

Analysis of the prognostic significance of lymph node related characteristics in papillary thyroid carcinoma patients presenting with pre- or intra-operative evidence of cervical lymph node metastases

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Abstract

Objective: To identify the prognostic significance of specific lymph node related characteristics for disease persistence and recurrence in patients with pre- or intra-operative evidence of neck metastases and no other risk factors.

Method and results Sixty-eight patients were identified; 50 per cent had persistent or recurrent disease. All underwent the same treatment strategy. There were no statistically significant differences in any of the patient- or tumour-related parameters when patients with and without persistence or recurrence were compared. Patients with recurrent or persistent disease had significantly larger (>3 cm) metastatic lymph nodes, but there were no differences regarding other lymph node related parameters (i.e. number, extracapsular extension, number of lymph nodes with extracapsular extension, and central vs lateral neck location). On multivariate analysis, however, none of the parameters were predictive of persistent or recurrent disease.

Conclusion: In papillary thyroid carcinoma patients with no other risk factors, pre- or intra-operative evidence of cervical metastases was associated with a very high rate of disease persistence or recurrence. Specific lymph node characteristics were not shown to have prognostic significance.

Key words: Thyroid Neoplasms; Papillary Thyroid Carcinoma; Neoplasm Metastases; Lymphadenopathy; Prognosis; Pathology

Introduction

Predictors of recurrence and mortality in papillary thyroid carcinoma have long been studied and analysed. Risk stratification is currently based on host-related factors (e.g. age or sex), tumour-related factors (e.g. size or extension) and the presence of distant metastases.¹ The presence of metastatic lymph nodes in the neck is one of the most important prognosticators in head and neck carcinomas, lowering survival rates by 50 per cent. However, the role of regional lymph node metastases in papillary carcinoma of the thyroid has been considered less significant.

The presence of lymph nodes is not a factor included in most prognostic scoring systems, such as: the age, grade of tumour, extent of tumour and size of tumour ('AGES') system; the age, distant metastasis, extent of tumour and size of tumour ('AMES') system; or

the metastasis, patient age, completeness of resection, local invasion, size of tumour ('MACIS') system. The tumour–node–metastasis scoring system, however, does include regional lymph node metastasis as a factor influencing prognosis, but only in those aged over 45 years; nonetheless, size, number and extracapsular extension are not taken into consideration.¹

Several recent studies have indicated that the presence of lymph node metastases can adversely affect the recurrence rate of papillary thyroid carcinoma and even survival.^{2–6} However, most of these findings were based on non-homogeneous samples that included: patients with and without distant metastases, those with clinical extrathyroid extension and primary tumour of various sizes, and the use of different treatment strategies.

A subgroup of papillary thyroid carcinoma patients present with pre- or intra-operative evidence of cervical

lymph node metastases, but without clinical (macroscopic) evidence of extrathyroid extension or distant metastases. In this subgroup, the clinical and histological predictors of recurrence, persistence or survival have scarcely been studied.^{7,8} The prognostic significance of lymph node related characteristics, such as the number of metastatic regional lymph nodes, the size of metastatic nodes and the presence of extracapsular extension, has not been thoroughly investigated in this subgroup.

The present study aimed to analyse the significance of these lymph node related characteristics for the unique subgroup of patients with papillary thyroid carcinoma and clinically evident cervical metastases. All patients in the present study underwent the same treatment strategy.

Materials and methods

Following approval of the study by the local institutional review board, the computerised database of a major tertiary medical facility was searched for all patients diagnosed with papillary carcinoma from 1993 to 2007 (using diagnosis codes from the International Classification of Diseases version 9). Only those patients treated with total thyroidectomy and concomitant neck dissection were selected. From this group, we excluded patients with radiological evidence of distant metastases, macroscopic extrathyroid extension, or aggressive histological features (tall cell and diffuse sclerosing types) so as to leave a homogeneous group with the experimental variable limited to the presence (specifically, the characteristics) of lymph node metastases.

The final study group consisted of 68 patients with locoregional disease at presentation. In all of these patients, there was clinical or radiological evidence of regional neck disease, which was confirmed pre-operatively by fine needle aspiration or intra-operatively by frozen section biopsy. Patients were then divided into two subgroups: one group were disease-free following surgery and radioiodine treatment (i.e. no clinical or imaging evidence of persistent or recurrent disease, a negative radioiodine scan, and undetectable thyroglobulin levels), and the other had evidence of recurrent or persistent disease.

Recurrent or persistent disease was determined on the basis of either clinical or sonographic evidence for neck nodes. Metastases of papillary carcinoma were confirmed by fine needle aspiration during follow up. A high level of stimulated thyroglobulin (>10 ng/ml), non-stimulated thyroglobulin (>1 ng/ml) or increased elevation of anti-thyroglobulin antibodies (in the presence of low thyroglobulin), along with a positive radioiodine scan or radiological evidence of disease, were also interpreted as recurrence or persistence of the disease.

The medical charts of the two patient subgroups were reviewed, and the patient, tumour and lymph node characteristics were analysed according to the absence or presence of disease recurrence and persistence.

Statistical analysis

Continuous data were expressed as means, ranges and 95 per cent confidence intervals. Categorical data were expressed as proportions. Comparisons were performed using the *t*-test for the continuous variables and the chi-square test for the categorical variables. For multivariate analysis, a logistic regression was carried out.

All reported *p* values are two-tailed; $p < 0.05$ was considered statistically significant. For statistical analyses, we used the Statistical Package for the Social Sciences software, version 15.0.1 (SPSS; Chicago, Illinois, USA).

Results

The study group consisted of 25 men and 43 women, with an average age of 44 years at presentation. Mean follow-up time was 6 years (range 1–15 years).

All patients underwent total thyroidectomy and neck dissection followed by radioiodine ablation at a dose of 150 mCi. Neck dissection was performed in the lateral neck (levels II, III and IV) with or without the central compartment in 60 patients, and in the central compartment only in 8 patients. (In 2005, central compartment dissection became standard practice in our department for every case of papillary carcinoma larger than 15 mm; prior to that period, dissection of the central compartment was performed only if there was clinical or sonographic evidence for metastases.) Nevertheless, there was no overall difference in the neck dissection type between the patients with recurrence or persistence and those who were disease-free following surgery and radioiodine ablation.

Thirty-four patients (50 per cent) had recurrent or persistent disease: 7 patients (10.3 per cent) had recurrent disease and 27 patients (39.7 per cent) had persistent disease. All patients were alive at the end of the follow-up period.

The factors analysed for their influence on disease recurrence and persistence are shown in Table I. No significant differences were found between the two groups of patients in either the patient- or tumour-related parameters investigated. However, the proportion of males that developed recurrent or persistent disease was higher compared with females (64 per cent vs 42 per cent, respectively); this was a near significant difference ($p = 0.078$).

Analysis of lymph node characteristics (number, size, presence of extracapsular extension and number of lymph nodes with extracapsular extension) revealed that patients with recurrent or persistent disease had significantly larger lymph nodes than those who were disease-free following surgery and radioiodine ablation ($p = 0.01$). Further analysis revealed that patients with lymph node metastases larger than 3 cm were at significantly higher risk of developing recurrent or persistent disease ($p = 0.032$). No significant differences were found between the two groups of patients in the other

TABLE I
PATIENT AND TUMOUR CHARACTERISTICS

Parameter	Disease-free pts*		Persistent or recurrent disease pts*		p
	Value	95% CI	Value	95% CI	
Age (mean (range); y)	41.8 (14–65)	37.4–46.2	46.3 (15–79)	40.5–52.2	0.214
Males (n (%))	9 (36)		16 (47)		0.078
Females (n (%))	25 (74)		18 (53)		
Multifocality (n (%))	20 (58)		25 (74)		0.2
Primary tumour size (mean (range); cm)	1.38 (0.1–4)	1.02–1.76	1.75 (0.1–5)	1.31–2.19	0.2
Microscopic extrathyroid extension (n (%))	17 (50)		19 (53)		0.8
Lymph node metastases (mean \pm SD; n)	4.9 \pm 5.0	3.11–6.70	6.4 \pm 6.0	4.47–8.65	0.2
Largest lymph node (mean (range); cm)	1.96 (0.45–4.00)	1.55–2.37	3.1 (0.5–9.5)	2.34–3.94	0.01
Pts with extracapsular extension (n)	10		10		1
Lymph nodes with extracapsular extension (mean (range); n)	2.2 (1–7)	0.78–3.62	2.1 (1–6)	0.86–3.54	1
Follow-up time (mean (range); y)	5.7 (1–13.9)	4.6–6.9	6.3 (0.4–15)	5.0–7.5	0.5

*n = 34. Pts = patients; CI = confidence interval; y = years; SD = standard deviation

lymph node parameters analysed. On multivariate analysis, none of the parameters were found to be significantly associated with outcome.

Discussion

Differentiated thyroid carcinoma tends to recur in about 30 per cent of patients, usually (in about 66 per cent of cases) within 10 years of initial therapy.² The two most important and consistently demonstrable patient-related factors known to influence the outcome of recurrent disease are age at presentation and tumour stage.^{2,3,9,10} Rates of recurrence are highest for patients younger than 20 years of age or older than 60 years.¹¹ Children typically present with more advanced disease and have more tumour recurrences after initial therapy than adults, yet their overall survival is good.^{12,13} Another important factor is tumour size. Papillary carcinomas smaller than 1 cm (microcarcinomas) are generally much less frequently associated with recurrence, and the cancer-specific mortality rate is close to zero.^{14,15} In general, smaller tumours are associated with one-third of the 30-year recurrence rates of larger tumours. There is a linear relationship between tumour size and recurrence or cancer-specific mortality,^{2,11,16–18} with prognosis growing incrementally poorer as tumour size increases.^{19,20} Extrathyroid extension and presence of distant metastasis have also been associated with recurrence and survival.^{10,16–18}

The prognostic importance of lymph node metastases has been a controversial issue. Some studies showed that nodal metastases had no effect on recurrence or survival.^{21–23} Some reported that nodal metastases are a risk factor for local tumour recurrence and cancer-specific mortality.^{2,5–6} Others reported a correlation between distant metastases and nodal metastases, particularly if these are bilateral neck or mediastinal metastases, or if there is extracapsular lymph node extension.^{2–4} It has also been reported that nodal involvement in older patients increases the risk of recurrence,²⁴ and that large (3 cm or greater) lymph node metastases in older patients influence survival.²⁵

Recently, several studies have consistently shown that the presence of metastatic neck lymph nodes is an independent risk factor for disease recurrence.^{26–29}

Nevertheless, few studies have analysed the factors that predict recurrence and persistence in patients presenting with locoregional disease. Spires *et al.*⁷ in a review of patients with regional disease at presentation who underwent neck dissection, found no significant difference in overall or disease-free survival between patients with and without nodal extracapsular extension. However, the authors did not exclude other negative prognostic factors, such as extrathyroid extension and distant metastases at presentation. Sex was the only significant parameter for disease-free survival; females had a significant advantage compared with males.

Leboulleux *et al.*⁸ studied 148 patients with papillary thyroid carcinoma and lymph node metastases or extrathyroid extension, all of whom underwent total thyroidectomy and neck dissection followed by radioiodine treatment. Neck dissection was performed routinely in all patients with thyroid carcinoma, regardless of the presence or absence of clinical or imaging evidence of lymph node metastases. They found that 5.4 per cent of patients had recurrent disease after a mean follow up of 4.7 years, and 22 per cent had persistent disease. The significant risk factors for recurrence were: more than 10 lymph node metastases at presentation, and extracapsular extension of the metastases in more than 3 lymph nodes. For persistent disease, the risk factors included: tumours larger than 4 cm and lymph node metastases in a central location.

In contrast to the study by Leboulleux *et al.*⁸ we excluded patients with known negative prognostic factors, such as large tumour size at presentation, macroscopic extrathyroid extension and distant metastases. In addition, we performed neck dissection only in those patients with pre- or intra-operative evidence of lymph node metastases. The latter fact may explain our finding of a high recurrence or persistence rate of 50 per cent within a mean follow-up period of

6 years (range 1–15 years). This is nearly twice the recurrence and persistence rates reported by Leboulleux *et al.* At the same time, similar to the findings of Spires and colleagues,⁷ comparison of the groups of patients with and without disease recurrence yielded no statistically significant differences in the presence of extracapsular extension in metastatic lymph nodes.

In the current study, univariate analysis revealed that patients with persistent or recurrent disease had significantly larger metastatic lymph nodes than disease-free patients. A metastatic lymph node larger than 3 cm was significantly associated with persistent or recurrent disease. We also noticed that males were more prone to develop recurrence or persistence, though this was not a significant finding. However, multivariate analysis revealed that none of the parameters were significantly associated with outcome.

We are aware that this is a retrospective case control study, comprising a limited number of patients, which may have prevented us from reaching more significant conclusions. Nonetheless, the findings highlight concerns that deserve attention in future studies and in the current clinical management of patients with papillary thyroid cancer.

- **This paper focuses on a subgroup of papillary thyroid carcinoma patients**
- **This subgroup present with pre- or intra-operative evidence of cervical lymph node metastases, and no other significant risk factors**
- **The prognostic significance of specific lymph node metastases characteristics has been little studied**
- **In our retrospective study, this subgroup had a high recurrence-persistence rate (50 per cent)**
- **This rate highlights the negative prognostic value of clinically evident lymph node metastases**
- **Specific lymph node characteristics (number, size and extracapsular extension) had no prognostic significance**

To summarise, this study showed that patients with papillary thyroid carcinoma, who were diagnosed with cervical lymph node metastases pre- or intra-operatively, with no evidence of macroscopic extrathyroid extension or distant metastases, had a very high rate of disease recurrence or persistence (50 per cent). This finding highlights the negative prognostic value of clinically evident lymph node metastases. Nonetheless, specific lymph node characteristics (number, size and extracapsular extension) were not found to have prognostic significance in this patient group.

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