

The Risk Factors for Contralateral Paratracheal Lymph Node Metastases in Papillary Thyroid Cancer

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ABSTRACT:

The risk factors for contralateral paratracheal lymph node metastases in papillary thyroid cancer

Objective: Lymph node metastasis is frequently seen in papillary thyroid cancer. In the present study, we aimed to evaluate the rate and risk factors for the contralateral paratracheal lymph node metastasis in papillary thyroid cancer and to evaluate the effect of risk factors on the extent of the lymphatic dissection.

Materials and Methods: Twenty-seven patients (19 female, 8 male) with a median age of 44 (range 16-75), who underwent total thyroidectomy with central neck dissection with or without therapeutical lateral neck dissection were examined. The effects of the age, gender, extrathyroidal extension, multifocality, bilaterality, lymphovascular invasion, T stage, prelaryngeal, pretracheal, ipsilateral paratracheal and lateral lymph node metastasis on the contralateral paratracheal metastasis were evaluated. 'Chi-square' and 'Fisher's exact' tests were used for statistical analyses.

Results: All patients underwent total thyroidectomy with bilateral central neck dissection. Additionally 12 patients out of 27 underwent therapeutical lateral neck dissection. T stages were classified as T1: 16 (59.3%), T2: 7 (25.9%), T3: 4 (14.8%) respectively. The occurrence of contralateral paratracheal metastasis was found significantly higher in the cases having lateral metastasis (100% vs 47.6; p=0.05).

Conclusions: Lymph node metastasis is frequently seen in papillary thyroid cancer and primarily occurs in the ipsilateral paratracheal area. The rate of contralateral paratracheal metastasis is higher in the patients with lateral lymph node metastasis. The lateral lymph node metastases detected pre or peroperatively should be considered for the bilateral central neck dissection.

Keywords: Contralateral paratracheal, lymph node, metastasis, papillary thyroid cancer

ÖZET:

Papiller tiroid kanserinde karşı paratrakeal lenf bezi metastazı gelişimi ile ilişkili risk faktörleri

Amaç: Papiller tiroid kanserinde lenf bezi metastazı sık görülür. Bu çalışmada; papiller tiroid kanserinde karşı paratrakeal lenf bezi metastazı oranı, karşı taraf lenf bezi metastazı için risk faktörleri ve bunların lenfatik diseksiyon alan genişliğine etkilerinin değerlendirilmesi amaçlandı.

Gereç ve Yöntemler: Papiller tiroid kanseri tanılı, tiroidektomi ile birlikte santral ve/veya terapötik lateral boyun diseksiyonu uygulanan, ortalama yaş 44 (16-75) olan 27 (19K, 8E) hastanın verileri incelendi. Karşı taraf paratrakeal metastaz gelişimi üzerine yaş, cinsiyet, ekstraparatrakeal yayılım, multifokalite, bilateralite, lenfovasküler invazyon, T evresi, prelaringeal metastaz varlığı, pretrakeal lenf bezi metastazı, aynı taraf paratrakeal lenf bezi metastazı, lateral metastaz varlığının etkisi değerlendirildi. İstatistik olarak "Ki-kare" ve "Fisher'in kesin olasılık" testleri kullanıldı.

Bulgular: Bu hastalara total tiroidektomiye ek olarak bilateral santral diseksiyon ve 12'sine ek olarak terapötik lateral boyun diseksiyonu uygulandı. T evresi sırasıyla T1: 16 (%59.3), T2: 7 (%25.9), T3: 4 (%14.8) idi. Karşı paratrakeal metastaz gelişimi lateral metastaz (%100 vs %47.6; p=0.05) varlığında anlamlı olarak yüksek bulundu.

Sonuç: Papiller tiroid kanserinde lenf nodu metastazı sık olup, öncelikle aynı taraf paratrakeal bölge lenf bezlerinde metastaz ortaya çıkmaktadır. Lateral metastazlı hastalarda karşı taraf paratrakeal metastaz gelişme riski daha yüksektir. Ameliyat öncesi veya peroperatif olarak lateral ve/veya lenf bezi metastazı saptanması, bilateral santral boyun diseksiyonu yapılmasında dikkate alınmalıdır.

Anahtar kelimeler: Karşı paratrakeal, lenf bezi, metastaz, papiller tiroid kanseri

Ş.E.E.A.H. Tıp Bülteni 2016;50(1):45-51



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Date of receipt / Geliş tarihi: December 14, 2015 / 14 Aralık 2015

Date of acceptance / Kabul tarihi: January 10, 2016 / 10 Ocak 2016

INTRODUCTION

Thyroid cancers account for approximately 1% of all cancers, and 1/3 of all head and neck tumors (1). Papillary thyroid cancer (PTC) is the most common histologic type, constituting 80-85% of all thyroid malignancies (2-4). PTC is seen both primarily, and incidentally at the examination of the thyroidectomy specimen, which is performed for other reasons (5). The incidence of clinical or occult metastases in regional lymph nodes in PTC is reported between 20-90% (6,7). Lymph node metastasis in PTC usually follows a sequential pattern (8). Lymph node metastasis in PTC primarily occurs to the central region, from here it spreads to ipsilateral lateral cervical lymph nodes, followed by contralateral lateral lymph nodes (2). Due to intense lymphatic drainage of thyroid with variances, the spreading pattern may not always follow this order, and sometimes without central metastasis, lateral skip metastases may occur (9). Due to sequential pattern, the most common metastasis occurs to the lymph nodes in the central region (10,11). Therapeutic central region neck dissection performed in patients with central lymph node metastasis, which is diagnosed with preoperative physical examination, imaging techniques and intraoperative findings is an accepted application, although the debate continues about its extensivity (11). Even in PTC cases with no clinical neck lymphatic metastasis, when prophylactic lymph node dissection is performed, occult central lymph node metastasis is often found at pathological examination (12). In the presence of clinicopathological factors such as out of thyroidal spreading, multifocality and lymphovascular invasion, risk of central metastasis is high (13).

It is still controversial to perform prophylactic central lymph node dissection and if performed, its extensivity, due to lack of evidence about its contribution to survival in PTC cases with clinically no metastasis.

It is reported that in patients with prophylactic bilateral central dissection, the most common occult metastasis is to ipsilateral paratracheal lymph nodes up to 50%, and to contralateral paratracheal lymph nodes between 3.9-13.3% (12,14,15). Central

dissection is a surgical procedure that increases the complication rates (16,17). Because the contralateral lymph node metastasis rates are less, some researchers suggest ipsilateral central lymph node dissection, and some, bilateral central neck dissection (7). In the absence of clinical lymph node metastasis in the central region or in the presence of unilateral clinical lymph node metastasis in the central region, the presence of predictive factors to detect if there is contralateral paratracheal lymph node metastasis present may prevent the unnecessary contralateral lymph node dissection and may contribute to reducing the complication rates. There are some studies conducted on this topic, and some factors have been reported (3,6,8,12,14,16,18).

In this study, evaluation of contralateral paratracheal lymph node metastasis rate, the risk factors for contralateral lymph node metastasis and its effects on lymphatic dissection extensivity in PTC were aimed.

MATERIAL AND METHOD

The data of 27 (19 Female, 8 Male) patients with a mean age of 44 (16-75) at T.R. Şişli Hamidiye Etfal Training and Research Hospital, Clinic of General Surgery, who were performed thyroidectomy with central, and if necessary, therapeutic lateral neck dissection with PTC diagnosis were examined retrospectively. The other malignancies of the thyroid were excluded. In all patients, PTC diagnosis was confirmed by preoperative fine needle aspiration biopsy (FNAB) or intraoperative frozen-section procedure. All patients underwent preoperative ultrasound, and when necessary, neck magnetic resonance imaging (MRI). In patients with suspected lateral metastasis clinically or with imaging techniques, and in patients with confirmed lateral metastasis with preoperative lymph node FNAB and/or thyroglobulin in the wash-out fluid in FNAB, lateral neck dissection was performed.

Central neck dissection: The anatomical and dissection descriptions of the central region were made according to the consensus report of American Thyroid Association, Surgery Working Group (19). The central region was defined as hyoid bone

superiorly, carotid artery at the lateral, innominate artery at the inferior right and at left, axial plane of innominate artery. The central region was assessed in itself as 4 separate groups as prelaryngeal, pretracheal, right and left paratracheal. Bilateral central dissection was defined as the extraction of the lymph nodes in these 4 parts in the central region; whereas unilateral central dissection is defined as the extraction of prelaryngeal, pretracheal, and paratracheal (right or left) lymph nodes at the dissection side. Therapeutic central neck dissection was defined as the dissection performed in the presence of lymph node metastasis detected clinically or with imaging techniques preoperatively or intraoperatively, and prophylactic central neck dissection was defined as the dissection performed when the lymph node metastasis is not detected clinically or with imaging techniques. Therapeutic central region dissection was performed bilaterally, and prophylactic central neck dissection was performed unilaterally. After the central dissection was completed, the specimen was separated and marked into 4 identified regions, and sent for pathological examination.

The patient data was divided into 2 groups as, lymph node metastasis present at the contralateral paratracheal region (Group 1) and absent (Group 2). The effects of age, gender, extrathyroidal extension, multifocality, bilaterality, lymphovascular invasion, T stage, prelaryngeal, pretracheal, ipsilateral paratracheal and lateral lymph node metastasis on the contralateral paratracheal metastasis were evaluated. In the presence of bilateral tumors, the lobe with the largest tumor focus was considered as

the tumor side. Postoperative complications (hypocalcemia, hypoparathyroidism and vocal cord paralyses) were evaluated.

Hypocalcemia was defined as the serum calcium levels below 8 mg/dl. Temporary hypoparathyroidism was defined when the function of parathyroid returns to normal range within 6 months, and permanent hypoparathyroidism was defined in cases when the supportive therapy is required more than 6 months and the parathormon levels stay in low levels.

All patients underwent preoperative and postoperative laryngoscopic vocal cord examination by an independent otolaryngologist. The vocal cord paralyses which resolved in less than 6 months are defined as temporary, and the ones that continue at the 6th month were defined as the permanent vocal cord paralyses.

“Chi-square” and “Fisher’s exact” tests were used statistically. p value ≤ 0.05 was considered as significant.

RESULTS

In addition to total thyroidectomy, 27 had bilateral central neck dissection and 16 had therapeutic lateral neck dissection. The age, gender, histopathological characteristics of the tumor, distribution of central metastasis, and the lateral metastasis states are given in Table-1. No significant difference was detected between the pairwise comparisons of patients in both groups in terms of age, gender, T stage, multicentricity, bilaterality, and prelaryngeal, pretracheal and paratracheal metastasis in the central region. In the

Table-1: Demographic data and clinicopathological factors (Group 1: Contralateral paratracheal lymph node metastasis present, group 2: Contralateral paratracheal lymph node metastasis absent)

	Number of patients (n=27) (%)	Group 1 (n=6) (%)	Group 2 (n=21) (%)	p
Mean age	44 (16-75)	52 (40-75)	42 (16-67)	0.195
Gender F/M	19 (70.4) / 8 (28.6)	3 (50) / 3 (50)	16 (76.2) / 5 (23.8)	0.319
T (T1/T2/T3)	16 (59.3) / 7 (25.9) / 4 (14.8)	3 (50) / 2 (33.3) / 1 (16.7)	13 (61.9) / 5 (23.8) / 3 (14.3)	0.864
Extrathyroidal metastasis present	15 (57.7)	2 (33.3)	13 (65)	0.348
Multicentricity present	20 (74.1)	4 (66.7)	16 (76.2)	0.633
Bilaterality present	17 (63)	5 (83.3)	12 (57.1)	0.363
Lymphovascular invasion present	23 (85.2)	6 (100)	17 (81)	0.341
Prelaryngeal met present	7 (25.9)	2 (33.3)	5 (23.8)	0.633
Pretracheal met present	10 (37)	4 (66.7)	6 (28.6)	0.153
Ipsilateral paratracheal met present	17 (63)	5 (83.3)	12 (57.1)	0.363
Lateral metastasis present	16 (59.3)	6 (100)	10 (47.6)	0.054

presence of lateral metastasis, lymph node metastasis at the contralateral paratracheal region was found to be significantly high ($p=0.05$). Temporary hypocalcemia rate was 47.7%, and permanent hypocalcemia rate was 4.5%. Temporary recurrent laryngeal nerve paralysis was seen in one patient, no permanent paralysis was detected. Demographic data and the clinicopathological factors are indicated in Table-1.

DISCUSSION

The lymphatic drainage pattern of thyroid is partly regular and lymph node spread in PTC follows a gradual spreading trend. Generally, cervical lymph node metastasis in PTC first affects the central region, then spreads to the ipsilateral region, followed by contralateral region and mediastinal lymph nodes (20,21).

Prophylactic central neck dissection for PTC is still controversial (14,16). Central region lymph node metastasis in PTC is the most common metastasis and in many patients with lateral region metastasis, there is central region lymph node metastasis present simultaneously (8,9,22). In our study also, the central metastasis rate is 96%, but because the study consisted only the patients who had therapeutic central dissection, this rate seems to be over the rates, reported in the literature. In the central region, the most commonly affected region was, as expected, ipsilateral paratracheal region, with a rate of 63%. Lateral metastasis rate was 59%. Due to the frequency of central region lymph node metastasis, therapeutic or prophylactic central neck dissection is performed generally with the therapeutic lateral neck dissection (7). However, to balance the risks and benefits of central neck dissection, the treatment options of the central lymph node metastasis region should be carefully considered (6).

The complication rates of central region lymph node dissection vary in various studies. Wang et al. (23) in their study with 188 patients, reported the whole postoperative complications rate as 5.3%, which of none is permanent, with 9 of them were reported to be temporary hypocalcemia, and one of them as temporary recurrent nerve paralysis.

According to the study of Zhu et al. (24), they reported that prophylactic neck lymph node dissection, in addition to the thyroidectomy, causes significant increase in the temporary hypocalcemia rates, compared to only thyroidectomy procedure alone. However, no significant difference was found in terms of permanent hypocalcemia and temporary-permanent recurrent nerve injury.

In the study of Segal et al. (25) with 503 patients, significant increase in the rates of permanent nerve paralysis and permanent hypoparathyroidism in reoperation were reported, compared to primary operation (5.8% vs 25%, and 5% vs 8.3%, respectively). However, Shen et al. (26) reported in their study that in primary or reoperative central neck lymph node dissection, they had similar complication and recurrence rates, and if the neck lymph node dissection is performed by an experienced surgeon, it might be safe as well as it is in the first operation. The complication rates of unilateral or bilateral central neck dissection varies. In Chae et al.'s study (16), no difference was found between unilateral and bilateral central lymphatic dissection in terms of major complications; temporary hypocalcemia rates were found as 31.8% vs 45.7% ($p=0.084$), and voice change rates as 7.6% vs 4.3% ($p=0.438$), which is opposite to the other study results.

Son et al. (27) in their study with 114 patients reported that temporary hypocalcemia was seen more in bilateral central neck dissection, compared to unilateral (48.3% vs 26.8%), and the decrease of parathormon postoperatively was more prominent; however, the other complications were in similar rates. In the same study, postoperative PTH levels reached to the similar levels 6 months later (11.8 vs 12.4 pg/mL) and it is reported that permanent hypocalcemia rates didn't show a significant difference.

In Giordano et al.'s study (28) with 1087 patients, which consisted of 3 groups in comparison, one with total thyroidectomy (1st group), one with unilateral central dissection in addition (2nd group), and one with bilateral central dissection in addition (3rd group), no significant difference was detected in the rates of temporary and permanent recurrent nerve paralysis. When compared with the group which

central dissection was not performed, the temporary hypoparathyroidism rates in the additional unilateral ($p=0.014$) and additional bilateral ($p<0.001$) dissection groups were found to be significantly higher. Permanent hypoparathyroidism rates were insignificant when the 1st and the 2nd groups were compared ($p=0.818$), and significant when the 1. and 3rd groups were compared ($p<0.001$).

When the bilateral central neck dissection is compared with unilateral central lymph node dissection, it is very important to evaluate the pattern of contralateral central lymph node metastasis and its predictive factors for setting the borders of central neck dissection in PTC, because it increases the postoperative morbidities such as hypoparathyroidism or recurrent laryngeal nerve paralysis (8).

In series, the rates of metastasis to the contralateral paratracheal lymph node, their predictions and their approaches show variances. In the literature, contralateral paratracheal lymph node metastasis rate is reported to be between 5-34% (7,18,22,29,30). In our study, contralateral lymph node metastasis rate was 22% similarly. In addition, in our study, contralateral paratracheal lymph node development was significantly higher in the presence of lateral lymph node metastasis ($p=0.05$). Even though the rate of the presence of contralateral paratracheal metastasis is higher when there is pretracheal metastasis (66.7% vs 28.6%), we believe that the insignificance of the difference is related to the low number of the patients ($p=0.153$).

The presence of lateral metastasis at the preoperative evaluation can be detected with a high accuracy rate (2,11). In our study, the relationship between the lateral metastasis and the contralateral paratracheal metastasis is controversial. Koo et al. reported in their study (8) that in PTC patients with ipsilateral metastasis, subtle contralateral central lymph node metastasis was relatively high and in these patients, multifocal tumor and the positive lymph node spreading in all lateral neck levels (II+III+IV) were reported to be independent risk factors for subtle contralateral central lymph node metastasis.

Keum et al. (7) suggest in their study that the imaging techniques with low sensitivity for

contralateral central region and high rates of subtle metastasis incline to bilateral therapeutic central neck dissection when therapeutic lateral neck dissection is performed.

However Roh et al. (22), reported that in patients with PTC, because the contralateral paratracheal lymph node metastasis is rare (8.9%), the optimum treatment may be the ipsilateral central and lateral region neck lymphatic dissection.

Ahn et al. (1) reported that generally in unilateral PTC, contralateral central lymph node metastasis rate is low, and contralateral central lymph node dissection is unnecessary, because it doesn't have an effect on the survival without disease. In the study, it is stated that contralateral central lymph node metastasis mostly develops in patients with ipsilateral macrometastasis or in patients with a tumor size of >1 cm, thus, bilateral central lymph node dissection should be preferred in these patients, in addition, in PTC patients with small tumor and who don't have an ipsilateral macrometastasis, prophylactic ipsilateral central lymph node dissection may be a satisfactory surgical extension.

Ito et al.'s study (31) with 759 patients reported a general metastasis rate of contralateral central region as 27.3%, and in tumors ≤ 1 cm in size as 9.8%.

Wada et al.'s study (32) with 259 patients reported that the most common affected region in central region metastasis was pretracheal (43.2%) and the ipsilateral region is affected more than the contralateral region (36.3% vs. 18.9%).

Eun et al. (18) in their study suggest that because the contralateral paratracheal lymph node metastasis is associated with ipsilateral paratracheal lymph node metastasis, this condition might be helpful in determining the extension of prophylactic central dissection in PTC patients. In other studies, ipsilateral paratracheal lymph node metastasis presence is detected to be an independent risk factor to predict contralateral paratracheal metastasis (3,12,14,18). Ipsilateral paratracheal lymph node metastasis presence is reported to be helpful in determining the extension of optimum prophylactic central lymphatic dissection in PTC patients (3,16,18).

Chen et al. (12) in their study with 218 patients, contralateral central lymph node metastasis is

significantly associated with ipsilateral lymph node metastasis ($p<0.001$), pretracheal lymph node metastasis ($p=0.002$), and prelaryngeal lymph node metastasis ($p=0.002$). In this study, ipsilateral central lymph node metastasis and prelaryngeal lymph node metastasis were detected to be independent risk factors for contralateral paratracheal lymph node metastasis. They state that therapeutic bilateral central lymph node dissection should be considered in patients with > 1 cm tumor size and with prelaryngeal lymph node or ipsilateral lymph node metastasis, especially in frozen section examination.

Chae et al. (16) stated that the positive frozen biopsy result in ipsilateral central lymph node ($p<0.001$), younger age ($p=0.002$) and out of thyroidal extension ($p=0.031$) is significantly associated with contralateral central lymph node metastasis. In patients with unilateral PTC, despite contralateral central lymph node metastasis risk, they recommend routine ipsilateral central lymphatic dissection and frozen section biopsy.

Wei et al. (6) in their study reported that >1 cm primary tumor size, capsular/extracapsular spreading, pretracheal, prelaryngeal lymph node metastasis and lateral lymph node metastasis might be predictive

factors for contralateral paratracheal lymph node metastasis in unilateral PTC (6).

Limitations: The small number of subjects and the retrospective characteristic of our study are of the main limitations.

CONCLUSION

Lymph node metastasis is often in papillary thyroid cancer, and metastasis occur primarily in the ipsilateral paratracheal region lymph nodes. In our study, contralateral paratracheal metastasis risk was found higher in patients with lateral metastasis. In the light of all these findings, lateral lymph node metastasis presence in the preoperative or intraoperative evaluation of central neck region should be taken into consideration in bilateral central neck dissection. We believe that central dissection should be performed bilaterally in patients with preoperatively detected lateral metastasis. More detailed studies are needed for the risks for contralateral paratracheal lymph node metastasis and therapeutic/prophylactic bilateral central lymph node dissection necessity in papillary thyroid cancer.

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