Research Article / Araştırma Makalesi

Warthin Tumor: Assessment of Association with Salivary Gland and Non-Salivary Gland Malignant Tumors Via Clinicopathological and Radiological Data

Warthin Tümörü: Tükürük Bezi ve Tükürük Bezi Dışı Malign Tümörler ile İlişkisinin Klinikopatolojik ve Radyolojik Veriler ile Değerlendirilmesi

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Abstract: This study aims to find out the incidence of malignant tumors originating from the salivary gland or other organs in patients with Warthin tumor (WT) and compare the clinicopathological, radiological, and demographic data of WT patients with or without malignant tumors. The study population consisted of 170 patients diagnosed with WT from cytology, surgery, and consultation materials between 2010 and 2021 in our hospital. Patient files were reviewed in terms of demographic data, smoking status, presence of malignant tumor, radiological findings, symptom duration, and operation procedure. A total of 40 malignant tumors were detected in 36 (21.2%) of 170 patients with WT. The most common localizations of malignant tumors were lung (35.0%), head and neck (35.0%), and genitourinary (12.5%) regions. The mean age of the patients with malignant tumor diagnosis (62.1±9.2) was higher than the patients without (56.5±9.8) (p=0.002). There was no significant difference between cases with and without malignant tumors in terms of gender, multifocality, bilaterality, amount of smoking, and pain complaints (p>0.05). The SUVmax of WTs ranged from 3 to 17.7 (median: 6.8, IQR: 5.5-11.0), and that of malignant tumors ranged from 2.7 to 16.2 (median: 8, IQR: 5.1-10.3) (p=0.756). This study demonstrates that WT can be seen with malignant tumors synchronously but also encountered before and after the malignant tumor diagnosis. This possibility should be considered, especially in the head and neck region, in patients diagnosed with malignant tumors or being investigated.
Keywords: Warthin tumor, Malignant tumor, Incidence, PET-CT

Özet: Bu çalışmanın amacı, Warthin tümörü (WT) olan hastalarda tükürük bezi veya diğer organlardan kaynaklanan malign tümörlerin görülme sıklığını bulmayı ve malign tümörü olan ve olmayan WT hastalarının klinikopatolojik, radyolojik ve demografik verilerini karşılaştırmayı amaçlamaktadır. Çalışma popülasyonunu 2010-2021 yılları arasında hastanemizde sitoloji, cerrahi ve konsültasyon materyallerinden WT tanısı alan 170 hasta oluşturmuştur. Hasta dosyaları demografik veriler, sigara içme durumu, malign tümör varlığı, radyolojik bulgular, semptom süresi ve operasyon şekli açısından incelendi. WT'li 170 hastanın 36'sında (%21.2) toplam 40 malign tümör tespit edildi. Malign tümörlerin en sık lokalizasyonları akciğer (%35.0), baş-boyun (%35.0) ve genitoüriner (%12.5) bölge idi. Malign tümör tanısı olan hastaların ortalama yaşı (62.1±9.2), olmayan hastalara göre (56.5±9.8) daha yüksekti (p=0.002). Malign tümörü olan ve olmayan olgular arasında cinsiyet, multifokalite, bilateralite, sigara içme miktarı ve ağrı şikayeti açısından anlamlı fark yoktu (p>0.05). WT'lerin SUVmaks'ı 3 ila 17.7 (medyan: 6.8, IQR: 5.5-11.0) arasında, malign tümörlerin SUVmaks'ı ise 2.7 ila 16.2 (medyan: 8, IQR: 5.1-10.3) arasında değişmekte idi (p=0.756). Bu çalışma, WT'nin malign tümörlerle eş zamanlı olarak görülebildiği gibi, malign tümör tanısı öncesinde ve sonrasında da karşılaşılabileceğini göstermektedir. Özellikle baş-boyun bölgesinde, malign tümör tanısı olan ya da araştırılan hastalarda bu olasılık göz önünde bulundurulmalıdır.
Anahtar Kelimeler: Warthin tümörü, Malign tümör, İnsidans, PET-CT

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1. Introduction

Warthin tumor (WT), or papillary cystadenoma lymphomatosum, is a benign tumor commonly affecting the parotid gland. It is the second most common salivary gland tumor after pleomorphic adenoma (PA), accounting for 5-21% of all salivary gland tumors [1-3]. It nearly always occurs in the parotid gland, but sometimes it originates from periparotid or cervical lymph nodes and rarely from the submandibular gland and minor salivary glands. It commonly affects individuals in their sixth and seventh decades of life, and male predominance has been reported in recent studies [3]. WT can occur as multiple or bilateral tumors, either synchronously or metachronously. Its association with tobacco smoking in both males and females has been shown [4, 5], and radiation exposure is linked as a tumorigenic factor [1].

WT most commonly presents as an asymptomatic, slowly growing swelling in the lower portion of the parotid gland. However, some are detected incidentally in routine examinations or imaging methods performed for unrelated reasons.

The association of WT with other salivary gland or non-salivary gland neoplasms has been previously reported. There are few studies on this subject in the literature, and the incidence of WT with salivary gland or non-salivary gland malignant tumors varies between 1.1-37% [6-11]. It is well known that WTs can cause hypermetabolic lesions on Positron Emission Tomography-Computed Tomography (PET-CT) imaging [12], and it can be seen synchronously or after diagnosis with benign or malignant tumors originating from salivary glands or tissues/organs other than salivary glands. Therefore, especially in oncological patients, high maximum standardized uptake values (SUV_{max}) of WTs may raise a suspicion of malignant processes [8, 12, 13].

This study aims to find out the incidence of malignant tumors originating from salivary glands or other organs in patients with WT and compare them with clinicopathological, radiological, and demographic data.

2. Materials and Methods

2.1. Patient selection and obtaining of the clinical data

The study population consisted of 170 patients diagnosed with WT from cytology, surgery, and consultation materials in our center between 2010 and 2021. Patient files were reviewed in terms of demographic data, smoking status, presence of malignant tumor, symptom duration, radiological findings, and operation procedure. The information about localization, diameter, multifocality, and bilaterality characteristics of the lesions was obtained by reviewing the radiological imaging [ultrasonography (USG), computed tomography (CT), magnetic resonance imaging (MRI), and PET-CT] and pathological examinations. SUV_{max} of malignant tumors and WTs were recorded. The highest value in multiple lesions was taken into account. The amount of smoking was calculated as pack years, and 20 pack years was accepted as the heavy smoking limit [5].

2.2. Statistical analysis

Results were expressed as mean±standard deviation (SD), median with Inter Quantile Range (IQR) for continuous variables, and the number (%) for categorical variables. The normality test (Shapiro-Wilk) was used to determine the distribution pattern of the data. According to the distribution, the Student's t-test or Mann-Whitney U test was used to determine the difference between the two groups of continuous variables. Chi-square analysis with Monte Carlo simulations (Pearson, Fisher's exact test, or Yates's correction for continuity) was applied to analyze categorical variables. IBM SPSS base system (SPSS, Version 25.0, USA) was used for statistical analysis. A two-tailed P-value <0.05 was considered statistically significant.

3. Results

One hundred seventy patients were identified, including 34 (20.0%) women and 136 (80.0%) men. The male/female ratio was 4. The mean age at the time of WT diagnosis ranged from

33 to 80 (mean: 57.6±9.9) years, with the highest incidence observed in the 6th and 7th decades (Figure 1).

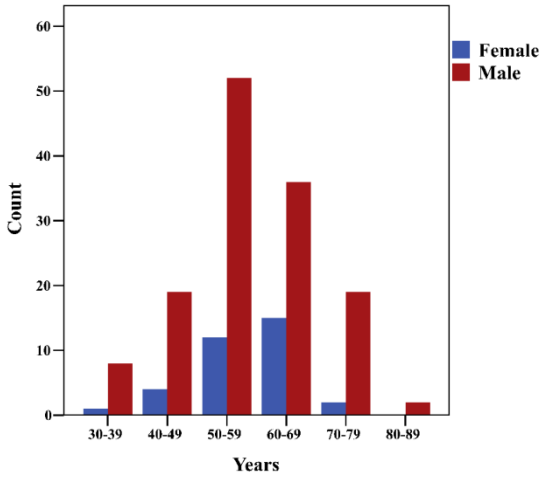

Figure 1. Age and gender distribution of patients with Warthin tumor.

A diagnostic procedure was parotidectomy (superficial, partial, or total) in 111 (65.3%) cases, fine needle aspiration (FNA) or incisional biopsy in 28 (16.5%) cases, excision after FNA or incisional biopsy in 21 (12.3%) cases, lymph node dissection in 8 (4.7%) cases and consultation in 2 (1.2%) cases (Table 1).

Table 1. Diagnostic procedures of Warthin tumors.

Procedures	**Number (%)**
Parotidectomy (Superficial, partial or total)	111 (65.3)
FNA or incisional biopsy	28 (16.5)
Excision after FNA or incisional biopsy	21 (12.3)
Lymph node dissection	8 (4.7)
Consultation	2 (1.2)
Total	**170 (100.0)**

FNA: Fine-Needle Aspiration

The ages of the patients ranged between 33 and 80 (mean: 57.6±9.9), and there was a male predominance (male/female: 4/1). The most common localization of the WTs was the parotid gland (96.5%); the most common symptom was a painless palpable mass in the parotid region. Only 13 (7.6%) patients had painful lesions. The duration of symptoms varied between 0.5 to 240 (median: 12, IQR: 4-36) months. WTs were found to be multifocal in 25 (14.7%) cases. Bilaterality was observed in 26 (15.3%) cases, of which 20 (11.8%) were synchronous and 6 (3.5%) were metachronous (interval between the two tumors: 9.3-180 months). Tumor diameter ranged from 0.8 to 8 (mean: 3±1.4) cm. In 6 (3.5%) patients, the mass reappeared in the same region 24-144 months after the first operation, and these cases were considered recurrence. Smoking data were available in 131 patients, and smoking was noted in 127 (96.9%) of them (median: 32.5 pack years, IQR: 27.5-40). Of the patients whose smoking amount was known (n=101), 82.2% were heavy smokers (>20 pack years). The clinicopathological features of the patients are shown in Table 2.

Table 2. The clinicopathological features of patients with Warthin tumor.

Characteristics	N	(%)	Range
Gender (male/female=4)			
Male	136	80.0	
Female	34	20.0	
Age (year)			mean: 57.6 ± 9.9 (range: 33-80)
Localization			
Parotid	164	96.5	
Periparotid lymph node	4	2.3	
Submandibular	2	1.2	
Symptom duration (months)			mean: 68.6 ± 97.0 (range: 2-180)
Pain			
Yes	13	7.6	
No	157	92.4	
Laterality			
Unilateral	144	84.7	
Bilateral	26	15.3	
Synchronous	20	11.8	
Metachronous	6	3.5	9.3-180 months
Focality			
Unifocal	145	85.3	
Multifocal	25	14.7	
Lesion diameter (cm)			mean: 3 ± 1.4 (range: 0.8-8)
Recurrence (months)			24-89.9
Yes	6	3.5	
No	164	96.5	
Smoking (pack-years)			median: 32.5 (IQR: 27.5-40)
Smoking status			
Yes	127	96.9	
No	4	3.1	
Malignant tumor co-existence			
Yes	36	21.2	
No	134	78.8	

A total of 40 malignant tumors were detected in 36 (21.2%) of 170 WT patients. Nineteen (47.5%) of them were before the diagnosis of WT (median: 13 months, IQR: 3.4-60), 12 (30.0%) at the same time with the diagnosis of WT, and 9 (22.5%) after the diagnosis of WT (median: 96 months, IQR: 52-140). The most common localizations of malignant tumors were lung (35.0%) and head and neck (35.0%). Squamous cell carcinomas (SqCC) (8 lung, three larynx, two oral cavity, one lip, one tonsil, and one skin) appear to be the most common (40.0%) malignant tumor type associated with WT. This is followed by lung adenocarcinomas (12.5%), papillary thyroid carcinomas (12.5%), urothelial carcinomas (5.0%), and breast carcinomas (5.0%), respectively. Two of the patients had more than one malignant tumor diagnosis. One of them had four different malignant tumor diagnosis [thyroid papillary carcinoma, mucinous tubular and spindle cell carcinoma (MTSCC) of the kidney, renal cell carcinoma, and urothelial carcinoma] and another one had two different malignant tumor diagnosis (breast carcinoma and prostate adenocarcinoma). Each of the remaining patients harbored a single malignant tumor. Interestingly, one patient with WT had papillary thyroid carcinoma developed in the thyroglossal duct synchronously. In addition, the patient was diagnosed with WT synchronously with MEC; MEC was located at the tongue base, and WT was detected in the neck dissection material of this patient's tumor excision specimen. The localization and histologic types of malignant tumors and their time relationship with WT are shown in Table 3.

Table 3. Malignant tumor types, localizations, and diagnostic intervals according to Warthin tumor.

Tumor localization and types	Prior (months)	Synchronous	After (months)	Total (%)
Lung				**14 (35.0)**
Adenocarcinoma	3 (5-40.3)	2	-	5 (12.5)
SqCC	3 (3-13)	4	1 (31.6)	8 (20,0)
NSCC	1 (10)	-	-	1 (2.5)
Head and neck				**14 (35.0)**
Papillary thyroid carcinoma	3 (48-60)	1	1 (52)	5 (12.5)
Larynx SqCC	2 (1.5-97)	1	-	3 (7.5)
Oral cavity SqCC	1 (156)	1	-	2 (5.0)
Lip SqCC	1 (106)	-	-	1 (2.5)
Tonsil SqCC	-	1	-	1 (2.5)
Mucoepidermoid carcinoma	-	1	-	1 (2.5)
Nasopharyngeal carcinoma	-	-	1 (12)	1 (2.5)
Genitourinary				**5 (12,5)**
Urothelial carcinoma	1 (9)		1 (96)	2 (5.0)
Prostate adenocarcinoma	1 (3)	-	-	1 (2.5)
Renal cell carcinoma	-	-	1 (72)	1 (2.5)
MTSC	-	-	1 (168)	1 (2.5)
Skin				**2 (5.0)**
Basal cell carcinoma	-	-	1 (180)	1 (2.5)
SqCC	1 (2)	-	-	1 (2.5)
Breast carcinoma	1 (156)	1	-	**2 (5.0)**
Hepatocellular carcinoma	-	-	1 (140)	**1 (2.5)**
Colon adenocarcinoma	1 (59)	-	-	**1 (2.5)**
Leukemia (AML-M3)	-	-	1 (115)	**1 (2.5)**
Total (%)	**19 (47.5)**	**12 (30.0)**	**9 (22.5)**	**40 (100.0)**

SqCC: Squamous cell carcinoma, NSCC: Non-small cell carcinoma, AML: Acute myeloid leukemia, MTSC: Mucinous tubular and spindle cell carcinoma

The mean age of the WT patients with malignant tumor diagnosis (62.1±9.2) was higher than the patients without (56.5±9.8) (p=0.002). There was no significant relationship between cases with and without malignant tumors in terms of gender, multiplicity, bilaterality, amount of smoking, and pain complaints (p>0.05). Moreover, there was no significant relationship between median pack-years (≤32.5 vs. >32.5) and heavy smoking (≤20 vs >20) and bilaterality, multiplicity, pain complaints, and malignant tumor incidence (p>0.05).

PET-CT images were available in 27 patients. In 16 of them, PET-CT images of both WTs (n=16) and malignant tumors (n=18) were available. Of the remaining patients, 10 had only WT images, and 1 had only malignant tumor images. The images were taken in 5 (18.5%, 5/27) patients for control or re-staging after malignant tumor diagnosis, in 13 (48.1%, 13/27) patients who harbored malignant tumors at the time of WT diagnosis, and in 2 (7.4%, 2/27) patients before the diagnosis of malignant tumors for diagnostic purposes. The images of the remaining 7 (26%, 7/27) patients without a malignant tumor diagnosis were taken due to clinical suspicion. As a result, PET-CT images of 26 WTs and 19 malignant tumors were assessed. The SUV_{max} of WTs ranged from 3 to 17.7 (median: 6.8, IQR: 5.5-11.0), and that of malignant tumors ranged from 2.7 to 16.2 (median: 8, IQR: 5.1-10.3) (p=0.756) (Figure 2).

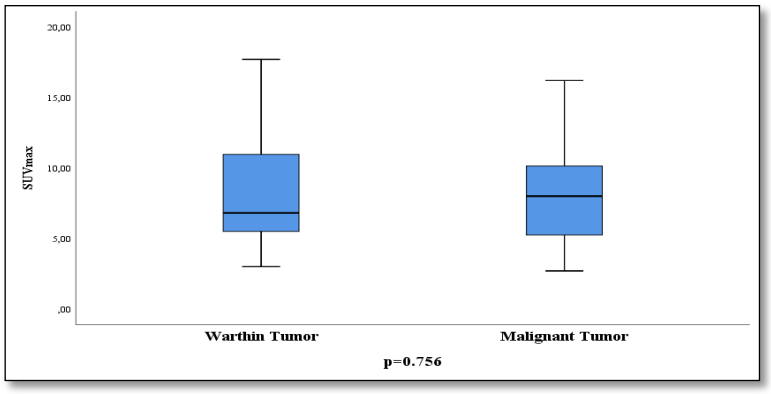

Figure 2. Relationship between Maximum Standardized Uptake Values (SUV_{max}) of Warthin and malignant tumors.

In cases with known SUV_{max} of both malignant tumors and WTs, the SUV_{max} of 7 malignant tumors [4 lung carcinoma, one papillary thyroid carcinoma, one urothelial carcinoma (Figure 3A, 3B), one prostate carcinoma] was lower than that of WTs.

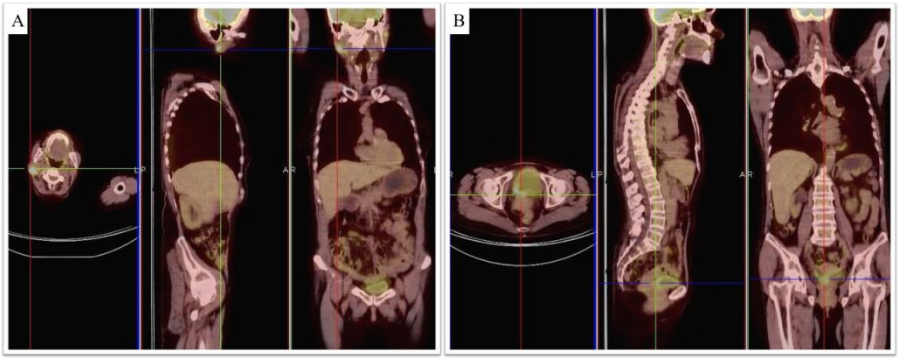

Figure 3. High-grade urothelial carcinoma of the bladder was diagnosed synchronously with Warthin tumor; A. Two foci with SUV_{max} were 11 and 4 in the right parotid, and a single focus with SUV_{max} was 7 in the left parotid. B. Increased FDG uptake with SUV_{max} of 8 was observed in wall thickening areas, more prominently in the posterior bladder wall.

4. Discussion and Conclusion

WT occurs most frequently in the 6th and 7th decades, and preference for men, association with smoking, and the high incidence of multifocality or bilaterality are some of the well-known features [14]. It accounts for 24-42.1% of all benign parotid gland tumors [2, 3, 15-18]. Although it was reported in many previous studies that it is the second most common salivary gland tumor after PA, recently, there has been an increase in studies reporting that the incidence of WT is higher than PA [19-21]. This supports the studies reporting that the incidence and ratio of WT have increased over the years [12, 16, 22].

WTs are histologically characterized by a lymphoid stroma that can often form germinal center structures between bilayered oncocytic epithelial cords [14]. By their nature, they form hot lesions on PET-CT images. This feature may raise the suspicion of metastasis or the second primary malignant tumor during diagnosis, staging, or control scans in oncological patients [13]. Many WTs exhibit high SUV_{max} values exceeding 3, a cut-off used to predict the malignant potential [23], ranging from 3.5 to 34.4 [24]. In addition, SUV_{max} values of WTs are often close to or even exceed the values of malignant tumors in patients who are examined for oncological

reasons [13, 25]. Makis et al. [25] reported incidental focal 18F-FDG uptake in the parotid gland in 31 of 7252 (0.4%) cancer patients imaged with PET/CT, and most of the biopsy-proven cases (40%) were WT. In their study, the SUV_{max} of WTs ranged from 4.2 to 18.3, and the mean SUV_{max} (10.3) of the WTs was higher than the malignant tumor (lymphoma) detected in the parotid gland. Consistent with the literature, SUV_{max} values of all WT cases in our study were ≥3 and were close to those of malignant tumors (p=0.752). Moreover, in patients with WT (n=16) whose malignant tumor images (n=18) also were available, the SUV_{max} values of 7 (38.9%) malignant tumors [4 lung carcinomas (2 adenocarcinomas, 1 SqCC, 1 NSCC), one papillary thyroid carcinoma, one urothelial carcinoma, one prostate adenocarcinoma] were lower than those in WTs.

Few studies have been conducted on the association of WT with salivary gland or non-salivary gland malignant neoplasms. The rate of malignant tumors in patients with WT (before, after, and at the time of diagnosis of WT) has been reported to be between 1.1-37% [6, 9, 14, 26]. Zaccarini and Khurana [6] found that 37.0% of patients with WT harbored extra-salivary gland malignant neoplasms. In this study, 70.4% of the malignant tumors were detected before the WT diagnosis (mean: 4.2 years; range: 6 days to 36 years), and 14.8% (4/27) of cases were diagnosed after the initial diagnosis of WT (mean: 5.4 years; range: 3 months to 10 years). In a series of Cardoso et al. [9], 20 (26.3%) of the patients with WT also developed other neoplastic diseases, most of which were malignant. These neoplastic diseases were mainly diagnosed before the WT diagnosis. In the present study of 170 WT patients, the rate of associated malignant neoplasms was 21.2%. Of them, 19 (47.5%) of malignant tumor diagnoses were before the diagnosis of WT, 12 (30.0%) were at the time of diagnosis of WT, and 9 (22.5%) were after the diagnosis of WT.

SqCC is the most common malignant tumor type in patients with WT, and its rate among malignant tumors is reported to be between 29.4 and 90.9% [6, 9, 14, 26]. Currently, we found that this ratio was 40.0% in this cohort. The most common sites of involvement for SqCC were reported as head and neck region and lung [6, 9, 14, 26]. Consistent with the literature, the most common sites of origin of SqCCs were found to be the lung (8 cases) and head and neck (7 cases) in our series. We also observed that lung carcinomas (8 cases of SqCC, 5 cases of adenocarcinoma, 1 case of non-small cell carcinoma) constituted 35% of all malignant tumor diagnoses and were detected in 14 (8.2%) patients with WT. White et al. [8] reported a concomitant diagnosis of lung cancer in 18.6% of patients with WT over five years. Smoking may explain some of these associations. Smokers are at eight times greater risk of developing WT compared with nonsmokers [4]. It is also well known that smoking increases the risk of development of cancers in various organs such as the lung, mouth, larynx, pharynx, esophagus, kidney, cervix, liver, urinary bladder, pancreas, stomach, and colon/rectum [27]. The evidence is suggestive but not sufficient to infer a causal relationship between tobacco smoke and breast cancer [28]. It is also reported to increase the risk of acute myeloid leukemia [27]. The range of malignant tumor types in our series, including breast carcinoma and leukemia, largely overlaps with the list of tumors just mentioned, and we suggest that a common etiology of smoking explains the association of WT and malignant tumors. However, although papillary thyroid carcinoma was not included in this list, it constituted 12.5% (5/40) of our malignant tumor diagnoses. This rate is reported as 3.7% (1/27) in the study of Zaccarini and Khurana [6], 5% (1/20) in the study of Cardoso et al. [9], and perhaps other etiological factors may play a role in this association. Other than smoking, obesity [18], hypertension [29], and radiation exposure [1] have been suggested to play a causative role in the development of WT. The limitation of our study is the lack of information about the presence of these factors in our study population. It should also be noted that, in some cases, the association of WTs with malignant tumors may also be coincidental.

The mean age of the patients with and without malignant tumors was 62.1±9.2 and 56.5±9.8, respectively. This difference was statistically

significant and was consistent with previous studies [6]. The age distribution (mean: 57.6±9.9), sex ratio (male/female: 4/1), lesion diameters (mean: 3±1,4), localizations, smoking rate (96.9%), bilaterality (15,3%), and multifocality characteristics of the patients were similar to the WT series in the literature [5, 6, 9, 10, 17, 18, 21, 26, 29]. Klussmann et al. [5] found the risk of bilateral development of WTs to be significantly associated with the level of cigarette consumption (p=0.003), but we could not support this finding.

Malignant transformation has been reported very rarely (at about 1%) in the epithelial or lymphoid component of WTs. While malignant transformation in the epithelial component is reported as case reports (SqCC, adenocarcinoma, and MEC) [26], the rate is reported as 2.2% [30] in the lymphoid component. No malignant transformation was detected in our cases' epithelial component or lymphoid stroma.

This study demonstrates that WT can be seen with malignant tumors synchronously but also encountered before and after the malignant tumor diagnosis. This possibility should be considered, especially in the head and neck region, in patients diagnosed with malignant tumors or being investigated.

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Ethics

Ethics Committee Approval: The study was approved by Eskişehir Osmangazi University Noninterventional Clinical Research Ethical Committee (Decision no: 8, Date: 03.11.2020).

Informed Consent: The authors declared that it was not considered necessary to get consent from the patients because the study was a retrospective data analysis.

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