The online version of this article is located at http://www.minervamedica.it

Minerva Chirurgica 2016 June;71(3):159-67

ORIGINAL ARTICLE

Role of prophylactic central neck dissection in cN0-papillary thyroid carcinoma: results from a high-prevalence area

Gregorio SCERRINO [1], Andrea ATTARD [2], Giuseppina Irene MELFA [1], Cristina RASPANTI [1], Silvia DI GIOVANNI [1*], Marco ATTARD [3], Angela INVIATI [1], Sergio MAZZOLA [4], Giuseppe MODICA [2], Gaspare GULOTTA[1], Sebastiano BONVENTRE[1]

[1]Unit of General and Emergency Surgery, Department of General, Emergency and Transplant Surgery, P. Giaccone Policlinico, Palermo, Italy; [2]Section of General and Thoracic Surgery, Department of General, Emergency and Transplant Surgery, P. Giaccone Policlinico, Palermo, Italy; [3]Unit of Endocrinology, V. Cervello Hospital, Palermo, Italy; [4]Political Sciences Faculty, University of Palermo, Palermo, Italy

*Corresponding author: Silvia Di Giovanni, Unit of General and Emergency Surgery, Department of General, Emergency and Transplant Surgery, P. Giaccone Policlinico, Via L. Giuffré 5, 90127, Palermo, Italy. E-mail: gregorio.scerrino@tiscali.it

ABSTRACT

BACKGROUND: Prophylactic, compartment-oriented central neck dissection (CND) for cN0 papillary thyroid carcinoma (PTC) is not widely practiced. We examined our results with this surgical approach.

METHODS: A cohort of 158 patients operated on for the classical variant of PTC at a follow-up of 1-22 years (mean: 6.6) were enrolled. The patients with a preoperative diagnosis of cN0 PTC (group A, 59 patients) underwent total thyroidectomy (TT) + CND. In the patients with incidental postoperative diagnosis of malignancy (group B, 99 patients) a TT alone was performed.

RESULTS: Ninety-six T1, 36 T2, 26 T3/T4 PTC patients were enrolled. The overall biochemical/scintigraphic recurrence rate (15 patients, 9.49%), was significantly higher in group B. Disease-free survival and need for postoperative radioiodine ablative treatment were more favorable in group A ($P<0.05$; $P<0.001$, respectively). The median radioiodine ablative treatment in the T2 cluster alone was lower in group A ($P<0.001$). The morbidity rate was similar in both groups.

CONCLUSION: Considering the acceptable morbidity, prophylactic CND seems to be advantageous in terms of recurrence rate and need for radioiodine treatment in this variant of PTC, at least in T2 or more advanced stages. The indolent behavior of PTC does not allow for reliable prognostic evaluations.

(*Cite this article as*: Scerrino G, Attard A, Melfa GI, Raspanti C, Di Giovanni S, Attard M. Role of prophylactic central neck dissection in cn0-papillary thyroid carcinoma: results from a high-prevalence area. Minerva Chir 2016;71:159-67)

Key words: Thyroid cancer, papillary - Thyroidectomy - Neck dissection - Recurrence - Therapeutics.

The classical variant of papillary thyroid carcinoma (PTC), the focus of this study, is one of the most common endocrine malignancies.[1, 2]. Though it is a highly indolent neoplasia, with an overall 10-year survival rate of more than 90%,[3, 4] lymph node metastases in central and lateral neck compartments are frequent; [4, 5] however, their impact on survival seems to be quite limited.[6]

The central neck compartment is defined as the anatomical area delimited from the hyoid bone, the sternal notch, and the innominate artery, and bilaterally from the common carotid arteries. The lymph nodes of this site include pretracheal, paratracheal, and precricoid (delphian) perithyroidal (including nodes along inferior laryngeal nerves) nodes. The cervicolateral compartments, right and left, are

the lymph node systems between the carotid sheaths and the trapezius muscles, and bilaterally, and between the subclavian vein to the hypoglossic nerve.[6, 7]

The surgical treatment of PTC is total thyroidectomy (TT),[1-4] though in some countries thyroid lobectomy is considered an acceptable surgical option for small, low risk PTCs.[5]

Treatment of central and/or lateral neck nodal metastases in PTC is generally accepted.[4, 5] Therapeutic neck dissection is performed in patients with known lymph node metastases. Ultrasonography (US) and even simple physical examination are commonly accepted diagnostic means for indicating this surgical approach.[8]

Prophylactic, compartment-oriented central neck dissection (CND) in cN0 PTC is widely accepted only in advanced stages of the disease. The 2009 American Thyroid Association (ATA) consensus statement recommends prophylactic CND only in T3-T4 stages of the disease.[9, 10] The evidence supporting the effectiveness of prophylactic CND in reducing recurrence and mortality in PTC is limited,[11] and the advantages of that extended excision in terms of survival or locoregional disease control remain unclear.[12-14] Our institutional protocol, until the end of 2002, for patients operated on for PTC required that they not undergo systematic CND. Effective at the beginning of 2003, and as a result of a re-evaluation of our results and a subsequent internal audit, all patients diagnosed preoperatively with PTC have systematically undergone a prophylactic CND, except those with "low risk" tumors,[15] *e.g.*, smaller than 1 cm.

The aim of this study was to determine whether systematic compartment-oriented CND is advantageous even in less advanced stages of PTC, and which advantages, if any, are associated with this practice.

Materials and methods

This retrospective cohort study was conducted as an institutional review of available data of patients who underwent total thyroidectomy±prophylactic CND for PTC between January, 1990 and September, 2012. We included all patients, traceable during the present follow-up, with a postoperative diagnosis of PTC (stages pT1-pT4) alive at follow-up, with or without signs of recurrence of disease, and for whom medical records were available, from the preoperative assessment to final data collection.

Patients who had previously undergone neck radiation, or under the age of 18, or suffering from a thyroid carcinoma different from papillary variant (included poorly differentiated and anaplastic carcinoma) were excluded. We also excluded papillary microcarcinomas (tumors smaller than 10 millimeters PTmC), multifocal PTC, and patients with a preoperative or intraoperative suspected or proven distant cancer spread, included lymph node involvement. Finally, patients with distant metastases at the postoperative scan following the first radioactive iodine (RAI) administration were also excluded. A total of 158 consenting patients (127 women, 31 men) were enrolled in the study. The demographic, clinical and pathologic data

TABLE I.—*Demographics data and tumor stage.*

	Total	Group A	Group B	P-value
Patients	158	59	99	
Age (mean)	47.29	49.35 (±12.21)	47.84 (±12.32)	P=0.67 (NS)
<45 yrs	58			
>45 yrs	100			
Gender				
Female	127 (80.38%)	46	81	
Male	31 (19.62%)	13	18	
T-Tumorstage				
T1	96 (60.76%)	33	63	P=0.4 (NS)
T2	36 (22.78%)	18	18	P=0.08 (NS)
T3/T4	26 (17.08%)	8	18	P=0.5 (NS)

TABLE II.—*Central compartment metastases in group A.*

	N. patients
Total (59 patients)	33 (57.6%)
T1 (33 patients)	13 (39.4%)
T2 (18)	12 (66.7%)
T3/T4 (8)	8 (100%)

and the stage division are reported in Table I. Fifty-nine patients (group A) had a preoperative diagnosis of PTC; in 99 (group B) a diagnosis of benign disease had been assumed. Table II shows the incidence of central compartment lymph node metastases found in group A. The two groups were similar in terms of age, gender, and tumor stage (Table I). Follow-up was carried out by outpatient consultation or direct, detailed telephone interview. The patients were followed for a mean of 6.6±1-22 years.

The present study was performed in accordance with the ethical standards of the Declaration of Helsinki (1964) and its later amendments.

The Ethics Committee of the Policlinico Universitario Paolo Giaccone approved this study.

Preoperative management

All patients had undergone a preoperative diagnostic protocol including clinical examination, laboratory tests (TSH, FT3, FT4, thyroid antibodies if a thyroid autoimmune disease was suspected), scintigraphy and/or ultrasound, as recommended in guidelines available at the time of inclusion.[5, 9] All patients with suspicious nodules underwent fine-needle aspiration (FNA) biopsy, with the aim of confirming a diagnosis of PTC. A preoperative fiber optic laryngoscopy was also performed.

Surgery

From 1990 to the end of 2002, all patients with a pre-operative diagnosis of PTC underwent surgery at the discretion of the attending surgeon. From 2003 on, all patients with this pre-operative diagnosis underwent TT+CND as per our department's protocol.

The thyroidectomy was always performed with the knot-tie technique, or, from the late 1990s on, with energy-based surgical instruments, such as ultrasound dissector or thermal device, that proved to have similar results in terms of postoperative complications (hypocalcemia, laryngeal nerve palsy) compared to conventional technique.[16, 17] Parathyroid glands and inferior laryngeal nerves were always identified. No thyroid tissue was purposely left in the surgical site.

The bilateral central lymph node dissection was done according to the compartment classification proposed by Dralle *et al.* [18] adapted to PTC, preserving at least both superior parathyroid glands and the controlateral inferior gland. In cases of removal or devascularization of a parathyroid gland, the gland was placed in cold saline solution. In as timely a way as possible, it was then sliced thinly, and the pieces reimplanted in a sterno-cleido-mastoid separate pocket, which was sutured with a black multifilament non-resorbable suture. The intraoperative frozen section was never performed.

Patients in whom a central compartment specimen contained less than 6 lymph nodes were excluded from the study.

A postoperative fiber optic laryngoscopy was repeated 24-48 hours after surgery. Calcium blood levels were always evaluated 12, 24 and 36-48 hours after surgery, or in cases of appearance of symptoms of hypocalcemia. A calcium-vitamin D treatment was administered if calcemia levels were ≤8 mg/dL (normal range: 8.6-10.2 mg/dL). The calcium-vitamin D supplement was pursued until calcemia settled into the normal range.

Radioiodine treatment

All patients received postoperative whole-body scan 50-90 days after surgery. When necessary, a postoperative RAI treatment after substitutive l-thyroxine treatment withdrawal (until a TSH value >30 mU/L was obtained) was given. Postoperative RAI treatment was not done in T1 PTC if the postoperative scan did not show a radioiodine uptake in the thyroid bed. The radioiodine dose was measured in MBq.

Follow-up

The goal of l-thyroxin substitutive treatment after surgery was to obtain TSH levels =0.1-0.5 mU/L. After these values were obtained, all patients underwent TSH dosage at least 6 months after surgery.

All patients underwent at least 1 clinical examination + stimulated thyroglobulin (Tg) + anti-thyroglobulin antibodies (ATA) + US scan 1 year after radioiodine treatment. Follow-up was repeated yearly. The Tg value was considered undetectable after TSH stimulation if it was < 2 ng/mL. If a value of 2-10 ng/mL was found, the exam was repeated in 6-12 months. If the value increased, it was considered recurrence, as it was if a palpable neck mass or a growing thyroid tissue at US scan were found. The criteria for recurrence were increasing Tg levels and/or thyroid tissue growing in the thyroid bed + positive cervical/whole body scan. The patients who suffered from recurrence were treated with radioiodine and/or re-surgery.

Study endpoints

The goals of the study were to evaluate the recurrence rate, the disease-free interval (DFI), the need for postoperative ablative radioiodine, and the retreatment (surgery, radioiodine) rate in each group of patients, stratified according to tumor size. In the case of retreatment, we considered the cumulative dose of radioiodine administered in these patients or the reoperations done in the surgical site. Finally, we examined the rate of transient (compressive hematoma) and permanent (vocal cord palsy; hypoparathyroidism) complications in both groups.

Statistical analysis

The analysis was done by calculating the relative risk (RR) for categorical variables (recurrence in groups A and B) because of the largeness of the cohort, and for which Fisher's exact text was not applicable. If the RR was <1, the risk of the recurrence was lower in group A (TT+CND). A Student's *t*-test for comparison of means was used only in patients who underwent RAI ablation (a total of 120 in groups A and B). Moreover, we compared all 158 patients with a nonparametric test (Kolmogorov-Smirnov) for a comparison of medians. Overall disease-free survival was calculated using the Kaplan-Meyer inverse method; the log rank test was used for comparison study groups. A P-value of 0.05 was used as the cut-off for statistical significance. The data were collected in a dedicated database (Microsoft Excel®, Microsoft Corporation, Redmond, WA, USA) and analyzed by a professional statistician. Statistical analyses were done with the STATA 12 software (StataCorp LP, 4905 Lakeway Drive, College Station, TX, USA).

Results

A total of 158 consenting patients (127 women, 31 men) were enrolled in the study. The demographic, clinical and pathologic data and the stage division are reported in Table I. Fifty-nine patients (group A) had a preoperative diagnosis of PTC; in 99 (group B) a diagnosis of benign disease had been assumed. Table II shows the incidence of central compartment lymph node metastases found in group A. The two groups were similar in terms of age, gender, and tumor stage (Table I).

Rate of recurrence

In all, in 15 patients (9.49%) we observed a recurrence, which was again treated in 11 cases with radioiodine, and in 4 cases with RAI ablation and, then, re-surgery. The patients in group B had a relevant increase in recurrence rate (13/99) compared with group A (2/59). The recurrences observed in the group A were always in the thyroid bed; the recurrences of the group B were: 5 in the thyroid bed; 5 in the central compartment (1 treated with re-surgery); 3 in the lateral compartment (reoperated on for radical modified lateral neck dissection). With the RR=0.258

TABLE III.—*Recurrence rate.*

	Recurrence	Group A	Group B	P.value
Overall Average	15/158 (9.49%)	2/59 (3.39%)	13/99 (13.13%)	<0.05
T1	5/96 (5.2%)	0	5	NS
T2	4/36 (11.1%)	0	4	NS
T3/T4	6/26 (23%)	2	4	0.62
<45 yrs	7	1	6	0.179
≥45 yrs	8	1	7	0.129
RAI (120)	14	1	13	<0.02

(<1), the risk of recurrence in group A was significantly lower than in group B (P<0.05). These results were confirmed in the cluster of patients who underwent postoperative RAI ablation (total=120) (P<0.02). Stratifying the cohort according to the T-stage, the small samples that we obtained did not allow for statistical significance in terms of recurrence. It is interesting to note that in T1 and T2 stages, in a total of 9 recurrences, none of the patients had undergone CND. Stratifying all the patients according to age (< 45y; ≥45y) no differences were found in terms of recurrence (Table III).

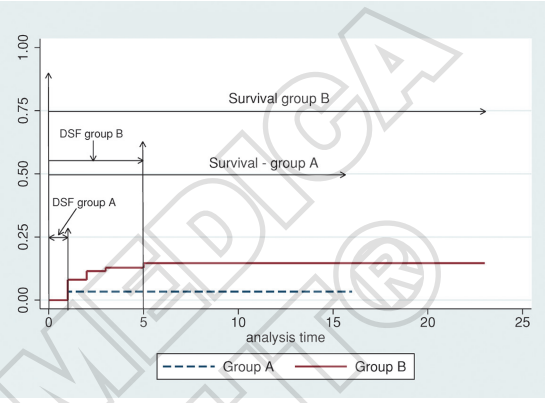

Figure 1.—Kaplan-Meier recurrence estimates.

Disease-free interval

Figure 1 (inverse Kaplan Meyer function) shows the time of recurrence, which corresponds to retreatment (radioiodine and/or surgery). In group A, the Kaplan-Meyer inverse function showed a recurrence probability of 3.4%, with a DFI of 0-1 year. In group B, this probability was 14.6%, with a DFI of 0-5 years. As a result, the probability of living without disease was =0.966, beginning with the second postoperative year in group A, and 0.854 with effect from the fifth postoperative year in group B. The difference between the two groups, verified by means of the log-rank test, was significant (P<0.05).

Postoperative RAI ablation

With the aim of verifying whether there were differences between the two groups in terms of need for postoperative RAI treatment (Table IV), we first first calculated the difference between the means of total amount of radioiodine in MBq administered in both groups, and found a statistically significant difference (P<0.002). Moreover, we calculated the same difference in terms of medians and once again found a statistically significant difference (P<0.001). In the cluster of patients at T2 stage, a difference in terms of median value of postoperative RAI was found (group A: median 1850 MBq; group B: median 3700 MBq) (P<0.001) (Table IV). The aggregation of results of T2+T3+T4 stages showed a statistically significant difference in terms of need for RAI treatment. A box-plot graph illustrates this result (Figure 2).

Postoperative complications

No significant postoperative bleeding causing compressive hematoma occurred in either group. Moreover, the rate of permanent complications was similar, though the rate of vocal cord palsy was of borderline statistical significance (TableV).

TABLE IV.—*Need for RAI (MBq).*

	Group A (59 patients)	Group B (99 patients)	P value
Overall average	1852.03	2229.75	<0.002
Patients treated with RAI	46	74	
MBq (Mean)	2375.40	2983.10	<0.002
Overall median	1850	2590	<0.001
T2 stage	18	18	
Median MBq in T2Stage	1850	3700	<0.001

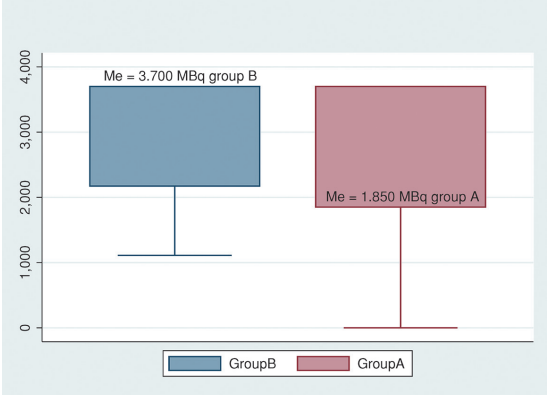

Figure 2.—Median radioiodine dosage in T2-T3-T4 stages. Conparison between the two groups.

TABLE V.—*Complications.*

	Group A (59 patients)	Group B (99 patients)	P value
RLN Palsy	4	1	0.06 (NS)
Hypoparathyroidism	3	5	0.6 (NS)

Discussion

Given the very good prognosis for PTC, the role of pCND as completion of TT remains controversial. This procedure is commonly accepted in advanced stages of the disease.[5, 9] Advocates of pCND cite the high incidence of metastases in the VI compartment, the higher recurrence rate in patients previously treated with TT alone, the better biochemical results in terms of Tg levels in patients who have undergone TT + CND, and the higher iatrogenic risk (hypoparathyroidism, inferior laryngeal nerve damage) in the re-operative approach for CND.[10, 19] The high incidence of nodal metastases in PTC has been well documented in several studies,[20-22] even in papillary thyroid microcarcinoma,[22, 23] though this type of cancer is not within the scope of our study. Few studies recommend pCND for all stages of PTC.[20, 21] Other studies suggest a risk-stratified selection of patients, with the aim of setting a limit on the indications for pCND.[24, 25] Several studies have underscored the fact that the prognostic impact of occult metastases or micrometastases on level VI lymph nodes, which has been reported in approximately 40% of cases,[26, 27] is clearly unfavorable. Moreover, the low rate of persistent or recurrent disease in the central compartment in short-term follow-up should be considered, and there is no evidence that pCND improves survival.[27, 28] Finally, one study provided evidence of the safety of a wait and watch approach for the central neck alone in terms of disease free survival, finding a very low rate of recurrence in the neck, no re-operation, and no mortality.[27]

Given the lack of data evidencing the advantages and disadvantages of pCND, several reviews, assessments of evidence, and meta-analyses have been published.[20, 29-31] The findings are once again controversial, with evidence of some moderate advantages of pCND, though these were generally not statistically significant.[30]

Other studies have considered the costs of pCND, attributable principally to longer duration and greater complexity of the surgical procedure, increase in rate of complications, and higher percentage of patients recruited for RAI ablation.[32] These studies, which are not in complete agreement, seem to indicate that pCND becomes cost-effective if the overall recurrence-rate is high (>10.3%), and the follow-up is >9 years.[33, 34]

With the aim of settling this question, a pro-

spective randomized controlled trial of pCND should be done, though it is probably not feasible.[14, 21]

Our study confirms that the pCND improves the overall results in terms of recurrence rate in all stages of PTC without a strong association with risk-stratification, even though we are conscious that in retrospective cohort studies considering extended follow-ups (1-22 years) some sources of bias, such as the changes in RIA protocols over a period of several years, or rotations in surgical teams, should be considered. Nevertheless, most of the criteria recommended in a recent consensus of ESES [24] were respected in our study. In fact, pCND was homogeneous in all our patients (formally complete, bilateral), therapeutic CND and the lateral neck dissections were not included, and the thyroglobulin measurement was homogeneous. Several risk criteria, such as age (<45 years; ≥45 years), though not statistically significant in our study, were also considered.

Our results confirm that the recurrence rate in the cohort considered as a whole is more favorable in patients who underwent TT+CND. Though in the groups stratified per tumor size no significant difference in recurrence was found, we observed that in T1 and T2 stages no recurrences were observed in the patients who underwent pCND. An interesting finding was offered by a Kaplan Meyer disease-free survival curve and related log rank test: in fact the patients who underwent TT alone had a higher risk of recurrence over a longer period of time. Moreover, the total amount of RAI treatment was lower in the group of patients treated with CND, in the T2-cluster considered separately, as well as in T2+T3+T4 aggregated stages. Our experience with pCND found it to be safe in terms of permanent complications, which were similar in both groups. We did not consider transient complications, evaluated in another study,[35] which have been reported as slightly higher than our experience, primarily concerning transient hypoparathyroidism.[36]

The varying reported experiences of teams in the presence of PTC naturally raise a question: is the variability attributable to the teams, or is PTC a non-homogeneous group of tumors that present with different features and, in particular, carry variable prognoses? It is extremely difficult to offer a conclusive answer to this question. Several genetic and molecular studies [37, 38] suggest that the behavior of PTC likely depends on different biomarkers of the tumor. Some studies [39-42] have identified the BRAF mutation as a molecular marker of aggressiveness of PTC. In some cases, this mutation could likely be a genetic abnormality induced by mutagenic environmental factors, such as a polluting element of volcanic origin.[43, 44]

The fact that our patients came from different areas of Sicily, the majority of whom were potentially exposed, in varying degrees, to volcanic pollution may explain the high rate of lymph node involvement (>40% in T1 PTC≥1 cm.), though more causes of this observation (genetic, environmental) could be involved.

Another series published [45] concluded that pCND does not improve long term disease control and recurrence. These results completely different from our experience could be explained with the different risk factors affecting the population and, subsequently, the different behavior of the PTC.

This is one of the primary factors that prompted us to routinely undertake pCND in the treatment of PTC≥1 cm. in our setting. The good results in terms of morbidity allowed us to continue this practice.

So, pCND is a practice that should be validated, ideally, with prospective randomized studies or, at least, with studies involving large cohorts with longer follow-up.

Conclusions

In the absence of more compelling data, the choice of routinely introducing this technique, which is burdened by a longer operative time and, generally speaking, by a higher level of complexity, depends on personal experience and skill of the surgical team. We introduced pCND into our routine practice because of the ascertainment, in patients at our institute, of the high incidence of lymph node involvement in the central compartment.

We are encouraged by our positive results

in reducing the recurrence rate, improving disease-free survival expectation, controlling radioiodine treatment (at least in T2 or more advanced stages), and the low incidence of post-surgical complications.

References

1. Ahmadieh H, Azar ST. Controversies in the management and follow-up of differentiated thyroid cancer:Beyond the guidelines. J Thyr Res 2012;2012:512401.
2. Ito Y, Fukushima M, Higashiyama T, Kihara M, Takamura Y, Kobayashi K, *et al*. Tumor size is the strongest predictor of microscopic lymph node metastasis and lymph node recurrence of N0 papillary thyroid carcinoma. Endocr J 2013;60:113-7.
3. Hundahl SA, Fleming ID, Fremgen AM, Menck HR. A national cancer data base report on 53,856 cases of thyroid carcinoma treated in the US, 1985-1995. Cancer 1998;83:2638-48.
4. Costa S, Giugliano G, Santoro L, Ywata De Carvalho A, Massaro MA, Gibelli B, *et al*. Role of prophylactic central neck dissection in cN0 papillary thyroid cancer. Acta Otorhinolaryngol Ital 2009;29:61-9.
5. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, *et al*. Management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2006;16:109-42.
6. Dralle H, Machens A. Surgical Approaches in thyroid cancer and lymph-node metastases. Best Pract Res Clin Endocrinol Metab 2008;22:971-87.
7. Musholt TJ. Classification of locoregional lymph nodes in medullary and papillary thyroid cancer. Langenbecks Arch Surg 2014;399:217-23.
8. Hartl DM, Mamelle E, Borget I, Leboulleux S, Mirghani H, Schlumberger M. Influence of prophylactic neck dissection on rate of retreatment for papillary thyroid carcinoma. World J Surg 2013;37:1951-8.
9. American Thyroid Association (ATA) Guidelines Taskforce on Thyroid Nodules and Differentiated Thyroid Cancer, Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, *et al*. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009;19:1167-214.
10. Hughes DT, Doherty GM. Central Neck Dissection for papillary thyroid cancer. Cancer Control 2011;18:83-8.
11. Tisell LE, Nilsson B, Mölne J, Hansson G, Fjälling M, Jansson S, *et al*. Improved survival of patients with papillary thyroid cancer after surgical microdissection. World J Surg 1996;20:854-9.
12. Shaha AR. Prophylactic central compartment dissection in thyroid cancer: A new avenue of debate. Surgery 2009;146:1224-7.
13. Carling T, Carty SE, Ciarleglio MM, Cooper DS, Doherty GM, Kim LT, *et al*. 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 2012;22:237-445.
14. Shaha AR. Central compartment dissection for papillary thyroid cancer. Brit J Surg2013;100:438-9.
15. Shaha AR, Loree TR, Shah JP. Intermediate risk-group for differentiated carcinoma of the thyroid. Surgery 1994;116:1036-41.
16. Cordón C, Fajardo R, Ramírez J, Herrera MF. A randomized, prospective, parallel group study comparing the harmonic scalpel to electrocautery in thyroidectomy. Surgery 2005;137:337-41.
17. Scerrino G, Paladino NC, Di Paola V, Morfino G, Matranga D, Gulotta G, *et al*. Total thyroidectomy performed with the Starion Vessel Sealing System versus conventional technique: A prospective randomized trial. Surg Innov 2010;17:242-7.
18. Dralle H, Damm I, Scheumann GF, Kotzerke J, Kupsch E, Geerlings H, *et al*. Compartment-oriented microdissection of regional lymph nodes in medullary thyroid carcinoma. Surg Today 1994;24:112-21.
19. Wong KP, Lang BHH. The role of prophylactic central neck dissection in differentiated thyroid carcinoma: issues and controversies. J Oncol 2011;2011:127929.
20. Barczynsky M, Konturek A, Stopa M, Nowak W. Prophylactic central neck dissection for papillary thyroid cancer. Brit J Surg 2013:100:410-8.
21. Wang Q, Chu B, Zhu J, Zhang S, Liu Y, Zhuang M, *et al*. Clinical analisis of prophylactic central neck dissection for papillary thyroid carcinoma. Clin Transl Oncol 2014;16:44-8.
22. Gyorki DE, Untch B, Tuttle RM, Shaha AR. Prophylactic central neck dissection in differentiated thyroid cancer: an assessment of the evidence. Ann Surg Oncol 2013;20:2285-9.
23. Lombardi CP, Bellantone R, De Crea C, Paladino NC, Fadda G, Salvatori M. Papillary thyroid microcarcinoma:Extrathyroidal extension, lymph node metastases, and risk factors for recurrence in a high prevalence of goiter area. World J Surg 2010;34:1214-21.
24. Sancho JJ, Lennard TW, Paunovic I, Triponez F, Sitges-Serra A. Prophylactic central neck dissection in papillary thyroid cancer: a consensus report of the European Society of Endocrine Surgeons (ESES). Langenbecks Arch Surg 2014;399:155-63.
25. Kim WW, Park HY, Jung JH. Surgical extent of central lymph node dissection in clinically node-negative papillary thyroid cancer. Head & Neck 2013;35:1616-20.
26. Hartl DM, Leboulleux S, Al Ghuzlan A, Baudin E, Chami L, Schlumberger M, *et al*. Optimization of staging of the neck with prophylactic central and lateral neck dissection for papillary thyroid carcinoma. Ann Surg 2012;255:777-83.
27. Nixon IJ, Ganly I, Patel SG, Morris LG, Palmer FL, Thomas D, *et al*. Observation of clinically negative central compartment lymph nodes in papillary thyroid carcinoma. Surgery 2013;154:1166-73.
28. Monchik JM, Simon CJ, Caragacianu DL, Thomay AA, Tsai V, Cohen J, *et al*. Does failure to perform prophylactic level VI node dissection leave persistent disease detectable by ultrasonography in patients with low-risk papillary carcinoma of the thyroid? Surgery 2009;146:1182-7.
29. Conzo G, Docimo G, Mauriello C, Gambardella C, Esposito D, Cavallo F, *et al*. The current status of lymph node dissection in the treatment of papillary thyroid cancer. A literature review. Clin Ter 2013;164:e343-6.
30. Wang TS, Cheung K, Farrokhyar F, Roman SA, Sosa JA. 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 2013;20:3477-83.
31. Calò PG, Medas F, Pisano G, Boi F, Baghino G, Mariotti S, *et al*. Differentiated thyroid cancer: indications and extent of central neck dissection-our experience. Int J Surg Oncol 2013;2013:625193.
32. Elfenbein D, Sippel RS. Prophylactic central neck dissection increases the costs of thyroid cancer care. Ann Surg Oncol 2014;21:354-5.
33. Zanocco K, Elabraj D, Sturgeon C. Routine prophy-

lactic central neck dissection for low-risk papillary thyroid cancer:a cost-effectiveness analysis. Surgery 2013;154:1154-5.
34. Wong CKH, Lang BHH. A cost-utility analysis for prophylactic central neck dissection in clinically nodal-negative papillary thyroid carcinoma. Ann Surg Oncol 2014;21:767-77.
35. Scerrino G, Di Giovanni S, Salamone G, *et al* Surgical Complications in prophylactic central neck dissection: preliminary findings from a retrospective cohort study. Minerva Chirurgica 2014;69(2 Suppl. 1):131-4.
36. Henry JF, Gramatica L, Denizot A, Kvachenyuk A, Puccini M, Defechereux T. Morbidity of prophylactic lymph node dissection in the central neck area in patients with papillary thyroid carcinoma. Langenbeks Arch Surg 1998;383:167-9.
37. McLeod DSA, Sawka AM, Cooper DS. Controversies in primary treatment of low-risk papillary thyroid cancer. The Lancet 2013;381:1046-57.
38. Xing M, Haugen BR, Schlumberger MT. Progress in molecular-based management of differentiated thyroid cancer. The Lancet 2013;381:1058-69.
39. Kimura ET, Nikiforova MN, Zhu Z, Knauf JA, Nikiforov YE, Fagin JA. High prevalence of BRAF mutations in thyroid cancer: genetic evidence for constitutive activation of the RET/PTC-RAF-BRAF signaling pathwayin papillary thyroid carcinoma. Cancer Res 2003;63:1454-7.
40. Nikiforova MN, Kimura ET, Gandhi M, Biddinger PW, Knauf JA, Basolo F. BRAF mutations in thyroid tumours are restricted to papillary carcinomas and anaplastic or poorly differentiated carcinomas arising from papillary carcinomas. J Clin Endocrinol Metab 2003;88:5399-404.
41. Xing M. Prognostic utility of BRAF mutationin papillary thyroid cancer. Mol Cell Endocrinol 2010;321:86-93.
42. Miccoli P, Basolo F. BRAF mutation status in papillary thyroid carcinoma: significance for surgical strategy. Langenbecks Arch Surg 2014;399:225-8.
43. Frasca F, Nucera C, Pellegriti G, Gangemi P, Attard M, Stella M, *et al*. BRAF(V600E) mutation and the biology of papillary thyroid cancer. Endocrine Related Cancer 2008;15:191-205.
44. Pellegriti G, De Vathaire F, Scollo C, Attard M, Giordano C, Arena S, *et al*. Papillary thyroid cancer incidence in the volcanic area of Sicily. J Natl Cancer Inst 2009;101:1575-83.
45. Moreno MA, Edeiken-Monroe BS, Siegel ER, Sherman SI, Clayman GL. In papillary thyroid cancer, preoperative central neck ultrasound detects only macroscopic surgical disease, but negative findings predict excellent long-term regional control and survival. Thyroid 2012;22:347-55.

*Acknowledgements***.—**The authors would like to thank Dr. Sergio Mazzola (Department of Political Sciences, University of Palermo) for planning and carrying out statistical analysis, and Warren Blumberg for editing the manuscript.

Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Manuscript accepted: June 3, 2015. - Manuscript revised: May 14, 2015.- Manuscript received: February 6, 2015.