumour was a predictive factor for a lower incidence of OLLNM in our study but in univariate analysis only. Ito et al. [31] studied the tumour capsule in a large cohort of 1,356 patients and came to the same conclusion for lateral OLLNM. Carcangiu et al. [32] reported that 56.6 % of patients with a non-encapsulated tumour were had histological lymph node metastasis versus 45 % with encapsulated tumours. In multivariate analysis, Mirallié et al. [23] showed that the

absence of a tumour capsule was a predictive factor for higher lymph node involvement.

In our series, tumour size was not a predictive factor for OLLNM. This was also reported by Mirallié et al. [23], McHenry et al. [25] and Hunt et al. [33], although they did not specifically study OLLNM. Other authors have reported an increase in rate of LNM and number of metastases with tumour size [5, 6, 15]. In papillary microcarcinoma, tumour size >5 mm was reported to be a strong predictive factor for central LNM [24]. Our series includes only supracentimetric PTC and considers only lateral nodes, which may explain our different findings.

Plurifocality and bilaterality of the tumour were significantly correlated with a high rate of OLLNM in univariate but not multivariate analysis. These factors were not considered predictive factors by Lee et al. [24] and Mirallié et al. [23] in univariate or multivariate analysis. Lin et al. [34], who studied PTC, reported that it was important to distinguish two types of multifocal tumour: multifocal-independent primary tumours and tumours with intrathyroid metastases. Only the latter are frequently associated with LNM. Our study did not differentiate these two types, which could explain our different findings.

This retrospective study has several limitations. First, although it covers a long period of time (1974–2006), during which improvements in imaging may have resulted in differences in the likelihood of detecting preoperative lymph node metastases and postoperative recurrence, the vast majority of diagnoses (86 %) were made after 1985, at a time in which ultrasonography was used routinely in our patients. Second, several predictive factors were not studied in this series like the histologic subtypes or the location of the tumour in the thyroid lobe [33] as well as the role of central lymph nodes in the likelihood of lateral nodes involvement. As already published, it is very likely that metastatic central nodes are predictive for lateral neck metastasis [15]. Due to our management of central lymph nodes where central ND is only performed in case of positive central exploration, these data were not usable in this study without inducing an important bias. However, our management of central neck nodes is in accordance with recent guidelines where prophylactic central ND is not mandatory, especially in small PTC [8]. Following the guidelines, the presence of metastatic central nodes could be unknown in clinical situations where central ND is not required. This situation would not impede the use of our predictive score.

Although we report interesting findings on OLLNM, this study does not address the issue of the impact on prognosis of patients with occult lateral lymph nodes. To our knowledge, no paper has been published on this subject. Nonetheless, a recent study has shown that occult lymph nodes in differentiated thyroid carcinoma have an impact on prognosis with more locoregional recurrence, but this study does not specifically address the issue of the lateral lymph nodes [35]. Meanwhile, international guidelines do not recommend prophylactic lateral ND in PTC because no benefit on survival or recurrence has been proved after this procedure [7, 8]. Studies with large cohorts of patients and clearly focusing on prognosis after prophylactic lateral ND are still needed.

Conclusion

The present study provides more information on lateral LNM in PTC N0 necks: OLLNM are present in 20 % of N0 patients and occurs mainly in patients <45 years of age, with TECS and with vascular invasion on histopathological examination. The findings from this study suggest that in cases where these predictive factors are absent, the incidence of lateral neck metastases may be low and further discussion with the patient regarding the risks and benefits of lateral nodal dissection may be warranted. While this study adds more insight into the frequency and characteristics of patients with lateral nodal spread from papillary thyroid cancer, larger studies are needed to better answer questions regarding the impact of these metastases on prognosis and survival.

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