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Multimodality treatment of undifferentiated pleomorphic soft tissue sarcoma of the extremity (eUPS) in the elderly

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ABSTRACT

Introduction: This subgroup analysis of undifferentiated pleomorphic soft tissue sarcoma of the extremity (eUPS) from the PERSARC collaborative group aimed to achieve a more personalized multimodality treatment approach for primary eUPS in elderly patients.
Material and methods: A multicenter retrospective study including primary high-grade eUPS surgically treated with curative intent between 2000 and 2016. Overall survival (OS), local recurrence (LR) and distant metastasis (DM) curves were calculated by Kaplan Meier analysis. Cox proportional hazard models were used to determine the effect of radiotherapy.
Results: From a total of 2511 patients with extremity soft tissue sarcoma (eSTS) of the PERSARC study collaborative; 703 patients with eUPS were included in this study. In elderly patients with eUPS 5-year OS, LR and DM were 35.4 (95%CI 29.3–42.8), 17.7 (95%CI 12.7–22.6) and 24.6 (95%CI 19.1–30.1). eUPS was significantly less treated with radiotherapy compared with other eSTS, especially in elderly patients. Patients with R1-R2 margins treated with radiotherapy had about half the risk of developing LR compared with patients treated without radiotherapy (HR = 0.454, p = 0.033).
Conclusion: Elderly patients with eUPS were less often treated with radiotherapy and showed higher LR. Nowadays, given an increasing life expectancy in elderly patients, multimodality treatment should be considered.

1. Introduction

Soft tissue sarcomas of the extremities (eSTS) are malignant tumours of mesodermal origin that constitute less than 1% of all malignant tumours [1]. Soft tissue sarcomas (STS) consist of more than 50 histological subtypes, which are all subsumed in the World Health Classification (WHO) of Tumours of Soft Tissue and Bone [2,3]. Malignant fibrous histiocytoma (MFH) was firstly described in the 1960's [4,5] and was considered to be one of the most common types of eSTS in adults [6–8]. In the 2002 WHO classification, MFH was declassified as a formal diagnostic entity and renamed to undifferentiated pleomorphic sarcoma (UPS) [9,10] Delisca et al.

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(2014) found no differences in oncologic outcome for sarcomas that remained in this unclassifiable UPS group as compared with the previously accepted MFH group [11].

UPS is one of the most common types of STS and accounts for approximately 10% of all adult STS [12] and one third of high-grade eSTS. UPS is diagnosed more often in elderly patients [13]. Due to the rarity of STS and the fact that there are more than 50 subtypes, most studies include all subtypes. This limits the interpretation of study results knowing that evidence indicates UPS has a poorer prognosis due to tumour characteristics such as deeper location, larger size and a high risk for local recurrence (LR) and distant metastasis (DM) compared with other STS. Therefore, this subtype may require a more individualized treatment approach [14–16].

Surgery in combination with radiotherapy (sporadically combined with chemotherapy in case of high-risk of development of metastasis) is the common therapy of choice for UPS, which is similar to the treatment of other STS [17]. Radiotherapy has a positive effect on local control but the effect of radiotherapy on overall survival (OS) remains under debate [18–20]. A recent paper concluded LR was an important predictor for OS in UPS of the extremities (eUPS). Radiotherapy and surgical margins were considered as predictors for local control. Surgical margin was also a prognostic factor for DM [14].

As eUPS most often is diagnosed in elderly, an individualized and balanced treatment plan for eUPS is crucial since research states that oncologic outcome in elderly patients with STS is worse and should be balanced to quality of life. Because the common opinion that elderly patients may poorly tolerate chemotherapy and radiotherapy remains, elderly patients are therefore often treated less aggressive [13,21–23]. Since the effect of chemotherapy in STS remains controversial and this treatment option is limited in elderly patients due to morbidity, toxicity and severe side effects this study will only focus on pre- and postoperative treatment with radiotherapy [24–27].

The aim of this study is to highlight one of the most common (and aggressive) subtypes of STS and compare patient and treatment characteristics of eUPS to eSTS from our international collaborative PERSARC database [28,29]. In addition, to achieve a more individualized and optimal treatment approach for primary, surgically treated eUPS in elderly patients, our secondary goal is to investigate the impact of age on chosen treatment strategies and its oncologic outcome.

2. Materials and methods

This multicenter study was centrally approved by the LUMC human subjects review board, and if applicable by local review boards abroad. The method of this study is based on our international database and has been published before [28,29].

2.1. Study population

In this study, patients (18 years or older) with histologically proven, primary high-grade soft tissue sarcomas of the extremities (eSTS) treated with curative intent were selected from one of the following collaborating sarcoma centers worldwide[(a-k)]. Patients after unplanned resection of the sarcoma undergoing re-resection in one of the collaborating centers were also included. Patients with LR or DM at presentation, patients receiving preoperative treatment other than radiotherapy or chemotherapy (e.g. isolated limb perfusion), patients who were censored or died before or at the day of surgery and intermediate malignancy tumours, Kaposi and paediatric sarcomas were excluded. In addition, patients of whom primary outcome measures, age or time-to-event data were missing were excluded. The guidelines of the European Society for Medical Oncology for STS follow-up (FU) were implemented in the collaborating specialized sarcoma centers[(a-k)] [30].

2.2. Study design

This is a retrospective observational cohort study. Existing prospective sarcoma databases (including documentation of clinic visits, operation reports, histology and radiographic reports) were used to collect clinical information retrospectively.

2.2.1. Variables

To achieve equal groups different age groups were divided as follows; young-aged patients: age $\leq$60 years, middle-aged patients: age 61–74 years and elderly patients: age $\geq$75 years.

Local recurrence was defined as the first clinical, radiological or pathological manifestation of tumour of the same histologic type within or contiguous to the previously treated tumour bed, 2 or more months after primary surgical treatment. DM was defined by clinical or radiological evident systemic spread of tumour outside the primary tumour bed, including nodal metastasis, 2 or more months after diagnosis. Margins were defined as follows: free (R0) when no residual tumour was found at the inked surface, marginal (R1) when microscopic residual tumour was found and intralesional (R2) when macroscopic residual tumour was detected.

See Appendix A for other variables based on our international database that has been published before [28,29].

2.2.2. Outcome

Overall survival, LR and DM were used as outcome measures.

2.3. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 25.0 [31]. $P < 0.05$ was considered statistically significant. The statistical program R version 4.0.2. was used for the competing risk analysis [32].

Descriptive statistics were used to summarize study variables by age group. For categorical or dichotomous variables absolute numbers and percentages within each group were reported. For continuous variables mean and standard deviation (SD) were reported in case of normally distributed data and median and interquartile range (IQR) were reported for non-normally distributed data. The groups were compared using the Chi-squared test or the Kruskal-Wallis test.

2.3.1. Oncological outcome

For different age groups, we retrospectively analysed OS, LR and DM by the Kaplan Meier (KM) method including 95% confidence intervals (CIs) and Log Rank test. The competing risk analysis with LR or DM as outcome and death as competing risk was used to model the time from surgery to developing a LR or DM. The effect of LR on OS and DM was analysed by using the Landmark approach [33]. In our study a landmark time of 24 months was chosen. Only patients who were alive and still in FU at landmark time were included in this analysis. At the landmark time patients were classified as LR in case they developed a LR within 24 months from date of surgery.

2.3.2. Treatment

Cause specific hazard ratios (HR) for the effect of radiotherapy on LR and DM were calculated by the Cox regression model.

Odds ratios (OR) for treatment with radiotherapy per age group were calculated by a binominal regression model.

3. Results

3.1. Study population

In this study cohort a total of 2511 patients with eSTS were analysed using data form 12 specialized Sarcoma centers participating in the PERSARC study group, including 703 patients with eUPS and 1808 patients with other eSTS. Twelve patients were excluded due to missing data.

Table 1 gives an overview of baseline patient characteristics of eUPS compared with other eSTS seen in our international data [29]. The mean age of patients with eUPS was 66 (SD 14.9) years at the date of surgery, this was significantly higher than the mean age for other eSTS of 59 (SD 17.6) years (Table 1).

eUPS were seen more often in males (55.6%), this was similar for other eSTS (54.3%). eUPS were significantly less often deep-seated (63.5%) compared with other eSTS (70.2%). Tumour size appeared to be smaller in eUPS compared with other eSTS, since tumour size in patients with eUPS averaged at 8.8 (SD 5.7) cm versus 9.1 (SD 5.6) cm in other eSTS, however this difference was not significant. Almost all eUPS (95.3%) were grade 3 tumours, in other eSTS this was 82.8% (Table 1).

3.2. Oncological outcome

3.2.1. Overall survival

The 5-year OS and 10-year OS for eUPS were 52.1% (95% CI 48.3–56.3) and 35.4% (95% CI 30.9–40.6), respectively. Patients who survived had a median FU of 65 (IQR 34–97) months. The 5-year OS and 10-year OS were significant (Log Rank: p = <0.001)

Table 1
Baseline patient characteristics undifferentiated pleomorphic sarcoma of the extremity (eUPS) compared with other soft tissue sarcoma of the extremity (eSTS).

	eUPS (*n = 703*)	**Other eSTS*** (*n = 1808*)	*p-value*
Gender			
Male	384 (54.6)	981 (54.3)	
Female	319 (45.4)	826 (45.6)	*0.880*
Missing	*0*	*1*	
Age *(mean,SD)*	66 (14.9)	59 (17.8)	*<0.001**
Depth			
Superficial	194 (36.5)	468 (29.8)	
Deep	337 (63.5)	1101 (70.2)	*0.004**
Missing	*172*	*239*	
Size (cm)			
< 5	158 (23.3)	444 (25.8)	
5-10	254 (37.5)	656 (38.1)	
>10	265 (39.1)	621 (36.1)	*0.118*
Missing	*26*	*87*	
Location			
Upper	190 (27.0)	428 (23.7)	
Lower	513 (73.0)	1379 (76.3)	*0.081*
Missing	*0*	*1*	
Margin (cm)	584 (87.6)	1496 (86.4)	*0.464*
R0	83 (12.4)	235 (13.6)	
R1-R2	*36*	*77*	
Missing			
Radiotherapy			
No	318 (46.5)	635 (35.7)	
Preop	84 (12.3)	234 (13.1)	
Postop	282 (41.2)	912 (51.2)	*<0.001**
Missing	*19*	*27*	
Chemotherapy			
No	612 (87.8)	1596 (89.2)	
Preop	19 (2.73)	46 (2.57)	
Postop	66 (9.47)	147 (8.22)	*0.327*
Missing	*6*	*19*	
Limb sparing			
Yes	600 (93.8)	1328 (91.1)	
No	40 (6.25)	129 (8.85)	*0.044**
Missing	*63*	*351*	
Grade			
II	33 (4.69)	275 (15.2)	
III	670 (95.3)	1497 (82.8)	
High-grade NFS	0 (0.00)	36 (1.99)	*<0.001**
Missing	*0*	*0*	
FU (months) *(median,IQR)*	41 (17–76)	45 (21–78)	*0.094*
Last known outcome			
No evidence of disease	290 (41.3)	860 (47.6)	
Alive with disease	19 (2.71)	89 (4.93)	
Alive, status unknown	30 (4.26)	115 (6.36)	
Dead of disease	85 (12.1)	327 (18.1)	
Dead of other cause	22 (3.13)	70 (3.87)	
Dead of unknown cause	257 (36.6)	347 (19.2)	*0.916*
Missing	*0*	*0*	

* Other eSTS included: leiomyosarcoma (n = 245), liposarcoma (n = 246), MF (n = 418), sarcoma not-otherwise-specified (n = 76), malignant peripheral nerve sheath tumour (n = 177), spindle cell sarcoma (n = 154), synovial sarcoma (n = 241), other sarcomas (n = 251). SD = standard deviation, NFS = not further specified, FU = follow-up, IQR = interquartile range.

lower in eUPS compared with other eSTS (Appendix Table B1. and Fig. B1).

3.2.2. Local recurrence

Of patients with eUPS 14.8% developed a LR. Median time to develop a LR was 12 (IQR 6–26) months. The 1-year LR and 5-year LR for patients with eUPS were 6.97% (95% CI 5.09–8.85) and 14.1% (95% CI 11.5–16.7), respectively. One year LR and 5-year LR were higher in eUPS compared with other eSTS, however this was not significant (Log Rank: p = 0.337, Appendix Table B1. and Fig. B2A).

With a landmark time at 24 months after surgery a total of 475 patients survived and were included whereof 44 (9.3%) of the patients had a LR within 24 months after surgery. Patients with eUPS who developed LR had significant lower OS compared with patients who did not develop LR (Log Rank: p = <0.001, Fig. 1A). Five-year OS decreased from 74.2 (95% CI 69.9–78.7) in patients without LR, to 30.0% (95% CI 18.6–48.4) in patients with LR.

Simultaneously, patients with eUPS who develop LR had significantly higher DM rates compared with patients who did not develop LR (Log Rank: p = <0.001, Fig. 1B). In patients with LR 5-year DM was 50.0 (95% CI 34.9–65.1). However, in patients without LR 5-year DM was only 21.3 (95% CI 17.5–25.2).

3.2.3. Distant metastasis

Of the patients with eUPS 30.1% developed DM. Median time to develop a DM was 11 (IQR 5–24) months. The 1-year DM and 5-year DM were 17.1% (95% CI 14.3–19.9) and 31.3% (95% CI 27.9–34.7), respectively. In patients with eUPS 1-year DM and 5-years DM were higher compared with other eSTS, however this was not significant (Log Rank: p = 0.772, Appendix Table B1. and Fig. B2B.).

3.3. Treatment

Patients with eUPS were significantly more often treated with limb-sparing surgery compared with other eSTS (p = 0.044, Table 1). Patients with eUPS were significantly less often treated with radiotherapy (p = <0.001, Table 1).

Patients with R1-R2 margins were more often treated with radiotherapy compared with patients resected with R0 margins (65.1% and 51.5%, respectively, Table 2).

Patients with R1-R2 margins treated with radiotherapy had about half the risk of developing LR (HR = 0.454, p = 0.033) compared with patients who were not treated with radiotherapy. The risk of developing DM was similar in both patients treated with or without radiotherapy (HR = 0.922, p = 0.818, Table 2).

Patients with R0 margins treated with radiotherapy had about 30% lower risk of LR (HR = 0.685) compared with patients who were not treated with radiotherapy, this difference was not significant (p = 0.113, Table 2). Patients with R0 margins treated with radiotherapy had about 30% higher risk on developing DM (HR = 1.348, p = 0.048, Table 2). However, when adjusting for age, depth, grade and size the risk on developing DM was only around 15% and this was not significant anymore (HR = 1.179 (95% CI 0.817–1.700), p = 0.379).

4. Age-related differences in eUPS

4.1. Age-related study population

At time of surgery, 220 (31.3%) of all patients with eUPS were aged 60 years or younger, 251 (35.7%) were aged between 61 and 74 years old and 232 (33.0%) were aged 75 years or older. Baseline characteristics by age groups are presented in Table 3.

As shown in Table 3, there were significant differences in grade, treatment with radiotherapy, treatment with chemotherapy and last known outcome in patients distributed in different age groups.

Elderly patients were significantly less often treated with radio- and chemotherapy. Only 42.7% of elderly patients were treated with radiotherapy compared with 58.5% in middle-aged and 59.2% in young patients (p = <0.001, Table 3). Even adjusted for size, depth and margin treatment with radiotherapy was less often administered to elderly patients compared with young patients (OR 0.589 (95% CI 0.363–0.954) and p = 0.032).

Less than one percent of elderly patients were treated with (postoperative) chemotherapy, compared with 18.0% of young patients (p=<0.001, Table 3).

4.2. Age-related oncological outcome

4.2.1. Overall survival

With an older age, the OS decreased significantly in patients with eUPS (Log-Rank: p = <0.001, Fig. 2 and Appendix Table B2). In elderly patients with eUPS the 5-year and 10-year OS were 35.4 (95% CI 29.3–42.8) and 12.9 (95% CI 7.99–20.9), respectively (Appendix Table B2).

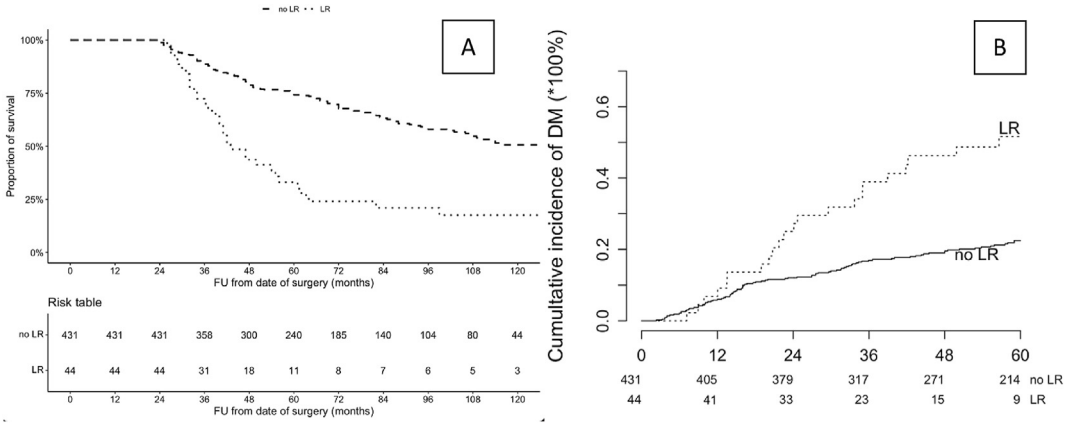

Fig. 1. A. Landmark analysis for overall survival (OS) in undifferentiated pleomorphic sarcoma of the extremity (eUPS) according to local recurrence (LR) status (Log Rank: p = <0.001). **B.** Landmark analysis with competing risk analysis for distant metastasis (DM) in undifferentiated pleomorphic sarcoma of the extremity (eUPS) according to local recurrence (LR) status (Log Rank: p = <0.001). FU = follow-up.

Table 2
Cause specific hazard of radiotherapy administration on local recurrence (LR) and distant metastasis (DM) stratified for surgical margin in undifferentiated pleomorphic sarcoma of the extremity (eUPS).

Margin	LR *(%)*	DM *(%)*	RTx *(%)*	LR	*p-value*	DM	*p-value*
n = 667				No RTx vs RTx		No RTx vs RTx	
R1-R2 *n = 83*	30 (*36.1*)	37 (*44.2*)	54 (*65.1*)	HR = 0.454 (95% CI 0.219–0.939)	*0.033**	HR = 0.922 (95% CI 0.463–1.837)	*0.818*
R0 *n = 584*	71 (12.2)	182 (*31.2*)	301 (*51.5*)	HR = 0.685 (95% CI 0.428–1.094)	*0.113*	HR = 1.348 (95% CI 1.003–1.837)	*0.048**

*R0 = no residual tumour, R1-2 = microscopic/macroscopic residual tumour, RTx = radiotherapy, LR = local recurrence, DM = distant metastasis.

Table 3
Baseline patient characteristics in undifferentiated pleomorphic sarcoma of the extremity (eUPS) by age group.

	≤ 60 years *(n = 220)*	**61–74 years** *(n = 251)*	**≥ 75 years** *(n = 232)*	*p-value**
Gender				*0.212*
Male	119 (54.1)	140 (55.8)	125 (53.9)	
Female	101 (45.9)	111 (44.2)	107 (46.1)	
Missing	*0*	*0*	*0*	
Age *(mean, SD)*	49 (9.83)	68 (3.97)	82 (4.82)	*<0.001**
Depth				*0.086*
Superficial	56 (33.9)	66 (33.0)	72 (43.4)	
Deep	109 (66.1)	134 (67.0)	94 (56.6)	
Missing	*55*	*51*	*66*	
Size (cm)				*0.362*
< 5	53 (25.5)	60 (24.5)	45 (20.1)	
5-10	82 (39.4)	82 (33.5)	90 (40.2)	
>10	73 (35.1)	103 (42.0)	89 (39.7)	
Missing	*12*	*6*	*8*	
Location				*0.309*
Upper	54 (24.5)	65 (25.9)	71 (30.6)	
Lower	166 (75.5)	186 (74.1)	161 (69.4)	
Missing	*0*	*0*	*0*	
Margin				*0.270*
R0	182 (88.8)	202 (84.9)	198 (88.4)	
R1-R2	21 (10.2)	36 (15.1)	26 (11.6)	
Missing	*15*	*13*	*8*	
Radiotherapy				*<0.001**
No	89 (40.8)	100 (41.5)	129 (57.3)	
Preop	31 (14.2)	33 (13.7)	20 (8.89)	
Postop	98 (45.0)	108 (44.8)	76 (33.8)	
Missing	*2*	*10*	*7*	
Chemotherapy				*<0.001**
No	164 (72.2)	217 (87.6)	231 (99.6)	
Preop	13 (5.96)	6 (2.43)	0 (0.00)	
Postop	41 (18.8)	24 (9.72)	1 (0.43)	
Missing	*2*	*4*	*0*	
Limb sparing				*0.590*
Yes	177 (95.2)	220 (93.6)	203 (92.7)	
No	9 (4.84)	15 (6.38)	16 (7.31)	
Missing	*34*	*16*	*13*	
Grade				*0.032**
II	17 (7.73)	7 (2.79)	9 (3.88)	
III	203 (92.3)	244 (97.2)	223 (96.1)	
Missing	*0*	*0*	*0*	
FU (months) *(median,IQR)*	54 (24–92)	43 (17–79)	31 (13–59)	*<0.001**
Last known outcome				*<0.001**
Alive with disease	7 (3.18)	7 (2.79)	5 (2.16)	
Alive, status unknown	13 (5.91)	12 (4.78)	5 (2.16)	
Dead of disease	23 (10.5)	37 (14.7)	25 (10.8)	
Dead of other cause	1 (0.45)	10 (4.0)	11 (4.74)	
Dead of unknown cause	54 (24.5)	75 (29.9)	128 (55.2)	
No evidence of disease	122 (55.5)	110 (43.8)	58 (25.0)	
Missing	*0*	*0*	*0*	

SD = standard deviation, FU = follow-up, IQR = interquartile range. R0 = no residual tumour, R1-2 = microscopic/macroscopic residual tumour.

4.2.2. Local recurrence

Elderly patients with eUPS developed more LR (19.0%) than younger age groups (middle-aged (14.7%) and young (10.5%) patients). Elderly patients had the longest median time to LR of 14 (IQR 7–33) months followed by 12 (IQR 4–23) months and 10 (IQR 6–28) months in middle-aged and young patients, respectively. Elderly patients with eUPS showed 1-year LR and 5-year LR of 7.76 (95% CI 4.32–11.2) and 17.7 (95% CI 12.7–22.6), respectively. In competing risk analysis, elderly patients with eUPS had significant higher 1-year LR and 5-year LR compared with younger age groups (Log Rank: p = 0.045, Fig. 3A and Appendix Table B2).

4.2.3. Distant metastasis

Elderly eUPS patients developed in only 24.6% DM, with the shortest time to DM of 8 (IQR 5–14) months. In middle-aged and young patients 35.5% and 36.4% developed DM, with median times

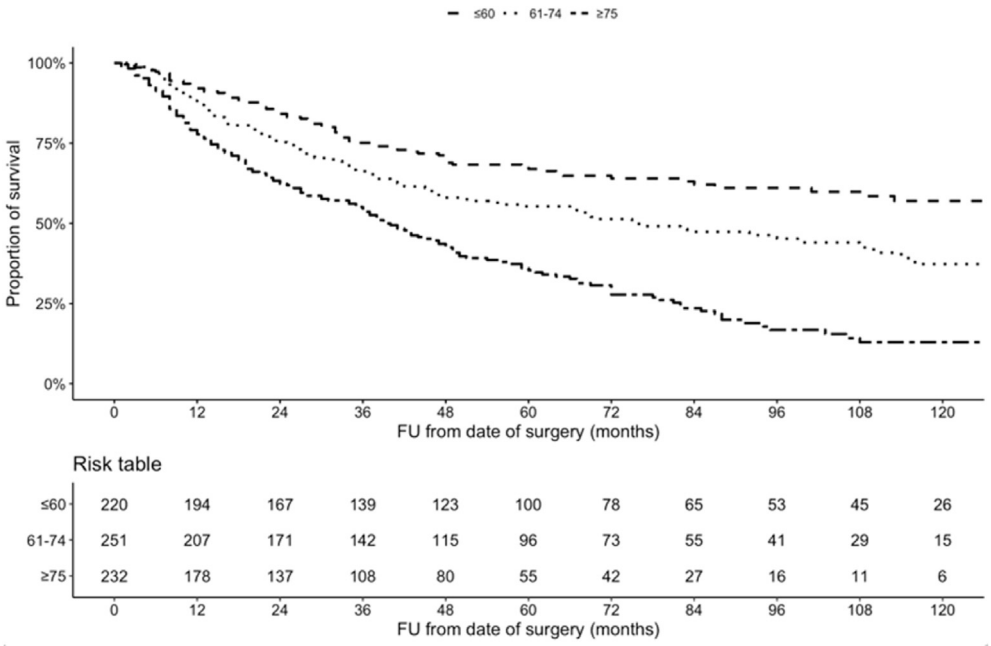

Fig. 2. Kaplan-Meier plot for overall survival (OS) in undifferentiated pleomorphic sarcoma of the extremity (eUPS) by different age groups (Log Rank: p = <0.001). FU = follow-up.

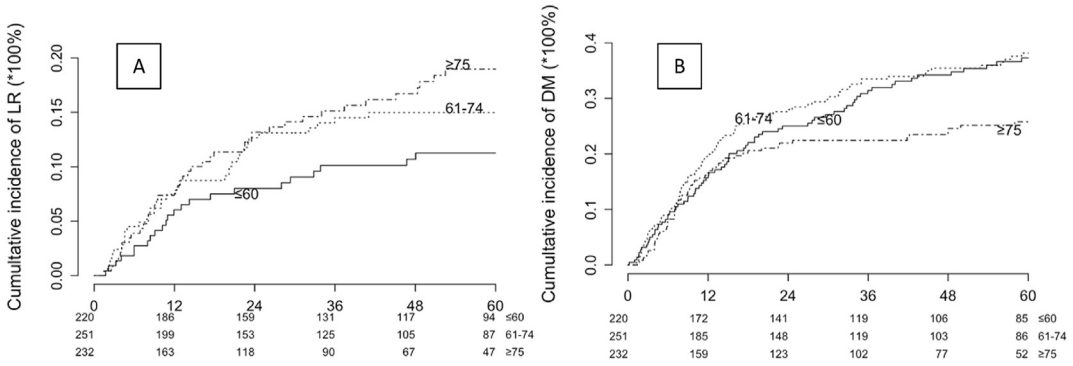

Fig. 3. A. Kaplan Meier plot with competing risk analysis for local recurrence (LR) in undifferentiated pleomorphic sarcoma of the extremity (eUPS) by different age groups (Log Rank: p = 0.045). **B.** KM plot with competing risk analysis for distant metastasis (DM) in eUPS by different age groups (Log Rank: p = 0.022).

to DM of 11 (IQR 6–24) and 15 (IQR 6–33) months, respectively. Elderly patients with eUPS showed 1-year and 5-year DM of 16.4 (95% CI 11.6–21.2) and 24.6 (95% CI 19.1–30.1), respectively. In competing risk analysis, elderly and young patients had almost similar 1-year DM, however, middle-aged patients had the highest 1-year DM. Five-year DM exceed in younger age groups, whereas older patients had significantly the lowest 5-year DM (Log Rank: p = 0.022, Fig. 3B and Appendix Table B2).

5. Discussion

In this large multicenter study on soft tissue sarcoma we highlighted eUPS, one of the most common subtypes of STS and formerly known as one of the most aggressive subtypes of STS due to high LR and DM [11,16,34–37]. We retrospectively analysed the oncological outcome of 703 patients with primary eUPS surgically treated with curative intent compared with 1808 patients with other eSTS from our international collaborative PERSARC database [28,29]. Our analysis aimed to better understand in which patients multimodal treatment with or without radiotherapy is indicated and whether age impacts chosen treatment strategies.

In contrast with the higher percentage of high-grade and larger tumours in eUPS compared to other eSTS DM and LR did not significantly differ in both sarcoma populations. OS was significantly lower in eUPS compared to other eSTS. Lower OS can be attributed to an older age of patients developing eUPS since age remains an important prognostic factor for OS [13,38]. This was further confirmed when dividing patients into different age groups which showed elderly patients had significant lower OS compared with younger age groups.

When dividing patients in different age groups we found that elderly patients with eUPS were less frequently treated with radiotherapy. Also elderly patients showed higher LR compared with younger patients, even when no significant differences were found in patient characteristics such as size, depth or margin. Higher LR in elderly patients can be attributed to less elderly patients treated with radiotherapy since treatment with radiotherapy is known as an important prognostic factor for LR [14].

Our results confirmed the benefits of radiotherapy after positive surgical margins as shown in previous literature [14,15]. In patients

with R1-R2 margins treated with radiotherapy the risk of developing LR halved.

Radiotherapy did not seem to have an effect on DM, however, in previous literature the effect of radiotherapy on DM remains debated [14,38]. In contrast, we found a significant higher risk of DM in patients with R0 treated with radiotherapy which could be explained by confounding bias due to unfavourable tumour characteristics in patients who were despite R0 resections treated with radiotherapy. When adjusting for age, depth, grade and size, this effect was not significant anymore.

Given an increasing life expectancy in elderly patients nowadays, a treatment with radiotherapy should (seriously) be considered to lower cancer-specific morbidity, improve local control and avoid debilitating tumours resulting in lower quality of life. Further research with data including co-morbidities, physical status and disease-specific survival should confirm this.

Limitations of this study are a retrospective design, resulting in patients with missing data that could introduce selection bias. Furthermore, we were unable to analyse disease-specific survival which could have given more insight in patients who actually died of eUPS. We also do not have data about co-morbidities and physical status of patients which could influence the decision of exposing (elderly) patients to a specific treatment (radiotherapy and/or chemotherapy). Last, we were not able to separate R1-R2 margins due to missing data, this could be important for analysing differences in the oncological outcome after treatment with radiotherapy in R1 versus R2 margins. Nevertheless, this multicenter study is the largest series examining primary surgically treated eUPS and gives a clear current update of the multimodal treatment and oncological outcome in eUPS as a continuation to previous literature about eUPS [11,16].

6. Conclusion

In conclusion, eUPS showed unfavourable biological features and lower OS compared with other eSTS. However, LR and DM did not differ even though eUPS was less treated with radiotherapy. Especially elderly patients with eUPS were less often treated with radiotherapy and also showed higher LR compared to younger patients. Nowadays, given our findings and an increasing life expectancy in elderly patients, treatment with radiotherapy should be considered.

Research data for this article

The data that has been used is confidential.

CRediT authorship contribution statement

Roos F. Bleckman: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft. **Ibtissam Acem:** Validation, Formal analysis, Investigation, Data curation, Writing – review & editing, Supervision. **Veroniek M. van Praag:** Conceptualization, Methodology, Validation, Investigation, Data curation, Writing – review & editing, Supervision, Project administration. **Desirée M.J. Dorleijn:** Writing – review & editing. **Cornelis Verhoef:** Resources, Writing – review & editing. **Yvonne M. Schrage:** Resources, Writing – review & editing. **Rick M.L. Haas:** Resources, Writing – review & editing. **Michiel A.J. van de Sande:** Conceptualization, Methodology, Validation, Formal analysis, Resources, Writing – review & editing, Supervision, Project administration. **the collaborative Persarc research group:** Resources, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

APPENDIX

A. Material and methods

A1. Variables

Survival was defined as the date of surgery to the time of death and, in case of survival, to the time of the last known FU date, which is based on the last contact with the department that is involved in the treatment of the eSTS. The same applies as for the last known outcome, unless the patient has died. LR was defined as the first clinical, radiological or pathological manifestation of tumour of the same histologic type within or contiguous to the previously treated tumour bed, 2 or more months after primary surgical treatment. Time to LR was defined as the date of first surgery to LR. DM was defined by clinical or radiological evident systemic spread of tumour outside the primary tumour bed, including nodal metastasis, 2 or more months after diagnosis. When no LR or DM was found, the date of the last clinical or radiological evolution was recorded. Tumour size was defined as the maximum diameter at pathologic analysis after the primary surgical treatment. When patients were treated with preoperative therapy tumour size defined as maximum diameter measured by CT or MRI before preoperative treatment. In patients who received preoperative therapy (radiotherapy and/or chemotherapy), tumour size was defined as the maximum diameter before treatment measured after radiological (MRI or CT) examination. Tumour grade was categorized as grade II or grade III based on established criteria of the Fédération Nationale des Centers de Lutte Contre le Cancer (FNCLCC), high-grade corresponds to grade II and III [39]. According to the World Health Organization (WHO) classification [40] 7 histological subtypes were retrospectively collected from pathology reports: leiomyosarcoma (LMS), liposarcoma (LPS), myxofibrosarcoma (MF), undifferentiated pleomorphic sarcoma (UPS), STS not-otherwise-specified (sarcoma-NOS), malignant peripheral nerve sheath tumour (MPNST), synovial sarcoma (SS) and other sarcomas. The category other sarcomas included adult rhabdomyosarcoma, angiosarcoma and other histological subtypes underrepresented in our data. Based on previous research [41], margins were defined as follows: free (R0) when no residual tumour was found at the inked surface, marginal (R1) when microscopic residual tumour was found and intralesional (R2) when macroscopic residual tumour was detected. Patients received FU by clinical and radiographic examinations, regularly scheduled as following: every 3–4 months in the first 2–3 years, every 6 months in the 3–4 years and yearly after 5 years. After 10 years of FU and without evidence of disease the FU ended for most of the patients.

B. Results

Table B1
Oncological outcomes for undifferentiated pleomorphic sarcoma of the extremity (eUPS) compared with other soft tissue sarcoma of the extremity (eSTS).

	eUPS		other eSTS	
	5-years	10-years	5-years	10-years
***Overall survival** (95% CI)*	52.1 *(48.3-56.3)*	35.4 *(30.9-40.6)*	61.1 *(58.7-63.6)*	44.8 *(41.5-48.3)*
	1-year	***5-years***	***1-year***	***5-years***
***Local recurrence** (95% CI)*	6.97 *(5.09-8.85)*	14.1 *(11.5-16.7)*	5.81 *(4.73-6.89)*	11.9 *(10.3-13.3)*
	1-year	***5-years***	***1-year***	***5-years***
Distant metastasis *(95% CI)*	17.1 *(14.3-19.9)*	31.3 *(27.9-34.7)*	15.8 (14.1–17.5)	29.9 *(27.9-34.7)*

CI = confidence interval.

Table B2
Age-related differences in oncological outcome for undifferentiated pleomorphic sarcoma of the extremity (eUPS).

	5-year OS (95% CI)	1-year LR (95% CI)	1-year DM (95% CI)
Young	66.9 (60.6–74.0)	5.91 (2.79–9.03)	15.5 (10.7–20.2)
Middle-aged	55.3 (49.1–62.3)	7.17 (3.79–10.4)	19.1 (14.2–24.0)
Elderly	35.4 (29.3–42.8)	7.76 (4.32–11.2)	16.4 (11.6–21.2)
	10-year OS (95% CI)	*5-year LR (95% CI)*	*5-year DM (95% CI)*
Young	57.0 (49.3–65.9)	10.5 (6.40–14.5)	34.1 (27.8–40.4)
Middle-aged	39.2 (31.5–48.7)	13.9 (9.65–18.2)	35.1 (29.1–41.0)
Elderly	12.9 (7.99–20.9)	17.7 (12.7–22.6)	24.6 (19.1–30.1)

LR and DM were both analysed by competing risk analysis with death as competing event. CI = confidence interval.

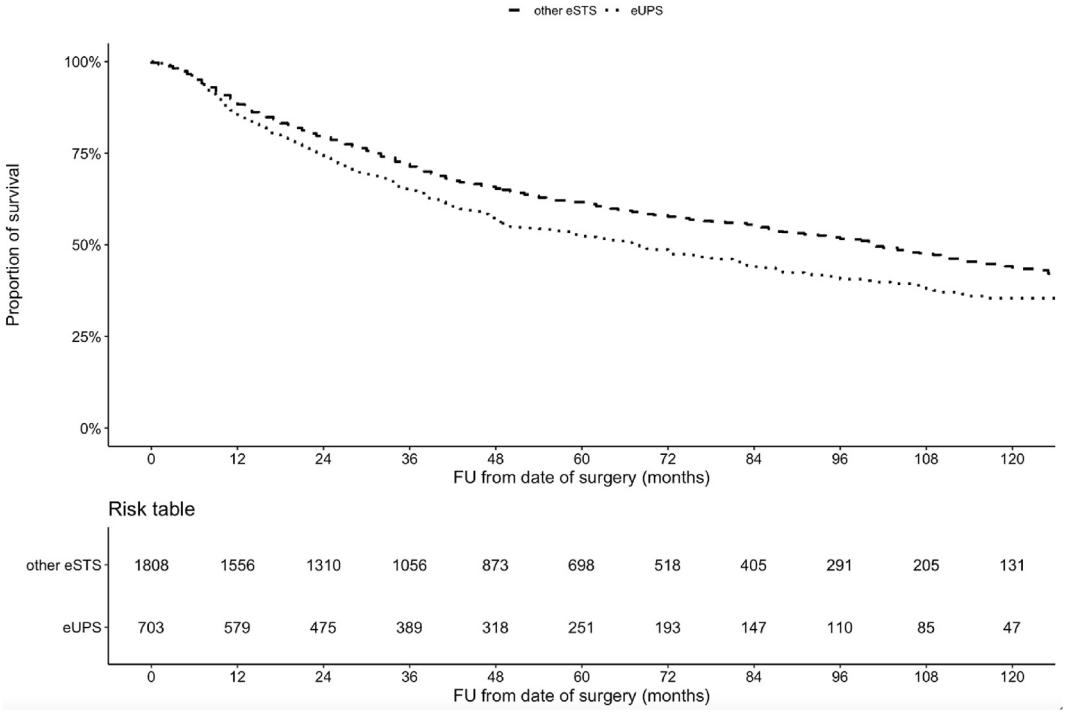

Fig. B1. Kaplan-Meier plot for overall survival (OS) in undifferentiated pleomorphic sarcoma of the extremity (eUPS) compared with other soft tissue sarcoma of the extremity (eSTS). Log Rank: p = <0.001.

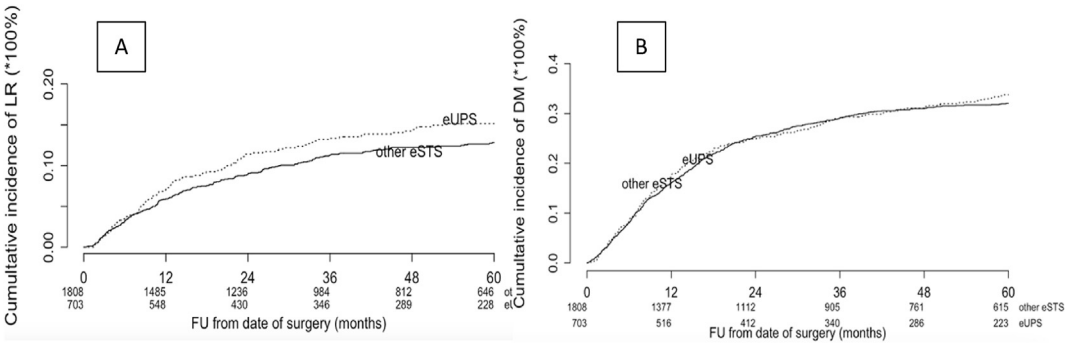

Fig. B2. A. Kaplan Meier plot with competing risk analysis for local recurrence (LR) in undifferentiated pleomorphic sarcoma of the extremity (eUPS) compared with other soft tissue sarcoma of the extremity (eSTS). Log Rank: p = 0.337. **B.** KM plot with competing risk analysis for distant metastasis (DM) in eUPS compared with other eSTS. Log Rank: p = 0.772.

References

[1] Boring CC, et al. Cancer statistics, 1993. CA Cancer J Clin 1993;43:7–26.
[2] Poremba C. [Soft tissue sarcomas: the role of histology and molecular pathology for differential diagnosis]. Verh Dtsch Ges Pathol 2006;90:59–72.
[3] Jo VY, Fletcher CD. WHO classification of soft tissue tumours: an update based on the 2013 (4th) edition. Pathology 2014;46:95–104.
[4] Kauffman SL, Stout AP. Histiocytic tumors (fibrous xanthoma and histiocytoma) in children. Cancer 1961;14:469–82.
[5] Ozzello L, et al. Cultural characteristics of malignant histiocytomas and fibrous xanthomas. Cancer 1963;16:331–44.
[6] Weiss SW, Enzinger FM. Malignant fibrous histiocytoma: an analysis of 200 cases. Cancer 1978;41:2250–66.
[7] Oda Y, et al. Reassessment and clinicopathological prognostic factors of malignant fibrous histiocytoma of soft parts. Pathol Int 2002;52:595–606.
[8] Bertoni F, et al. Malignant fibrous histiocytoma of soft tissue. An analysis of 78 cases located and deeply seated in the extremities. Cancer 1985;56:356–67.
[9] Fletcher CD. The evolving classification of soft tissue tumours - an update based on the new 2013 WHO classification. Histopathology 2014;64:2–11.
[10] Fletcher CDMBJ, Hogendoorn P, et al., editors. WHO classification of tumours of soft tissue and Bone (ed 4). Lyon, France: IARC Press; 2013.
[11] Delisca GO, et al. MFH and high-grade undifferentiated pleomorphic sarcoma-what's in a name? J Surg Oncol 2015;111:173–7.
[12] Henderson MT, Hollmig ST. Malignant fibrous histiocytoma: changing perceptions and management challenges. J Am Acad Dermatol 2012;67:1335–41.
[13] Hoven-Gondrie ML, et al. Worse survival in elderly patients with extremity soft-tissue sarcoma. Ann Surg Oncol 2016;23:2577–85.
[14] Kamat NV, et al. The outcome of patients with localized undifferentiated pleomorphic sarcoma of the lower extremity treated at stanford university. Am J Clin Oncol 2019;42:166–71.
[15] Goertz O, et al. The impact of surgical margins and adjuvant radiotherapy in patients with undifferentiated pleomorphic sarcomas of the extremities: a single-institutional analysis of 192 patients. Cancers 2020;12:362.
[16] Lehnhardt M, et al. MFH revisited: outcome after surgical treatment of undifferentiated pleomorphic or not otherwise specified (NOS) sarcomas of the extremities – an analysis of 140 patients. Langenbeck's Arch Surg 2009;394:313–20.
[17] Widemann BC, Italiano A. Biology and management of undifferentiated pleomorphic sarcoma, myxofibrosarcoma, and malignant peripheral nerve sheath tumors: state of the art and perspectives. J Clin Oncol 2018;36:160–7.
[18] Gingrich AA, et al. Neoadjuvant radiotherapy is associated with R0 resection and improved survival for patients with extremity soft tissue sarcoma undergoing surgery: a national cancer database analysis. Ann Surg Oncol 2017;24:3252–63.
[19] Beane JD, et al. Efficacy of adjuvant radiation therapy in the treatment of soft tissue sarcoma of the extremity: 20-year follow-up of a randomized prospective trial. Ann Surg Oncol 2014;21:2484–9.
[20] Callegaro D, et al. Impact of perioperative chemotherapy and radiotherapy in patients with primary extremity soft tissue sarcoma: retrospective analysis across major histological subtypes and major reference centres. Eur J Cancer 2018;105:19–27.
[21] Biau DJ, et al. Adverse effect of older age on the recurrence of soft tissue sarcoma of the extremities and trunk. J Clin Oncol 2011;29:4029–35.
[22] Balducci L. Geriatric oncology: challenges for the new century. Eur J Cancer 2000;36:1741–54.
[23] Fentiman IS, et al. Cancer in the elderly: why so badly treated? Lancet 1990;335:1020–2.
[24] Pervaiz N, et al. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. Cancer 2008;113:573–81.
[25] Adjuvant chemotherapy for localised resectable soft tissue sarcoma in adults. Sarcoma Meta-analysis Collaboration (SMAC). Cochrane Database Syst Rev; 2000, Cd001419.
[26] Woll PJ, et al. Adjuvant chemotherapy with doxorubicin, ifosfamide, and lenograstim for resected soft-tissue sarcoma (EORTC 62931): a multicentre randomised controlled trial. Lancet Oncol 2012;13:1045–54.
[27] Chen H, et al. Can older cancer patients tolerate chemotherapy? A prospective pilot study. Cancer 2003;97:1107–14.
[28] Rueten-Budde AJ, et al. Dynamic prediction of overall survival for patients with high-grade extremity soft tissue sarcoma. Surg Oncol 2018;27:695–701.
[29] Acem I, et al. Age-related differences of oncological outcomes in primary extremity soft tissue sarcoma: a multistate model including 6260 patients. Eur J Cancer 2020;141:128–36.
[30] Group Teesnw. Soft tissue and visceral sarcomas: ESMO clinical practice guidelines for diagnosis taf-uAOSie.
[31] Ibm Corp. Released. IBM SPSS statistics for windows, version 25.0. Armonk, NY: IBM Corp; 2017.
[32] R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2020. URL, https://www.R-project.org/.
[33] Van Houwelingen HC. Dynamic prediction by landmarking in event history analysis. Scand J Stat 2007;34:70–85.
[34] Stojadinovic A, et al. Analysis of the prognostic significance of microscopic margins in 2,084 localized primary adult soft tissue sarcomas. Ann Surg 2002;235:424–34.
[35] Zagars GK, et al. Prognostic factors for patients with localized soft-tissue sarcoma treated with conservation surgery and radiation therapy: an analysis of 1225 patients. Cancer 2003;97:2530–43.
[36] Callegaro D, et al. Development and external validation of two nomograms to predict overall survival and occurrence of distant metastases in adults after surgical resection of localised soft-tissue sarcomas of the extremities: a retrospective analysis. Lancet Oncol 2016;17:671–80.
[37] Pisters PW, et al. Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcomas of the extremities. J Clin Oncol 1996;14:1679–89.
[38] Vodanovich DA, et al. Predicting the prognosis of undifferentiated pleomorphic soft tissue sarcoma: a 20-year experience of 266 cases. ANZ J Surg 2019;89:1045–50.
[39] Guillou L, et al. Comparative study of the National Cancer Institute and French Federation of Cancer Centers Sarcoma Group grading systems in a population of 410 adult patients with soft tissue sarcoma. J Clin Oncol 1997;15:350–62.
[40] (WHO) WHO. WHO classification of tumours of soft tissue and bone. fourth ed. IARC; 2013.
[41] Wittekind C, et al. TNM residual tumor classification revisited. Cancer 2002;94:2511–6.