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Original Research

Increased survival of non low-grade and deep-seated soft tissue sarcoma after surgical management in high-volume hospitals: a nationwide study from the Netherlands

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KEYWORDS
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Abstract ***Background:*** Diagnosing and treating soft tissue sarcomas (STSs) remains challenging, stressing the urgency for centralisation. This nationwide survey aimed to evaluate the centralisation of STS surgery and its effect on survival.
Methods: Patients operated for primary STS from 2006 to 2015 were queried from the Netherlands Cancer Registry. Hospitals in which STS surgery was performed were allocated into three categories: low-volume (1–9 resections per year), medium-volume (10–19 resections) or high-volume (≥20 resections). Differences in tumour characteristics and outcome were calculated. A multivariable regression analysis was performed to adjust for case-mix.
Results: Of the 5282 identified patients, 42% was treated in low-volume hospitals, 7.7% in medium-volume hospitals and 51% in high-volume hospitals, with a significant trend over time towards treatment in a high-volume hospital ($p < 0.01$). In high-volume hospitals, more often patients with non low-grade, large and deep-seated tumours were treated than in low-volume hospitals. For the whole group, there was no survival benefit for patients treated in high-volume hospitals, with 10-year net survival rates of 76% (low-volume), 68% (medium-volume) and 68% (high-volume). However, subgroup analysis for patients with non low-grade and deep-seated tumours did reveal a benefit from treatment in a high-volume hospitals with 10-year survival rates of 54% (high-volume), 49% (low-volume) and 42% (medium-volume) and a relative risk of 1.3 (high-volume versus low-volume, $p = 0.03$).
Conclusion: Centralisation of STS surgery has increased in the past decade. Surgery in a high-volume hospital improved survival of patients with non low-grade and deep-seated tumours, and therefore these patients should be referred to such a hospital.

1. Introduction

Soft tissue sarcomas (STSs) are a group of rare mesenchymal tumours and comprise approximately 1% of all adult malignancies. Within the group of STS, over 50 different malignant histological subtypes have been described, with a broad variety in biological behaviour, presentation, treatment approach and prognosis. Owing to the rarity of these tumours, it is estimated that a general practitioner in the Netherlands only sees one patient with STS every 20 years and a surgeon in a general hospital only once every 4 years, which makes it difficult to gain sufficient clinical experience in diagnosing and treating these patients [1,2].

These observations highlight the urgency for centralisation of sarcoma care, in both diagnosis and treatment. Within the Netherlands, we strive to centralise sarcoma care into dedicated STS expertise centres, but centralisation until 2011 was limited and in need of improvement [3].

The aim of this nationwide study was to determine whether centralisation of STS care has increased over time and whether this has affected survival and other surgical outcomes, such as the proportion of 'whoops' resections, by using data of the Netherlands Cancer Registry (NCR).

2. Methods

2.1. Data collection

All patients diagnosed with primary STS and who underwent surgery during the time interval 2006–2015 were identified and queried from the NCR. Gastrointestinal stromal tumours (GISTs), visceral sarcomas, Kaposi sarcomas and children (age at diagnosis <18 years) were excluded. Data on patient characteristics, tumour characteristics and primary treatment were obtained directly from patients' medical records by data managers of the Netherlands Comprehensive Cancer Organisation, which hosts the NCR.

The STS were categorised according to the World Health Organisation-classification and graded according to the Fédération Nationale des Centres de Lutte Contre Le Cancer (FNCLCC) [1]. Grade I tumours were labelled as low-grade tumours. Grade II tumours, grade III tumours and tumours in which grading is not applicable were pooled and labelled as non low-grade tumours. Tumour subtypes and localisations were recorded in the NCR following the International Classification of Diseases for Oncology (third version) (ICD-O-3) morphology and ICD-O-3 topography codes. There was no central pathology review. Tumours were classified as superficial when located entirely above the fascia or as deep-seated when located beneath the fascia or with invasion of the fascia.

For assessing patients' survival, information on their vital status during follow-up was obtained through linkage with the Municipal Personal Records Database. The most recent linkage for the current study was performed in February 2018.

Potential 'whoops' resections were identified by coinciding dates of first pathological confirmation and surgical resection. They were named 'potential' because not all these resections may have been unplanned but instead deliberately be performed without prior biopsy (i.e. diagnostic excision). Resection margins were classified as

R0 (microscopically negative margins), R1 (microscopically positive margins), R2 (macroscopically positive margins) or Rx (unknown/margins not assessed). The proportion of patients requiring multiple procedures (i.e. re-resections) included patients who underwent more than one operation as part of their primary treatment.

Owing to the nature of our data source, no data were available regarding comorbidities/medical history, local recurrence rate, distant metastasis rate or causes of death/disease-specific survival (DSS).

2.2. Hospitals performing STS surgery

The hospitals in which the patients were treated were allocated into three categories based on the number of STS resections performed annually: 1–9 resections (low-volume), 10–19 resections (medium-volume) or ≥20 resections per year (high-volume).

2.3. Statistical analyses

Trends in STS treatment and in centralisation of STS surgery over the study period were tested for significance using the np-trend test [4]. Age of the different subgroups was presented as medians with corresponding interquartile ranges (IQRs). To estimate the impact of surgical volume on survival, net survival rates were calculated as an approximation of—and perhaps more robust alternative to [5]—DSS. Accordingly, crude survival rates were adjusted for the expected survival in the general population according to persons' age, sex and birth year by applying the lifetable approach. In other words, the crude survival rates were adjusted for mortality in a comparable 'healthy' population of equal age and gender as a proxy for DSS, since the NCR does not register information on recurrence and DSS. For high-volume and low-volume hospitals, the Pohar Perme method [6] was used to estimate the net survival rates, while for medium-volume hospitals, the Ederer-II method [7] was chosen to prevent overcorrection because of the low number of patients in this subgroup. The univariable impact of surgical volume was displayed graphically, and a multivariable Poisson regression model was developed to assess the effect of surgical volume adjusted for established prognostic factors (age, STS subtype, grade, depth and size). Subsequently, the same analyses were performed for the subgroup of patients with non low-grade and deep-seated tumours. All tests were two-sided, and p-values <0.05 were considered statistically significant. Statistical analyses were performed using Stata version 14.1 (StataCorp, College Station, Texas).

3. Results

3.1. Patient characteristics

In total 5282 patients who were diagnosed with primary STS and who underwent STS surgery between 2006 and 2015 were identified, with a median age of 61 year (IQR 47–73). The most common subtypes were liposarcoma, leiomyosarcoma and fibrosarcoma, and the extremity and trunk were the most frequently observed localisations. Most tumours were non low-grade, superficially located and larger than 5 cm (Supplementary table S1). Most patients underwent surgery only (61%), and approximately a third of the patients received radiotherapy. A small subgroup received systemic therapy as part of their primary treatment (5.9%) (Table 1).

3.2. Hospitals performing STS surgery

On annual average, in 76 hospitals STS surgery was performed. This number decreased from 82 hospitals in 2006–2007 to 66 in 2014–2015 ($p = 0.05$), mainly because of a decrease in the number of low-volume hospitals (72 to 56) (Table 1). Of the hospitals in which STS surgery was performed, 88% of the hospitals were low-volume hospitals in which 42% of all STS patients were treated, 3.9% were medium-volume hospitals in which 7.7% of all STS patients were treated, and 7.9% were high-volume hospitals in which 51% of all STS patients were treated (Table 1, Fig. 1A, Fig. 1B). Patients treated in low-volume hospitals had a median age of 64 years (IQR 49–77), patients treated in medium-volume hospitals had a median age of 62 years (IQR 46–72), and patients treated in high-volume hospitals had a median age of 59 years (IQR 46–70). During the study period, there was a significant trend over time towards treatment in a high-volume hospital, from 43% of the patients in 2006–2007 to 62% of the patients in 2014–2015 being treated in a high-volume hospital ($p < 0.01$) (Table 1, Fig. 1B).

We observed a skewed distribution of patients across the hospitals in which STS surgery was performed, although a significant change over time was observed ($p < 0.01$) (Fig. 2). While in 2006–2007 10.3% of all hospitals accounted for half of all STS resections, this proportion decreased to 6.0% in 2014–2015. In 2014–2015, 75% of the STS resections were performed in 21% of the hospitals (35% in 2006–2007), and 90% of the resections in 46% of the hospitals (59% in 2006–2007). The last 10% of resections are widely spread over the remaining 40–55% of the hospitals.

3.3. Case-mix in hospitals performing STS surgery

In high-volume and medium-volume hospitals, mainly patients with non low-grade STS (73% and 75%) were treated, while the proportion of patients with non low-grade tumours treated in low-volume hospitals was 56%. In high-volume centres also mainly patients with large tumours (70%) were treated, whereas this number was lower in medium-volume hospitals (61%) and low-volume hospitals (46%). At last, in low-volume hospitals, mainly patients with superficial tumours (76%) were

Table 1
Trends in the treatment and centralisation of patients diagnosed with soft tissue sarcoma and undergoing surgery in the Netherlands during the study period (2006–2015).

Factor	2006–2007	2008–2009	2010–2011	2012–2013	2014–2015	Total period	p-value[c]
No. of STS patients with primary surgery	1052	969	1050	1064	1147	5282	
Primary treatment regimen, n (%)							p < 0.01
Surgery only	611 (58%)	596 (62%)	643 (61%)	660 (62%)	735 (64%)	3245 (61%)	
Surgery + RTx	364 (35%)	305 (32%)	352 (34%)	337 (32%)	367 (32%)	1725 (33%)	
Surgery + RTx + CTx	37 (3.5%)	24 (2.5%)	31 (3.0%)	37 (3.5%)	22 (1.9%)	151 (2.9%)	
Surgery + CTx	40 (3.8%)	44 (4.5%)	24 (2.3%)	30 (2.8%)	23 (2.0%)	161 (3.0%)	
No. of patients treated per surgical volume, n (%)							p < 0.01
1–9 resections/year (low-volume)	502 (48%)	472 (49%)	453 (43%)	406 (38%)	363 (32%)	2196 (42%)	
10–19 resections/year (medium-volume)	101 (9.6%)	54 (5.6%)	92 (8.8%)	85 (8.0%)	75 (6.5%)	407 (7.7%)	
≥20 resections/year (high-volume)	449 (43%)	443 (46%)	505 (48%)	573 (54%)	709 (62%)	2679 (51%)	
Mean no. of hospitals performing STS surgery[a]	82	80	77	77	66	76	p = 0.05[d]
Total no. of hospitals performing STS surgery[b]	87	89	86	88	83	105	p = 0.09
Mean no. of hospitals performing STS surgery per surgical volume, n (%)							p = 0.29
1–9 resections/year (low-volume)	72 (88%)	72 (90%)	67 (87%)	67 (87%)	56 (86%)	67 (88%)	
10–19 resections/year (medium-volume)	4 (4.9%)	2 (2.5%)	4 (5.2%)	3 (3.9%)	3 (4.6%)	3 (3.9%)	
≥20 resections/year (high-volume)	6 (7.3%)	6 (7.5%)	6 (7.8%)	7 (9.1%)	7 (11%)	6 (7.9%)	
Proportion of operations in top quartile of hospitals	69%	71%	74%	80%	77%	76%	p < 0.01

STS, soft tissue sarcoma; RTx, radiotherapy; CTx, chemotherapy.
[a] Mean over period.
[b] Including mergers.
[c] Tested for trend over total study period using the np-trend test.
[d] Tested for trend over total study period using a linear regression analysis.

treated, whereas in medium-volume and high-volume hospitals, the distribution between superficial and deep-seated tumours was more equal (medium-volume: 57% superficial versus 43% deep; high-volume: 54% superficial versus 46% deep) (Table 2).

Over the years, in low-volume and medium-volume hospitals, significantly less patients with deep-seated tumours were operated (low-volume: 25% in 2006–2007 to 21% in 2014–2015, $p < 0.01$; medium-volume: 60% to 53%, $p = 0.01$), and significantly less patients with large tumours were operated (low-volume: 50% to 36%, $p < 0.01$; medium-volume: 79% to 50%, $p < 0.01$). On the contrary, in high-volume hospitals, the proportion of patients with deep-seated tumours increased (44% to 48%, $p < 0.01$), while the proportion of patients with large tumours remained stable (70% 68%, $p = 0.35$). There were no significant changes over time in the proportions of patients with non low-grade and low-grade tumours (low-volume: $p = 0.93$, medium-volume: $p = 0.74$, high-volume: $p = 0.48$) (Table 2).

3.4. Shift in use of treatment modalities

Most probably related to this case-mix, the use of neoadjuvant/adjuvant radiotherapy and chemotherapy raised as the annual surgical volume increased ($p < 0.001$). Whereas in low-volume hospitals, 75% of the patients were treated with surgery alone, this proportion was 61% in medium-volume hospitals and 50% in high-volume hospitals. Subsequently, the proportion of patients receiving neoadjuvant/adjuvant radiotherapy increased from 23% in low-volume hospitals to 35% in medium-volume hospitals and 46% in high-volume hospitals. The proportion of patients receiving chemotherapy also increased from 2.1% in low-volume hospitals to 6.1% in medium-volume hospitals and 9.0% in high-volume hospitals (Table 3).

3.5. STS surgery–Potential 'whoops' resections, resection margins and multiple procedures

The proportion of patients undergoing a potential 'whoops' resection was lower as the annual surgical volume increased: 62% in low-volume hospitals, 44% in medium-volume hospitals and 29% in high-volume hospitals ($p < 0.01$). For medium-volume and high-volume hospitals, there were no significant changes in this proportion over time ($p = 0.17$ and $p = 0.76$), but for low-volume hospitals, this proportion increased from 58% in 2006–2007 to 66% in 2014–2015 ($p = 0.02$) (Table 2).

Considering R1/R2 resections, the number of non-radical resections was higher when patients were treated in high-volume hospitals (19%) than in medium-volume (16%) and low-volume (14%) hospitals ($p < 0.01$). Over time, the amount of non-radical resections was stable for low-volume hospitals ($p = 0.76$) but decreased for medium-volume (26%–16%, $p = 0.01$) and high-volume hospitals (22%–15%, $p = 0.01$) (Table 2).

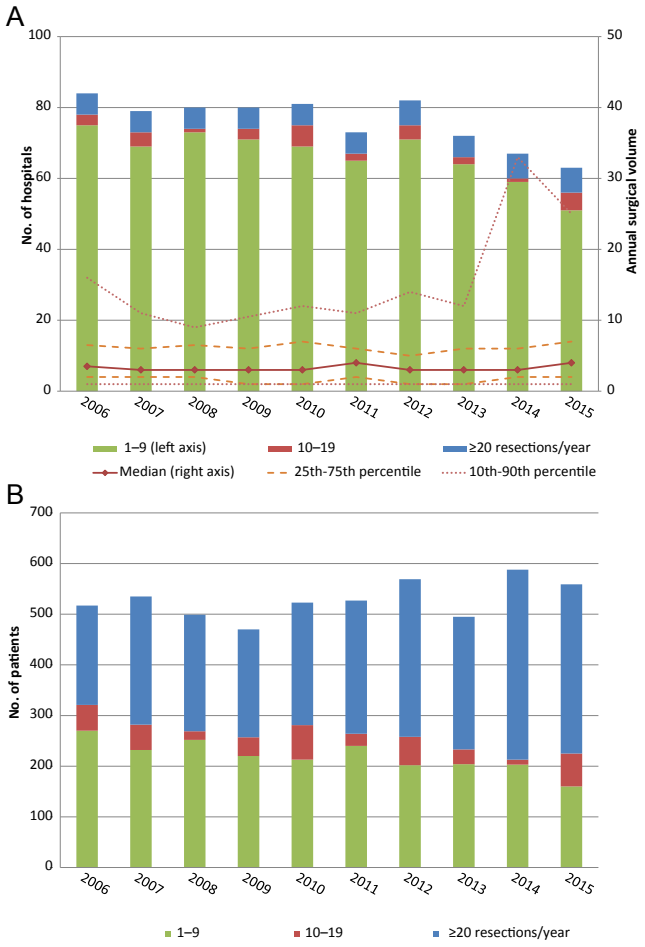

Fig. 1. Trends in centralisation of STS surgery of patients diagnosed in the Netherlands from 2006 to 2015 stratified by surgical volume (low-volume: 1–9 resections, medium-volume: 10–19 resections, high-volume: ≥20 resections). **(A)** Number of hospitals performing STS surgery. **(B)** Number of patients undergoing STS surgery. STS, soft tissue sarcoma.

The number of patients requiring multiple procedures varied from 29% in high-volume hospitals and in medium-volume hospitals to 36% in low-volume hospitals ($p < 0.01$). These proportions remained stable over time (low-volume: $p = 0.99$, medium-volume: $p = 0.70$, high-volume: $p = 0.70$) (Table 2).

3.6. Effects on survival

Univariable net survival rates were significantly higher for patients treated in low-volume hospitals than for those treated in medium-volume and high-volume hospitals, with 10-year net survival rates of 76% versus 68% and 68% respectively and relative rates of 1.5 (medium-volume versus low-volume, 95% confidence interval [CI] 1.2–2.0, $p = 0.001$) and 1.5 (high-volume versus low-volume, 95% CI 1.3–1.7, $p < 0.001$) (Fig. 3A). However, after adjustment for other prognostic factors, a multivariable Poisson regression analysis did not show any impact of surgical volume on

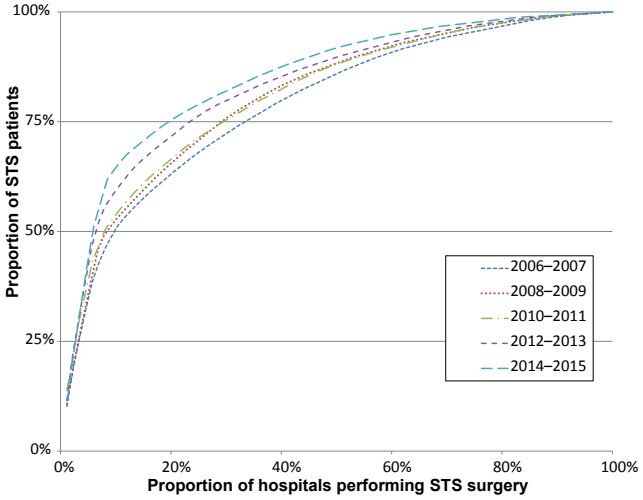

Fig. 2. Allocation of patients undergoing STS surgery in the Netherlands from 2006 to 2015 across the hospitals performing STS surgery. Trend over time was tested by a test for equality of the regression coefficients of the fitted values. STS, soft tissue sarcoma.

net survival (medium-volume versus high-volume: relative rate [RR] 1.2, 95% CI 0.93–1.4, $p = 0.20$; low-volume versus high-volume: RR 1.01, 95% CI 0.87–1.2, $p = 0.91$) (Table 4A).

Since in high-volume hospitals more often patients with non low-grade, large and deep-seated tumours were treated (Table 2), which is associated with more complex surgery, a subgroup analysis was performed including only patients with non low-grade and deep-seated STS (median age 61 years, IQR 48–71). The univariable analysis on patients with non low-grade and deep-seated tumours ($n = 1222$) did not show a difference in survival anymore, with net survival rates of 49%, 42% and 54%, respectively and relative rates of 1.03 (medium-volume versus low-volume, 95% CI 0.76–1.4, $p = 0.84$) and 0.83 (high-volume versus low-volume, 95% CI 0.69–1.01, $p = 0.06$) (Fig. 3B). However, in multivariable analysis, surgery in a high-volume hospital did show a significant and beneficial effect on net survival compared with surgery in a low-volume hospital (RR 1.3, 95% CI 1.02–1.6, $p = 0.03$). The same impact was observed in comparison with medium-volume hospitals, although this failed to reach statistical significance (RR 1.3, 95% CI 0.98–1.8, $p = 0.07$) (Table 4B). The full results of the multivariable Poisson regression analysis are shown in Supplementary Table S2.

4. Discussion

We observed a significant effect of surgery in a high-volume hospital on net survival rate for patients with non low-grade and deep-seated tumours (i.e. tumours for which more complex surgery and more multidisciplinary treatment is required) and an increase in referring and treating STS patients to/in high-volume

Table 2
Tumour characteristics and surgical characteristics of patients undergoing surgery for soft tissue sarcoma in the Netherlands from 2006 to 2015 stratified by hospital volume.

Factor	2006–2007	2008–2009	2010–2011	2012–2013	2014–2015	Total period	p-value[d]
Surgery in low-volume hospitals (1–9 resections/year)	502	472	453	406	363	2196	
Tumour grade[a], n (%)							p = 0.93
Low grade	184 (44%)	154 (40%)	177 (49%)	143 (46%)	104 (40%)	762 (44%)	
Non low-grade	236 (56%)	228 (60%)	184 (51%)	165 (54%)	156 (60%)	969 (56%)	
Tumour size[b], n (%)							p < 0.01
≤5 cm	148 (50%)	140 (47%)	161 (53%)	164 (56%)	181 (64%)	794 (54%)	
>5 cm	149 (50%)	159 (53%)	140 (47%)	130 (44%)	102 (36%)	680 (46%)	
Tumour depth[c], n (%)							p < 0.01
Superficial	333 (75%)	289 (70%)	333 (77%)	290 (76%)	271 (79%)	1516 (75%)	
Deep	110 (25%)	122 (30%)	98 (23%)	93 (24%)	70 (21%)	493 (25%)	
Potential 'whoops' resections, n (%)	293 (58%)	282 (60%)	298 (66%)	256 (63%)	239 (66%)	1368 (62%)	p = 0.02
Potential 'whoops' resections for large, deep-seated and non low-grade tumours, n(%)	20 (40%)	28 (48%)	25 (48%)	17 (36%)	16 (55%)	106 (45%)	p = 0.83
Patients with R1/R2 resection, n (%)	72 (14%)	65 (14%)	66 (15%)	53 (13%)	57 (16%)	313 (14%)	p = 0.76
Patients requiring multiple procedures, n (%)	175 (35%)	163 (35%)	182 (40%)	151 (37%)	119 (33%)	790 (36%)	p = 0.99
Surgery in medium-volume hospitals (10–19 resections/year)	101	54	92	85	75	407	
Tumour grade[a], n (%)							p = 0.74
Low grade	20 (22%)	10 (24%)	20 (26%)	24 (32%)	11 (18%)	85 (25%)	
Non low-grade	72 (78%)	32 (76%)	56 (74%)	50 (68%)	49 (82%)	259 (75%)	
Tumour size[b], n (%)							p < 0.01
≤5 cm	17 (22%)	14 (33%)	28 (40%)	32 (54%)	32 (50%)	123 (39%)	
>5 cm	62 (78%)	29 (67%)	42 (60%)	27 (46%)	32 (50%)	192 (61%)	
Tumour depth[c], n (%)							p = 0.01
Superficial	37 (40%)	26 (52%)	60 (69%)	58 (77%)	33 (47%)	214 (57%)	
Deep	55 (60%)	24 (48%)	27 (31%)	17 (23%)	37 (53%)	160 (43%)	
Potential 'whoops' resections, n (%)	37 (37%)	23 (43%)	42 (46%)	43 (51%)	33 (44%)	178 (44%)	p = 0.17
Potential 'whoops' resections for large, deep-seated and non low-grade tumours, n(%)	7 (20%)	2 (13%)	4 (27%)	3 (30%)	5 (31%)	21 (23%)	p = 0.74
Patients with R1/R2 resection, n (%)	26 (26%)	10 (19%)	8 (8.7%)	8 (9.4%)	12 (16%)	64 (16%)	p = 0.01
Patients requiring multiple procedures, n (%)	25 (25%)	17 (32%)	27 (29%)	30 (35%)	18 (24%)	117 (29%)	p = 0.70
Surgery in high-volume hospitals (≥20 resections/year)	449	443	505	573	709	2679	
Tumour grade[a], n (%)							p = 0.48
Low grade	107 (26%)	101 (26%)	112 (25%)	144 (29%)	164 (27%)	628 (27%)	
Non low-grade	301 (74%)	292 (74%)	336 (75%)	357 (71%)	444 (73%)	1730 (73%)	
Tumour size[b], n (%)							p = 0.35
≤5 cm	109 (30%)	106 (30%)	114 (28%)	139 (30%)	197 (32%)	665 (30%)	
>5 cm	257 (70%)	247 (70%)	299 (72%)	330 (70%)	410 (68%)	1543 (70%)	
Tumour depth[c], n (%)							p < 0.01
Superficial	218 (56%)	193 (51%)	260 (56%)	303 (57%)	352 (52%)	1326 (54%)	
Deep	171 (44%)	184 (49%)	204 (44%)	232 (43%)	330 (48%)	1121 (46%)	
Potential 'whoops' resections, n (%)	128 (29%)	132 (30%)	147 (29%)	170 (30%)	198 (28%)	775 (29%)	p = 0.76
Potential 'whoops' resections for large, deep-seated and non low-grade tumours, n(%)	19 (18%)	16 (14%)	9 (8%)	18 (14%)	24 (12%)	86 (13%)	p = 0.51
Patients with R1/R2 resection, n (%)	98 (22%)	86 (19%)	103 (20%)	118 (21%)	105 (15%)	510 (19%)	p = 0.01
Patients requiring multiple procedures, n (%)	132 (29%)	133 (30%)	141 (28%)	164 (29%)	204 (29%)	774 (29%)	p = 0.70

[a] Excluding unknown grade.
[b] Excluding unknown size.
[c] Excluding unknown depth.
[d] Tested for trend over total study period using the np-trend test.

Table 3
Use of the different treatment modality of patients undergoing surgery for soft tissue sarcoma in the Netherlands from 2006 to 2015, stratified by surgical volume.

Treatment	Low-volume, n (%)	Medium-volume, n (%)	High-volume, n (%)	Total, n (%)
Surgery alone	1656 (75%)	250 (61%)	1339 (50%)	3245 (61%)
Surgery + RTx	493 (22%)	132 (32%)	1100 (41%)	1725 (33%)
Surgery + RTx + CTx	14 (0.6%)	11 (2.7%)	126 (4.7%)	151 (2.9%)
Surgery + CTx	33 (1.5%)	14 (3.4%)	114 (4.3%)	161 (3.0%)

χ^2-test: $p < 0.001$.
RTx: radiotherapy, CTx: chemotherapy.

hospitals, although STS surgery is still highly fragmented across the country. This increase in centralisation was mainly the result of the more frequent referral of patients with deep-seated and large tumours from low-volume and medium-volume hospitals to high-volume hospitals, whereas there was no increase in the referral of non low-grade STS.

Previous studies regarding centralisation of STS care mainly reported not only on improvements in surgical outcomes [3,8–10] and disease-free, relapse-free or progression-free survival [11–15] but also on improvements in overall survival after treatment at expert sites/high-volume hospitals [10,14–16]. The added value of this study to these studies on centralisation of STS care is the nationwide set-up, and the use of net survival rates as an alternative to and proxy for DSS [5], especially since many patients with low-grade STS are included who most probably will not die from their STS. In the current study, we could confirm an effect on net survival, but only in the subgroup of patients with poor

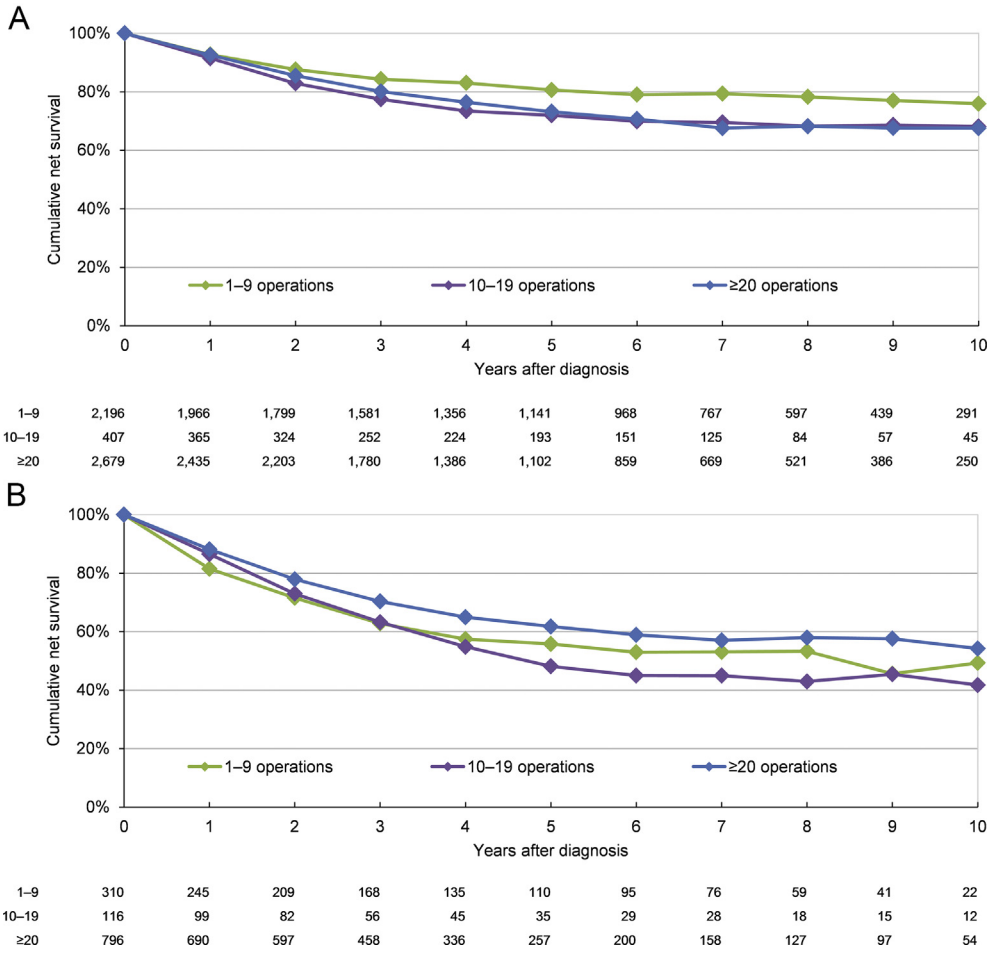

Fig. 3. Net survival curves of patients undergoing STS surgery in the Netherlands from 2006 to 2015 stratified by surgical volume (low-volume: 1–9 resections, medium-volume: 10–19 resections, high-volume: ≥20 resections). **(A)** Net survival rate of all patients undergoing STS surgery (medium-volume versus low-volume: RR 1.5, 95%CI 1.2–2.0, p = 0.001; high-volume versus low-volume: RR 1.5, 95%CI 1.3–1.7, p≤0.001). **(B)** Net survival rate of patients undergoing STS surgery for non low-grade and deep-seated tumours (n = 1222) (medium-volume versus low-volume: RR 1.03, 95%CI 0.76–1.4, p = 0.84; high-volume versus low-volume: RR 0.83, 95%CI 0.69–1.01, p = 0.06). STS, soft tissue sarcoma; RR, relative rate; 95% CI, 95% confidence interval.

Table 4
Effect of surgical volume on survival after adjustment for case-mix (age, STS subtype, size, grade and depth) in a multivariable Poisson regression analysis. Results of the total study cohort (A) and of the subgroup analysis including only patients with non low-grade and deep-seated tumours (B). Full results with all covariates are shown in Supplementary Table S2.

Hospital volume	RR	95% CI	p-value
(A)			
≥20 (high)	Ref		
10-19 (medium)	1.2	0.93–1.4	0.20
1-9 (low)	1.01	0.87–1.2	0.91
(B)			
≥20 (high)	Ref		
10-19 (medium)	1.3	0.98–1.8	0.07
1-9 (low)	1.3	1.02–1.6	0.03*

STS, soft tissue sarcoma; RR, relative rate; 95% CI, 95% confidence interval.
* means statistically significant/$p<0.05$.

prognostic characteristics, such as non low-grade and deep-seated tumours.

Notably, we observed a large proportion of and an increase in the number of potential 'whoops' resections in low-volume hospitals, although the absolute number of 'whoops' resections decreased over time. It should be remarked that this proportion includes resections of large and deep-seated tumours as well as resections of small and superficial tumours. Especially the latter category, 'whoops' resections of a small and superficial STS, cannot be prevented at all times and are 'all-in-the-game', considering that benign soft tissue lesions are 100 times more prevalent [1]. Furthermore, some of these resections might deliberately have been performed without prior histological confirmation by biopsy (i.e. diagnostic excision). The increase in the proportion of 'whoops' resections in low-volume hospitals even might be the result of centralisation itself. The proportion of tumours that are unrecognised as an STS probably will be stable over time. When low-volume hospitals perform less surgeries, the proportion of these 'whoops' resections will increase. Nonetheless, in a considerable part of these patients suboptimal surgical approaches are chosen [17,18], with unclear/inadequate resection margins [17–19], and these patients will need to undergo a re-resection to remove residual tumour and obtain adequate margins [19,20]. This is also reflected in the current study, where patients treated in low-volume hospitals significantly more often needed to undergo re-resection than patients treated in high-volume hospitals.

The higher number of irradical resections in high-volume hospitals, although decreasing over time, is most probably because these hospitals more often operate on large and deep-seated tumours. They might perform planned R1-resections more often, after neoadjuvant radiotherapy, to spare surrounding vital structures, such as the neurovascular bundle, or even to prevent amputation. This hypothesis is also supported by the observation that patients treated in high-volume hospitals more often receive neoadjuvant/adjuvant radiotherapy, instead of surgery alone.

It has been shown that simple referral guidelines (referral of all deep-seated tumours and all superficial tumours ≥5 cm) can result in nearly complete referral of STS patients to expertise centres, with an acceptable surplus referral of benign tumours [21]. Currently, the guidelines in the Netherlands list a set of requirements that hospitals have to meet in order to treat STS patients, rather than indicate when to refer patients to an STS expertise centre regarding size, localisation or depth of the tumour [22]. Three of these requirements state that hospitals have to perform at least 10 primary STS resections annually, that all patients have to be discussed in an STS multidisciplinary team regarding diagnostic and treatment procedures and that the formulated advice during these multidisciplinary meetings is mandatory to follow. These referral guidelines allow general surgeons to consult an STS expertise centre for diagnostic and treatment advice without necessarily referring the patient in person. Remarkably, over 85% of the hospitals in which STS surgery is performed do not meet the specific requirement of at least 10 STS resections per year. Unfortunately, the rationales behind deviating from the guidelines are not registered in the NCR. For various reasons, such as travel distance, the patient's own wish, unawareness of the existence of STS expertise centres or based on the (binding) advice of the multidisciplinary tumour board, patients are treated in low-volume hospitals.

On top of the beneficial effect on survival of patients with non low-grade and deep-seated STS and the lower number of 'whoops' resections and re-resections, treatment in a high-volume and expertise centre also might improve STS care on other levels. For example, patients will be treated by more experienced clinicians with more insight into the heterogeneity of the disease, its diagnosis and the rapidly evolving treatment options. Other examples include patient counselling regarding treatment decision-making and inclusion in clinical trials, which might be more optimal in high-volume multidisciplinary hospitals than in low-volume hospitals. However, in order to establish the best possible care for these patients, centralisation of STS care into high-volume hospitals should be paired with improving the diagnostic work-up for soft tissue tumours of unknown origin and creating more awareness, since centralisation is not only a result of high-volume hospitals recruiting these patients but mostly relies on the alertness and willingness of physicians in low-volume and medium-volume hospitals to refer their patients.

5. Conclusion

Centralisation of STS surgery has increased in the past 10 years, although it is still highly fragmented across the

country. Treatment in a high-volume hospital had a beneficial effect on net survival rates for patients with non low-grade and deep-seated STS on a population-level, and it most probably also does reduce surgery-related morbidities reflected by the lower number of potential 'whoops' resections and re-resections. Therefore, we plea for centralisation of STS care into dedicated multidisciplinary expertise centres and for more strict referral guidelines, stating that all patients with suspected or confirmed STS have to be at least discussed in an expertise centre. Patients with suspected non low-grade and deep-seated STS based on imaging—and subsequently more complex surgeries and more multidisciplinary treatment required—have to be referred to a high-volume hospital for a imaging-guided biopsy prior to start of treatment.

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Conflicts of interest statement

None of the authors has any conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.01.005.

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