Journal of American Science

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Role of Prophylactic Central Neck Dissection for Early Papillary Thyroid Cancer

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Abstract: The role of prophylactic central lymph node dissection in the management of PTC is still a controversy. There is no convincing evidence that prophylactic central neck dissection provides an improvement in overall survival, recurrence rate, or any clinically significant variable when applied without discrimination to all PTC patients. The recurrence rate found in this study of 5% confirms the rarity of lymph node recurrence and leaves many doubts regarding the usefulness of prophylactic central neck dissection. Also, the ATA presented many contradictions for emerging PCND in routine TT surgery for PTC patients, however its recommendations is based on the risks and stages of tumor. Our study does not show significant increase in morbidity with prophylactic central neck dissection than with Thyroidectomy alone. On the other hand, PCND upgraded 35% of the patients included in our study to N1, and this is regarded by many as over-diagnosis and may lead to overtreatment in the form of higher doses of RAI. Therefore, in our opinion, until conclusive evidence emerges of the actual benefit of prophylactic central neck dissection procedure in the treatment of PTC without suspicious enlarged nodes, it may be avoided. In conclusion, Total Thyroidectomy appears to be the adequate treatment for clinically node-negative PTC. Based on current literature and our results, we support the American Thyroid Association's recommendations that prophylactic central neck dissection should be reserved only for the use in high risk patients and advanced (T3 and T4) papillary thyroid cancers and could be considered for the more appropriate selection of patients for radioiodine treatment. Unfortunately, no pathological or clinical factors are able to predict with any degree of certainty the presence of nodal metastasis. The potential use of molecular markers will hopefully offer a further tool to stratify the risk of recurrence in patients with PTC and allow a more specific approach to offer prophylactic central neck dissection to patients with the most benefit. Multi-institutional larger studies with longer follow-up periods are necessary to provide definitive conclusions.

[Emad El-Din Farid Ibrahim, Shaaban Mohamed Mohamed Abdulmaged, Dina Hany Ahmed, Ahmed Serag El-Din Hessein, Sameh Wagdy Abdel Ghaffar Hussein. **Role of Prophylactic Central Neck Dissection for Early Papillary Thyroid Cancer.** *J Am Sci* 2019;15(11):102-109]. ISSN 1545-1003 (print); ISSN 2375-7264 (online). http://www.jofamericanscience.org. 10. doi:10.7537/marsjas151119.10.

Keywords: Prophylactic, Central, Neck, Dissection Papillary, Thyroid, Cancer

1. Introduction

Papillary thyroid cancer is the most common form of differentiated thyroid cancer, comprising approximately 90% of the 44,670 estimated new cases of thyroid cancer in the United States in 2012 ***(Jemal et al.,2012).***

The established primary treatment of papillary thyroid cancer per American Thyroid Association (ATA) guidelines is total thyroidectomy for all tumors larger than 1 cm. The ATA consensus statement also recommends therapeutic central neck dissection in patients with clinically involved nodes and prophylactic central neck dissection in advanced primary tumors (T3 or T4) without evidence of nodal involvement ***(Haugen et al., 2016).***

Radioactive iodine ablation plays an important role in adjuvant treatment following thyroidectomy for some subgroups of patients based on risk of recurrence. This treatment algorithm achieves extremely low death rates; however, the rates for cervical lymph node metastasis and recurrence remain significant. Despite the ATA recommendations, there is controversy regarding the ideal surgical management of the central neck lymph nodes in patients with papillary thyroid cancer ***(Haugen et al, 2016).***

Papillary thyroid cancer and the follicular variant of papillary thyroid cancer have a propensity for cervical lymphatic spread that occurs in 20% to 50% of patients on standard review of surgical pathologic specimens and in 90% of those examined for micro metastases. The spread of tumours cells occurs in a predictable pattern that initiates in the perithyroidal lymph nodes of the central neck and progresses to the lymph nodes of the lateral cervical compartments and the superior mediastinum ***(Lundgren et al., 2016).***

"Skip" metastases to the lateral compartment without central neck nodal involvement are rare but do occur. Patients with nodal metastases have higher rates of persistent and recurrent disease during postoperative surveillance. The impact of nodal metastases on overall survival remains debatable; several studies have demonstrated no difference in mortality, while two large population-based studies have shown increased mortality in patients with regional lymph node metastasis ***(Lundgren et al., 2016).***

Prophylactic or routine central neck dissection for patients with papillary thyroid carcinoma is defined as complete excision of the level VI and VII lymph nodes in patients with no evidence of nodal involvement after preoperative clinical and imaging evaluation. The role of prophylactic central neck dissection remains a contentious issue regarding its benefits and risks, and several reports have reviewed this subject. Several single-institution retrospective cohort studies on total thyroidectomy alone vs with prophylactic neck dissection, as well as a meta-analysis of these studies, have reported mixed results ***(Chisholm et al., 2009).***

Proponents of prophylactic central neck dissection at the time of initial thyroidectomy cite the high incidence of cervical lymph node metastases and the associated increase in recurrence rates with the possibility of decreased survival. The low sensitivity of preoperative ultrasound evaluation and intraoperative assessment to accurately detect lymph node involvement is also used as rationale for routine central neck dissection. The addition of central neck dissection to initial total thyroidectomy can provide valuable staging information and has been shown to upstage approximately a third of patients older than 45 years of age to stage III disease in two retrospective reviews ***(Hughes et al., 2011).***

The addition of prophylactic central neck dissection appears to provide important staging information that can affect radioactive iodine ablation treatment, but the evidence regarding recurrence and survival benefits remain limited and conflicted. The argument against prophylactic central lymph node dissection at the time of initial thyroidectomy for papillary cancer, focus on the unproven benefit and the possibility of increased complications ***(Sywak et al., 2006).***

The relevance of subclinical cervical lymph node metastases on rates of recurrence and survival has been questioned by some retrospective studies. Additionally, there is lack of proven benefit in outcomes after prophylactic central node dissection. The possibility of increased complications rates with central neck dissection has been addressed, although again by only small retrospective studies. Higher rates of temporary hypoparathyroidism with central neck dissection seem consistent between these studies, while the rates of permanent hypoparathyroidism and nerve injury rates are statistically similar compared with total thyroidectomy alone. The debate on the role of routine central neck dissection in the treatment of papillary thyroid carcinoma is likely to continue until a large randomized trial with long-term follow-up can be completed ***(Sywak et al., 2016).***

Aim of the Work

The aim of this work is to compare the risk-benefit of total thyroidectomy with prophylactic central neck dissection (level VI) in clinically and radiologically node negative early (T1 or T2) papillary thyroid carcinoma, with total thyroidectomy without central neck dissection.

2. Patients and Methods

This prospective study includes 40 patients with early Papillary Thyroid Carcinoma (T1 or T2) without evidence of nodal involvement, in group (I) 20 patients will undergo total thyroidectomy without central neck dissection and in group (II) 20 patients will undergo total thyroidectomy with prophylactic central neck dissection.

Study was done in the following steps:

1. Determination of the target disease.
2. Identification of the target patients.
3. Preoperative assessment of the patients.
4. Postoperative follow-up of the patients.
5. Data collection.
6. Data analysis.
7. Reporting and interpretation (Results).
8. Discussion and conclusion.

I) Aim of the work:

The aim of this study is to compare the risk-benefit of total thyroidectomy without prophylactic central neck dissection (Group I), with total thyroidectomy with central neck dissection (level VI) (Group II) in node negative (Clinically and Radiologically) early (T1 or T2) papillary thyroid carcinoma.

Inclusion criteria:

1- Stage: T1 and T2 papillary thyroid cancer
2- Age: Any adult age
3- Sex: Male and Female

Exclusion criteria:

1- T3 and T4 papillary thyroid cancer
2- Preoperative lymph nodes metastases N1
3- Distant metastases M1

II) Preoperative assessment of the patients:

1- History and full clinical examination including vocal cord examination.
2- Full Thyroid Profile plus Serum Thyroglobulin and Thyroglobulin Antibodies.
3- Ultrasound Neck.
4- Radionuclide Thyroid scan.

5- Fine needle aspiration.
6- CT scan of the Neck, Chest.

III) Postoperative follow-up:

1-Monitor complications in the form of recurrent laryngeal nerve injury and permanent hypoparathyroidism.

2-Monitor recurrence of the disease every 3 month for one year by

A) Ultrasound Neck.
B) Serum Thyroglobulin level.
C) Full-Body Radioisotope scan.

IV) Data collection:

Information was gathered from both groups of patients included in the study who underwent total thyroidectomy with and without central neck dissection.

V) Data analysis:

Statistical methods:

Statistical presentation and analysis of the present study was conducted using the mean, standard Deviation, unpaired student t-test and chi-square tests by ***SPSS V20.***

3. Results

Patients were divided randomly into two groups. Group I performed Total Thyroidectomy without Central Neck Dissection. Group II performed Total Thyroidectomy with Central Neck Dissection.

Preoperative data:

Group I involved 16 Females, and 4 Males, while group II involved 15 Females and 5 Males, with a total of 31 Females and 9 Males in both groups. The p-value was 0.705 showing no significance.

The age range in group I was between 24 and 53 years of age, while in group II was between 19 and 60 years of age. The p-value was 0.460 showing no significance.

The preoperative staging in group I showed, 9 patients were (T1N0M0), while 11 patients were (T2N0M0). In group II 12 patients were (T1N0M0), while 8 patients were (T2N0M0). The p-value was 0.342 showing no significance.

Preoperative Serum Thyroglobulin level in group I was elevated in 14 patients, while in group II it was elevated in 15 patients. The p-value was 0.723 showing no significance.

Preoperative Serum Thyroglobulin antibody level in group I was elevated in 6 patients, while in group II it was elevated in 3 patients. The p-value was 0.256 showing no significance.

Postoperative data and complications:

The postoperative staging in group I showed, 6 patients were (T1N0M0), while 14 patients were (T2N0M0). In group II 8 patients were (T1N0M0), while 5 patients were (T2N0M0), and 7 patients were (T2N1MO). The p-value was 0.0031 showing significance.

Patients were assessed for complications as a direct result for the surgical intervention.

Vocal cord mobility was assessed after removal of the endotracheal tube. Voice assessment was performed and it was based on the patient's subjective report and physician's objective assessment of voice in the office, and the assessment was done 2 month after the surgical intervention.

In group I, one case showed unilateral RLN injury, while in group II also one case showed unilateral RLN injury. The p-value was 1.000 showing no significance.

Permanent Hypoparathyroidism (***low serum iPTH (<1.4 pmol/L or <13 pg/ml) and need for calcium and vitamin D replacement 1 year after surgical intervention)*** as a complication of surgery.

In group I no cases were diagnosed with Permanent Hypoparathyroidism as a direct result for the surgical intervention, while in group II one case was diagnosed with Permanent Hypoparathyroidism as a direct result for the surgical intervention. The p-value was 0.311 showing no significance.

Follow-up

All the patients in the two groups received RAI ablation. P-value was 1.000, showing no significance.

At three month after surgery and RAI treatment, serum thyroglobulin (Tg) measurements were undetectable (<0.1 ng/ml) in all the patients in the two groups. Also clinical examination and Ultrasound neck showed no recurrence in all the patients. P-value was 1.000, showing no significance.

At six month after surgery one case of disease recurrence was detected by rising Tg levels and confirmed by Ultrasound neck and whole body scan as cervical lymph nodes metastasis in group I. In group II serum thyroglobulin (Tg) measurements were undetectable (<0.1 ng/ml) in all the patients, and clinical examination, and Ultrasound neck showed no recurrence. P-value was 0.311, showing no significance.

At twelve month after surgery in group II one case of disease recurrence was detected by rising Tg levels and confirmed by Ultrasound neck and whole body scan as cervical lymph nodes metastasis. In group I serum thyroglobulin (Tg) measurements were undetectable (<0.1 ng/ml) in all the patients other than the case detected at six month, and clinical examination, and Ultrasound neck showed no recurrence. P-value was 0.311, showing no significance.

Overall disease Recurrence was one case in group I, and one case in group II. P-value was 1.000, showing no significance.

Table (1): Preoperative Serum Thyroglobulin by Group.

Preoperative Serum Thyroglobulin		Groups					
		Group I		Group II		Total	
		No.	%	No.	%	No.	%
Elevated		14	70.0	15	75.0	29	72.5
Normal		6	30.0	5	25.0	11	27.5
Total		20	100.0	20	100.0	40	100.0
Chi-square	X^2	0.125					
	P-value	0.723					
	Significance	No Significance					

Table (2): Preoperative Serum Thyroglobulin antibody by Group

Preoperative Serum Thyroglobulin antibody		Groups					
		Group I		Group II		Total	
		No.	%	No.	%	No.	%
Elevated		6	30.0	3	15.0	9	22.5
Normal		14	70.0	17	85.0	31	77.5
Total		20	100.0	20	100.0	40	100.0
Chi-square	X^2	1.290					
	P-value	0.256					
	Significance	No Significance					

Table (3): Preoperative and postoperative TNM by Group.

T		Groups						
		Group I		Group II		Chi-square		
		No.	%	No.	%	X^2	P-value	Significance
Pre	T1	9	45.0	12	60.0	0.902	0.342	No Significance
	T2	11	55.0	8	40.0			
Post	T1	6	30.0	8	40.0	0.440	0.507	No Significance
	T2	14	70.0	12	60.0			
Chi-square	X^2	0.960		1.600				
	P-value	0.327		0.206				
	Significance	No Significance		No Significance				

Table (3): Postoperative TNM Classification by group.

TNM	Group I	Group II	Chi-square	P-value	Significance
T1N0M0	6	8	11.549	0.0031	Significant
T2N0M0	14	5			
T2N1M0	0	7			

Table (4): Recurrent Laryngeal Nerve Injury by Group.

Recurrent laryngeal nerve injury		Groups					
		Group I		Group II		Total	
		No.	%	No.	%	No.	%
No		19	95.0	19	95.0	38	95.0
Yes		1	5.0	1	5.0	2	5.0
Total		20	100.0	20	100.0	40	100.0
Chi-square	X^2	0.000					
	P-value	1.000					
	Significance	No Significance					

Table (5): Permanent Hypoparathyroidism by Group.

Permanent hypoparathyroidism		Groups					
		Group I		Group II		Total	
		No.	%	No.	%	No.	%
No		20	100.0	19	95.0	39	97.5
Yes		0	0.0	1	5.0	1	2.5
Total		20	100.0	20	100.0	40	100.0
Chi-square	X^2	1.026					
	P-value	0.311					
	Significance	No Significance					

Table (6): Disease Recurrence within One Year by Group.

Disease recurrence within one year		Groups					
		Group I		Group II		Total	
		No.	%	No.	%	No.	%
No		19	95.0	19	95.0	38	95.0
Yes		1	5.0	1	5.0	2	5.0
Total		20	100.0	20	100.0	40	100.0
Chi-square	X^2	0.000					
	P-value	1.000					
	Significance	No Significance					

4. Discussion

The fundamental goals of initial therapy for patients with PTC are to improve overall and disease-specific survival, permit accurate disease staging and risk stratification, reduce the risk of persistent/recurrent disease and associated morbidity, while minimizing treatment-related morbidity and unnecessary therapy. The specific goals of initial therapy are to:

Eliminate the primary tumor, disease that has extended beyond the thyroid capsule and clinically significant lymph node metastases. Total surgical resection is an important determinant of outcome, while residual metastatic lymph nodes represent the most common site of disease persistence/recurrence ***(Wang et al., 2004).***

Minimize the risk of metastatic spread and disease recurrence. Adequate surgery is the most important treatment variable affecting prognosis, while TSH suppression, RAI treatment, and other modalities of treatment each play adjunctive roles in at least some patients ***(Mazzaferri et al., 2010).***

Facilitate postoperative treatment with RAI, where appropriate. For patients who require RAI remnant ablation or RAI treatment of potential (adjuvant therapy) or known (therapy) residual or metastatic disease, removal of all normal thyroid tissue is an important element of preliminary surgery ***(Haugen et al., 2016).***

Provide accurate staging and risk stratification of the disease. Because risk stratification and disease staging should be used to guide initial prognosis, disease management, and follow-up strategies, accurate post-operative risk assessment is a crucial element in the management of patients with PTC ***(Haugen et al., 2016).***

Permit accurate long-term surveillance for disease recurrence.

Minimize treatment-related morbidity. The experience of the surgeon and the extent of surgery both play important roles in determining the risk of surgical complications ***(Gourin et al., 2010).***

Regional lymph node metastases are present at the time of diagnosis in the majority of the patients with papillary thyroidcarcinomas and a lesser extent in patients with follicular carcinomas. The frequency of micrometastases (<2 mm) nearly 90%, depending on the sensitivity of the type of detection method ***(Randolph et al., 2012)***.

However, the clinical implications of micrometastases are likely less significant compared to macrometastases. Preoperative US identifies suspicious cervical adenopathy in 20%–31% of cases, potentially altering the surgical approach in as many as 20% of patients. However, preoperative US identifies only half of the lymph nodes found at surgery, due to the presence of the overlying thyroid gland ***(O'Connell et al., 2013).***

The location of the lymph nodes may also be useful for decision-making. Malignant lymph nodes are much morelikely to occur in levels III, IV, and VI than in level II, although this may not be true for PTC tumors arising in the upper pole of the thyroid, which have a higher propensity to demonstrate skip metastases to levels III and II ***(Park et al., 2012).***

Even though PTC lymph node metastases are reported by many to have no clinically substantial effect on the outcome for low risk patients, a study of the SEER database found, among 9904 patients with PTC, that lymph node metastases, distant metastasis, age >45 years, and large sized tumor markedly predicted poor overall survival outcome in a multi-variable analysis. All-cause survival at 14 years was 82% for PTC without lymph node metastases and 79% with nodal metastases ($p < 0.05$). Another SEER study concluded that cervical lymph node metastases conferred an independent risk of increased mortality, but that's in patients with follicular cancer and patients with papillary cancer above the age of 45.

However, the characteristics of lymph node metastases can also discriminate the risk of recurrence to the patient, especially in patients with clinically evident metastasis, larger metastases, multiple metastases, and/or extracapsular nodal extension, in comparison to those with more limited microscopic nodal disease ***(Randolph et al., 2012)***.

A recent comprehensive analysis by the National Cancer Data Base and SEER, however, showed a small but significantly decreased survival in patients younger than 45 years with lymph node metastases in comparison to younger patients without lymph nodes affection, and that having incrementally more metastatic lymph nodes up to six involved nodes adds mortality risk in this age group. This study highlights the importance of meticulous preoperative screening for nodal metastases and potentially raises questions about current thyroid cancer staging systems. Common to all of these studies is the conclusion that the effect of the presence or absence of lymph node metastases on overall survival, if present, is small ***(Adam et al., 2015).***

The role of therapeutic lymph node dissection for treatment of thyroid cancer nodal metastases is well accepted for cN1 disease. However, the value of routine prophylactic level VI (central) neck dissection for cN0 disease remains unclear. Central compartment dissection (therapeutic or prophylactic) can be achieved with low morbidity by experienced thyroid surgeons. The value for an individual patient depends upon the utility of the staging information to the treatment team in specific patient circumstances ***(Sancho et al., 2014).***

Based on limited and imperfect data, prophylactic dissection has been suggested to improve disease-specific survival, local recurrence, and post-treatment Tg levels. It has also been used to inform the use of adjuvant RAI and improve the accuracy of the estimates of risk of recurrence. However, in several studies, prophylactic dissection has shown no improvement in long-term patient outcome, while increasing the likelihood of temporary morbidity, including hypocalcaemia, although prophylactic dissection may decrease the need for repeated RAI treatments ***(Barczynski et al., 2013).***

The removal of cN0 level VI lymph nodes detects a substantial number of patients with pN1 disease, upstaging many patients over age 45 from American Joint Committee on Cancer (AJCC) stage I to stage III. However, the direct effect of this on long-term outcome is small at best as microscopic nodal positivity does not carry the recurrence risk of macroscopic clinically detectable disease. The use of staging information for the planning of adjuvant therapy depends upon whether this information will affect the team-based decision-making for the individual patient. For these reasons, groups may elect to include prophylactic dissection for patients with some prognostic features associated with an increased risk of metastasis and recurrence (older or very young age, larger tumor size, multifocal disease, extrathyroidal extension, known lateral node metastases) to contribute to decision-making and disease control ***(Sancho et al., 2014).***

Alternatively, some groups may apply prophylactic level VI dissection to patients with better prognostic features if the patient is to have a bilateral thyroidectomy, and if the nodal staging information will be used to inform the decision regarding use of adjuvant therapy **(*Laird et al., 2012).***

Finally, for some groups it appears reasonable to use a selective approach that applies level VI lymph node dissection at the time of initial operation only to patients with clinically evident disease based on preoperative physical exam, preoperative radiographic evaluation, or intraoperative demonstration of detectable disease (cN1) ***(Gyorki et al., 2013).***

The preceding recommendations should be interpreted in light of available surgical expertise. For patients with small, noninvasive, cN0 tumors, the balance of risk and benefit may favor thyroid lobectomy and close intraoperative inspection of the central compartment, with the plan adjusted to total thyroidectomy with compartmental dissection only in the presence of involved lymph nodes.

The rationale for pCND is based on the assumption that patients have high rates of metastases and regional recurrence in the central neck and that reoperation for central neck recurrence is difficult and carries an increased risk of hypocalcaemia and unintentional RLN injury. However, improvements in survival and locoregional recurrence rates have not been consistently demonstrated with pCND. Although some studies have reported a decrease in neck recurrence after pCND, others do not demonstrate any effect ***(Haugen et al., 2016).***

In our study, pCND did not show any advantage related to locoregional recurrence in cN0 disease

during the follow-up period of one year. There was no significant trend toward less recurrence in the central compartment in patients who underwent TT plus pCND compared to those who had TT only. The biological behavior of LNM may not always be predictable. While central LNM is often high, the recurrence rate remains low (0-15%), even in patients who underwent TT. It has not been possible to explain this difference, but it might be related to the extreme aggressiveness of cancers, in which recurrence would not only depend on local procedures such as pCND. Our results were consistent with the majority of the other studies that concluded the lack of benefit from pCND. The indication for pCND in PTC patients with cN0 is less well defined and remains controversial.

According to Mazzaferri the incidence of transient hypoparathyroidism after CND ranges between 14% and 44% (***Mazzaferri, et al.2009).*** For White the rate of permanent hypoparathyroidism after total thyroidectomy with prophylactic CND is between 0% and 14.3%***(White et al. 2006).*** Our data did not show any significant difference in incidences of transient or permanent symptomatic hypocalcaemia between the two groups, as with group I it was 0%, and group II it was 5% (P-value=0.311), which is different to the other studies, but limited by the small number included in the study.

Many studies showed an increased risk of RLN paralysis in patients undergoing CND, with rates of recurrent lesions ranging between 1% and 12% ***(Hughes et al., 2011).*** Pereira reports increments from 3% to 6% of RLN lesions between TT only and TT with pCND ***(Pereira el al., 2005).***

Segal et al. reported a higher rate of permanent nerve injury (5.8% versus 25%) for second surgery compared to first operations (5.8% versus 25%) ***(Segal et al. 1995).***

According to Popadich, the percentage of RLN transient paralysis increased from 1.8% after TT to 2.3% after TT with pCND, whereas the definitive rates range from 0.4% to 1.8% ***(Popadich et al., 2011).***

For Giordano transitional cases range from 3.6% to 5.5%, the definitive from 1% to 2.3% ***(Giordano et al., 2012).***

In our experience, there was no significant difference between the two groups as the incidence of RLN injury was the same in both groups at 5%.

The results of this study should be interpreted with caution because of some limitations. First, the study is not of the highest-quality evidence, and such data might lead to less powerful results. Second, the number of patients in our studies is small, which may not reflect the real situation. Third, the follow-up period in the study was relatively short. Because PTC has the characteristics associated with slow-growth, some patients might not have detectable LNM until many years after initial surgery. This might be a bias for clearly evaluating postoperative recurrence.

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10/27/2019