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Are Clinical Predictors of Oral Malignancy Risk Changing? A Sample Study

Ağız Kanserinin Klinik Belirteçleri Değişiyor mu? Bir Örneklem Çalışması

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Abstract

Objective: Our study assesss the clinical features of oral lesions that require histological examination and patient-reported symptoms to estimate the risk of malignancy and to determine the presence of any altered features.

Materials and Methods: Demographic characteristics of 70 patients and clinical features of lesions were analyzed using chi-square test, Fisher's Exact test of Independence and discriminant function analysis.

Results: Margins, lymphadenopathy, patient's self-awareness of the lesion associated with mass effect, surface texture, colour, ulceration, loss of function and pain were significant parameters indicating the risk of malignancy ($p<0.05$). Analyses of the parameters related to the high risk of malignancy have led to a statistical model for clinical differentiation of benign lesions from malignancies with an accuracy of 91.4% ($p=0.016$). The statistical model demonstrated that the most important discriminative features were margins, surface texture, patient's self-awareness, lymphadenopathy, loss of function, ulceration, colour, and pain, respectively.

Conclusion: In our study, age, gender, duration and localization did not anticipate the nature of the lesion. Our statistical model showed that irregular/indistinct margins and surface textures and the presence of lymphadenopathy have a higher risk of malignancy.

Keywords
Oral lesion, oral malignancy, malignancy risk

Öz

Amaç: Çalışmanın amacı histopatolojik inceleme gerektiren oral lezyonların klinik özellikleri ve hastaların sübjektif semptomları değerlendirilerek, malignite riski ile ilişkili parametrelerin ve farklılık sergileyen klinik özelliklerin belirlenmesidir.

Gereç ve Yöntemler: Yetmiş hastaya ait demografik veriler, lezyonların klinik özellikleri ve hastaların sübjektif semptomları ki-kare testi, Fisher bağımsızlık ve diskriminant analizi ile değerlendirildi.

Bulgular: Lezyonun sınırları, rengi, lenfadenopati varlığı, lezyon farkındalığı, yüzey özellikleri, ülserasyon, fonksiyon kaybı ve ağrı malignite riski açısından önemli parametreler olarak belirlendi ($p<0,05$). Verilerin analizi sonrası, lezyonları klinik açıdan benign ve malign olarak %91,4 doğrulukla ayırt edebilen istatistiksel bir model geliştirildi ($p=0,016$). Değişkenlerin diskriminant özellikleri incelendiğinde sırasıyla, lezyon sınırları, yüzey özellikleri, hastanın lezyon farkındalığı, lenfadenopati, fonksiyon kaybı, ülserasyon, lezyon rengi ve ağrı en önemli parametreler olarak saptandı.

Sonuç: Örneklem grubumuzda yaş, cinsiyet, lezyonun süresi ve lokalizasyonu gibi özellikler malignite riski ile ilişkili bulunmadı. Geliştirilen istatistiksel modele göre, klinik olarak sınırları düzensiz/belirsiz, yüzeyi düzensiz/mikst lezyonların ve lenfadenopati varlığının malignite açısından daha yüksek risk taşıdığı belirlendi.

Anahtar Kelimeler
Oral lezyon, oral malignite, malignite riski

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Introduction

A detailed oral examination which includes a thorough head and neck evaluation, visual inspection and palpation is considered as the primary step to detect any oral mucosal change (1-3). Clinical features of oral lesions and practitioner's impressions are of vital importance in detection of any oral mucosal lesion, especially for oral potentially malignant disorders (OPMD) and oral squamous cell carcinoma (OSCC). Clinically, these lesions may present with changes in surface, color and contour, loss of surface integrity, altered mobility of affected oral structures, delayed healing after dental extraction, or as exophytic and verrucous growths and persisting ulceration (4,5).

OPMD and initial OSCC lesions may be asymptomatic or minimally symptomatic and patients may not report bleeding, mobility of teeth, neck mass, difficulty in oral functions etc., which are usually observed in advanced stages (5). Thus, presence of symptoms, that could be associated with malignancy may be misinterpreted by the patient and the clinician, resulting in a diagnostic delay (2). It has been reported that over 30% of patients with OSCC and oropharyngeal cancer had received oral cancer screening within three years prior to the diagnosis of OSCC (6). Late-stage diagnosis correlates with prognosis of the disease: the survival rate is over 80% for stage 1, 2 lesions, 56% for lesions diagnosed at late stages (stage 3, 4) and 33.5% for metastasized lesions (1). Even with assistance of adjuncts for early detection of oral lesions, it is still very challenging to accurately differentiate OPMDs and OSCCs from benign reactive inflammatory analogs (2). Additionally, patient characteristics, prevalence, localization, and prognosis of OPMD and OSCC have been reported to vary in time (7-10) due to changes in etiological factors such as tobacco use, human papilloma virus, and immunosuppression (11,12).

In this prospective study, the aim was to evaluate patient reported findings and clinical characteristics of oral lesions that required incisional/excisional biopsy and histological examination following treatment/elimination of any causative factors, to investigate whether there is a changing trend in patient and lesion profiles that may alter the assessment of the risk of malignancy of oral lesions.

Materials and Methods

Patients who applied to Faculty of Dentistry, Ege University between June 2017 and June 2018 were included. All patients received clinical extraoral and intraoral examination under incandescent overhead illumination and a thorough head and neck evaluation by an experienced oral medicine specialist (B.K.). Inclusion criteria were presence of an oral lesion that required incisional/excisional biopsy and subsequent histological examination after elimination of any possible causative factor, and patient's consent to participate. Patients who were previously diagnosed and received treatment for oral cancer, who were currently on radiotherapy or chemotherapy due to head-neck cancer and who had medically compromised conditions which contraindicated biopsy were excluded. The study protocol was approved by the Clinical Research Ethics Committee of Ege University (decision no: 18-1/23, date: 09.01.2018). All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Each participant signed a detailed informed consent form. Following clinical examination, images of all oral mucosal lesions were obtained under standard conditions. Patient demographics, lesion characteristics, and patient self-reported signs and symptoms were recorded (Table 1).

Each lesion received standard surgical procedures for histological examination by oral surgeons within the same facility. Histological diagnoses were determined by two independent pathologists, and if agreement was not present, consensus obtained with another pathologist. When required, direct immunofluorescent testing was utilized. The lesions were grouped as benign and malignant (the latter also includes lesions with increased risk of malignancy) according to histological diagnoses.

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0 (SPSS, Inc, Chicago, IL). Chi-square test and Fisher's Exact test of Independence were used to determine the significance of the relationships between variables. Discriminant function analysis was utilized to develop a statistical model which can aid to

Table 1. Data analysis including the scoring system and the significance between benign and malignant lesions

Clinical features and patient self-reported findings		All lesions (n, %)	Benign (n, %)	Malignant/ increased risk of malignancy (n, %)	Significance of difference
Color	Normal	3 (4.3%)	3 (100%)	0 (0%)	p=0.161
	White	25 (35.7%)	20 (80%)	5 (20%)	p=0.017*
	Red	6 (8.6%)	4 (66.7%)	2 (33.3%)	p=0.783
	Mixed	36 (51.4%)	16 (37.2%)	20 (74.1%)	p=0.003*
Texture	Smooth	21 (30.0%)	20 (46.5%)	1 (3.7%)	p=0.000*
	Verrucous	16 (22.9%)	9 (56.2%)	7 (43.8%)	p=0.628
	Velvety	5 (7.1%)	3 (60%)	2 (40%)	p=0.946
	Irregular/mixed	28 (40.0%)	11 (39.3%)	17 (60.7%)	p=0.002*
Ulceration	No ulceration	39 (55.7%)	30 (69.8%)	9 (33.3%)	p=0.003*
	Non-elevated borders	13 (18.6 %)	7 (53.8%)	6 (46.2%)	p=0.534
	Elevated borders	18 (25.7%)	6 (33.3%)	12 (66.7%)	p=0.004*
Margins	Regular	32 (45.7%)	29 (90.6%)	3 (9.4%)	p=0.000*
	Irregular	29 (41.4%)	12 (41.4%)	17 (58.6%)	p=0.004*
	Indistinct	9 (12.9%)	2 (22.2%)	7 (77.8%)	p=0.010*
Location	High risk (FOM, lateral tongue, posterior oral cavity)	23 (32.9%)	13 (56.5%)	10 (43.5%)	p=0.555
	Other	47 (67.1%)	30 (43.5%)	17 (56.5%)	
Lymphadenopathy	Absent	39 (55.7%)	31 (79.5%)	8 (20.5%)	p=0.380
	Present	31 (44.3%)	12 (38.7%)	19 (61.3%)	p=0.000*
Lymph node size	<1 cm	17 (54.8%)	8 (47.1%)	9 (52.9%)	p=0.293
	1-1.5 cm	11 (35.5%)	4 (36.4%)	7 (63.6%)	p=0.842
	>1.5 cm	3 (9.7%)	0 (0%)	3 (100%)	p=0.265
Lymph node texture	Soft	9 (29.3%)	7 (77.8%)	2 (22.2%)	p=0.004*
	Firm	9 (29.3%)	1 (11.1%)	8 (88.9%)	p=0.044*
	Rubbery	7 (22.6%)	3 (42.8%)	4 (51.7%)	p=1.000
	Hard	6 (19.4%)	1 (16.7%)	5 (83.3%)	p=0.363
Lymph node mobility	Mobile	20 (64.5%)	11 (55%)	9 (45%)	p=0.012*
	Immobile	11 (35.5%)	1 (9%)	10 (90.9%)	
Pain	None	35 (50%)	28 (80%)	7 (20%)	p=0.001*
	Mild	16 (22.9%)	7 (43.8%)	9 (56.2%)	p=0.098
	Moderate	11 (15.7%)	6 (54.5%)	5 (45.5%)	p=0.609
	Severe	8 (11.4%)	2 (25%)	6 (75.0%)	p=0.025*
Duration	<2 weeks	4 (5.7%)	2 (50%)	2 (50%)	p=0.629
	2-4 weeks	9 (12.9%)	6 (66.6%)	3 (33.3%)	p=0.729
	>4 weeks	57 (81.4%)	35 (61.4%)	22 (38.5%)	p=0.993
Loss of function	None	38 (54.3%)	29 (67.4%)	9 (33.4%)	p=0.005*
	Mild	19 (27.1 %)	11 (57.9%)	8 (42.1%)	p=0.711
	Moderate	4 (5.8%)	1 (25.0%)	3 (75.0%)	p=0.123
	Severe	9 (12.8%)	2 (22.2%)	7 (77.8%)	p=0.010*
Patient self-awareness	Not aware	26 (37.1%)	22 (84.6%)	4 (15.3%)	p=0.002*
	Aware	31 (44.3%)	18 (58.1%)	13 (41.9%)	p=0.606
	Aware and associated with mass effect	13 (18.6%)	3 (23.1%)	10 (76.9%)	p=0.002*

*p<0.05. FOM: Floor of mouth

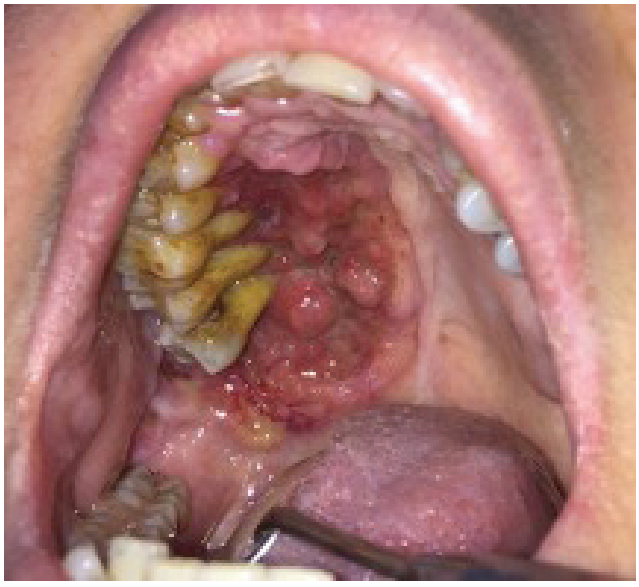

Figure 1. A large ulceration with elevated borders and irregular margins located at right maxillary area which was histologically diagnosed as SCC (Patient #: 46)
SCC: Squamous cell carcinoma

identify the discriminative variables for malignant and benign lesion groups. In all tests, p was set at 0.05.

Results

Seventy patients who fulfilled the inclusion criteria were enrolled. Results of data analysis including differences between benign and malignant lesions are presented in Table 1.

Forty-three lesions were histologically diagnosed as benign, and 27 lesions were malignant (Figure 1). Differences between the preliminary clinical diagnoses and the histological diagnoses were statistically significant (p=0.016).

The study group included 39 males (55.7%) and 31 (44.3%) females. The number of benign lesions (n=43) were similar for males (n=21, 48.8%) and females (n=22, 51.2%). Malignant lesions were more common among males (n=18, 66.7%) compared to females (n=9, 33.3%), however the difference was not statistically significant (p=0.144). Patient's age ranged from 21 to 81 years (mean: 56.41 years); mean age of patients with benign lesions was 53.81 years, while for the malignant group, it was calculated as 60.56 years (p=0.065).

The majority of mixed colored lesions were histologically malignant (74.1%), which represented a potential indicator of malignancy (p=0.003). A smooth texture was an indicator of benign nature (p=0.000). Both verrucous or velvety surface textures were not predictive of subsequent histology (p=0.628 and p=0.946, respectively), whereas irregular/mixed texture represented a clinical feature associated with malignant potential (p=0.002). Presence of ulceration was associated with malignant lesions (p=0.003). The ulcers with elevated borders were observed significantly more frequently in the malignant group. (p=0.004). Lesions with regular margins were more likely to be benign (p=0.000), while most of the malignant lesions presented with irregular margins (p=0.004). Additionally, indistinct margins were more common among malignant lesions (p=0.010).

43.5% of lesions located on "higher risk areas" (floor of mouth, lateral tongue and posterior oral cavity) were histologically confirmed as malignant, while 56.5% of them were benign. Thus, statistical analysis did not reveal a significant difference between the location of benign and malignant lesions (p=0.555). Presence of lymphadenopathy was more common among malignant lesions (p=0.000). Soft texture of lymph nodes was suggestive of benign lesions (p=0.004), and firm texture was more common among malignant lesions (p=0.004). In addition, lack of lymph node mobility (fixed) was associated with malignant lesions (p=0.012).

Of all patients, 50% reported pain, and lack of pain was more common in patients with benign lesions (p=0.001), while 75% of patients with severe pain had malignant lesions (p=0.025). Duration of the lesion was not suggestive of histological nature in the present study (p=0.993). Malignant lesions were associated with loss of function (p=0.010) and in the malignant group, patients were aware of the lesion associated with a mass effect (p=0.002).

The discriminant function analysis was used for assessment of the risk of malignancy, which revealed that margins (p=0.000), lymphadenopathy (p=0.000), texture (p=0.000), color (p=0.001), presence of ulcer (p=0.001), patients' self-awareness of the lesion associated with mass effect (p=0.000), loss of function (p=0.001) and pain (p=0.002) were important parameters in suggesting clinical risks of malignancy.

Box's Test of Equality of Covariance Matrices was applied to the above-mentioned features (to parameters with significant differences between benign and malignant lesions) and has led to a clinical

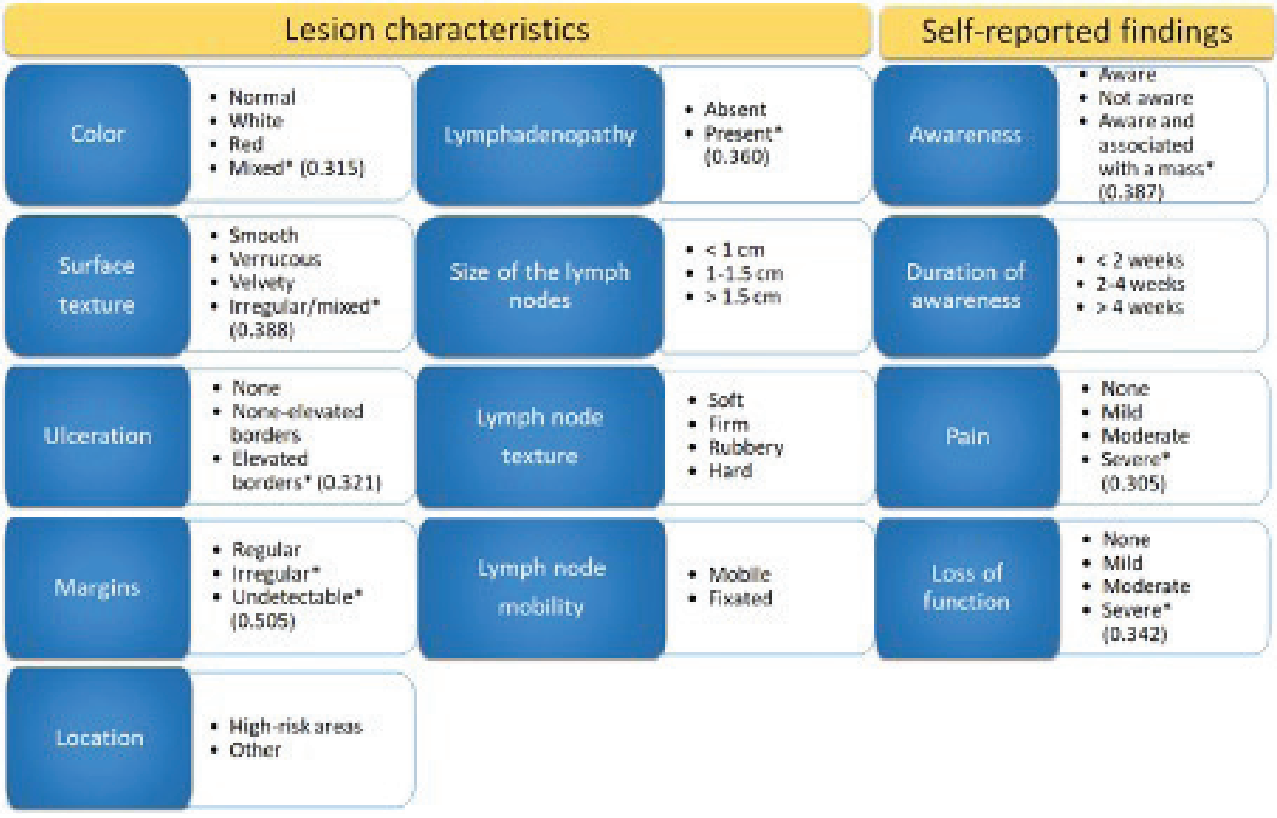

Figure 2. The discriminant characteristics of oral mucosal lesions with higher malignancy risk as observed in the statistical model (discrimination value 92.6%)
*The most powerful discriminative features and corresponding correlation values

model which discriminated all lesions with an accuracy of 91.4% (the discrimination value was 90.7% for benign and 92.6% for malignant lesions). The Pearson correlations between predictors and standardized canonical discriminant functions pointed the conclusion that, irregular or indistinct margins was the most powerful discriminator regarding the nature of an oral mucosal lesion (0.505) in our statistical model, followed by irregular/mixed surface texture (0.388), patients' self-awareness of the lesion associated with mass effect (0.387), presence of lymphadenopathy (0.360), severe loss of function (0.342), presence of ulcer with elevated borders (0.321), mix color (0.315) and severe pain (0.305) (Figure 2).

Discussion

Clinical presentations of various oral lesions are well described, yet to minimize the diagnostic delays, it is vital to recognize that presentation of a lesion may vary over time, and a lesion which may be present for extended periods of years may come forward with sudden progression to malignancy (5). Our results reveal that there may be clinical features that require more attention and further investigation to diagnose or rule out any suspicion of malignancy.

It should be emphasized that oral cancer presents with different epidemiological and clinical patterns which vary due to individual and cultural differences and environmental factors (13). Additionally, the current knowledge regarding localization with high risk of malignancy is changing and the incidence of malignant tumors at locations with lower risk has been increasing (9). Changes in gender and age of the patients with OPMD have also been reported (10). This assumption is reflected in poor overall efficacy of clinical oral examination to predict oral dysplasia or OSCC (14). Non-invasive, chair-side and inexpensive methods are needed to assist in diagnosis. However, the most critical influence upon detection and diagnosis remains the experience and training of the clinician (9,15).

The present paper assessed clinical features of various oral mucosal lesions and patient reported findings to investigate whether there is a changing trend in patient and lesion profiles. Three most relevant discriminating features that may support clinical evaluation to determine the risk of malignancy were "irregular or indistinct margins", followed by "irregular/mixed texture" and "self-awareness associated with mass effect. Regular lesion margins were suggestive of a benign lesion, whereas irregular or indistinct margins were indicators of malignant potential, which is in accordance with previous studies. An important aspect is that oral mucosal malignancies have horizontal (surface) and vertical (depth) components and even though these lesions may appear as mucosal surface alterations, malignant tissue changes may be confined in the lower layers of the epithelium or extend into the underlying stroma (15). Thus, when asymptomatic or minimally symptomatic, these lesions may be overlooked (2). Variability in the occurrence, severity and perception of pain has been previously reported and may be related to nature of lesion, biology of pain, presence of ulceration or mass have also been cited (7). As reported in the literature, severe pain was noted to be an indicator of malignant lesions (8).

Age, gender, duration and localization of the lesion did not predict the nature of the lesion, which contrasted with some other papers in the literature. It has been reported that malignant lesions are more common among older and male patients (3,5,10,16). However, comparable results were presented as well, either stating equal incidence of OSCC in females and males (8) or higher incidence of OSCC in female patients, especially among those less than 40 years of age (3). Our study may also reflect the increasing incidence of OSCC in females similar to those reported mainly in less developed countries (7). Likewise, lesion location did not assist in differentiating benign from malignant lesions in our study sample, which is in contrast with the literature but has also been noted by others (8). The ventrolateral aspects of the tongue and the floor of the mouth, followed by buccal and retromolar mucosa have been stated as the most frequent location for OSCC (1,5). Yet, a study reported that although tongue had the highest transformation rate, no significant relationship was observed between site and malignant transformation risk. The variation in the locations of oral malignant lesions has also been reported with increasing incidence in the "lower risk" regions, possibly due to changes in epidemiological and etiological factors (8,9).

White lesions primarily reflected benign lesions, whereas mixed color was a potential indicator of increased risk of malignant nature of oral lesions, as previously suggested in the literature (14). Ulcerations with elevated borders were significantly associated with malignant lesions. Differentiation of ulcerative lesions from the oral mucosal lesions that may have malignancy potential requires a careful assessment of borders. This finding is consistent with the literature. The chronic ulcer with elevate borders is described as a clinical feature of malignancy that should not be overlooke (14).

It is recommended that oral mucosal lesions persisting for more than 2-3 weeks require follow up and biopsy to carry out diagnosis (5,15). However, our study showed that duration of the lesion was not a predictor of the nature of the lesion. Considering that the oral lichen planus or oral lichenoid lesions and any other lesions present for extended periods may show the rapid malignant transformation, we need to revise conventional statements regarding the duration of the lesion: if an ulcerative lesion or a swelling is not resolved within 2-3 weeks after elimination of the causative factor and/or treatment, biopsy should be performed regardless of the duration. Once histological diagnosis is confirmed, active surveillance is needed with repeat/subsequent biopsy when changes in the nature of the lesion or in symptoms are observed.

Despite careful analysis of data, lack of other potentially confounding variables such as tobacco and alcohol use, diet, family history, other systemic conditions, oral status (decayed/missing/filled teeth, periodontal inflammation, mechanical irritation of mucosa etc.) are recognized among limitations of our study. On the other hand, the strength of this paper is the histological diagnosis being confirmed by a panel of blinded pathologists.

Conclusion

Our results revealed important clinical features of oral lesions and patient self-reported findings which were different than those commonly accepted for oral malignant entities. However, histopathological examination remains the gold standard for definitive

diagnosis. It is known that a lesion can appear clinically innocent but may harbor epithelial dysplasia, whereas a histologically benign lesion may still possess molecular risk of malignant progression. Therefore, molecular analyses shall be incorporated into the tissue examination in future investigations. Thanks to development in molecular biomarkers spesific to oral mucosal malignancies, eventually clinicians can accurately predict the nature and prognosis of epithelial disorders eventually.

Ethics

Ethics Committee Approval: The study protocol was approved by the Clinical Research Ethics Committee of Ege University (decision no: 18-1/23, date: 09.01.2018).

Informed Consent: Each participant signed a detailed informed consent form.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: U.A., Concept: B.K., P.G., Design: N.E.Ö., B.K., C.G., P.G., Data Collection or Processing: N.E.Ö., C.G., Analysis or Interpretation: B.K., H.B., P.G., Literature Search: N.E.Ö., B.K., Writing: N.E.Ö., B.K., P.G.

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