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Use of Intraoperative Gamma Probe in Selective Neck Dissection for Papillary Thyroid Cancer with Neck Metastasis Patients

Boyun Metastazlı Papiller Tiroid Kanseri Hastalarında Selektif Boyun Diseksiyonunda İntraoperatif Gama Prob Kullanımı

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ABSTRACT Objective: The purpose of this study is to investigate the selective neck disection with use of intraoeprative gamma probe technique of which is performed due to determine dissection levels and extension, regards to reduce recurrence rates and complications. **Material and Methods:** The patients were divided two groups, of which first group designed as recurrent patients instead second group as non recurrent. The independent samples t-test was then used to compare the parameters with a normal distribution, according to the presence of a relapse, and the Mann-Whitney U test was used to compare the results with a non-normal distribution. **Results:** The study included 41 patients who underwent selective neck disection with use of gamma probe and total thyroidectomy with papillary thyroid cancer. In total, 12 (29.3%) patients' disease recurred. The presence of recurrence did not depend on gender (p=0.398). While 12.5% of males (n=1) had recurrence, 33.3% of females (n=11) had recurrence. No statistically significant difference was obtained between the median values of the total number of malignant lymph nodes according to groups (p=0.174). There was no statistically significant difference between the median values of number of follow-up months according to patient group (p=0.148). **Conclusion:** The use of preoperative United States-mapping with intraoperative gamma probe in selective neck disection for patients with metastatic differentiated thyroid cancer is technically safe, and effective for determining the borders of the neck dissection of which is related with unnecessary surgical extension.

Keywords: Thyroid; papillary thyroid cancer; neck metastasis; neck dissection

ÖZET Amaç: Bu çalışmanın amacı, kansersiz sağkalımı sürdürmek ve komplikasyon oranını azaltmak amacıyla intraoperatif gamma prob tekniği kullanılarak yapılan selektif boyun diseksiyonunun etkinliğinin araştırılmasıdır. **Gereç ve Yöntemler:** Hastalar iki gruba ayrıldı; birinci grup nüks hastaları, ikinci grup ise nüks olmayan hastalar olarak tasarlandı. Daha sonra normal dağılıma sahip parametrelerin nüks varlığına göre karşılaştırılmasında bağımsız örneklem t-testi, sonuçların normal dağılıma uymayan durumlarla karşılaştırılmasında ise Mann-Whitney U testi kullanıldı. **Bulgular:** Çalışmaya papiller tiroid kanseri nedeniyle gama prob kullanılarak selektif boyun diseksiyonu ve total tiroidektomi uygulanan 41 hasta dâhil edildi. Toplamda 12 (%29,3) hastanın hastalığı tekrarladı. Nüks varlığı cinsiyete bağlı değildi (p=0,398). Erkeklerin %12,5'inde (n=1) nüks görülürken, kadınların %33,3'ünde (n=11) nüks görüldü. Toplam malign lenf nodu sayısının gruplara göre ortanca değerleri arasında istatistiksel olarak anlamlı bir fark elde edilmedi (p=0,174). Hasta grubuna göre takip ay sayısı ortanca değerleri arasında istatistiksel olarak anlamlı fark yoktu (p=0,148). **Sonuç:** Metastatik diferansiye tiroid kanserli hastalarda selektif boyun diseksiyonunda intraoperatif gama prob kullanımı, teknik olarak güvenli ve boyun diseksiyonu sınırlarını belirlemeye yardımcı bir metot olarak kullanılabilinir.

Anahtar Kelimeler: Tiroid; papiller tiroid kanseri; boyun metastazı; boyun diseksiyonu

Differentiated thyroid cancers are rare, representing approximately 1% of all malignant neoplasms; however among endocrine neoplasms, they are the most common.[1] Between 30% and 80% of patients with well-differentiated thyroid cancer have cervical lymph node metastases during the preopera-

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tive period.[2] The lateral and central neck compartment metastases are involved with similar frequencies (62.1% vs. 68.8%); furthermore, lymph node metastases are present in both compartments in 67% of cases, and are limited to the central compartment in only 20%.[2]

Although thyroidectomy (total or lobectomy) is widely accepted as the primary treatment for papillary and follicular carcinomas, the indications for locoregional lymphadenectomy are debated. The prophylactic surgery for occult lymph node metastases, especially for papillary carcinomas, has not yet been defined. Total thyroidectomy, followed by radiometabolic therapy, are widely accepted treatment procedure. Neck dissections must be performed in patients with proven lateral or central cervical lymph node metastases to improve the regional control of the disease. Central neck dissection, extensive excision of prelaryngeal and pretracheal nodes, with at least one paratracheal lymph node basin, modified radical neck dissection, limited neck dissection, selective or supraselective nodal excisions, and compartment procedures, such as focused removal, may all be applied in order to control occult or proven neck metastases. Sentinel lymph node biopsy, using both vital dyes and radioisotopes, has been developed as an alternative to elective lymph node dissection in patients with clinically node-negative disease.[3]

The complication rate in thyroid surgeries varies in large-scale studies done in different institutions. Campbell et al. reported a 28% complication rate among 1094 patients, in contrast, Ley et al. reported a 2.4% overall rate among 124 patients.[4,5] Post-thyroidectomy complications that can lead to prolonged hospitalization include bilateral recurrent laryngeal nerve injury and neck hematoma, both of which are related to a risk of life-threatening clinical conditions, besides hypocalcemia and airway obstruction. Permanent disabilities subsequent to recurrent laryngeal nerve damage and hypoparathyroidism due to excessive neck dissection, especially with the central compartment dissection, can lead complications during neck dissection.[6]

Our objective was to contribute to the literature by comparing the number of lymph nodes removed and the recurrence rates with using gamma probe-guided selective neck disection and total thyroidectomy method for thyroid papillary cancer. The aim of this surgical method was to reduce recurrences and to maintain cancer-free survival together with lower complication rates among differentiated thyroid carcinoma patients with proven or suspicious nodal metastasis. Further, we planned to determine statistically the advantages and disadvantages of our approach by comparing different neck dissection methods, namely radical neck dissection, functional neck dissection, and supraselective nodal excision with another study.

MATERIAL AND METHODS

DATA COLLECTION

All 41 patients who underwent above-mentioned surgery between 2010 and 2021 for differentiated thyroid cancer with neck metastasis were identified retrospectively. Preoperative, operative, and follow-up data for these patients were collected. The diagnosis, malignancy type, preoperative and postoperative data regarding lymph nodes, upper and lower levels of the neck dissection, follow-up period, and recurrence were documented. In particular, the stage of the disease and its spread to the neck lymph nodes according to neck level were also documented in details related to the preoperative and postoperative pathology results.

The patients were divided into two groups. The first group included patients with recurrence and the second group included patients with non-recurrence. Gender related recurrence, total number of metastatic lymph nodes, follow-up time, and number of metastatic lymph nodes at each neck level were compared. In addition, frequency distributions and descriptive statistics for the above-mentioned data were collected.

SURGICAL METHOD

All suspicious thyroid nodules and lymph nodes revealed by the ultrasonography, which had been performed by the same nuclear medicine doctor, and were biopsied under ultrasonography guidance, using the free-hand method and a 10 mL standard syringe

with a 22 gauge needle. If there were several thyroid nodules, only the most suspicious one was biopsied. Most of the suspicious lymph nodes in the uppermost and lowermost levels of neck were also biopsied to confirm the metastases. Only patients with papillary and follicular carcinomas with lymph node metastases in the central and lateral compartments were included in the study.

Following the biopsies, cytopathological diagnoses were made, and the patients were prepared for total thyroidectomy and selective neck dissection. On the morning of the surgery, a sketch was drawn showing the nodules and lymph nodes and any reference points (previous surgical scar, clavicle, trachea, common carotid artery, etc.). Fine needle aspiration-confirmed metastatic lymph nodes were shown, together with their size, on the neck map and numbered to facilitate documentation of the final histopathological results. Tc-99m-labeled macro-aggregated albumin was then injected into the lesions at the center of each biopsy-proven lesion. This radiopharmaceutical was prepared and formed according to the manufacturers' recommendations, and 80,000 to 100,000 particles were injected with the desired volume and activity. If there were several lesions in the immediate vicinity, the uppermost and lowermost pathological lymph nodes in the lateral and central cervical areas were selected for radio-labeling. The injected lymph nodes were marked on the pre-drawn neck map to provide anatomical references for nearby non-injected lymph nodes. During the surgery, the probe was placed in direct contact with the skin and with the maximum count rate were marked with the help of the drawn neck map. Dissection boundaries were determined in relation to the activity measured with the gamma probe. Even higher count rates were noted during the surgical exploration.

The aim of the neck dissection was to perform an excision that included the lymph nodes marked at the uppermost and lowermost levels. No neck dissections were performed beyond these marked lymph nodes. Measurements were made in the removed lymph nodes with the gamma probe, and it was ensured that all marked lymph nodes had been removed. After the neck dissection, a gamma probe was used to measure the residual activity in the surgical area and once it could be shown that no residual marked lymph node remained, the surgical procedure was completed. Regardless of having radioiodine therapy, all patients were selected by below-mentioned criterion.

Inclusion Criteria

1) Neck dissection due to papillary or follicular thyroid carcinoma.

2) Having undergone the surgical technique described.

3) Access to data concerning the preoperative and postoperative examinations of patients.

4) Patients have been reached by phone or face-to-face in order to evaluate the current status of the patients.

Exclusion Criteria

1) Having undergone thyroidectomy or neck dissection for reasons other than thyroid cancer.

2) Patients who underwent surgery for anaplastic thyroid carcinoma or medullary thyroid carcinoma.

3) Being unable to access the patient's data to be used for comparative purposes.

4) Failure to reach the patient at the contact number given to learn about their current status.

STATISTICAL ANALYSIS

The study protocol was approved by the ethics committee of Gülhane Training and Research Hospital wit the number of 2021/126 (08.04.2021). Following evaluation of the normality of the data distribution, appropriate parametric and non-parametric tests were performed. The data were analyzed using IBM SPSS V23 (USA). The Shapiro-Wilk test was used to examine compliance with a normal distribution. The independent samples t-test was then used to compare the parameters with a normal distribution, according to the presence of a relapse, and the Mann-Whitney U test was used to compare the results with a non-normal distribution. Fisher's exact test was used to examine for categorical data. The analysis results were presented as frequencies (percentages) for the categorical variables, and as a mean±standard deviation and median (minimum-maximum) for the quantitative variables. The significance level was taken as

p<0.050.

RESULTS

The study was conducted in accordance with the Declaration of Helsinki. Of the 41 participants, 19.5% were male, 80.5% female. The average age of the patients was 46.83 years. The average number of malignant lymph nodes in the 2nd level of the neck was 1.47, the average number of malignant lymph nodes in the 3rd level of neck was 2.18, the average number of malignant lymph nodes in the 4th level of neck was 2.33, the average number of malignant lymph nodes in the 5th neck level was 1, and the average number of malignant lymph nodes in the central compartment of the neck was 2.11. The average number of total malignant lymph nodes per patient was 4.08. The average number of follow-up months for the participants was 40.37 months. The shortest follow-up time was 8 months, on the contrary the longest follw-up period was 118 months. Frequency distributions and descriptive statistics of the variables are shown in Table 1.

There was no statistically significant difference between the median values of the number of level 2 malignant lymph nodes according to group (p=0.533). The median value obtained was 1, both in those with and without recurrence. There was no statistically significant difference between the median values of the number of level 3 malignant lymph nodes according to group (p=0.940). The median value was obtained as 2 in those both with and without recurrence. There was no statistically significant difference between the mean values of the number of level 4 malignant lymph nodes according to group (p=0.890). While the average value was 2.25 in those with recurrence, the average value was 2.38 in those without. The total number of malignant lymph nodes in level 5 was one. No statistical analysis could thus be made. There was no statistically significant difference between the median values of the number of central region malignant lymph nodes according to group (p=0.632). The median value was 1.5 in those with recurrence and 1 in those without. There was no statistically significant difference between the median values of the total number of malignant lymph nodes according to groups (p=0.174). The median value was 4.5 in those with recurrence and 1.5 in those without. There was no statistically significant difference between the median values of number of follow-up months according to patient group (p=0.148). The median value was 27.5 in those with recurrence and 37 in those without. A comparison of the quantitative variables according to groups is shown in Table 2.

TABLE 1: Frequency distributions and descriptive statistics of the variables in the study.

	Frequency	Percentage
Groups		
Recurrent (Group 1)	12	29.3%
Non-recurrent (Group 2)	29	70.7%
Gender		
Male	8	19.5%
Female	33	80.5%
	$\bar{X}$±SD	Median (minimum-maximum)
Age	46.83±14.75	45 (22-74)
Malignant lymph nodes 2nd region	1.47±0.96	1 (1-5)
Malignant lymph nodes 3rd region	2.18±1.74	2 (1-9)
Malignant lymph nodes 4th region	2.33±1.37	2 (1-5)
Malignant lymph nodes 5th region	1±0	1 (1-1)
Malignant lymph nodes central compartment	2.11±1.55	1 (1-6)
Total number of malignant lymph nodes	4.08±3.51	3 (1-14)
Follow-up time (monhts)	40.37±20.27	36 (13-89)

SD: Standard deviation.

Recurrence occurred in 29.3% (n=12) of the patients in the study. There was no statistically significant difference between the average age of the participants according to groups (p=0.946). While the average age of those with recurrence was 46.58, for those without recurrence average age was 46.93. The presence of recurrence did not depend on gender (p=0.398). While 12.5% of males (n=1) had recurrence, 33.3% of females (n=11) had recurrence. In Group 1, only one, out of a total of 12 patients with recurrence, had contralateral thyroid tissue recurrence and thyroid lobectomy had been performed on this patient due to micropapillary carcinoma. 11 out of the 12 patients with recurrence had cervical lymph node metastatic recurrence. Distribution of recurrence by gender is shown in Table 3.

DISCUSSION

This retrospective study revealed that the recurrence

TABLE 2: Comparison of quantitative variables according to groups.

	Groups					
	Recurrent (Group 1)		Non-recurrent (Group 2)			
	X̄±SD	Median (minimum-maximum)	X̄±SD	Median (minimum-maximum)	Statistical test	p value
Age	46.58±16.18	44 (22-69)	46.93±14.42	48 (22-74)	t=-0.068	0.946
Malignant lymph nodes 2nd region	1.43±0.53	1 (1-2)	1.5±1.17	1 (1-5)	U=36.000	0.533
Malignant lymph nodes 3rd region	2±1.15	2 (1-4)	2.27±1.98	2 (1-9)	U=51.500	0.940
Malignant lymph nodes 4th region	2.25±1.26	2 (1-4)	2.38±1.51	2 (1-5)	t=-0.142	0.890
Malignant lymph nodes 5th region	1±0	1 (1-1)	1±0	1 (1-1)	---	---
Malignant lymph nodes central compartment	2.3±1.83	1.5 (1-6)	2±1.41	1 (1-5)	U=81.000	0.632
Total number of malignant lymph nodes	4.92±3.42	4.5 (1-13)	3.71±3.55	1.5 (1-14)	U=123.500	0.174
Follow-up time (monhts)	34.67±23.27	27.5 (13-89)	42.72±18.83	37 (18-84)	U=123.500	0.148

t: Independent sample t-test; U: Mann-Whitney U test; SD: Standard deviation.

TABLE 3: Distribution of recurrence in gender.

	Group			
	Recurrent (Group 1)	Non-recurrent (Group 2)	Statistical test	p value
Gender				
Male	1 (12.5)	7 (87.5)	---	0.398
Female	11 (33.3)	22 (66.7)		

rate was not affected negatively by using a gamma probe to display the metastatic lymph nodes preoperatively to define the borders of the neck dissection. According to the results and observations in the present study, we might conclude that this method can be used as a reliable method with loco-regional metastatic differentiated thyroid cancer patients, however, it was not compared with other possible neck dissection surgeries in this study.

The literature reports variable rates regarding the recurrence of thyroid cancer. Our recurrence rate was 29.3% and the mean follow-up time for the recurrent patients was 34.67 months compared with 42.72 in non-recurrent group, a difference that lacked statistical significance. In the recurrence group, the median value for metastatic lymph nodes was 4.5 compared to 1.5 in the nonrecurrence group, again without statistical significance. Although these two criterion showed no statistical significance, we might conclude that having more metastatic lymph nodes may lead to a greater likelihood of recurrence. That is why it is necessary that neck dissections should be adequate and precise. Additionally, all neck levels had minimal differences regarding the number of metastatic lymph nodes, and there was no statistical significance. Despite the fact that there were fewer patients in the recurrence group, their total number of metastatic lymph nodes was not statistically different compared with those of the non-recurrence group. This reveals that recurrence may be related to the number of metastatic lymph nodes.

The most common reason for secondary surgery was recurrence of the disease in the neck lymph nodes, and it was associated with prolonged hospitalization and higher rates of complication. According to our study results, recurrence was predominantly due to neck metastasis. Liang et al. found that lateral cervical lymph nodes (36.5%) and central plus lateral cervical lymph node metastases (26.3%) were the main reasons for secondary surgeries among their patients.[7] A number of studies have reported recurrence rates for differentiated thyroid cancer patients with locoregional metastasis: Hollenbeak et al. reported a recurrence rate of 39% among well-differentiated thyroid carcinoma patients, with extended duration of the disease and older age nega-

tively impacting the rate.[8] Bi and Zhang et al. found lower recurrence rates among total thyroidectomy and lobectomy patients, with rates of 1.87% and 2.20% respectively, as evaluated from eight studies.[9] The updated 2015 American Thyroid Association guidelines, report a recurrence risk of <1% to 5% for low-risk patients.[10] The primary reason for recurrence are an inability to perform adequate lymph node dissections initially and/or residual tumor following lymph node dissection and reoperations frequently may result in damage to the cervical nerves. During reoperation procedures in the central lymph node compartment, more than 20% of cases suffer inferior laryngeal nerve damage and, in more than 30%, permanent hypoparathyroidism may develop.[11] In the current study, 1 of out of 41 patients experienced recurrent laryngeal nerve paralysis, and 3 out of 41 patients had to commence treatment due to temporary hypoparathyroidism after their secondary surgery.

In papillary thyroid cancer metastases occur often and early, with some studies reporting high rates of regional disease as high as 80%.[2,11] Although it is now accepted that macroscopic nodal metastases affect prognosis, the impact of occult regional disease is far more limited.[12] For this reason, cervical lymph node dissection is important in preventing recurrence, particularly if certain metastasis is shown. The first cascade lymph nodes of the thyroid gland are in the central compartment of the neck (Level VI), and drainage then occurs into the lower jugular chain (Level IV) and the upper mediastinum (Level VII). Our results resemble findings reported in the literature regarding positive lymph node counts and sites, and they confirm the pattern of lymph node metastasis identified in former studies. Regional lymph node dissection is a widely accepted practice for all patients with clinically evident central or lateral metastatic nodal disease. Cervical lymph node treatment options include modified radical neck dissection and limited neck dissections, such as selective and supra-selective nodal excisions. Levels III, IV, and VI are the most common sites for metastatic disease in well-differentiated thyroid cancer, while Level V has been shown to harbor metastatic disease in 25% to 60% of therapeutically dissected necks.[13] The prophylactic dissection of Level V is considered controversial because of the accompanying morbidity of the spinal accessory nerve.[13]

Currently, the primary treatment for papillary thyroid carcinoma is surgical intervention, which varies according to the thyroid nodule characteristics, and may involve either lobectomy or total thyroidectomy.[14] The optimal treatment for lymph node metastases, especially for papillary carcinoma, has not yet been defined. In approximately 80% of cases, lymph node micrometastases can be demonstrated without any agreement on their clinical significance.[15] Beom Heo et al. reported that 5 or more central lymph node micrometastases may not require immediate complete thyroidectomy.[15] Some publications in the literature report that when total thyroidectomy and radiometabolic therapy are applied, lymph node involvement has no effect on survival or local recurrence; however, there is other evidence indicating that survival and local recurrence are affected.[16,17] As a result, some studies routinely recommend total thyroidectomy plus central compartment lymphadenectomy. Other studies recommend thyroidectomy plus radically modified regional lymphadenectomy to reduce the incidence of local recurrence and ensure the optimal effect for radiometabolic therapy.[17] Adequate cervical lymph node dissection is important to reduce the amount of tissue to which radioiodine can potentially be fixed, thereby improving the effects of radiometabolic therapy. Aliyev et al. concluded that recurrent tumor can be localized correctly using [^{18}F] fludeoxyglucose-positron emission tomography/computed tomography and a surgical gamma probe when performing total thyroidectomy with neck dissection for metastatic thyroid cancer.[18]

There is general consensus that, for node-positive thyroid cancer patients, neck dissection is obligatory instead of node-negative thyroid cancer patients.[19] The surgical resection options vary regarding node-negative thyroid cancer, especially for neck treatment. This variability leads excessive neck dissection related to higher complication rates. It is significant that more than 20% of inferior laryngeal nerve damage and more than 30% of permanent hypoparathyroidism develop following reoperation procedures necessitated by recurrence and residual

tumors.[11,20] Marian et al. also reported incidental parathryoidectomy following thyroidectomy as 15.3% especially related with completion thyroidectomies among 3,065 patients.[21] A 25% incidence of postoperative shoulder dysfunction has been reported in patients undergoing lateral neck dissection for well-differentiated thyroid cancer.[13,22] In order to reduce the comorbidities of neck dissection and the recurrence rates, we determined our surgery plan preoperatively in terms of its extent and the borders of the neck dissection by using a gamma probe to identify the uppermost and lowermost metastatic lymph nodes. This technique is generally classified as selective neck dissection; however it is far more objective and predictable than most selective neck dissections due to the preoperative probing.

There were several limitations in this study. First, because this was a single center and a retrospective study, the cohort was relatively small. In addition, the study did not compare the success rates and recurrence following other types of surgery than that described. Finally, the study did not include further follow-up information on patients subsequent to secondary surgeries.

CONCLUSION

The use of preoperative United States-mapping with intraoperative gamma probe in patients with metastatic differentiated thyroid cancer is technically safe, and it is effective for determining the borders of the selective neck dissection both preoperatively and intraoperatively. The surgical technique described above provides better information, making it possible to get better oncological results and to reduce recurrence and persistence. However, the compartment-oriented dissection generally used by surgeons should not be omitted, particularly in patients with preoperatively documented multiple metastatic foci. We suggest that morbidity, surgical extension and surgery time could be reduced through surgical modifications such as the method described without causing recurrence; however, long-term follow-up is needed to validate these results.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Mehmet Burak Aşık, Ramazan Yıldız;* ***Design:*** *Mehmet Burak Aşık, Ramazan Yıldız;* ***Control/Supervision:*** *Mehmet Burak Aşık, Ramazan Yıldız;* ***Data Collection and/or Processing:*** *Mehmet Burak Aşık, Ramazan Yıldız;* ***Analysis and/or Interpretation:*** *Mehmet Burak Aşık, Ramazan Yıldız;* ***Literature Review:*** *Mehmet Burak Aşık;* ***Writing the Article:*** *Mehmet Burak Aşık;* ***Critical Review:*** *Ramazan Yıldız;* ***References and Fundings:*** *Mehmet Burak Aşık, Ramazan Yıldız;* ***Materials:***

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