International Journal of Surgery 12 (2014) S57–S62

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

Original research

Central neck dissection in papillary thyroid carcinoma: Results of a retrospective study

F. Tartaglia [a, *], S. Blasi [a], A. Giuliani [b], M. Sgueglia [a], L. Tromba [a], S. Carbotta [a], G. Carbotta [a], G. Tortorelli [a]

[a] Department of Surgical Sciences, "Sapienza" University of Rome, Rome, Italy
[b] Istituto Superiore di Sanità, Rome, Italy

ARTICLE INFO

Article history:
Received 23 March 2014
Accepted 3 May 2014
Available online 23 May 2014

Keywords:
Papillary thyroid carcinoma
Central neck dissection
Total thyroidectomy

ABSTRACT

Aims of the study: The aim of this retrospective study was to appraise the impact of central neck dissection (CND) when treating papillary thyroid carcinoma (PTC) and identifying predictors of tumour recurrence by analysing the results and complications related to this surgical procedure.
Materials and methods: The study examined the histories of 347 patients with PTC, divided into two groups: group A including 284 patients who underwent total thyroidectomy (TT) only; group B including 63 patients who underwent TT and CND and possible lateral neck dissection (LND).
Results: The patients in the B group were younger than those in the A group (an average of 44.5 vs. 48.6; $p = 0.03$) and their tumours were larger (1.91 cm vs 1.27 cm, $p = 0.001$). Multifocality, extra-capsular extensions of the neoplastic mass and high cell histological variant were more prevalent in the B group. The incidence of permanent hyperparathyroidism was higher in group B than in group A (25.4% vs 9.5%, $p = 0.0006$). Recurrence of disease and the numbers requiring reoperation were also higher in group B: (24.1% in group B vs 6.6 in group A, $p < 0.0001$). Patients classified as clinically N0 at their first operation and who were most probably clinically N1, totalled 6.6%.
Conclusions: Our data show that only extra-capsular extension may be considered a predictor of recurrence. The findings of our study support the idea of carrying out "therapeutic" CND only in cases of preoperative or macroscopic intraoperative clinical evidence of lymph-node involvement.

1. Introduction

Papillary thyroid carcinoma (PTC) accounts for about 80% of all thyroid cancers and is the sixth most common cancer with an increased incidence in the case of females [1]. PTC presents a high incidence of lymph-node metastases, particularly in the central compartment (level VI). The presence of clinically evident lymph-node metastases in the central compartment requires, besides total thyroidectomy (TT), also central neck dissection (CND). CND carried out (clinically or availing of radiology) to remove apparent metastatic lymph-nodes in the central compartment (cN1a) is called "therapeutic central neck dissection" while central lymphadenectomy performed in the absence of suspected lymph-node metastases (cN0) is defined "prophylactic" or "elective" [2]. In the presence of cN1a carcinomas, almost all agree in associating therapeutic CND and TT, whereas in the case of cN0, and, therefore, for "prophylactic" CND the issue is quite controversial. Many factors should be considered when deciding whether and when to perform prophylactic CND: the T of the tumour, gender, age, histological subtype, the involvement of the capsule and so on. Personal conviction is supported by rates of reoperation due to recurrence, survival over time, laboratory index trends. Unfortunately, there isn't any decisive contribution to the discussion due to the lack of randomized prospective trials and the explanations of this lack have been explained quite thoroughly in a recent article regarding this issue [3]. Therefore, we wish to make a contribution by expounding our convictions starting from our personal experience. The purpose of this retrospective study was, therefore, to assess the impact of the CND in the treatment of PTC's by identifying factors predicting tumour recurrence and analysing the oncological results and complications related to the surgical procedure.

* Corresponding author. Largo Pannonia 48, 00183 Rome, Italy.
E-mail address: francesco.tartaglia@uniroma1.it (F. Tartaglia).

http://dx.doi.org/10.1016/j.ijsu.2014.05.053
1743-9191/

2. Materials and methods

This retrospective study was carried out by examining the case histories of patients who underwent thyroid surgery in the years between 2000 and 2010 at the Department of Surgical Sciences of "Sapienza" University of Rome. We included all patients with histological–pathological PTC diagnoses. We excluded from the study all patients who had undergone surgery for benign thyroid disease, surgery for non-papillary thyroid carcinomas, previous radiation therapy of the neck, simultaneous surgery for hyperparathyroidism, completion thyroidectomy. The patients were divided into two groups. The first group (group A) included all patients with clinically negative lymph nodes (cN0) who underwent TT. The second group (group B) included all patients who underwent TT and CND and/or lateral neck dissection (LND) with preoperative or intraoperative clinical evidence of lymph-node metastases both in the central and lateral cervical compartments (cN1a and cN1b). Preoperative assessment was carried out by clinical examination, ultrasound exam of the neck, fine needle aspiration, measurements of serum calcium, phosphorus, PTHi, Tg, anti-Tg antibodies. The motility of the vocal cords was assessed by preoperative and postoperative indirect or fibre optics laryngoscopy. Temporary recurrent laryngeal nerve dysfunction was defined as decreased or absent vocal cord mobility resolving within 6 months of surgery. Permanent recurrent nerve paralysis was defined as vocal cord dysfunction persisting beyond 6 months after initial surgery. Temporary hypocalcaemia was defined as a decrease in serum calcium levels of <8.0 mg/dl. Definitive hypoparathyroidism was defined as the presence of intact PTH values of <10 pg/ml persisting one year after surgery. Phosphorus concentrations were evaluated only after ruling out any concomitant causes of hyper-or hypophosphatemia that might invalidate the assessment [4]. All patients were subjected to whole-body scintigraphy after surgery and/or radioiodine ablation therapy according to the ATA guidelines of 2009. All the patients data gathered over the years were entered into a database. The data included the demographic characteristics of the patients, the histological–pathological features of their primary tumours and lymph nodes and postoperative complications The follow up of all the patients was carried out by monitoring serum thyroglobulin, anti-thyroglobulin antibodies, serum calcium, phosphorus and iPTH, annual neck ultrasonography, total body scintigraphy. Data regarding the number of reoperations were also collected and these were classified according to the lymph node compartment removed: central (level VI), lateral (levels I–IV), both (levels I–VI). Recurrence of neoplastic disease was defined as the presence of neoplastic disease 6 months after the first surgical operation.

Statistical analyses were carried out using SAS 6.1 software. The quantitative variables were expressed as ±SD averages and qualitative variables as proportions and percentages. The Student's *t*-test and the Mann–Whitney *U*-test were used to compare quantitative variables, respectively, with or without normal distribution. The chi-square test was used to investigate differences between qualitative variables. The value of $p < 0.05$ was considered significant. The analysis of variance was performed to determine whether gender, age ≥45, high cell variant, multifocality, extra-capsular extension, hyperfunction, tumour size ≥1 cm and chronic thyroiditis may be considered predictors of tumour recurrence.

3. Results

Three hundred and forty-seven patients fulfilled the study's inclusion criteria. Group A included 284 patients, who underwent TT only. Group B included 63 patients who underwent both TT and CND and in some cases LND too. A summary of the demographic and clinical characteristics of the two groups is provided in Table 1.

The patients in group B were younger on average than those in group A (average age of 44.5 vs. 48.6, $p = 0.03$). The gender distribution rate was similar for both groups. Two hundred and eight subjects underwent preoperative cytology (Table 2). The sizes of the tumours were greater in group B compared to group A (1.91 cm vs. 1.27 cm, $p = 0.001$). Multifocality and extra-capsular extension of the tumour occurred significantly more frequently in group B. The higher frequency of extra-capsular extension and larger tumour size in the group B was proved by the greater frequency of cases rated pT3, and pT4 in group B (respectively 17.2% vs 34.9% and 5.6% vs 19%, $p < 0.0001$) (Table 3). Lymphocytic thyroiditis was apparently more frequent in group A than in group B (21.9% vs 12.7%), but again the statistical significance was low ($p = 0.09$). A summary of histological variants distribution between the two groups are provided in Table 4. The most frequent and classical histological variant was practically the same in both groups and was, therefore, statistically insignificant: 60.5% in group A vs 60.3% in group B ($p = 0.97$). A high cell variant rate was prevalent in group B: 7.9% vs. 2.46% ($p = 0.03$). The follicular variant was slightly more frequent in group A (23.9% vs 15.9%) and was statistically significant ($p = 0.16$).

A summary of the postoperative complications for both groups is provided in Table 5. Bleeding requiring reoperation occurred only in group A and in 5 patients only (1.76%). In the case of the entire sample, transient recurrent lesion occurred in 4.9% instances and proved definitive in 2.6% cases. The average values for serum calcium and phosphorus during the first and second days and one year after surgery, as well as the mean values for iPTH one year after surgery are provided in Table 6. Occurrence of transient hypocalcaemia does not differ significantly between group A and group B (10.9% vs. 12.7%, respectively, $p = 0.6$) although the mean values for serum calcium during the first and second postoperative days are lower for group B (8.1 mg/dl vs 7.8 mg/dl, $p = 0.007$). All the patients in our sample had normal preoperative phosphorus levels, which mean that any early and late postoperative changes could reasonably be considered as side-effects of surgery. No statistically significant results emerged from the data analysed, with the exception of the one-year phosphorus concentrations in the symptomatic patients. The cumulative incidence of definitive hypoparathyroidism in the entire sample was 12.4%, but revealed a higher prevalence in group B than in group A (25.4% vs 9.5%, $p = 0.0006$). The average values for iPTH a year after surgery were lower in group B than in group A (24.08 pg/ml vs 33.3 pg/ml, $p < 0.0001$). The presence of parathyroid during final histological examinations was shown to be more frequent in group B than in group A (19.7% vs. 14.7%, $p = 0.18$). In the B group the parathyroid was never replanted, in group A at least one parathyroid gland was replanted (in 12 cases). The average values for thyroglobulin and

Table 1
Demographic data.

Variables	Group A ($N = 284$)	Group B ($N = 63$)	Odds ratio B/A	*P* value
Age (in years)	48.6 ± 13.7	44.5 ± 15.4	_	0.03
Male %	59 (20.8)	16 (25.4)	0.8	0.4
Female %	225 (79.2)	47 (74.6)	1	
Tumour Size (mm)	1.27 ± 1.4	1.9 ± 1.16	_	0.001
Tumour multifocality %	69 (24.3)	29 (46.0)	1.9	0.0005
Extra-thyroidal extension %	52 (18.3)	35 (55.6)	3.0	0.0001
Hyperthyroidism %	18 (6.3)	1 (1.6)	0.2	0.13
Hashimoto thyroiditis %	62 (21.9%)	8 (12.7%)	0.6	0.09

N = numbers of subjects. Age and tumour size are expressed as means ± standard deviations.

Table 2
Preoperative cytological diagnosis.

Preoperative cytology	Group A ($N = 162$)	Group B ($N = 46$)	P value
Thy 1%	5 (3.1)	0 (0)	0.22
Thy 2%	30 (20.5)	1 (2.2)	0.03
Thy 3%	30 (18.5)	2 (4.3)	0.019
Thy 4%	90 (55.6)	26 (56.5)	0.85
Thy 5%	7 (4.3)	17 (36.9)	0.0001

Distribution of preoperative cytological features for the two groups.

anti-thyroglobulin antibodies in patients who completed follow-up, measured during the preoperative phase, and after initial postoperative ablation, at one year and 5 years after surgery, are shown in Table 7. The data show average values of post-operative thyroglobulin to be higher in group B than in to group A (29.08 vs 21.05 ng/ml, $p = 0.001$). The data show that average post-operative thyroglobulin values were higher in the B group than in the A group (29.08 vs 21.05 ng/ml, $p = 0.001$). The average values of thyroglobulin after initial ablative treatment did not differ significantly while one year after surgery thyroglobulin values were lower in group A than in group B (0.85 vs 1.4 ng/ml). Five years after surgery, a follow-up involving 226 people from the A group and 62 patients belonging to the B group was carried out. There weren't any significant differences in average thyroglobulin values for both groups, which in both cases was <1 ng/ml.

Recurrent disease requiring reoperation occurred more frequently in group B : 24.1% in group B vs 6.6% in group A, $p < 0.0001$. Therefore, the percentage of patients clinically N0 at the time of the first surgical treatment who were probably N1 was 6.6%. The two groups were significantly different in the type of reoperations performed: in group B, LND was performed in 12 patients who had been previously subjected to TT and CND (19.3% vs 0.3%) and in two cases there was also removal of locally relapsed neoplastic tissue (Table 8). Reoperation was performed in the first group after 34.08 ± 7.6 months, in the second group 20.75 ± 5.2 months. The average number of positive lymph nodes in the first group was 13.81 ± 0.33, in the second group 13.79 ± 3.17. The size of the tumour was significantly related to the probability of developing recurrent neoplastic disease when measuring more than 1 cm ($p = 0.004$).

Variance analysis was carried out to determine whether gender, age ≥45 years, the high cell variance, multifocality, extra-capsular extension, hyper-function, tumour size ≥1 cm, lymphocytic thyroiditis may be considered as being predictors of lymph-node cancer recurrence. Our data show that only extra-capsular extension may be considered as a predictor of relapse, while in the case of men the correlation is minimal (Table 9).

4. Discussion

Indications for lymphadenectomy “on principle” or “necessary” in the treatment of PTC are the subject of lively debate in literature. Several authors wrote of their experiences but there isn't any prospective randomized trial decisive contribution to the discussion [3]. Indication for prophylactic CND in cN0 appears to be correlated with incidences of postoperative complications. Dralle reports a significant risk of postoperative hypoparathyroidism after CND [5], but suggests that prophylactic central lymph node dissection improves prognosis for papillary thyroid cancer [6]. According to Mazzaferri the incidence of transient hypoparathyroidism after CND ranges between 14% and 44% [7]. For White the rate of permanent hypoparathyroidism after total thyroidectomy with prophylactic CND is between 0% and 14.3% [8], notwithstanding the application of correct surgical techniques providing for recognition and conservation of the entire cervical parathyroid [9]. Our data don't show any significant difference in incidences of transient symptomatic hypocalcaemia between the two groups although the average values for serum calcium on the first and second post-operative days were lower in the group B (8.1 mg/dl vs 7.8 mg/dl, $p = 0.007$). It appears that phosphorus finds it difficult to return to preoperative values in patients who develop postoperative hypocalcaemia symptoms and may therefore be considered a more sensitive parameter in long-term follow-up. In our experience, incidence of permanent hypoparathyroidism for the entire sample studied was similar to the data provided by literature (about 12.4%), but there was a higher prevalence in the group that underwent CND. In addition, the average values for iPTH a year after surgery were higher in the group submitted to total thyroidectomy only (33.3 pg/ml vs 24.08 pg/ml, $p < 0.0001$).

Many studies showed an increased risk of recurrent paralysis in patients undergoing CND, with rates of recurrent lesions ranging between 1% and 12% [10]. Pereira reports increments from 3% to 6% of recurrent lesions between TT only and TT + CND [11]. Segal et al. reported a higher rate of permanent nerve injury (5.8% versus 25%) for second surgery compared to first operations (5.8% versus 25%) [12]. According to Popadich, the percentage of recurrent transient paralysis increased from 1.8% after TT to 2.3% after TT + CND, whereas the definitive rates range from 0.4% to 1.8% [13]. For Giordano transitional cases range from 3.6% to 5.5%, the definitive from 1% to 2.3% [14]. In our experience, there was no significant difference between the two groups.

The disease recurrence rate was the subject of many studies reported in literature. Patients with locally advanced disease have a greater risk of relapse even if they don't have clinically evident cervical lymph-node metastases. Unlike patients with small tumours, high rates of recurrence risk depend essentially by the initial N stage: if the risk of recurrence in N0 patients is low, N1a or N1b present a high risk recurrence level [15,16]. Some authors report a recurrence risk rate ranging from 0% to 9% for clinically N0 PTC patients [17], others report a probability <5% recurrence for PTC cN0 patients or those with micro-metastases (metastases <0.2 cm in a lymph node) [18] In our experience, evidence of neoplastic disease recurrence was more frequent in the group receiving CND than in the group receiving TT only (24.1% vs 6.6%, $p < 0.0001$). Furthermore, surgical procedure most frequently applied to group B was LND. So, the percentage of clinical N0 patients who was probably N1 at the time of the first surgery was 6.6%. Reoperation was performed in the first group after 34.08 ± 7.6 months, in the second after 20.75 ± 5.2 months. Our finding is in keeping with the literature as the majority of reoperations occurs within the first three years of follow-up.

The core issue is the downstaging of cN0 patients. One of the main objectives of prophylactic CND in patients with small tumours is to provide accurate staging of the disease (N0 or N1a) in order to choose which patients require postoperative radioiodine treatment [19]. To this end, in our experience, the method of the “sentinel” [20] lymph-node method proved of little avail also because of the well-known skip metastasis phenomenon. On the contrary, in the case of patients with locally advanced tumours, the main aim of prophylactic CND is to eliminate any residual disease from the central compartment in order to improve the effectiveness of postoperative therapy with radioactive iodine. In our experience, about 6.6% of PTC patients was downstaged at the time of first surgery, a percentage lower compared to that reported in literature which is about 30% [21,22]. Moreover, all patients who underwent to second surgery were finally free from disease.

Another crucial controversy regards the size of tumour. Dralle support the use of routine central lymph-node dissection for PTC >10 mm in diameter [6]. Kutler and colleagues [23] in a

Table 3
T stage in groups A and B.

T stage	Group A $N = 284$	Group B $N = 63$	Odds ratio B/A	*P* value
pT1a %	150 (52.8)	8 (12.7)	0.24	0.0001
pT1b %	47 (16.55)	15 (23.8)	1.24	0.17
pT2 %	20 (7)	6 (9.5)	1.28	0.49
pT3 %	50 (17.6)	22 (34.9)	2	0.002
pT4 %	17 (5.6)	12 (19.0)	3.8	0.001

retrospective study of 83 subjects revealed no statistically significant difference regarding the risk of metastatic spread to the central compartment between patients with microcarcinomas and patients with tumours larger than 1 cm. Furthermore, this study showed that even microcarcinomas <5 mm might be associated with an 18.8% incidence of metastatic disease. In fact, recurrence rate was 4.8% despite the CND and the post-operative radioactive iodine treatment. Data conflicting with this study were reported by Teixeira and colleagues [24] who declare the absence of nodal micro metastases in patients with PTC's diameter <0.5 cm. Wada evaluated prophylactic CND useless in papillary thyroid microcarcinomas without palpable lymphadenopathy [25]. The different positions about the opportunity of performing CND in patients with tumours <1 cm led some authors to propose CND hemicompartment, ipsi-lateral to the tumour, believing that reduction of the CND extent could decrease postoperative complications. In our experience, the univariate statistical test correlated significantly the size of the tumour >1 cm to the likelihood of developing recurrent neoplastic disease ($p = 0.004$).

Other factors being implicated in the indications for prophylactic CND are gender, age, multifocality, extra-capsular invasion of the tumour and histological type. The data in literature regarding age and gender are conflicting, some authors didn't report any statistically significant differences between males and females [26] although some studies stated that risk of recurrence disease in men was greater than women [27,28.] Some authors consider age <45 years a risk factor, others hold that the risk increases in patients ≥45 years [28–30]. Multifocality and extra-thyroidal extension were associated with an increased risk of lymphatic metastasis including the laterocervical area [28,31] and a higher mortality rate and neoplastic relapse [32]. The risk of tumour recurrence varies in the case of multifocality from 1% to 2% in unicentric papillary micro carcinoma, 4–6% in multifocal papillary micro-carcinoma [33,34], 8–10% in >4 cm intra-thyroidal PTC [35]. In our study, analysis of variance revealed that only extra-capsular extension may be considered a predictor of relapse. It is important to refer to aggressive variants of papillary carcinoma and, in particular, to high-cell and diffused-sclerosis carcinomas. Some variants of papillary carcinoma present more aggressive pathological features, as extra-capsular spread and lymph node metastases. TT and CND treatment might be warranted if the diagnosis were made pre-or intraoperatively [36]. In this study the most common histological variant was the classic one, equally distributed in both groups and without any significant statistical difference: 60.5% in group A vs 60.3% in group B ($p = 0.97$). The high-cell variant was prevalent in group B: 7.9% vs. 2.46% ($p = 0.03$). The follicular type was more frequent in group A (23.9% vs 15.9%), but did not reach statistical significance ($p = 0.16$). Furthermore the familial nonmedullary thyroid carcinomas (FNMTC) have an increased risk of multifocal disease and lymph node involvement with higher recurrence rates and decreased disease-specific survival rates [37]. Moreover some Authors have shown the correlation between the presence of a BRAF-V600 mutation and the incidence of central compartment lymph node metastasis [38].

Table 4
Distribution of histological variants of papillary carcinoma of the thyroid.

Variant	Group A ($N = 284$)	Group B ($N = 63$)	Odds ratio B/A	*P* value
Classic variant %	172 (60.5)	38 (60.3)	1.1	0.97
Tall cell-variant %	7 (2.46)	5 (7.9)	3.2	0.03
Follicular variant %	68 (23.9)	10 (15.9)	0.65	0.16
Diffuse sclerosing variant %	29 (10.2)	7 (11.1)	1.1	0.6
Insular variant %	8 (2.8)	3 (4.7)	1.4	0.4

Table 5
Complications.

Complications	Group A ($N = 284$)	Group B ($N = 63$)	Odds ratio B/A	*P* value
Postoperative temporary hypocalcaemia	31 (10.9)	8 (12.7)	1.2	0.6
Permanent hyperparathyroidism	27 (9.5)	16 (25.4)	2.8	0.0006
Postoperative temporary vocal cord palsy	13 (4.6)	4 (6.3)	1.4	0.5
Postoperative permanent vocal cord palsy	8 (2.8)	1 (1.6)	0.5	0.6
Seroma	9 (3.1)	0 (0)	–	0.15
Haemorrhage	5 (1.7)	0 (0)	–	0.06
Parathyroid glands in the specimen	42 (14.7)	12 (19.7)	4.5	0.18
Parathyroid glands transplanted	12 (4.23)	0 (0)	–	0.7

In the follow up of PTC a crucial role is played by thyroglobulin measurements. Because thyroglobulin is produced only by follicular cells, after surgery it unequivocally indicates persistent disease, and should lead to further tests aimed to discover the lesion producing it [39–45]. On the contrary, if there are no detectable serum thyroglobulin levels, the patient may be considered in clinical remission [46]. In our study, the average Tg values were higher in the group that underwent CND (29.08 vs. 21.05 ng/ml, $p = 0.001$). One year after surgery, thyroglobulin values were lower for group A than for group B (0.85 vs 1.4 ng/ml). The 5-year follow-up was completed by 226 patients in group A and 62 patients in group B. There were no significant differences in average thyroglobulin values between the groups, both of which yielded values of <1 ng/ml. Thyroglobulin is, in our opinion, a reliable marker of disease recurrence with higher average values for group B, where recurrence rate was higher.

5. Conclusions

Our retrospective study shows that the 6.6% of patients staged as clinically N0 was really N1 at the time of first surgery. This means

Table 6
Average values for serum calcium, phosphorus, intact PTH.

Variables	Group A ($N = 284$)	Group B ($N = 63$)	*P* value
Serum calcium 1^d	8.07 ± 0.68	7.81 ± 0.65	0.007
Serum calcium 2^d	8.1 ± 0.75	7.84 ± 0.68	0.003
Serum calcium 1^y	8.8 ± 0.36	8.7 ± 0.36	0.31
Phosphorus 1^d	3.8 ± 0.66	4.1 ± 0.78	0.01
Phosphorus 2^d	4.05 ± 1.8	3.9 ± 0.69	0.67
Phosphorus 1^y	4.2 ± 0.39	4.4 ± 0.39	<0.0001
PTH 1^y	33.06 ± 16.78	24.08 ± 16.66	<0.0001

The values are presented as mean ± Std. Dev. Serum calcium 1^d = mean values for serum calcium on postoperative day 1. Serum calcium 2^d = mean values for serum calcium on postoperative day 2. Serum calcium 1^y = mean values for serum calcium a year after surgery. Fosforo1^d = average values for phosphorus on postoperative day 1. Phosphorus 2^d = average values of phosphorus on postoperative day 2. Phosphorus 1^y = average values for serum phosphate one year after surgery. PTH 1^y = average values for intact parathyroid hormone one year after surgery.

Table 7
Average thyroglobulin (ng/ml) and anti-tyroglobulin antibody values (IU/ml).

Variables	Group A ($N = 284$)	Group B ($N = 63$)	P value
Preop Tg	21.5 ± 22.05	29.08 ± 15.46	0.001
Pre-ablation Tg	1.98 ± 0.85	1.97 ± 0.97	0.9
Tg 1^{y}	0.85 ± 0.95	1.4 ± 0.85	<0.0001
Preop. Anti-Tg	37.82 ± 63.13	38.25 ± 16.43	0.9
3 months Anti-Tg	14.68 ± 10.8	14.14 ± 8.38	0.6
Anti-Tg 1^{y}	10.57 ± 7.38	9.33 ± 14.49	0.51
Variables	Group A ($N = 224$)	Group B ($N = 62$)	P value
Tg 5^{y}	0.11 ± 0.84	0.12 ± 0.07	0.46
Anti Tg 5^{y}	5.01 ± 7.28	3.11 ± 5.44	0.025

Tg 1^{y} = average values for thyroglobulin one year after surgery. Anti-Tg 1^{y} = mean values of anti-thyroglobulin one year after surgery. Tg 5^{y} = average values of thyroglobulin 5 years after surgery. Anti-Tg 5^{y} = average values of thyroglobulin 5 years after surgery. Data are expressed as mean ± Std. Dev.

Table 8
Disease recurrence requiring reoperation.

	Group A ($N = 289$)	Group B ($N = 63$)	P value
Reoperation	19 (6.6%)	14 (24.1%)	<0.001
Mean time to reoperation (months)	34.08 ± 7.6	20.75 ± 5.2	0.0002
CND	12 (4.2%)	0 (0%)	0.1
LND	1 (0.3%)	12 (19.3%)	<0.0001
CND + LND	6 (2.11%)	1 (1.61%)	0.8
Removal of local recurrence	0	2 (3.23%)	0.002
Mean no. positive nodes	0.33 ± 13.81	3.17 ± 13.79	<0.001

The average reoperation time-lapse and the average number of positive lymph nodes expressed as mean ± Std. Dev. **CND** = central neck dissection. **LND** = lateral neck dissection.

Table 9
Variance analysis factors influencing disease recurrence rates.

Variable	DF	Parameter estimate	Standard error	T value	Pr < (t)
Gender	1	−0.09	0.04	−2.31	0.021
Variant	1	−0.19	0.09	−2.12	0.03
Tumour multifocality	1	−0.04	0.03	−1.14	0.25
Extra-thyroidal extension	1	0.18	0.04	4.61	<0.0001
Hyperthyroidism	1	−0.031	0.07	−0.43	0.66
Patient age (≥45 years)	1	−0.017	0.03	−0.52	0.62
Hashimoto thyroiditis	1	−0.003	0.04	−0.52	0.6
Tumour size (≥1 cm)	1	0.03	0.03	0.96	0.33

that, according to our samples, a 6.6% of the PTC patients at the time of first surgery were probably downstaged, but this percentage is lower than that reported in literature, that is about 30%. Moreover, patients who underwent to second surgical treatment for recurrent tumour were finally free of disease at follow up.

Our findings support the idea of carrying out "therapeutic" CND only in the presence of clinical evidence of preoperative or intraoperative macroscopic lymph node involvement. We also believe that level VI is an anatomical functional whole and that central hemicompartment lymphadenectomy is not oncologically correct.

Prophylactic CND should be taken into account in case preoperative tests rate tumours T3 and T4. We don't consider gender or age ≥45 discriminatory factors for prophylactic CND since our data are discordant with those of literature.

Ethical approval

This is a retrospective study based only on the analyses of recorded data and then no Ethical Approval was necessary.

Author contribution

Francesco Tartaglia: Participated substantially in conception, design, and execution of the study, and in the analysis and interpretation of data; performed surgery; revised the study and approved the final version of the manuscript.

Sara Blasi: Participated substantially in conception, design, and execution of the study and in the data base construction.

Alessandro Giuliani: statistical analysis and interpretation of data.

Monica Sgueglia: postoperative data collections.

LucianaTromba: data collections and patient's follow-up at 60 days.

Sabino Carbotta: drafting and editing of the manuscript.

Giovanni Carbotta: bibliographical research and editing of the manuscript.

Giovanni Tortorelli: writing the manuscript.

Conflict of interest/financial support

The authors have no conflict of interest or any financial support.

References

[1] R.M. Cisco, W.T. Shen, J.E. Gosnell, Extent of surgery for papillary thyroid cancer: preoperative imaging and role of prophylactic and therapeutic neck dissection, Curr. Treat. Options Oncol. 13 (1) (2012 Mar) 1–10.
[2] L.H. Sobin, M. Gospodarowicz, C. Wittekind (Eds.), UICC International union against cancer. TNM classification of malignant tumors, seventh ed., Wiley, West Sussex, UK, 2010, pp. 58–62.
[3] T. Carling, S.E. Carty, M.M. Ciarleglio, D.S. Cooper, G.M. Doherty, L.T. Kim, R.T. Kloos, E.L. Mazzaferri Sr., P.N. Peduzzi, S.A. Roman, R.S. Sippel, J.A. Sosa, B.C. Stack Jr., D.L. Steward, R.P. Tufano, R.M. Tuttle, R. Udelsman, American Thyroid Association Surgical Affairs Committee. American Thyroid Association design and feasibility of a prospective randomized controlled trial of prophylactic central lymph node dissection for papillary thyroid carcinoma, Thyroid 22 (3) (2012 Mar) 237–244.
[4] F. Tartaglia, S. Minisola, M. Sgueglia, S. Blasi, D. Brunelli, E. Degli Effetti, A. Maturo, A. Cola, F. Custureri, F.P. Campana, Tumor-induced hypophosphatemic osteomalacia associated with tertiary hyperparathyroidism: a case report, G. chir. 27 (1–2) (2006) 9–13.
[5] H. Dralle, Postoperative hypoparathyroidism: central neck dissection is a significant risk factor, Chirurg 83 (12) (2012 Dec) 1082.
[6] H. Dralle, Prophylactic central lymph node dissection improves prognosis for papillary thyroid cancer, Chirurg 84 (2) (2013 Feb) 149.
[7] E.L. Mazzaferri, G.M. Doherty, D.L. Steward, The pros and cons of prophylactic central compartment lymph node dissection for papillary thyroid carcinoma, Thyroid 19 (7) (2009 Jul) 683–689.
[8] M.L. White, P.G. Gauger, G.M. Doherty, Central lymph node dissection in differentiated thyroid cancer, World J. Surg. 31 (2007) 895–904.
[9] F.P. Campana, M. Marchesi, M. Biffoni, F. Tartaglia, G. Nuccio, F. Stocco, M.O. Jaus, M. Millarelli, Tecnica della tiroidectomia totale. Suggerimenti e proposte di pratica chirurgica (Total thyroidectomy technique: suggestions and proposals of surgical practice), Ann. ital. chir. 67 (5) (1996) 627–635.
[10] D.T. Hughes, G.M. Doherty, Central neck dissection for papillary thyroid cancer, Cancer Control 18 (2) (2011 Apr) 83–88.
[11] J.A. Pereira, J. Jimeno, J. Miquel, M. Iglesias, A. Munné, J.J. Sancho, A. Sitges-Serra, Nodal yield, morbidity, and recurrence after central neck dissection for papillary thyroid carcinoma, Surgery 138 (6) (2005 Dec) 1095–1100.
[12] K. Segal, R. Friedental, E. Lubin, J. Shvero, J. Sulkes, R. Feinmesser, Papillary carcinoma of the thyroid, Otolaryngol. Head Neck Surg. 113 (4) (1995 Oct) 356–363.
[13] A. Popadich, O. Levin, J.C. Lee, S. Smooke-Praw, K. Ro, M. Fazel, A. Arora, N.S. Tolley, F. Palazzo, D.L. Learoyd, S. Sidhu, L. Delbridge, M. Sywak, M.W. Yeh, A multicenter cohort study of total thyroidectomy and routine central lymph node dissection for cN0 papillary thyroid cancer, Surgery 150 (6) (2011 Dec) 1048–1057.
[14] D. Giordano, R. Valcavi, G.B. Thompson, C. Pedroni, L. Renna, P. Gradoni, V. Barbieri, Complications of central neck dissection in patients with papillary thyroid carcinoma: results of a study on 1087 patients and review of the literature, Thyroid 22 (9) (2012 Sep) 911–917.
[15] A. Shaha, Treatment of thyroid cancer based on risk groups, J. Surg. Oncol. 94 (8) (2006 Dec 15) 683–691.
[16] M. Schlumberger, F. Pacini, W.M. Wiersinga, A. Toft, J.W. Smit, F. Sanchez Franco, P. Lind, E. Limbert, B. Jarzab, F. Jamar, L. Duntas, O. Cohen, G. Berg, Follow-up and management of differentiated thyroid carcinoma: a European

perspective in clinical practice, Eur. J. Endocrinol. 151 (5) (2004 Nov) 539–548.
[17] D.S. Cooper, G.M. Doherty, B.R. Haugen, R.T. Kloos, S.L. Lee, S.J. Mandel, E.L. Mazzaferri, B. McIver, F. Pacini, M. Schlumberger, S.I. Sherman, D.L. Steward, R.M. Tuttle, American Thyroid Association Guidelines Taskforce on thyroid nodules and differentiated thyroid Cancer. Revised American Thyroid Association Guidelines for patients with thyroid nodules and differentiated thyroid cancer, Thyroid 19 (2009) 1167–1214.
[18] G.W. Randolph, Q.-Y. Duh, K.S. Heller, V.A. LiVolsi, S.J. Mandel, D.L. Steward, R.P. Tufano, R.M. Tuttle, The prognostic significance of nodal metastases from papillary thyroid cancer can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension: report of the ATA Surgical Affairs Committee, Thyroid 22 (11) (2012 Nov) 1144–1152.
[19] S. Vergez, J. Sarini, J. Percodani, E. Serrano, P. Caron, Lymph node management in clinically node-negative patients with papillary thyroid carcinoma, Eur. J. Surg. Oncol. 36 (8) (2010 Aug) 777–782.
[20] N. Peparini, A. Maturo, F.M. Di Matteo, F. Tartaglia, M. Marchesi, F.P. Campana, Blue-dye sentinel node mapping in thyroid carcinoma: debatable results of feasibility, Acta Chir. Belg. 106 (5) (2006) 523–527.
[21] A. Bozec, O. Dassonville, E. Chamorey, G. Poissonnet, A. Sudaka, I. Peyrottes, F. Ettore, J. Haudebourg, F. Bussière, D. Benisvy, P.Y. Marcy, J.L. Sadoul, P. Hofman, S. Lassale, J. Vallicioni, F. Demard, J. Santini, Clinical impact of cervical lymph node involvement and central neck dissection in patients with papillary thyroid carcinoma: a retrospective analysis of 368 cases, Eur. Arch. Otorhinolaryngol. 268 (8) (2011 Aug) 1205–1212.
[22] K.P. Wong, B.H. Lang, The role of prophylactic central neck dissection in differentiated thyroid carcinoma: issues and controversies, J. Oncol. 2011 (2011), 127929.
[23] D.I. Kutler, A.D. Crummey, W.I. Kuhel, Routine central compartment lymph node dissection for patients with papillary thyroid carcinoma, Head Neck 34 (2) (2012 Feb) 260–263.
[24] G. Teixeira, T. Teixeira, F. Gubert, H. Chikota, R. Tufano, The incidence of central neck micrometastatic disease in patients with papillary thyroid cancer staged preoperatively and intraoperatively as N0, Surgery 150 (6) (2011 Dec) 1161–1167.
[25] N. Wada, Q.Y. Duh, K. Sugino, H. Iwasaki, K. Kameyama, T. Mimura, K. Ito, H. Takami, Y. Takanashi, Lymph node metastasis from 259 papillary thyroid microcarcinomas: frequency, pattern of occurrence and recurrence, and optimal strategy for neck dissection, Ann. Surg. 237 (3) (2003 Mar) 399–407.
[26] Wendong Wang, Jialei Gu, Jinbiao Shang, Kejing Wang, Correlation analysis on central lymph node metastasis in 276 patients with cN0 papillary thyroid carcinoma, Int. J. Clin. Exp. Pathol. 6 (3) (2013) 510–515.
[27] M.R. Pelizzo, I.M. Boschin, A. Toniato, A. Piotto, C. Pagetta, M.D. Gross, A. Al-Nahhas, D. Rubello, Papillary thyroid carcinoma: 35-year outcome and prognostic factors in 1858 patients, Clin. Nucl. Med. 32 (6) (2007) 440–444.
[28] Parameswaran Rajeev, Sohail Ahmed, Tarek M. Ezzat, Gregory P. Sadler, Radu Mihai, The number of positive lymph nodes in the central compartment has prognostic impact in papillary thyroid cancer, Langenbecks Arch. Surg. 398 (3) (2013 Mar) 377–382.
[29] B.Y. Cho, H. Choi, Y.J. Park, J.A. Lim, H.Y. Ahn, E.K. Lee, K.W. Kim, K.H. Yi, J.K. Chung, Y.K. Youn, N.H. Cho, D.J. Park, C.S. Koh, Changes in the clinicopathological characteristics and outcomes of thyroid cancer in Korea over the past 4 decades, Thyroid 23 (7) (2013 Jul) 797–804.
[30] D.S. Cooper, G.M. Doherty, B.R. Haugen, R.T. Kloos, S.L. Lee, S.J. Mandel, E.L. Mazzaferri, B. McIver, S.I. Sherman, R.M. Tuttle, American Thyroid Association Guidelines Taskforce. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer, Thyroid 16 (2) (2006 Feb) 109–142.
[31] Y. Wu, The clinical application of central neck lymph node dissection, J. Surg. Concepts Pract. 8 (2003) 293.
[32] S. Ortiz, J.M. Rodríguez, T. Soria, D. Pérez-Flores, A. Piñero, J. Moreno. Extrathyroid spread in papillary carcinoma of the thyroid: clinicopathological and prognostic study. Otolaryngol. Head Neck Surg., 124 (3), 261–265.
[33] E. Roti, E.C. degli Uberti, M. Bondanelli, L.E. Braverman, Thyroid papillary microcarcinoma: a descriptive and meta-analysis study, Eur. J. Endocrinol. 159 (6) (2008 Dec) 659–673.
[34] E.L. Mazzaferri, Management of low-risk differentiated thyroid cancer, Endocr. Pract. 13 (5) (2007 Sept) 498–512.
[35] Y. Ito, T. Kudo, M. Kihara, Y. Takamura, K. Kobayashi, A. Miya, A. Miyauchi, Prognosis of low-risk papillary thyroid carcinoma patients: its relationship with the size of primary tumors, Endocr. J. 59 (2) (2012) 119–125.
[36] E.J. Kuo, P. Goffredo, J.A. Sosa, S. Roman, Aggressive variants of papillary thyroid microcarcinoma are associated with extrathyroidal spread and lymph node metastases: a population-level analysis, Thyroid 19 (2013 Apr).
[37] A. Hillenbrand, J.E. Varhaug, M. Brauckhoff, R. Pandev, S. Haufe, C. Dotzenrath, R. Köberle, R. Hoffmann, G. Klein, M. Kadmon, T. Negele, T. Hagieva, D. Henne-Bruns, M. Luster, T. Weber, Familial nonmedullary thyroid carcinoma-clinical relevance and prognosis. A European multicenter study. ESES Vienna presentation, Langenbecks Arch. Surg. 395 (7) (2010 Sep) 851–858.
[38] G.M. Howell, M.N. Nikiforova, S.E. Carty, M.J. Armstrong, S.P. Hodak, M.T. Stang, K.L. McCoy, Y.E. Nikiforov, L. Yip, BRAF V600E mutation independently predicts central compartment lymph node metastasis in patients with papillary thyroid cancer, Ann. Surg. Oncol. 20 (1) (2013 Jan) 47–52.
[39] F. Pacini, L. Agate, R. Elisei, M. Capezzone, C. Ceccarelli, F. Lippi, E. Molinaro, A. Pinchera, Outcome of differentiated thyroid cancer with detectable serum Tg and negative diagnostic 131I whole body scan: comparison of patients treated with high 131I activities versus untreated patients, J. Clin. Endocrinol. Metab. 86 (2001) 4092–4097.
[40] M. Schlumberger, F. Mancusi, E. Baudin, F. Pacini, 131I therapy for elevated thyroglobulin levels, Thyroid 7 (1997) 273–276.
[41] J. Pineda, T. Lee, K. Ain, J. Reynolds, J. Robbins, Iodine-131 therapy for thyroid cancer patients with elevated thyroglobulin and negative diagnostic scan, J. Clin. Endocrinol. Metab. 80 (1995) 1488–1492.
[42] B. Amato, R. Compagna, L. Sivero, V. Salvati, M. Amato, G. Vigliotti, A. Rocca, M. Donisi, Lymphectomy for elderly in thyroid surgery, Chirurgia 26 (4) (2013 Aug) 303–306.
[43] G. Romano, E. Luna, G. Cocchiara, F. Calderone, C. Zumbino, M. Muzio, M.C. Lo Nigro, A.I. Lo Monte, G. Buscemi, Di Bernardo C, N. Napoli, The surgical treatment of nodular thyroid lesions: our experience. Analysis of 462 cases, G. Chir. 25 (1–2) (2004 Jan-Feb) 23–26 (Review).
[44] A. Sanguinetti, G. Docimo, M. Ragusa, F. Calzolari, F. D'Ajello, R. Ruggiero, D. Parmeggiani, A. Pezzolla, E. Procaccini, N. Avenia, Ultrasound scissors versus electrocautery in axillary dissection: our experience, G. Chir. 31 (4) (2010 Apr) 151–153. PubMed PMID: 20444331.
[45] R. Gervasi, G. Orlando, M.A. Lerose, B. Amato, G. Docimo, P. Zeppa, A. Puzziello, Thyroid surgery in geriatric patients: a literature review, BMC Surg. 12 (Suppl. 1) (2012) S16, http://dx.doi.org/10.1186/1471-2482-12-S1-S16.
[46] F. Pacini, M. Capezzone, R. Elisei, C. Ceccarelli, D. Taddei, A. Pinchera, Diagnostic Iodine-131 whole-body scan may be avoided in thyroid cancer patients who have undetectable stimulated serum Tg levels after initial treatment, J. Clin. Endocrinol. Metab. 87 (2002) 1499–1501.