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Original Research Article

Papillary thyroid carcinoma, evaluation of prophylactic central compartment's dissection versus conservative management: a prospective study

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ABSTRACT

Background: Papillary thyroid carcinoma (PTC) is one of the commonest thyroid cancers. While there is consensus of block node dissection in nodal positive patients, there is controversy in dealing with nodal negative patients regarding the need of block node dissection. We aimed to evaluate prophylactic central lymph node dissection (pCLND) versus conservative management in PTC with N0 neck.
Methods: This was a prospective randomized study conducted at General Surgery Department, Sohag University Hospital, from August 2013 to September 2017. It included fifty-five patients diagnosed to have PTC with N0 neck randomly divided into two groups; (Group A) included 25 patients who underwent total thyroidectomy (TT) alone and (Group B) included 30 patients who underwent TT with pCLND. We compared both groups regarding the operative and post-operative outcomes.
Results: There was temporary hypoparathyroidism with an incidence of 12% for Group A and 23% for Group B (P=0.01). Permanent hypocalcemia occurred in 1 patient in each group (P=0.75). Unilateral recurrent laryngeal nerve (RLN) temporary palsy occurred in 10% for Group B patients and in 8% for Group A patients, (P=0.46). Node metastases were observed in 43% in group B upstaging the disease. Both univariate and multivariate analyses showed that CLN metastasis was significantly associated with age <45, male gender, tumor size >2.0cm, bilaterality, and multifocality. Locoregional recurrence was observed in 4% of patients in group A and in 0% in B.
Conclusions: TT+pCLND is a safe treatment in patients with N0 PTC and it can be done without a high complication rate and without recurrence compared to TT without CLND.

Keywords: Central node dissection, Papillary thyroid carcinoma, Risk factors, Total thyroidectomy

INTRODUCTION

PTC is the most common well differentiated thyroid carcinoma (WDTC) and is considered a relatively indolent tumor.[1] This relatively benign Behavior has led to a concept that CLND would not affect survival rates.[2] Despite this, regional lymph node (LN) metastases are frequent in PTC occurring in 20% to 90% of patients.[3] The pattern of LN metastasis takes place in a sequential manner; involving the central compartment (level VI) first with a frequency reaching 90% including micro-metastases, followed by the ipsilateral lateral compartment and then the contralateral lateral compartment and the mediastinal LN.[4,5]

Although there is consensus of block node dissection in node positive patients there is controversy about the benefits of elective CLND in N0 PTC.[6] Patients have a

comparable ten-year survival without consideration of the type of surgical treatment, this fact advocates application of limited surgical intervention, but the high incidence of regional LN metastases makes surgeons rethink of performing TT+CLND as a standard surgical procedure in those patients.[6,7] As evaluation of the CLND specimen advances the disease stage in 30% of the patients, CLND might be an important first line treatment that would improve the accuracy of staging and would affect the survival rate in long term.[8] The central region is the first and most frequent area of thyroid carcinoma metastasis and constitutes one of the most important prognostic markers for recurrence.[9] In the same time it has been advocated that pCLND would decrease central compartment reoperation by performing a definitive and more radical initial surgical treatment as revision surgery still represents the main treatment for known recurrent/persistent disease in central compartment which are associated with higher complication rates compared to initial surgery. Besides providing objective information about LN status, CLND has also value to reduce postoperative Tg levels and local recurrence rates.[10,11] Secondary benefit of pCLND would be minimizing patients' anxiety about a secondary operation.[2] Add to this the low accuracy of preoperative diagnostic tools in identifying nodal involvement, led several authors to consider CLND especially when dealing with recurrent disease.[12]

In the other side, The American Thyroid Association (ATA) 2015 guidelines states that the impact of pCLND on survival is unclear and by all means is excellent overall.[4] Also, the effect of pCLND on recurrence rates for PTC appears to be negligible and those undergoing pCLND required fewer repeated doses of radioactive iodine (RAI), but significantly higher rates of permanent hypoparathyroidism.[13,14] Add to this some would argue that in case of CLN metastases, there would also be metastases at level VII; thus CLND would not be sufficient treatment.[15]

This study aimed to compare the outcome of pCLND versus no dissection in case of PTC with N0 neck.

METHODS

This was a prospective randomized study comparing TT without pCLND and TT+ pCLND for patients in N0 PTC neck at General Surgery Department, Sohag University Hospital from August 2013 to September 2017. Fifty-five patients were enrolled into the study. Institutional Ethical Committee approval was taken prior to commencement of study. A written and informed consent was taken from all patients after explaining details of operative procedures.

Inclusion criteria

Inclusion criteria were patients with PTC, diagnosed pre-operative by cytological diagnosis, with N0 neck either clinically, following US and confirmed after intra-operative inspection.

Patients were subjected to history and clinical examination, neck US, indirect laryngoscopy, fine needle aspiration cytology or Tru-Cut™ needle biopsy, thyroid function tests, thyroglobulin, calcitonin, Chest x-ray, CT scan, and MRI were done to detect any extra-thyroidal extension.

Exclusion criteria

The exclusion criteria were patients diagnosed as PTC with clinically palpable, radiological suspicious LN involvement, or after operative exploration, angiolymphatic invasion, evidence of extra thyroidal extension, locoregional extension, and aggressive histological subtypes.

The included patients were divided randomly by the closed envelop method into two groups.

- *Group A:* 25 patients who underwent TT alone
- *Group B:* 30 patients who underwent TT+pCLND whether ipsilateral or bilateral according to the tumor bilaterally

The term CLND (level VI), as defined by the ATA consensus, implies removal of prelaryngeal (Delphian nodes), pretracheal lymphatic tissue and at least one paratracheal LN.[16] Care must be taken not to injure the inferior thyroid artery during dissection as it supplies both parathyroid glands. RLN should be directly visualized throughout the nodal dissection in order to avoid injury. Author compared operative time, complication rates, local recurrence rate, disease free survival and mortality in-between both groups.

Postoperative follow-up included indirect laryngoscopy, measurement of serum calcium 24 hours and 48 hours postoperatively, calcium and vitamin D were administered prophylactically the second day postoperative together with suppressive L- Thyroxine therapy was routinely administrated. RAI ablation was considered when tumor size >10mm. The resected surgical specimens were histopathologically examined with comment on the final pathological diagnosis and LN status. Serum Tg and Tg antibody levels were assayed every 6 months together with neck US.

Follow-up was continued until the end of August 2017, ranged from 18 months to 48 months with a mean duration of 22±2.1 months. It was conducted monthly for the first 6 months then every 6 months throughout the rest of follow up period via clinical examination, laboratory, and imaging procedures for determination of the primary outcome measures; morbidity and recurrence of the disease.

Statistical analysis

Statistical analysis was done using IBM Statistical Package for Social Sciences version 22, 2014 (SPSS Inc., Chicago, Illinois, USA).

Qualitative data were expressed as number and percentages, and quantitative data were expressed as mean and SD. For comparison of percentages in qualitative variables, a χ^2-test was used for parametric (normally distributed) data and Fisher's exact test was used for nonparametric (non-normally distributed) data. For comparison of means in quantitative variables, a Student t-test was used.

Univariate analyses were performed by the Pearson chi-square $\chi 2$-test or one-way ANOVA. Multivariate analysis was employed by binary logistic regression to assess the relationships between clinical and pathological characteristics, which were found to be significant by univariate analysis, and CLN metastasis. The results were presented as ORs with 95% confidence intervals and P values. For all of these tests, the cutoff for significance of all used statistical analyses was rated as P ≤0.05, P value = 0.001 was rated as highly significant, and P value >0.05 was rated as not significant. Recurrence free survival was examined using Kaplan-Meier curves, Graphs were produced by using STATA intercooled version 12.1 program.

RESULTS

Table 1: Demographics and clinical features of patients.

Variable	Group A (25)	Group B (30)	P value
Sex ratio (F:M) 3.2:1	4:1	2.75:1	0.052
Age at diagnosis			
<45	13	20	0.137
≥45	12	10	
Mean age (years) 30±2.5	31±2.6	30±1.2	0.624
Mean duration of goiter (years)	3.25±1.5	4±1.30	0.241
Lesion Number			
Solitary thyroid nodule	5 (20%)	10 (33%)	0.170
Multi-nodular goiter	20 (80%)	20(67%)	
Lesion location			
Unilateral	14 (56%)	20 (67%)	0.153
Bilateral	11 (44%)	10 (33%)	
Tumor size (largest dimension in centimeters)			
≤2.0 cm	18(72%)	17(57%)	0.215
>2.0 cm	7 (28%)	13(43%)	

(P-value ≤0.05) = significant

This study included 55 patients suffering from PTC with N0 neck underwent either TT without pCLND (Group A); 25 patients (45%) or TT with pCLND (Group B) comprised 30 patients (55%) after exclusion of 6 patients lost to follow-up. The demographics and clinical features of both study groups are shown in Table 1.

All patients included in this study showed normal vocal cord mobility, normal thyroid function tests and normal levels of serum calcium before surgery.

The mean operative time for Group A was shorter (85.1±11.2 min), while for Group B the mean operative time was (96.8±15.7 min). The difference in-between both groups was significant (P=0.001). Add to this the postoperative hospital stay was shorter in Group A (5.3±2.5 days) versus (7.8±3.1 days) in Group B. The difference in-between both groups was significant (P=0.004) (Table 2).

Among the entire series, there was no permanent RLN palsy, although 5 patients (9%) had unilateral temporary palsy occurred; 3 patients (10%) in Group B and 2 patients (8%) in Group A (P=0.46). Measurement of serum calcium showed temporary hypocalcemia occurred in 10 (18%) patients distributed as 3 patients (12%) in Group A and 7 patients (23%) in Group B (P=0.01). Permanent hypocalcemia occurred in 1 patient in each group (P=0.75). However, only 4 (7.3%) patients had the symptoms of hypocalcemia distributed as 1 patient (4%) in Group A and 3 Patients (10%) in Group B (Table 2).

Postoperative hemorrhage requiring emergency surgery occurred in 2 patients (6.7%) of Group B and in 1 patient (4%) of Group A. The difference in-between both groups was insignificant (P=0.68) (Table 2).

Table 2: Surgical treatment, outcomes.

	Group A Number=25	Group B Number=30	P value
Operative time (minutes)	85.1±11.2	96.8±15.7	0.001
Postoperative hemorrhage	1 (4%)	2 (6.7%)	0.68
Wound infection	0	0	
Postoperative hospital stays (days)	5.3±2.5	7.8±3.1	0.004
Temporary hypoparathyroidism	3 (12%)	7 (23%)	0.01
Permanent hypoparathyroidism	1 (4%)	1 (3.3%)	0.75
Temporary RLN injury	2 (8%)	3 (10%)	0.46
Operative mortality	0	0	
Postoperative RAI	12 (48%)	18 (60%)	0.35
Regional recurrence	1 (4%)	0	

(P-value ≤0.05) = significant; NS = not significant

In Group B, histopathological study of the specimens containing the CLN showed that they were positive for malignancy in 13 patients (43%), the frequency of LN metastases was greater in men affecting 8 patients (62%)

than in women affecting 5 patients (38%) (P=0.02). So, after pCLND occult LN metastasis of this group thus upstaged (43%) and thus, changed the decision for those patients to receive post-operative RAI. In Group B; Univariate analysis of the different variables which may be responsible for CLN metastasis showed that CLN metastasis of patients with N0 PTC was significantly associated with age <45, male gender, tumor size >2.0cm, bilaterality, and multifocality. No significant correlation was found between CLN metastasis and capsular invasion (Table 3).

Table 3: Univariate analysis of risk factors associated with CLN metastasis.

	Central lymph node metastasis		P value
	Positive (%)	Negative (%)	
Gender			
Male	5 (62.5%)	3 (37.5%)	0.002
Female	8 (36%)	14 (64%)	
Age (Y)			
<45	15 (75%)	5 (25%)	0.000
≥45	4 (40%)	6 (60%)	
Ultrasonographic tumor size (cm)			
≤2.0 cm	9 (53%)	8 (47%)	0.007
>2.0 cm	10 (77%)	3 (33%)	
Bilaterality			
No	11 (55%)	9 (45%)	0.001
Yes	9 (90%)	1 (10%)	
Multifocality			
No	11(55%)	9 (45%)	0.003
Yes	8 (80%)	2 (20%)	
Capsular invasion			
No	13 (65%)	7 (35%)	0.973
Yes	6 (60%)	4 (40%)	

(P-value ≤0.05) = significant

Table 4. Multivariate logistic regression of independent risk factors affecting CLN metastasis.

Variable	Odds ratio	(95% confidence interval)	P value
Male gender	4.9	(1.6–15.2)	0.002
Age (Y) <45	6.2	(1.7–22.7)	0.000
Tumor size >2.0cm	3.37	(1.43 – 7.96)	0.007
Bilaterality	6.25	(3.45 – 11.36)	0.001
Multifocality	3.18	(1.64 – 6.17)	0.003

Multivariate logistic regression analysis revealed that age <45 years (P=0.000), ultrasonographic tumor size >2cm (P=0.025), and bilaterality (P=0.000) were independent risk factors of CLN metastasis in patients with N0 PTC (Table 4).

Follow-up was continued until the end of August 2017, from 18 months to 48 months with a mean duration of 22 months, and no operative mortalities occurred in both groups. Also, we did not face any patient with distant metastasis or extrathyroidal invasion, but there was only one disease local recurrence (4%) in Group A (P=0.30) (Figure 1).

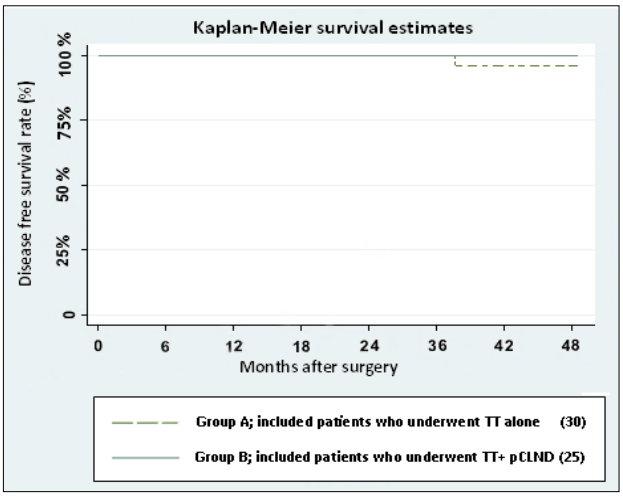

Figure 1: Disease-free survival of papillary carcinoma patients who underwent TT alone and those who underwent TT+ pCLND.

DISCUSSION

While PTC carries the best prognosis among the variable types of thyroid carcinomas with survival rates ranging from 92% to 95% at 5 years and from 89% to 90% at 10 years, the effect of cervical nodal metastasis on survival is difficult to assess.[17,18] In the absence of a survival benefit, potential morbidities and medical economics, the value of the conventional use of neck dissection is unaccepted.[18] PCLND in clinically node-negative WDTC patients remains controversial.[19]

Patients with PTC are usually young, and cervical metastases are not uncommon.[20] The mean age of our patients was 30±2.3 years, which is comparable to other studies.[21,22] The female to male ratio was also similar to previous studies as 3.2:1.[23]

In accordance with previous studies, CLND revealed metastasis in 43% of patients experienced neck dissection.[24] Also, other studies recorded this occult metastasis to be between 40 and 90%.[25] So many surgeons consider the necessity of CLND for PTC patients because the high rate of CLN metastasis.

LN metastases are considered as the important prognostic factor for PTC patients aged ≥45 years. However, in a study of patients <45 years with PTC, the presence and number of LN metastases were associated with compromised survival.[26] Add to this, ages <45 years were an independent risk factors for the presence of CLN metastasis, which allowed for selective pCLND in PTC.[27] Although some studies deny this association, in present study, CLN metastasis was detected in 75% of patients aged <45 years, while CLN metastasis was detected in

only 40% of patients aged ≥45 years.[28] This difference was statistically significant (P=0.000) which in line with other studies.[29] Author concluded that ages <45 years was significantly associated with increased incidence of CLN metastasis of patients with N0 PTC.

Previous studies have evaluated the risk factors related to central and/or lateral LN involvement and it showed that women were more susceptible to PTC which may be related to the estrogen level in women.[30] While other studies showed that the incidence of male patients' LN metastasis was significantly higher as they are exposed to unhealthy lifestyles and harmful environmental factors, such as smoking and drinking.[31] In present study, men were determined to be significantly more related to LN metastasis. So et al. reported that male sex, tumor multifocality, and extrathyroidal tumor extension; all were independent predictors of occult CLN metastases.[32]

Considering tumor size as a risk factor for CLN metastasis, previous studies showed that larger tumor size was a risk factor for the presence of CLN metastasis in patients with PTC.[33] However, the size cutoffs differed in those studies but Suman et al, reported that larger tumors (tumor size >2cm) were significantly associated with CLN metastasis.[27] Ito et al. reported that PTC of >2cm was the strongest independent risk factor for both microscopic central and lateral LN metastasis.[34] The presence of LN metastasis has been recorded to be 2-6 fold higher in patients with tumors of >4cm in comparison with smaller tumors.[35] In present study, CLN metastasis was more frequent in patients with tumor size >2cm and detected in 77% of patients, in comparison to patients with tumor size ≤2cm CLN metastasis was detected in 53% of patients (P=0.007). Multivariate logistic regression analysis revealed that tumor size >2cm was an independent predictor of CLN metastasis in patients with N0 PTC.

The relationship between tumor bilaterality and CLN metastasis in patients with PTC is controversial. Some studies reported that bilaterality was not significantly associated with CLN metastasis.[36] Others showed that bilaterality is an important risk factor of CLN metastasis.[37] In present study, the incidence of CLN metastasis in patients with bilateral tumors was 89%, significantly higher than 52.4% in patients with unilateral tumor. This difference was statistically significant (P=0.001). Multivariate logistic regression analysis showed bilaterality was an independent risk factor of CLN metastasis in patients with N0 PTC. The multifocality increase the risk of LN metastasis.[35] In present study, CLN metastasis was found to be significantly high when there is multifocality (P=0.003) which detected in 80% of patients, in comparison to patients without multifocality CLN metastasis was detected in 55% of patients.

Also, bilateral lesions were found to be a risk factor for LN metastasis in comparison with unilateral lesions.[35] In present study, CLN metastasis was found to be significantly high in the presence of bilateral lesions which detected in 89% of patients, in comparison with patients with unilateral tumors CLN metastasis was detected in 52.4% of patients. This difference was statistically significant (P=0.001).

Author do not have any permanent RLN palsy in both groups, and the rate of temporary RLN palsy in TT+CLND group was similar to the previous studies. PCLND also has been recorded to cause a higher rate of temporary RLN injury. However, in a previous study, no significant differences were found between thyroidectomy alone in comparison to TT+CLND regarding temporary RLN palsy.[38] In present study, there was no permanent RLN palsy, and temporary RLN palsy was found in 10% of Group B patients.

The incidence of hypoparathyroidism varies among centers and its prevalence ranges from 16 to 55%, but still the only significant complication of CLND.[39,40] Although the extent of surgery does not influence the number of parathyroid glands the possible mechanism behind hypocalcemia is devascularization of the glands.[41] Our temporary and permanent hypoparathyroidism rates are much lower in comparison to the previous studies.[42] Biochemical hypocalcemia (<8mg/dl) was observed in 18% of patients, and symptomatic hypocalcemia was observed in only 7.3% of these patients. This is because we followed a strategy of giving calcium and vitamin D in the first postoperative day aiming at reducing the risk of transient hypocalcemia without causing parathyroid hormone inhibition.[43]

CLN metastasis is considered the most important risk factor for local recurrence.[44] Also it decreases survival and it is related to distant metastasis.[45,46] Bardet et al, stated that the risk of recurrence was low in patients without macroscopic LN involvement; even if pCLND was not applied.[47] Nevertheless, recurrence was determined in 4% of Group A patients but due to the low number of patients statistical analysis could not be made.

Our results proved that CLN metastatis is prevalent in patients with N0 PTC with upstaging of the disease. The results also suggest that TT+CLND is a safe treatment in patients with N0 PTC in experienced hands and it can be done without a high complication rate. The basic limitations of this study were the little number of patients and we could not evaluate the effect of occult CLN metastasis identified by pCLND on oncological outcomes of those patients, because the relatively short follow-up time in this study.

CONCLUSION

In conclusion, metastatic disease to CLN is prevalent in patients with N0 PTC. Ages <45 years, male gender, tumor size >2cm, multifocality, and bilaterality; are

independent risk factors of CLN metastasis, which allow for selective CLND in patients with N0 PTC.

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