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Risk factors for central neck lymph node metastases in follicular variant vs. classic papillary thyroid carcinoma

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Abstract

Purpose Histological variants of papillary thyroid carcinoma (PTC) have been advocated as possible risk factors for central neck nodal metastases (CNM). A lower incidence of CNM in follicular variant of papillary thyroid carcinoma (fvPTC) when compared with classic PTC (cPTC) has been observed. We aimed to compare risk factors for CNM in patients with fvPTC and cPTC.

Methods The medical records of 1737 patients with a diagnosis of cPTC or fvPTC were reviewed. Demographic, clinical and pathological findings were prospectively registered. Risk factors for CNM were evaluated by univariate and multivariate analysis in cPTC vs. fvPTC patients.

Results Six hundred and fifty-two patients (37.5%) had fvPTC. The diagnosis was incidental in 69.5% of the fvPTC and in 29.4% of the cPTC patients. Overall, 26.3% cPTC and 8.3% fvPTC patients showed CNM ($p < 0.001$). In both cPTC and fvPTC patients at univariate analysis age <45 years, nonincidental diagnosis, tumor size >5 mm, multifocality, angioinvasion and extracapsular invasion were risk factors for CNM. At multivariate analysis independent risk factors for CNM in both cPTC and fvPTC patients were age <45 years ($p < 0.01$), nonincidental diagnosis ($p < 0.001$), multifocality ($p < 0.001$) and extracapsular invasion ($p < 0.001$).

Conclusions No differences were observed between cPTC and fvPTC with regard to risk factors of CNM. fvPTC seems associated with a lower incidence of CNM, presumably because of the higher rate of incidental diagnosis. With the exception of age, in patients with a preoperative diagnosis of PTC, no preoperatively available clinical parameter is a reliable predictor of CNM.

Keywords Lymph node metastases · Papillary thyroid carcinoma · Follicular variant of papillary thyroid carcinoma

Introduction

Papillary thyroid carcinoma (PTC) frequently metastasizes to lymph nodes in the central neck compartment. Central neck nodal metastases (CNM) may negatively affect recurrence rate and, probably, survival [1–4]. A therapeutic compartment oriented central neck dissection (level VI dissection) is considered the standard treatment option when central neck involvement is found at preoperative work up or intraoperative inspection [5, 6]. Some concerns still exist regarding the role of prophylactic central compartment neck dissection in patients with clinically node negative (cN0) PTC [7–17]. Demographic, histological and clinical features have been advocated as possible clinical risk factors for CNM in PTC [18, 19] suggesting a more or less aggressive surgical approach basing on these parameters [20–24]. Follicular variant of PTC (fvPTC) is the second most common subtype of PTC [25–27] accounting for 9–41% of pathological proven PTC [28–31]. Several studies showed a lower incidence of cervical lymph node metastases and aggressive behavior in fvPTC when compared with classic PTC (cPTC) [22, 25, 28, 32–36].

Despite it may be challenging to preoperatively diagnose a fvPTC, even basing on more recent molecular and genetic analysis [37–43], such findings could imply a less

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aggressive surgical approach when dealing with pre- or intraoperatively proven fvPTC.

However no conclusive results are available in the literature, mainly because the pathological diagnosis of fvPTC changed over time and is not univocal in the published literature [36–38]. Moreover, published series usually included patients recruited over large time period frames, implying different diagnostic and management protocols in the same Institution.

For this reason we designed the present study, aiming to compare risk factors for central neck nodal involvement in patients with fvPTC and cPTC in a single Institution during a relatively short study period.

Materials and methods

Patients population

From January 2008 to September 2014, a total of 2211 patients underwent surgery for PTC at our Institution. Among them, the medical records of 1737 consecutive patients who underwent total thyroidectomy (TT) (with or without concomitant central and/or lateral neck lymph node dissection) with a pathologic diagnosis of cPTC or fvPTC were reviewed. Exclusion criteria were: age less than 18 years, radiation history, previous neck surgery, preoperative evidence of distant metastases and other PTC histological variants.

Study design

The following parameters were prospectively registered in a specifically designed database (Microsoft Excel®, Microsoft Corporation, Redmond, WA, USA): age, sex, type of diagnosis (incidental or nonincidental), extent of surgical procedure (TT with/without ipsilateral or bilateral central neck node dissection with/without ipsilateral or bilateral lateral neck dissection), tumor size, pathological diagnosis, extracapsular invasion, angioinvasion, multifocal disease, concomitant autoimmune thyroiditis at pathological examination, TNM staging [44].

Study end point

To compare risk factors for central neck nodal involvement in patients with fvPTC and cPTC.

Definitions

According to World Health Organization Classification of Tumors, cPTC was defined as tumor characterized by "complex papillae with thin fibrovascular cores that sometimes become edematous" and fvPTC, as composed "entirely or almost entirely of follicles lined by cells exhibiting nuclear features of papillary thyroid carcinoma" [38].

PTC was defined as incidental in the case of incidental diagnosis at final histology for patients operated on for disease not related to thyroid malignancy. PTC was considered nonincidental in the case diagnosis was preoperatively proven or suspected.

PTC was considered multifocal if two or more foci were found in one or both lobes. In case of uni- or bilateral multiple tumor foci, the dimension of the largest one was used for statistical analysis.

TT was defined as total bilateral extracapsular thyroid removal.

The nodal status was evaluated preoperatively and intraoperatively in all the patients with nonincidental diagnosis. Compartment oriented neck dissection (bilateral central neck dissection with/without lateral neck dissection) was accomplished in all the patients with preoperative or intraoperative proven central and/or lateral neck node metastases with a therapeutic intent. In cN0 PTC patients (absence of any pre- or intra-operative evidence of lymph node disease) no lateral neck dissection was performed and the decision-making regarding whether to perform any forms of prophylactic central neck node dissection was based on surgeons' and patients' preferences (no central dissection vs. ipsilateral central neck dissection with or without frozen section examination vs bilateral central neck dissection) [14–16].

Bilateral central compartment neck dissection included the removal of pre-laryngeal, pretracheal and both the right and left paratracheal nodal basins [45]. Ipsilateral central compartment neck dissection included pre-laryngeal, pretracheal and the paratracheal nodal basins on the side of the tumor [45]. Lateral neck dissection was defined as compartment oriented functional lateral neck dissection, including levels II to V [46].

All the surgical procedures were performed by an experienced endocrine surgeon or by a resident operating under supervision. Pathological tumor staging was defined in accordance with the 2010 7th edition of the American Joint Committee on Cancer pTNM staging system [44]. Patients in whom no lymph node dissection was performed or the number of removed lymph nodes was less than six were classified as having undetermined nodal status (pNx). Nx patients showing no macroscopic evidence of node metastases were considered as node negative for statistical analysis.

Statistical analysis

Statistical analysis was performed using a commercially available software package (SPSS 15.0 for

Windows®–SPSS Inc., Chicago, IL, USA). The χ^2 test was used for categorical variables, and the *t* test was used for continuous variables. Significant variables at univariate analysis were further assessed for evaluating their independence with multiple linear regression analysis. A *P* value less than 0.05 was considered significant.

Results

There were 390 males (22.5%) and 1347 (77.5%) females with a mean age of 46.9 ± 13.5 years (range:18–85). As mentioned above all the patients underwent TT. Overall, a bilateral central neck lymph node dissection was accomplished in 515 patients (29.6%); 138 patients underwent ipsilateral central neck dissection (7.9%). One hundred and twenty-three patients (7.1%) required a lateral neck lymph node dissection, bilateral in 14 cases.

Regarding the "pN stage", 1181 patients (68%) were classified as Nx, 201 N0 (11.6%) and 355 N1 (20.4%). Sixteen patients with pre- or intraoperative proven lateral neck node metastases (13 and 3 cases, respectively), who underwent TT plus bilateral central compartment neck dissection plus lateral neck dissection, showed lateral neck lymph node metastases without CNM (skip metastases). In this subgroup of patients, nodal metastases were found at level II, III, IV, and V in 6/16 (37.5%), 13/16 (81.2%), 9/16 (56.2%) and 2/16 patients (12.5%), respectively.

Demographic, clinical, operative, and pathological characteristics of all the included patients are reported in Table 1.

Six hundred and fifty-two patients (37.5%) had fvPTC and the remaining 1085 (62.5%) had a cPTC.

No differences were observed between cPTC and fvPTC patients regarding sex, concomitant autoimmune thyroiditis, and/or angioinvasion at pathological examination ($p = \text{NS}$) (Table 1). cPTC patients were younger and had smaller tumors when compared with fvPTC patiens (mean age 45.2 vs. 47.4 years, respectively, $p < 0.01$; mean tumor size 10.5 vs. 12.2 mm, respectively, $p < 0.001$) (Table 1). Comparing cPTC cases and fvPTC, multifocality and extracapsular invasion were more often observed in cPTC patients (46.1% vs. 30.4%, respectively, $p < 0.001$; 25.2% vs. 9.0%, $p < 0.001$, respectively) (Table 1).

The diagnosis of thyroid carcinoma was incidental in 453 (69.5%) of the fvPTC. In these cases pre-operative diagnosis was: undetermined follicular lesion in multinodular goiter in 248 cases, multinodular goiter in 170 cases, toxic multinodular goiter in 24 cases, Basedow's disease in 11 cases. The diagnosis of thyroid carcinoma was incidental in 319 (29.4%) of the cPTC patients. In these cases pre-operative diagnosis was: undetermined follicular lesion in multinodular goiter in 177 cases, multinodular goiter in 111 cases, toxic multinodular goiter in 19 cases, Basedow's disease in 12 cases.

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

	All	cPTC[a]	fvPTC[b]	*P* value
Patients	1737	1085	652	
Age (±SD[c]) (range) years	46.0 ± 13.5 (18–85)	45.2 ± 13.4 (18–85)	47.4 ± 13.6 (18–80)	<0.01
<45 years/ ≥ 45 years	856/881	577/508	279/373	<0.001
Male/Female	390/1347	240/845	150/502	NS*
Incidental/ Nonincidental diagnosis	772/965	319/766	453/199	<0.001
Extent of central neck node dissection				
Not performed	1084	553	531	<0.001
Ipsilateral central neck dissection	138	111	94	<0.05
Bilateral central neck dissection	515	421	27	<0.001
Extent of lateral neck node dissection				
Not performed	1614	980	634	<0.001
Unilateral neck dissection	109	93	16	<0.001
Bilateral neck dissection	14	12	2	NS*
Tumor size (± SD[c]) (range) mm	11.1 ± 9.5 (1–110)	10.5 ± 7.6 (1–50)	12.2 ± 12.0 (1–110)	<0.001
Microcarcinoma	1069	692	377	<0.05
≤5 mm/>5 mm	479/1258	264/821	215/437	<0.001
pT stage				
T1/T2/T3/T4	1236/147/ 349/5	747/59/ 275/4	489/88/ 74/1	<0.001
Extracapsular invasion	332	273	59	<0.001
Multifocality	698	500	198	<0.001
Thyroiditis	122	82	40	NS*
Angioinvasion	91	61	30	NS*
pN stage				
Nx/N0/N1	1181/201/ 355	632/155/ 298	549/46/57	0.001

[a]*cPTC,* classic papillary thyroid carcinoma

[b]*fvPTC,* follicular variant papillary thyroid carcinoma

[c]*SD,* standard deviation

**NS*, not significant

Overall, 339 patients (19.5%) showed CNM: 285/1085 cPTC (26.3%) and 54/652 fvPTC (8.3%) patients ($p < 0.001$).

In cPTC patients at univariate analysis male sex ($p < 0.001$), age <45 years ($p < 0.001$), nonincidental diagnosis ($p < 0.001$), tumor size >5 mm ($p < 0.001$), multifocality ($p < 0.001$), angioinvasion ($p < 0.001$), extracapsular

Table 2 Risk factors for CNM in cPTC patients: univariate analysis

	No CNM[a]	CNM[a]	*P* value
Patients	800	285	
Age (±SD[b]) (range) years	47.4 ± 13.2 (18–82)	39.0 ± 12.3 (18–85)	<0.001
<45 years/ ≥45 years	371 (46.4%)/429 (53.6%)	206 (72.3%)/79 (27.7%)	<0.001
Male/Female	155 (19.4%)/645 (80.6%)	85 (29.8%)/200 (70.2%)	<0.001
Incidental/Nonincidental	308 (38.5%)/492 (61.5%)	11 (3.9%)/274 (96.1%)	<0.001
Tumor size (± SD[b]) (range) mm	9.4 ± 7.2 (1–50)	13.6 ± 8.0 (1–50)	<0.001
Microcarcinoma	575 (71.9%)	117 (41.1%)	<0.001
≤5 mm/ >5 mm	230 (28.8%)/570 (71.2%)	34 (11.9%)/251 (88.1%)	<0.001
pT stage			
T1/T2/T3/T4	606(75.8%)/40(5%)/153 (19.1%)/1(0.1%)	141(49.5%)/19(6.7%)/122 (42.8%)/3(1%)	<0.001
Extracapsular invasion	150 (18.7%)	123 (43.2%)	<0.001
Multifocality	313 (39.1%)	187 (65.6%)	<0.001
Thyroiditis	72 (9%)	10 (3.5%)	<0.01
Angioinvasion	22 (2.7%)	39 (13.7%)	<0.001

[a]*CNM*, central neck nodal metastases

[b]*SD*, standard deviation

Table 3 Risk factors for CNM in fvPTC patients: univariate analysis

	No CNM[a]	CNM[a]	*P* value
Patients	598	54	
Age (± SD[b]) (range) years	47.9 ± 13.5 (18–80)	42.1 ± 14.4 (20–77)	<0.01
<45 years/ ≥45 years	244 (40.8%)/354 (59.2%)	35 (64.8%)/19 (35.2%)	<0.01
Male/Female	136 (22.7%)/462 (77.3%)	14 (25.9%)/40 (74.1%)	NS*
Incidental/Nonincidental	443 (74.1%)/155 (25.9%)	10 (18.5%)/44 (81.5%)	<0.001
Tumor size (±SD[b]) (range) mm	12.0 ± 12.1 (1–110)	14.1 ± 9.9 (2–60)	NS*
Microcarcinoma	353 (59.0%)	24 (44.4%)	NS*
≤5 mm/ >5 mm	209 (35.0%)/389 (65.0%)	6 (11.1%)/48 (88.9%)	<0.001
pT stage			
T1/T2/T3/T4	460(76.9%)/86(14.4%)/51 (8.5%)/1(0.2%)	29(53.7%)/2(3.7%)/23 (42.6%)/0(0%)	<0.001
Extracapsular invasion	37 (6.2%)	22 (40.7%)	<0.001
Multifocality	159 (26.6%)	39 (72.2%)	<0.001
Thyroiditis	39 (6.5%)	1 (1.8%)	NS*
Angioinvasion	22 (2.7%)	8 (14.8%)	<0.001

[a]*CNM*, central neck nodal metastases

[b]*SD*, standard deviation

**NS*, not significant

invasion ($p < 0.001$) and absence of concomitant autoimmune thyroiditis at pathological examination ($p < 0.01$) were risk factors for central neck involvement (Table 2).

In fvPTC patients at univariate analysis age <45 years ($p < 0.01$), nonincidental diagnosis ($p < 0.001$), tumor size >5 mm ($p < 0.001$), multifocality ($p < 0.001$), angioinvasion ($p < 0.001$), and extracapsular invasion ($p < 0.001$) were risk factors for CNM (Table 3).

At multivariate analysis independent risk factors for CNM in cPTC patients were age <45 years ($p < 0.01$), nonincidental diagnosis ($p < 0.001$), multifocality ($p < 0.001$) and extracapsular invasion ($p < 0.001$). Similarly, at multivariate analysis independent risk factors for central neck nodal involvement in fvPTC patients were age <45 years ($p < 0.01$), nonincidental diagnosis ($p < 0.001$), multifocality ($p < 0.001$) and extracapsular invasion ($p < 0.001$).

When excluding from the analysis patients with incidental diagnosis and those with unknown nodal status (pNx patients) and considering only the 653 patients with non-incidental diagnosis (532 cPTC and 121fvPTC) who underwent ipsilateral or bilateral central neck dissection with therapeutic or prophylactic intent, no significant difference was found concerning the rate of CNM between cPTC and fvPTC (285/532 vs. 54/121, $p = \text{NS}$). In this subgroup of patients, risk factors for CNM in cPTC patients were male sex ($p < 0.001$), age <45 years ($p < 0.001$), multifocality ($p < 0.001$), angioinvasion ($p < 0.001$), extracapsular invasion ($p < 0.001$) and absence of concomitant autoimmune thyroiditis at pathological examination ($p < 0.01$), while in fvPTC were multifocality ($p < 0.001$) and extracapsular invasion ($p < 0.001$). At multivariate analysis independent risk factors for CNM in cPTC patients were male sex ($p < 0.001$), age <45 years ($p < 0.001$), multifocality ($p < 0.001$), angioinvasion ($p < 0.01$) and extracapsular invasion ($p < 0.001$) and in fvPTC patients were multifocality ($p < 0.001$) and extracapsular invasion ($p < 0.001$).

Discussion

CNM are common in patients with PTC and may negatively affect recurrence rate and, probably, survival [1–4].

Some concerns still exist regarding the role of central compartment neck dissection in PTC patients, especially those with clinically node negative (cN0) PTC [5–17]. The demographic and clinical factors predictive of central lymph node metastases in PTC patients remain uncertain [18]. It has been suggested that central compartment neck dissection should be risk-stratified [3] basing on demographic, histopathological and clinical characteristics (age, sex, tumor size, histological variant), but several studies showed discordant results probably because of the heterogeneous patients' populations [18–24].

In particular, studies comparing histological variants of PTC showed a lower incidence of cervical lymph node metastases and less aggressive behavior in fvPTC when compared with cPTC [22, 25, 28, 32–36].

Obviously, a decreased rate of CNM in patients with fvPTC could imply a less aggressive management protocol in this subgroup of PTC patients when compared with cPTC.

However, it is worthy to underline that the published studies have the main limitations of including heterogeneous patients population, mainly due to the long study period, implying different management protocols and tumor classification [22, 25, 28, 32–36].

For this reason, we designed the present retrospective study to compare risk factors for central neck node involvement in patients with fvPTC and cPTC treated at a single Institution over a relatively short study period and using an homogeneous surgical approach.

As expected we observed a lower incidence of central neck nodal involvement in fvPTC patients (8.3%) when compared with cPTC patients (26.3%) ($p < 0.001$). However this finding was presumably due to the higher rate of incidental diagnosis in the fvPTC group.

Indeed, fvPTC is the second most common subtype of PTC [28–33] accounting for 9–41% of pathological proven PTC [28–31], but its pre- and intraoperative diagnosis may be challenging due to the lack of unequivocal cytological characteristics of malignancy and the low accuracy of frozen section examination [39, 40]. In our series, fvPTC represented 37.5% of the PTC cases, but about two thirds of the incidentally diagnosed PTC. Since nonincidental diagnosis was found to be independent risk factor for CNM in both fvPTC and cPTC, the higher rate of incidentally diagnosed tumors could explain the lower rate of CNM in the fvPTC group. Of note, when excluding from the analysis patients with incidental diagnosis of PTC the rate of CNM did not differ between the two groups. In our opinion, this findings is of utmost importance. Indeed, if the role of other independent risk factors for both fvPTC and cPTC we found (i.e., age < 45 years, multifocality and extracapsular invasion) are well established in the literature, the type of presentation (incidental vs. nonincidental) is less analyzed in the published studies.

It is clear that incidental diagnosis implies less aggressive tumours which at the time of the operation have not determined clinical manifestation yet. However, our data suggest that there is no difference between fvPTC and cPTC in terms of CNM rate when a preoperative diagnosis of PTC is established.

Some studies have tried to further classify fvPTC into completely encapsulated, well-circumscribed and infiltrative subtypes demonstrating variable clinico-pathologic aggressiveness [36, 41]. However, these features are not available preoperatively and are not useful for planning the surgical procedure [36, 41]. From a theoretical point of view, molecular markers, such as BRAF mutation evaluation in the cytological specimens, could help in the pre-operative assessment. Indeed, it has been proposed that BRAF negative tumors could be associated with a less aggressive, encapsulated variant [33]. However, conflicting results have been reported in the literature [33, 42, 43].

Basing on our results, it could be speculated that, even if the diagnosis of fvPTC is preoperatively established, based on cytological and molecular markers [25, 33, 34, 39], the surgical approach to the central neck should not differ from that adopted for cPTC patients.

It is clear, that one of the main limitation of the present study is the lack of molecular and genetic analysis that

could probably give additional information regarding the aggressiveness of the tumors, independently from their histological characteristics. This reflects the retrospective nature of the study.

In spite of these limitations, we think that the value of the present study resides in the evaluation of a relatively large series of patients consecutively treated at a single Institution during a relatively short period of time with the same operative approach and using the same pathological classification.

In conclusion we observed no differences between cPTC and fvPTC with regard to risk factors of CNM. fvPTC seems associated with a lower incidence of CNM, presumably because of the higher rate of incidental diagnosis. Our data suggest that with the exception of age, in patients with a pre-operative diagnosis of PTC, no preoperatively available clinical parameter is a reliable predictor of CNM.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study were in accordance with ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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