Original Article
Pattern of nodal involvement in papillary thyroid cancer: a challenge of quantitative analysis

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Abstract: Introduction: Backgrounds of this study were to examine and analyse the relationship among the number of lymph nodes with metastases harvested in central and lateral compartments, the characteristics of tumours and patients, and the recurrences rate. Methods: A retrospective review of 118 patients treated for a papillary thyroid cancer and underwent to neck dissection, including in all cases both central and lateral compartment, was realised. A quantitative analysis, on this homogeneous cohort of patients, was performed to hypothesize the minimum number of cervical lymph nodes to be necessarily excised in order to obtain an adequate management of these patients. Results: The mean follow-up time was 75.9 months. Five-year overall survival was 96.6%. The correlation among the metastatic lymph node number of the ipsilateral central compartment, isolated or pooled with those of the ipsilateral lateral compartment, age of patient and tumour size revealed a statistical significance (P=0.01); both parameters, tumour size and age, may be considered as dependent predictor variables. Conclusion: We suppose, notwithstanding the limited number of patients, that the number of lymph nodes harvested to achieve an optimal cervical dissection may be superior to 8 and 11 in central and lateral compartments, and 6 and 10 in contralateral ones, respectively. Moreover we recommend the bilateral dissection of central nodes compartment in presence of tumour localised in the isthmus.

Keywords: Papillary thyroid cancer, lymph node metastases, cervical dissection, quantitative analysis

Introduction

Thyroid cancer represents about 1% of all malignancies, but an increasing incidence has been reported worldwide [1, 2]. In Europe, it raised up to an average of 5 and 13 new cases per year per 100,000 inhabitants, in male and female respectively [3]. The commonest histotype of the differentiated thyroid malignancy is papillary thyroid cancer (PTC), typical of which is the frequent spread to locoregional lymph nodes [1]. Cervical metastases frequently occur first in the central compartment and subsequently in the lateral one [4, 5]. Recurrences of the PTCs are more frequent if the nodal involvement is extensive [4, 6]. Currently, thyroid cancer is staged using the Tumour Node Metastases (TNM) staging [1, 7]. Total thyroidectomy (TT) with cervical nodes dissection is the treatment of choice for PTC [8], but the correct management of nodal excision remains controversial [6, 9, 10]. The aims of this study were to evaluate and analyse the relationship among the number of metastatic lymph nodes harvested in the central and lateral compartments with the tumour size, age and gender of patients, taking also into account the incidence rate of recurrences and, as a consequence, the adequacy of the surgical procedure.

Patients and methods

We retrospectively reviewed 118 patients treated for a PTC, out of a total of 1491 thyroid surgical procedures, from January 2007 to December 2009 at an Endocrine French Surgery Unit. All selected patients, never previously submitted to neck surgery, underwent a TT under general

Table 1. Patients and tumour characteristics

	Upper Third n=23 (19.5%)	Middle Third n=65 (55.1%)	Lower Third n=30 (25.4%)	Total n=118
Mean age (years)	48.4±11.5	48.8±15.6	44.3±15.1	47.5±14.7
Range (years)	26-66	19-86	17-75	17-86
Sex ratio (m/f)	4/19	13/52	8/22	25/93
Stage I	9 (39.1%)	31 (47.7%)	18 (60.0%)	58 (49.2%)
Stage II	1 (4.4%)	2 (3.1%)	2 (6.7%)	5 (4.2%)
Stage III	13 (56.5%)	27 (41.5%)	8 (26.6%)	48 (40.7%)
Stage IV	-	5 (7.7%)	2 (6.7%)	7 (5.9%)
T1	10 (43.5%)	24 (36.9%)	20 (66.7%)	54 (45.8%)
T2	3 (13.0%)	9 (13.9%)	6 (20.0%)	18 (15.3%)
T3	10 (43.5%)	29 (44.6%)	4 (13.3%)	43 (36.4%)
T4	-	3 (4.6%)	-	3 (2.5%)
Size (mm)	13.9±7.9	20.6±14.3	13.8±7.1	17.6±12.1
Range (mm)	5-40	1-65	4-35	1-65
Multifocality (%)	9 (39.1%)	16 (24.6%)	12 (40.0%)	37 (31.3%)

anaesthesia with a selective cervical dissection, including always both lateral and central compartment. Lateral cervical lymph nodes were defined as the nodal tissue in levels II-V, and central lymph nodes as the nodal tissue in level VI.

All patients were from the central county of Orleans (population approximately 270,000), which is an iodine-deficient area of France with three nuclear power plants placed within a range of 50 km from the county town. All subjects were admitted after having been investigated pre-operatively by routine and hormone laboratory tests, neck ultrasound scan, and ultrasound-guided fine-needle aspiration cytology (FNAC). A supplementary enhanced computed tomography of the neck and a ^{99m}Technetium scintigram of the thyroid were performed in 15/118, and 8/118 equivocal cases, respectively. Otorhinolaryngologic examinations, by indirect laryngoscopy, were negative for vocal cord mobility disorders in all patients. The American Society of Anaesthesiologist (ASA) physical status classification system was assessed in all patients: 35 were ASA 1, 56 ASA 2 and 27 ASA 3. Hypertension was the most frequent co-morbidity. Sternocleidomastoid muscles, internal jugular nerves, and spinal accessory nerves were preserved in all cases.

In our experience, the criteria adopted to extend the lymph node dissection (therapeutic

and prophylactic), in ipsilateral and contralateral side, were as follows: i) pre-operative FNAC nodal positivity or radiological findings suggestive for metastases; ii) intra-operative detection, either by visual inspection or touch, of suspect nodes; iii) multifocal and advanced tumours confirmed at the intra-operative frozen section examination of the thyroid gland; iv) in the case of multifocal neoplasm localised also in the isthmus, a supplementary prophylactic contralateral central compartment dissection was done. Recurrent nerves and parathyroid glands were identified in all cases. All procedures were performed by 3 surgeons highly trained, with a minimum of ten-year experience in thyroid surgery. An accurate haemostasis was done, and thyroid bed was systematically drained. The muscle was partly closed with a resorbable suture, and metal clips or topical skin adhesive were used for surgical wound closure. Disease staging was performed according to TNM criteria. All patients were addressed to the Endocrinology Unit for the adjuvant radio-ablation, and a post-operative clinical, instrumental, and laboratory surveillance.

The number of lymph nodes metastases (LNMs) were categorised into 4 groups namely: IC) ipsilateral central; CC) contralateral central; IL) ipsilateral lateral; CL) contralateral lateral. Tumour size was indicated in millimetres (mm) and age expressed in years.

The results are expressed as mean ± standard deviation (SD) and 95% confidence interval (CI), or as median. Differences between means were analysed using the analysis of variance (ANOVA). The Pearson's correlation was calculated to examine the association among the number of metastatic nodes harvested, the tumour size and the patient gender. When appropriate, a Spearman's rank test was used. The stepwise regression analysis was utilised to detect dependent variables. The level for statistical significance was set at P<0.05, and the statistical software utilised was SPSS (version 13.0).

Table 2. Correlation among the number of LNMs, with tumour size, age and gender of patients

		IC N=66	CC N=8	IL N=47	CL N=4	IC+IL N=113
Tumour size	rho	0.29	0.05	0.07	0.77	0.21
	P	0.01*	0.90	0.65	0.22	0.02*
Patients Age	rho	-0.31	0.17	-0.10	0.25	-0.22
	Total p	0.01*	0.67	0.49	0.74	0.01*
Gender	rho	-0.04	-0.54	-0.02	0.57	-0.06
	P	0.73	0.16	0.83	0.42	0.51
Tumour size	rho	0.38	0.63	-0.13	n.v.	0.18
	P	0.05	0.36	0.62		0.23
Patients Age	rho <45	-0.19	0.10	0.11	n.v.	-0.09
	P	0.33	0.89	0.68		0.54
Gender	rho	-0.05	0.94	-0.16	n.v	-0.11
	P	0.39	0.05	0.55		0.47
Tumour size	rho	0.38	-0.33	0.08	0.86	0.27
	P	0.01*	0.66	0.63	0.33	0.02*
Patients Age	rho >45	0.004	0.73	-0.08	0.90	0.04
	P	0.97	0.26	0.65	1.00	0.73
Gender	rho	-0.19	0.27	-0.04	0.50	-0.15
	P	0.13	0.72	0.81	0.60	0.21

*statistically significant (P value<0.05). rho: Spearman's correlation coefficient; n.v.: not value; LNM: lymph node metastases; IC group: ipsilateral central; CC group: contralateral central; IL group: ipsilateral lateral; CL group: contralateral lateral.

Results

Overall, patients were 93 females aged 46.9±14.5 years (range 17-86) and 25 males aged 50.2±15.9 years (range 23-82), with 75/118 patients (63.6%) being over 45-years old at time of TT. All tumours were classified according to their localisation in the thyroid gland, and differentiated in upper, middle, or lower third. Isthmus lesions were counted as middle third. If the cancer was multifocal, we considered the largest neoplasm (**Table 1**). In the whole cohort, the localisation of the cancer was 23 (19.5%), 65 (55.1%), or 30 (25.4%) to the upper, middle, or lower third, respectively. The corresponding localisation in the 75 patients aged over 45 was: 18 (24.0%; 16 females and 2 males), 41 (54.7%; 33 females and 8 males), 16 (21.3%; 11 females and 5 males).

At the histopathological examination, the maximum diameter of the malignant nodule averaged 17.6±12.1 mm, neoplasm multifocality was recorded in 37 patients, with involvement of the upper, middle or lower thyroid third in 9 (24.3% of 37; 7 females, 2 males), 16 (43.2%; 11 females, 5 males) and 12 cases (32.4%; 10 females, 2 males), respectively (**Table 1**) Hashimoto's thyroiditis was histologically present in 16 patients (13.5%). Cervical drainage, which was bilateral in 10 patients, was generally removed in the first post-operative day, except for 3 patients, in whom it was delayed on the next day for slight bleeding.

No mortality was observed. Early complications were transient hypocalcaemia in 19 (16.1%), transient recurrent laryngeal nerve injuries in 7 (5.9%) and cervical haematomata in 2 (1.7%). Only 2 patients (1.7%) developed permanent hypoparathyroidism, in which they required permanent substitutive treatment with oral calcium and cholecalciferol. Discharge occurred on the first, second or third postoperative day in 71, 42 or 5 patients, respectively.

The mean follow-up time was 75.9±9.2 months (range 61-98), equivalent to 6.3±0.7 years. The 5-year overall survival was 96.6% (114/118), because 3 patients (2.5%) died for distant recurrences, and 1 died for unrelated causes (severe multiple trauma in a road accident). In the whole cohort, local recurrences occurred in 7 patients (5.9%), of whom 6 required a surgical second-look and 1 a supplementary radioiodine therapy.

Nodal metastases were found in 66/118 patients in the IC, 8/14 in the CC, 47/118 in the IL and 4/10 in the CL group, respectively (**Table 2**).

A concordance between lymph node positivity for metastases in central and lateral compartment was found in 7 of 23 cases (30.4%) when the cancer was in the upper third of thyroid, in 26 of 65 cases (40%) when the cancer was in the middle third and in 6 of 30 cases (20%) when the cancer was in the lower third, but differences were not statistically significant. The LNMs in the IC group, either isolated or pooled with those of the IL group, were statistically related to age and tumour size (P=0.01), particularly in patients over 45 years (**Table 2**). In these lymph nodes groups, tumour size and

Table 3. Adequacy judgement of cervical lymph node dissection in PTC patients

Cervical Node Dissection	Adequacy Judgement		
Lymph node metastases/ Total lymph nodes harvested Total lymph nodes: mean ± SD	Insufficient	Good	Optimal
IC 182/655 (27.8%) 5.5±2.9	<3	3-8	>8
CC 22/60 (36.7%) 4.3±2.2	<2	2-6	>6
IL 114/966 (11.8%) 8.2±3.7	<5	5-11	>11
CL 5/87 (5.7%) 8.7±1.8	<6	6-10	>10

PTC: Papillary Thyroid Carcinoma.

age may be considered as sensible dependent predictor variables. Instead, the other CC and CL groups were unrelated to tumour size, age and gender (**Table 2**). The number of lymph nodes to be removed to reach an optimal adequacy of treatment was assessed considering the average number of lymph node harvested ± SD values (e.g. considering A (average) ± B (SD), we reckoned the lymph node dissection insufficient if <B, good if comprised between A and B, and optimal if > than A plus B values) (**Table 3**).

Discussion

PTC spreads to cervical nodal metastases in 30 to 80% of patients [4]. Patients with nodal involvement have an increased recurrence of PTC and a decreased survival rate [11, 12]. Accordingly, the appropriate surgical treatment of overt and occult nodal metastases improves overall survival [13], and indeed cervical node dissection represents the recommended treatment for the advanced thyroid malignant diseases [8]. Controversies remain on the correct management to achieve an adequate neck dissection and on the cervical lymph node levels that require excision [4, 6]. In accord to the international guidelines for the management of differentiated thyroid cancer, the initial surgical treatment for PTC is TT with synchronous central node compartment dissection [8]. Such dissection is therapeutic if lymph nodes are clinically involved or prophylactic if thyroid cancer is advanced, i.e. stage T3 or T4 [8]. However, literature reports a large variability of results about the total number of lymph nodes removed

and the nodal levels included in the dissections [4, 6, 9, 11]. Due to occult lymph node metastases a routine prophylactic central node compartment dissection can be carried out in all PTC patients, even if in absence of preoperative imaging suggestive for metastases or suspect nodes during the intra-operative research [14-18].

The prophylactic lateral node dissection is not recommended in absence of cytological diagnosis of tumour [8], despite more analysis showed a concordance of the involvement in central and lateral compartment [19-21]. However, a few studies report that maximisation of the number of lymph nodes removed is unnecessary and unrelated to the recurrences [6, 22]. The lateral compartment dissection increases the complications rate for a raised surgical invasiveness [13, 21]. Some authors report a concordance between tumours localisation and nodal compartment involvement, particularly between superior lobe and lateral compartment [23, 24]. Others underlined the usefulness of the sentinel node biopsy to better assess the lateral neck compartment status for the purpose of detecting the occult lesions [25]. Recently, new surgical techniques for haemostasis and use of nerve-sparing devices have been introduced to reduce complications arising from monopolar diathermy thermal injury [26, 27].

On considering our low rate recurrences occurred during the follow-up period, and on the basis of our experience, we suggest that: i) the number of lymph nodes harvested to consider a cervical dissection as optimal may be accounted more than 8 and 11 in central and lateral compartments, and 6 and 10 in contralateral sides, respectively; ii) when tumour is localised either only or even in the isthmus, a supplementary prophylactic contralateral central compartment dissection is recommended, due to the increased spreading trend toward the locoregional lymph nodes.

Furthermore, we confirm that central lymph nodes compartment must be always removed, lateral lymph nodes compartment may be either removed in case of ipsilateral central nodes positivity or cleared despite of the pres-

ence of uninvolved central nodes, at least in more advanced diseases, and contralateral lymph nodes compartments should be inspected and removed only on the evidence of gross node metastases.

In our retrospective analysis, we worked up data from the above said 118 cases hypothesized and suggested which minimum number of lymph nodes better applies to achieve a quantitatively adequate cervical dissection. However, further studies with an increasingly larger number of patients are necessary to better strengthen and confirm this hypothesis as a future method of evaluation.

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Disclosure of conflict of interest

None.

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