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Original Paper

Predictive Factors for Node Involvement in Papillary Thyroid Carcinoma. Univariate and Multivariate Analyses

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For patients with papillary thyroid carcinoma, lymph node involvement is a common complication, resulting in node dissection and its resulting morbidity. To determine means of limiting lymph node dissections, we attempted to define intra-operative criteria predictive of node metastasis and so identify the patients likely to benefit from this procedure. This retrospective study concerned 158 patients (118 female) treated between 1974 and 1996 for papillary thyroid carcinoma by total thyroidectomy associated with bilateral (central and lateral) ($n = 119$) or unilateral ($n = 39$) dissection. The following criteria were used to study the predictive value of node involvement: age, sex, tumour size, tumour site, uni- or multifocality, existence or not of a tumour capsule, existence or not of perithyroid involvement and presence or not of vascular invasion. 99 patients (63%) had node involvement. Four factors showed predictive value for node involvement in univariate analysis: vascular invasion ($P = 0.02$), male sex ($P = 0.008$), absence of a tumour capsule ($P < 0.0001$) and perithyroid involvement ($P < 0.0001$). Two factors were predictive in multivariate analysis: absence of a tumour capsule and perithyroid involvement. Our results enabled us to calculate the risk of node involvement for each patient as a function of the existence of a peritumoral capsule and/or perithyroid involvement and to determine the indication for dissection. When neither of these factors was present, the risk of node involvement was 38.3% and dissection was not considered essential. If both risk factors were found, the risk was 87.1% and dissection was considered necessary. © **1999 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

AMONG DIFFERENTIATED thyroid carcinomas, papillary forms are considered to spread to lymphatic tissues more so than follicular forms [1–3]. In various patient series treated by systematic node dissection, the rates of node involvement have ranged from 47% to more than 80% [1, 4–6], i.e. 20–53% of patients had an unnecessary procedure. The morbidity of thyroid surgery is increased when neck dissection is performed. The rate of permanent complications (hypocalcaemia or recurrent laryngeal nerve palsy) reaches 17.3% compared with 6.1% for total thyroidectomy [7]. The purpose of this study was to determine the factors predictive of node involvement that can serve as intra-operative criteria for the selection of patients likely to benefit from dissection.

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PATIENTS AND METHODS

This retrospective study concerned 158 patients (118 female, 75%), with a mean age of 43 years (standard deviation 16.5 years), who underwent surgery for papillary thyroid carcinoma between 1974 and 1996. All patients had total thyroidectomy associated with central bilateral lymph node dissection. A lateral modified radical dissection of both sides was received by 119 patients and a unilateral procedure (i.e. on the tumour side) by 39.

In most cases (91%, $n = 143$), node dissection was performed at the same time as thyroidectomy. It was deferred (within 2 months) when extemporaneous examination indicated a benign lesion or the patient had been referred from another centre. The decision to perform node dissection was taken in principle in the presence of a papillary tumour greater than 1 cm in diameter or when there was pre-operative evidence of metastatic lymph nodes. During this period, 481 papillary cancers were surgically treated. Some patients operated upon during the same period had neither bilateral nor unilateral modified radical dissection and were not included in the study. Dissection was not performed for one of the following reasons: a tumour measuring less than 1 cm in diameter and with no palpable node; advanced age; the convictions of the surgeon; or the presence of a known histologically (on definitive examination) demonstrated tumour in a patient who refused to be re-operated upon. Patients who underwent secondary dissection for cervical recurrence were also excluded.

All slides of histological examinations of thyroids and nodes were re-interpreted by a single histopathologist (C.S.). The following characteristics were studied: tumour size (or that of the largest nodule), tumour site (unilateral, bilateral, isthmic), uni- or multifocality, existence or not of a tumour capsule, existence or not of perithyroid involvement (micro- or macroscopic extrathyroid tumour invasion), the presence or not of vascular invasion, and the presence or not of node metastases. According to the histological data, patients were classified into two groups: N+ (existence of node metastasis) or N− (absence of node metastasis). Among N+ patients, we did not distinguish microlymph node metastases from palpable metastases.

Statistics

Results are expressed as means (± standard deviation, S.D.). Univariate analysis of the two groups of patients, with and without lymph node metastasis, was done using Student's *t*-test for quantitative parameters and the chi-square test for qualitative parameters. Statistical significance was set at $P < 0.05$. Parameters significant between patients with and without lymph node metastasis in univariate analysis were included in a multivariate logistic regression study. Independent significant parameters were identified using stepwise logistic regression. Threshold values for independent significant parameters were determined according to the terciles of each parameter. The odds ratios for these threshold values were calculated for lymph node metastasis.

Table 1. *Predictive factors for node involvement in univariate analysis*

	N+ patients *n* (%)	*P* value
Vascular invasion		0.02
Present	23 (82)	
Absent	76 (60)	
Sex		0.008
Male	32 (80)	
Female	67 (57)	
Tumour capsule		< 0.0001
Absent	68 (76)	
Present	30 (45)	
Perithyroid involvement		< 0.0001
Yes	60 (85)	
No	37 (47)	

RESULTS

33 (21%) patients had palpable lymph nodes before surgery. None had bilateral palpable involvement. There were 97 unilateral thyroid tumours, 52 bilateral and 9 isthmic, with a mean size of 31 mm (S.D., 19.8; range 3–170). 9 patients had tumours smaller than or equal to 10 mm. The lesions were multifocal in 64 cases (41%), and encapsulated in 67 cases (43%) (non-encapsulated in 89 (57%) (data available for 156 patients). Perithyroid involvement was noted in 71 cases (47%) (data available for 150 patients). Vascular invasion were found in 28 cases (18%) (data available for 154 patients). Metastatic nodes occurred in 99 patients (63%), and these were more frequent in multifocal tumours (68.7 versus 59.1%). The localisation of node involvement (central or lateral) was not determined in this study. The mean number of nodes removed was known (51, range 11–131) in the 119 patients who underwent bilateral resection. In N+ patients, the mean number of involved nodes was 7.2 (range 1–42).

Univariate analysis

Mean age was not significantly related to the existence of node metastases (42.7 years for N+ versus 43.7 years for N− $P = 0.71$) nor were age groups (0–20, 21–40, 41–60 and over 61 years; $P = 0.11$). However, 11 of the 12 patients under 20 years of age were N+. The mean tumour size was not significantly different in the two groups (32.2 mm for N+ versus 30.3 mm for N−; $P = 0.57$). The uni- or bilateral nature of tumours was not predictive of node metastasis ($P = 0.13$), nor the multifocality of lesions (68.7 versus 59.1%; $P = 0.22$).

In univariate analysis, four factors were significantly related to node involvement (Table 1) male sex ($P = 0.008$), presence of vascular invasion ($P = 0.02$), absence of a tumour capsule ($P < 0.0001$) and perithyroid involvement ($P < 0.0001$). Absence of a tumour capsule was a significant factor even in comparison with the group of patients with extracapsular tumour growth (76 versus 50% for N+; $P = 0.0005$).

The fact that perithyroid involvement was significantly related to the presence of a peritumoral capsule ($P < 0.0001$), male sex ($P = 0.038$) and the presence of vascular invasion ($P = 0.015$) made it essential to perform a multivariate analysis.

Multivariate analysis

In logistic regression studies, the four significant factors determined in univariate analysis showed two significant independent factors differentiating patients with and without node metastasis: absence of a tumour capsule ($P = 0.023$) and

Table 2. *Predictive factors of node involvement in multivariate analysis*

Parameters	Estimate	Odds ratio (95% CI)	*P* value
Absence of tumour capsule	1.081	2.519 (5.586–1.135)	0.023
Perithyroid involvement	1.464	4.324 (1.853–10.088)	0.001

CI, confidence interval.

perithyroid involvement ($P = 0.001$). The relative risks of node metastasis were calculated independently for each of these factors (Table 2).

After adjustment using the logistic regression model, the probability of node involvement was calculated for the four groups defined by the presence or absence of one or both risk factors determined by multivariate analysis (Table 3).

Univariate analysis of the 51 patients in the first group (probability of node involvement: 38.3%) showed that N+ patients had more multifocal tumours (52.9% N+ versus 29.4% N− patients), were younger (34 years N+ versus 39.8 years N−), had smaller tumours (27.7 mm N+ versus 33.3 mm N−) and had more bilateral tumours (52.9% N+ versus 23.5% N−). None of these differences was statistically significant (Table 4). The only significant difference was sex: 41.1% of N+ patients were male versus 14.7% of N− patients ($P = 0.03$).

DISCUSSION

The role of dissection in the treatment of papillary thyroid cancer is debatable. Although it is generally performed only when node involvement is evident macroscopically, interpretation of suspect features in intra-operative conditions may be unreliable [4, 6, 8]. Node involvement is currently considered to be indicative of a poor prognosis for local recurrences [2, 9–13] and survival [5, 14]. In a few series, node dissection has resulted in a reduction in local recurrence in N+ patients [5, 10, 12] and sometimes improves survival [5].

The purpose of this study was to determine the criteria predictive of node metastasis and reduce the rate of unnecessary dissections. In our series, macroscopic metastases were not distinguished from microscopic ones since published studies do not indicate the prognostic values for these two types of node metastases. Since the end of this study, we have verified that these criteria could be analysed intra-operatively. During extemporaneous examination, the pathologist was able to specify whether the patient had extrathyroid involvement or a peritumoral capsule. However, the histological subtypes of papillary cancers could not be distinguished during extemporaneous examination and were thus not determined. This series was homogeneous with respect to treatment since all patients had total thyroidectomy associated with at least unilateral modified radical dissection. Patients who had less complete dissections were excluded since we could not determine with certainty the nature of their nodal state. The proportion of bilateral resections in this series (75%) depended on the practices of the different surgeons.

The factors predictive of node involvement have rarely been studied in the literature. Some authors have noted that patients under 40–45 years of age were more often N+ than others [4, 5, 15]. The involvement of cervical nodes in children and adolescents has often been reported [8, 16, 17]. In our series, the frequency of node involvement was greater (but not significantly) in patients under 20 years of age, although this result was probably due to the small number ($n = 12$) included.

Our series confirmed that tumour size is not predictive of node involvement [7, 11]. In this respect, the reported frequency of node metastasis is the same for microcarcinomas [18] as for larger tumours [11, 17], although a greater number of metastatic nodes have been found in N+ patients when tumour diameter increases [4, 5]. The only cases of microcarcinoma included in this series were those with palpable nodes. However, the true rate of node involvement for these patients could not be determined.

Unlike Henry and associates [19], we found no predictive value for tumour multifocality, although node metastases were more frequent with a multifocal lesion (68.7 versus 59.1%). However, Noguchi and associates [6] reported that multifocal tumours were associated with a higher rate of bilateral involvement than unifocal tumours. Ahuja and colleagues [15] noted a greater (but non-significant) frequency of node involvement for multifocal tumours (52.4 versus 33.5%).

Male sex was a predictive factor in univariate analysis in our series, and Ahuja and colleagues [15] found that this factor was predictive for patients under 20 and over 40 years of age. For Carcangiu and colleagues [17], sex had no predictive value.

The existence of a peritumoral capsule has been studied as a risk factor for node involvement. Carcangiu and colleagues [17] noted that 56.5% of patients with non-encapsulated tumours were N+ versus 45% with encapsulated tumours. This was an important predictive factor in our study. Even when tumour growth was extracapsular, the frequency of node involvement remained lower than that in patients with a non-encapsulated tumour.

Though Ozaki and colleagues [1] found that the frequency of node involvement was independent of extrathyroid involvement, this factor generally has important predictive value. For McHenry and associates [11], the frequency of node involvement was five times greater with extrathyroid disease. Simon and associates [10] found rates among N+ patients of 61% and 56% for T1 and T2 and 88% and 85% for T3 and T4 tumours (i.e. those with perithyroid involvement). Henry and associates [19] noted that the frequency of node involvement doubled when the perithyroid capsule was involved (44.6 versus 22.4%). In our series, this factor had the highest predictive value.

After surgery, we provided systematic treatment with ^{131}I for patients with tumours larger than 1 cm in diameter, which allowed the destruction of thyroid residues [20, 21]. We consider that surgery is more efficient than ^{131}I treatment for

Table 3. Probabilities of node metastasis

Group	Absence of tumour capsule	Perithyroid involvement	Probability of node involvement (CI)
1: $n = 51$	–	–	38.3% (26.7–51.4)
2: $n = 27$	+	–	61% (43.9–75.8)
3: $n = 13$	–	+	72.9% (53–86)
4: $n = 58$	+	+	87.1% (77.3–93.1)

CI, confidence interval.

Table 4. Predictive factors in group 1 (without any risk factors): univariate analysis

	N+	N−	*P*-value
Tumour size	27.7 mm	33.3 mm	0.15
Age (years)	34	39.8	0.15
Bilateral tumours	52.9%	23.5%	0.07
Multifocality	52.9%	29.4%	0.10
Male sex	41.1%	14.7%	0.03

node involvement. In fact, some involved nodes do not take up ^{131}I [22, 23].

Our study indicates that it is possible intra-operatively to estimate the risk of node involvement for patients. For those with no risk factors of node involvement (one-third of our patients), it would seem possible not to perform dissection in the absence of macroscopic node involvement since the probability of involved nodes was only 38.3%. In this group, the frequency of node metastasis is more important for male patients and those with a bilateral tumour. For those with two risk factors (one-third of our patients), the probability of node metastasis (87.1%) was great enough to warrant dissection. For those with a single risk factor (absence of a tumour capsule or perithyroid disease), the probability of node involvement was 61 and 72.9% respectively. Node dissection would seem preferable in these patients because of its efficacy in reducing local recurrences and probably in prolonging survival, especially if the risk factor is perithyroid involvement. These guidelines should help reduce the number of unnecessary dissections. We found that the most frequently involved node sites were the homolateral and contralateral paratracheal, homolateral jugular and supra clavicular (data not shown). We consider that nodes in these four sites should be resected. When the tumour is located at the upper pole of the thyroid lobe, the subdigastric nodes may also be involved.

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