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Rationality in prophylactic central neck dissection in clinically node-negative (cN0) papillary thyroid carcinoma: Is there anything more to say? A decade experience in a single-center

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Rationality in prophylactic central neck dissection in clinically node-negative (cN0) papillary thyroid carcinoma: Is there anything more to say? A decade experience in a single-center

C. Dobrinja [a, *], M. Troian [a], T. Cipolat Mis [a], G. Rebez [a], S. Bernardi [b], B. Fabris [b], L. Piscopello [c], P. Makovac [a], F. Di Gregorio [d], N. de Manzini [a]

[a] Division of General Surgery, Department of Medical, Surgical and Health Sciences, Cattinara Teaching Hospital, Strada di Fiume, 34149, Trieste, Italy
[b] SS Endocrinologia (UCO Medicina Clinica), Azienda Ospedaliero-Universitaria di Trieste, Department of Medical, Surgical and Health Sciences, Cattinara Teaching Hospital, Strada di Fiume, 34149, Trieste, Italy
[c] Division of Endocrinology, Azienda Ospedaliero-Universitaria di Trieste, Maggiore Hospital, Piazza dell'Ospitale, Trieste, Italy
[d] Nuclear Medicine Unit, Ospedale S. Misericordia Udine, Italy

HIGHLIGHTS

- The role of prophylactic central neck dissection (PCND) remains a matter of debate in patients with clinically node-negative (cN0) PTC.
- Overall complication rate was significantly higher in the group of patients undergoing PCND.
- Overall survival and recurrence rates did not differ between those undergoing PCND and those undergoing total thyroidectomy alone.
- Accurate patient selection is important to achieve the best results.

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ABSTRACT

Aim: Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy. Despite its extremely favorable prognosis, cervical lymph node metastases are a common feature of PTC and a known independent risk factor for local recurrence. However, the role of prophylactic central neck dissection (PCND) remains a matter of debate in patients with clinically node-negative (cN0) PTC. To better clarify the current role of PCND in the surgical treatment of PTC, evaluating advantages and disadvantages of PCND and outcome of cN0 PTC patients who have been treated with either total thyroidectomy alone or in combination with PCND. A review of recent literature data is performed.
Methods: Between January 2000 and December 2015, 186 consecutive patients with cN0 PTC were identified to be included in the present study. 74 of these underwent total thyroidectomy associated with PCND, while 112 patients underwent total thyroidectomy alone. The epidemiological and clinical-pathological data of all patients included were collected at diagnosis and during follow-up.
Results: Overall complication rate was significantly higher in the group of patients undergoing PCND (39.2% vs. 17.8%, $p = 0.0006$). To be specific, they presented a considerably increased risk of temporary recurrent laryngeal nerve injury ($p = 0.009$) and of permanent hypothyroidism ($p = 0.016$). Overall survival and recurrence rates did not differ between those undergoing PCND and those undergoing total thyroidectomy alone ($p = 1.000$ and $p = 0.715$, respectively).
Conclusions: The results of the present study do not support the routine use of PCND in the treatment of cN0 PTC patients.

1. Introduction

Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy, accounting for approximately 80% of all thyroid cancers. Its incidence is rapidly increasing worldwide, partially due to

* Corresponding author. Division of General Surgery, Department of Medical, Surgical and Health Sciences, Cattinara Teaching Hospital, Università degli Studi di Trieste, Strada di Fiume 447, 34149, Trieste, Italy. Tel.: +39 3472514845, +39 0403994152 (phone).
E-mail address: ch_dobrinja@yahoo.it (C. Dobrinja).

increased detection because of more sensitive imaging techniques. The overall prognosis for treated PTC is generally good, with a 10-year survival rate exceeding 90% [1–3]. However, cervical lymph node metastases are a common feature of PTC, occurring in 20–50% of patients in the central compartment of the neck (level VI) and in 10–30% of patients in the lateral compartment of the neck (level II-V), while micrometastases are reported in up to 80% of cases, especially in young patients [4–15]. The role of prophylactic central neck dissection (PCND) remains a matter of debate in patients with clinically node-negative (cN0) PTC. Proponents of PCND support its routine use as it has the advantage of increasing accuracy in TNM staging and reducing local recurrence and surgical morbidity associated with re-operation [4–6,8–14,16]. Conversely, those against the routine use of PCND claim that the clinical impact of occult micrometastases has yet to be demonstrated and it may lead to an overstaging of disease and a consequent risky overuse of radioactive iodine (RAI) ablation without clear evidence of reduction in recurrence or added benefit survival. Moreover, the risk for postoperative complications and morbidity has to be taken into account [4,8–12,16–18].

In order to better clarify the current role of PCND in the surgical treatment of PTC, we aimed to evaluate the advantages and disadvantages of PCND and the outcome of cN0 PTC patients who have been treated with either total thyroidectomy alone or in combination with PCND.

2. Material and methods

This study is a retrospective cohort analysis of prospectively recorded data extracted from the Institutional Register of Thyroid Surgery of the Department of General Surgery, University Hospital of Trieste.

Between January 2000 and December 2015, 878 patients underwent thyroid surgery and 236 presented with PTC. Of these, 186 consecutive patients with clinically node-negative (cN0) PTC were identified to be included in the present study, regardless of the size of the malignant nodule.

Most of the operations were performed in the last 5–10 years. A small part of the interventions was made before 2005. In particular, from 2000 to 2005 were performed 25 interventions (13.4%), between 2005 and 2010, 44 interventions (23.6%), and from 2010 to 2015, 117 (63%) interventions.

Since 2005 all surgical procedures were performed by the same surgical team consisting of 1 or 2 surgeons dedicated to endocrine surgery.

Exclusion criteria included: histotypes other than PTC, evidence of lymph node metastases on preoperative clinical examination and/or ultrasound (US), evidence of distant metastases at the time of diagnosis. Patients undergoing therapeutic lymph node dissection beyond the central compartment were also excluded, as well as those with incidental histologic finding of papillary microcarcinoma <4 mm in diameter and patients with incomplete follow-up data.

All patients underwent total thyroidectomy (TT) with curative intent.

The patients were staged T1 or T2 at the preoperative evaluation, and none patients presented preoperative evidence of lymph node involvement (N0). PCND was introduced in our surgical practice in 2007 and was not performed routinely but according to the surgeon's judgement of the surgical field and potential risk factors, i.e. sex, age, familiarity, BRAFV600E mutation status (when available), tumor diameter (larger than 10 mm), extrathyroidal extension and suspicious lymph nodes at the time of surgery. When performed, the central compartment neck dissection aimed at removing the nodes of the prelaryngeal, pretracheal, and paratracheal basins according to American Thyroid Association (ATA) Guidelines [4].

All patients with evidence of central and/or lateral neck lymph node metastases on preoperative clinical examination and/or ultrasound (US) were not included in the study since they underwent therapeutic lymph node dissection. We included patients with clinically lymph node-negative (cN0) PTC with negative preoperative imaging for lymph node disease. It was decided to make the PCND in patients with BRAFV600E mutation at the FNAC, and/or with tumor with a diameter greater than 1 cm, even in the absence of lymph nodes macroscopically suspicious at the cervical surgical exploration.

Therefore, for the purpose of this study, patients were divided into group A, consisting of those who underwent TT associated with prophylactic level VI lymph node dissection (unilateral or bilateral, beginning 2007), and group B, including patients who underwent TT alone (from 2000 through all 2015).

The data gathered for each patient included: age, gender, histopathologic characteristics of the primary tumor (i.e. size, histotype, lymph node status, TNM classification, AJCC stage), postoperative complication rates, postoperative radioactive iodine (RAI) ablation therapy, local recurrence rates, overall survival, tumor-specific survival, and disease-free survival.

For each patient, the preoperative work-up consisted of: high-resolution US of the neck by a skilled sonographer, US-guided fine-needle aspiration cytology (FNAC), serum measurement of free thyroid hormone (FT3, FT4), and thyrotropin (TSH). Direct fiber optic laryngoscopy was performed in all patients immediately before and within three weeks after surgery to assess cord motility. Recurrent laryngeal nerve (RLN) injury was considered permanent when the cord palsy persisted 6 months after surgery. Calcium levels were measured postoperatively during the first 48 h and one week after surgery, and measurement was repeated whenever necessary. Supplementation of calcium and calcitriol was administered only in symptomatic patients and/or those with hypocalcemia confirmed by laboratory test results and defined by serum total calcium level of less than 8.0 mg/dL. Hypoparathyroidism was considered permanent when it lasted for more than six months, even if asymptomatic.

Patients were routinely follow-up every three months during the first postoperative year and on a yearly basis thereafter. During each follow-up visit, the patient received a routine physical examination, neck US, and assays for Tg and TgAb levels. Whole-body scintigraphy was performed within three months after surgery and in patients with indications for RAI ablation therapy. According to ATA Guidelines, postsurgical thyroid remnant ablation with low radioiodine (^{131}I) activities, ranging from 50 mCi to 200 mCi, was offered to all patients when indicated and subsequent treatments were administered when required.

The patients were considered to be free of disease when serum Tg levels were less than 1 ng/mL, neck US was negative, and TgAb levels were undetectable. The patients who did not undergo ^{131}I remnant ablation were considered to be free of disease when neck US was negative and serum Tg levels and TgAb were undetectable and/or stable during follow-up. Patients who were not considered to be free of disease underwent subsequent ^{131}I therapy and/or other surgical treatments if necessary.

2.1. Statistical analysis

Quantitative results were reported in terms of mean and standard deviation for normal distributions and median and interquartile range for non parametric distributions. Qualitative variables were reported in terms of absolute frequencies and percentages. Categorical variables were assessed using the Fisher's

exact test or Chi-squared test, when appropriate. Continuous variables were evaluated by using the Student T-test or Mann-Whitney *U* test, when appropriate. The Kaplan-Meier method was used to generate survival curves and comparison relied on Log-rank test. A *p*-value of less than 0.05 was considered to be statistically significant. All statistical analyses were performed using a commercially available software named R (the R Foundation for Statistical Computing, Version 3.0.3).

3. Results

Group A encompassed 74 patients who underwent total thyroidectomy associated with prophylactic central neck dissection. Group B consisted of 112 patients who underwent total thyroidectomy alone. Although not randomized, the two groups were similar regarding epidemiological and clinical data. Characteristics of all included patients are reported in Table 1.

No statistically significant difference was found in terms of gender ($p = 0.22$), with a prevalence of females in both groups (84% in group A and 74% in group B, respectively).

Mean tumor diameter was significantly smaller in the thyroidectomy only group, being 11 mm (range 7–16 mm) versus 13 mm (range 9–18 mm) in the prophylactic lymphadenectomy set ($p = 0.03$). The majority of patients in both groups presented with either pT1 or pT2 lesions (62.2% in group A and 77.7% in group B, respectively), whereas pT3 or pT4 lesions were found in 37.8% ($n = 28$) of patients in group A and in 22.3% ($n = 25$) of patients in group B. This difference was found to be significant on statistical analysis ($p = 0.003$). When considering the N status of those who underwent PCND, nodal involvement was found in 32 patients (43.2%), and 24 of these (32.4%) presented with micrometastases (75% of the N+ patients in group B).

As for TNM staging, a significant difference between the two groups was found only for stage I disease (55.4% in group A and 71.4% in group B, $p = 0.04$).

As far as postoperative complications are concerned, overall complication rate was significantly higher in the group of patients undergoing PCND (39.2% versus 17.8%, $p = 0.0006$). Data are reported in detail below and are summarized in Table 2.

Table 1
Epidemiological characteristics and tumor data.

Variable	Group A (TT + PCND)	Group B (TT)	*p*-value
Number of patients	74 (40%)	112 (60%)	
Gender			
M	12 (16.2%)	29 (25.9%)	0.22
F	62 (83.8%)	83 (74.1%)	
Age (years)	53 ± 16.25 [23–86]	57 ± 14.63 [16–84]	0.11
Age < 45 years	26 (35.1%)	27 (24.1%)	0.21
Tumor diameter (mm)	13 [9–18]	11 [7–16]	**0.03**
T status			
pT1	37 (50.0%)	65 (58.1%)	0.3
pT2	9 (12.2%)	22 (19.6%)	
pT3	25 (33.8%)	21 (18.7%)	**0.03**
pT4	3 (4.0%)	4 (3.6%)	
N status			
Nx	–	112 (100%)	n.s.
N0	42 (56.8%)	–	
N1	32 (43.2%)	–	
Micrometastases	24 (32.4%)	–	
Stage			
I	41 (55.4%)	80 (71.4%)	**0.04**
II	6 (8.1%)	9 (8.0%)	0.99
III	20 (27.0%)	18 (16.1%)	0.10
IV	7 (9.5%)	5 (4.5%)	0.29

Bold denotes the *p*-value of less than 0.05 was considered to be statistically significant.

Table 2
Postoperative complications and survival rates.

Variable	Group A (TT + PCND)*	Group B (TT)*	*p*-value
Follow-up (months)	37 [22–66]	76 [35–112]	<**0.0001**
Postoperative complications	29 (39.2%)	20 (17.8%)	**0.0006**
Hypoparathyroidism	17 (23.0%)	10 (8.9%)	**0.0032**
Temporary	11 (14.9%)	9 (8.0%)	0.065
Permanent	6 (8.1%)	1 (0.9%)	**0.016**
RLN injury	10 (13.5%)	4 (3.6%)	**0.0035**
Temporary	7 (9.5%)	3 (2.7%)	**0.009**
Permanent	3 (4.0%)	1 (0.9%)	0.303
Other complications	2 (2.7%)	6 (5.3%)	0.29
RAI*	43 (58.1%)	55 (49.1%)	0.23
Doses of ^{131}I			0.50
50 mCi*	1 (2.3%)	1 (1.8%)	
100 mCi*	42 (97.7%)	52 (94.6%)	
150 mCi*	0 (0.0%)	1 (1.8%)	
200 mCi*	0 (0.0%)	1 (1.8%)	
Tumor recurrence	4 (5.4%)	4 (3.6%)	0.715
Surgery for recurrence	2 (2.7%)	2 (1.8%)	1.000
Tumor-related death	1 (1.3%)	1 (0.9%)	1.000

Bold denotes the *p*-value of less than 0.05 was considered to be statistically significant.
Abbreviations: *RAI = radioactive iodine; TT = Total thyroidectomy; PCND = prophylactic central neck dissection; mCi = radioactive iodine doses.

Hypoparathyroidism was recorded in 17 patients (23.0%) in group A: of these, 11 patients (14.9%) presented with a temporary condition, whereas 6 patients (8.1%) endured a permanent condition. In group B, hypoparathyroidism was recorded in 10 patients (8.9%), the vast majority of which ($n = 9$) experienced temporary disorders. Statistical analysis showed a significant increased risk of permanent hypoparathyroidism in PCND patients ($p = 0.016$), whereas temporary hypoparathyroidism was not considered to be quite significantly different between the two groups ($p = 0.07$).

RLN injury was reported in 10 patients (13.5%) in group A and in 4 patients (3.6%) in group B ($p = 0.0035$). In this case, the difference was notably different in terms of temporary nerve palsy, since it involved 7 patients (9.5%) in group A versus 3 patients (2.7%) in group B ($p = 0.009$). Permanent damage was not found to be significantly different on statistical analysis (4.1% in group A versus 0.9% in group B, $p = 0.30$).

Other complications recorded included wound complications (i.e. hematoma, seroma) and did not noticeably differ between the two considered sets ($p = 0.29$).

When further subdividing the patients in group A between those who received ipsilateral PCND ($n = 40$) and those who underwent bilateral PCND ($n = 34$), no significant difference could be found in terms of overall postoperative complication rate ($p = 0.10$).

Mean follow-up period was 37 months (range 22–66 months) in group A and 76 months (range 35–112 months) in group B ($p < 0.0001$).

RAI ablation therapy was performed in 43 patients (58.1%) in group A and 55 patients (49.1%) in group B ($p = 0.23$), with a mean ^{131}I dose of 50–100 mCi and no significant differences between the two groups ($p = 0.50$).

Examining our series, Group A (TT + PCND) consisted of 74 patients. 28 patients were classified as pT3-pT4 and were treated with RAI ablation. The remaining 46 patients were classified as pT1-pT2. In such cases in our institution the indication to RAI ablation is maintained only in presence of unfavorable histological features (for example: tall cells, oncogenic mutations as BRAF or NRAS, vascular invasion) or lymph node metastasis. These conditions were present in only 15 patients and therefore will reach the number of 43 patients which corresponds to 58% of the group A.

As regards survival rates, overall survival was not significantly different between the two groups of patients and well exceeded

90% at 10 years (93% in group A and 91% in group B, respectively; $p = 1.000$). Tumor-related deaths are reported in 1.3% of cases (1 patient) in group A and 0.9% of cases (1 patient) in group B ($p = 1.000$). Recurrence rate is 5.4% (4 patients) in group A and 3.6% (4 patients) in group B, with no significant differences between the two sets ($p = 0.71$). In both groups, half of the patients diagnosed with local recurrence underwent surgical excision, whereas the other half underwent radioiodine therapy. Survival curves are illustrated in Fig. 1.

In Fig. 1 there are represented the Comparison of Survival Curves between two groups and the events reported after 100 months are related to group B (mean follow-up 76 months, ranging from 35 to 112 months) and not group A, where the highest follow-up time point has been stated with 66 months because PCND was performed since 2007.

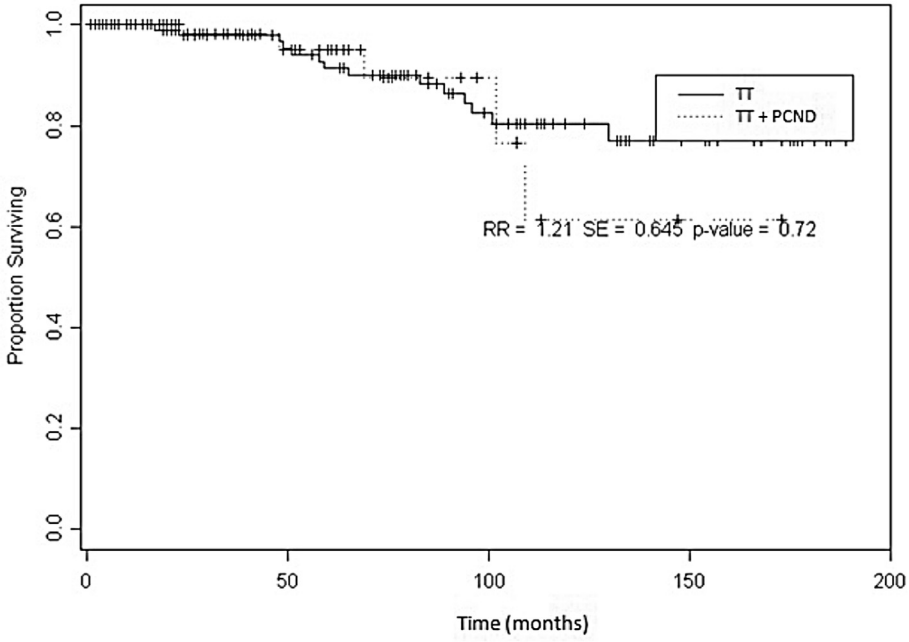
4. Discussion

Differentiated thyroid cancer is a relatively uncommon neoplasm, accounting for 1–2% of all human malignancies [1]. During the last decades, its incidence has surprisingly increased worldwide, in part related to improved imaging techniques [2].

Papillary thyroid carcinoma represents nearly 80% of all thyroid cancers [1–3]. Localized PTCs exhibit an extremely favorable prognosis with a 5-year survival rate exceeding 99%. However, being a lymphotropic tumor, PTC frequently presents with neck node metastases. Indeed, micrometastases are found in up to 80% of cases and in 20–50% of patients the central neck compartment is involved [1–8,10,11]. Positive regional lymph nodes decrease 5-year survival to 97% and are associated with higher recurrence rates [2–8,11–15]. Although surgery, namely in the form of a TT has been accepted as the treatment of choice for most patients with thyroid cancer, the best indications of lymph node dissection are still controversial [4–8,10–12,19,20]. Management guidelines agree in regard to treating patients with clinically evident nodal disease, while PCND remains a matter of debate in cN0 PTC patients [4–12,17,18]. The lack of prospective randomized clinical trials on the subject and the heterogeneity of study populations are the main limiting factors to draw clear conclusion as to whether or not PCND is indicated for the treatment of patients with cN0 PTC.

According to its proponents, PCND reduces the risk of local recurrence and increases long-term survival by increasing accuracy in TNM staging and improving stratification of RAI ablation therapy, thus enhancing chances of cure. Moreover, preoperative imaging modalities are not always reliable where lymph nodes of the central compartment are concerned, and PCND reduces the need for reoperation in central recurrence, which might be associated with greater morbidity [4–6,8–14,16,21]. A retrospective study by Barczyński M. et al [5]. examined 640 patients with cN0 PTC and found that bilateral PCND followed by personalized adjuvant RAI therapy improved both the 10-year disease-specific survival and loco-regional control, without increasing the risk for permanent morbidity. In addition, regional recurrence was significantly lower in patients who had TT with PCND, and this was true also among those who did not receive radioiodine treatment. A trend toward lower recurrence rates in PCND patients is reported also by other studies [16,22], suggesting that routine PCND should be considered in the hands of high-volume surgeons treating cN0 PTCs.

Beyond recurrence rates, another argument in favor of PCND is the staging information it provides, which can guide the use of RAI ablation therapy. Hughes DT et al [23]. showed that routine central lymph node dissection for the treatment of PTC leads to upstaging of nearly one third of patients aged over 45 years, thereby changing the dose of radioactive iodine ablative therapy. Moreover, the additional information provided by PCND can be used to tailor RAI treatment as patients without nodal metastasis after central neck dissection (pN0) may be able to safely receive lower doses of ^{131}I or not receive it at all [21,24–26]. Conversely, the potential upstaging from PCND can lead to overtreatment with RAI, which is not devoid of morbidity risks (e.g. salivary and lacrimal gland dysfunction,



Comparison of Survival Curves between two groups. Mean follow-up period was 37 months (range 22-66 months) in group A and 76 months (range 35-112 months) in group B ($p < 0.0001$)

Fig. 1. Comparison of survival curves.

dysphagia, secondary malignancies) [27]. In the present study, no significant difference was found in terms of indication to RAI ablation therapy and ^{131}I dose of administration, although our results may be limited by the small sample size.

A risky overuse of radioiodine administration is just one of the arguments of those against the routine use of PCND. Opponents also claim that to date there is no clear evidence to support that PCND improves survival [4,8–12,16–18]. The natural good prognosis of this form of thyroid cancer, as well as the generally short-term follow-up and heterogeneity of population in many studies, may certainly hinder the ability to demonstrate a significant difference in terms of disease-free survival and recurrence rates between TT with PCND and TT alone [11,22,28,29]. Although this issue could be resolved with a prospective randomized clinical trial, an ATA special subcommittee found that the sample size and length of follow-up required for a statistically significant outcome make it not readily feasible [30]. Anyhow, Nixon IJ et al [17]. recently published the results of an observational study which aimed to describe the outcomes for 1798 patients with PTC who did not undergo PCND. The authors reported a 5-year disease-specific survival of 100%, whereas 5-year recurrence-free survival and central-neck recurrence-free survival were 96.6% and 99.1%, respectively. More than 80% of reoperation for thyroid cancer were performed within the first 2 years of postoperative follow-up, suggesting that the described median follow-up of 46 months should have been considered adequate to identify the majority of recurrences in this cohort of patients. In the present study, overall mean follow-up period was 56.5 months and it was significantly longer in the TT alone group. This can be easily explained by considering that the TT alone group encompassed patients operated over a 15-year time-frame beginning 2000, whereas TT with PCND group included patients over a 8-year interval beginning 2007. In any case, no major difference was found between the two groups in terms of overall survival, tumor-specific survival and recurrence rates, thus supporting what previously reported by other literature data [7–12,17–22,27–30].

Another issue of controversy is that the clinical impact of subclinical central lymph node metastasis is yet to be demonstrated. Lymph node metastasis is a known significant predictor of overall survival, especially in older patients [4,31]. This is reflected also in the AJCC TNM staging system, in which lymph node metastasis in a patient aged older than 45 years moves the stage from I to III [4]. However, the TNM classification does not differentiate between macro- ($\geq$2 mm) and micrometastatic (<2 mm) lymph nodes. Indeed, the risk of recurrence has been shown to relate to the primary tumor characteristics and patient age, but also the size, number, extracapsular spread and location of metastatic lymph nodes play a significant role in predicting recurrence, with lower disease-free survival rates in patients with macrometastases when compared to those with micrometastases [4–8,11,32–35]. In a prospective randomized controlled single institution trial performed by Viola et al. [7], after 5 years of follow-up no difference was observed in the outcome of patients treated by means of TT with PCND when compared to those treated by TT alone. In particular, although almost 50% of the patients with PTC had micrometastatic lymph nodes in the central compartment, none of the presurgical features analyzed, including BRAF mutation, was able to predict their presence, nor to be aware of their presence seemed to have any effect on the outcome. Therefore, the identification of microscopic nodal disease, while frequent, must be carefully used when staging a patient since it may cause an unnecessary increase in radioactive iodine utilization. In our case series, micrometastases were found in about one third of PCND patients and they represented 75% of all pN + cases. Although micrometastic lymph node appreciably added on a more accurate staging of disease, a significant difference was found only for AJCC stage I and no considerable discrepancy was found in terms of overall survival, disease-free survival and RAI treatment.

A potential bias of our study is represented by the fact that the CND was not performed routinely but according to the surgeon's judgment of the surgical field and potential risk factors, i.e. sex, age, familiarity, BRAFV600E mutation status (when available), tumor diameter (larger than 10 mm), extrathyroidal extension and suspicious lymph nodes at the time of surgery. We want to stress that it was decided to make the PCND in patients with potential risk factors, even in the absence of lymph nodes macroscopically suspicious at the cervical surgical exploration. Group A encompassed also cN0 patients who on operative assessment were discovered to have suspicious and/or enlarged lymph nodes. Although they underwent *de facto* a bilateral therapeutic lymphadenectomy, for the purpose of this study and in accordance with previously published trials [36–44], these patients were still included in the prophylactic set. In addition, we underline the, although lymph nodes may have appeared suspicious or enlarged on macroscopical evaluation, histopathologic examination did not always revealed tumor disease in the surgical specimen.A further important matter of consideration in regard to PCND is the associated risk for postoperative complications even when performed by skillful and experienced hands [4,8–12,16–18]. In our study, overall complication rate was drastically higher in the group of patients undergoing PCND, whose incidence was almost doubled when compared to the TT alone group (39.2% vs. 17.8%, $p = 0.0006$). In particular, statistical analysis showed that PCND patients presented a considerably increased risk of temporary RLN injury ($p = 0.009$) and permanent hypoparathyroidism ($p = 0.016$), whereas permanent RLN injury and temporary hypoparathyroidism did not reach statistical significance ($p = 0.303$ and $p = 0.069$, respectively). These results are comparable to other published analyses [7–12,18,22,27,36]. Overall, literature data agree in stating that, although relatively safe in the hands of experienced surgeons, PCND carries a not negligible risk of long-term morbidities, especially in terms of transient and permanent hypoparathyroidism. To address this issue, in recent years several authors have introduced a more limited (ipsilateral) central neck dissection as an alternative treatment for patients with unilateral PTC in order to reduce the morbidity associated with PCND [36–44].

In our study, when further subdividing the PCND group between ipsilateral and bilateral central neck dissection, no significant difference was found neither in terms of RLN injury nor in terms of hypoparathyroidism ($p = 0.23$ and $p = 0.25$, respectively).

When considering published literature data, most studies concur in reporting for ipsilateral PCND similar short-term oncologic outcomes and lower risk of postoperative complications, namely transient hypocalcemia [37,39]. However, it does not go unnoticed that ipsilateral central neck dissection may imply the risk of overlooking contralateral metastases in up to one fourth of the patients [37,41,43,44]. For this reason, frozen section examination (FSE) has been proposed to identify who could benefit from bilateral central compartment node dissection. In particular, Raffaelli M. et Al [45]. demonstrated that frozen section examination on the ipsilateral central neck nodes is highly accurate in predicting node metastases in clinically unifocal cN0 PTC patients and can be useful in determining the extension of central compartment node dissection.

False-negative results were reported mainly in case of micrometastases which, as already stated, have limited clinical implications [44,45].

Since there is no consensus regarding routine PCND in cN0 PTC patients, it appears blatantly clear how identification of prognostic factors for central lymph node metastases could assist surgeons in

determining whether the procedure should be performed.

Our study evaluated the potential benefits of performing prophylactic central neck dissection (CND) with total thyroidectomy in management of papillary thyroid carcinoma patients who were clinically node-negative (cN0) at presentation (stage T1 or T2 at the preoperative evaluation).The limit of our study, we comprehend, is that the study is not completely prospective, because only patients enrolled since 2007 underwent PCND. In addition the patients weren't randomly assigned to two groups: TT + PCND group (group A) or TT group (group B). Nevertheless, in our opinion, our study represents a prospective long-term trial and may be useful to validate the benefits of prophylactic central compartment lymph node dissection in papillary thyroid cancer (PTC). After 15 years of follow-up, no difference was observed in the outcome of the two groups. However, a higher prevalence of permanent hypoparathyroidism was observed in Group A ($P = 0.016$).

Although results are conflicting due to variation in the study settings and heterogeneity of population, most papers agree in recognizing the following variables as independent preoperative risk factors for central lymph node metastases: age <45 years, male sex, $BRAF^{V600E}$ mutation, familiarity, multifocality, tumor size >1 cm, and aggressive pathological variants. These characteristics should be considered in association with lymphovascular invasion, capsular invasion and extrathyroidal extension, which are intra- or postoperatively acquired [8,9,46–53]. However, more prospective clinical trials are needed to unquestionably define clear benefits on long-term outcomes.

5. Conclusion

The risk for postoperative complication is significantly increased in PCND patients, without clear evidence of reduction in recurrence or added benefit survival. Therefore, though existing literature data are still conflicting, it is our firm belief that PCND should be avoided in the treatment of cN0 PTCs, reserving the procedure to “high-risk” patients to reduce the local recurrence rate. More studies are needed to determinate preoperative and postoperative predictive risk factors useful in planning tailored therapeutic approaches.

Ethical approval

The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

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Author contribution

Chiara Dobrinja: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Marina Troian: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Tommaso Cipolat Mis: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Giacomo Rebez: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data and patients' follow-up.

Stella Bernardi: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Bruno Fabris: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Lanfranco Piscopello: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Petra Makovac: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Fernando Di Gregorio: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Nicolò de Manzini: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Note: Chiara Dobrinja and Marina Troian equally contributed to this work.

Conflicts of interest

All Authors have no conflict of interests.

Guarantor

Chiara Dobrinja.

Research registration unique identifying number (UIN)

I registered my study but I'm waiting for the UIN.

Informed consent

Informed consent has been obtained from all individuals included in this study.

References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics 2016, CA Cancer J. Clin. 66 (2016) 7–30.

[2] K.D. Miller, R.L. Siegel, C.C. Lin, A.B. Mariotto, J.L. Kramer, J.H. Rowland, K.D. Stein, R. Alteri, A. Jemal, Cancer treatment and survivorship statistics 2016, CA Cancer J. Clin. 66 (2016) 271–289.

[3] American Cancer Society, Cancer Facts and Figures, 2015. http://www.cancer.org/cancer/thyroidcancer/.

[4] B.R. Haugen, E.K. Alexander, K.C. Bible, G.M. Doherty, S.J. Mandel, Y.E. Nikiforov, F. Pacini, G.W. Randolph, A.M. Sawka, M. Schlumberger, K.G. Schuff, S.I. Sherman, J.A. Sosa, D.L. Steward, R.M. Tuttle, L. Wartofsky, 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer, Thyroid 26 (1) (2016) 1–133.

[5] M. Barczyński, A. Konturek, M. Stopa, W. Nowak, Prophylactic central neck dissection for papillary thyroid cancer, Br. J. Surg. 100 (2013) 410–418.

[6] M. Barczyński, A. Konturek, M. Stopa, W. Nowak, Nodal recurrence in the lateral neck after total thyroidectomy with prophylactic central neck dissection for papillary thyroid cancer, Langenbecks Arch. Surg. 399 (2014) 237–244.

[7] D. Viola, G. Materazzi, L. Valerio, E. Molinaro, L. Agate, P. Faviana, V. Seccia, E. Sensi, C. Romei, P. Piaggi, L. Torregrossa, S. Sellari-Franceschini, F. Basolo, P. Vitti, R. Elisei, P. Miccoli, Prophylactic central compartment lymph node dissection in papillary thyroid carcinoma: clinical implications derived from the first prospective randomized controlled single institution study, J. Clin. Endocrinol. Metab. 100 (2015) 1316–1324.

[8] G. Conzo, E. Tartaglia, N. Avenia, P.G. Calò, A. de Bellis, K. Esposito, C. Gambardella, S. Iorio, D. Pasquali, L. Santini, M.A. Sinisi, A.A. Sinisi, M. Testini, A. Polistena, G. Bellastella, Role of prophylactic central

compartment lymph node dissection in clinically N0 differentiated thyroid cancer patients: analysis of risk factors and review of modern trends, World J. Surg. Oncol. 141 (2016) 149.
[9] C. Gambardella, E. Tartaglia, A. Nunziata, G. Izzo, G. Siciliano, F. Cavallo, C. Mauriello, S. Napolitano, G. Thomas, D. Testa, F. Rossetti, A. Sanguinetti, N. Avenia, G. Conzo, Clinical significance of prophylactic central compartment neck dissection in the treatment of clinically node-negative papillary thyroid cancer patients, World J. Surg. Oncol. 142 (2016) 247.
[10] J.J. Sancho, T.W. Lennard, I. Paunovic, F. Triponez, A. Sitges-Serra, Prophylactic central neck dissection in papillary thyroid cancer: a consensus report of the European Society of Endocrine Surgeons (ESES), Langenbecks Arch. Surg. 399 (2014) 155–163.
[11] E. Mamelle, I. Borget, S. Leboulleux, H. Mirghani, C. Suárez, P.K. Pellitteri, A.R. Shaha, M. Hamoir, K.T. Robbins, A. Khafif, J.P. Rodrigo, C.E. Silver, A. Rinaldo, A. Ferlito, D.M. Hartl, Impact of prophylactic central neck dissection on oncologic outcomes of papillary thyroid carcinoma: a review, Eur. Arch. Otorhinolaryngol. 272 (2015) 1577–1586.
[12] 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 (2012) 1–10.
[13] Y. Ito, T. Kudo, K. Kobayashi, A. Miya, K. Ichihara, A. Miyauchi, Prognostic factors for recurrence of papillary thyroid carcinoma in the lymph nodes, lung, and bone: analysis of 5,768 patients with average 10-year follow-up, World J. Surg. 36 (2012) 1274–1278.
[14] Y. Ito, A. Miyahuchi, K. Kobayashi, M. Kihara, A. Miya, Static and dynamic prognostic factors of papillary thyroid carcinoma, Endocr. J. 61 (2014) 1145–1151.
[15] A.S. Alzahrani, M. Xing, Impact of lymph node metastases identified on central neck dissection (CND) on the recurrence of papillary thyroid cancer: potential role of $BRAF^{V600E}$ mutation in defining CND, Endocr. Relat. Cancer 20 (2013) 13–22.
[16] T.A. Moo, J. McGill, J. Allendorf, J. Lee, T. Fahey III, R. Zarnegar, Impact of prophylactic central neck lymph node dissection on early recurrence in papillary thyroid carcinoma, World J. Surg. 34 (2010) 1187–1191.
[17] I.J. Nixon, L.Y. Wang, I. Ganly, S.G. Patel, L.G. Morris, J.C. Migliacci, R.M. Tuttle, J.P. Shah, A.R. Shaha, Outcomes for patients with papillary thyroid cancer who do not undergo prophylactic central neck dissection, Br. J. Surg. 103 (2016) 218–225.
[18] P.G. Calò, G. Pisano, F. Medas, J. Marcialis, L. Gordini, E. Erdas, A. Nicolosi, Total thyroidectomy without prophylactic central neck dissection in clinically node-negative papillary thyroid cancer: is it an adequate treatment? World J. Surg. Oncol. 12 (2014) 152.
[19] K.Y. Bilimoria, D.J. Bentrem, C.Y. Ko, A.K. Stewart, D.P. Winchester, M.S. Talamonti, C. Sturgeon, Extent of surgery affects survival for papillary thyroid cancer, Ann. Surg. 246 (2007) 375–384.
[20] G. Conzo, N. Avenia, G.L. Ansaldo, P. Calò, M. De Palma, C. Dobrinja, G. Docimo, C. Gambardella, M. Grasso, C.P. Lombardi, M.R. Pelizzo, A. Pezzolla, L. Pezzullo, M. Piccoli, L. Rosato, G. Siciliano, S. Spiezia, E. Tartaglia, F. Tartaglia, M. Testini, G. Troncone, G. Signoriello, Surgical treatment of thyroid follicular neoplasms: results of a retrospective analysis of a large clinical series, Endocrine 55 (2017) 530–538.
[21] A.R. Glover, J.S. Gundara, O. Norlén, J.C. Lee, S.B. Sidhu, The pros and cons of prophylactic central neck dissection in papillary thyroid carcinoma, Gland. Surg. 2 (2013) 196–205.
[22] T.S. Wang, K. Cheung, F. Farrokhyar, S.A. Roman, J.A. Sosa, A meta-analysis of the effect of prophylactic central compartment neck dissection on locoregional recurrence rates in patients with papillary thyroid cancer, Ann. Surg. Oncol. 20 (2013) 3477–3483.
[23] D.T. Hughes, M.L. White, B.S. Miller, P.G. Gauger, R.E. Burney, G.M. Doherty, Influence of prophylactic central lymph node dissection on postoperative thyroglobulin levels and radioiodine treatment in papillary thyroid cancer, Surgery 148 (2010) 1100–1106.
[24] D.B. Evans, Papillary carcinoma of the thyroid: balancing principles of oncology with emerging technology, Surgery 150 (2011) 1015–1022.
[25] S. Bonnet, D. Hartl, S. Leboulleux, E. Baudin, J.D. Lumbroso, A. Al Ghuzlan, L. Chami, M. Schlumberger, J.P. Travagli, Prophylactic lymph node dissection for papillary thyroid cancer less than 2 cm: implications for radioiodine treatment, J. Clin. Endocrinol. Metab. 94 (2009) 1162–1167.
[26] D.M. Hartl, S. Leboulleux, A. Al Ghuzlan, E. Baudin, L. Chami, M. Schlumberger, J.P. Travagli, Optimization of staging of the neck with prophylactic central and lateral neck dissection for papillary thyroid carcinoma, Ann. Surg. 255 (2012) 777–783.
[27] D.E. Gyorki, B. Untch, R.M. Tuttle, A.R. Shaha, Prophylactic central neck dissection in differentiated thyroid cancer: an assessment of the evidence, Ann. Surg. Oncol. 20 (2013) 2285–2289.
[28] T. Zetoune, X. Keutgen, D. Buitrago, H. Aldailami, H. Shao, M. Mazumdar, T.J. Fahey III, R. Zarnegar, Prophylactic central neck dissection and local recurrence in papillary thyroid cancer: a meta-analysis, Ann. Surg. Oncol. 17 (2010) 3287–3293.
[29] V. Marotta, C. Sciammarella, M. Capasso, A. Testori, C. Pivonello, M.G. Chiofalo, C. Gambardella, M. Grasso, A. Antonino, A. Annunziata, P.E. Macchia, R. Pivonello, L. Santini, G. Botti, S. Losito, L. Pezzullo, A. Colao, A. Faggiano, Germline polymorphisms of the VEGF-pathway predict recurrence in non-advanced differentiated thyroid cancer, J. Clin. Endocrinol. Metab. (2016 Nov 16), http://dx.doi.org/10.1210/jc.2016-2555 [Epub ahead of print], PMID: 27849428.
[30] T. Carling, S.E. Carty, M.M. Ciarleglio, D.S. Cooper, G.M. Doherty, L.T. Kim, R.T. Kloos, Mazzaferri EL. Sr, P.N. Peduzzi, S.A. Roman, R.S. Sipperl, J.A. Sosa, B.C. Stack Jr., D.L. Steward, R.P. Tufano, R.M. Tuttle, R. Udelmans, 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, Thryoid 22 (2012) 237–244.
[31] Y.D. Podnos, D. Smith, L.D. Wagman, J.D. Ellenhorn, The implication of lymph node metastasis on survival in patients with well-differentiated thyroid cancer, Am. Surg. 71 (2005) 731–734.
[32] G.W. Randolph, Q.Y. Duh, K.S. Heller, V.A. LiVolsi, S.J. Mandel, D.L. Steward, R.P. Tufano, R.M. Tuttle, American Thyroid Association Surgical Affairs Committee's Taskforce on Thyroid Cancer Nodal Surgery, The prognostic significance of nodal metastases from papillary thyroid carcinoma can be stratified based on the size and number of metastatic lymph nodes, as well as the presence of extranodal extension, Thyroid 22 (2012) 1144–1152.
[33] I.M. Cranshaw, B. Carnaille, Micrometastases in thyroid cancer. An important finding? Surg. Oncol. 17 (2008) 235–238.
[34] R. Ducoudray, C. Trésallet, G. Godiris-Petit, F. Tissier, L. Leenhardt, F. Menegaux, Prophylactic lymph node dissection in papillary thyroid carcinoma: is there a place for lateral neck dissection? World J. Surg. 37 (2013) 1584–1591.
[35] B.H. Lang, A.H. Tang, K.P. Wong, T.W. Shek, K.Y. Wan, C.Y. Lo, Significance of size of lymph node metastasis on postsurgical stimulated thyroglobulin levels after prophylactic unilateral central neck dissection in papillary thyroid carcinoma, Ann. Surg. Oncol. 19 (2012) 3472–3478.
[36] 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 (2012) 911–917.
[37] M. Raffaelli, C. De Crea, L. Sessa, P. Giustacchini, L. Revelli, C. Bellantone, C.P. Lombardi, Prospective evaluation of total thyroidectomy versus ipsilateral versus bilateral central neck dissection in patients with clinically node-negative papillary thyroid carcinoma, Surgery 152 (2012) 957–964, http://dx.doi.org/10.1016/j.surg.2012.08.053.
[38] M.R. Pelizzo, I.M. Boschin, M. Variolo, G. Carrozzo, C. Pagetta, O. Lora, A. Piotto, C. Dobrinja, Central node neck dissection for papillary thyroid carcinoma: clinical implications, surgical complications and follow up. A prospective vs a restrospective study, J. Clin. Exp. Pathol. 5 (2015) 259, http://dx.doi.org/10.4172/2161-0681.1000259.
[39] P.G. Calò, G. Conzo, M. Raffaelli, F. Medas, C. Gambardella, C. De Crea, L. Gordini, R. Patrone, L. Sessa, E. Erdas, E. Tartaglia, C.P. Lombardi, Total thyroidectomy alone versus ipsilateral versus bilateral prophylactic central neck dissection in clinically node-negative differentiated thyroid carcinoma. A retrospective multicenter study, Eur. J. Surg. Oncol. (2016) 30931–30933. S0748-7983.
[40] P.G. Calò, F. Medas, G. Pisano, F. Boi, G. Baghino, S. Mariotti, A. Nicolosi, Differentiated thyroid cancer: indications and extent of central neck dissection—our experience, Int. J. Surg. Oncol. 2013 (2013) 625193.
[41] Y.I. Son, H.S. Jeong, C.H. Baek, M.K. Chung, J. Ryu, J.H. Chung, Y.K. So, J.Y. Jang, J. Choi, Extent of prophylactic lymph node dissection in the central neck area of the patients with papillary thyroid carcinoma: comparison of limited versus comprehensive lymph node dissection in a 2-year safety study, Ann. Surg. Oncol. 15 (2008) 2020–2026.
[42] B.S. Koo, E.C. Choi, Y.H. Yoon, D.H. Kim, E.H. Kim, Y.C. Lim, Predictive factors for ipsilateral or contralateral central lymph node metastasis in unilateral papillary thyroid carcinoma, Ann. Surg. 249 (2009) 840–844.
[43] B.H. Lang, K.P. Wong, K.Y. Wan, C.Y. Lo, Impact of routine unilateral central neck dissection on preablative and postablative stimulated thyroglobulin levels after total thyroidectomy in papillary thyroid carcinoma, Ann. Surg. Oncol. 19 (2012) 60–67.
[44] M. Raffaelli, C. De Crea, L. Sessa, P. Giustacchini, R. Bellantone, C.P. Lombardi, Can intraoperative frozen section influence the extension of central neck dissection in cN0 papillary thyroid carcinoma? Langenbecks Arch. Surg. 398 (2013) 383–388.
[45] M. Raffaelli, C. De Crea, L. Sessa, G. Fadda, C. Bellantone, C.P. Lombardi, Ipsilateral central neck dissection plus frozen section examination versus prophylactic bilateral central neck dissection in cN0 papillary thyroid carcinoma, Ann. Surg. Oncol. 22 (2015) 2302–2308.
[46] H. Qu, G.-R. Sun, Y. Liu, Q.-S. He, Clinical risk factors for central lymph node metastasis in papillary thyroid carcinoma: a systematic review and meta-analysis, Clin. Endocrinol. 83 (2015) 124–132.
[47] J.W. Lee, B.S. Koo, The prognostic implication and potential role of BRAF mutation in the decision to perform elective neck dissection for thyroid cancer, Gland. Surg. 2 (2013) 206–211.
[48] D.L.S. Danilovic, E.U. Lima, R.B. Domingues, L.G. Brandão, Hoff Ao, S. Marui, Pre-operative role of BRAF in the guidance of the surgical approach and prognosis of differentiated thyroid carcinoma, Eur. J. Endocrinol. 170 (2014) 619–625.
[49] T.P. de Castro, W. Waissmann, T.C. Simões, R.C. de Mello, D.P. Carvalho, Predictors for papillary thyroid cancer persistence and recurrence: a retrospective analysis with a 10-year follow-up cohort study, Clin. Endocrinol. (Oxf) 85 (2016) 466–474.
[50] P. Suman, C.H. Wang, S.S. Abadin, T.A. Moo-Young, R.A. Prinz, D.J. Winchester,

Risk factors for central lymph node metastasis in papillary thyroid carcinoma: a National Cancer Data Base (NCDB) study, Surgery 159 (2016) 31–39.
[51] H. Yan, X. Zhou, H. Jin, X. Li, M. Zheng, X. Ming, R. Wang, J. Liu, A study on central lymph node metastasis in 543 cN0 papillary thyroid carcinoma patients, Int. J. Endocrinol. 2016 (2016) 1878194.
[52] B. Ma, Y. Wang, S. Yang, Q. Ji, Predictive factors for central lymph node metastasis in patients with cN0 papillary thyroid carcinoma: a systematic review and meta-analysis, Int. J. Surg. 28 (2016) 153–161.
[53] W. Sun, X. Lan, H. Zhang, W. Dong, Z. Wang, L. He, T. Zhang, S. Liu, Risk factors for central lymph node metastasis in cN0 papillary thyroid carcinoma: a systematic review and meta-analysis, PLoS One 10 (2015) e0139021.