

The Evaluation of Routine Central Nodal Dissection in Radiologically Node Negative Differentiated Thyroid Carcinoma

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ABSTRACT

Background: thyroid cancer is the most common malignant disease in endocrine system and is rapidly increasing in incidence. The use of routine prophylactic central neck dissection for the treatment of differentiated thyroid cancer has been an area of debate over the past few decades. **Aim of the Work:** the primary aim of surgery was to resect disease, minimize the chance of recurrence and achieve this with minimal morbidity. Selecting the appropriate procedure is critical as not only does surgery provide initial therapy, but also optimizes the patient for adjuvant radioactive iodine (RAI) therapy when required. **Patients and Methods:** this study was conducted to evaluate the efficacy of prophylactic central lymph nodal dissection in patients diagnosed with differentiated thyroid carcinoma from several points of view including operative time, hospital stay, postoperative complications and most importantly the recurrence. Our patients were operated upon between August 2016 and August 2017 with minimal follow up of 6 months and follow up extended to 2 years after surgery. **Results:** Operative time was significantly higher in group B with a mean time of 141.68 ± 12.72 as compared to group A. The most outstanding difference in terms of complications was detected in transient hypoparathyroidism that occurred in 16% of group B patients. A single case of recurrence was detected at 12 month in group A that was confirmed by fine needle aspiration cytology which required reoperation. **Conclusion:** there was no convincing evidence that pCND leads to an improvement in recurrence rate, overall survival, or any clinically significant variable when applied indiscriminately to DTC patients.

Keywords: Differentiated thyroid cancer, papillary thyroid carcinoma, radioactive iodine

INTRODUCTION

Thyroid cancer is the most common endocrine malignancy, and its incidence is increasing at the highest rate among cancers worldwide⁽¹⁾. Differentiated thyroid cancer (DTC), which derives from follicular epithelial cells, includes papillary and follicular cancer; DTC accounts for more than 90% of all thyroid cancers⁽²⁾. Lymph node metastases are a common finding in papillary thyroid carcinoma (PTC), occurring in 20–50 % of patients in the central compartment of the neck (level VI) and in 10–30 % in the lateral compartment of the neck (levels II –V)⁽³⁾. However, despite good prognosis, loco-regional recurrence is relatively common after curative surgery. With recognition of the step-wise progression of metastasis from central (level VI) to lateral (levels II–V) compartments, routine prophylactic central neck dissection (pCND) has been advocated at the time of total thyroidectomy to minimize loco-regional recurrence⁽⁴⁾. The central compartment is bounded by the hyoid bone (superior), carotid artery (lateral), and sternal notch or innominate artery (inferior). The American Thyroid Association (ATA) defines central compartment neck dissection as “comprehensive, compartment-oriented removal of the prelaryngeal

and pretracheal nodes and at least one paratracheal lymph node basin⁽¹⁾. The inability to diagnose lymph node metastases accurately by preoperative ultrasonography (low sensitivity) or intraoperative inspection, the high incidence of lymph node metastases, the decreased risk of local recurrence and need for reoperation and its morbidity, the improved ability to justify radioactive iodine (RAI) treatment, the better thyroglobulin (Tg) surveillance, and the failure of I^{131} ablation in approximately 30% of cases are considered factors that favor routine (or prophylactic) central lymph node dissection⁽⁵⁾. Given the excellent overall survival rates associated with PTC and the potential morbidity associated with reoperative cervical surgery, prophylactic CND may seem to be appropriate, as it may decrease the disease recurrence rate by extirpating level VI lymph nodes⁽⁶⁾.

AIM OF THE WORK

This work aimed at prospectively comparing between total thyroidectomy alone and total thyroidectomy combined with central node dissection in clinically and radiologically negative lymph nodes in cases of differentiated thyroid carcinoma.

PATIENTS AND METHODS

1) Patients: This study was a randomized prospective study conducted at Ain-Shams university Hospitals on 50 patients diagnosed as node negative differentiated thyroid carcinoma. They were randomly divided into 2 groups and operated upon between August 2016 and August 2017 with minimal follow up of 6 months postoperatively. An informed consent was taken from all patients who accept to participate in the study. **The study was approved by the Ethics Board of Ain Shams University.** **Inclusion criteria:** Preoperative pathological diagnosis of DTC by ultrasonography guided fine-needle aspiration cytology. Clinical stage T1 or T2 DTC. No clinical nor radiological evidence of neck node involvement (central or lateral). **Exclusion criteria:** Any other type of thyroid cancers other than primary differentiated thyroid cancer. Clinical or radiological evidence of nodal or distant metastasis at presentation. Previous thyroid surgery. Patients with a mixed tumor. All the patients in this study were under the care of one surgical team under supervision of consultant surgeon and were randomly divided into two groups. Randomization was done using serial number of patient presentation to the treating team, where odd numbers were involved in group A, and even numbers were involved in group B. **The first group (A):** include 25 patients who underwent total thyroidectomy alone. **The second group (B):** include 25 patients who underwent total thyroidectomy and central lymph node dissection. **Statistical Analysis:** Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges when their distribution found parametric and median with inter-quartile range (IQR) when their distribution found non-parametric. Also qualitative variables were presented as number and percentages. The comparison between the groups regarding qualitative data was done by using **Chi-square test**. The comparison between the two independent groups with quantitative data and parametric distribution were done by using **Independent t-test** while non parametric data were compared using **Mann-Whitney test**. The confidence interval was set to 95% and the margin of error accepted was set

to 5%. So, the p-value was considered significant at the level of < 0.05.

RESULTS

Table (1): Comparison between the two groups as regards Preoperative serum thyroglobulin, Operative time and Hospital stay.

	Group A		Group B		Test value	P-value	Sig.
	No. = 25	No. = 25					
Preop. Tg Range	Mean±SD 3 – 23	11.70 ± 3.40	Mean±SD 3.5 – 26	11.81 ± 3.05	-0.069	0.945	NS
Operative Time Range	Mean±SD 86 – 150	119.64 ± 17.23	Mean±SD 120 – 160	141.68 ± 12.72	-5.145	0.000	HS
Hospital stay Range	Mean±SD 24 – 60	40.80 ± 8.49	Mean±SD 36 – 72	44.16 ± 8.98	-1.360	0.180	NS

P-value > 0.05: Non significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant

Table (2): Postoperative complications.

Postop. Complications	Group A		Group B		Test value	P-value	Sig.
	No.	%	No.	%			
None	21	84.0%	16	64.0%	1.587	0.207	NS
Transient RLN palsy	2	8.0%	2	8.0%	0.000	1.000	NS
Hematoma	1	4.0%	3	12.0%	1.087	0.297	NS
Transient hypoparathyroidism	0	0.0%	4	16.0%	4.348	0.037	S
Permanent hypoparathyroidism	1	4.0%	0	0.0%	1.020	0.312	NS

Table (3): Pathological types

Pathology	Group A		Group B		Test value	P-value	Sig.
	No.	%	No.	%			
Follicular variant PTC	0	0.0%	1	4.0%	1.02	0.312	NS
FTC	3	12.0%	2	8.0%	0.222	0.637	NS
Hurthle cell carcinoma	0	0.0%	1	4.0%	1.02	0.312	NS
microPTC	2	8.0%	0	0.0%	2.083	0.148	NS
Multifocal PTC	1	4.0%	0	0.0%	1.02	0.312	NS
PTC	19	76.0%	21	84.0%	0.5	0.479	NS

Table (4): sTg level at 1, 6 & 12 months.

	Group A		Group B		Test value	P-value	Sig.
	No.	%	No.	%			
Tg 1 month	Median (IQR)	1.7 (0.3 – 2.6)	0.9 (0.1 – 1.4)	1.777	0.076	NS	
Tg 6 months	Median (IQR)	0.1 (0.1 – 0.1)	0.1 (0.1 – 0.1)	1.472	0.141	NS	
Tg 12 months	Median (IQR)	0.1 (0.1 – 0.1)	0.1 (0.1 – 0.1)	1.768	0.077	NS	

Table (5): Follow up by Neck U/S and incidence of recurrence.

		Group A		Group B		Test value	P-value	Sig.
		No.	%	No.	%			
US 6 months	Negative	25	100.0%	25	100.0%	0.000	1.000	NS
	Positive	0	0.0%	0	0.0%			
US 12 months	Negative	24	96.0%	25	100.0%	1.020	0.312	NS
	Positive	1	4.0%	0	0.0%			
Recurrence	Negative	24	96.0%	25	100.0%	1.020	0.312	NS
	Positive	1	4.0%	0	0.0%			

DISCUSSION

One of the most controversial issues in the treatment of thyroid cancer is the management of the central neck nodes in patients with PTC⁽⁷⁾. Thyroid tumor cells are spread through the lymphatic system in a sequential fashion: thyroid gland to central compartment to ipsilateral lateral compartment to contralateral lateral and mediastinal compartments. However, cases of “skip” metastases to the lateral compartment without central compartment involvement have been reported. Involvement of the suprathyroid region, namely the submental and submandibular nodes, is a rare phenomenon⁽²⁾. The ATA consensus statement regarding the terminology and classification of the central neck defines the central compartment nodal dissection as all perithyroidal and paratracheal soft tissue and lymph nodes with borders extending superiorly to the hyoid bone, inferiorly to the innominate artery, and laterally to the common carotid arteries⁽⁸⁾. It is well known that unrecognized, occult, or microscopic metastases may be found in 31–62% of the patients who undergo elective central neck dissection for PTC, but such lymph node involvement appears to have little or no impact on the clinical outcome⁽⁹⁾. Concerns have been raised regarding the use of the sTg as a surgical outcome measure because it is not clear in the published studies whether lesser levels of sTg in patients undergoing PCND are related to the removed microscopic metastases or to a more complete total thyroidectomy⁽¹⁰⁾. One argument that favors PCND is in the difficulty to define pre-(with ultrasonography and clinical examination) and intraoperatively the lymph node involvement, although the surgeon’s assessment of the central neck is an accurate predictor of which patients with PTC would benefit from central neck dissection^(11,12). To decrease the risk of postoperative complications related to PCND, unilateral central

neck dissection has emerged as an alternative approach to bilateral central neck dissection. Ipsi-PCND appears to be a safe, efficacious, and interesting alternative to Bil-PCND, especially for small PTC⁽¹³⁾. In clinical unifocal, cN0 PTC without evidence of extracapsular invasion, a more limited approach has been proposed to reduce the complications rate associated with bilateral CND: ipsilateral CND⁽⁷⁾. Ipsilateral CND (IpsiCND) includes elective removal of pre-laryngeal, pre-tracheal, and the paratracheal nodes on the side of the tumor and was proposed in patients with clinical unilateral PTC. Comparative studies have suggested that IpsiCND may be an effective alternative option to bilateral CND for cN0 PTC because of the similar short-term oncologic outcome and the lower risk of postoperative complications, namely, transient hypocalcaemia⁽⁹⁾. Routine ipsilateral CLND with intraoperative reading of the frozen section can be employed to assess the risk of contralateral CLN metastasis. This information should be of value in deciding whether to perform contralateral CLND or not⁽¹⁴⁾. TT followed by RAI administration and TSH suppression therapy guaranteed optimal long-term results and a low incidence of locoregional lymph node recurrence that was similar to the incidence that has been reported for a RCLD series⁽⁵⁾. Some studies stated that there is no convincing evidence that prophylactic central neck dissection leads to an improvement in recurrence rate, overall survival, or any clinically significant variable when applied indiscriminately to all PTC patients. Moreover, PCND is associated with increased morbidity, even when performed by experienced surgeons: in particular, it is associated with a higher rate of transient complications, mostly hypoparathyroidism⁽¹⁵⁾. This study was conducted to evaluate the efficacy of prophylactic central lymph nodal dissection in patients diagnosed with differentiated thyroid carcinoma from several points of view including operative time, hospital stay, postoperative complications and most importantly the recurrence. Our patients were operated upon between August 2016 and August 2017 with minimal follow up of 6 months and follow up extended to 2 years after surgery. Serum Tg levels was measured preoperatively and postoperatively at 1, 6 and 12 months. The preoperative mean value for the two groups was similar. The levels of sTg showed a remarkable

drop through the mentioned period to reach a median of 0.1 for both groups. These findings were different from those found by **Popadich et al.**⁽¹⁶⁾ where Tg levels were measured pre initial I^{131} ablation and at 6 months postablation. Patients undergoing TTx alone had significantly higher preablation stimulated Tg reading compared with the cohort undergoing routine CLND. Perioperative data regarding operative time and hospital stay were comparable to **Raffaelli et al.**⁽⁹⁾ where they classified their study group according to procedure into 3 groups: total thyroidectomy (TT), TT plus ipsilateral PCND (Ipsi-PCND), and TT plus bilateral PCND (Bil-PCND). The mean hospital stay was greater for patients in the Bil-PCND group. Similarly, Operative time was greater for the Bil-PCND than in the Ipsi-PCND and TT groups (78.9 ± 23.3 minutes vs 64.3 ± 17.1 minutes vs 57.9 ± 15.4 minutes). In terms of postoperative complications, **Conzo et al.**⁽⁵⁾ conducted a large retrospective study and showed that the incidence of permanent hypoparathyroidism and permanent unilateral vocal fold palsy was 1% and 0.8% in group A and 3.6% and 1.7% in the group B, respectively. Our results were quite similar to those data except that we didn't record any cases of permanent vocal cord palsy. We both agreed in the significance of transient hypoparathyroidism that was higher in group B. The incidence of transient unilateral recurrent laryngeal nerve palsy in the study was 8% in both groups (2 cases in each group). These results were comparable with those of **Calò et al.**⁽¹⁵⁾, where transient recurrent laryngeal nerve palsy was observed in 3 patients in group A (1.36%) and in 2 patients in group B(3.07%) ($P = 0.69$). No cases of permanent or bilateral recurrent laryngeal paralysis were observed. **Wang et al.**⁽¹⁷⁾ conducted a focused study where PTC patients were subjected to PCND only as proven by frozen section analysis. For each patient, an average of three lymph nodes was obtained. Pathological examination showed that central lymph node metastases were found in 83 patients (83/188, 44.1 %). Postoperative complications happened in 10 patients (10/188, 5.3%), in which 9 (9/188, 4.8 %) had temporary hypocalcemia and 1 patient had transient recurrent laryngeal nerve palsy (1/188, 0.5 %). These findings confirm our results that transient hypoparathyroidism is the most common complication to occur in the PCND group with

high significance. **Shen et al.**⁽¹¹⁾ findings coincide with most of prospective studies regarding postoperative complications. Transient hypocalcemia occurred in 11% and 38% in group A and B respectively. The rate of permanent vocal cord paralysis was 1% and 2% respectively. The only contradiction to our study was the incidence of transient hoarseness which was surprisingly lower in group B (4% and 2% respectively), yet, still statistically insignificant. By far, the most common histological type is PTC (84% in group A & 76% in group B). This is comparable with that of **Calò et al.**⁽¹⁵⁾ where the rate of classical type PTC was 60.9% and 67.7% in group A and B respectively, followed by follicular variant (32% and 23%). Whereas, the least popular type was Hurthle cell variant (3.1%) which is comparable to our results (4% in total). In terms of recurrence, **Conzo et al.**⁽⁵⁾ stated that, 6 months after RAI treatment, cervical US did not identify suspiciously enlarged lymph nodes, and serum Tg levels were <2 ng/ mL. This is consistent with our data which recorded no recurrence within the same period in either group. At a mean follow of 9.5 ± 3.5 years, no patient developed distant recurrence. Nodal recurrences were observed in 15 of 390 of the group A patients (3.8%; 6 central recurrences [VI] and 9 ipsilateral recurrences [IIIV]) and in 12 of 362 of the group B patients [3.3%]; five central recurrences [VI] and seven ipsilateral recurrences [III-IV]). **White et al.**⁽²⁾ conducted a systematic review of literature using evidence-based criteria. They concluded that CLND may decrease recurrence of PTC (Levels IV and V data, no recommendation) and likely improves disease-specific survival (grade C recommendation). Limited level III data suggested survival benefit with the addition of prophylactic dissection to thyroidectomy (grade C recommendation). However, there may be a higher rate of permanent hypoparathyroidism and unintentional permanent nerve injury when CLND is performed with total thyroidectomy than for total thyroidectomy alone (grade C recommendation). Our data agree with all that previously mentioned in literatures, no difference in terms of recurrence was detected between both groups. The incidence of complications was comparable especially transient hypoparathyroidism in the central lymph nodal dissection group. The low recurrence rate (4%) combined with the non-negligible incidence of

complications leads us to sustain that prophylactic central lymph node dissection should not be carried out on a routine basis in the treatment of PTC. Instead, it may be more useful to develop criteria for the identification of high risk patients for whom central neck dissection could be of benefit. The problem that remains is how to define the assessment criteria of high-risk patients, considering the fact that only the size of the tumor can be assessed preoperatively, while the locoregional infiltration and multifocality can usually only be identified after surgery. We believe that a prophylactic central neck dissection should not be routinely recommended for smaller tumors (≤ 1 cm) while it may be advisable for larger tumors (>2 cm), especially if cytological suspicion of a high risk subtype arises or if there are intraoperative signs of extra-capsular spread. Although the compared groups were similar in terms of clinical and pathologic findings, the incidence of microcarcinoma and extensive use of RAI ablation were the main limitations of the present study and preclude the drawing of definitive conclusions. The current study has another limitation related to the relatively small number of pooled patients and to overcome this limitation, we recommend a further study on a larger scale with larger number of study population. The average follow-up of just 12 months which is reasonable for detecting early recurrences but prevent us from evaluating late recurrences. The debate over the benefits of RCLD for the treatment of DTC without suspicious enlarged lymph nodes in terms of recurrence rate and overall survival is likely to continue until conclusive evidence can be provided. Therefore, we believe that prophylactic neck dissection should be used selectively to avoid the minimal potential for morbidity.

CONCLUSION

In the absence of data supporting the favorable effects of RCLD, we believe that, in the treatment of DTC without a suspicious enlarged lymph node, it is not indicated, and more prospective, randomized controlled studies with large sample and sufficient follow-up are needed in the attempt to better define its clinical significance and demonstrate its prognostic impact. In addition, in identifying high-risk patients, more accurate and

definite criteria might be investigated for a better preoperative assessment and a tailored surgery.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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