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Research Article

The Prognostic Benefit of Early Postoperative Radiotherapy and Diagnostic Value of Serologic Markers on Women with Uterine Sarcoma and Carcinosarcoma

Eva Meixner[1-3*], Philipp Hoegen[1-3], Laila König[1-3], Elisabetta Sandrini[1-3], Robert Wolf[1-3], Laura L. Michel[3,4], Katharina Smetanay[3,4], Carlo Fremd[3,4], Andreas Schneeweiss[3,4], Jürgen Debus[1-3,5,6], Juliane Hörner-Rieber[1-3,6]

[1]Department of Radiation Oncology, University Hospital Heidelberg, Im Neuenheimer Feld, Heidelberg, Germany

[2]Heidelberg Institute of Radiation Oncology (HIRO), Heidelberg, Germany

[3]National Center for Tumor diseases (NCT), Im Neuenheimer Feld, Heidelberg, Germany

[4]Department of Gynecology and Obstetrics, Heidelberg University Hospital, Heidelberg, Germany

[5]Heidelberg Ion Therapy Center (HIT), Im Neuenheimer Feld, Heidelberg, Germany

[6]Clinical Cooperation Unit Radiation Oncology, German Cancer Research Center (DKFZ), Im Neuenheimer Feld, Heidelberg, Germany

[*]**Corresponding author:** Eva Meixner, Department of Radiation Oncology, Heidelberg University Hospital, Im Neuenheimer Feld 400, 69120 Heidelberg, Germany

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Abstract

Introduction: Women with uterine sarcoma represent a rare heterogenous group with unproven evidence regarding the optimal adjuvant treatment. We aimed to evaluate outcomes and the impact of postoperative radiotherapy (RT).

Methods: We retrospectively identified 51 patients, treated with curative adjuvant pelvic radio(chemo)therapy for carcinosarcoma (n=30), leiomyosarcoma (n=14) and endometrial stromal sarcoma (n=7) between 2001-2021. Blood counts and serologic markers were documented prior to surgery, pre- and post-RT.

Results: With a median follow-up of 34.7 months, overall survival (OS) 1-, 2- and 5-year rates were 89.9%, 73.3% and 51.7%, respectively, and significantly inferior with positive nodal and resection status, cervical and parametrial infiltration, with higher age and FIGO-stage. A shorter time interval from surgery to RT and normal preoperative leukocyte counts were identified as significantly favorable. Distant control (DC) rates were 84.0% and 60.7% and local control (LC) were 93.7% and 88.2% for 1 and 5 years, respectively, and significantly inferior with a higher FIGO stages, positive resection margins and serosal involvement. DC was poor for cervical infiltration, positive nodal status and with higher Glasgow-Prognostic-Scores. Treatment caused strong declines in leukocyte and hemoglobin levels; however, only moderate toxicity was observed (CTCAE grade <4).

Conclusion: RT shortly (≤8 weeks) after hysterectomy was well tolerated achieving efficient LC, but with a significant decrease in blood counts. This study confirms the poor OS of uterine sarcoma due to high failures in DC and shows evidence for the correlation of preoperative leukocyte count and pre-RT Glasgow-Prognostic-Score for prognosis.

Keywords: Uterine neoplasm; Blood counts; Glasgow Prognostic Score; Nutritional Index; HDR brachytherapy; Sequential radio-chemotherapy; Hematotoxicity

Abbreviations: 3D: 3-Dimensional; BMI: Body Mass Index; BT: Brachytherapy; CI: Confidence Interval; CRP: C-Reactive Protein; CTCAE: Common Terminology Criteria For Adverse Events; DC: Distant Control; EBRT: External Beam Radiotherapy; EQD2: Equivalent Dose In 2 Gy Fractions; FIGO: International Federation Of Obstetrics and Gynecology; GPS: Glasgow Prognostic Score; HR: Hazard Ratio; IMRT: Intensity-Modulated Radiotherapy; LC: Local Control; LDH: Lactate Dehydrogenase Enzyme; NI: Nutritional Index; OS: Overall Survival; RT: Radiotherapy; SIRI: Systemic Inflammation Response Index

Introduction

Uterine malignancies represent the fourth most common cancer in women with rising death rates between 2011 and 2015 of about 2% per year and an increasing number of carcinosarcoma among endometrial cancers [1-3]. Within this, uterine sarcoma is rare and accounts for only 3-7% of the uterine neoplasms mostly affecting elderly women aged over 50 years [4-7]. From a pathological view, up to the year 2009, the most common histologic subtypes of uterine sarcoma were carcinosarcoma (50%, also known as malignant mixed Müllerian tumor), followed by leiomyosarcoma (30%), endometrial stromal sarcoma (15%) and adenosarcoma [5,7]. Over time, histologic classification has evolved with emerging integration of molecular subtyping, and the International Federation of Obstetrics and Gynecology (FIGO) 2009 re-classification [7,8] of carcinosarcoma currently considers it to be nearer to metaplastic carcinoma than sarcoma due to epithelial to mesenchymal transition9.

For primary curative treatment, surgery with radical hysterectomy and bilateral salpingo-oophorectomy without tumor rupture provides the cornerstone of curative therapy [10]. However, there is little evidence regarding the optimal adjuvant treatment as well as high-risk factors as prospective data are sparse. Adjuvant oncologic regimens vary broadly with little consensus on the benefits of the addition of adjuvant radiotherapy (RT) or chemotherapy to optimize oncologic outcome and the application of systemic therapy regimens for improvement of the disease-free survival remains controversial [11-14]. The same debate is ongoing about postoperative radiotherapy: Prior studies showed a significant reduction in the risk of locoregional failure with superior 5-year local control (LC) rates of 87% and 5-year disease-specific survival after adjuvant RT as well as superior overall survival (OS) rates for uterine carcinosarcoma [15-19]. Further, brachytherapy (BT) added therapeutic value to the treatment of uterine sarcoma as it allows for better sparing of the surrounding tissue while maintaining high doses with conformal applicators and improving LC efficiently for 5-year rates of up to 91% [20]. However, even in the multimodal treatment of uterine sarcoma, the OS remains poor with 5-year rates of 25 – 41% [5,6,15,21] and the role of postoperative RT has been questioned by other studies in early stages for not showing improvement of oncologic outcome or LC. Until now, there have been heterogenous findings of prognostic clinical or pathological high-risk markers. Large tumor sizes, higher stages, an older age, adnexal spread, lymph node metastases, deep myometrial invasion or lymphatic vascular involvement represent the most common forms associated with a poorer outcome [4-6,16,17,22].

Overall, current research has shed more light on the identification of biomarkers which are argued to reflect meaningful factors within the immune system's reaction to carcinogenesis and treatment response. While the presence of such gene-based biomarkers as tumor suppressor gene p53 in endometrial cancer has been shown to be correlated with worse outcomes [23], evidence is lacking for the impact of blood-based serologic markers and changes of laboratory data during treatment, and none have yet been implemented in clinical routine.

Given this lack of data for uterine sarcoma, we aimed to analyze oncologic outcomes and treatment-related toxicity as well as to identify serologic inflammatory prognostic markers and indices and their changes during treatment in the adjuvant setting with radiotherapeutic approaches.

Materials and Methods

Patient and treatment characteristics

Between March 2001 and June 2021, 86 women with uterine sarcoma were treated with RT at a single center. Metastasized patients or palliative treatment settings were excluded, leading to the identification of fifty-one women who received curative postoperative pelvic RT for their primary lesion with upfront hysterectomy. This retrospective analysis was approved by the local ethics committee (S-453/2021). Patient demographic and treatment as well as pathological and surgical data were reviewed and included the results of clinical examinations or radiological reports and oncologic staging according to the FIGO classification of 2018 [7,24] for uterine sarcoma and endometrial carcinoma for carcinosarcoma.

Radio(chemo)therapy

Recommendation for oncologic therapy was pre- and postoperatively discussed in an interdisciplinary tumor conference. The indication for adjuvant RT or radio-chemotherapy and the application of the sequence after upfront radical hysterectomy was defined individually for each patient according to risk factors, pathological criteria and clinical performance status as well as limiting comorbidities. Six cycles of sequential chemotherapy

with carboplatin and paclitaxel were intended for selected cases. The application and monitoring were incumbent upon the local gynecologic oncologists. Pelvic RT was ap-plied once daily, using external beam radiotherapy (EBRT) with 3-dimensional conformal (3D) or intensity-modulated RT (IMRT) techniques and 6 to 23 MV photon linear accelerators. The delineation of the clinical target volume was extrapolated from contouring guidelines from endometrial carcinoma [25,26] and adapted to each's patient specifics including a risk-adapted length of the vagina, the vaginal cuff, parametrial and paravaginal compartments as well as regional lymph nodes, including the external, internal and common iliac up to the bifurcation of the aorta. Taking into account the variability of irradiation techniques used, individual organ movements or the use of an internal target volume, a varying margin of 0.5 to 1.5 cm was applied for the planning target volume. A vaginal cuff high-dose-rate (HDR) brachytherapy with Iridium-192 was used for dose escalation with a single or multichannel applicator at a prescription depth of 5mm. For better comparison of total values, base and boost doses were calculated and summed to an equivalent dose in 2 Gy fractions (EQD2). An α/β ratio of 10 was applied for the tumor and the following linear quadratic model was used:

EQD2Gy = fractional dose x number of fractions x (fractional dose + a/ß) / (2Gy+ a/ß).

Prognostic scores, blood counts and serologic markers

Values of blood counts and serologic markers were documented at three timepoints: preoperatively for baseline, prior to the start and at the end of RT. The assessed parameters included leukocyte (norm: 4 – 10 /nl) and platelet counts (norm: 150 – 440 / nl) as well as hemoglobin levels (norm: 12 – 15 g/dl). Further, serum albumin (norm: 30 – 50 g/l), lactate dehydrogenase enzyme (LDH) (norm: < 248 U/l) and C-reactive protein (CRP) levels (norm: < 5 mg/l) were assessed. We calculated the scores of the commonly used Nutrition-al Index (NI = Albumin/CRP) [27] as well as the Glasgow Prognostic Score (GPS) [28], grouping elevated CRP (≥10 mg/l) and hypoalbuminemia (<35 g/l) concentrations into three categories: 0 points for best prognosis with serum values within normal ranges, intermediate prognosis with 1 point in case of only one parameter in the normal range and poor prognosis for a score of 2 with elevated CRP and hypoalbuminemia. Pre- and post-RT body weight was assessed with calculation of the Body Mass Index (BMI (kg/m²) = weight / height x height).

Toxicity and oncologic follow-up

For each patient, the evaluation of treatment response included follow-up visits with clinical data, referring physician notes and radiology. Clinical outcome including OS, LC, and DC was assessed. OS was defined from the time of surgery until last contact or date of death. LC was considered until the occurrence of any tumor progression at the original site or local pelvic lymph nodes. DC was specified as the development of metastatic lesions occurring outside the pelvis. Acute (≤90 days) and late (>90 days) toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0).

Statistical analysis

Kaplan–Meier analysis and the log-rank test or Cox regression were utilized to calculate survival curves and further to compare subgroups, with a p-value of less than 0.05 being statistically significant. Uni- and multivariate Cox-proportional hazards ratios (HR) with a 95% confidence interval (95%CI) were used to assess the influence of cofactors. Patient and treatment characteristics as well as laboratory data were compared using the Mann–Whitney–U tests or Pearson Chi-Square tests for continuous or categorical data and ANOVA with repeated measures and the t-test, respectively. Receiver operating characteristic curve analysis was performed to calculate cut-off values. IBM statistical software was used for statistical calculations (versions 25 and 28, Armonk, NY, USA).

Results

Fifty-one women with a median age of 65 years met the inclusion criteria and were included in our study. The most common histology was carcinosarcoma (n=30, 58.8%), followed by leiomyosarcoma (n=14, 27.5%) and endometrial stromal sarcoma (n=7, 13.7%). About two-thirds of the patients were diagnosed with FIGO stage 1 or 2 (68.6%); the remaining high-stage cancers consisted of eight carcinosarcoma (FIGO stage 3), six leiomyosarcoma (FIGO 3: n=4, FIGO 4: n=2) and two endometrial stromal sarcoma (FIGO stage 3). All patients were treated in a curative setting with EBRT with a median dose of 50.4 (range: 43.2 – 58.8) Gy in 24 to 28 fractions. Vaginal surface brachytherapy boost was applied in 40 patients with a median boost dose of 10 (range: 5 – 20) Gy in 1 to 4 fractions. The summed cumulative median total EQD2 dose (α/β=10) was 62.06 (range: 44.25 – 74.56) Gy. Detailed patient and treatment characteristics are presented in Table 1.

Characteristics	Values (range or percentage)
Median age	65 (30 – 85) years
Menopausal status	
premenopausal	8 (15.7%)
postmenopausal	43 (84.3%)
Histological subtype	
carcinosarcoma	30 (58.8%)
leiomyosarcoma	14 (27.5%)
endometrial stromal sarcoma / (undifferentiated, low-grade, high-grade)	7 (13.7%) / (4, 2, 1)
FIGO stage	
1/2	35 (68.6%)
3/4	16 (31.4%)
Nodal status	
N+	7 (13.7%)
N0	44 (86.3%)
Cervical infiltration	
positive	14 (27.5%)
negative	36 (70.6%)
Parametrial infiltration	
positive	10 (19.6%)
negative	41 (80.4%)
Serosal infiltration	
positive	8 (15.7%)
negative	43 (84.3%)
Resection margin status	
R1	8 (15.7%)
R0	43 (84.3%)
Median Body-Mass-Index prior to RT	26.4 (18.2 – 47.8) kg/m²
Median Karnofsky performance score prior to RT	90 (60 – 100) %
Median time from surgery to start of RT	63 (26 – 230) days
Adjuvant treatment concept	
Radiotherapy only	33 (64.7%)
Sequential radiochemotherapy	18 (35.3%)
Sequence after hysterectomy	

RT prior to chemotherapy	7 (38.9%)
Chemotherapy prior to RT	11 (61.1%)
Median treatment time	40 (33 – 51) days
Brachytherapy boost	
yes	40 (78.4%)
no	11 (21.6%)
Extended field radiation	
Pelvic plus para-aortic region	3 (5.9%)
no extended field	48 (94.1%)
EBRT technique	
IMRT	33 (64.7%)
3D-RT	18 (35.3%)

3D-RT: 3-dimensional conformal radiotherapy, EQD2: equivalent dose in 2 Gy fractions, FIGO: International Federation of Obstetrics and Gynecology, IMRT: intensity-modulated radiotherapy, RT: radiotherapy

Table 1: Patient and treatment characteristics.

Overall survival

With a median follow-up of 34.7 (range: 6.6 – 201.5) months, OS rates for the overall cohort for 1, 2 and 5 years were 89.9%, 73.3% and 51.7%, respectively (Figure 1A). At the end of the observation period, 28 women (54.9%) were still alive, while the remaining women, consisting of 15 with carcinosarcoma, 6 with leiomyosarcoma and 2 with stromal sarcoma, had died after a median follow-up time of 21.0 (range: 6.6 – 62.5) months. In more detail, OS rates for 1, 2 and 5 years for carcinosarcoma were 96.4%, 66.8% and 42.0%, 85.7%, 78.6% and 57.1% for leiomyosarcoma, and 71.4% each for stromal sarcoma, respectively.

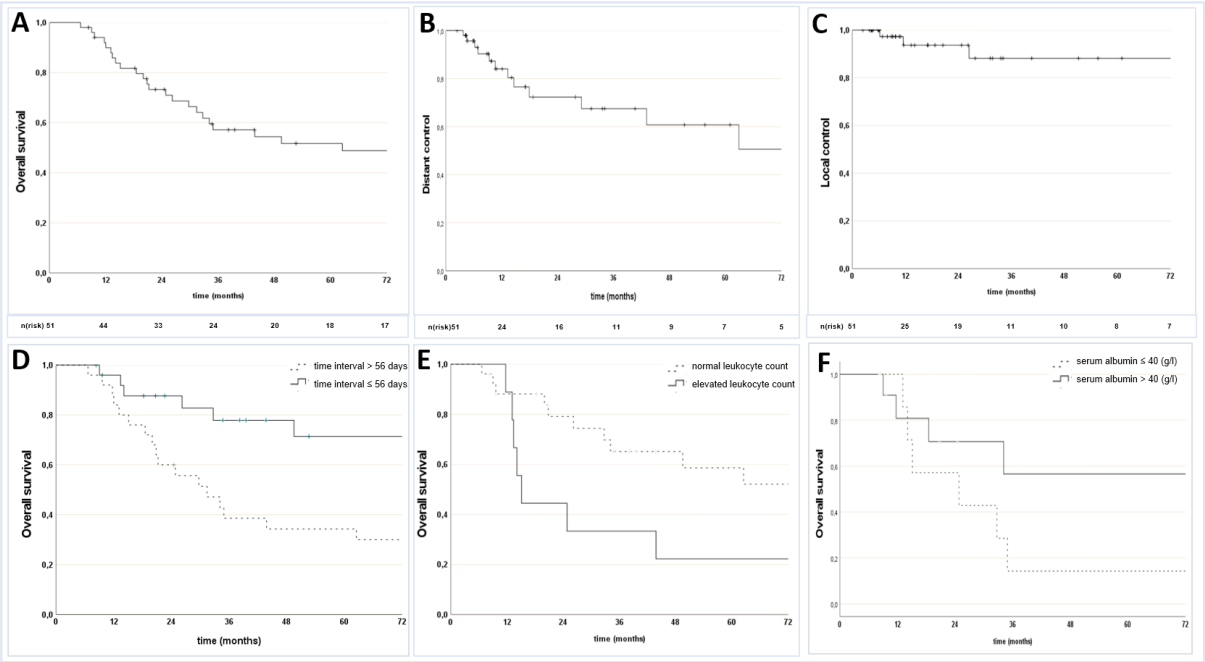

Figure 1: Kaplan–Meier curves for A) overall survival, B) distant control, C) local control, D) overall survival depending on the time interval (≤ 8 weeks vs. > 8 weeks) between surgery and the start of radiotherapy, E) overall survival depending on the leukocyte count (leukocytosis vs. normal ranges) prior to surgery, F) overall survival depending on pre-radiotherapy serum albumin levels (≤ 40 g/l vs. > 40 g/l). n(risk): number at risk.

Table 2 represents the findings of the univariate Cox proportional hazards ratio analysis. Inferior OS was significantly correlated to older patients (p=0.020), higher FIGO stages (p=0.026), positive regional nodal status (p=0.010), cervical (p<0.0001) and parametrial infiltration (p=0.023) and positive resection margins (p=0.001). Patients with a higher pre-RT Karnofsky performance score of 90 or 100% showed a trend of superior OS, without being statistically significant (p=0.052). Clinical and pathological factors of post- or premenopausal status, the Body Mass Index (normal vs. obese), a deep myometrial in-filtration or the presence of lymphangiosis or vascular hemangiosis did not influence the OS. Neither did treatment-related factors with the application of a BT boost, the RT technique (IMRT vs. 3D-RT), the overall RT treatment time, nor the use of chemotherapy or the sequence of adjuvant treatment regimen administration significantly influence OS.

While the time interval between chemotherapy and RT had no impact on oncologic outcome, OS was superior in patients with a shorter time interval from surgery to the start of radiotherapy (p =0.047), with a cut-off value of ≤8 weeks. (Figure 1D).

Multivariate analysis revealed that highly reliable factors for inferior prediction of prognosis for OS were: a higher age (p=0.015, HR 1.099, CI: 1.019 – 1.186), a higher FIGO stage (p=0.044, HR 0.179, CI: 0.034 – 0.956), positive resection margins (p=0.009, HR 50.316, CI: 2.691 – 940.928) and cervical infiltration (p=0.003, HR 24.806, CI: 3.014 – 204.160). A positive lymph node status only showed a trend for a poorer outcome in multivariate analysis (p=0.057, HR 8.834, CI: 0.935 – 83.504).

Characteristics	Overall survival		Distant control		Local control	
	HR 95%CI	p	HR 95%CI	p	HR 95%CI	p
Age	1.046 (1.007 – 1.087)	**0.020**	0.989 (0.937-1.004)	0.689	1.001 (0.896-1.117)	0.993
Menopausal status	2.732 (0.638-11.704)	0.176	0.280 (0.083-0.952)	**0.041**	25.739 (<0.1-40937240)	0.656
Body-Mass-Index	1.173 (0.485-2.833)	0.723	0.542 (0.161-1.820)	0.322	1.656 (0.150-18.300)	0.681

Karnofsky performance score	0.430 (0.183-1.008)	0.052	0.972 (0.208-4.548)	0.972	0.476 (0.043-5.270)	0.545
Preoperative leukocyte count	1.227 (1.082 – 1.393)	**0.001**	1.049 (0.900 – 1.223)	0.538	1.064 (0.762 – 1.485)	0.715
Pre-RT serum albumin	0.878 (0.771 – 0.999)	**0.048**	0.955 (0.840 – 1.087)	0.488	0.797 (0.606 – 1.048)	0.104
Pre-RT Glasgow-Prognostic-Score	0.989 (0.271 – 3.601)	0.986	5.845 (0.679 – 50.294)	**0.011**	0.103 (<0.1-100995)	0.747
FIGO stage	1.494 (1.050-2.125)	**0.026**	1.865 (1.128-3.083)	**0.015**	3.210 (1.066-9.669)	**0.038**
Tumor size	1.462 (0.520-4.106)	0.471	1.011 (0.989-1.034)	0.339	10.430 (0.933-116)	0.057
Histologic subtype	0.623 (0.324-1.200)	0.157	1.161 (0.581-2.319)	0.672	0,975 (0.233-4.074)	0.972
Nodal status	3.968 (1.389-11.336)	**0.010**	5.838 (1.626-20.963)	**0.007**	0.042 (<0.1-1251365)	0.719
Resection margin	4.520 (1.829-11.168)	**0.001**	7.828 (2.340-26.186)	**0.001**	22.298 (1.949-255.122)	**0.013**
Cervical infiltration	5.297 (2.163-12.975)	**<0.0001**	3.775 (1.111-12.835)	**0.033**	1645.623 (<0-1.925^12)	0.487
Parametrial infiltration	3.003 (1.160-7.774)	**0.023**	3.077 (0.921-10.283)	0.068	3.629 (0.328-40.117)	0.293
Serosal infiltration	2.125 (0.776-5.822)	0.143	3.964 (1.105-14.223)	**0.035**	12.274 (1.093-137.866)	**0.042**
Deep myometrial infiltration	1.322 (0.490-3.566)	0.581	33.698 (0.145-7826)	0.206	28.826 (<0.1-5742730)	0.589
Lymphangiosis	1.028 (0.395-2.678)	0.955	1.919 (0.422-8.723)	0.399	1.491 (0.135-16.455)	0.744
Vascular hemangiosis	0.710 (0.232-2.175)	0.549	4.126 (0.828-20.575)	0.084	2.316 (0.207-25.965)	0.496
RT vs. radiochemotherapy	0.523 (0.192-1.422)	0.204	0.958 (0.302-3.034)	0.942	0.663 (0.059-7.401)	0.738
Adjuvant sequence of RT and chemotherapy	1.481 (0.781-2.805)	0.229	1.478 (0.618-3.532)	0.379	0.929 (0.244-3.547)	0.915
Time interval between chemotherapy and RT	0.978 (0.930-1.029)	0.390	0.965 (0.907-1.028)	0.270	0.955 (0.820-1.112)	0.553
Time interval between surgery and start of RT	0.989 (0.979-1.000)	**0.047**	0.989 (0.973-1.004)	0.145	1.002 (0.985-1.019)	0.838
Brachytherapy (yes vs. no)	1.189 (0.439-3.217)	0.733	0.455 (0.143-1.452)	0.183	0.159 (0.014-1.771)	0.135
Cumulative dose EQD2 (α/β=10)	1.056 (0.987-1.131)	0.113	0.976 (0.901-1.058)	0.555	0.924 (0.800-1.091)	0.391
RT technique	0.950 (0.408-2.211)	0.906	0.787 (0.239-2.596)	0.694	0.027 (<0.000->755.1)	0.489
Duration of RT treatment	0.986 (0.895-1.085)	0.770	0.932 (0.804-1.082)	0.355	0.763 (0.532-1.095)	0.142

CI: confidence interval, , EQD2: equivalent dose in 2 Gy fractions, FIGO: International Federation of Obstetrics and Gynecology, HR: hazard ratio, RT: radiotherapy. A p-value of <0.05 was considered statistically significant

Table 2: Univariate analyses of prognostic factors.

Local and distant control

Distant progression-free survival was poor with 1-, 2- and 5-year DC rates of 84.0%, 72.3% and 60.7%, respectively (Figure 1B). After a median time of 13.3 (range: 3.7 – 121.3) months, 13 women (25.5%, n=4 carcinosarcoma, n=6 leiomyosarcoma, n=3 stromal sarcoma) were diagnosed with distant failures due to single (n=2) or multiple (n=11) metastases in the lung (n=6), liver (n=6), and lymph nodes outside the pelvis (n=6), bone (n=2), brain (n=2), peritoneum (n=2) and pleural (n=1). Three patients (5.9%, n=1 carcinosarcoma, n=2 leiomyosarcoma) experienced local failures after a median time of 11.5 (range: 6.2 – 26.4) months, resulting in 1-, 2-, and 5-year LC rates of 93.7%, 88.2% and 88.2%, respectively (Figure 1C).

The results of the univariate analysis of prognostic factors on LC and DC are listed in Table 2. LC was inferior for patients with a higher FIGO stage (p=0.038), positive resection margins (p=0.013) and serosal involvement (p=0.042). A larger tumor size (mm) led to a trend to inferior LC, but without reaching statistical significance (p=0.057).

Distant control was identified to be worse for premenopausal women (p=0.041) and for patients with a higher FIGO stage (p=0.015), positive nodal status (p=0.007), cervical infiltration (p=0.033), positive resection margins (p=0.001) and serosal involvement (p=0.035). Patients with the presence of parametrial infiltration only showed a trend of slightly inferior distant control (p=0.068).

Toxicity and prognostic blood values

Preoperative blood values were assessed with a median time of 2 (range: 0 – 18) days prior to surgery, 5 (range: 0 – 20) days prior to RT and 4 (range: 0 – 16) days at the end of RT. Figure 2 shows the median values and quartiles of peripheral blood leukocyte and platelet counts and hemoglobin levels and their changes during the course of treatment. Absolute leukocyte counts (Figure 2A) were assessed to have changed significantly (p=0.021) at all three timepoints, with median preoperative leukocyte counts of 7.9 (4.1 – 24.4) (per nl) without the presence of leukopenia, median pre-RT leukocyte counts of 5.6 (3.5 – 16.2) (per nl) with six cases of leukopenia, and median post-RT leukocyte counts of 4.8 (3.0 – 9.2) (per nl) with nine women suffering from leukopenia, respectively. These significant effects were consistent even when patients with chemotherapy prior to RT were excluded. A leukocyte count that was not within normal ranges in nine patients with leukocytosis prior to surgery significantly reflected an inferior OS (p=0.001) (Table 2 and Figure 1E), while the same effect could not be shown for pre-RT (p=0.640) or post-RT (p=0.850) leukocyte levels.

The median preoperative hemoglobin levels were 13.1 (6.7 – 16.3) g/dl with anemia in 10 women, which decreased significantly after surgery (p=0.045) to a median pre-RT hemoglobin level of 12.5 (9.2 – 15.2) g/dl and anemia in 16 women. No significant changes during RT (p=0.591) were seen regarding the hemoglobin levels, resulting in a median post-RT hemoglobin level of 12.3 (9.2 – 14.9) g/dl with anemia in 20 patients (Figure 2B). Platelet counts (Figure 2C) did not change significantly after surgery or during RT (p=0.200) with median values of 286 (125 – 654) (per nl) prior to surgery, with one woman suffering from thrombopenia, a median value of 269 (129 – 551) (per nl) prior to RT and one case of thrombopenia and 253 (155 – 535) (per nl) post RT without thrombopenia. Of note, due to the retrospective nature of the study, preoperative blood values were not assessable in 12 patients. Transfusion of erythrocytes or platelets or granulocyte-stimulation factor were not administered during the course of RT.

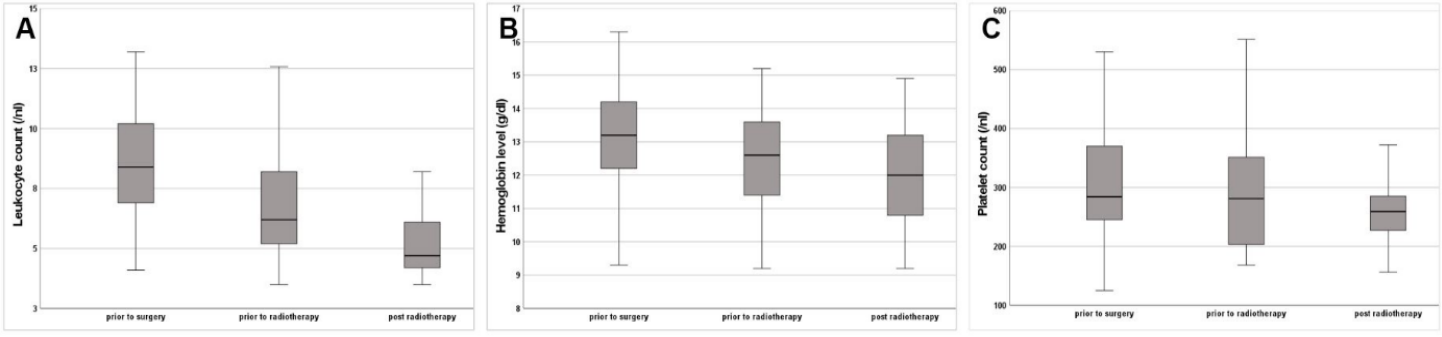

Figure 2: Boxplots with first and third quartiles, minimum, maximum and median values without statistical outliners of peripheral blood cell count with A) leukocyte count (per nl) B) hemoglobin levels (g/dl) C) platelet count (per nl) at three time points: prior to surgery, prior to radiotherapy and after radiotherapy.

Neither absolute values of hemoglobin (preoperative p=0.478/pre-RT p=0.869/post-RT p=0.232) nor platelets (preoperative p=0.343/pre-RT p=0.924/post-RT p=0.762) were found to be reliable significant biomarkers for the prediction of OS at any of the three timepoints.

Within the assessed serologic markers, the pre-RT albumin levels were significantly (p=0.048, Table 2) correlated to the prediction of a superior OS for cut-off values of above 40 g/l (Figure 1F), but not for DC and LC. Serum CRP (preoperative p=0.785/pre-RT p=0.990/post-RT p=0.378), albumin (preoperative p=0.410/post-RT p=0.271) or LDH (preoperative p=0.294/pre-RT p=0.163/post-RT p=0.174) levels did not predict OS. The same was assessed for the influence on the prediction of LC and DC.

The application of the Glasgow Prognostic Score showed a significant prediction (p=0.011, Table 2) of an inferior outcome for distant control with higher scores at the start of RT, while this could not be confirmed prior to surgery (p=0.918) or at the end of RT (p=0.273). The assessment of the Nutritional Index did not provide any prediction of OS prior to surgery (p=0.930), prior to RT (p=0.946) or after RT (p=0.627), nor did it provide any prognostic information on LC or DC.

In addition to the above-mentioned hematologic toxicity, only moderate toxicity to local organs at risk was observed, with no patients having documentation of high-grade toxicity (CTCAE grade ≥ 4). The most common acute toxicities were grade 1/2 including gastrointestinal disorders with diarrhea (n=18, 35.3%), abdominal pain (n=14, 27.5%), obstipation (n=3, 5.9%) and nausea (n=3, 5.9%), as well as genitourinary side-effects consisting of dysuria (n=17, 33.3%), urgency (n=5, 9.8%), nycturia (n=4, 7.8%), vaginal mucositis (n=7, 13.7%) and discharge (n=2, 3.9%) as well as fatigue (n=28, 54.9%).

Higher-grade acute toxicity (CTCAE grade 3) consisted of three cases with gastrointestinal disorders with severe diarrhea and electrolyte imbalance leading to unplanned inpatient treatment and a one-day interruption of RT treatment in one woman. The extent of toxicity was not significantly correlated to the RT technique used. Further, the body weight and BMI did not change significantly during the course of RT treatment and a median weight loss of -1.0 (range: -11.5 to +7.0) kilogram was assessed. All patients completed treatment with the intended dose as planned.

Discussion

Our study consists of a rare group of women with uterine sarcoma in the adjuvant setting who were treated with radiotherapy or radio-chemotherapy after hysterectomy. It provides new evidence on the optimal postoperative treatment sequence and the beneficial impact of RT applied early (≤ 8 weeks) after surgery and on the prediction of oncologic outcomes with the use of blood markers with preoperative leukocyte levels and pre-RT albumin and Glasgow-Prognostic-Score.

Therapeutic adjuvant recommendations for women with uterine malignancies vary broadly when uterine sarcoma is the underlying diagnosis. While uterine sarcoma consist of heterogenous histologic subtypes, given their aggressiveness and rarity, they have in many studies to date been grouped and analyzed together. Moreover, during the period under review, classification and affiliation for carcinosarcomas has changed from a sarcoma to an endometrial carcinoma entity with sarcomatous components [4,6]. Despite this, they are still accompanied by more aggressive behavior than high-risk endometrial cancers, leading to poor 3- and 5-year OS rates of 45% and 25-35% [29,30], respectively. Nonetheless, all subtypes of identified uterine tumors in our study suffered from extremely poor prognosis concerning OS and DC and improvement of the therapy is greatly needed.

With regard to local control, the application of adjuvant EBRT and BT in our study led to efficient 5-year LC rates of 88.2%, which is in line with prior studies with 5-year LC rates of 91% [20]. Even though the majority of subtypes in our study were carcinosarcomas, only one woman with this histology and two patients with leiomyosarcoma suffered from the overall three (5.9%) local failures. The local recurrence rate had previously been reported to be lower for carcinosarcoma than for leiomyosarcoma (53% vs. 71%) [4] which may be due to a superior benefit of RT [17]. While leiomyosarcoma was reported to have a poor prognosis of only 51% (stage 1) or 25% (stage 2) for 5-year OS [6], our study proved a comparable outcome of 57.1%, but of note, with 42.9% of leiomyosarcoma patients having a higher FIGO stage 3 or 4. Endometrial stromal sarcoma represents the most favorable sarcoma subgroup, with 5- and 10-year survival rates of 98% and 89% for stage 1 tumors, whereas high-grade and undifferentiated subgroups with the inferior outcome of 83% for the 5-year rate [6,31,32] also exist. Given their rarity, only seven women with a 5-year OS of 71.4% could be included, but this made subgroup analysis impossible.

When we analyzed the effectiveness of radiation on the improvement of LC, a time interval from surgery to the start of RT below 8 weeks was identified to be significantly correlated with superior OS. Kodiyan, et al. [33] showed similar results when RT was delayed, with inferior OS in the treatment of adjacent cancer patients with early-stage cervical cancer treated with upfront surgery, while subsequent chemotherapy could not build up enough of this advantage. Taking into mind that surgery is the most effective upfront local option, it is our guess that this trend of rapid RT initiation after surgery contributes to “complete” the local treatment, especially in cases with residual tumor.

Poor OS is mostly caused by failures in distant control as previously reported with 5-year rates of disease-free survival of 64% [30], which was comparably apparent in a quarter of the

women in our study. While the application of systemic therapy regimens re-mains controversial, current research and randomized studies analyze targeted therapy in the adjuvant treatment for the improvement of distant progression-free survival [11-13]. Consistent with previous studies [13], the lung was one of the most common organs for metastases. While OS remains poor, long-term survival after the resection of pulmonary metastases, especially in oligometastases of leiomyosarcoma, should be considered in reasonable cases as showing promising results [34].

The development of molecular profiles and immune modulation targeted therapies is increasingly dominating cancer treatment and diagnostics. The immune system represents a dynamic interplay of systemic and local pro- and anti-inflammatory markers. While there is only weak evidence for uterine sarcoma, such markers have been studied in other cancers including gynecological tumor entities. Chao, et al. [35] confirmed an in-crease in the preoperative–postoperative ratio of systemic inflammation response index (SIRI) with neutrophil, monocyte and lymphocyte counts correlated with inferior OS for uterine cervical cancer. Wang, et al. [36] hypothesized that the ratios of neutrophil to lymphocyte and platelet to lymphocyte were useful for the prediction of distant and lymph node metastases in uterine cervical cancer. For endometrial cancer, however, studies on biological tissue have shown an increased infiltration of immune cells (macrophages, neutrophils, B- and T-cells) into the tumor environment and abnormal isoenzyme shifts or elevated LDH values in the diagnostic of malignant uterine sarcoma with elevated CRP levels in leiomyosarcoma being associated with impaired OS, but these were assessed in the pretreatment situation only [37-41].

However, due to the rarity of the disease, only limited pre-treatment evidence exists concerning quantitative values in uterine sarcoma. In our retrospective study, we focused on serum albumin, CRP and LDH levels, the Glasgow Prognostic Score and Nutritional Index as well as absolute blood counts, with additional analyses of changes and prognostic value over the course of treatment and at various timepoints. Leukocytosis prior to surgery was a prognostic marker for inferior OS, which may reflect the pro-inflammatory tumor environment or expression of tumor-caused infection, whereas CRP levels were not proven as a significant factor at any timepoint. Further, the pre-RT GPS score was found to significantly reflect distant control, while pre-RT serum albumin, a component of the GPS score, was an important predictor for OS. Similar results were shown in cervical cancer by Nishida, et al. [42] during concurrent chemo-radiation for the prediction of outcomes in cervical cancer. While increased pre-RT serum LDH and CRP levels and pre-/post ratios were associated with inferior OS in the treatment of cervical cancer [43], our results did not confirm this for uterine sarcoma. The extrapolation and transfer of results of prognostic biomarkers, even in the case of adjacent cancers can therefore not be generalized and must be validated for each marker and entity in future research.

While the nutritional status and sarcopenia has been described to have an impact on survival in endometrial cancer [44], this could not be confirmed for the BMI in our cohort of uterine sarcoma. Since the absolute value of a single marker does not always give an indication of the prognosis, we further applied the Nutritional Index that had been previously described to go along with inferior oncologic outcomes in gastrointestinal and lung cancer [27], but neither a prediction of OS nor LC or DC was found.

Significant hematologic changes in the leukocyte counts after surgery and during RT as well as hemoglobin levels after surgery have been presented in our study. This decrease in leukocyte counts during RT was consistent even when patients with chemotherapy prior to RT were excluded and might most likely be explained by considering the results of prior studies in cervical cancer patients [45,46] with hematologic toxicity and decreases in neutrophil, lymphocyte and platelet counts due to bone irradiation that goes along with pelvic RT and similar target volumes. Our study could not confirm a significant reduction in platelet counts for uterine sarcoma, but of note, cervical cancer radiotherapy is ad-ministered with concurrent weekly cisplatin compared to RT only in uterine sarcoma, which might mostly likely have contributed to increased toxicity. Taking into account the given poor distant control in uterine sarcoma, the likelihood of upcoming required adjuvant hematotoxic systemic therapy is high. Special respect in the treatment of these women should therefore be given to minimize hematologic toxicity and bone marrow-sparing pelvic RT treatment with proposed dose-volume concepts of V40Gy<28% to pelvic and lumbal bone marrow [46].

Some limitations of the study include its limited number of heterogenous patients with uterine sarcoma, but this is a consequence of the rarity of the disease. Of note, definitive conclusions, especially for subgroup analyses and Kaplan–Meier estimates, must therefore be interpreted cautiously. Due to the retrospective design of the study, differential blood counts with absolute values of neutrophils or lymphocytes were not routinely assessed and preoperative values were only reliably available for a subset of women. Further, absolute values and normal ranges of blood marker or serum levels may vary among laboratories, which could influence the prediction possibility and the interpretation of ab-solute cut-off values. Lastly, as FIGO classification has changed several times during the time of observation, reporting and comparison of outcomes may differ [47].

Future research needs to focus on the interaction between tumor cells and the immune system and consecutive inflammation mediators that could be triggered by carcinogenesis itself or be treatment induced to provide more diagnostic or prognostic knowledge to clinical routine and implementation into cancer

therapy for uterine sarcoma. Given the heterogeneity of radiation techniques and treatment sequence regimens used to treat uterine sarcoma, further input to the sparse existing evidence in the adjuvant setting is urgently needed.

Conclusion

Postoperative radiotherapy in uterine sarcoma achieved efficient LC and even superior OS when RT was applied shortly (≤8weeks) after hysterectomy. Treatment was well tolerated with only low-grade RT-induced toxicity, but it resulted in a significant decrease in the leukocyte counts after surgery and during the course of RT. This study confirms classic risk factors and the poor OS of uterine sarcoma due to high failures in DC and offers new evidence of hematologic changes during RT and the impact of blood biomarkers for a significant correlation between preoperative leukocyte count, pre-RT Glasgow-Prognostic-Score and pre-RT serum albumin levels for the prediction of prognosis in uterine sarcoma.

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