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ORIGINAL ARTICLE

Can intraoperative frozen section influence the extension of central neck dissection in cN0 papillary thyroid carcinoma?

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Abstract
Purpose Ipsilateral central compartment node dissection has been proposed to reduce the morbidity of prophylactic bilateral central compartment node dissection in papillary thyroid carcinoma (PTC), but it carries the risk of contralateral metastases being overlooked in approximately 25 % of patients. We aimed to verify if frozen section examination (FSE) can identify patients who could benefit from bilateral central compartment node dissection.
Methods All the consenting patients with clinically unifocal PTC, without any preoperative evidence of lymph node involvement, observed between September 2010 and September 2011 underwent total thyroidectomy plus bilateral central compartment node dissection. Ipsilateral central compartment nodes were sent for FSE.
Results Forty-eight patients were included. Mean number of removed nodes was 13.2±6.8. Final histology showed lymph node metastases in 21 patients: ipsilateral in 15, bilateral in 6. FSE accurately predicted lymph node status in 43 patients (27 node negative, 16 node positive). Five node metastases were not detected at FSE: three were micrometastases (≤2 mm). Sensitivity, specificity and overall accuracy of FSE in definition of N status status were 80.7, 100, and 90 %, respectively.
Conclusions FSE is accurate in predicting node metastases in clinically unifocal node negative PTC and can be useful in determining the extension of central compartment node dissection. False-negative results are reported mainly in case of micrometastases, which usually have limited clinical implications.

Keywords Papillary thyroid carcinoma · Elective central neck dissection · Prophylactic central neck dissection · Frozen section examination

Introduction

Central neck nodal metastases are common in papillary thyroid carcinoma (PTC) [1]. Nodal metastases are associated with an increase in recurrence rate and may impact negatively on survival [2, 3]. As a consequence, when central nodal disease is detected at preoperative work up or during the intraoperative inspection, therapeutic compartment-oriented central neck dissection (level VI dissection) is considered the standard treatment option [4]. On the other hand, in patients with clinically node negative (cN0) PTC the role of prophylactic central neck dissection (PCND) remains unclear and a matter of debate [5–7].

In spite of a recent trend towards a more aggressive surgical treatment, some experts consider that PCND should be avoided because of the little clinical significance of microscopic lymph

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node involvement (occurring in 31–62 % of the patients undergoing elective central neck dissection) and the high risk of postoperative complications [5–9].

Recently published systematic reviews and meta-analyses did not reach an unequivocal conclusion concerning the management of cN0 PTC patients [1, 2, 10]. Indeed, also the last published revision of the American Thyroid Association (ATA) management guidelines continues to reflect the controversy regarding this point [11].

As the risks of complications following PCND are the main consideration against the elective removal of central neck nodes, in recent years several authors have introduced a more limited (ipsilateral) central neck dissection, including the elective removal of pre-, para-tracheal, and recurrential nodes on the affected side, as an alternative treatment for patients with unilateral PTC [12–17].

Comparative studies have suggested that ipsilateral PCND may be an alternative treatment, and even preferable, option to bilateral PCND for cN0 PTC, because of the similar short-term oncologic outcome and the lower risk of postoperative complications, namely transient hypocalcemia [12–18]. On the other hand, ipsilateral central neck dissection implies the risk overlooking contralateral metastases. Recently published studies demonstrated that bilateral central node metastases occur in 20–50 % of the cases [13, 14, 18]. Despite the risk of bilateral metastases being high for larger tumors with ipsilateral central neck metastases [13], at present it is hard to define which patients would develop clinically significant bilateral central node metastases and would benefit from a bilateral PCND. It has been suggested that frozen section examination on the ipsilateral central neck nodes can be employed to assess the risk of contralateral central neck metastases and to subsequently modulate the extension of the PCND [15, 18].

In this study, we aimed to verify if frozen section examination (FSE) is able to identify patients with clinically unifocal and cN0 PTC who could benefit from bilateral central neck dissection.

Material and methods

Study end points The primary end point of the study was to determine the accuracy of FSE in detecting occult ipsilateral central neck nodal disease in patients with clinically unifocal and cN0 PTC. The secondary aim of the study was to determine the rate of bilateral occult nodal disease in patients with clinically unifocal and cN0 PTC. The study protocol was preliminarily submitted and approved by the Institutional Ethical Committee.

Patients population Among 195 patients who underwent surgery with a diagnosis of PTC between September 2010 and September 2011, 48 consenting patients with clinically unilateral and cN0 PTC were included in the present study. Exclusion criteria were: clinically bilateral and multifocal PTC, previous neck surgery, macroscopically infiltrating tumors, evidence of lymph node involvement, and/or distant metastases.

Study design Included patients underwent total thyroidectomy plus prophylactic bilateral central neck dissection. After terminating the surgical procedure, ipsilateral and contralateral nodes were separated. FSE was performed on the ipsilateral central neck nodes in all the cases and includes all ipsilateral nodes. The results of the FSE did not influence the extension of the surgical procedure. The following parameters were prospectively registered in a specifically designed database (Microsoft Excel®, Microsoft Corporation, Redmond, WA, USA): age, sex, nodule size, operative time, postoperative complications, hospital stay, pathological lesion size, pathological diagnosis, multifocal disease, number of removed and metastatic lymph nodes, and TNM staging [19].

Definitions PTC were defined clinically unifocal and cN0 in the absence of any pre- (i.e., clinical and ultrasound examination) or intra-operative evidence of multifocal disease or lymph node involvement, respectively. Bilateral central neck dissection included the removal of prelaryngeal, pretracheal, and both the right and left paratracheal nodal basins [20]. Ipsilateral central neck nodes, included prelaryngeal, pretracheal, and the paratracheal nodal basins on the side of the tumor [20]. Occult lymph node metastases were defined micrometastases if they measured ≤2 mm in their maximum diameter [21].

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 seventh edition of the American Joint Committee on Cancer pTNM staging system [19].

Postoperative management Postoperative serum calcium and phosphorus levels were measured in all the patients. Hypocalcemia was defined as a serum calcium level below 8.0 mg/dl, even in one single measurement. Laryngoscopy was performed preoperatively and postoperatively in all patients 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 χ^2 test was used for categorical variables, and the t test was used for continuous variables. A P value less than 0.05 was considered significant. Sensitivity, specificity, and overall accuracy of FSE in detecting occult ipsilateral node metastases were calculated.

Results

Demographic, clinical, operative, and pathological characteristics of all the included patients are reported in Table 1. There were 7 males and 41 females with a mean age of 40.9± 12.8 years (range, 19–65). Mean lesion size, as evaluated by preoperative neck ultrasound, was 14.1±8.0 mm (range, 5–47). Mean operative time was 73.1±26.5 min (range, 40–140).

Post-operative complications included three transient recurrent laryngeal nerve palsies (3.1 % of the nerves at risk), 25 transient hypocalcemias (52.1 %), one definitive hypoparathyroidism (2.1 %), and one self-limiting lymphatic leakage (2.1 %), which was conservatively treated. No other complications occurred. In particular, no definitive laryngeal nerve palsy was observed. Mean hospital stay was 4.3±2.1 days (range, 2–10). When excluding the patient with lymphatic leakage the mean hospital stay was 3.9±1.5 days (range, 2–7).

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

Patients	48
Age (±SD) (range), years	40.9±12.8 (19–65)
Male/female	7 (14.6 %)/41 (85.4 %)
Lesion size (±SD) (range), mm	14.1±8.0 (5–47)
Operative time (±SD) (range), min	73.1±26.5 (40–140)
Tumor size (±SD) (range), mm	13.3±6.7 (5–30)
pT stage	
T1/T2/T3	33 (68.7 %)/4 (8.3 %)/11 (22.9 %)
pN stage	
N0/N1	27 (56.3 %)/21 (43.7 %)
Microscopic multifocal disease	24 (50 %)
Microcarcinoma	24 (50 %)
Removed lymph nodes (±SD) (range)	13.2±6.8 (6–33)
Metastasized lymph nodes (±SD) (range)	1.2±2.0 (0–10)
Bilateral node metastases	6 (28.6 % of pN1 patients)
Nodes examined at FSE	7.6±4.1 (3–23)
FSE[b]	
Positive/negative	16 (33.3 %)/32 (66.7 %)
Concordance with final histology: yes/no	43 (89 %)/5 (11 %)
Hospital stay (±SD) (range), days	4.3±2.1 (2–10)
Complications	
Transient hypocalcemia	25 (52.1 %)
Definitive hypoparathyroidism	1 (2.1 %)
Transient laryngeal nerve palsy	3 (3.1 % of the nerves at risk)
Definitive laryngeal nerve palsy	0
Lymphatic leakage	1 (2.1 %)

SD standard deviation, *FSE* frozen section examination

The mean pathologic lesion size was 13.3±6.7 mm (range, 5–30). Final histology revealed 33 (68.7 %) pT1 (22 microcarcinomas, 16 multifocal), four (8.3 %) pT2 (one multifocal), and 11 (23.0 %) pT3 (two microcarcinomas with extrathyroidal tumor extension, seven multifocal). The mean number of removed and metastatic nodes was 13.2±6.8 (range, 6–33) and 1.2±2.0 (range, 0–10), respectively. The mean number of lymph nodes examined at FSE was 7.6±4.1 (range, 3–23). Overall, occult lymph node metastases were found in 21 patients (43.7 %): 15 with pT1 and 6 with pT3 PTC. Micrometastases were observed in seven out of these 21 patients (33.3 %). Bilateral nodal involvement was observed in six patients (one of whom with micrometastases): 12.5 % of all the included patients and 28.6 % of the patients with central compartment lymph node metastases.

FSE of the ipsilateral central neck nodes showed lymph node metastases in 16 patients (including four patients with micrometastases) and was negative for metastatic nodal disease in the remaining 32 cases. Final histology confirmed lymph node metastases in all the 16 patients with positive FSE; in four of them, lymph node metastases were found also in the contralateral nodes. Reactive changes were confirmed at final histological examination in 27 patients among the 32 (84 %) with a negative FSE. In the remaining five patients with negative FSE, final histology showed nodal involvement; three of them had micrometastases. Bilateral nodal disease was found in two out of these five patients, one of whom had bilateral micrometastases.

No significant difference was found between pN0 and pN1 patients concerning demographic, clinical and pathologic characteristics (Table 2). The sensitivity, specificity and overall accuracy of FSE in detecting ipsilateral central neck lymph node metastases were 80.7, 100, and 90 %, respectively.

Discussion

The role for elective or prophylactic central neck dissection in patients with cN0 PTC has not clearly defined yet [7]. Recently published systematic reviews and meta-analyses did not reach equivocal conclusions concerning the management of cN0 PTC patients [1, 2, 10]. Even the revised ATA management guidelines reflect the controversy regarding this debated point [22].

PCND could have the potential benefit to improve accuracy in staging, to decrease postoperative serum thyroglobulin levels, to allow a better selection of patients for radioiodine treatment, and to reduce the recurrence rate in patients with cN0 PTC. On the other hand, PCND implies a higher risk of postoperative complications, namely transient and permanent hypoparathyroidism and unintentional laryngeal nerve injury, in the absence of any significant data confirming its advantages, especially in terms of recurrence

Table 2 Comparative analysis between pN0 and pN1 patients

	pN0	pN1	*P* value
Number of patients	27	21	NS
Age±SD (years) (range)	41.2±13.3 (19–62)	40.4±12.5 (19–65)	NS
Male/female	3/24	4/17	NS
Tumor size±SD (mm) (range)	13.4±7.1 (5–30)	13.1±6.5 (6–30)	NS
pT stage			
T1	18	15	NS
T2	4	0	NS
T3	5	6	NS
Microcarcinoma yes/no	14/13	10/11	NS
Multifocal disease yes/no	10/17	14/7	NS
Removed nodes	11.8±5.9 (6–33)	15.0±7.6 (6–33)	NS

SD standard deviation, *NS* not significant

and survival rate, in patients with occult lymph node involvement [1].

Moreover, one of the arguments to favor PCND resides in the difficulty to pre- (with ultrasound and clinical examination) and intra-operatively evaluate lymph node involvement [10], even if it has been demonstrated that surgeons assessment of the central neck is an accurate predictor of which patients with PTC would benefit from a central neck dissection [23].

In order to reduce the risk of postoperative complications related to PCND, unilateral central neck dissection emerged as an alternative approach to bilateral central neck dissection [20]. Ipsilateral PCND appeared to be a safe, efficacious, and interesting alternative to bilateral PCND, especially for small (≤1 cm) PTC, but no conclusive data are available [12–17].

In a recently published prospective study [18], comparing total thyroidectomy, total thyroidectomy plus ipsilateral PCND and bilateral PCND in patients with clinically unifocal cN0 PTC, we demonstrated that even if total thyroidectomy appears an adequate treatment option, PCND could be considered for a more accurate staging and more appropriate selection of patients for radioiodine treatment. Since bilateral PCND is associated with an increased risk of transient complications (i.e., hypocalcemia), a longer operative time and a longer hospital stay, ipsilateral PCND could be a valid treatment option, basing of the fact that the risk of complications did not significantly differ from that of total thyroidectomy alone. On the other hand, it carries the risk of contralateral metastases being overlooked in approximately one fourth of the patients. Indeed bilateral central neck node metastases were found in 23 % of patients who underwent bilateral PCND [18]. In the present series of clinically unifocal cN0 PTC bilateral neck nodes metastases were found in 12.5 % of the cases.

It has been recently suggested that clinically unilateral and cN0 PTC larger than 1 cm have a higher risk of bilateral central neck node metastases [14] and the presence of ipsilateral central neck lymph node metastases is the only independent predictor of contralateral nodal involvement [13]. Unfortunately, it is hard to define which patients would have ipsilateral central lymph nodes involvement and would benefit from a bilateral PCND.

Chae et al. [15] have recently investigated the reliability of FSE of the ipsilateral central neck nodes in patients with cN0 PTC in detecting central neck node metastases. In their study FSE was highly accurate (91.1 %) in diagnosing ipsilateral central neck node metastases. Only patients with positive FSE underwent contralateral central neck dissection and contralateral metastases were found in 30.4 % of them [15]. Basing on their findings, they suggested that FSE can be useful to modulate the extension of central neck dissection [15]. However, not all the included patients underwent bilateral central neck dissection. As a consequence, the status of the contralateral nodes was known only in a minority of patients (22.7 %) with lymph node metastases found at FSE [15].

Of note, some authors have reported isolated contralateral central compartment nodal metastases in 3.6 % of the patients [13]. In order to have a precise indication of the contralateral nodal status, in the present study, all the patients underwent bilateral PCND. We found no isolated contralateral nodal metastases. Probably this was partially due to the fact that only patients with clinically unifocal and cN0 PTC were included, even if microscopic multifocal disease was observed in 50 % of the cases. On the other hand, bilateral central neck nodal metastases were found in 12.5 % of the patients and in 28.6 % of those who staged as pN1. These results confirm our previous observation that about one fourth of the patients with occult nodal metastases have bilateral nodal involvement if bilateral PCND is performed [18]. Altogether these findings seem to confirm that the presence of ipsilateral nodal metastases is the main predictor for contralateral central neck node metastases in patients with clinical unifocal and cN0 PTC [13].

The results of the present study also confirm that it is hard to pre- or intraoperatively define which patients are at

risk of having central neck node metastases and could benefit of central neck node dissection based on clinical data, in the absence of FSE. Indeed, no significant difference was found between patients with and without central neck node metastases in terms of demographic, clinical and pathologic findings (Table 2).

On the other hand, FSE was highly accurate in defining the nodal status of patients pre- and intraoperatively classified as N0. Sensitivity, specificity, and overall accuracy were 80.7, 100, and 90 %, respectively. These results are similar to those obtained from Chae et al. [15] who reported a sensitivity of 78.3 %, a specificity of 100 %, and an overall accuracy of 91.1 %.

Most of the false-negative results we observed were obtained in case of micrometastases, which are usually of little clinical significance [21]. As a consequence, FSE of the ipsilateral node could be suggested as a reliable method to intraoperatively assess the nodal status of cN0 patients and to define the extent of the central neck dissection. Since the risk of complications of bilateral PCND can be exceedingly high, even in experienced hands, as also underlined by the results of the present study, the possibility to intraoperatively define the nodal status is of utmost value.

It is evident that the major limitation of the present study is the small number of patients included and the lack of follow up data. Nonetheless, it is hard to define the adequate follow up period for patients with PTC, since recurrence may occur even decades after the first operation. Moreover, the aim of the present study was not to investigate about the completeness of the surgical resection or the recurrence rate, but to evaluate if FSE is accurate in predicting central neck lymph node metastases and could be used to intraoperatively modulate the extent of central neck dissection.

Conclusion

The results of the present study demonstrated that FSE on the ipsilateral central neck nodes is accurate in predicting node metastases in clinically unifocal and N0 PTC and can be useful in determining the extension of central compartment node dissection. False-negative results are reported mainly in case of micrometastases, which usually have limited clinical implications. Ipsilateral PCND plus FSE of the ipsilateral nodes could be considered a valid alternative to bilateral PCND, in order to reduce morbidity, limiting the risk of overlooking central neck node metastases. Bilateral central neck dissection should be performed in case of positive FSE, because of the high risk of contralateral central node metastases. Nonetheless, we need further prospective comparative studies to evaluate and eventually validate this intraoperative decision making approach.

Conflicts of interest None.

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