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Professional Paper

TOTAL THYROIDECTOMY WITH CENTRAL NODE DISSECTION IS A VALUABLE OPTION IN PAPILLARY THYROID CANCER TREATMENT

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SUMMARY – *Introduction:* Papillary thyroid cancer is one of the cancers with favorable prognosis, although the long-term recurrence rate in the paratracheal region is reported to be as high as 30%. The use of ^{131}I is considered to be a reliable treatment option for lymph node metastases in the paratracheal region. According to the majority of internationally accepted guidelines, it is not recommended to perform central node dissection (CND) routinely. Total thyroidectomy (TT) remains an adequate treatment for these patients. According to many studies, CND is associated with higher rates of hypoparathyroidism. However, CND improves staging. *Methods:* We performed a retrospective study. We included 248 patients treated for papillary thyroid cancer during a 20-year period. Data were collected on patient (age, sex) and tumor (size, focality) characteristics, presence of metastases in the central neck compartment, incidence of postoperative hypoparathyroidism, and locoregional failure. We divided patients into two groups based on pathological analysis: those without positive lymph nodes (N0) and those with positive paratracheal lymph nodes (N1). We compared patient and tumor characteristics and risk of recurrence between the two groups. *Results:* There were 39.5% patients with central neck metastases in our series. In the central neck dissection specimen, 5.5 nodes were found on average. Hypoparathyroidism was found in 23.4% of patients and remained permanent in 3.2% of patients. Female and older patients had a lower chance of central compartment metastases, as did patients with smaller and unifocal tumors. Recurrence risk was doubled for the N1 group. All tested differences between the groups reached statistical significance. *Discussion and conclusion:* In our hands, CND was a safe and effective surgical procedure. It improved staging and postsurgical management. Efforts should be made to improve the preoperative work-up in order to more accurately identify high-risk patients.

Key Words: *differentiated thyroid cancer, total thyroidectomy, central compartment lymph node dissection*

Introduction

The overall incidence of papillary thyroid cancer (PTC) is increasing, with increases in the incidence rate and thyroid cancer mortality rate for advanced-stage papillary thyroid cancer[1]. PTC is generally considered to have a favorable prognosis[2]. Some authors have proposed adjustments in workup, diagnosis, and management of PTC to accommodate the discovery that many thyroid cancers are low-risk and do not require aggressive, immediate intervention[3]. Others have been pointing out that more than 10% of patients who died from thyroid cancer had tumors

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smaller than 2 cm and underwent treatment[4]. The problem is how to recognize the group of patients at risk for an aggressive clinical course.

Involvement of lymph nodes is very common, and, lymph node micrometastases are observed in up to 80% of cases[5]. The long-term recurrence rate in the paratracheal region has been reported as being up to 30%. Currently, there are no non- or minimally-invasive methods that are completely reliable for detecting all of the metastases[6]. The radiological diagnostics of paratracheal space can represent a problem. It is a well-established fact that ultrasound (US) is an excellent method for assessing lateral neck compartments. Additionally, it helps guide fine needle aspiration, which is vital for diagnosis and staging. However, the identification of lymph nodes in the central compartment is not always that simple. The percentage of lymph nodes detected in this region is reported to be up to 23.9%[7] in the hands of an experienced radiologist using a high-quality high-resolution ultrasound. A number of the lymph nodes go undetected due to their position beneath the thyroid gland. Furthermore, some nodes may be hard to detect because they may be overshadowed by artifacts due to bone structures or air. This is true for some nodes in region VI, and it creates a particular problem in assessing region VII involvement. As much as half of the nodes later found in surgery can be missed during the initial US examination[8]. The assessment can also be compromised by the quality of the ultrasound machine as well as the subjectivity of the radiologist performing the US.

During recent decades, the role of routine central lymph node dissection (CND) in the treatment of PTC has been an object of much study and remains controversial[9]. According to the majority of internationally accepted guidelines, it is not recommended to perform CND routinely. According to some authors, paratracheal metastases impact survival and CND lowers recurrence risk and prolongs disease free survival. Calo et al. compared rates of locoregional recurrence in patients treated with total thyroidectomy (TT) alone or in combination with bilateral or ipsilateral CND, but found no statistically significant differences between the groups[10]. TT with CND is associated with higher complication rates compared with TT alone, more often resulting in hypoparathyroidism than recurrence nerve palsy[10]. The risk-benefit analysis of neck dissection in patients with low-risk DTC showed no benefits in terms of complete remission or occurrence of progression, and risk of complications seems to be higher in patients with neck dissection[11]. Total thyroidectomy (TT) remains an adequate treatment for patients with PTC. The use of ^{131}I is considered a reliable treatment for lymph node metastases in the paratracheal region[12,13].

CND improves staging, however. Better preoperative work-up and recognition of patients with higher risk for development of neck metastases could improve our surgical management. Ipsilateral CND could bring the benefit of better staging without burden of a rising complication rate[6,10].

Methods

We performed a retrospective study. We analyzed the records of 248 patients treated for PTC at the Department of Head and Neck Surgery in the Institute for Tumors of the "Sestre milosrdnice" University Hospital during a 20-year period. We included all the patients that had preoperatively diagnosed PTC without clinical suspicion of either central or lateral neck metastases. All the patients received TT and CND. Indication for CND was based on preoperative PTC diagnosis and intraoperative finding of suspicious lymph nodes. Ipsilateral paratracheal and pretracheal spaces were routinely dissected. If any suspicious lymph nodes were observed in pretracheal or contralateral paratracheal space, contralateral dissection was also performed. All the patients received follow-up of at least one year. None of the patients had signs of disseminated disease during follow-up.

Data was collected on patient (age, sex) and tumor (size, focality) characteristics, number of dissected lymph nodes, presence of metastases in the central neck compartment, incidence of postoperative hypoparathyroidism, and locoregional failure. We divided patients into two groups based on pathological analysis: those without positive paratracheal lymph nodes (N0) and those with positive paratracheal lymph nodes (N1). We compared patient (age, sex) and tumor characteristics and risk of recurrence between the two groups.

Descriptive statistical methods were used to describe the study population. The chi-square test was used to test for 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

We performed TT with CND in 248 patients with PTC.

There were 150 patients (60.5%) without and 98 patients (39.5%) with central neck metastases.

In the whole group of patients, the mean age was 49.4 (median 51, range 11 to 86 years); 150 patients (60.5%) were younger than 55 and 98 (39.5%) were 55 or older. There were 48 men (19.4%) and 200 women (80.6%).

Average tumor size was 14.3 mm (median 12 mm, range 3 to 60 mm); 44.8 % of tumors were up to 10 mm in size and 55.2% were larger than 10 mm. The majority of tumors was unifocal (68.1%).

CND was performed in all patients. On average, 5.5 nodes were found per CND specimen, range 0-28 per specimen, median 4. We found central neck metastases in 39.1% of patients.

Hypoparathyroidism manifested in 23.4% of patients. Eight patients (3.2%) had permanent hypoparathyroidism requiring vitamin D supplements.

We observed lateral neck recurrence in 17 patients during follow-up. In this group of patients, 4 had both central compartment and lateral neck recurrence. Overall recurrence risk was 6.9%.

Further analysis was performed comparing the N0 and N1 groups of patients.

In the N0 group of patients, we observed a higher proportion of older (70.4%) and female patients (64%) (Figure 1). The difference was statistically significant for both age (χ^2=6.168; df=2; p=0.013) and sex (χ^2=4.205; df=2; p=0.04). In the group of patients with tumors up to 1 cm in size we found metastases in 26.1% of the patients, whereas in the group of patients with tumors larger than 1 cm metastases were found in almost 50% of patients. The difference between the groups was statistically significant (χ^2=14.23; df=2; p<0.001), (Figure 2). Similarly, metastases were found in 32.5% of patients that had unifocal tumors and in 53.2% of patients with multifocal tumors. The difference between groups was statistically significant (χ^2=9.612; df=2; p=0.002) (Figure 2).

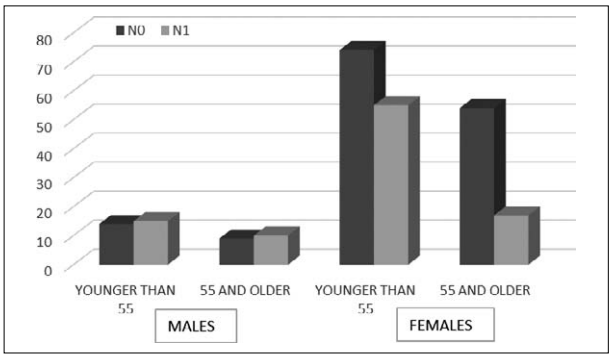

Figure 1. Patient age and sex in the N0 and N1 patient groups.

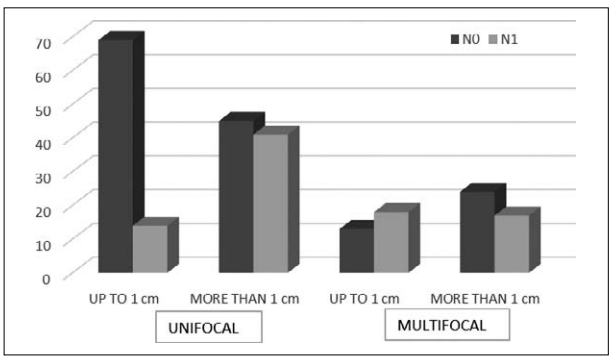

Figure 2. Size and focality of tumors in the N0 and N1 patient groups.

Risk of recurrence was doubled for N1 patients, and the difference between the N0 and N1 groups was statistically significant (χ^2=18.49; df=2; p<0.001).

Discussion

Despite the overall favorable prognosis, some patients have PTC with a clinically aggressive course. Our goal was to try to identify patients who are at risk and treat them more aggressively, possibly improving the course of the disease.

Our finding of nearly 40% central compartment neck metastases in patients with PTC is consistent with literature data of 20-50% of lymph node involvement in most series. Metastases can be present even when the primary tumor is small and intrathyroidal[14].

According to the literature, PTC is diagnosed in women twice as often than in men, with a median age at diagnosis of about 45 years[5]. The median age was higher in our series, and only one fifth of the patients

were men. This difference can be explained by the selection of a study group as clinically N0 PTC, because one expects more female and older patients in the group of patients with PTC with N0 lymph node status.

Compared with the series of Machens et al., average tumor size in our series was smaller, the proportion of tumors smaller than 10 mm was higher, and multifocality was seen in more patients[15]. Although all tumor characteristics differ among published series, tumor multifocality shows the highest variability and is described in up to 85% of patients[5].

It has been shown that the number of lymph nodes in the CND specimen is important in predicting central compartment recurrence[16]. The expected number of lymph nodes in the central neck compartment, according to a cadaveric study, is four (range 1-16)[17]. In our series, we found 5.5 nodes per central neck dissection specimen, demonstrating the high quality of dissections.

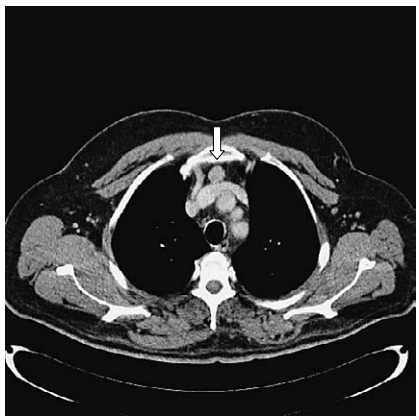

Figure 3. Contrast-enhanced MSCT (arrow points to an enlarged region VII lymphnode).

All studies found greater rates of temporary hypoparathyroidism with CND[6]. Surgical treatment of thyroid carcinoma is associated with a greater rate of hypoparathyroidism when CND is added to thyroidectomy[6]. Transient hypoparathyroidism appeared in 23.4% of patients in our series and became permanent in 3.2% of patients. Our result is comparable to other studies[6,18,19]. Use of different surgical techniques does not change the complication rates significantly[20].

Ryu et al. showed that male sex, tumor size larger than 1cm, positive lymph nodes, lymphovascular invasion, and extrathyroidal extension are significantly associated with lateral neck LN recurrence[21]. Data in our series were consistent with published data – risk of recurrence is doubled for N1 patients.

Although we are able to recognize tumors with higher metastatic potential after surgery and immunohystochemical analysis, this does not help preoperative decision making. Some authors mention angiogenesis[22], or more precisely matrix metalloproteinases and their inhibitors, regarding the development of lymph node metastases[23].

Diagnostic work up can also be improved in order to help the surgeon decide on the optimal operation plan for every patient. After identifying a patient with higher risk of central compartment metastases, multislice computed tomography (MSCT) can be performed (Figure 3). This diagnostic procedure is usually

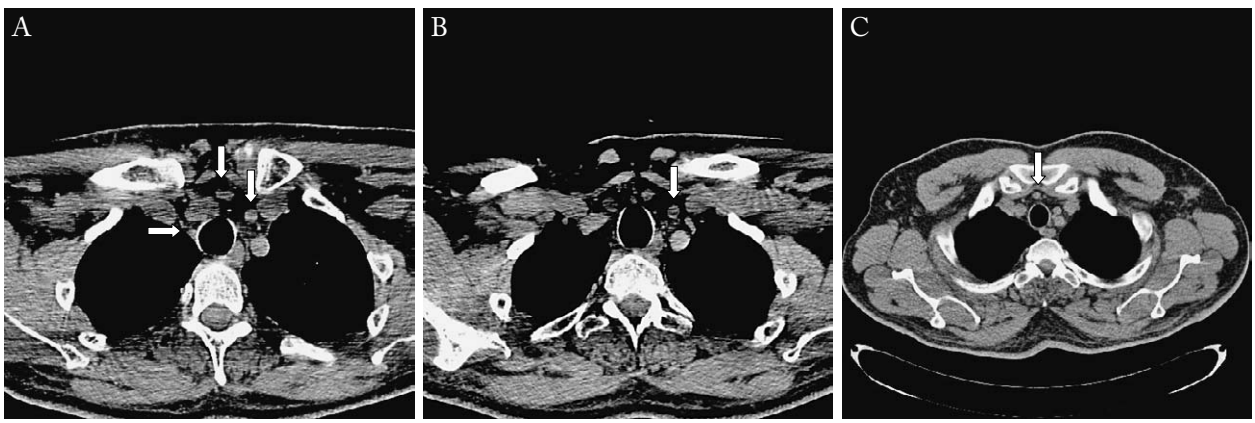

Figure 4. (A, B, C) Non enhanced MSCT. The figure shows good visibility of paratracehal and pretracheal lymphnodes even on a MSCT without intravenous contrast (arrows).

avoided in patients with PTC because it is in most cases performed using an intravenous contrast agent which, consequently, delays the administration of radioactive iodine (RAI). However, the delay is 4-8 weeks at most, with literature stating that a 4-week delay is sufficient[24]. This delay should not be considered a contraindication for performing MSCT since the data acquired from the procedure can change patient management. It is an especially important diagnostic procedure for patients with large tumors, tumors with extrathyroidal spread, or patients with widely distributed nodal disease already identified with US. In these patients, MSCT detects possible involvement of not typically affected regions such as mediastinal, infra-clavicular, retropharynegeal and parapharyngeal regions, which cannot be adequately evaluated using US. MSCT is also more accurate in assessing the central compartment[25], especially region VII which cannot be visualized with US alone. Suspicious lymph nodes in this region seen on MSCT should alter the surgical approach. Furthermore, this particular region can be also adequately assessed using a non-contrast MSCT scan (Figure 4). The anatomy of the region allows an experienced radiologist to detect lymph nodes as small as 3 mm, even without the use of a contrast agent, thus eradicating the need for delay of RAI treatment in patients where it is necessary to administer the RAI treatment as soon as possible.

Conclusion

In our hands, CND has been a safe and effective surgical procedure. The question that has to be answered is whether it should be indicated in all patients with PTC and whether we can improve preoperative work-up to more accurately identify high-risk patients.

At the moment, CND significantly improves staging and enables more precise postsurgical management of patients with PTS.

Further analyses are necessary to answer whether ipsilateral CND can bring the benefit of better staging without the burden of a rising complication rate.

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Sažetak

TOTALNA TIROIDEKTOMIJA S DISEKCIJOM CENTRALNE REGIJE VRATA U LIJEČENJU PAPILARNOG KARCINOMA ŠTITNJAČE

M. Pastorčić Grgić, B. Stubljar, P. Perše, M. Zekan Vučetić i S. Šitić

Uvod: Papilarni karcinom štitnjače spada u tumore s povoljnom prognozom unatoč opisivanoj stopi recidiva u paratrahealnoj regiji i do 30% slučajeva. Radiojodna ablacija se smatra pouzdanom metodom liječenja metastaza u paratrahealnim čvorovima. Većina međunarodno prihvaćenih smjernica ne preporuča rutinsko izvođenje disekcije regije VI (CND) već se samo totalna tireidektomija (TT) smatra adekvatnim liječenjem u ovoj skupini bolesnika. Prema mnogim studijama CND je povezana s višom pojavnošću hipoparatireoidizma. S druge strane, CND pomaže u utvrđivanju točnog staginga bolesti. *Metode:* Proveli smo retrospektivnu studiju u koju smo uključili 248 bolesnika koji su liječeni zbog papilarnog karcinoma štitnjače tijekom 20 godina. Podaci su analizirani temeljem karakteristika bolesnika (dob, spol), tumora (veličina, uni – i mutifokalnost), prisustva metastaza u centralnoj regiji vrata, incidencije postoperativnog hipoparatireoidizma i stope lokoregionalnog povrata bolesti. Na osnovu patohistološkog nalaza podijelili smo bolesnike u dvije skupine: bolesnike bez pozitivnih limfnih čvorova u regiji VI (N0 skupina) kao i one s pozitivnim limfnim čvorovima u regiji VI (N1 skupina). Uspoređivali smo osobine bolesnika i karakteristike tumora kao i rizik lokalnog recidiva bolesti između ove dvije skupine. *Rezultati:* U našoj seriji bilo je 39.5% bolesnika s metastazama u regiji VI vrata čiji su disektati u prosjeku sadržavali 5.5 limfnih čvorova. Postoperativni hipoparatireoidizam je verificiran kod 23.4% bolesnika, a ostao trajan u 3.2% bolesnika. Žene i bolesnici starije životne dobi imali su manji rizik od metastaza u regiju VI, isto kao i bolesnici s manjim i unifokalnim tumorima. Rizik povrata bolesti bio je udvostručen za N1 skupinu bolesnika. Sve analizirane razlike između skupina pokazale su statističku značajnost. *Rasprava i zaključak:* U našoj ustanovi CND smatramo sigurnom i učinkovitom operacijom koja poboljšava staging bolesti i time unapređuje daljnje liječenje bolesnika. Nužno je poboljšati preoperativnu obradu kako bismo prepoznali bolesnike visokog rizika.

Ključne riječi: *papilarni karcinom, disekcija regije VI*