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SURGICAL SYMPOSIUM CONTRIBUTION

Risk Factors for Central Neck Lymph Node Metastases in Micro- Versus Macro- Clinically Node Negative Papillary Thyroid Carcinoma

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Abstract

Background Tumor size has been advocated as possible risk factors for occult central lymph node metastases (CNM) in papillary thyroid carcinoma (PTC) patients. This prospective study evaluated factors that could identify patients at higher risk of occult CNM, especially comparing micro-PTC and macro-PTC.

Methods One hundred and eighty-six patients were recruited. All the patients had cN0 clinically unifocal PTC and underwent total thyroidectomy and bilateral prophylactic central neck dissection. Risk factors for occult CNM in micro- and macro-PTC patients were evaluated.

Results Eighty-two patients showed CNM. The rate of CNM did not differ among different sizes cut off (≤20 mm, ≤10 mm, ≤5 mm P = NS). Significantly more pN1a than pN0 patients had pT3 tumors (35/82 vs. 26/104) ($P < 0.05$), extracapsular invasion (35/82 vs. 22/104) ($P < 0.01$) and microscopic multifocal disease (50/82 vs. 47/104) ($P < 0.05$). Independent risk factors for CNM were extracapsular invasion and multifocality at multivariate analysis. Risk factors for CNM in 77 micro-PTC were extracapsular invasion (16/31 pN1 vs. 10/46 pN0, $P < 0.05$) and multifocality (21/31 pN1 vs. 16/46 pN0, $P < 0.01$). Among 109 macro-PTC, risk factors for CNM were angioinvasion (15/51 pN1 vs. 7/58 pN0, $P < 0.05$) and classic PTC at the final histology (PTC vs. tall cell variant vs. follicular variant PTC) ($P < 0.05$).

Conclusions Risk factors for CNM can differ between micro- and macro-PTC, but no preoperatively known clinical parameter is predictor of CNM in cN0 clinically unifocal PTC.

Introduction

Papillary thyroid carcinoma (PTC) frequently metastasizes to lymph nodes in the central neck compartment [1, 2]. In patients with clinically node-negative (cN0) PTC, the role of prophylactic central compartment neck dissection remains unclear and still matter of debate [3–6].

It is hard to define which patients with PTC would benefit from a prophylactic central compartment neck dissection because of the difficulty defining pre- (with ultrasonography and clinical examination) [7] and intra-operatively, by the surgeon's assessment, the central neck lymph node involvement [8, 9].

The demographic and clinical factors predictive of central lymph node metastases (CNM) in patients with cN0 PTC remain uncertain [10]. It is suggested that prophylactic central compartment neck dissection should be risk stratified [3]. In this regard, several authors [3, 11–13] and some guidelines [14, 15] suggest at least a personalized

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decision-making approach in "high-risk" patients basing on demographic and clinical characteristics (male gender, age more than 45 years or less than 15 years, tumor size >4 cm, aggressive histological variant, radiation history, known distant metastases, extrathyroidal disease). On the other hand, to date there is no high level evidence on this topic and the studies available [3, 11–13, 16–20] report discordant results, probably because of the heterogeneous patients' populations concerning operative and clinicopathologic features (prophylactic vs. therapeutic central neck dissection, clinical unifocal vs. clinical multifocal PTC, unilateral vs. bilateral central neck dissection) source of uncontrolled bias [3, 11–13, 16–20].

In the present study, we aimed to prospectively evaluate factors that could identify clinically unifocal and cN0 PTC patients at higher risk of occult CNM, especially comparing micro-PTC and macro-PTC.

Materials and methods

Patients

Among 732 patients who underwent surgery with a preoperative cytological proven PTC between March 2008 and July 2012, 186 consenting patients cN0 and with clinically unilateral PTC were prospectively recruited. Exclusion criteria were: clinically suspicious multifocal PTC, previous surgery of the neck, radiation history, clinically infiltrating tumors, evidence of clinical (evaluated by preoperative ultrasound and intraoperative inspection) central and/or lateral lymph node involvement, evidence of distant metastases.

Study design

Included patients underwent total thyroidectomy and prophylactic bilateral central neck dissection. Age, sex, thyroid weight, tumor size, pathological diagnosis, extracapsular invasion, angioinvasion, multifocal disease, concomitant autoimmune thyroiditis at pathological examination, number of removed and metastatic lymph nodes, TNM staging [21] were prospectively registered in a specifically designed database.

Study end point

The study end point was to identify risk factors for CNM in clinically unifocal cN0 PTC able to indicate patients at higher risk of occult nodal disease, with particular regard to lesion size (micro-PTC vs. macro-PTC).

Definitions

PTC were defined clinically unifocal and cN0 in the absence of any pre- (i.e., clinical and ultrasound examination) or intraoperative evidence of lymph node involvement or multifocal disease. Total thyroidectomy was defined as total bilateral extracapsular thyroid resection. Bilateral central neck dissection included prelaryngeal, pretracheal and both the right and left paratracheal nodal basins [22]. Micro-PTC was defined as PTC $\leq$10 mm in its maximum diameter. Macro-PTC was PTC $>$ 10 mm in its maximum diameter. Tumors were considered multifocal if two or more foci were found in one (unilateral) or both lobes (bilateral). In these cases, the dimension of the one foci was registered.

Pathological tumor staging was defined using the 2010 7th edition of the American Joint Committee on Cancer pTNM staging system [21].

Postoperative management

Postoperative serum calcium and phosphorus levels were measured in all the patients, and hypocalcemia was defined as a serum calcium level below 8.0 mg/dl. Laryngoscopy was performed preoperatively in all the patients and postoperatively in all patients who present objective or subjective dysphonia to check vocal cord motility.

Statistical analysis

Statistical analysis was performed using a commercially available software package (SPSS 15.0 for Windows®—SPSS Inc., Chicago, IL, USA). The *t* test was used for continuous variables, and the Chi-square test was used for categorical variables. Multiple linear regression analysis was used to assess the independence of the significant variables at univariate analysis.

Results

Demographic, clinical, operative and pathological data of the study population are reported in Table 1.

There were 38 males and 148 females with a mean age of 42.6 ± 14.5 years (range 16–85).

The mean nodule size as evaluated preoperatively by ultrasound was 16.3 ± 9.1 mm (range 5–50).

Postoperative complications included 93 transient hypoparathyroidism, 3 definitive hypoparathyroidism, 4 transient and 2 definitive recurrent laryngeal nerve palsies, and 1 lymphatic leak, which was conservatively treated. No other complications occurred.

Table 1 Demographic, clinical, operative and pathological characteristics of the patients

Patients	186
Age (±SD) (range) years	42.6 ± 14.5 (16–85)
<45 years/≥45 years	107 (57.5%)/79 (42.5%)
Male/female	38 (20.4%)/148 (79.6%)
Thyroid weight (± SD) (range) gr	21.3 ± 12.6 (5–97)
Tumor size (± SD) (range) mm	14.7 ± 9.2 (2–50)
≤5 mm/>5 mm	12 (6.5%)/174 (93.5%)
≤2 cm/>2 cm	152 (81.7%)/34 (18.3%)
Microcarcinoma	77 (41.4%)
pT stage	
T1/T2/T3	104 (55.9%)/21 (11.3%)/61 (32.8%)
Extracapsular invasion	57 (30.6%)
Microscopic unilateral multifocal	97 (52.1%)
Microscopic bilateral multifocal	31 (16.7%)
Thyroiditis	15 (8.1%)
Angioinvasion	27 (14.5%)
Histological subtypes	
Classic PTC	143 (76.9%)
Follicular variant	39 (21%)
Tall cell variant	4 (2.1%)
pN stage	
N0/N1	104 (55.9%)/82 (44.1%)
Removed lymph nodes (± SD) (range)	12.5 ± 5.7 (6–33)
Metastasized lymph nodes (± SD) (range)	1.1 ± 1.7 (0–6)

SD standard deviation; *PTC* papillary thyroid carcinoma

The mean pathologic lesion size was 14.7 ± 9.2 mm (range 2–50). The mean thyroid weight was 21.3 ± 12.6 grams (range 5–97).

The final histology revealed 104 (55.9%) pT1 (51 microcarcinomas, 61 multifocal), 21 (11.3%) pT2 (6 multifocal) and 61 (32.8%) pT3 (26 microcarcinomas, 30 multifocal).

Overall, the mean number of removed and metastatic nodes was 12.5 ± 5.7 (range 6–33) and 1.1 ± 1.7 (range 0–6), respectively. Overall, occult CNM were found in 82 patients (44.1%): 41 with pT1, 6 with pT2 and 35 with pT3 PTC. The mean number of metastatic nodes in pN1a patients was 2.5. ± 1.6 (range 1–6). No significant difference was observed between pN0 and pN1a patients concerning mean age [44.2 ± 14.5 (range 18–78) versus 40.6 ± 14.2 (range 16–85), respectively, P = NS], number of patients with age less than 45 years (56/104 vs. 51/82, respectively, P = NS), sex (male/female ratio 16/88 vs. 22/60, respectively, P = NS), thyroid weight [21.7 ± 13.5 (range 5–97) vs. 20.7 ± 11.2 (range 5–71), respectively, P = NS], microscopic bilateral multifocal disease (14/104 vs. 17/82, respectively, P = NS), mean number of removed nodes [12.4 ± 5.4 (range 6–33) vs. 12.5 ± 6.1 (range 6–33), respectively, P = NS], histological subtypes (classic PTC vs. follicular variant vs. tall cell variant: 73/27/4 vs. 70/12/0, respectively, P = NS), angioinvasion (12/104 vs. 15/82, respectively, P = NS) and thyroiditis (11/104 vs. 4/82, respectively, P = NS) (Table 2). No significant difference was observed between pN0 and pN1a patients concerning mean tumor size [15.0 ± 10.1 (range 2–50) vs. 14.2 ± 8.0 (range 4–45), respectively, P = NS] (Table 2). The rate of nodal metastases did not significantly differ among different sizes cutoff (≤5 mm: 8/104 pN0 vs. 4/82 pN1a; ≤10 mm: 46/104 pN0 vs. 31/82 pN1a; ≤20 mm: 83/104 pN0 vs. 69/82 pN1a, respectively, P = NS) (Table 2). Significantly more pN1a than pN0 patients had pT3 tumors (35/82 vs. 26/104) ($P < 0.05$), extracapsular invasion (35/82 vs. 22/104) ($P < 0.01$) and microscopic multifocal disease (50/82 vs. 47/104) ($P < 0.05$). Independent risk factors for CNM were extracapsular invasion and multifocality at multivariate analysis.

The mean number of removed and occult metastatic nodes was similar between macro- and micro-PTC pN1 patients (13.2 ± 5.9 and 2.7 ± 1.6 vs. 11.5 ± 6.4 and 2.3 ± 1.7, respectively, P = NS).

Table 2 Comparative analysis between pN0 and pN1a patients

	pN0	pN1a	*P* value
Patients	104	82	
Age (±SD) (range) years	42.2 ± 14.5 (18–78)	40.6 ± 14.2 (16–85)	NS*
<45 years/≥ 45 years	56 (53.8%)/48 (46.2%)	51 (62.2%)/31 (37.8%)	NS*
Male/female	16 (15.4%)/88 (84.6%)	22 (26.8%)/60 (73.2%)	NS*
Thyroid weight (±SD) (range) gr	21.7 ± 13.5 (5–97)	20.7 ± 11.2 (5–71)	NS*
Tumor size (±SD) (range) mm	15.0 ± 10.1 (2–50)	14.2 ± 8.0 (4–45)	NS*
≤5 mm/>5 mm	8 (7.7%)/96 (92.3%)	4 (4.9%)/78 (95.1%)	NS*
≤2 cm/>2 cm	83 (79.8%)/21 (20.2%)	69 (84.1%)/13 (15.8%)	NS*
Microcarcinoma	46 (44.2%)	31 (37.8%)	NS*
pT stage			
T1	63 (60.6%)	41 (50%)	NS*
T2	15 (14.4%)	6 (7.3%)	NS*
T3	26 (25%)	35 (42.7%)	< 0.05
Extracapsular invasion	22 (21.1%)	35 (42.7%)	< 0.01
Microscopic unilateral multifocal	47 (45.1%)	50 (61%)	< 0.05
Microscopic bilateral multifocal	14 (13.5%)	17 (20.7%)	NS*
Thyroiditis	11 (10.6%)	4 (4.9%)	NS*
Angioinvasion	12 (11.5%)	15 (18.3%)	NS*
Histological subtypes			
Classic PTC	73 (70.2%)	70 (85.4%)	NS*
Follicular variant	27 (26%)	12 (14.6)	NS*
Tall cell variant	4 (3.8%)	0 (0%)	NS*
Removed nodes (± SD) (range)	12.4 ± 5.4 (6–33)	12.5 ± 6.1 (6–33)	NS*

*NS** not significant; *SD* standard deviation; *PTC* papillary thyroid carcinoma

Among 109 macro-PTC, risk factors for CNM were angioinvasion (15/51 pN1 vs. 7/58 pN0, $P < 0.05$) and classic PTC at the final histology (PTC vs. tall cell variant vs. follicular variant) ($P < 0.05$) (Table 3).

Risk factors for CNM in 77 micro-PTC were extracapsular invasion (16/31 pN1 vs. 10/46 pN0, $P < 0.05$) and multifocality (21/31 pN1 vs. 16/46 pN0, $P < 0.01$) (Table 4).

Discussion

Occult nodal PTC metastases may be found in 31–62% of the patients who undergo elective central neck dissection [3, 20]. Indeed, one argument that favors prophylactic central neck dissection is the difficulty predicting the central neck nodal status pre- (ultrasonography and clinical examination) [7] and intraoperatively [8, 9].

As suggested in several studies [23, 24], tumor size alone is not a reliable indicator of PTC aggressiveness, since local and nodal recurrences, distant metastases and cases of disease-related death have been reported in patients with micro-PTC [23, 24].

Macroscopic lymph node involvement may negatively affect recurrence and survival in patients with PTC [6, 25, 26]. On the other hand, some studies suggest that microscopically positive nodes do not appear to progress to recurrence [27, 28]. However, occult nodal disease is not always a "microscopic disease" and this aspect should be better defined in studies regarding this topic [25, 29].

The reliability of demographic and clinical factors in predicting CNM in patients with cN0 PTC remains uncertain [10].

We designed this prospective study to identify PTC patients at higher risk of CNM basing on clinical findings. In the present patients series, we did not find any preoperative clinical parameter able to reliably predict the nodal disease in clinically unifocal cN0 PTC. Independent risk factor for CNM was extracapsular invasion and multifocality.

In the subset analyses, considering separately macro- and micro-PTC, the risk factors for CNM were different. In micro-PTC, extracapsular invasion and microscopic

Table 3 Comparative analysis between pN0 and pN1a macro-PTC patients

	pN0	pN1a	*P* value
Patients	58	51	
Age (± SD) (range) years	45.2 ± 15.6 (18–78)	40.2 ± 15.4 (16–85)	NS*
< 45 years/≥ 45 years	30/28	32/19	NS*
Male/female	9/49	14/37	NS*
Tumor size (± SD) (range) mm	20.9 ± 10.1 (11–50)	18.1 ± 7.9 (11–45)	NS*
≤2 cm/>2 cm	37/21	38/13	NS*
pT stage			
T1/T2/T3	27/15/16	26/6/19	NS*
Extracapsular invasion	12	19	NS*
Microscopic unilateral multifocal	31	29	NS*
Microscopic bilateral multifocal	10	12	NS*
Thyroiditis	4	2	NS*
Angioinvasion	7	15	<0.05
Histological subtypes			
Classic PTC	37	44	<0.05
Follicular variant	17	5	<0.05
Tall cell variant	4	2	NS*
Removed nodes (± SD) (range)	12.4 ± 5.7 (6–32)	13.2 ± 5.9 (6–26)	NS*

*NS** not significant; *SD* standard deviation; *PTC* papillary thyroid carcinoma

Table 4 Comparative analysis between pN0 and pN1a micro-PTC patients

	pN0	pN1a	*P* value
Patients	46	31	
Age (± SD) (range) years	42.9 ± 13.0 (19–71)	41.2 ± 12.4 (20–72)	NS*
< 45 years/≥ 45 years	26/20	19/12	NS*
Male/female	7/39	8/23	NS*
Tumor size (± SD) (range) mm	7.6 ± 2.1 (2–10)	7.9 ± 1.9 (4–10)	NS*
≤5 mm/>5 mm	8/38	4/27	NS*
pT stage			
T1/T2/T3	36/0/10	15/0/16	<0.05
Extracapsular invasion	10	16	<0.05
Microscopic unilateral multifocal	16	21	<0.01
Microscopic bilateral multifocal	4	5	NS*
Thyroiditis	7	2	NS*
Angioinvasion	5	0	NS*
Histological subtypes			
Classic PTC[b]	36	24	NS*
Follicular variant	10	7	NS*
Tall cell variant	0	0	NS*
Removed nodes (± SD) (range)	12.4 ± 5.2 (6–33)	11.5 ± 6.4 (6–33)	NS*

*NS** not significant; *SD* standard deviation; *PTC* papillary thyroid carcinoma

multifocal disease have been confirmed as main risk factors for CNM. Conversely, excluding micro-PTC from the statistical analysis, we did not find any significant difference between pN0 and pN1 macro-PTC patients regarding microscopic multifocal disease and extracapsular invasion. Risk factors for occult CNM in macro-PTC were microscopic angioinvasion and histological subtypes. In particular, macro-PTC patients with classic PTC have a higher

risk of CNM when compared with patients with follicular variant PTC. This is in accordance with several studies showing a lower incidence of CNM in follicular variant PTC when compared with classic PTC [13, 30]. However, to date it is challenging to preoperatively diagnose a follicular variant PTC, even relying on recent molecular and genetic analysis [13, 30–33]. As a consequence, in the clinical practice, in the subset of patients with preoperatively proven PTC, it is very rare to correctly modulate the indication or the extension of central neck dissection basing on the expected histological subtypes.

The major limitation of the present study is the small number of patients included. Indeed, the selection criteria we used were very strict, excluding patients with known multifocal and bilateral PTC, infiltrating tumors, evidence of lateral lymph node involvement and/or distant metastases, patients with previous radiation and/or neck surgery history, in order to avoid the common bias, due to heterogeneous patients' series. Among 732 patients admitted at our institution with a preoperative cytological diagnosis of PTC in the study period, we included only 186 patients (25.4%). Further prospective studies with larger series of patients and without preventable clinical bias are needed to validate our results.

Other limitation of the study is the lack of follow-up data. Nonetheless, in patients with PTC the recurrence may occur even many years after the initial diagnosis and surgical treatments, and for this reason it is hard to define the sufficient follow-up period. Moreover, the study end point was to identify risk factors for CNM in clinical unifocal cN0 PTC patients, especially comparing micro-PTC and macro-PTC.

The lack of data assessing the genetic cancer profiles in this subset of patients could be considered also a limitation. On the other hand, the role of BRAF V600E mutation, the most investigated genetic parameter, as prognostic factor of lymph node metastasis at diagnosis and of the long-term outcome in PTC patients remains to be clarified [28, 31–33].

Further studies are needed to obtain more accurate preoperative biomolecular parameters in order to modulate surgical aggressiveness, therapeutic strategies and follow-up in patients with PTC [33].

In spite of the limitations of the present study, we think that the value of the study resides in the prospective recruitment and analysis of patients treated at a single center during a relatively short period with the same surgical strategy.

The risks of complications after prophylactic bilateral central neck dissection are the main argument against the elective removal of central neck nodes. For this reason, a limited (ipsilateral) central compartment neck dissection, including elective removal of prelaryngeal, pretracheal and the paratracheal nodes on the side of the tumor, was proposed in patients with clinical unilateral PTC [19, 20, 25].

In comparative studies, ipsilateral central neck dissection showed similar short-term oncologic outcome and lower risk of postoperative hypocalcaemia with respect to bilateral central compartment neck dissection [19, 20]. Since ipsilateral central neck dissection implies the theoretical risk of missing contralateral node metastases [19], it has been suggested that frozen section examination on the ipsilateral central neck nodes can be used to intraoperatively assess the ipsilateral nodal status and to modulate the extension of the central compartment neck dissection [20, 25].

Recently, we prospectively compared the results of an intraoperative decision-making approach based on ipsilateral central compartment neck dissection and frozen section examination with those of standard prophylactic bilateral central neck dissection in patients with cN0 clinically unifocal PTC. We found that in clinically unifocal cN0 PTC routine ipsilateral central compartment neck dissection and frozen section examination of the ipsilateral nodes could be a valid alternative to prophylactic bilateral central neck dissection since it allows accurate staging and it may reduce morbidity [29].

Further prospective studies with larger series of patients and long follow-up data are needed to validate this intraoperative decision-making approach, but, because of the impossibility to define preoperatively clinical parameter as reliable predictor of nodal disease in clinically unifocal cN0 PTC, in the absence of suspect extracapsular invasion, we think reasonable to perform, in this subset of patients, ipsilateral central compartment neck and frozen section examination to intraoperatively modulate the extension of the central neck clearance.

In conclusion, in our experience, risk factors for CNM differ between micro- and macro-PTC, but no preoperatively clinical parameter is predictor of CNM in cN0 clinically unifocal PTC.

Authors' contribution MR, CDC, RB contributed to study conception and design. LS, CDC, SET took part in acquisition of the data. LS, CDC, CPL, SET involved in analysis and interpretation of data. LS, MR, CDC, CPL contributed to drafting of manuscript. MR, CPL, RB participated in critical revision of manuscript.

Compliance with ethical standards

Conflict of interest No conflict of interest is declared for this paper

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