Cervical Lymph Node Dissection for Papillary Thyroid Cancers: A Decade Experience of a Single Surgical Team

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Abbreviations:

US - Ultrasound;
FNAC - Fine Needle Aspiration
Cytology;
PCND - Prophylactic Central Neck
Dissection;
LND - Lateral Node Dissections;
PTC - Papillary Thyroid Carcinoma;
cNO - Clinical Node-negative;
RLN - Recurrent Laryngeal Nerve;
TT - Total Thyroidectomy;
TT+CND - Total Thyroidectomy with
Therapeutic Central Neck Dissection;
TT+PCND - Total Thyroidectomy with
Prophylactic Central Neck Dissection;
TT+CLND - Total Thyroidectomy with
Central and Lateral Neck Dissection.

Rezumat

Limfadenectomia cervicală în carcinomul papilar tiroidian: zece ani de experiență a unei singure echipe chirurgicale

Premize: Pacienții cu operații tiroidiene trebuie evaluați ecografic preoperator iar în cazul leziunilor suspecte puncția aspirativă cu ac fin (FNA) trebuie să completeze investigațiile. În țările vestice, chirurgii endocrini efectuează de rutină ecografiile cervicale. Rolul limfadenectomiei profilactice de compartiment central (LPCC) în cazul carcinoamelor papilare tiroidiene (CPT) rămâne controversat. În anul 2014 am efectuat o schimbare de strategie în tratamentul CPT: introducerea LPCC efectuată pe baza criteriilor European Society of Endocrine Surgeons (ESES) și ecografia preoperatorie efectuată de către chirurg (S-US).

Material și Metodă: Pentru înțelegerea rolului jucat de cele două metode nou introduse am efectuat un studiu retrospectiv a două perioade succesive de 5 ani, din baza noastră de date menținută prospectiv.

Rezultate: Cele două grupuri analizate au fost similare din punct de vedere epidemiologic și clinic. FNA s-a efectuat la doar 21,66% dintre pacienți. Diagnosticul de CPT a fost stabilit la majoritatea cazurilor prin examen histopatologic extemporaneu (EHE). S-US au ghidat limfadenectomia laterocervicală selectivă ducând astfel la îndepărtarea unui număr mai mare de ganglioni metastazați, având în plus și o valoare predictivă pozitivă superioară celor efectuate de către endocrinologi. Rata de complicații a LPCC a fost semnificativ mai mare doar pe seama hipoparatiroidismului tranzitor.

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Concluzii: S-US este un instrument util în tratamentul CPT. Diagnosticul prin FNA sau cel prin EHE sunt obligatorii. LPCC este o metoda sigură de tratament și stadializare a CPT.

Cuvinte cheie: carcinom papilar tiroidian, ecografie efectuată de chirurg, limfadenectomie profilactică, puncție aspirativă cu ac fin

Abstract

Background: All patients undergoing thyroid operations should be subjected to preoperative neck ultrasound (US) followed by fine needle aspiration cytology (FNAC) of suspicious lesions. In Western countries, thyroid surgeons routinely perform neck ultrasound. The role of prophylactic central neck dissection (PCND) remains a topic of debate. For treatment of papillary thyroid carcinoma (PTC), in 2014 we introduced two new adjuncts: PCND based on criteria of the European Society of Endocrine Surgeons (ESES) consensus group and surgeon-performed US (S-US).

Methods: In order to better understand the role of these two adjuncts in our shift of strategy we aimed to evaluate the outcomes of our patients in two successive 5-year time periods based on a retrospective analysis of our prospectively maintained database (total of 286 patients were included in this study).

Results: The two groups were similar regarding epidemiological and clinical data. FNAC was done in only 21.66% of all PTC cases. PTC diagnosis was done in the majority of suspicious cases by FS. S-US guided the selective lateral node dissections (LND), leading to more lymph node metastases detections and it also surpassed endocrinologist performed US (E-US) in terms of PPV. PCND rate of complications was significantly higher due only to transient hypoparathyroidism.

Conclusions: Preoperative surgeon-performed ultrasonography is a useful tool in the arsenal of PTC treatment. The systematic preoperative FNAC diagnosis and intraoperative frozen sections in uncertain cases are mandatory. PCND is a safe method of treatment and staging in PTC.

Key words: papillary thyroid carcinoma, surgeon-performed ultrasound, prophylactic node dissection, fine needle aspiration cytology

Introduction

Papillary thyroid carcinoma (PTC) is the most frequent thyroid carcinoma accounting for more than 80% of all thyroid cancers. Worldwide its incidence is rising probably due to increased detection by more efficient imaging techniques (1). Cervical lymph node metastases are common for PTC occurring in 20-50% in the central compartment of the neck and in 10-30% in the lateral one (2-5).

According to current guidelines, all patients undergoing thyroid operations should be subjected to preoperative neck ultrasound (US) of the thyroid and central plus lateral neck compartments, followed by fine needle aspiration cytology (FNAC) of suspicious lesions (6). In

Western countries, surgeons specialized in thyroid surgery routinely perform neck ultrasound as part of the physical exam.

The role of prophylactic central neck dissection (PCND) remains subject to debate in patients with clinical node-negative (cN0) PTC. Also the criteria of selecting patients for PCND varies worldwide in national and international consensus groups (7,8).

In 2014 we changed strategy by introducing two new adjuncts in the treatment of patients with papillary thyroid carcinoma: PCND based on criteria of the European Society of Endocrine Surgeons (ESES) consensus group and preoperative neck US performed by one of our surgeons (9).

In order to better understand the role of

these two adjuncts in our shift of strategy we aimed to evaluate the outcomes of our patients in two successive 5-year time periods.

Material and Methods

This is a retrospective cohort analysis of a prospectively maintained database recorded in 3 different hospitals: Surgery Clinic IV, Surgery Clinic II and Humanitas Hospital Cluj-Napoca. Between April 2010 and March 2019 a total of 3552 thyroid operations were performed by the same surgical team, 350 (9.85%) of them for thyroid malignancies. Exclusion criteria included histotypes other than PTC, reinterventions for PTC, patients with incidental histological finding of papillary microcarcinoma and patients with incomplete data recorded. All patients underwent total thyroidectomy with curative intent. According to our shift of strategy in 2014, patients were divided into two cohorts: group A (131 patients) (April 2010 and March 2014) and group B (155 patients) (April 2014-March 2019).

For each patient, preoperative work-up consisted of endocrinologist-performed US (E-US) of the neck, serum measurement of free thyroid hormones (FT3, FT4) and thyrotropin (TSH), laryngoscopy for vocal chord evaluation. The diagnosis of PTC was confirmed preoperatively with FNAC or intraoperatively with frozen section (FS).

Postoperative, all patients received prophylactic oral calcium and vitamin D (CalciviD) for 10 days. Patients were discharged in the first or second postoperative day.

Criteria for PCND as stated by The European Society of Endocrine Surgeons were: patients with T3-T4 tumors, age <15 or > 45, male gender, bilateral or multifocal disease or known lateral neck lymph node metastases.

Follow-up was routinely done at 6 weeks, 3 months and 6 months after surgery, consisting of a routine physical examination, neck ultrasound, laryngoscopy (at 6 weeks) and assays for TSH, calcium, PTH, Tg and TbAb.

Calcium and PTH levels were first measured postoperatively at the 6-week follow-up or whenever symptoms of hypocalcemia occurred.

Hypoparathyroidism was considered permanent when it lasted for more than six months after surgery. Recurrent laryngeal nerve (RLN) injury was considered permanent when the chord palsy persisted 6 months after surgery.

The data recorded for each patient included age, gender, type of operation, total thyroidectomy (TT) alone, total thyroidectomy with therapeutic central neck dissection (TT+CND), total thyroidectomy with prophylactic central neck dissection (TT+PCND), total thyroidectomy with central and lateral neck dissection (TT+CLND), histopathologic report (TNM classification) and postoperative complications.

Statistical analysis was done using GraphPad online calculator. Qualitative variables were reported in terms of absolute frequencies and percentages. Categorical variables were assessed using Fisher's exact test, Chi-squared test or Chi-squared test with Yates' correction when appropriate. P-value less than 0,05 was considered to be statistically significant.

Results

The Cohort A of patients consisted of 131 PTC, operated between April 2010 and March 2014, and Cohort B of 155 patients operated between April 2014-March 2019. Although not randomized, the two groups were similar regarding epidemiological and clinical data. Their characteristics are reported in *Table 1*.

No statistically significant difference was found in terms of gender ($p=0.644$) with the prevalence of females in both groups (70% in the first cohort and 79.35% in the second). The majority of patients in both cohorts were over 45 years of age, without statistically significant difference regarding the relevant age cut-point of 45.

FNAC of the US suspicious tumor or lymph nodes was done in 11 (8.40%) of the 131 patients in Cohort A and in 51 (32.90%) of the 155 patients in Cohort B ($p<0.001$). Intraoperative PTC diagnosis by FS was obtained significantly more often ($p<0.001$) in Cohort A. In 51 patients of cohort B neither FNAC nor FS diagnosis was done.

The majority of the patients in both groups

Table 1. Epidemiological, clinical and pathological data of PTC patients

Variable	Cohort A	Cohort B	p-value
No. of patients	131	155	
Gender			
Male	30 (22.90%)	32 (20.65%)	0.644
Female	101 (70.10%)	123 (79.35%)	
Age			
< 15 years	0	2 (1.29%)	n.s.
15-45 years	46 (35.11%)	57 (36.77%)	0.708
> 45 years	85 (64.89%)	96 (61.94%)	
FNAC diagnostic	11 (8.40%)	51 (32.90%)	<0.001
Pathological T status			
pT1	70 (53.44%)	93 (60%)	0.579
pT2	20 (15.27%)	22 (14.19%)	
pT3	38 (29.01%)	35 (22.58%)	
pT4	3 (2.29%)	5 (3.23%)	
Surgical Procedure			
TT	100 (76.33%)	51 (32.90%)	<0.001
TT + Node Dissections	31 (23.66%)	104 (67.10%)	
TT+PCND	-	33 (21.29%)	
TT+CND	20 (15.27%)	39 (25.16%)	
TT+CLND	11 (8.40%)	32 (20.65%)	0.620
Pathological N status			
pN0	13 (41.94%)	35 (33.65%)	0.397
pN+	18 (58.06%)	69 (66.35%)	

had either pT1 or pT2 lesions (68.71% in Cohort A and 74.19% in Cohort B respectively), with pT4 lesions being observed in less than 3%. No statistical difference regarding tumor size was recorded in the two cohorts ($p=0.579$).

Analyzing the two cohorts we observed a statistically significant difference regarding the total number of lymph node dissections performed in favor of Cohort B ($p<0.001$). This was due to significantly more CND performed in the second period ($p=0.007$). When comparing the outcomes (pN0 versus pN+) of lymph node dissections performed in the two cohorts, there

were no significant differences ($p=0.397$).

We found a significant increase of pN+ node dissections in the second analyzed period ($p=0.029$), but after excluding the patients diagnosed preoperatively with lymph node FNAC (7 cases, all of them in Cohort B) the difference was not quite significant at 90% CI ($p=0.057$). The outcomes of LND are presented in *Table 2*.

Preoperative US performed by the surgeon (S-US) was done in 119 (76.77%) patients of cohort B: 51 patients diagnosed preoperatively via FNAC and 68 patients with E-US cancer

Table 2. Outcomes of Central and Lateral Lymph Node Dissections (CLND)

Variable	Cohort A	Cohort B	p-value
TT+CLND	11	32	
pN0	4 (36,36%)	2 (6,25%)	0,029
pN+	7 (63,64%)	30 (93,75%)	
TT+CLND without FNAC	11	25	
pN0	4 (36,36%)	2 (8%)	0,057
pN+	7 (63,64%)	23 (92%)	

suspicion but without FNAC. In 5 patients it only raised suspicion of metastatic lymph node involvement and in 16 patients it confirmed the E-US suspicion. For the 25 patients without FNAC diagnosed lymph node metastases in whom E-US and S-US raised suspicion of N+, pathological confirmation came in 22 (88%) patients. Two (8%) US suspicions of lymph node involvement, all raised by E-US, were not confirmed by the pathologist. Positive predictive value of S-US was 100% while of E-US it was 90%. Details are presented in *Tables 3* and *4*.

In order to evaluate the outcome and complications of PCND done according to the

ESES consensus criteria we analyzed two subgroups of the Cohort B: TT+PCND (33 patients) versus TT (51 patients). Their characteristics are reported in *Table 5*. No statistically significant difference was found in terms of gender or age. The majority of patients in both groups had pT1-pT2 tumors whereas pT3-pT4 tumors were found almost three times more frequently in the TT+PCND group (21.21% vs. 7.84%). This difference was statistically significant ($p=0.0141$). Nodal involvement (pN+) was found in 54.55% of the patients who underwent TT+PCND.

The overall complication rate was

Table 3. Outcome of 25 TT+CLND patients with suspicious lymph node involvement (N+) on US examination

Variables	E-US + S-US	S-US only	E-US only	Total
cN+ (US)	16 (64%)	5 (20%)	4 (16%)	25 (100%)
pN0	0	0	2	2 (8%)
pN+	16	5	2	23 (92%)

Abbreviations: E-US = endocrinologist performed ultrasound; S-US = surgeons performed ultrasound

Table 4. Predictive values of S-US and E-US in finding N+ nodes

Variable	N+	NO	PV
S-US only	TP=16+5 FN=2	FP=0 TN=2	PPV=21/21+0=1 (100%) NPV=2/2+2=0,5 (50%)
E-US only	TP=16+2 FN=5	FP=2 TN=0	PPV=18/18+2=0,9 (90%) NPV=0/0+2=0 (0%)

Abbreviations: TP = true-positive, FP = false-positive, FN = false-negative, TN = true-negative, PV = predictive value, PPV = positive predictive value, NPV = negative predictive value

Table 5. Epidemiological and pathological data of Cohort B patients with TT+PCND vs. TT alone

Variable	TT+PCND	TT	p-value
No. of patients	33 (39,29%)	51 (60,71%)	
Gender			
Male	8 (24,24%)	15 (29,41%)	0,788
Female	125 (75,76%)	36 (70,59%)	
Age			
< 45 years	11 (33,33%)	21 (41,18%)	0,469
> 45 years	22 (66,67%)	30 (58,82%)	
Pathological T status			
pT1 - pT2	23 (78,79%)	47 (92,16%)	0,014
pT3 - pT4	10 (21,21%)	4 (7,84%)	
Pathological N status			
pNx	-	51 (100%)	n.s.
pN0	15 (45,45%)	-	
pN+	18 (54,55%)	-	

Table 6. Postoperative complications in Cohort B patients with TT+PCND vs. TT alone

Variable	TT+PCND	TT	p-value
No. of patients	33 (39,29%)	51 (60,71%)	
Total complications	12 (36,36%)	7 (13,73%)	0,031
Hypoparathyroidism	11 (33,33%)	5 (9,80%)	0,010
Temporary	10 (30,30%)	5 (9,80%)	0,021
Permanent	1 (3,03%)	0	n.s.
RLN injury	1 (3,03%)	1 (1,96%)	1,000
Temporary	1 (3,03%)	1 (1,96%)	1,000
Permanent	0	0	-
Other complications	0	1 (1,96%)	n.s.

significantly higher in the TT+PCND group (36.36% vs 13.73%, $p=0.031$) due to temporary hypo-parathyroidism, which was also significantly higher in the same group. We did not experience any permanent RLN injury in our patients. Data is summarized in *Table 6*.

Discussions

PTC account for approximately 80% of all thyroid carcinomas (2) and have an extremely favorable prognosis. However, it frequently bares lymph node metastases of the central neck compartment in 20-50% of the cases (9-12), and in 10-30% in the lateral one. Micrometastases are found in up to 80% of the patients. Positive lymph nodes are associated with higher recurrence rates and decreased 5-year survival (13,14).

Preoperative neck ultrasound is the recommended imaging modality for rising suspicion of thyroid tumors and enlarged neck lymph nodes and combined with FNAC for diagnosing and staging PTC. US is traditionally performed by radiologists and endocrinologists but surgeons who routinely perform preoperative neck ultrasound and FNAC are uniquely qualified to evaluate not only the tumor but also the lateral neck, sometimes obtaining extra-information to guide the future operation in the sense of selective CLND or PCND. Surgeon-performed US is increasing because of inadequate or incomplete imaging performed by radiologists (15). S-US has proven to be a reliable and consis-

tent tool to assess the thyroid nodule risk stratification, thus surgeons should recognise the potential of this tool and its implementation (16).

In our experience, not only that S-US guided the selective LND leading to more (although not quite statistically significant) lymph node metastases detections after its implementation but it also surpassed E-US in terms of PPV and NPV providing for more-comfort and confidence while performing TT+CLND.

Fine needle aspiration cytology (FNAC) is considered the most reliable and cost-effective method for the diagnosis of malignant thyroid nodules, with excellent sensitivity and specificity (17). When compared with frozen section (FS), FNAC has shown to have a comparable sensitivity and positive predictive value for PTC (18,19) and without the disadvantage of prolonging the operation. Also, benign FS does not entirely exclude the possibility of malignancy, because more than half of benign FSs show malignancy on final pathologic exam. In addition, FS may also bare the potential risk of undertreating patients in the event of a benign FS diagnosis, and also may affect the tissue available for a final diagnosis analysis (20).

In our pool of patients FNAC was done in only 21.66% of all PTC cases. PTC diagnosis was done in the majority of cases by FS. FNAC of the US suspicious tumor or lymph nodes was done only in 8.40% of the 131 patients in Cohort A and in 32.90% of the 155 patients in Cohort B. Moreover, 51 patients in cohort B

where neither diagnosed preoperatively by FNAC nor intraoperatively by FS thus excluding them from applying PCND criteria on them. The reasons why such small percentage of FNAC performed is in part due to the fact that only a few endocrinologists perform FNAC but also because a lot of patients refuse it.

While there is general acceptance that clinically evident nodal disease should be removed for therapeutic purposes, there is strong debate among endocrine surgeons regarding PCND (3,6,9,12,21,22). According to its proponents, PCND lowers the risk of local recurrence and increases long-term survival without increasing the risk of permanent morbidity (23). Moreover, in TT-PCND patients needing surgery for lymph node recurrent disease, the dissection the central compartment dissection can be avoided, thus decreasing the risks of RLN injury or parathyroid complications. On the other hand, different studies claim that there is no hard evidence to support the above statements (6,10,12,15,16).

The advantages obtained by PCND whether in the line of confirmation/information of lymph node involvement or in the line of minimizing the biochemical burden of the disease, can be used to tailor radioiodine (RAI) treatment (24,25). Still, there are authors that claim that the potential upstaging resulted from PCND is leading to overtreatment with RAI with its associated complications (26).

This controversy is also augmented by the varying recommendations from national and international consensus groups (6,9,27). Moreover, The American Thyroid Association (ATA) estimated that it would take over 5000 subjects and over 15 Million \$ to perform a randomized controlled trial to evaluate the benefits of PCND.

In our study we observed that introducing PCND according to the 2014 ESES consensus criteria, significantly increased the number of lymph node dissections associated to TT. The lymph node metastases were found in 18 (54.55%) out of the 33 patients with TT+PCND. However, when comparing the two cohorts, the

difference in lymph node metastases on pathological examination was not significant. Moreover, the rate of complications, although transient, was significantly higher in the PCND group. The potential advantage in our patients, is that the 33 (21.29%) patients with PCND benefited from a better risk stratification before deciding RAI treatment and the fact that more than half of them were exempted of possible reinterventions in the central neck compartment.

Although done on a prospectively maintained database our study has several limitations: small sample size and not prospective or randomized. Also, it lacks the analysis of RAI treatment, recurrence and 10-year survival rates in our population of patients in order to be able to draw clear conclusions on the real benefit of PCND.

Conclusions

Prophylactic lymph node dissection in patients with PTC according to the 2014 ESES consensus criteria didn't result in a significant increase in lymph node metastases found on pathological examination, but it added useful information for improved risk stratification in line with RAI treatment. There were no permanent RLN lesions or permanent hypoparathyroidism in TT+PLND patients making PCND a safe method of treatment.

Preoperative surgeon performed ultrasonography was a useful tool to identify more patients with lymph node metastases in the lateral neck and to direct the selective lymph node dissections. The systematic preoperative FNAC diagnosis and intraoperative frozen sections in uncertain cases are mandatory in the treatment of PTC. In the future, more FNACs are needed to preoperatively diagnose PTC in order to decrease the need of more operative time consuming FSs.

Author's Contributions

RS, VM: concept & design; VM, RS, DC, DS: provision of study material or patients; RS,

VM: data analysis and interpretation; RS, VM, DC: manuscript writing; VM: final approval of manuscript.

Conflict of Interest

The authors declare no conflicts of interests.

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