



ELECTIVE CENTRAL COMPARTMENT LYMPH NODE DISSECTION DOES NOT INCREASE THE RISK OF POSTOPERATIVE HYPOPARATHYROIDISM IN PATIENTS TREATED FOR DIFFERENTIATED THYROID CANCER

Boris Stubljar¹, Marija Pastorčić Grgić¹, Ljiljana Mayer²,
Pavao Perše¹ and Tomislav Tomičević¹

¹Division of Head and Neck Surgery, Department of Surgical Oncology, University Hospital for Tumors, Sestre Milosrdnice University Hospital Centre;

²Laboratory Diagnostics Division, University Hospital for Tumors, Sestre Milosrdnice University Hospital Centre

SUMMARY – Aim: The aim of this study was to compare the incidence of postoperative hypoparathyroidism in two groups of patients who were treated for differentiated thyroid cancer. **Methods:** A retrospective analysis of 179 patients who were treated for differentiated thyroid cancer in our institution from January 2011 until December 2018 was performed. Only patients initially treated with total thyroidectomy and those who did not have preoperatively confirmed central compartment and lateral neck lymph node metastases were included in this study. Two main groups of patients were analysed. The patients who were treated with total thyroidectomy and elective central compartment lymph node dissection simultaneously were included in the first group. The patients who were treated only with total thyroidectomy were included in the second group. The rate of transitory and persistent postoperative hypoparathyroidism was compared between the two groups. **Results:** A total of 117 patients (65.4%) underwent total thyroidectomy and elective central compartment lymph node dissection simultaneously (TT + CCLNd group). The remaining 62 patients (34.6%) underwent total thyroidectomy only (TT group). A total of 22.6% patients in the TT group developed postoperative hypoparathyroidism compared with 25.6% in the TT + CCLNd group. The rate of persistent hypoparathyroidism in the TT and TT + CCLNd groups was 3.2% and 6.0%, respectively. The difference in the rate of transient and persistent postoperative hypoparathyroidism was not statistically significant between the two groups. Within the TT + CCLNd group, 82.9% of patients underwent ipsilateral paratracheal lymph node dissection and 17.1% underwent bilateral paratracheal lymph node dissection. The rate of postoperative hypoparathyroidism was analysed in those two subgroups of patients and did not prove to be statistically significant. **Discussion:** While its impact on the local recurrence rate is still controversial, elective central compartment lymph node dissection could be a great tool for selection of patients who could profit from adjuvant radioiodine treatment. On the other hand, central compartment lymph node dissection could potentially increase the risk of hypoparathyroidism due to involuntary injury to parathyroid glands and/or their blood supply. Our study did not find a statistically significant difference regarding postoperative hypoparathyroidism between patients who underwent central compartment lymph node dissection compared with patients who underwent total thy-

Corresponding author: Boris Stubljar, MD, Division of Head and Neck Surgery, Department of Surgical Oncology, University Hospital for Tumors, Sestre Milosrdnice University Hospital Centre, Ilica 197, 10000 Zagreb
E-mail: bstubljar@yahoo.com

roidectomy only. Our data are not in accordance with some of the previously published studies. **Conclusion:** Our results demonstrated that elective central compartment lymph node dissection is a safe procedure and does not significantly increase the risk of postoperative hypoparathyroidism when it is performed simultaneously with total thyroidectomy.

Key Words: differentiated thyroid cancer, total thyroidectomy, central compartment lymph node dissection, paratracheal dissection, postoperative hypoparathyroidism

Introduction

Thyroid cancer is the most common endocrine malignancy and its incidence rate has been increasing over the past several decades^{1,2}. Papillary thyroid carcinoma and follicular thyroid carcinoma both arise from the follicular cells and they are the most common types of thyroid cancer. Together they are known as differentiated thyroid cancer (DTC) and account for as much as 90% of all malignancies found in the thyroid gland^{3,4}. While its incidence is high, the overall mortality for DTC remains very low. On the other hand, the risk of locoregional recurrence remains significantly high and metastases to regional lymph nodes are known to be an independent prognostic factor for it⁵⁻⁸. The other negative prognostic factors for locoregional recurrence after DTC treatment are tumor size, multifocality, and extrathyroidal extension⁷.

DTC shows a high tendency to metastasize to central compartment lymph nodes (CCLN) rather than to lateral cervical lymph nodes⁹. Anatomical boundaries of the central neck compartment are the hyoid bone superiorly, the sternal notch inferiorly, and the medial borders of both carotid sheaths laterally. Besides the thyroid gland and lymph nodes (centrally located prelaryngeal and pretracheal and bilaterally located paratracheal nodes), other structures found in this compartment are the esophagus, trachea, parathyroid glands, and recurrent laryngeal nerves^{10,11}. The inferior thyroid artery that supplies both superior and inferior parathyroid glands is also found in the paratracheal space¹².

The rate of metastatic CCLN involvement recognized on preoperative high-resolution ultrasound is not higher than 30 %¹³⁻¹⁵. On the other hand, the rate of occult CCLN metastases detected on pathological specimens after elective central compartment lymph node dissection (CCLNd) varies from 20 to up to 60%¹⁶⁻¹⁸.

There are still controversies about adequate DTC treatment regarding both the operation of the primary

tumor and management of clinically negative CCLN. The treatment strategy varies from thyroid lobectomy as a definitive procedure to total thyroidectomy (TT) plus elective CCLNd. The main complication of TT is postoperative hypoparathyroidism, and synchronous elective CCLNd can even increase its incidence.

The aim of this study was to analyze the impact of elective CCLNd on the incidence of postoperative hypoparathyroidism in two groups of patients who were treated for DTC.

Methods

We performed a retrospective analysis of 179 patients who were treated for DTC in our institution from January 2011 until December 2018. Only patients initially treated with TT were included in this study. All patients treated with less than TT and those treated in two-stage completion thyroidectomy were excluded from analysis. Patients with synchronous lateral neck metastases and patients with associated hyper- or hypoparathyroidism were excluded from the study as well.

All patients underwent neck ultrasound examination with special focus on the thyroid gland, CCLN, and lateral neck lymph nodes as a standardized preoperative protocol. All suspicious lymph nodes were further analysed with fine needle aspiration cytology (FNAC). None of the patients included in this study had CCLN or lateral neck metastases confirmed on preoperative neck ultrasound and/or FNAC.

Two main groups of patients were created and analysed separately. All the patients who were initially treated only with TT were placed in the first group (TT group). The patients who underwent elective CCLNd simultaneously with TT were placed in the second group. (TT + CCLNd group). The decision on whether or not to perform an elective CCLNd simultaneously with TT was left to the surgeon's preference.

The rate of transitory and persistent postoperative hypoparathyroidism was compared between the two groups.

A blood sample for PTH determination was collected in a 5 mL Vacuette Z serum separator clot activator tube (Greiner Bio-One GmbH, 4550 Kremsmünster, Austria). After centrifugation of the samples at 3500 rpm/10 minutes we measured PTH concentration by electrochemiluminescence immunoassay on the Cobas e411 analyzer (Hitachi, Tokyo, Japan) using the original manufacturer's reagents, calibrators, and controls from the Roche company (Roche Diagnostics GmbH, D-68298 Mannheim, Germany). The laboratory continuously implements two independent systems for assessment of external quality control: Cro-Qalm (Croatian Society of Medical Biochemistry and Laboratory Medicine) and Labquality (Helsinki, Finland).

Transitory hypoparathyroidism was considered when the serum PTH level was below the reference range and patients received vitamin D or/and calcium supplementation in the period after the discharge from the hospital up to one year after surgery. All the patients dependent on supplementation therapy for more than one year after surgery were diagnosed with permanent hypoparathyroidism.

The chi square test was used to compare the differences between the groups, except in small observed frequencies when the Yates corrected chi-square test was used. Statistical significance was set at $p < 0.05$.

Results

Out of 179 patients included in this study, there were 142 women (79%) and 37 men (21%) with a mean age of 51 (range 20-86 years of age) (Table 1).

A total of 117 patients (65.4%) underwent simultaneous TT and elective CCLNd (TT + CCLNd group). The remaining 62 patients (34.6%) only underwent TT (TT group).

Out of 62 patients within the TT group, 14 (22.6%) developed postoperative hypoparathyroidism. Within the TT + CCLNd group the rate of postoperative hypoparathyroidism was slightly higher (30 of 117 patients or 25.6%), but there was no significant statistical difference between the two groups ($\chi^2=0.205$; $df=2$; $p=0.651$).

Persistent hypoparathyroidism after at least one year of clinical follow-up was confirmed in 2 patients in the TT group (3.2%) and 7 patients in the TT + CCLNd group (6.0%). The difference was not statisti-

Table 1. Characteristics of study patients

Total No = 179	
Sex	
Male	37 (21%)
Female	142 (79%)
Age, mean (range)	51 (20-86)
Operation	
Total thyroidectomy	62 (34.6%)
Total thyroidectomy + central compartment lymph node dissection	117 (65.4%)
Type of central compartment lymph node dissection	
Pretracheal + ipsilateral paratracheal	97 (82.9%)
Pretracheal + bilateral paratracheal	20 (17.1%)

cally significant (Yates $\chi^2 = 0.197$; $df=2$; $p=0.957$). Three patients in the TT group (4.8%) and 3 patients within TT + CCLNd group (2.6%) were lost to follow-up (Figure 1).

Within the TT + CCLNd group, 97 patients (82.9%) underwent ipsilateral paratracheal lymph node dissection and 20 patients (17.1%) underwent bilateral paratracheal lymph node dissection. Pretracheal lymph nodes were removed in all the patients.

The incidence of postoperative hypoparathyroidism was 24.7% and 30.0% in the ipsilateral and bilat-

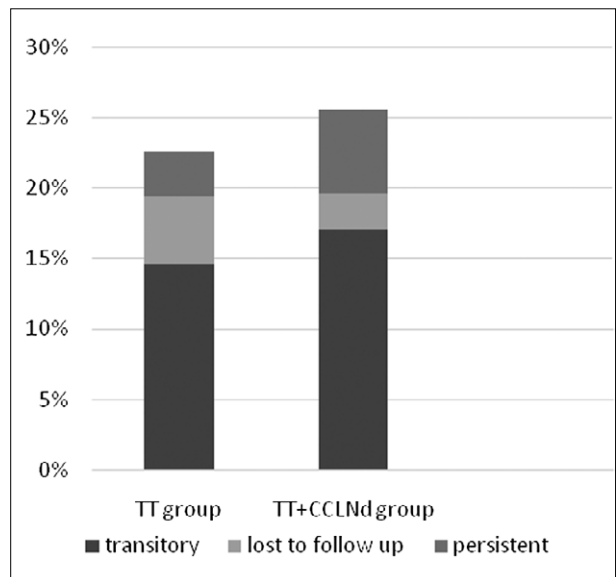


Figure 1. The rate of transitory and persistent hypoparathyroidism between the TT and TT + CCLNd groups.

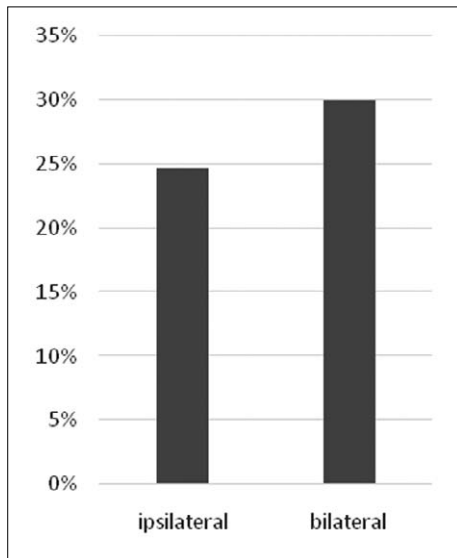


Figure 2. The rate of postoperative hypoparathyroidism compared between group of patients who underwent ipsilateral and bilateral paratracheal dissection.

eral dissection groups, respectively. Although expected, the difference was still not found to be significant ($\chi^2=0.24$; $df=2$; $p=0.624$) (Figure 2).

Within the TT + CCLNd group, 45 patients (38.5%) were diagnosed with metastatic lymph nodes on the final pathological report (positive subgroup). In the remaining 72 patients (61.5%), no positive lymph nodes were found in the pathological specimen (negative subgroup).

The incidence of postoperative hypoparathyroidism in the positive and negative subgroup was 31.1% and 22.2% respectively, and the difference was also not shown to be statistically significant ($\chi^2=1.148$; $df=2$; $p=0.284$).

Discussion

The incidence of DTC has been increasing over the past decades. Despite its generally excellent prognosis, DTC may also present with the more aggressive tumor features, including multifocality, local nodal metastasis, and extrathyroidal spread. Consequently, there is still an ongoing debate about the appropriate surgical management for DTC. Some authors are in favor of unilateral lobectomy as an adequate surgical treatment for all tumors up to 4 centimeters in diameter and without any adverse pathological features (multifocal-

ity, extrathyroidal spread, lateral neck metastases). The majority of other authors consider only TT to be the optimal treatment strategy for all tumors greater than 1 centimeter¹⁹⁻²¹. Even microcarcinomas are treated with TT by some surgeons²⁰. Similarly, management of regional CCLN remains controversial. Metastatic CCLN involvement on preoperative clinical or imaging assessment is a well-established indication for therapeutic dissection¹⁰. On the other hand, validity of an elective CCLN dissection is still the subject of an open discussion. Kutler *et al.* documented that CCLN dissection is a safe procedure and may decrease the need for further reoperations because of the local recurrence²³. In direct contrast, a meta-analysis by Shan *et al.* found no benefit in performing TT with CCLNd versus TT alone with regard to locoregional recurrence. They instead demonstrated a higher risk of postoperative complications⁹.

A decision to perform routine CCLN dissection may have implications on the postoperative treatment. A study by Bonnet *et al.* found that precise staging of CCLN led to a change in TNM classification in 30.5% of patients and that it can play a role in further decisions to treat these patients with radioactive iodine²⁴.

Postoperative hypoparathyroidism and hypocalcemia are the most common complications after TT and often result in prolongation the hospital stay and decreased quality of life. The incidence of transitory hypoparathyroidism after TT is described to be within a wide range from 6.9-46.0%^{25,26}. The incidence of persistent hypoparathyroidism is reported to be 0-9%²⁷.

CCLNd potentially increases the risk of hypoparathyroidism due to involuntary injury of parathyroid glands and/or the inferior thyroid artery that runs through paratracheal space. There are numerous reports showing that TT with elective CCLNd is associated with a higher rate of postoperative hypoparathyroidism^{9,28,29}.

In contrast, we could not find any statistically significant difference between the two analyzed groups of patients in our study. The incidence of postoperative transitory and persistent hypoparathyroidism did not differ statistically in the group of patients who underwent CCLNd compared with the group of patients who underwent TT only. Surprisingly, the incidence was not higher even in the subgroup of patients who underwent bilateral paratracheal dissection compared with ipsilateral or in the subgroup of patients with confirmed metastatic lymph nodes.

Some of the above data are in contradiction with many of the previous studies^{9,30,31}.

Based on our data, we think that CCLNd is a safe procedure in hands of a well-trained surgeon and that it does not significantly increase the incidence of postoperative hypoparathyroidism. While its significance on the local recurrence rate is still the subject of discussion, elective CCLNd could be a great tool for selection of patients with occult metastatic lymph nodes who are candidates for further radioiodine ablation. Although our data indicate otherwise, we would still advocate unilateral paratracheal dissection rather than bilateral, in order to reduce the risk of postoperative hypoparathyroidism. Bilateral paratracheal dissection should only be considered in cases where there are multifocal tumors localized in both lobes or centrally localized isthmic tumors, and when suspicious lymph nodes are found bilaterally.

From our perspective, the main downside of our study is the randomization of patients into two main groups. Rather than blindly, their randomization was based on the surgeon's preference in performing elective CCLNd, which could potentially lead to bias.

Conclusion

When performed routinely, CCLNd is a safe procedure that does not significantly increase the risk of postoperative hypoparathyroidism. Furthermore, it can select patients for postoperative radioiodine treatment. We strongly advocate referral of all patients with thyroid cancer to highly-volume centers where CCLNd can be performed safely and effectively.

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Sažetak

ELEKTIVNA DISEKCIJA REGIJE VI NE POVEĆAVA RIZIK
POSTOPERATIVNOG HIPOPARATIREOIDIZMA
KOD BOLESNIKA LIJEČENIH ZBOG DOBRO DIFERENCIRANOG KARCINOMA ŠTITNJAČE

B. Stubljar, M. Pastorčić Grgić, Lj. Mayer, P. Perše i T. Tomičević

Cilj: Cilj rada je usporediti incidenciju postoperativnog hipoparatireoidizma između dvije skupine bolesnika liječenih zbog dobro diferenciranog karcinoma štitnjače. **Metode:** Retrospektivno smo analizirali 179 bolesnika koji su u našoj ustanovi liječeni zbog dobro diferenciranog karcinoma štitnjače u periodu od siječnja 2011 do prosinca 2018. U studiju su bili uključeni samo bolesnici kod kojih je inicijalno učinjena totalna tiroidektomija te oni koji na osnovu preoperativne obrade nisu imali potvrđene metastaze na lateralnom vratu i u regiji VI. Analizirane su dvije skupine bolesnika. U prvu skupinu su uključeni bolesnici kod kojih je u istom aktu učinjena totalna tiroidektomija i disekcija regije VI. Svi ostali bolesnici kod kojih je učinjena samo totalna tiroidektomija uključeni su u drugu skupinu. Stopa tranzitornog i trajnog hipoparatireoidizma je uspoređivana između dvije skupine. **Rezultati:** Kod ukupno 117 bolesnika (65,4%) učinjena je disekcija regije VI istodobno s totalnom tiroidektomijom. (TT + CCLNd skupina). Kod preostalih 62 bolesnika (34,6%) učinjena je samo totalna tiroidektomija. (TT skupina). Ukupno 22,6% bolesnika iz TT skupine je razvilo postoperativni hipoparatireoidizam usporedno s 25,6% bolesnika iz TT + CCLNd skupine. Stope trajnog hipoparatireoidizma u TT i TT + CCLNd skupinama su iznosile 3,2 i 6 %. Stopa tranzitornog kao i trajnog postoperativnog hipoparatireoidizma nije bila statistički značajna između dvije skupine. Unutar TT + CCLNd skupine, kod 82,9% bolesnika je učinjena disekcija ipsilateralnih paratrahealnih limfnih čvorova, za razliku od 17,1% bolesnika kod kojih je učinjena disekcija bilateralnih paratrahealnih čvorova. Stopa postoperativnog hipoparatireoidizma je analizirana u dvjema podskupinama i nije se pokazala statistički značajnom. **Rasprava:** Iako je utjecaj elektivne disekcije regije VI na lokoregionalno recidiviranje i dalje kontroverzan, ona može biti odličan alat za probir bolesnika koji mogu imati korist od adjuvantne radiojodne ablacije. S druge strane, disekcija regije VI potencijalno može povećati rizik hipoparatireoidizma zbog nenamjerne ozljede doštitnih žlijezda ili/i njihove krvne opskrbe. Naša studija nije pokazala statistički značajnu razliku u stopi postoperativnog hipoparatireoidizma između skupine bolesnika kod kojih je učinjena disekcija regije VI u usporedbi sa skupinom bolesnika kod kojih je učinjena samo totalna tiroidektomija. Naši podaci su u proturiječju s nekim ranije publiciranim studijama. **Zaključak:** Naši rezultati su pokazali da je elektivna disekcija regije VI sigurni postupak i značajno ne povećava rizik postoperativnog hipoparatireoidizma kada se izvodi istodobno s totalnom tiroidektomijom.

Ključne riječi: *dobro diferencirani karcinom štitnjače, totalna tiroidektomija, disekcija regije VI, paratrahealna disekcija, postoperativni hipoparatireoidizam*