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Original Research

Age-related differences of oncological outcomes in primary extremity soft tissue sarcoma: a multistate model including 6260 patients

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Abstract ***Purpose:*** No studies extensively compared the young adults (YA, 18–39 years), middle-aged (40–69 years), and elderly (≥70 years) population with primary high-grade extremity soft tissue sarcoma (eSTS). This study aimed to determine whether the known effect of age on overall survival (OS) and disease progression can be explained by differences in tumour characteristics and treatment protocol among the YA, middle-aged and elderly population in patients with primary high-grade eSTS treated with curative intent.
Methods: In this retrospective multicentre study, inclusion criteria were patients with primary high-grade eSTS of 18 years and older, surgically treated with curative intent between 2000 and 2016. Cox proportional hazard models and a multistate model were used to determine the association of age on OS and disease progression.
Results: A total of 6260 patients were included in this study. YA presented more often after 'whoops'-surgery or for reresection due to residual disease, and with more deep-seated

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tumours. Elderly patients presented more often with grade III and larger (≥10 cm) tumours. After adjustment for the imbalance in tumour and treatment characteristics the hazard ratio for OS of the middle-aged population is 1.46 (95% confidence interval [CI]: 1.22–1.74) and 3.06 (95% CI: 2.53–3.69) in the elderly population, compared with YA.

Discussion: The effect of age on OS could only partially be explained by the imbalance in the tumour characteristics and treatment variables. The threefold higher risk of elderly could, at least partially, be explained by a higher other-cause mortality. The results might also be explained by a different tumour behaviour or suboptimal treatment in elderly compared with the younger population.

1. Introduction

Soft tissue sarcomas (STSs) are a group of rare heterogeneous tumours of mesenchymal origin with various histologic and clinical features. The estimated incidence of STS is less than 4.7 per 100,000 persons in Northern Europe per year [1]. STSs may occur in all age groups, with a relatively high incidence in patients younger than 40 years compared with other malignancies [1,2]. STS represent approximately 1–2% of all adult malignancies (2, 3) and 7–8% of all malignancies in adolescents and young adults (AYAs) [3,4].

In the past, clinical trials mainly focused on the middle-aged population, in which STS is the most prevalent [3], whereas the AYAs and elderly population remained underrepresented in these trials [5,6]. The lack of enrolment in clinical trials of the AYAs and elderly population limits our knowledge of tumour behaviour and effectiveness of STS management in these populations.

Several studies have shown relative lack of improvement in clinical outcomes in the AYA population compared with their older and younger counterparts (4, 7) and poorer disease-specific survival of the elderly patients compared to the younger counterparts [8]. With the increasing referrals for treatment of elderly patients with STS, as well as the lack of improvement in the AYA population, further evaluation of factors influencing outcome for the different age groups might help in the decision-making regarding treatment strategies for the different patient groups [4,7,9,10].

Therefore, the primary aim of this study is to evaluate differences in overall survival (OS) and disease progression among age groups of patients with a primary high-grade eSTS treated with a curative intent. The secondary aim is to determine whether potential differences in outcome can be explained by differences in tumour and treatment characteristics among the different age groups.

2. Methods

2.1. Study design and population

This is a retrospective multicentre study of surgically treated patients with primary high-grade eSTS. Local institutional ethics board approval was obtained before the study. Patients were identified from 21 participating specialized sarcoma centres or registries (Appendix A).

All patients with primary high-grade (FNCLCC II/III) eSTS of 18 years and older that were surgically treated with curative intent between 2000 and 2016 with correctly registered time-to-events were included. Patients undergoing re-excision after unplanned sarcoma excision were also included. Exclusion criteria were:

- presentation with local recurrence (LR) or distant metastasis (DM)
- intermediate malignancy tumours, Kaposi and paediatric sarcomas
- patients receiving (neo)adjuvant treatment other than radiotherapy (RTX) or chemotherapy (CTX) (e.g. isolated limb perfusion)
- patients who died or were censored at the day of definitive surgery
- patients of whom age or time-to-event data were missing.

2.2. Variables

Patient information, tumour characteristics, treatment-related variables and survival data were obtained from medical records or sarcoma registries. Age was determined as age at time of surgery. Patients were categorized into three age groups (YA: 18–39, middle-aged: 40–69, elderly: 70+). Size was measured as the maximum diameter of tumour mass on imaging-techniques or based on pathological report. The Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading-system was used for tumour grading. A tumour partially or entirely deep to the investing fascia was classified as deep. Histological subtypes were retrieved from pathology reports and were classified into 7 categories according to the World Health Organization classification [11]: leiomyosarcoma (LMS), liposarcoma (LPS), myxofibrosarcoma (MF), undifferentiated pleomorphic sarcoma and (pleomorphic) STS not-otherwise-specified (UPS/NOS), malignant peripheral nerve sheath tumour (MPNST), synovial sarcoma (SS) and other. The 'other'-category included angiosarcoma, adult rhabdomyosarcoma and other histological subtypes underpresented in our data.

A 'whoops'-surgery was defined as a surgical procedure in which the mass was assumed to be benign but final pathologic diagnosis after surgery showed an STS. Surgical margin was classified as R0 (negative, defined as no ink on tumour) or R1-2 (microscopically/macroscopically positive). No central pathology review for the diagnosis and surgical margin was performed in this study. Owing to the retrospective and multicentre nature of this study, it was not possible to centrally review 6260 eSTS cases. Because only expert centres were included in this study, we believe central review would not significantly improve the article to warrant such an effort. All centres generally adhered to the ESMO-guidelines for diagnosis, treatment and follow-up [12].

LR was defined as the first radiological evidence of malignant recurrence at or near the primary tumour bed. DM was defined as the first radiological or pathological evidence of recurrence at any other side outside the primary tumour bed. For the date of LR and DM, the date of tissue biopsy was used if the diagnosis was pathologically confirmed, otherwise the date of radiological examination was used.

End points of the study were OS, LR and DM.

2.3. Statistical analysis

All statistical analyses were performed in the statistical program R (version 3.6.3) [13]. Patient demographics and baseline characteristics were described with proportions for categorical variables and means with standard deviations or medians with interquartile ranges (IQRs). Differences in categorical variables were tested with the chi-square test or Fisher's exact test. Bonferroni-correction for differences in tumour and treatment variables between the age groups was used to account for multiple testing.

OS was defined as the time interval between definitive surgery and date of death or date of last follow-up. Time-to-LR and time-to-DM was defined as the time interval between definitive surgery and date of LR or DM, respectively, or date of last follow-up. Median survival was computed with the reversed Kaplan-Meier estimator. Kaplan-Meier plots for OS and cumulative incidence of LR (CILR) and cumulative incidence of DM (CIDM) plots were constructed to compare the YA, middle-aged and elderly age groups. The CILR and CIDM were estimated using competing risk analyses, with death as competing event. Differences in time-to-event outcomes were evaluated with the log-rank test or the Peto-Wilcoxon test if the proportional hazard (PH) assumption was violated. Missing values were imputed for the Cox PH models using multiple imputation (m = 20). Pooled estimates were computed using Rubin's rules.

A multistate model was built to assess the association between age and disease progression. A multistate model is an extension of competing risk analyses, in which transitions to and from intermediate events are modelled [14]. Fig. 1 depicts the multistate model used in this study. Every patient starts in the initial state after definitive surgery, alive with no evidence of disease (ANED). A patient stays in this state until disease progression, death or censoring. If a patient first develops a LR and afterwards a DM, the patient will move from ANED to LR to DM. If a patient first develops a DM and afterwards a LR, the patient will move from ANED to DM and remains in DM. If a patient is diagnosed with a LR and DM simultaneously (synchronous relapse) the patient will move directly to the DM-state.

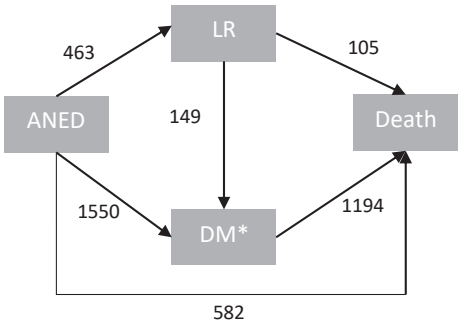

Fig. 1. **Disease progression of eSTS in a multistate model along with number of patients moving from one state to another.** The states are indicated by blocks and the transitions are indicated by arrows. * Patients with synchronous relapse (LR + DM) move to the DM-state. If a patient first develops a DM and afterwards a LR, the patient will remain in the DM-state. ANED = alive no evidence of disease, LR = local recurrence, DM = distant metastasis.

Multivariable Cox PH models were used to estimate the effect of age on OS and for each transition. The models were adjusted for tumour and treatment characteristics. The tumour characteristics were histology, grade, size, depth and tumour site. The treatment characteristics were surgical margin, radiotherapy and chemotherapy. We assessed the PH-assumption visually using the Schoenfeld-residuals. We used state occupancy plots to visualize the probability of being in a state at different time point after surgery for the three age groups.

P-values ≤ 0.05 were considered statistically significant. Results from the Cox PH models were described in hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). All statistical tests were two-sided. The packages 'mstate', 'mcprsk' and 'survival' were used for the multistate model and survival analyses, and the package 'mice' was used for multiple imputations.

3. Results

3.1. Patient population

A total of 6268 patients were eligible for this study. Two patients due to missing age, three patients due to missing time-to-event data and three patients without follow-up were excluded, resulting in 6260 patients that were

included (Fig. 2). The ages ranged between 18 and 100 years (median, IQR: 63, 49–74). The population was categorized into three age groups: the YA (n = 841, 13.4%), the middle-aged (n = 3217; 51.4%) and the elderly population (n = 2202; 35.2%) (Table 1). The female:male ratio in the total population was 1:1.24. The median follow-up time was 49.4 months (95% CI: 47.1–52.3).

3.2. Differences in tumour characteristics

YA presented more often after 'whoops'-surgery or for reresection due to residual disease compared with both the middle-aged and elderly population. Also, YA had significantly more deep-seated tumours compared with the middle-aged, and elderly population, while elderly presented more often with grade III and large (≥10 cm) tumours compared with the YA and middle-aged population.

SS, MPNST and LPS were significantly more often diagnosed in YA compared with the middle-aged and elderly population, whereas UPS and NOS were diagnosed more often in elderly compared with the YA and middle-aged population. LMS and MF were more frequent in the middle-aged and elderly population compared with YA. No significant difference was found between the middle-aged and elderly population for LMS and MF (Table 1). Fig. 3 describes the age distribution for the main histologic subtypes.

3.3. Differences in treatment

Elderly had significantly more R1-R2 resections compared with the YA and middle-aged population. RTX and CTX were more often offered in the YA and middle-aged population compared with elderly. In addition, there was a significant difference in CTX use between the YA and middle-aged population.

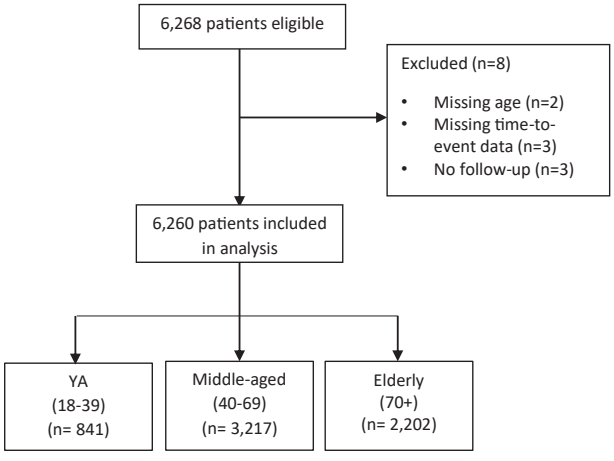

Fig. 2. Consort diagram for patients included in the study. YA = young adults.

3.4. Differences in outcome

There was a significant difference among the age groups for all oncological outcomes (Fig. 4). The 5-year OS in the YA, middle-aged and elderly population, is 78.4% (95% CI: 75.0–81.9), 70.3% (95% CI: 68.4–72.3) and 50.0% (95% CI: 47.3–52.9), respectively (Table 2).

Age was significantly associated with OS in the univariate model (Fig. 4a). After adjustment for the presentation and treatment variables, the association between age and OS decreased but remained significant (HR middle-aged: 1.46 (95% CI: 1.22–1.74), HR elderly: 3.06 (95% CI: 2.53–3.69), YA as reference) (Table 3).

Age demonstrated a significant effect on the cause-specific hazard of LR (Fig. 4b). The difference in the cause-specific hazard of LR between the YA and middle-aged population could entirely be explained by the imbalance in tumour and treatment characteristics (HR middle-aged: 1.38 (95% CI: 0.978–1.95), YA as reference). Difference in the cause-specific hazard of LR between the YA and elderly population could partially be explained by the imbalance in tumour and treatment characteristics (HR elderly: 2.20 (95% CI: 1.53–3.16), YA as reference) (Table 3, transition 1). In addition, age demonstrated a significant effect on the cause-specific hazard of DM (Fig. 4c). The imbalance in tumour and treatment characteristics does not seem to explain the difference in the cause-specific hazard of DM among the age groups (HR middle-aged: 1.26 (95% CI: 1.07–1.49), HR elderly: 1.23 (95% CI: 1.02–1.48), YA as reference) (Table 3, transition 2). HRs for the elderly were the highest for transition 3 (ANED → Death) and 5 (LR → Death) (Table 3). Cumulative incidence plots for LR and DM stratified by age group and histology are depicted in appendix C.

3.5. State occupancy probabilities

The probability of occupying the LR state is similar for each age group over time. The probability of occupying the DM-state in the first year after definitive surgery is the highest in elderly patients compared with the YA and middle-aged population. The probability of occupying the DM decreases after a year because of people moving to the death state (Fig. 5).

4. Discussion

This study showed significant differences among the YA, middle-aged and elderly population in tumour characteristics, treatment strategies and all oncological outcomes. The differences in OS among the age groups could partially be explained by the imbalance in tumour and treatment characteristics. The difference in LR rates between the YA and middle-aged could

Table 1
Tumour and treatment characteristics.

Variable		All patients (n = 6260)	YA (n = 841)	Middle-aged (n = 3217)	Elderly (n = 2202)	P[a]
Gender	Male	3466 (55.4)	464 (55.2)	1815 (56.4)	1187 (53.9)	
	Female	2793 (44.6)	377 (44.8)	1401 (43.6)	1015 (46.1)	0.182
	Missing	*1*		*1*		
Histology	LMS	657 (10.5)	50 (5.95)	336 (10.5)	271 (12.3)	
	LPS	1002 (16.0)	191 (22.7)	569 (17.7)	242 (11.0)	
	MF	1095 (17.5)	42 (4.99)	599 (18.6)	454 (20.6)	
	UPS and NOS	1948 (31.1)	96 (11.4)	959 (29.8)	893 (40.6)	
	MPNST	353 (5.64)	98 (11.7)	186 (5.79)	69 (3.14)	
	SS	570 (9.11)	267 (31.7)	254 (7.90)	49 (2.22)	
	Other	631 (10.1)	97 (11.5)	312 (9.70)	222 (10.1)	<0.001
	Missing	4		2	2	
Grade	2	1008 (24.6)	169 (29.2)	585 (27.3)	254 (18.4)	
	3	3096 (75.4)	410 (70.8)	1560 (72.7)	1126 (81.6)	<0.001
	High-grade (not further specified)	2156	262	1072	822	
Size	<5 cm	1510 (24.9)	239 (29.7)	802 (25.8)	469 (21.9)	
	5–10 cm	2383 (39.3)	323 (40.2)	1199 (38.5)	861 (40.2)	
	≥10 cm	2165 (35.7)	242 (30.1)	1112 (35.7)	811 (37.9)	<0.001
	Missing	*202*	*37*	*104*	*61*	
Depth	Deep	4095 (70.1)	601 (76.3)	2126 (71.0)	1368 (66.6)	
	Superficial	1744 (29.9)	187 (23.7)	870 (29.0)	687 (33.4)	<0.001
	Missing	421	53	221	147	
Site	Lower extremity	4750 (75.9)	647 (76.9)	2501 (77.8)	1602 (72.8)	
	Upper extremity	1509 (24.1)	194 (23.1)	715 (22.2)	600 (27.2)	<0.001
	Missing	*1*		*1*		
Presentation	Primary	3814 (78.8)	489 (73.2)	1928 (78.1)	1397 (82.0)	
	Whoops/residue	1028 (21.2)	179 (26.8)	542 (21.9)	307 (18.0)	<0.001
	Missing	*1418*	*173*	*747*	*498*	
Type of surgery	Limb sparing	5059 (93.9)	674 (95.1)	2590 (93.9)	1795 (93.4)	
	Amputation	330 (6.12)	35 (4.94)	169 (6.13)	126 (6.56)	0.306
	Missing	*871*	*132*	*458*	*281*	
Resection margin	R0	5338 (87.9)	737 (89.8)	2769 (89.2)	1832 (85.4)	
	R1-R2	732 (12.1)	84 (10.2)	336 (10.8)	312 (14.6)	<0.001
	Missing	*190*	*20*	*112*	*58*	
Radiotherapy	No	3016 (48.2)	379 (45.1)	1460 (45.4)	1177 (53.5)	
	Yes	3239 (51.8)	461 (54.9)	1753 (54.6)	1025 (46.5)	<0.001
	Missing	*5*	*1*	*4*		
Chemotherapy	No	5240 (83.7)	593 (70.5)	2526 (78.5)	2121 (96.3)	
	Yes	1019 (16.3)	248 (29.5)	690 (21.5)	81 (3.68)	<0.001
		1		*1*		
Radiotherapy (detailed)	No RT	3017 (48.6)	379 (45.4)	1459 (45.8)	1179 (53.8)	
	Adjuvant	2033 (32.7)	262 (31.4)	1062 (33.4)	709 (32.4)	
	Neoadjuvant	1135 (18.3)	190 (22.8)	647 (20.3)	298 (13.6)	
	Neo- and adjuvant	24 (0.387)	4 (0.479)	16 (0.503)	4 (0.183)	<0.001
	Missing	*51*	*6*	*33*	*12*	
Chemotherapy (detailed)	No CT	5241 (84.1)	593 (70.8)	2529 (79.1)	2119 (96.4)	
	Adjuvant	560 (8.98)	109 (13.0)	394 (12.3)	57 (2.59)	
	Neoadjuvant	190 (3.05)	64 (7.65)	119 (3.72)	7 (0.318)	
	Neo- and adjuvant	243 (3.90)	71 (8.48)	156 (4.88)	16 (0.728)	<0.001
	Missing	*26*	*4*	*19*	*3*	

LMS, leiomyosarcoma; LPS, liposarcoma; MF, myxofibrosarcoma; NOS, not-otherwise-specified; UPS, undifferentiated pleomorphic sarcoma; MPNST, malignant peripheral nerve sheath tumour; SS, synovial sarcoma.
[a] Global *P* value for differences in distribution across the age groups.

entirely be explained by the imbalance in these baseline characteristics, but the difference between the YA and elderly population could only partially be explained by the imbalance. Differences in DM rates among the age groups seem not to be explained by the imbalance in tumour and treatment characteristics among the groups.

It is noteworthy that YA presented more often after 'whoops'-surgery. This is in line with the findings of Younger *et al.* [15] which showed that AYA were more vulnerable to incorrect diagnosis compared with the elderly population. This could be explained by the overall lower prevalence of malignant tumours in YA which makes medical professionals less aware

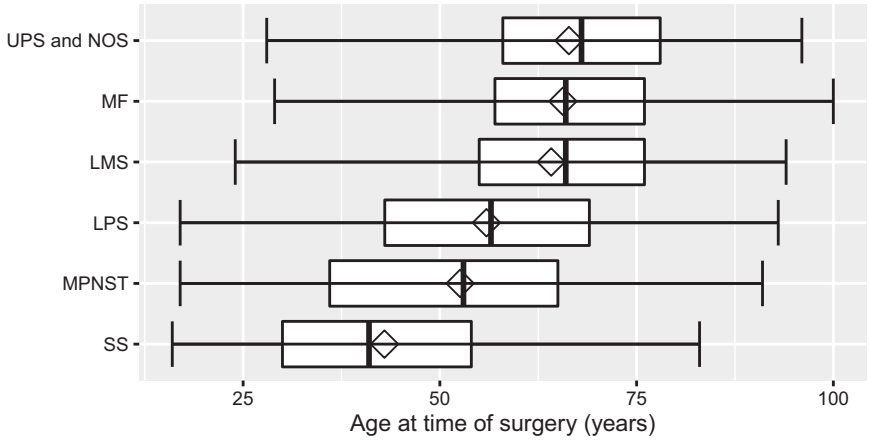

Fig. 3. **Age distribution for histologic subtypes.** Boxes represent the 25th 50th and 75th quartiles, end of horizontal bars represent 1.5 times the interquartile range. Rhombus represents the mean. UPS, undifferentiated pleomorphic sarcoma; NOS, not-otherwise-specified; MF, myxofibrosarcoma; LMS, leiomyosarcoma; LPS, liposarcoma; MPNST, malignant peripheral nerve sheath tumour; SS, synovial sarcoma.

that STS can also affect YA. Another explanation for the higher 'whoops' rates in the YA compared with the elderly is that YA presented with smaller tumours, which might mistakenly be considered benign more frequently.

This study showed a higher overall mortality in the elderly population compared with their younger counterparts, which is in accordance with previous studies [8,16]. In addition, elderly have a more than six and five times higher risk of dying in the ANED and LR state, respectively. Because OS was taken as an end point rather than disease-specific survival, this was to be expected because elderly obviously have a higher risk of dying of natural causes. However, other studies have also shown an increased sarcoma-specific mortality in the older population [8,9,16,17].

The elderly presented with larger (≥10 cm) and more grade III tumours compared with the YA and middle-aged population. In addition, the variation in histological subtypes in the elderly was different than in the younger populations. Elderly were more frequently diagnosed with UPS and NOS, which tend to be more aggressive tumours [18]. All these tumour characteristics could partly explain the impaired OS in the elderly.

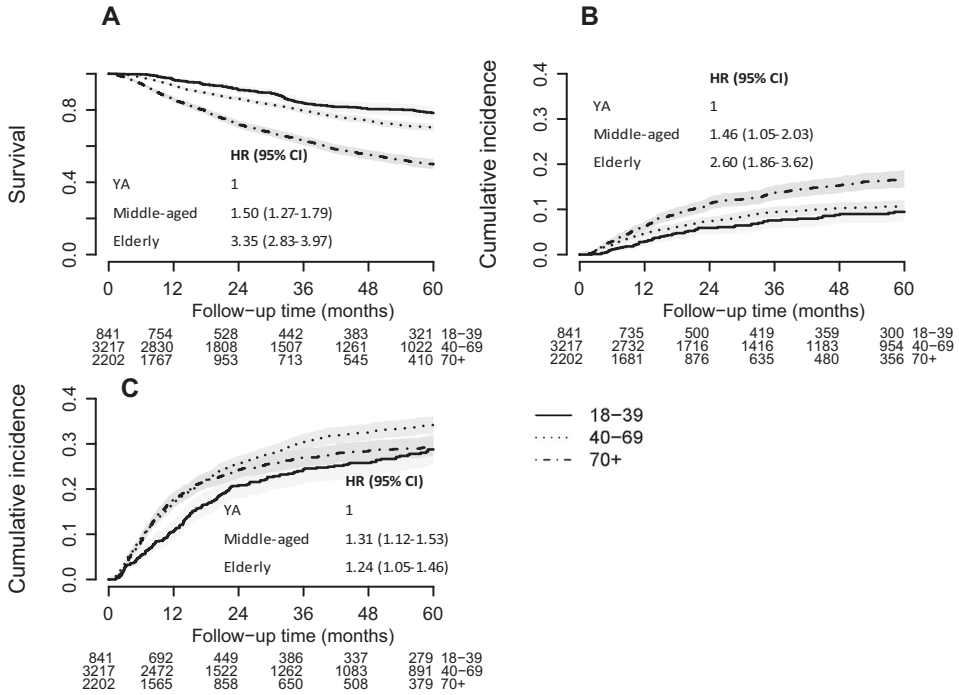

Fig. 4. **Kaplan-Meier curves.** (A) Overall survival (log-rank: $p < 0.001$). (B) Cumulative incidence of local recurrence (log-rank: $p < 0.001$). (C) Cumulative incidence of distant metastasis (Peto-Wilcoxon: $p = 0.001$).

Table 2
Oncological outcome stratified by age group.

Oncological outcome	YA (95% CI)	Middle-aged (95% CI)	Elderly (95% CI)
Overall survival			
2 year	91.1% (89.1–93.3)	86.2% (84.9–87.5)	71.8% (69.8–74.0)
5 year	78.4% (75.0–81.9)	70.3% (68.4–72.3)	50.0% (47.3–52.9)
10 year	66.7% (61.5–72.3)	58.4% (55.6–61.2)	23.7% (20.3–27.7)
Cumulative incidence of LR			
1 year	2.91% (1.76–4.05)	4.67% (3.94–5.41)	6.33% (5.30–7.35)
2 year	5.90% (4.19–7.61)	7.34% (6.39–8.30)	11.2% (9.79–12.6)
5 year	9.45% (7.14–11.8)	10.7% (9.46–11.9)	16.6% (14.7–18.5)
Cumulative incidence of DM			
1 year	10.8% (8.64–12.9)	17.0% (15.7–18.3)	17.6% (16.0–19.2)
2 year	20.8% (17.9–23.8)	25.6% (24.0–27.2)	24.1% (22.2–26.0)
5 year	28.8% (25.2–32.3)	34.2% (32.3–36.1)	29.4% (27.2–31.6)
Overall survival after first LR			
1 year	79.8% (69.8–91.3)	66.7% (61.3–72.6)	59.9% (54.0–66.4)
2 year	54.0% (41.6–70.0)	49.1% (43.2–55.9)	45.5% (39.4–52.5)
5 year	41.5% (29.3–58.8)	32.0% (25.9–39.5)	22.7% (17.2–29.8)
Overall survival after first DM			
1 year	70.1% (63.9–76.9)	59.6% (56.4–63.0)	35.9% (31.8–40.4)
2 year	42.4% (35.7–50.4)	37.1% (33.8–40.7)	15.8% (12.6–19.8)
5 year	21.7% (15.9–29.6)	16.8% (14.0–20.1)	6.28% (4.19–9.42)

YA = young adults, LR = local recurrence, DM = distant metastasis, ANED = alive with no evidence of disease.

in addition, elderly had more positive resection margins. This might be due the fact that elderly presented more often with unresectable tumours, or that surgeons chose to perform less extensive resections to improve quality of life in the elderly. In addition, elderly patients are less often offered radiation or chemotherapy, probably due to pre-existing comorbidities and reduced physical and psychological reserves [9,10,19].

The lower rates of RTX use in the elderly might explain the higher LR rates in this age group, as this study showed a HR of 0.56 for the transition from ANED → LR in those who received RTX. In addition, RTX was associated with an improvement in OS (HR: 0.85). CTX was not associated with an improvement in OS but was associated with the transition from ANED → DM (HR: 1.3). This could probably be explained by confounding by indication, as patients with higher risk of developing a DM are more likely to receive CTX.

After adjustment for the imbalance in tumour and treatment variables, the association between age and OS decreases, suggesting that worse OS in the elderly may only partially be explained by the imbalance of tumour and treatment variables. However, it has been suggested that elderly have a more aggressive tumour biology and a weaker tumour-specific immune response [20,21], which might be another explanation for decreased survival. This is supported by the finding that the probability of developing DM in the first year after surgery is higher for the elderly compared with the younger counterparts with the same tumour and treatment characteristics. Besides elderly have a higher risk of developing a DM, they also have a higher risk of dying after DM. The 1-year OS after first DM was 35.9% in

Table 3
HRs of age for overall survival and all transitions in the multistate model.

Variable	OS	TRANS 1 ANED → LR	TRANS 2 ANED → DM	TRANS 3 ANED → Death	TRANS 4 LR → DM	TRANS 5 LR → Death[b]	TRANS 6 DM → Death
Age	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
- YA	1	1	1	1[a]	1	1	1
- Middle-aged	1.46 (1.22–1.74)	1.38 (0.978–1.95)	1.26 (1.07–1.49)		1.26 (0.703–2.25)	1.40 (0.506–3.89)	1.26 (1.03–1.54)
- Elderly	3.06 (2.53–3.69)	2.20 (1.53–3.16)	1.23 (1.02–1.48)	5.93 (4.85–7.25)	0.792 (0.419–1.49)	4.54 (1.66–12.4)	2.20 (1.76–2.74)

Adjusted for histology, grade, size, depth and tumour site, surgical margin, (neo)adjuvant radiotherapy and (neo)adjuvant chemotherapy.

[a] For transition 3 (ANED → Death), the YA and middle-aged group were combined in one group due to the relatively small number of patients in this transition for these age groups.

[b] For transition 5 (LR → Death), we only adjusted for tumour characteristics due to the relatively small number of patients in this transition.

Appendix B includes the full multistate model including het HRs of the adjusted variables.

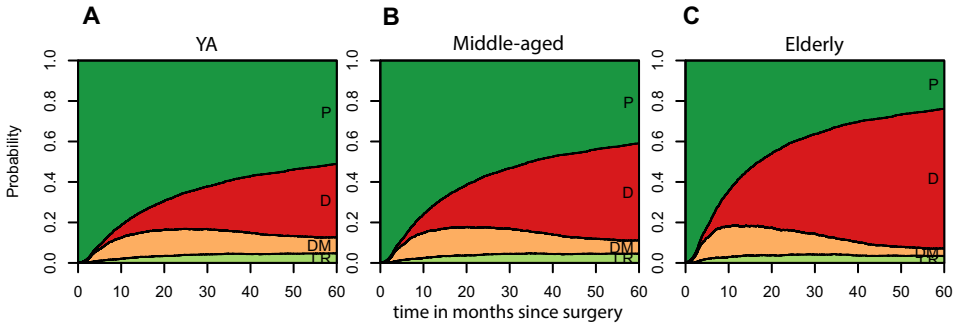

Fig. 5. State occupation probabilities for three patients with the same profile in each age group. Panel A: patient in the YA group with a grade III, deep-seated, Malignant peripheral nerve sheaeth tumour of 10 cm of the lower limb treated with RT and R0-resection. Panel B: patient in the middle-aged group with the same patient profile as A. Panel C: patient in the elderly group with the same patient profile as A. The distance between two curves denotes the probability of being in a specific state at a specific time after surgery. YA = young adults, P = alive no evidence of disease, D = death, DM = distant metastasis, LR = local recurrence.

the elderly compared with 59.6% in the middle-aged population. We did not have any information about the treatment regimens after disease progression, but a potential explanation for the declined OS in elderly could also be a less aggressive treatment approach in this population.

This study found an increased risk of LR in the elderly population compared with YA, in accordance with previous reports [8,22], Also, an increased but less evident risk of DM was found in the middle-aged and elderly population compared with YA. After adjustment for tumour and treatment characteristics, the difference in cause-specific hazard of LR among the age groups decreased. However, the association for the cause-specific hazard of DM remained the same after adjustment, suggesting that the imbalance in measured tumour and treatment characteristics does not explain the difference in DM rate. These findings are in line with a previous report of Biau *et al.* [22], which showed that the effect of age on DM could hardly be explained by presentation and treatment variables. Yet, unmeasured or not-fully modelled explanatory confounders could also, at least partially, explain the remaining association. However, our study included more than twice as many patients compared with Biau *et al.* [22] which made it possible to adjust for more variables without overfitting the models.

4.1. Limitations and strengths

This study has several limitations due to its retrospective design. First, missing data and patients lost to follow-up were present in our data set, probably resulting in selection bias due to selective lost to follow-up. We have used multiple imputations to reduce the bias. Furthermore, the association among the age groups and clinical outcome could be explained by other variables as we did not include in our analysis, such as treatment characteristics of progressive disease, resulting in residual confounding. In addition, we combined patients with R1 and R2 resections in one group, as more detailed information about surgical margins was not available in all centres. Finally, we were unable to assess the disease-specific survival which would provide more insight into the influence of tumour and treatment characteristics on the effect of age. Nevertheless, to our knowledge, this is the largest multicentre study to date examining age-related differences in oncological outcome for patients with primary high-grade eSTS surgically treated with curative intent.

5. Conclusion

In this large multicentre study, we have observed a significant decrease in OS and increase in LR and DM rate with increasing age. This can only partially be explained by differences in tumour and treatment characteristics, suggesting that eSTS may have a more aggressive tumour behaviour in elderly patients when compared with their younger counterparts, which may coincide with a weaker tumour-specific immune response in elderly patients.

Author contributions

I.A. contributed to writing – Original Draft, methodology, formal analysis, and visualization. C.V. contributed to Conceptualization, Methodology, Writing – Review and Editing. A.J.R.-B. contributed to Formal analysis, Writing – Review & Editing. D.J.G. contributed to Conceptualization, Methodology, Writing – Review & Editing. W.J.v.H. contributed to Conceptualization, Methodology, Writing – Review & Editing. PERSARC research group contributed to Conceptualization, Investigation,

Writing – Review & Editing. M.A.J.v.d.S. contributed to Supervision, Conceptualization, Methodology, Writing – Review & Editing.

Conflict of interest statement

None declared.

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Appendix A–C. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.09.021.

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