



Predictive Factors of Thyroid Cancer in Geriatric Patients

Geriatrik Hastalarda Tiroit Kanserinin Prediktif Faktörleri

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Abstract

Aim: Although age is not a contraindication for thyroid surgery, decision for surgery should be made carefully in geriatric patients. The aim of this study was to determine the diagnostic value of cytological and ultrasonographic findings in geriatric patients with thyroid pathology.

Methods: Records of patients above 65 years, who underwent thyroid surgery in our clinic between 2014 and 2019, were retrospectively analyzed. Demographic data, biopsy findings according to the Bethesda System, ultrasonography findings (nodule size, echogenicity, margin, micro-calcification, elastography values, peripheral halo and its echogenicity) and pathology results were recorded.

Results: A total of 295 patients (58 males and 237 females) with the mean age of 69.13 years (range; 65-82) were included in the study. When benign and malignant groups were compared, suspicion of malignancy, presence of irregular margins, micro-calcification, elastography score of above 3, hypo-echogenicity and hypo-echoic halo were found to be significant predictive factors for malignancy ($p<0.001$). When ultrasonography parameters were evaluated with regard to the malignancy risk, specificity was found to be 0.92 for micro-calcification, 0.97 for irregular contour and 0.95 for elastography score above 3.

Conclusion: The indication for surgery should be supported by ultrasonography and ultrasound elastography findings in patients with atypia/follicular lesion of unknown significance or whose fine needle aspiration biopsy result is non-diagnostic.

Keywords: Thyroid cancer, geriatric, elastography, irregular margins, microcalcification

Öz

Amaç: Yaş, tiroit cerrahisi için bir kontrendikasyon olmamasına rağmen, geriatrik hastalarda operasyon kararı dikkatli bir şekilde verilmelidir. Bu çalışmanın amacı tiroit patolojisi olan geriatrik hastalarda sitolojik ve ultrasonografik bulguların tiroit kanserindeki tanısal değerini belirlemektir.

Yöntemler: 2014-2019 yılları arasında kliniğimizde tiroit cerrahisi geçiren 65 yaş üstü hastaların kayıtları retrospektif olarak incelendi. Demografik veriler, Bethesda Sistemi'ne göre biyopsi sonuçları, ultrasonografi bulguları (nodül boyutu, ekojenite, sınır, mikrokalsifikasyon, elastografi değerleri, periferik halo ve ekojenitesi) ve patoloji sonuçları kaydedildi.

Bulgular: Yaş ortalaması 69,13 (dağılım; 65-82) olan 295 hasta (58 erkek ve 237 kadın) çalışmaya dahil edildi. Benign ve malign gruplar karşılaştırıldığında biyopside malignite şüphesi, görüntülemeye düzensiz sınırların varlığı, mikrokalsifikasyon, için üzerinde elastografi skoru, hipoekojenite ve hipoekoik halo malignite için anlamlı bulundu ($p<0,001$). Ultrasonografi parametreleri malignite riski açısından değerlendirildiğinde, özgüllük mikrokalsifikasyon için 0,92, düzensiz sınır için 0,97 ve için üzerindeki elastografi skoru için 0,95 olarak bulunmuştur.

Sonuç: İnce iğne aspirasyon biyopsisi sonucu tanısal olmayan veya önemi bilinmeyen atipi/foliküler lezyon olan hastalarda operasyon endikasyonu ultrasonografi ve ultrason elastografi bulguları ile desteklenmelidir.

Anahtar Sözcükler: Tiroit kanseri, geriatrik, elastografi, düzensiz sınırlar, mikrokalsifikasyon

Introduction

The prevalence of thyroid nodules increases with age. The rate of nodular thyroid diseases is above 50% in patients over 65 years of age (1,2). While the vast majority

of undifferentiated thyroid cancers are seen in individuals aged 60 years or over, the course of differentiated thyroid cancers is more aggressive in geriatric patients (3).

Life expectancy and quality of life increased with the developments in diagnosis and treatment of chronic

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diseases, which are common in the geriatric age group, namely cardiovascular diseases, pulmonary diseases and Diabetes mellitus. Although age is not a contra-indication for thyroid surgery, the decision for operation should be made carefully due to certain morbidities (4).

Indications for thyroidectomy include compressive symptoms such as dysphagia or dyspnea, suspicion of malignancy, substernal goiter, hyperthyroidism resistant to treatment and cosmetic reasons (5). Among these, suspicion of malignancy is the most important and the most challenging indication.

Fine needle aspiration biopsy (FNAB) is the most valuable diagnostic method in decision making for surgery for the treatment of thyroid nodules (6). The Bethesda System for reporting cytopathology is the most commonly used tool for thyroid cytopathology (7). However, this system is not always helpful in decision making for surgery due to the inconsistencies among different centers with regard to the malignancy risk in the categories of nondiagnostic cytology, benign cytology and atypia of undetermined significance/follicular lesion of undetermined significance [atypia of undetermined significance (AUS)/follicular lesion of undetermined significance (FLUS)] (8). Ultrasound findings and clinical features should also be evaluated for surgical decision making in these patients.

The aim of this retrospective study was to determine the diagnostic value of cytological and ultrasonographic findings in patients above 65 years with thyroid pathology.

Methods

Records of patients above 65 years, who underwent thyroid surgery in our clinic between 2014 and 2019, were retrospectively analyzed. Demographic data, biopsy results according to the Bethesda System, ultrasound findings (nodule size, echogenicity, margin, micro-calcification, elastography values, peripheral halo and its echogenicity) and pathology results were recorded. Patients with hyperthyroidism, recurrent thyroid pathology and medullary carcinoma, who had undergone surgery due to definitive regional or distant metastasis and complementary thyroidectomy and thyroidectomy due to parathyroid pathologies, were excluded. A complete physical and laboratory examination was performed pre-operatively in all patients. Vocal cord mobility was evaluated and recorded before surgery. Only patients, who had temporal or permanent vocal cord paralysis, were evaluated with flexible fiberoptic laryngoscopy post-operatively.

In our institution, decision for thyroidectomy is made by a multi-disciplinary endocrinology committee composed of experienced cytopathologists, pathologists, endocrinologists and surgeons. The indications for surgery

include nodular goiter, thyrotoxicosis, suspected or verified malignancy, and large and retro-sternal goiter causing tracheal compression. The length of stay in hospital and intensive care unit and the post-operative complications were evaluated in the post-operative period.

Hypocalcemia (<8 mg/dL) persisting for more than 6 months post-operatively was defined as "persistent hypocalcemia".

All procedures performed in studies involving human subjects were in accordance with the ethical standards of the institutional review board (reference no: 54/09) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Surgical Technique

The patient was positioned with hyperextension of the neck following general anesthesia induction. Kocher's incision was made in all cases. The strap muscles were not routinely cut. First, the median vein was ligated and cut, so as to mobilize the gland to the medial. After the upper pole vessels had been isolated, the superior thyroid artery and vein were ligated twice in distal of the bifurcation and above the thyroid capsule. The veins of the inferior pole were ligated individually and cut. The recurrent laryngeal nerve was found at the point where it crossed the thyroid artery and preserved through following along its trace. The parathyroid glands seen in normal location or detected on thyroid capsule were preserved during dissection. No additional dissection was made for the parathyroid glands that could not be visualized. A suction drain was installed in all patients.

Statistical Analysis

All statistical analyses were performed using the SPSS 22.0 statistical package (SPSS, Chicago, IL, USA). In the descriptive statistics, the data were expressed as mean (standard deviation) for continuous variables, and as frequencies and percentages (%) for nominal variables. Normality was evaluated with the Kolmogorov-Smirnov test. The χ^2 test was used to assess the presence of significant differences in risk factors between malignant and benign groups. Multiple logistic regression analysis was performed for significant correlations. Receiver operating characteristic (ROC) curves were formed for analysis of the relationship between the risk factors and malignancy. Areas under the curve (AUC), sensitivity and specificity values, Youden index, diagnostic odds ratio (DOR), and positive and the negative likelihood ratio (LR) were determined for each risk factor. Higher AUC, positive LR, and DOR indicated a stronger relationship between the risk factor and malignancy (Figure 1). A p value of less than 0.05 was considered statistically significant.

Results

A total of 295 patients (58 males and 237 females) with the mean age of 69.13 years (range; 65-82) were included in the study. The patients were divided into two groups as benign and malignant according to the final pathology results. There was no significant difference in mean age between the benign and malignant groups. Of the patients, 285 had pre-operative biopsy results including non-diagnostic (n=32), benign (n=124), AUS (n=72), suspicious for follicular neoplasm (n=22), suspicious for malignancy (n=27) and malignant (n=8). All patients were evaluated with ultrasonography pre-operatively. The mean nodule size was 2.9 cm, microcalcification was found in 100 patients, solid nodule in 23, hypoechogenicity in 48 and hypoechoic nodule in 59 patients. The elastography score was found to be 3 and above in 69 out of 136 patients in whom elastography was performed (Table 1).

When benign and malignant groups were compared, suspicion of malignancy, presence of irregular margins, microcalcification, an elastography score of above 3, hypoechogenicity and hypoechoic halo were found to

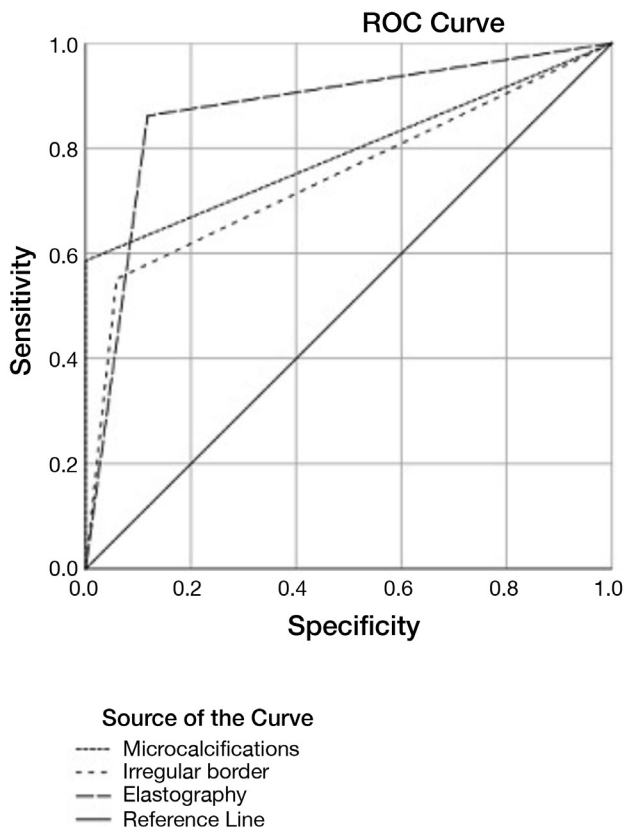


Figure 1. Higher AUC, positive LR, DOR was indicate a stronger relationship between malignancy risk and evaluation method

AUC: Area under the curve, LR: Likelihood ratio, DOR: Diagnostic odds ratio, ROC: Receiver operating characteristic

be significant predictive factors for malignancy ($p < 0.001$) (Table 2).

When ultrasonography parameters were evaluated with regard to the malignancy risk, specificity was found to be 0.92 for microcalcification, 0.97 for irregular contour and 0.95 for elastography score above 3 (Table 3).

Total thyroidectomy was performed in all patients. The pathology results were reported as benign in 167 patients,

Table 1. US findings and biopsy characteristics of patients	
Variables	Total, [n=295 (100%)]
Age, mean	69.13
FNA cytology	
Absent	10
Non diagnostic	32
Benign	124
AUS	72
sFN	22
sM	27
Malign	8
Microcalcification	
Present	100
Absent	195
Irregular margins	
Present	63
Absent	232
Solitary nodule	
Present	23
Absent	272
Elastography scores	
≥3	69
<3	67
Not evaluated	159
Echogenicity	
Hypoechoic	48
Isoechoic	64
Mix	171
Hiper	12
Gender	
Male	58
Female	237
Nodule size	
≥2 cm	201
<2 cm	94
Hypoechoic halo	
Present	59
Absent	236

FNA: Fine needle aspiration, AUS: Atypia of undetermined significance, sFN: Suspicious for follicular neoplasm, sM: Suspicious for malignancy, US: Ultrasonography, n: Number

Variables	Total, [n=295 (100%)]	Benign group, [n=167 (56.6%)]	Malignant group, [n=128 (43.4%)]	p value
Age, mean	69.13	69.08	69.20	0.731
FNA cytology				
Absent	10	4	6	0.282
Non diagnostic	32	22	10	0.143
Benign	124	99	25	0.001
AUS	72	33	39	0.034
sFN	22	7	15	0.015
sM	27	2	25	<0.001
Malign	8	0	8	0.001
Microcalcification				
Present	100	12	88	<0.001
Absent	195	155	40	
Irregular margins				
Present	63	4	59	<0.001
Absent	232	163	69	
Solitary nodule				
Present	23	10	13	0.121
Absent	272	157	115	
Elastography scores				
≥3	69	3	66	<0.001
<3	67	57	10	
Echogenicity				
Hypoechoic	48	7	41	<0.001
Isoechoic	64	43	21	
Mix	171	108	63	
Hiper	12	9	3	
Gender				
Male	58	34	24	0.731
Female	237	133	104	
Nodule size				
≥2 cm	201	118	83	0.343
<2 cm	94	49	45	
Hypoechoic halo				
Present	59	14	45	<0.001
Absent	236	153	83	
FNA: Fine needle aspiration, AUS: Atypia of undetermined significance, sFN: Suspicious for follicular neoplasm, sM: Suspicious for malignancy, n: Number				
Significant p values are shown in bold				

	AUC	Sen.	Spc.	LR+	LR-	DOR	YI
Presence of microcalcification	0.793	0.68	0.92	9.57	0.34	9.23	0.60
Presence of irregularity	0.746	0.45	0.97	19	0.56	33.92	0.42
Elastography scores ≥3	0.872	0.86	0.95	17	0.14	121.42	0.81
AUC: Area under curve, Sen: Sensitivity, Spc: Specificity, LR: Likelihood ratio, DOR: Diagnostic Odds ratio, YI: Youden index							

papillary micro-carcinoma in 62, papillary carcinoma in 55 and follicular carcinoma in 11 patients.

The post-operative complications included temporally dysphonia (1-2%), permanent hypocalcemia (1-2%) and transient hypocalcemia (30%). While re-exploration was necessary in two patients due to post-operative hemorrhage, the rate of wound site infection was 1.5%. No permanent dysphonia and death occurred.

While the mean length of hospital stay was found to be 3.1 days (range; 2-7), the mean intensive care unit length of stay was 1.4 days (range; 1-3) in 18 patients who required intensive care.

Discussion

Recent studies have indicated that thyroid surgery could be performed with low mortality and morbidity rates even in the elderly (9,10). However, it is essential to make an individual risk and benefit analysis in elective thyroid surgery, particularly in geriatric patients (10,11). The vast majority of thyroidectomy indications are composed of high suspicion of malignancy, resistant thyrotoxicosis and large thyroid leading to compression symptoms in geriatric patients. While it is easy to make a diagnosis of thyrotoxicosis and compression symptoms, it is necessary to use clinical, cytological and ultrasonographic properties in cases suspicious for malignancy and their predictive values should be great.

FNAB is accepted as the most reliable diagnostic tool for discrimination of benign and malignant thyroid nodules. It has a high specificity (72-100%) and sensitivity (65-98%). While the false positive rate of this method is 0-7% for detection of malignant tumors, the false negative rate is 1-11%. The diagnostic value of the method increases when performed under ultrasound guidance. FNAB is the first choice in the diagnosis of thyroid nodules due to having low complication rates, being well tolerated by the patients and cost-effective, not requiring hospitalization and yielding accurate results (6,12).

The Bethesda System is a reporting system created for cytopathology reports of fine needle aspiration biopsies of the thyroid gland. The system aims at standardizing the diagnoses by making a categorization and improving communication between pathologists and clinicians. This reporting system was first introduced in 2009 and revised in 2017. The diagnosis groups, which are still being used, were preserved after the revision. While the malignancy risk of AUS was 5-15% according to the Bethesda System, the rate of malignancy was found to be 54.1% in our study. While the malignancy risk is 15-30 in patients undergoing surgery due to the diagnosis of follicular lesion, this rate was 68.1% in our study. In a meta-analysis of eight studies performed by Bongiovanni in 2012, the

rate of malignancy was reported to be 15.9% and 26.1% for AUS and FLUS, respectively (13-15). However, there are also studies reporting opposite results. In their study analyzing the results of 3207 FNABs, Theoharis et al. (16) reported that the risk of malignancy was 48% and 34% for AUS and FLUS, respectively. The striking high rates of AUS and FLUS were associated with the fact that only some part (30%) of these patients had undergone surgery. The malignancy rates were reported as 18.9% and 45.7%, respectively, in a study by Onder et al. (17), which investigated the effectiveness of the Bethesda System for detecting malignancy risk in undetermined cases. The high rates in our study could be associated with the fact that we considered ultrasonography findings and elastography findings besides the diagnosis of AUS when deciding the indications for operation.

In the literature, benign thyroid nodules have been reported to be sharp and well demarcated, and malignant nodules have been reported to be irregular and poorly demarcated. Although the histological characteristics consistent with the contour structure of the nodule could not be clearly explained, irregular and speculated contour structure has been reported to be specific for malignant nodules (18). In our study, while the absence of an irregular margin was significant in benign nodules, it was not found to be statistically significant in malignant nodules.

It has been reported that calcification could be detected in 10-15% of all thyroid nodules; however, the pattern and the location of the calcification rather than its presence was important for discrimination of malignancy. Intrinsic microcalcifications have been reported to increase the suspicion of malignancy in thyroid nodules (19). In our study, while the rate of malignancy was 88% in the presence of microcalcification on ultrasonography, this rate was 20.5% in the absence of microcalcification. Ultrasound elastography is an imaging method developed for noninvasively assessing the tissue firmness. The method evaluates the distortion developing with an external compression (20). Elastography is an imaging method used for evaluating the mechanic and elastic properties of soft tissue and is mainly based on the structural organization and composition of macromolecules. Pathological processes change the tissue structure and consequently its elastic properties. Malignant thyroid nodules are usually firmer than benign nodules. This characteristic is more evident in papillary carcinoma. In our study, while the elastography score was >3 in 69 patients, the rate of malignancy was 95% and the rate of benign nodules was 85% in those with an elastography score of <3 . Although the rates found in our study were consistent with the literature, the mean values vary between 45% and 89% in the literature (21-23).

In the literature, ultrasound and cytopathological features of malignant nodules in geriatric patients mostly seem the same as in young patients (24). In our study, the rate of malignancy was higher in the postoperative pathology, since ultrasound elastography was used and the operation decision was made more selectively.

The results of the study helped us make a diagnosis for operation strongly in patients whose FNAB result was non-diagnostic or AUS.

In studies evaluating complications, no significant difference could be found between young and elderly patients who had undergone a thyroid surgery. Passler et al. (9) compared the results of 55 patients aged 75 years and over (mean; 80) with 683 younger ones and found that the rate of early complications in patients older and younger than 75 years was 25.5% and 21.8, respectively. While the rates of hematoma, seroma, transient or permanent recurrent nerve palsy, transient and permanent hypocalcemia were found to be similar between young and elderly patients in the literature, the incidence of temporal dysphonia, permanent dysphonia, transient hypocalcemia and permanent hypocalcemia was found to be 1-2%, 0%, 30% and 1-2%, respectively, in our study. While 2 patients were re-explored due to post-operative hemorrhage, the rate of wound site infection was 1.5%. Despite the risk of morbidity is high in the elderly, the rate in our study is consistent with the literature (9). There was no mortality in our study and this was consistent with the literature (25).

Study Limitations

Our study has several limitations. The study was retrospective, small sample size of patients and lack of data from the young group, and also in our study, making the operation decision more clearly in the geriatric group had a positive effect on our study.

Conclusion

Thyroidectomy has better morbidity and mortality rates compared to other elective operative procedures in the elderly due to being quite a safe surgical procedure. Age is not a contra-indication alone for surgeons experienced in thyroid surgery and it should be evaluated together with comorbid diseases. The indication for surgery should be supported by ultrasonography and ultrasound elastography findings in patients whose FNAB result is AUS. A well preoperative preparation would decrease the risk of complications and mortality. Further studies evaluating the influence of age on complications in elderly patients are needed.

Authorship Contributions

Concept: S.T. Design: S.T. Data Collection or Processing: S.T., H.K. Analysis or Interpretation: S.T. Literature Search: S.T., H.K. Writing: S.T., H.K.

Conflict of Interest: The authors have no conflict of interest to declare.

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