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Clinical characteristics of uterine sarcoma: Retrospective analysis of a single center

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Abstract

To examine the histopathological features and treatment modalities in patients with uterine sarcoma according to subgroups (uterine leiomyosarcoma, low grade/high grade endometrial stromal sarcoma, adenosarcoma, undifferentiated uterine sarcoma) and to determine the factors affecting mortality rates. We retrospectively evaluated patients diagnosed with uterine sarcoma in our center between March 2012 and December 2019. We compared the clinicopathological characteristics and treatment modalities of the subgroups and investigated the factors affecting mortality rates using logistic regression analysis. There was no difference between the subgroups in terms of age, body mass index, menopausal status, comorbidity, presenting complaint, primary diagnosis, surgical treatment protocol, adnexal and lymph node involvement and tumor size (p> 0.01). However, there were higher rates of hormone therapy administration in the low grade endometrial stromal sarcoma group (p: 0.000). There were comparable rates of local and distant metastases between subgroups, however, no difference was found between chemotherapy and radiotherapy protocols (p> 0.01). It was found that in all US groups, stage was the only parameter which affected mortality rates (OR: 15.7 (95% CI 2.8-29.6) p = 0.002). Stage is the most important factor affecting mortality in all uterine sarcomas. Despite their different histopathological features, subgroups do not have distinctive features such as demographic features, presenting complaints, primary diagnosis and surgical treatment protocols.

Keywords: Uterine sarcomas, adenosarcoma, leiomyosarcoma, endometrial stromal sarcomas, undifferentiated uterine sarcomas

Introduction

Uterine sarcomas (US), which account for less than 10% of all cancers of the uterine corpus, originate from the connective tissue elements of the myometrium or endometrium [1]. According to the 2014 World Health Organization (WHO) classification system based on the origin and differentiation/growth patterns of neoplastic cells, USs were classified into the following categories: uterine leiomyosarcoma (uLMS; 65%), endometrial stromal sarcoma [ESS; 21%, low grade (LG) and high grade (HG)], adenosarcoma (AS, 5%) and undifferentiated uterine sarcoma (USS; 5%) [2, 3]. Among the defined risk factors of USs are tamoxifen use and the history of pelvic radiation exposure [4, 5]. Since US has no specific finding, most cases are diagnosed after myomectomy or hysterectomy. Therefore, there is no reliable diagnostic tool other than histopathological examination [6].

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Treatment is based on complete surgical removal of the uterus. Systemic lymphadenectomy, on the other hand, is controversial for patients except for those with extrauterine involvement and clinically enlarged lymph nodes [7, 8], whereas, it has been found to be associated with increased survival in patients with HG-ESS [9]. The clinical and pathological variations of US subgroups require an individualized adjuvant therapy modality, consisting of options including hormone therapy, chemotherapy, and radiotherapy [3].

Because of the low incidence of US, many centers treat only a few patients per year, which poses a challenge to conducting randomized controlled trials. In addition, multidisciplinary studies reveal different diagnostic and therapeutic approaches. This single-center study aimed to evaluate the histopathological features and treatment modalities of US and to determine the prognostic factors affecting mortality rates.

Materials and Methods

We retrospectively analyzed the data of 82 patients who were diagnosed with US in our center between March 2012 and December 2019 through the records on the hospital automation system. Patients who were treated primarily by surgery and

diagnosed with LMS, LG-ESS, HG-ESS, UUS and AS based on pathological examination were included in the study. We excluded patients (n:30) who had a concomitant malignant disease, had no surgical treatment, had incomplete clinical records, and were diagnosed with carcinosarcoma. We recorded data such as age, body mass index (BMI; kg / m2), additional systemic diseases and presenting symptoms. Moreover, we investigated the surgical treatment modality [myomectomy, hysterectomy, bilateral salpingo-oophorectomy (BSO) and systemic lymphadenectomy (SLN)], recurrent surgical interventions, morcellation, and the presence of residual tumor. We reviewed the results of pathological investigations and thus performed tumor staging based on the International Federation of Gynecology and Obstetrics (FIGO) system [10].

Post-treatment follow-ups were made at 3-month intervals for the first 2 years, at 6-month intervals between 2-4 years and then annually. A complete physical examination, detailed gynecological examination, and laboratory tests (complete blood count, renal and liver function tests, and chest radiography) were performed at all follow-up visits. Imaging methods (thoracic computerized tomography (CT) scan/ abdominal USG imaging± abdominal CT scan) were used if clinically necessary. Overall survival (OS) is the time from initial diagnosis to the time of death or the last follow-up visit, while disease-free survival (DFS) is the time from the end of the treatment process to the detection of recurrence or the last follow-up visit (months). We evaluated radiotherapy, hormone therapy and chemotherapy applications during the entire follow-up period. All treatments and follow-ups were carried out by the same gynecological oncology team.

This study was reviewed and approved by the local Research and Ethics Committee of the University (Project no: KA20/292) and in accordance to the Declaration of Helsinki.

Statistical analysis

Statistical analysis was performed using the statistical package SPSS software (Version 23.0, SPSS Inc., Chicago, IL, USA). For each continuous variable, normality was checked by Kolmogorov Smirnov and Shapiro-Wilk tests and by histograms. All numerical data are expressed as median values (minimum-maximum) or as proportions.

Comparisons between groups were applied using Student T test for normally distributed data and Mann Whitney U test were used for the data not normally distributed. The categorical variables between the groups was analyzed by using the Chi square test. It was considered significant when $p<0.01$ with the Bonferroni correction.

Overall survival was analyzed using the Wald test, and the log-rank test was used to examine their relationship when different parameters were applied. The survival curve was plotted using the standard Kaplan-Meier methodology. Cases that did not develop death or recurrence during the follow-up period were marked as censored in the survival graphics.

Results

A total of 48 patients who met the inclusion criteria were included in the study. The demographic data and clinicopathological characteristics of the patients are described in Table 1. Of the patients, 58% were diagnosed with LMS (n=28), 10% with LG-ESS (n=5), 10% with HG-ESS (n=5), 15% with AS (n=7) and 6% with UUS (n=3). The mean age of the whole group was 52.3±10.9 years, with no difference between the mean age of subgroups (p=0.062). There was no difference between the comorbidities and BMI of the groups (p = 0.079). The most common presenting complaint was menometrorrhagia (35.4%) in patients with US, and postmenopausal bleeding in AS and UUS subgroups (p=0.027; Table 1). Probe curettage was performed at 19 (39.6%) of these patients, of whom 47.4% [n=9 (18.8% of the entire group)] were found to have malignant tumors. In 50% of the patients, histopathological diagnosis was established by paraffin-section examination after the hysterectomy procedure, whereas the highest rate of diagnosis using probe curettage was in the UUS subgroup (66.7%). In 75% of the patients, Ca-125 was <35 U / mL, while Ca-125 levels were not different between the subgroups (p= 0.992). Also, there was no difference between the groups in terms of surgical procedure type. In addition, almost all of the patients had non-visible tumor debulking surgery. An optimal debulking of less than 1 cm was achieved in 2 patients (1 patient LG-ESS, 1 patient HG-ESS), whereas non-visible tumoral debulking was achieved in all other patients. Of the 3 patients who underwent laparoscopic myomectomy, 1 (n = 1 LMS) had in-bag morcellation and 2 had open morcellation (n = 1 LG-ESS, n = 1 LMS). All 3 patients had stage 1 tumor at the time of diagnosis. In pathology specimens, tumor diameter was >7cm in 62% of the patients. There was no difference between the subgroups in terms of tumor diameter and adnexal/omental/lymph node involvement (p> 0.05). Except for US and UUS subgroups, other subgroups had FIGO stage 1 cancer at the time of diagnosis. Of the patients, 57.8% had chemotherapy and 51.1% received radiotherapy, with no difference between subgroups in this regard. Sixty percent of the patients in the HG-ESS subgroup had hormone therapy. Of the patients who received chemotherapy after diagnosis (n=29; 60.4%), 16 (55.2%) had gemcitabine (900 mg/m2 over 90 minutes) on days 1 and 8 plus docetaxel (75mg/m2) on day 8 every 21 days (LMS, n = 11; HG-ESS, n = 2; AS, n = 2; and UUS, n = 1), and 9 (31%) had ifosfamide (5 g / m2) and doxurobucin (75 mg / m2) (IMA) (LMS, n= 6; HG-ESS, n= 2; AS, n= 1). Five of the 9 patients with IMA developed a relapse and received gemcitabine-docetaxel (LMS n = 4, HG-ESS n = 1) as second-line chemotherapy.

In the entire US group, the rate of 5-year OS was 51.2% and the rate of DFS was 39.9% (Table 2, Figure 1-2). All patients survived after 5 years in the LG-ESS subgroup, whereas all patients died in the UUS subgroup (Table 2 and Figure 3). In 21 patients who died (43.7%), the rates of adnexal involvement (p = 0.045), lymphovascular invasion (LVSI) (p = 0.005), paraaortic lymph node involvement (LNM) (p = 0.012) and advanced stage tumor (p = 0.001) were significantly higher compared to patients who survived. The logistic regression analysis, which were conducted on clinical and histopathological features and treatment modalities, and which aimed to evaluate the factors affecting the mortality rate, showed that only the stage was effective on the mortality rate in the whole US group [OR: 15.7 (95% CI, 2.8-29.6) p = 0.002].

Table 1. AClinicopathological baseline characteristics of patients with uterine sarcomas

	Entire Group N=48	LMS n= 28 (58%)	LG-ESS n=5 (10%)	HG-ESS n=5 (10%)	AS n=7 (15%)	UUS n=3 (6%)	p
Age (year)	52.3±10.9	51.6.±10.6	44±4.6	48.4±13.3	59±8.2	63.6±10.7	0.063
COMORBIDITIES							
DM±HT	16(33%)	6(21.5%)	1(20%)	2(40%)	5(71%)	2(66.5%)	0.079
Others	6(12.5%)	3(10.5%)	-	2(40%)	2(29%)	-	
BMI(kg/m2)	29.2±5.4	27.7±4.0	30.2±4.8	28.9±7.0	35.4±6.2	28.9±7.8	0.643
Premenopause	22(45.8%)	13(46.4%)	5(100%)	3(60%)	1(14.3%)	-	
Postmenopause	26(54.2%)	15(53.6%)	-	2(40%)	6(85.7%)	3(100%)	0.020
SYMPTOMS							
Asymptomatic	2 (4.2%)	-	-	-	2(28.6%)	-	
Menometrorrhagia	17 (35.4%)	10 (58.8%)	3(60%)	3(60%)	1(14.3%)	-	0.027
Postmenopausal bleeding	9(18.8%)	4 (14.3%)	-	-	3(42.9%)	2 (66.7%)	
Pain	6(13.4%)	6 (21.4%)	-	-	-	-	
Mass	14(29.2%)	8 (28.6%)	2 (40%)	2 (40%)	1(14.3%)	1(33.3%)	
INITIAL DIAGNOSIS							
Endometrial curattage	9 (18.8%)	2(7.1%)	-	1(20%)	4 (57.1%)	2 (66.7%)	
Paraffin after myomectomy	8 (16.7%)	7 (25%)	1 (20%)	-	-	-	0.041
Paraffin after hysterectomy	50 (50%)	14 (50%)	2(40%)	4(80%)	3(42.9%)	1(33.3%)	
Frozen	7 (14.6%)	5 (17.9%)	2(40%)	-	-	-	
Ca125 (U/mL)							
<35	27(75%)	14(73.7%)	4(80%)	3(75%)	4(80%)	2(66.7%)	0.992
>35	9(25%)	5(26.3)	1(20%)	1(25%)	1(20%)	1 (33.3%)	
SURGERY TYPE							
TAH ± BSO	128(25.5)	8(28.6)	2(40%)	1(25%))	1(14.3%)	--	0.702
TAH ± BSO ± cytoreduction	35(74.5%)	20(71.4%)	3(60%)	3(75%)	6(85.7%)	3(100%)	
TUMOUR SIZE							
< 7cm	16(38%)	9(37.5)	-	2(66.7%)	3(42.9%)	2(66.7%)	0.265
> 7cm	26(62%)	15(62.5%)	5(100%)	1(33.3)	4(57.1%)	1(33.3%)	
Adnexal involvement	12(28.6%)	5(20.8%)	2(40%)	1(33.3%)	2(28.6%)	1(33.3%)	0.526
Omental involvement	-	-	1(25%)	-	-	-	-
Lymph node involvement	6(15.8%)	2(9.5%)	-	1(33.3%)	1(16.7%)	2(66.7%)	0.088
FIGO STAGE							
Stage 1	33(68.8%)	21(75%)	3(60%)	3(60%)	6(85.7%)	-	
Stage 2	6(12%)	2(7.1%)	2(40%)	1(20%)	1(14.3%)	-	0.039
Stage 3	5(10.4%)	3(6.3)	-	-	-	2(66.7%)	
Stage 4	4(8.3%)	2(7.1%)	-	1(20%)	-	1(33.3)	
ADJUVANT THERAPY							
Chemotherapy	26(57.8%)	15(55.6%)	-	4(80%)	4(66.7%)	3(100%)	0.063
Radiotherapy	23(51.1%)	14(51.9%)	2(40%)	2(49%)	3(50%)	1(33.3%)	0.969
Hormonotherapy	10(22.2%)	2(7.4%)	4(8.9%)	3(60%)	1(16.7%)	-	0.000
FIRST LINE CHEMOTHERAPY PROTOCOL							
Gemstabin-docetaksel	16(55.2%)	11(57.6%)	-	2(50%)	2(66.7%)	1(33.3%)	
Ifosfamide- doxurobucin	9(31%)	6(31.6%)	-	2(50%)	1(11.1%)	-	0.175
Others	4(13.8%)	2(10.5)	-	-	-	2(66.7%)	
RECURRENCE TOTAL	25	16	1	4	1	3	
Locoregional	8(32%)	3(18.8%)	1(100%)	3(75%)	1(100%)	-	0.035
Distant	17(68%)	13(81.2%)	-	1(25%)	-	3(100%)	

Abbreviations: LMS Leiomyosarcoma, HG- ESS High Grade Endometrial stromal sarcoma, LG-ESS: High Grade Endometrial stromal sarcoma UUS Undifferentiated uterine sarcoma, BMI: body mass indeks, FIGO International Federation of Oncology and Obstetrics, TAH-BSO: Total abdominal hyterectomy-bilateral salpingo-oophorectomy.

Table 2. Survival rates

			95% Confidence Interval					
	Estimate Mean	**Std. Error**	**Lower Bound**	**Upper Bound**	**1st year survivor %**	**3rd year survivor %**	**5th year survivor %**	**p**
Overall Survival	129.7	17.0	94.5	161.2	82.5	65.9	51.2	-
Disease Free Survival	71.7	11.7	48.8	94.7	58.9	46.4	39.9	-
Subgroup's Overall Survival								
LMS	67.8	8.3	51.5	84.1	84.2	71.1	50.2	
LG-ESS	-	-	-	-	100	100	100	
High Grade-ESS	18.8	8.3	7.0	30.6	60.0	40.0	40.0	0.001
Adenosarcoma	66.1	10.7	45.2	87.1	85.7	71.4	71.4	
Undifferentiated uterine sarcoma	56.0	6.9	47.8	75.2	33.3	33.3	0.0	

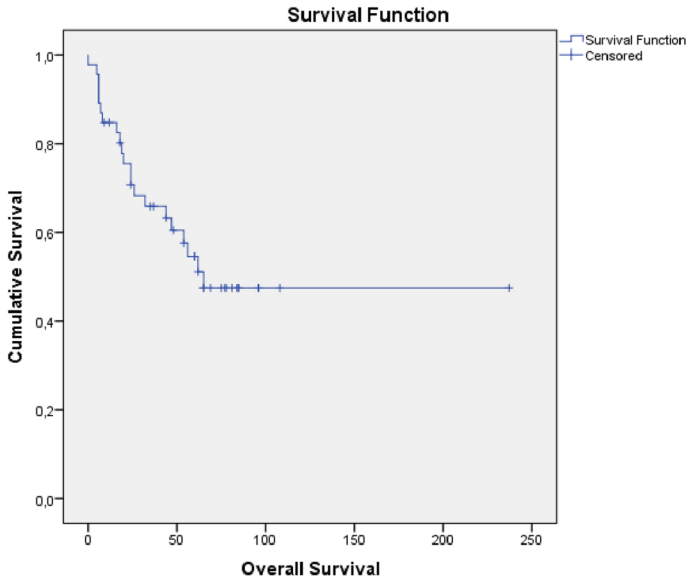

Figure 1. Entire Group overall survival

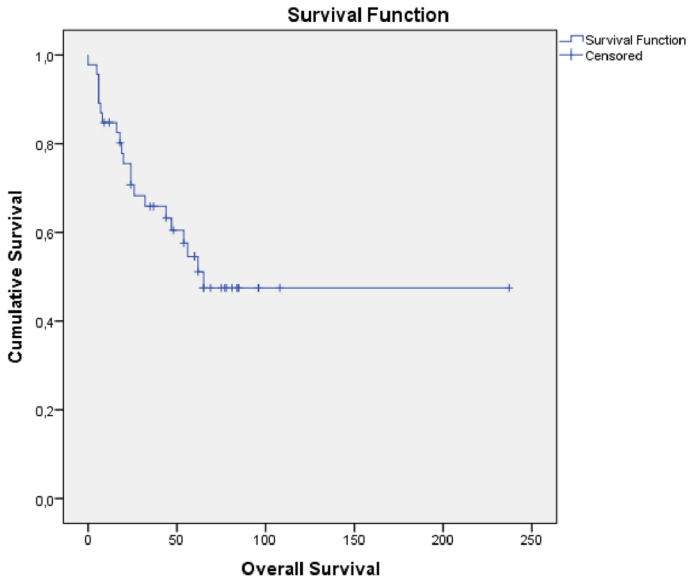

Figure 2. Entire Group disease free survival

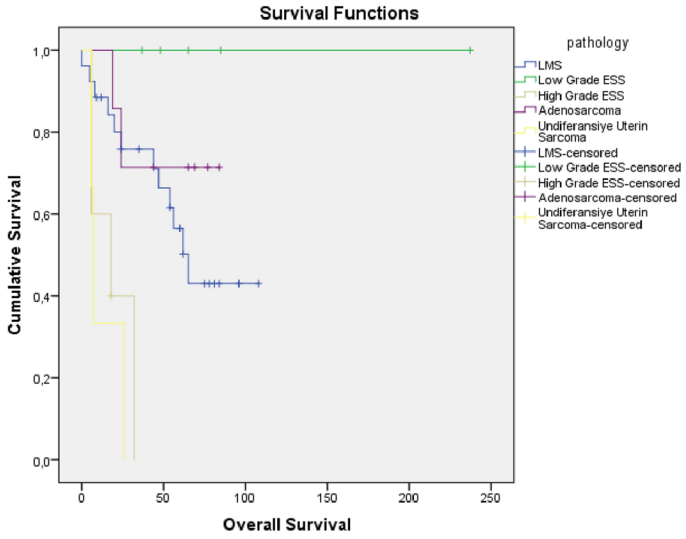

Figure 3. Subgroup's overall survival

Discussion

The histopathological diversity and rarity of uterine sarcomas complicate to reach a consensus on determining adjuvant therapies and prognostic factors. Our study showed that stage is the most important parameter affecting the prognosis in patients with US, whose treatment and follow-up are carried out in our clinic.

Although each of the subgroups has unique epidemiological, clinical and pathological features, the low incidence of these subgroups complicates their individual assessment. Uterine sarcomas typically present after the age of 40 years, with a reported mean age at diagnosis of 52 years[11]. Similarly, in our study, the mean age was 52.3±10.9 years, and more aggressive subtypes were observed with increasing years of age (LG-ESS: 44±4.6 years vs UUS: 63.6±10.7 years, p= 0.01). Consistent with the literature, abnormal uterine bleeding (menometrorrhagia+ abnormal uterine bleeding 54%, n= 26) was the most common symptoms in all subgroups. Moreover, the diagnosis was most often established by paraffin-section examination after the hysterectomy procedure (50%, n = 24) [6, 12]. In only 9 (47.3%) of 19 patients who underwent probe curettage procedure, malignancy diagnosis could be made in the preoperative period. In a study evaluating the histopathological results of 68 endometrial biopsy specimens in

152 LMS patients, Hinchcliff et al. reported that 51.5% of biopsy examinations resulted in a diagnosis of sarcoma, of which 35.5% showed a specific subtype[13]. The absence of a relationship between the levels of CA125 and the histological subtype, limits the use of tumor markers for differential diagnosis. While there are studies, which report that high level of CA125 is associated with extrauterine spread of the tumor, especially in LMS, there are no studies investigating the differences between subgroups [1]. In 62.5% of patients with LMS, the size of the tumor was> 7 cm, which was not significantly different from that of other sarcoma subtypes.

While non-visible tumor resection surgery was the main treatment modality in all US subgroups, there was a difference in the efficacy of adjuvant chemotherapy, hormone therapy, and radiotherapy among subgroups. A successful non-visible tumoral debulking was achieved in almost all patients in our study. The decision for adjuvant therapy for subgroups was made by a multidisciplinary team. In a study evaluating 259 LMS patients from 53 centers, Takehara et al. reported a significantly higher 5-year OS in stage-1 patients who received adjuvant chemotherapy compared to those who did not (67.8% vs 46.7%, P = 0.0461) [14]. However, the effect of radiotherapy on LMS could not be demonstrated in a phase 3 randomized controlled study [15]. While LG-ESS, which is characterized by late recurrences, was found sensitive to hormone therapy, it has been shown that chemotherapy and radiotherapy increase survival in HG-ESS [(time ratio (TR) (95% CI): 1.36 (1.17–1.58), p < 0.001) for chemotherapy and (TR (95% CI): 1.57 (1.32–1.87), p < 0.001) for radiotherapy] [9]. In adenosarcomas, it is recommended to decide on adjuvant treatment by evaluating age, sarcomatous overgrowth, myometrial invasion and lymph node involvement, which are the most important prognostic factors [16].

Despite all treatment modalities, USs have a very poor prognosis due to the high potential of locoregional and systemic metastasis. USs constitute 26% of deaths due to uterine corpus malignancies. Although OS could not be calculated in subgroups due to insufficient number of patients, the 5-year survival in low-grade ESS patients was 100%, whereas all UUS patients died. Studies in the literature have reported that prognostic factors include advanced stage and age, high grade and mitotic index. In our study, logistic regression analysis showed that stage was the only parameter affecting survival rates [17-19]. In a study of 73 patients with US, Barquet-Munoz et al. similarly identified stage as the most important independent risk factor affecting overall survival rate [20]. A study by Hosh et al. on the highest number (13,089) of US patients using the National Cancer Institute Surveillance, Epidemiology, and End Result (SEER) database, reported that older age, black race, advanced tumor grade, and stage were associated with worsened survival, however, 53% of this study group consisted of carcinosarcoma patients [21].

Regarding the evaluation of subgroups, a study on 208 patients with LMS, which constitutes 1-2% of all uterine malignancies, reported tumor grade and stage as prognostic factors [22]. However, D'Angelo et al. reported that tumor size and mitotic index are significant prognostic factors according to univariate (p = 0.018 and p = 0.003, respectively) and multivariate (p = 0.006 and p = 0.001) analyzes [23]. Multivariate analysis in a study of 165 patients with AS showed that the sarcomatous component, lymphovascular invasion, age, and FIGO stage are among significant prognostic factors affecting OS and DFS [24]. In a study, which included the highest number of patients with LG-ESS and HG-ESS by using the 1998-2013 records of National Cancer Database, negative prognostic factors have been reported as increased age and tumor size in LG-ESS, and additionally distant or nodal metastasis, neglect of lymphadenectomy, and pathologically positive surgical margins in HG-ESS. However, the stage was not included in the evaluation [9].

Our study presents US patients diagnosed, treated and followed up by the same gynecological oncology team in a single reference center in a short period of time, which ensures the formation of a homogeneous patient group. Similar to many studies in the literature, the most important limitations of the study are the inclusion of retrospective data and the limited number of patients with US.

As shown in our study, stage is the most important prognostic factor for USs. Randomized controlled trials (RCTs) are needed to investigate the effects of different histopathological features and diagnostic and therapeutic modalities on prognosis in USs, which have many unknown aspects regarding diagnosis, prognosis and treatment. However, difficulty of conducting RCTs in extremely rare subgroups underlines the importance of multicenter studies or reviews that include studies presenting experiences similar to our study.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
The authors declared that this study has received no financial support.

Ethical approval
This study was reviewed and approved by the local Research and Ethics Committee of the University (Project no: KA20/292) and in accordance to the Declaration of Helsinki.

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