

# **Original Article**

# **Prophylactic Central Lymph Node Dissection** in Differentiated Thyroid Cancer - Benefits and **Risks**

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#### **Abstract**

Introduction: Papillary thyroid cancer is the most common thyroid malignancy. Lymph nodes involvement is common in differentiated thyroid cancer, and cervical lymph node micrometastases are observed in up to 85% of patients with papillary thyroid cancer during surgery. While the therapeutic central lymph node dissection has been accepted, the debate on the prophylactic in differentiated thyroid carcinoma (DTC) continues.

Aim: To evaluate the benefits and risk of prophylactic central lymph node dissection in differentiated thyroid cancer.

Materials and methods: Between January 2014 and December 2018, 223 total thyroidectomies due to papillary thyroid cancer were performed in the Kaspela University Hospital in Plovdiv. The patients were allocated into two groups: group A consisting of 36 patients with total thyroidectomy alone, and group B - 178 patients with total thyroidectomy and prophylactic central lymph node dissection.

Results: In 36 (21.6%) patients, we found metastases only in ipsilateral side. In 24 (13.4%) of them we found metastatic spread in both ipsilateral and contralateral lymph nodes. In 7 (3.9%) patients, the metastasis was found only in the contralateral nodes. A pre-laryngeal lymph node was found and removed in 79 patients. Metastases were found in 12 of these 79 nodes. Analysis of complications showed no significant differences in its rate in patients with TT+ PCLND vs. patients with TT alone.

Conclusions: The present study suggests that the realization of total thyroidectomy with prophylactic central lymph node dissection in papillary thyroid cancer patients has neither substantial advantages nor significant complications for the short period of observation.

#### **Keywords**

papillary thyroid cancer, prophylactic central neck lymph node dissection

# INTRODUCTION

The rate of differentiated thyroid carcinoma (DTC) has increased in the past decade. The papillary thyroid cancer (PTC) makes up approximately 70%-85% of all thyroid cancers.<sup>[1]</sup> Up to 40% of patients with DTC have cervical lymph node metastases, and up to 80% of them possess undetectable micrometastases in the cervical lymph nodes. Pre-operative imaging have limited sensitivity at detecting them.<sup>[2]</sup> Patients with this disease have high overall survival and an excellent prognosis, but usually the concerns are associated with the local recurrences. Recurrence most commonly occurs in the cervical lymph nodes and is generally managed with surgical resections.<sup>[3]</sup> Pro-



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phylactic central neck lymph node dissection (PCNLD) is performed to remove occult nodal metastases which are not detected during clinical examination and by imaging. Neck ultrasound (US) and contrast enhanced computed tomography (CT) are widely used for preoperative imaging to visualise and evaluate metastatic neck lymph nodes. However, they are not particularly accurate, with low sensitivities of 23%-53.2% and 41%-66.7%, respectively, and impossibility to detect micrometastases. After surgical removal micrometastases can be found in the central cervical lymph nodes in 40%-60% of cases.<sup>[4]</sup> PCNLD also offers better staging of the disease, reduction of the risk of central neck recurrence; it may lower postoperative thyroglobulin levels leading to more effective detection of persistent or recurrent disease; it reduces the need for re-surgeries in the central neck which are associated with increased risk of injury to the recurrent laryngeal nerve (RLN) and parathyroid glands. It should be noted that a PCNLD also carries a risk of RLN and parathyroid glands injury which is pointed to by the opponents of prophylactic dissections. The indications and role of PCNLD in thyroid cancer management remain controversial.<sup>[5]</sup>

Central neck lymph node dissection (CLND) includes level VI, the anatomic area bounded by the hyoid bone superiorly, the sternal notch inferiorly, and the medial borders of the carotid sheaths laterally. The structures in this compartment are the esophagus, recurrent laryngeal nerves, trachea, parathyroid glands, thymus, and the thyroid gland. The included lymph nodes are the pre-tracheal, para-tracheal and pre-laryngeal (also called Delphian). The lymph nodes found below the sternal notch to the level of the innominate vein are described as level VII; these must also be removed during CNLD.<sup>[5]</sup>

The dissection might be therapeutic or prophylactic.

Therapeutic lymph node dissection involves the removal of abnormal lymph nodes that are clinically or radiographically suspected for metastatic disease, or cytologically or histologically proven. This dissection is based on the need of regional disease control to prevent future morbidity from tumour spread, maintain quality of life, and possibly maximise survival.

Prophylactic lymph node dissection is the removal of lymph nodes that are normal on physical examination and radiographic imaging. Dissection of clinically and radiographically normal lymph nodes is based on the theory that early detection and removal of microscopic disease in regional lymph nodes may prevent recurrence and improve survival. The decision to proceed with this dissection is based on assessment of the risks and benefits of the procedure. Morbidity of regional lymph node dissection varies with the anatomic region of the body and can include postoperative hemorrhage requiring re-surgery, seroma, nerve injury, and the cosmetic complications of a scar. These complications must be balanced against the potential benefits of the procedure. [6]

# **AIM**

To evaluate the benefits and risk of prophylactic central lymph node dissection in differentiated thyroid cancer.

#### MATERIALS AND METHODS

This study is a retrospective cohort analysis of data extracted from the Institutional Register of Thyroid Surgery of the Department of General Surgery, Kaspela University Hospital in Plovdiv. Between January 2014 and December 2018, 401 patients were operated on for papillary thyroid cancer in our facility. Twenty-seven patients with lobectomy alone as well as 38 patients with MRND were excluded from the study

Of the remaining 336 PTC patients, 77 were also excluded as they met our exclusion criteria. The focused group included 223 patients with total thyroidectomies due to thyroid cancer in the Kaspela University Hospital in Plovdiv. The patients were divided into two groups: group A consisting of 36 patients with total thyroidectomy alone, and group B - 178 patients with total thyroidectomy and PCNLD. Pre- and postoperative indirect laryngoscopy and laryngeal ultrasound in both groups were performed. PTH and calcium level in the 12 post-op hours was measured. The inclusion criteria for enrolment were as follows: (1) patients undergone a total thyroidectomy; (2) preoperative diagnosis of PTC by ultrasonography guided fine needle aspiration (FNA) cytology; (3) clinical stage T1, T2, or T3 PTC without gross extra thyroidal extension; (4) no clinical evidence of neck node involvement (central or lateral); (5) patients aged ≥18 years.

The exclusion criteria were as follows: (1) a diagnosis other than PTC; (2) patients with a mixed tumour; (3) patients with previous thyroid surgery; (4) patients with inadequate follow-up data; (5) patients with preoperative evidence of nodal disease or who had undergone lymph node dissection of any lateral compartment during the initial surgery.

Every patient in either group received a drainage tube, and each patient was discharged two days after surgery if there were no significant complications requiring hospital treatment. All surgeries were performed by one surgeon.

Each patient underwent a preoperative evaluation: FNA biopsy of the primary tumour and evaluation of the lymph node status by physical examination and dedicated neck ultrasonography. Vocal cord movement was assessed routinely by preoperative and postoperative indirect and direct laryngoscopy as well as laryngeal ultrasound in female patients.

Temporary vocal cord palsy was defined as decreased or absent vocal cord mobility which resolved within 6 months after surgery. Permanent vocal cord palsy was defined as vocal cord dysfunction persisting for more than 6 months after the initial surgery. Serum calcium levels were obtained at the following time points: preoperatively and then once a day. Parathyroid hormone (PTH) levels also were measured once a day. Normal PTH levels are between 12–88 pg/ml. Symptomatic hypocalcemia (such as perioral and digital paresthesia, tetany, and palpitation) was regarded as being present if the calcium level was lower than 2.17 mmol/l and patient complained of any of the above symptoms, irrespective of the duration of their hospital stay. Routine calcium supplementation was given to all patients with total thyroidectomy. Permanent hypocalcemia or hypoparathyroidism was defined as an ongoing need for calcium or vitamin D supplementation that lasted more than 12 months.

# Statistical analysis

Quantitative results were reported as the mean and standard deviation for normal distributions and median and interquartile range for nonparametric distributions. Qualitative variables were reported in terms of absolute frequen-

# **RESULTS**

This study enrolled a total of 223 PTC patients who were assigned to two groups (36 in the TT group and 178 in the TT plus CND group). The two groups were matched in age, sex ratio, follow-up duration, and tumour size (p=0.267, p=0.314, p=0.268, and p=0.738, respectively). Additionally, the two groups of patients had almost similar operation times. Postoperative pathology results showed no significant difference in the T stage of patients in each group (p=0.514) (**Table 1**).

In group B, of 178 patients, in 67 (37.6%) patients we found a metastatic spread in central compartment (Fig. 1).

In 36 (21.6%) patients, the metastases were only in the ipsilateral side, in 24 (13.4%) patients - in the ipsilateral and contralateral sides, and in 7 (3.9%) cases only in the contralateral side (**Fig. 2**). Pre-laryngeal lymph node was found and removed in 79 patients and metastases were found in 12 patients (**Fig. 3**). Analysis of complications showed no significant differences in patients with TT + PCNLD vs. patients with TT alone.

Table 1. Demographics and perioperative data

	TT n=36	TT plus CNLD n=178	P value
Age	53.7±3.8	51.3±2.7	0.267
Sex ratio (M:F)	1:5.1	1:4.4	0.314
Follow-up duration (months)	47.9±15.9	48±14.2	0.268
Tumour size (cm <sup>3</sup> )	1.6±1.4	1.7±1.2	0.738
Operation time (min)	78.2±23.4	88.9±16.9	0.058
T stage			0.514
pT1	(56.7%)	(52.2%)	
pT2	(17.4%)	(20.9%)	
pT3	(25.9%)	(26.9%)	
N stage			
pN0	NA	(71.2%)	
pN1a	NA	35 (28.8%)	
Multiplicity	(32.7%)	(37.9%)	0.497

cies and percentages. Categorical variables were assessed using the Fisher's exact test or chi-squared test, when appropriate. Continuous variables were evaluated by using the t-test or the Mann-Whitney U test, when appropriate. A *p*-value of less than 0.05 was considered to be statistically significant. All statistical analyses were performed using IBM SPSS Statistics v. 22.

#### **Ethics statements**

This study was approved by the Institutional Review Board of Kaspela University Hospital, Plovdiv (IRB No. 2019-12-04).

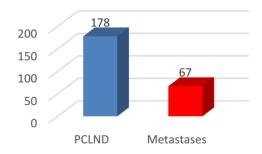
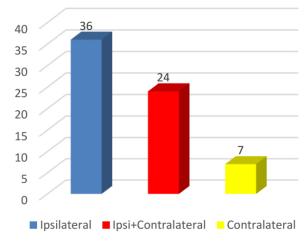
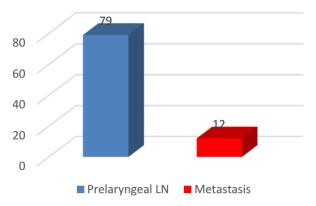


Figure 1. Metastases in lymph nodes after PCND.



**Figure 2.** Central compartment lymph node involvement.



**Figure 3.** Prelaryngeal lymph node metastasis.

However, the complications rate in the TT plus CNLD group wasn't significantly higher than that in the TT group, especially the occurrence of transient hypocalcemia (p=0.817). Additionally, there weren't higher incidences of transient or permanent vocal cord paralysis, postoperative bleeding, and seroma, in the TT plus CNLD group (**Table 2**).

Table 2. Complications

	TT	TT+PCNLD	P value
Vocal cord paralysis			
Transient	4 (11.1%)	14 (7.8%)	0.112
Permanent	0	0	
Hypoparathyroidism			
Transient	5 (13.89%)	23 (12.9%)	0.817
Permanent	1 (2.78%)	5 (2.80%)	0.704
Bleeding	1 (2.78)	3 (1.68%)	0.387
Seroma	1 (2.78)	6 (3.37%)	0.572

# **DISCUSSION**

It is difficult to identify patients that can be candidates for PCNLD. Many studies have tried to identify risk factors that necessitate its implementation. These include tumour size, infiltration of the capsule of the gland, patient age, some oncogenes, p53, BRAF, etc.<sup>[7]</sup> ATA recommends thyroidectomy and CNLD in all cases with proven DTC and clinically positive lymph nodes, as well as in high-risk for micrometastasis patients with T3-T4 tumours or established metastatic nodes in the lateral compartments. This is how the various guides change over the years (**Table 3**).

Potential complications in the implementation of CNLD include hypoparathyroidism, damage to the recurrent laryngeal nerve, damage to the external branch of the superior laryngeal nerve, injury to the trachea, esophagus, and, very rarely, damage to the large vessels.<sup>[8,9]</sup>

The incidence of permanent hypoparathyroidism in DTC patients according to White et al. ranges from 1-2% when total thyroidectomy is performed and in 0-14.3% in patients with TT and PCNLD. According to the same author, permanent RLN paresis is reported in 0-5.5% of the patients in the first group and 0-5.7% in the second group. According to other researchers, there are statistically significant differences in the two groups only when temporary hypoparathyroidism and transient RLN paresis were compared. [10]

The results of our study show that treatment of DTC with TT+CNLD does not result in higher rates of postoperative complications compared with the complication rates seen when using TT alone. Usually, a higher rate of complications often occurs even when TT+CNLD is performed by a high-volume thyroid surgeon. Sosa et al. were the first investigators to report a significant association between surgical volume and patient outcomes following thyroidectomy, and several subsequent reports have confirmed that a surgeon's experience and volume are significantly correlated with the surgical outcomes.<sup>[11]</sup> In our research, all procedure were performed by one experienced surgeon.

According to Bozec et al., Rosenbaum et al., and Shindo et al., comparing the incidence of transient and permanent hypoparathyroidism, temporary and permanent damage to RLN in patients with TT and TT+CNLD, they do not find statistically significant differences and recommend PCNLD as an effective and safe procedure especially performed by an experienced endocrine surgeon. [12] We have obtained similar results (Table 2).

When evaluating and comparing RLN damage and parathyroid function, according to a number of endocrine surgeons, it is imperative that these indicators have to be compared with the incidence of complications in patients with re-surgery caused by relapse of diseases in central compartment lymph nodes. [13] We observe this situation in 3/36 (8.33%) in the group with TT alone in median follow-up  $(47.9\pm15.9)$  (Fig. 4).

Implementation of PCNLD has been found to lead to more accurate staging, determines the need for radioiodine therapy, and improves prognosis especially in patients un-

**Table 3.** Summary of recommendations from consensus groups regarding performance of prophylactic central neck lymph node dissection (CLND) for papillary thyroid cancer (PTC). Lawrence A. Shirley et al, Front Oncol 19 June 2017, Table 1.

Consensus group	Year	Recommendations for prophylactic CLND for PTC
American Thyroid Association	2015	Consider for T3/T4 tumours or clinically involved lateral neck nodes or if the information will impact further steps in therapy
National Comprehensive Cancer Network	2016	Consider for patients with T3/T4 tumours, but must weigh against the risk of hypoparathyroidism and nerve injury
British Thyroid Association	2014	Benefit is unclear in high-risk patient, such that decision-making should be personalized. Bilateral CLND should be performed over ipsilateral CLND
European Society of Endocrine Surgeons	2014	To be considered for patients with high-risk features, including T3/T4 tumours, extremes of age, male gender, bilateral/multifocal disease, clinically positive lateral lymph nodes. To be performed in specialized centres
Japanese Society of Thyroid Surgeons / Japanese Association of Endocrine Surgeons	2011	To be performed routinely



**Figure 4.** Re-surgery for relapse of diseases in central lymph nodes.

der the age of 45 and with other risk factors. Shindo et al., comparing the incidence of central compartment lymph node involvement in patients with papillary carcinoma under and over 45 years of age, found that 28% of them were insufficiently staged due to the "saving" of lymphatic dissection in adults.<sup>[12]</sup> In our research, this percentage is 16.8% in patients with TT alone.

On the other hand, rapid recurrence of the disease is much more common in geriatric groups. It is believed that because of biological changes of tumour cells in lymph nodes, they are less susceptible to radioiodine therapy due to the reduced utilization of radioisotope with advancing age. In support of this claim, Schlumberger et al. found that radioiodine uptake in patients <40 years old was found in almost 90% of them, whereas in the age group >40 years, only 53% of them accumulated it. For this reason, the use of iodine therapy is with dubious results in the adult population and CNLD is the only alternative. Also PCNLD has been shown to result in a significant decrease in the 131I doses required

for ablation and therapy.<sup>[14]</sup> We observed rapid recurrence in a single case in the group with TT and the patient was 62 years old but this result failed to reach statistical significance.

Roh et al., in a retrospective analysis of 184 patients with unilobar localized papillary carcinoma without physical and ultrasound data of metastasis in central cervical lymph nodes and with prophylactic CNLD, found metastases in the ipsilateral compartment in 42.9% of cases and in 9.2% in the contralateral. [15] We observed less metastatic spread in ipsilateral side in 21.6%, 13.4% in both ipsilateral and contralateral lymph nodes, and similar result in contralateral lymph nodes 3.9% (Fig. 3).

There is a serious debate about the implementation of unilateral or bilateral PCNLD. Moo et al., in a study of 104 patients with bilateral PCNLD, detected in 47 of them metastases in the contralateral compartment and supported the need for prophylactic dissection. Their results are supported by Koo et al.  $^{[16]}$ 

According to a number of studies, the incidence of "skip" metastases is not so rare and occurs in 12.0%–19.7% of cases, so they recommend mandatory PCNLD. On the other hand, PCNLD usually removes lymph nodes with micro metastases, and its implementation does not significantly affect the prognosis of the disease, but affects the frequency of local relapses and the need for re-surgery. [17] In our study, this percentage is significantly low.

The role of sentinel node biopsy is also under investigation and is currently used in some thyroid centres. However, given the high rates of lymph node metastasis with PTC, it may not be an effective operative strategy in selecting patients for PCNLD. Because of the association of prophylactic central lymph node dissection with an increased incidence of complications, many authors have been trying to find criteria that justify its implementation. Siddiqui et al., evaluating their own results and the results from ten more studies, tried to summarise the main risk factors for metastasis in central lymph nodes level VI and leads to need of PCNLD:

age, gender, tumour size, multifocal, bilateral, thyroid background, and extra hyoid invasion. [18]

Our study has several limitations that should be mentioned. First, this study includes relatively short follow-up time that may have biased the results. We were unable to evaluate the long-term outcomes of patients who received prophylactic CNLD and to compare it with those in the TT group. If it were available, long term disease recurrence and survival data might have also affected our final results. Also due to the small cohort size and short follow-up time in our current study, we were unable to perform subgroup analyses to examine whether any patient subgroup may have benefitted from treatment with prophylactic CNLD. The study seeks to evaluate the benefits of prophylactic CNLD in treatment of PTC patients.

# CONCLUSIONS

The present study suggests that the realization of total thyroidectomy with prophylactic central lymph node dissection in papillary thyroid cancer patients has neither substantial advantages nor significant complications for the short period of observation.

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# **Competing Interests**

The authors have declared that no competing interests exist.

## **Ethical Statement**

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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# Профилактическая диссекция центрального лимфатического узла при дифференцированном раке щитовидной железы – преимущества и риски

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#### Резюме

**Введение:** Папиллярный рак щитовидной железы является наиболее распространённым злокачественным новообразованием щитовидной железы. Вовлечение лимфатических узлов часто встречается при дифференцированном раке щитовидной железы, а микрометастазы в шейные лимфатические узлы наблюдаются у 85% пациентов с папиллярным раком щитовидной железы во время операции. В то время как терапевтическая диссекция центрального лимфатического узла уже принята, дебаты о профилактических мерах при дифференцированной карциноме щитовидной железы (ДРЩЖ) продолжаются.

**Цель:** Оценить пользу и риск профилактической диссекции центрального лимфатического узла (ПДЦЛУ) при дифференцированном раке щитовидной железы.

**Материалы и методы:** В период с января 2014 г. по декабрь 2018 г. в Университетской больнице "Каспела" в Пловдиве было выполнено 223 тотальные тиреоидэктомии по поводу папиллярного рака щитовидной железы. Пациенты были разделены на две группы: группу А, состоящую из 36 пациентов с применением только тотальной тиреоидэктомией, и группу Б – 178 пациентов с применением тотальной тиреоидэктомией и профилактической центральной лимфодиссекцией.

**Результаты:** У 36 (21.6%) пациентов мы обнаружили метастазы только на ипсилатеральной стороне. У 24 (13.4%) из них мы обнаружили метастатическое распространение как в ипсилатеральные, так и в контралатеральные лимфатические узлы. У 7 (3.9%) больных метастазы обнаружены только в контралатеральных лимфатических узлах. Преларингеальный лимфатический узел был обнаружен и удалён у 79 пациентов. Метастазы обнаружены в 12 из этих 79 узлов. Анализ осложнений не показал существенных различий в их частоте у пациентов с ТТ+ПДЦЛУ по сравнению с пациентами с ТТ.

**Заключение:** Проведённое исследование свидетельствует о том, что выполнение тотальной тиреоидэктомии с профилактической центральной лимфодиссекцией у больных папиллярным раком щитовидной железы не имеет существенных преимуществ и существенных осложнений за короткий период наблюдения.

#### Ключевые слова

папиллярный рак щитовидной железы, профилактическая центральная лимфодиссекция шеи

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