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Central Node Neck Dissection for Papillary Thyroid Carcinoma: Clinical Implications, Surgical Complications and Follow up. A Prospective vs a Restrospective Study

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Abstract

Introduction: The treatment and particularly the extension of surgical therapy of papillary thyroid carcinoma (PTC) remain still controversial in some issues, especially for the lack of preoperative information or variables that allow predicting the level of aggressiveness of the tumor.

Aim of the study: The purpose of the study was to assess the impact of the central node neck dissection (CNND) on surgical outcome and disease free- follow up of PTC- patients operated on at our center by evaluation of postoperative complications (parathyroid and recurrent nerve damage, hemorrhage rates) and pts rates presenting detectable serum Thyroglobulin (TG) or TG-Antibodies (TG-AB) values, at the time of ^{131}Iodine treatment and subsequently at 6-12 months, combined with neck high-resolution ultrasound (HRUS) The results of a prospective study on 149 pts preoperatively diagnosed and HR-US staged N0-PTC who underwent total thyroidectomy and CNND were compared with the results of a retrospective study on 114 similar postoperatively diagnosed PTC-pts who received total thyroidectomy, without nodes dissection.

Materials and methods: 149 patients who underwent total thyroidectomy (TT)+CNND from March 2012 to August 2013 (group-A) and 114 patients who underwent TT from January to December 2011 (group-B) were compared on the following variables: gender, age, histological variant of PTC, tumor size, TNM stage, multifocality, vascular invasion, thyroiditis, expression of BRAF mutation, surgical complications (transient postoperative hypocalcemia and hypoparathyroidism, temporary or permanent dysphonia and hemorrhage), values of TG and anti-TG Ab in suspension or under TSH stimulus, in pre-ablation and on the last clinical and instrumental evaluation of the patient. Statistical analysis was performed using the Student t-test and Fisher. A p value less than 0.05 was considered statistically significant.

Results: Comparing the patients of group-A with group-B the following variables present with statistically significant differences: transient postoperative hypocalcemia (group-A 50.3% vs group-B 21.9% , p<0.0001) , association with lymphocitary chronic thyroiditis (group-A 63.1% vs group-B 37.7%, p<0.0001), median postoperative serum TG value (group-A 1,05 ng/L vs group-B 2,4 ng/L , p=0.01), median postoperative anti-TG antibodies value (group-A 903 kU/L vs group-B 118.5 kU/L, p=0.006), median value of anti-TG antibodies at the last follow up after radioiodine therapy (group-A 481,5 kU/L vs group-B 35 kU/L, p=0.0001).

The following variables do not present statistically significant differences: gender (females 83.2% group-A vs group-B 82.5%, p ns), mean age at diagnosis (>45 years group-A 59.7% vs group-B 53.1%, p ns) , the histological subtypes (p ns), microcarcinomas (group-A 29,5% vs group-B 35%, p ns) , pT (p ns) , presence of multifocal lesions (group A 45.6% vs group B 55.3%, p ns), temporary dysphonia (7,4% group-A vs. group B 2.6%, p ns), definitive dysphonia (group-A 1,3% vs group-B 0,9%, p ns), post-operative hemorrhage (group-A 2% vs group-B 1.8%, p ns), radioiodine therapy (group-A 80.6% vs group-B 80.7%, p ns), rhTSH (group-A 88.3% vs group-B 82.6%, p ns), median value of TG at the last follow up after radioiodine therapy (group-A 0,2 ng/ml vs group-B 0,3 ng/ml, p ns), median value of TG at the last follow-up in patients not receiving therapy (group-A 0.4 ng/ml vs group-B 0.3 ng/ml, p ns).

Discussion and conclusion: In our study we observed that the CNND has allowed a more complete postoperative staging, the TG values after surgery were lower in patients in group A vs group B patients (p<0.0001). Moreover, in group-A any recurrence occurred whereas in group B it was observed a case of relapse at 8 months.

Introduction

The role of central lymph node neck dissection (CNND) in the treatment of papillary thyroid carcinoma (PTC) is still debated because its possibility of increased morbidity with uncertain benefits [1-3]. While is widely accepted that patients with clinically apparent lymph nodes metastases should undergo compartment-oriented neck dissection, controversy exists about the need for central neck dissection in clinically node-negative PTC patients [1-6].

Prophylactic central lymph node dissection (pCLND) for clinically node negative (cN0) PTC is controversial. This is most likely due to lack of uniformity of findings and relatively low yield rate encountered in many papers [1-6]. The benefits of prophylactic central compartment lymph node dissection (pCLND) in PTC are still under investigation. This treatment seems to reduce PTC recurrence/mortality rates but has a higher risk of surgical complications. Identification of risk factors for central lymph node metastasis (CLNM) in patients with PTC might assist surgeons in determining whether to perform selective pCLND [7].

The purpose of the study is to assess the therapeutic role of the central node neck dissection (CNND) in the PTC, sono-graphically classified cN0, the impact of such treatment on surgical outcome and on the follow up of patients, which is implemented by mean value of serum TG and serum Anti-TG Ab, high-resolution ultrasonography, and ^{131}I total-body scintigraphy.

Materials and Methods

Inclusion criteria

Group-A: Patients having FNAC suggesting for PTC (preoperative diagnosis), without preoperative evidence of lymph nodes disease, sono-graphically classified cN0, were prospectively included. All these patients underwent preoperative neck sono-graphy to exclude neck lymph nodal involvement. All these patients underwent total thyroidectomy and ipsilateral/ bilateral central node neck dissection.

Group-B (control group): Patients collected retrospectively, with similar characteristics as group A, with postoperative histological diagnosis of PTC, who underwent total thyroidectomy, served as matched controls.

We excluded patients with poorly differentiated thyroid carcinoma, preoperative evidence of cervical lymph node metastasis at physical examination or on preoperative neck sonography, those with metastatic disease (M1), with R1 thyroidectomy; patients who underwent completion thyroidectomy, and patients who underwent concomitant lateral neck dissection due to preoperative or intraoperative evidence of lymph nodes disease.

Data collection

149 patients who underwent total thyroidectomy (TT)+CNND from March 2012 to August 2013 (group A) and 114 patients who underwent TT from January to December 2011 (group-B) were compared on the following variables: gender, age, histological variant of PTC, tumor size, TNM stage (7th Edition 2009) [7], mono/plurifocality, vascular invasion, thyroiditis, the presence of the BRAF mutation (in group A), postoperative complications (transient or permanent postoperative hypoparathyroidism, temporary or permanent dysphonia and hemorrhage), radio-Iodine doses (in suspension or with rhTSH), and outcome (serum TG and TG-Ab levels, in pre-ablation and on the last clinical and instrumental patient's evaluation recurrence rates).

Surgical technique

All surgical procedures were performed by an experienced endocrine surgeon. The procedure consisted in total extracapsular thyroidectomy and level VI omo or bilateral lymph node clearance. The prelaryngeal lymph nodes were dissected at time of mobilization of the thyroid pyramidal lobe and isthmus. The remaining level VI lymph nodes in the paratracheal and pretracheal spaces were dissected en-bloc with the thyroid gland l. The superior limit of dissection was the cricoid cartilage; the lateral limits were the medial border of the carotid arteries. In all cases the recurrent laryngeal nerve were exposed. Any parathyroid gland that could not be preserved was re-implanted into the sternomastoid muscle.

Assessment of complications

In this study we considered, as major related complications: laryngeal nerve injuries, postoperative hypocalcaemia, and any event leading to substantial morbidity and disability, increasing the level of care, or resulting in substantially lengthened hospital stay (postoperative bleeding, wound hematoma or wound infection). Laryngeal nerve injuries were documented with postoperative laryngoscopy proving altered vocal cord mobility. Definitive laryngeal nerve damage was defined when the altered vocal cord mobility persisted during the six months after the operation. Hypocalcaemia was defined as a serum calcium<2.10 mmol/L in the second postoperative day. Hypocalcemics patients were discharged with substitutive therapy. Criteria to define definitive hypo-parathyroidism were presence of hypocalcaemia during at least six months.

Postoperative follow-up

Complete follow-up, ranged from 18 to 36 months (median 16 months), was possible in all patients.

In all cases, TSH, serum TG and TG-AB levels were checked 2 to 4 months after surgery after thyroid hormone withdrawal/after suspension of substitutive thyroid therapy (levothyroxine) (TSH>30 μUI/ml) or after rhTSH administration (rhTSH).

The completeness of the procedure was also determined in all patients by neck sonographic imaging and in 186 by ^{131}Iodine whole body scan (WBS) (87.7%).

Patients with pT1N0 tumours whose WBS revealed no thyroid remnants didn't receive radioiodine therapy.

Ablation with 50 or 150 mCi ^{131}I was then performed to destroy remnants of functional thyroid tissue, according to the American Thyroid Association (ATA) Guidelines [8]. In these patients WBS was repeated 4 days after ^{131}I administration to visualize any thyroid remnant or metastases, followed by thyroid hormone supplementation.

The mean period of time elapsed between the thyroidectomy and ^{131}I administration for postsurgical remnant ablation was 2-4 months.

The criteria for successful thyroid ablation were defined as the disappearance of any visible area of uptake in the thyroid bed (≤ 1%) and an undetectable serum TG levels off levothyroxine (TSH >30 μUI/ml).

We evaluated how many patients didn't performed radioiodine therapy and the patients who underwent to radioiodine therapy. We evaluated serum TG levels and anti-thyroglobulin antibody measurements in all patients and the presence of increased anti-thyroglobulin antibody levels without detectable TG levels was not considered for relapse disease.

We considered as cut off of normality: Tg levels<1 ng/ml and Ab anti Tg levels<100 kU/L.

Statistical analysis

Comparison of categorical variables was performed by Student t test and Fisher exact test when appropriate. Statistical analysis was performed using a statistical software package (Statistica 7) for Windows. All P values<0.05 were considered significant.

Results

We enrolled 149 patients who underwent TT+CNND from March 2012 to August 2013 (group-A) and 114 patients who underwent TT from January to December 2011 (group-B).
Group-A (TT with CNND) was composed of 124 women and 25 men, with a median age of 48.5 years (range: 8-83), group B (TT; n=114) comprised 94 women and 20 men with a median age of 50 years (range: 11-86). Tumor size ranged from 3 mm to 60 mm in group A (median 15 mm) and from 3 mm to 68 mm in group-B (median=15.08 mm) [p=0.11].

The rate of micro papillary thyroid carcinoma (major longitudinal diameter less than 1 cm) was respectively in two groups: 29.5% (44/149) in group A vs 35% (40/114) in group-B [p ns]. There were 81 (54,3%) plurifocality in group-A, and 51(44.7%) in group-B respectively [p ns]. Final histology is illustrated in Table 1 of those patients who underwent to CNND (group A) 62 (41.6%) had metastatic lymph nodes. The association with lymphocitary chronic thyroiditis was major in group A than in group B (63.1% vs 37.7% respectively). 29/149 (19.4%) patients with pT1N0 tumours in whose WBS revealed no thyroid remnants didn't receive radioiodine therapy.

Variables	Group-A: TT+CNND	Group-B: TT	*P value*
Number of patients	149	114	N.S.
Gender : F/M	124 (83.2%)/ 25 (16.8%)	94 (82.5%)/ 20 (17.5%)	N.S.
Age (years)	48.5	50	N.S.
Age ≤ 45 years/> 45 years	59 (39.6%)/ 90 (60.4%)	54 (46.9%)/60 (53.1%)	N.S.
Tumor diameter in mm	15 (3-60)	15.08 (3-68)	N.S.
Rate of microPTC	29.5% (44/149)	35% (40/114)	N.S.
Hisological variant	149 pz	114 pz	N.S.
Follicular thyroid carcinoma	19 (12.8%)	27 (23.7%)	p 0.02
pT1a	33 (22.1%)	26 (22.8%)	N.S.
pT1b	31 (20.8%)	27 (23.7%)	
pT2	16 (10.7%)	15 (13.1%)	
pT3	69 (46.4%)	46 (40.4%)	
N0	87 (58.4%)	/	/
N1a	62 (41.6%)	/	/
I	93 (62.4%)	67 (58.8%)	N.S.
II	6 (4%)	0 (0%)	N.S.
III	50 (33.6%)	13 (11.4%)	N.S.
Plurifocality	81/149 (54%)	51/114 (44.7%)	N.S.
Association with LCT	94/149 (63%)	42/114 (37%)	p <0.0001
Postoperative morbidity	82/149(55%)	29/114 (25.4%)	p <0.0001
Transient hypoparathyroidism	75 (50.3%)	25 (21.9%)	p <0.0001
Permanent hypoparatiroidism	2 (1.3%)	2 (1.8%)	N.S.
Transient laringeal nerve palsy	11 (7.4%)	3 (2.6%)	N.S.
Pemanent laringeal nerve pasy	2 (1.3%)	1 (0.9%)	N.S.
Hemorrhage	3/149 (2%)	2/114 (1.8%)	N.S.
Mean follow-up (months)	15 (7-30) 120 pts	22 (8-42) 92 pts	N.S.
^{131}I radioiodine therapy	120/149 (80.6%)	92/114 (80.7%)	N.S.
^{131}I radioiodinetherapy dose (mCi)	89.16 (50-150)	100.49 (50-150)	N.S.
No.of radioiodine treatment	1 (1)	1 (1)	N.S.
Postoperative TG levels ng/ml	1.05 ng/L	2.4 ng/L	p=0.02
Postoperative Ab anti TG levels (kU/L)	903	118,5	p=0.006
post radioablation TG levels	0.2 ng/L	0.3 ng/L	N.S.
Post radioablation Ab anti TG levels (kU/L)	481.5	35	p=0.0001
Neck recurrence	0	1	N.S.

Table 1: Final histology of those patients who underwent to CNND.

On the contrary, ablation with 50 or 150 mCi ^{131}I was performed to destroy remnants of functional thyroid tissue in 120/149 (80.6%) in group A and 92/114 (80.7%) in group-B (p=N.S).

Totally, after surgery and before ^{131}I radioidine treatment there were 24 patients in group-A (16%) and 33 patients (29%) in group B with detectable levels of TG and negativity of anti TG antibodies.

Particularly, considering patients with undosable levels of AB anti TG, there were 102 patients with TG<0.1 ng/ml, 86 patients with TG range 0.1-1 ng/ml and 57 patients with TG > 1 ng/ml.

There were, after surgery and before ^{131}I radioidine treatment respectively in two groups, 13 patients (8.7%) and 3 (2.6%) patients with only AB anti TG levels detectable, with undosable TG levels.

There were only 2 patients (1.3%) in group A with either detectable TG levels and Ab anti TG levels after surgery and before ^{131}I radioidine treatment.

No relapse disease was registered. In group-B, one neck recurrence/residual disease occurred in one patient in group-B. This patient needed a reoperation and underwent to lymph nodes lateral neck dissection at a mean time of 8 months and now is alive and disease free. Any patients deceased for thyroid disease. The overall morbidity rates were statistically significant different among two groups [p<0.0001]. Comparing the patients of group-A with group-B the following variables present with statistically significant differences: transient postoperative hypocalcemia (group A 50.3% vs group B 21.9% , p<0.0001) , association with lymphocitary chronic thyroiditis (group-A 63.1% vs group-B 37.7%, p<0.0001) , median postoperative serum TG value (group-A 1,05 ng/L vs group-B 2,4 ng/L , p=0.01), median postoperative anti-TG antibodies value (group-A 903 kU/L vs group-B 118.5 kU/L, p=0.006) , median value of anti-TG antibodies at the last follow up after radioiodine therapy (group A 481,5 kU/L vs group B 35 kU/L, p=0.0001).

The following variables do not present statistically significant differences: gender (females 83.2% group-A vs group-B 82.5%, p ns), mean age at diagnosis (>45 years group-A 59.7% vs group B 53.1%, p ns) , the histological subtypes (p ns), microcarcinomas (group-A 29.5% vs group B 35%, p ns) , pT (p ns) , presence of multifocal lesions (group-A 45.6% vs group-B 55.3%, p ns), temporary dysphonia (7.4% group-A vs. group-B 2.6%, p ns), definitive dysphonia (group-A 1,3% vs group-B 0,9%, p ns), post-operative hemorrhage (group-A 2% vs group-B1,8%, p ns), radioiodine therapy (group A 80.6% vs group-B 80.7%, p ns), rhTSH (group-A 88.3% vs group-B 82.6%, p ns), median value of TG at the last follow up after radioiodine therapy (group-A 0.2 ng/ml vs group-B 0.3 ng/ml, p ns), median value of TG at the last follow-up in patients not receiving therapy (group-A 0.4 ng/ml vs group-B 0.3 ng/ml, p ns).

Discussion

Papillary thyroid carcinoma (PTC) is the most common type of thyroid cancer, accounting for approximately 80% of cases. Its incidence has nearly doubled over the last 30 years and is thought to be due in part to earlier diagnosis of subclinical disease [8-11].
The prognosis for treated PTC is generally good, with 10-year overall survival rates exceeding 90 per cent. It is approved that total thyroidectomy is the procedure of choice for all PTC with diameter greater than 10 mm [9]. Lymph node metastases are common in PTC, occurring in 20-50% of cases, more frequently in the central compartment of the neck [12]. Lymph node involvement are known to be an independent risk factor for local recurrence [10,11], but not disease-specific death [13]. The role of central compartment lymphadenectomy of the neck is much debated today and particularly the best surgical strategy to be adopted in case of PTC, ultrasound CN0, is still questioned. While it's determined that patients with metastases to central compartment lymph nodes should undergo to therapeutic neck dissection [8], there is concern to effectiveness of prophylactic central compartment lymphadenectomy. Several studies, both retrospective and prospective, were performed to evaluate the real impact of prophylactic central neck dissection in PTC on long-term survival, locoregional control, and indication for ^{131}I radioiodine therapy [1-6,15,16]. Arguments in favor of the DCCN "in principle" are the incidence between 50% and 70% of cases of metastasis to the central and lateral compartment's lymph nodes and the concomitant rate of local recurrence and mortality [17-20]. Some Authors show better prognosis in patients receiving concomitant DCCN, but other Authors not confirms this [21-25]. Sywak et al. [26] show that the TT associated with the DCCN gets a greater reduction in postoperative serum TG levels and a faster and higher rate of subjects with undetectable TG levels in the next 6 months after surgery; showing that this trend may be correlate with the lower risk of cancer recurrence. The potential increase in postoperative complications, particularly hypoparathyroidism and recurrent laryngeal nerve injury, and the lack of benefit in terms of overall survival demonstrated by some studies, decreased the enthusiasm for the prophylactic DCCN [27-28].

Some authors demonstrated that the grater morbidity is only temporary [26,30,31] and moreover some Authors, supported the need for a prophylactic DCCN to avoid re-interventions for recurrent or persistent disease leading major rates of complications [28-32].

Probably, the existing debate among surgeons towards central lymph node excision will never end because extremely favourable prognosis of the PTC and because the poor data available in literature. In particular, there are many difficulties to perform studies with a follow-up long enough to assess the benefits of pCLND on overall survival and mortality [33,34]. .

Certainly, we must to consider the proven increase in morbidity, especially regarding the hypoparathyroidism, either definitive or transitory, and the increased recurrent paralysis. The risk of exposing patients to an overtreatment is high and then we must reserve the pCLND to selected cases only where the CLND are justified by certified risk factors of patients or by intraoperative evidence of proven central node metastases.

Regarding the risk factors for CLNM, in a study reported by Suman P et al., in 39.562 patients with T1-4cN0M0 PTC, 61% underwent pCLND. 15.6% of patients had CLNM. On adjusted multivariable logistic regression, age ≤ 45 years, Asian race, male sex, and larger tumors are associated with the presence of CLNM, which allows for selective pCLND in PTC [7].

Concerning the choice in which patients perform the lymphadenectomy, we can find the answer in the study performed Raffaelli M et al. who performed an ipsilateral central compartment node dissection (IpsiCCD) plus frozen section examination in order to determining nodal status and to modulating the extension of the central neck clearance [35].

In 2015 Viola D et al. Realized a study in which a total of 181 patients with PTC without evidence of preoperative/intraoperative lymph node metastases (cN0) were randomly assigned to either Group A (n=88) and treated with total thyroidectomy (TTx) or Group B (n=93) and treated with TTx+pCCND. After 5 years of follow up, no difference was observed in the outcome of the two groups. However, a higher percentage of Group A were treated with a higher number of (131) I courses (P=0.002), whereas a higher prevalence of permanent hypoparathyroidism was observed in Group B (P=0.02). No preoperative predictors of central compartment lymph node metastases (N1a) were identified. Only three patients were upstaged, and the therapeutic strategy changed in only one case. The Authors concluded that cN0 patients with PTC treated either with TTx or TTx

+pCCND showed a similar outcome. One advantage of TTx+pCCND was a reduced necessity to repeat (131) I treatments, but the disadvantage was a higher prevalence of permanent hypoparathyroidism. Almost 50% of patients with PTC had micrometastatic lymph nodes in the central compartment, but none of the presurgical features analyzed, including BRAF mutation, was able to predict their presence; moreover, to be aware of their presence does not seem to have any effect on the outcome [36].

The present study aimed to be randomized and prospective in its data collection and follow-up. Probably, its major limit consists in the short follow-up, and in the type of DNNC (ipsilateral or bilateral) which was an intraoperative choice (bias).

The follow-up of patients who underwent TT alone (group B) is longer than those in group-A only because they have been treated in a previous period compared to patients of group-A. The first consideration analyzing our results is that, 149 patients in group-A underwent TT and DNNC, they were all N0 after high-resolution ultrasound (hrN0). Of these, 41.6% (62/149) were histologically N+, N + subjects 21.5% (32/149) were aged>45 years and were therefore classified as stage III, rather than stage I. Finally, the presence of involved central neck lymph nodes upstaged 21.5% of patients in the TT+CLND group to the stage III of the disease. The importance of the DNNC is stressed by the fact that about 42% (62/149) of patients, at definitive histological examination, resulted having a lymph node involvement, even if they were preoperative classified as hrN0.

The acknowledge of lymph node status is indispensable in the staging of patients, especially those over 45 years, in which the histologically proved lymph nodal involvement leads a change of patient's staging (transition from stage I to stage III) (in our series 21.5% (32/149) of patients). This up-staging may have an impact on the choice of the radioiodine amount administered to the patients, although there were no statistically significant differences in doses of 131 I administered in the 2 groups (p ns). According to the ATA guidelines [9] the serum TG levels (marker of malignancy) and the serum levels of anti-TG Ab during suppressive therapy and then in suspension or after rhTSH stimulation, combined with high resolution sonography, seem to be the two best methods to ensure proper follow-up.

Our study, like Sywak [26] and Low [37] showed that in the group of patients who underwent TT+DNNC the serum TG values were lower (<0.1 ng/ml) than those of patients with TT alone (p=0.03), even excluding the possible bias correlated to the presence of Ab anti-TG; nevertheless, this difference, did not persisted after the radioiodine ablation (p=0.09). Probably, the tendency to achieve undetectable TG levels is due to a higher dose of radioiodine therapy in up-staged patients.

This study shows that the characteristics of patients the two groups are comparable. In particular, the gender, the mean age at diagnosis, the distribution of histological subtypes, the diameter and the multifocality of lesions, were well matched between the two groups (table I).

Another consideration analysing our data is that, the rate of LCT was greater in group A. Thus is a consequence of fact that probably the presence of lymph node enlargements, also if not involved by tumor, induced the surgeons to perform a CNND both unilateral of bilateral (group-A). The importance to perform the DCCN isn't only determining which patients would benefit from radioiodine therapy, but maybe prevent radioiodine treatment in patients with tumors below 20 mm (T1), as demonstrated by Bonnet et al [31], which showed that 42% of patients with tumor below 20 mm, can avoid radioiodine treatment, in case of lack of angioinvasion, favorable histological variant, and N0 at histological evaluation.

A further concern is the real impact of the DNNC in the overall survival of PTC patients. In Literature there were been reported very good results of radioiodine therapy in the treatment of nodal micro metastases, moreover several Authors reports higher morbidity in patients treated with DNNC [14]. In our series, temporary postoperative hypocalcemia was higher in group A (50.3%) than in group B (21.9%), [p<0.0001], but the definitive hypoparathyroidism did not reached a significant difference between the two groups (2% group A, group B vs. 1.8%, p ns). In addition, there were any differences in postoperative laryngeal nerve palsies among the two groups (1.3% group-A vs 0.9% group B, p ns). Therefore, the DCCN in PTC appears to be important as it improves the accuracy of staging, especially in patients over 45 years, and seem to remove the residual microscopic disease. Patients with metastatic lymph nodes would be treated with higher doses of ^{131}I, which would lead to a lowering of TG levels similar to those of patients without lymph node involvement. On the other hand, patients without lymph node involvement (N0), with small size tumor (T1-2), and with favorable histological variant, could avoid radioiodine therapy and its correlated complications without sacrificing low TG levels.

Considering our follow-up data, the mean postoperative stimulated serum TG levels, excluding patients with anti-TG AB, were statistically significant lower in group A than that of group B patients (group A 1.05 ng/ml vs. group B and 2.4 ng/ml, p=0.01) reflecting that the CNND produced the decrease of TG levels respect to the TT alone, but nevertheless there was no significant difference in loco-regional control rates after TT with CNND and TT only.

In the follow-up none of the patients in group A underwent reoperation for recurrence. In group B, one patient underwent reoperation for recurrent upper mediastinal lymph node.

Our data demonstrated lower TG levels in patients with DCCN. Considering the inverse relationship between TG levels and extent of lymph node dissection demonstrated by Low [37], we can maybe presume a lower recurrence and less persistence of disease in these patients, which is difficult to prove for the need of further prospective and randomized studies with longer follow-up [17]. The debate concerning the prophylactic dissection of the central compartment will continue, but it is important remembering to the surgical community the following statements "let the treatment is worse than the disease" and "primum non nocere" [37,38].

Conclusion

The addition of routine CNND in cN0 papillary thyroid carcinoma results in lowers postoperative and post-ablation of TG levels. Prophylactic CNND optimizes staging providing a basis for a personalized approach for adjuvant radioiodine. Moreover, prophylactic CNND may be helpful in decreasing short-term locoregional recurrence in patients with clinically node-negative PTC and may reduce the need for reoperation in the central compartment.

CNND provided an up-staging of more than 20% of patients with a clinically N0 neck, but was associated with significant morbidity regarding parathyroid function. The risk of transient hypocalcemia may increase after CNND but central neck dissection did not increase permanent morbidity and revealed a significant rate of non-clinically evident node metastases. In experienced hands, central neck dissection

should be routinely combined with total thyroidectomy in the primary treatment of pre- or intraoperatively diagnosed papillary thyroid cancer.

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