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## **Incidence of unplanned excisions of soft tissue sarcomas in the Netherlands: a population-based study**

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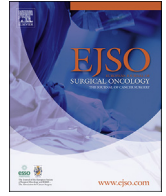
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## Incidence of unplanned excisions of soft tissue sarcomas in the Netherlands: A population-based study



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### ABSTRACT

**Introduction:** Timely recognition of soft tissue sarcomas (STS) remains challenging, potentially leading to unplanned excisions (also known as ‘whoops procedures’). This population-based study charted the occurrence of unplanned excisions and identified associated patient, tumour, and treatment-related characteristics. Furthermore, it presents an overview of the outcomes and clinical management following an unplanned excision.

**Methods:** From the Netherlands Cancer Registry (NCR) database, information was obtained on 2187 adult patients diagnosed with STS in 2016–2019 who underwent surgery. Tumours located in the mediastinum, heart or retroperitoneum were excluded, as well as incidental findings. Differences between patients with planned and unplanned excisions were assessed with chi-square tests and a multivariable logistic regression model.

**Results:** Overall, unplanned excisions comprise 18.2% of all first operations for STS, with a quarter of them occurring outside a hospital. Within hospitals, the unplanned excision rate was 14.4%. Unplanned excisions were more often performed on younger patients, and tumours unsuspected of being STS prior to surgery were generally smaller ( $\leq 5$  cm) and superficially located. Preoperative imaging was omitted more frequently in these cases. An unplanned excision more often resulted in positive margins, requiring re-excision. Patients who had an unplanned excision outside of a sarcoma centre were more often discussed at or referred to a sarcoma centre, particularly in case of residual tumour.

**Discussion:** Potential improvement in preventing unplanned excisions may be achieved by better compliance to preoperative imaging and referral guidelines, and stimulating continuous awareness of STS among general surgeons, general practitioners and private practices.

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## 1. Introduction

Soft tissue sarcomas (STS) are a heterogeneous group of malignancies that account for less than 1% of all adult cancers, with world age-standardised incidence rates of approximately 2.0–3.0/

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100,000 persons in most European countries [1]. At the same time, benign soft tissue tumours are much more common, considered to outnumber STS with at least a factor 100 [2], and even higher ratios for particular localisations such as the extremities [3]. Consequently, there is a considerable risk of STS being mistaken for benign tumours and hence excised without proper diagnostic workup—preoperative imaging and a biopsy—and surgical planning, resulting in inadequate surgical margins [4], potentially worsened by contamination of adjacent tissue. These unplanned excisions, also known as ‘whoops procedures’, generally require second surgery that may be more extensive, including amputation [5,6], and are associated with increased local recurrence rates [7,8], particularly in high-grade STS [9].

Although STS should preferably be managed within specialised centres or reference networks sharing multidisciplinary expertise and experience, clinical suspicions of STS are most warranted for deep lesions of soft tissues, or large (diameter >5 cm) superficial ones [10]. In addition, excisional biopsies may be allowed as the most practical option for superficial lesions smaller than 3 cm. Following from this, unplanned excisions often seem to concern smaller and superficial STS [11,12].

The extent to which unplanned excisions occur in clinical practice is difficult to determine. Rates reported in the literature vary from approximately one-fifth to over half of STS resections [4,12–16]. These estimates, however, are often derived from specialised centres, and therefore highly depend on local referral patterns. A study using older data (1992–2011) from the Surveillance, Epidemiology, and End Results (SEER) Medicare linked dataset reported 36.9% of procedures to be unplanned, although this analysis was conducted on elderly patients only [17]. Recently, a nationwide evaluation established a mean unplanned excision rate of 11.3% for Japan over an 11-year period (2006–2016), with a slight decrease over time [18].

The present study aims to chart the population-based occurrence of unplanned excisions of STS for the Netherlands using its national cancer registry, and to identify risk factors in terms of patient and tumour characteristics in this setting. Furthermore, it provides an overview of the clinical management and outcomes of patients with STS following an unplanned excision. In the context of current discussions regarding centralisation of care in the Netherlands, results were also evaluated with respect to care delivery by dedicated sarcoma centres. The analyses focus on adult patients since paediatric oncology has already been centralised for several decades.

## 2. Methods

### 2.1. Database

The Netherlands Cancer Registry (NCR) covers a population of 17.4 million inhabitants as of January 1st, 2020. Its database, hosted and maintained by the Netherlands Comprehensive Cancer Organisation (Integraal Kankercentrum Nederland; IKNL), contains information on newly diagnosed cancer patients since 1989 (with a coverage of approximately 90%–95%, depending on tumour site) [19]. Case notification of STS is received from all pathology laboratories in the Netherlands, after which IKNL data managers acquire information on patient, tumour, and treatment-related characteristics from hospitals' electronic medical records. Consent for the study design, data abstraction process, and storage protocols was acquired from the supervisory committee of the NCR.

Tumour site and morphology are coded according to the International Classification of Diseases for Oncology (ICD-O, third edition) [20] and classified according to the World Health Organisation (WHO) classification 2013 [2]. Tumour size is partly coded using the

TNM classification system of the Union for International Cancer Control (UICC) [21]. Due to changes in the 8th edition of the TNM classification, information on tumour depth is available until 2017. The surgical margins are classified as R0 (negative margins), R1–R2 (microscopically or macroscopically positive margins) or RX (unknown margins/margins not assessed). As the NCR registers the specific hospital of each treatment, it was possible to determine whether management took place in a sarcoma centre. Sarcoma centres are characterized by their participation in the European Organisation for Research and Treatment of Cancer (EORTC) sarcoma group, or designated as such by The Netherlands Federation of University Medical Centres (Nederlandse Federatie van Universitair Medische Centra; NFU).

As of 2016, the NCR has extended its registry with additional data items specifically for STS. These include the intention of surgery, which allows for distinguishing unplanned from planned excisions. A procedure is considered unplanned when, according to patients' medical records, a soft tissue tumour was (partially) removed in the absence of a suspicion of malignancy. Accordingly, excisional and incisional biopsies do not qualify as unplanned excisions.

### 2.2. Patient selection

All adult patients ( $\geq 18$  years) diagnosed with an STS (excluding Kaposi's sarcoma; see [Supplementary table A](#) for selected subtypes) in 2016–2019 and who underwent surgery as part of their primary treatment, including those who had surgery performed by a general or private practitioner, were retrieved from the NCR and included in the study. Patients with an STS located in the viscera, including those in the mediastinum, heart, retroperitoneum and/or peritoneum, and gynaecological sarcomas were excluded, as were incidental findings of STS. For one sarcoma centre, no information regarding the intent of surgery was available, and all cases with a first surgical procedure in this centre were excluded. From another centre, information was only available from 2017, and patients treated here were included from that year on.

### 2.3. Statistical analyses

In assessing differences between patients with unplanned and patients with planned excisions, the analyses were focused on information that was available prior to surgery. This included patients' sex and age (at time of diagnosis, in groups 18–49/50–64/65–74/75 years and over, and median and interquartile range), tumour site (head and neck/trunk/upper extremities/lower extremities), clinical tumour size ( $\leq 5$  cm/ $> 5$  cm), tumour depth (for 2016: superficial/deep), the use of preoperative imaging (yes/no), and whether first surgery took place in a sarcoma centre (sarcoma centre/other hospital/general practitioner or private practice). Categorical variables were evaluated using chi-square tests, and the Mann-Whitney *U* test was employed for comparing the difference in median age between the groups. Time trends for unplanned excisions were assessed by calculating a chi-squared test statistic for Pearson's correlation coefficient.

Independent predictors for unplanned excisions were identified using a multivariable logistic regression model, following their selection based on a *p*-value of  $< 0.1$  in the univariable analyses. Since sarcoma centres serve patients who are more suspect of having a STS, the analyses were also performed for patients who had their first surgery outside one of these centres. The results of the logistic regression analyses were presented as odds ratios (OR) with their corresponding 95% confidence intervals (95%CI). Tests results with a *p*-value of  $< 0.05$  were considered statistically significant. All analyses were performed using Stata (version 16.1, StataCorp, College Station, Texas).

Additionally, the rate of unplanned excisions assessed in this study was compared to prior estimations made with the NCR database [22,23]. These had been based on a proxy for ‘potential unplanned resections’ defined by equal dates of STS surgery and the tumours’ first histopathological confirmation. Although the risk of overestimating the number of unplanned excisions using this proxy was acknowledged, the extent of overestimation remained unknown.

### 3. Results

#### 3.1. Patient and tumour characteristics

In total, information on 2187 adult patients diagnosed with STS in 2016–2019 who had undergone surgery was extracted from the NCR (Fig. 1). The study population included 1293 (59.1%) male and 894 (40.9%) female patients, with a median age at diagnosis of 66 years (interquartile range 51–77); 30.8% of the patients was aged 75 years and over (Table 1). Most tumours were localized in the lower extremity (33.1%) and the trunk (30.8%). Most patients presented with smaller tumours (46.0%) while clinical size could not be determined in about one-eighth of cases (12.3%). Preoperative imaging was carried out for the majority of tumours (57.5%) and, on the basis of cases registered in 2016, about two-third (65.8%) of cases concerned superficial tumours. First surgeries for STS more often took place outside a sarcoma centre in other hospitals (56.1%), and a minority of procedures (4.5%) was performed by a general or

private practitioner.

#### 3.2. Unplanned excision

Overall, unplanned excisions occurred in 399 (18.2%) of first surgeries. Following univariable analyses, patients with an unplanned excision were younger compared to those who underwent a planned procedure (median age 63 versus 67 years;  $p < 0.01$ ; among patients aged 65 years and over, 15.5% had an unplanned excision). Their tumours were more often found in the upper extremity (18.1% versus 13.0%;  $p < 0.01$ , with unplanned excisions comprising 23.6% of all procedures performed for STS at this site), were smaller ( $\leq 5$  cm: 60.9% versus 42.7%;  $p < 0.01$ ) and more often superficially located (84.3% versus 62.0%;  $p < 0.01$ ). Furthermore, preoperative imaging was omitted more than twice as often (73.7% versus 35.6%;  $p < 0.01$ ). The unplanned excision rate was 14.4% within hospitals, with only a minority of first surgeries performed in a sarcoma centre being unplanned (3.0%), while these comprised over one fifth of first surgeries in other hospitals (22.4%). Unplanned excisions seemed to occur more often over time, with a statistically significant trend for procedures performed in non-sarcoma centre hospitals ( $p = 0.04$ ; Fig. 2). General practitioners and private practices accounted for approximately a quarter of unplanned excisions over the total study period (24.6%).

In the overall multivariable logistic regression, first surgery performed in a sarcoma centre was the most predominant determinant (Table 2A), with unplanned resections being much less

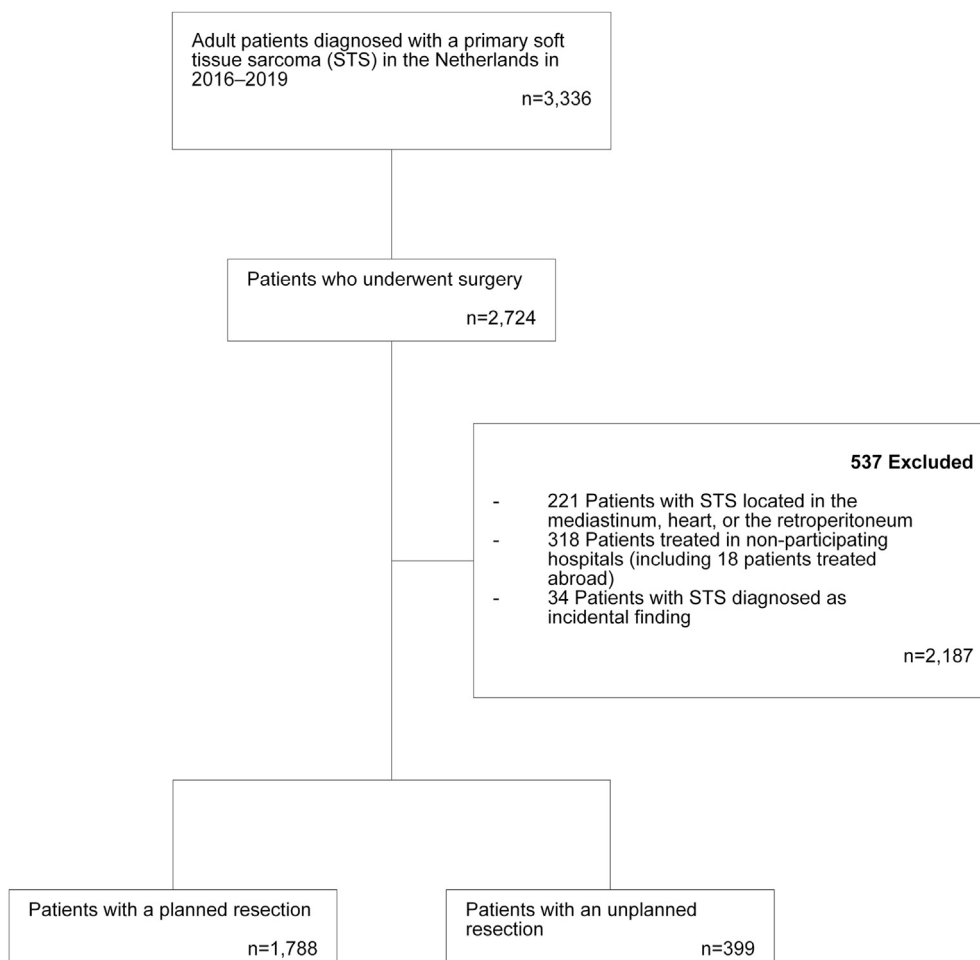


Fig. 1. CONSORT diagram of patient selection.

**Table 1**  
Univariable analyses of determinants of planned and unplanned excisions for adult patients with a primary soft tissue sarcoma (STS).

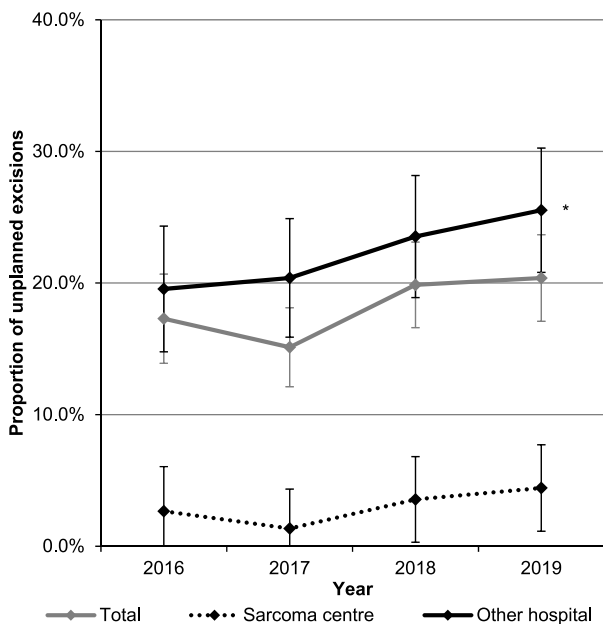
	Total (n = 2187)		Planned excision (n = 1788; 81.8%)		Unplanned excision (n = 399; 18.2%)		
	n	%	n	%	n	%	p
<b>Sex</b>							0.57
Male	1293	59.1%	1052	58.8%	241	60.4%	
Female	894	40.9%	736	41.2%	158	39.6%	
<b>Age at diagnosis, years</b>							<0.01
18–49	500	22.9%	382	21.4%	118	29.6%	
50–64	518	23.7%	418	23.4%	100	25.1%	
65–74	495	22.6%	432	24.2%	63	15.8%	
≥75	674	30.8%	556	31.1%	118	29.6%	
median (interquartile range)	66 (51–77)		67 (53–77)		63 (47–76)		
<b>Tumour site</b>							<0.01
Head and neck	486	22.2%	385	21.5%	101	25.3%	
Trunk	673	30.8%	546	30.5%	127	31.8%	
Upper extremities	305	14.0%	233	13.0%	72	18.1%	
Lower extremities	723	33.1%	624	34.9%	99	24.8%	
<b>Clinical tumour size</b>							<0.01
≤5 cm	1007	46.0%	764	42.7%	243	60.9%	
>5 cm	911	41.7%	848	47.4%	63	15.8%	
Unknown	269	12.3%	176	9.8%	93	23.3%	
<b>Tumour depth (2016)</b>							<0.01
Superficial	316	65.8%	246	62.0%	70	84.3%	
Deep	137	28.5%	128	32.2%	9	10.8%	
Unknown	27	5.6%	23	5.8%	4	4.8%	
<b>Preoperative imaging</b>							<0.01
No	930	42.5%	636	35.6%	294	73.7%	
Yes	1257	57.5%	1152	64.4%	105	26.3%	
<b>Location of first surgery</b>							<0.01
Sarcoma centre	862	39.4%	836	46.8%	26	6.5%	
Other hospital	1227	56.1%	952	53.2%	275	68.9%	
General practitioner/private practice	98	4.5%	0	0.0%	98	24.6%	

likely compared to first surgeries in another location (OR 7.77; 95% CI: 5.07–11.91). Tumour depth was excluded from the model as it was not evaluated as a significant determinant in an analysis

focusing on cases diagnosed in 2016 only (data not shown). The analysis excluding the sarcoma centres (Table 2B) identified that elderly patients (OR 0.55 for those aged 65–74 years; 95% CI: 0.37–0.83; OR 0.56 for those aged 75 years or over; 95% CI: 0.39–0.80 compared to those aged 18–49 years) and larger tumours were less likely involved in an unplanned excision (OR 0.48; 95% CI: 0.33–0.69 compared to those with smaller tumours). Also, preoperative imaging was significantly associated with a lower odds of an unplanned excision after adjustment for the other factors (OR 0.38, 95% CI: 0.28–0.52). Tumour sites of the head and neck region and upper extremity appeared to approach statistical significance compared to the trunk, for a decreasing (OR 0.71, 95% CI: 0.49–1.02) and an increasing effect (OR 1.45, 95% CI: 0.98–2.14), respectively.

### 3.3. Postsurgical management

Outcomes of surgery were determined for 2103 patients (96.2%), of whom 391 (18.6%) had undergone an unplanned excision. The majority of unplanned excisions resulted in residual disease: microscopic disease at the margin (R1) was observed in 58.8% of cases compared to 28.9% after planned procedures (p < 0.01; Table 3), and macroscopic margins (R2) in 6.4% compared to 2.0% (p < 0.01). As a result, more patients underwent a re-excision following a primary unplanned excision (68.0%) than after a planned resection (18.3%; p < 0.01), and adjuvant radiotherapy was more often administered (18.4% versus 10.4%, p < 0.01). After an initially unplanned excision outside a sarcoma centre, the majority of patients (67.4%) was referred to or discussed with a sarcoma centre (compared to 39.8% in case of a planned procedure). This proportion was even higher for patients left with residual disease following an unplanned excision (72.3%, compared to 53.0% in case of a planned procedure).



\* statistically significant trend over time

**Fig. 2.** Proportion of unplanned excisions in sarcoma centres and other hospitals over time, with 95%-confidence intervals\* statistically significant trend over time.

**Table 2A**  
Overall multivariable analysis of determinants of unplanned excisions.

		n	Odds ratio	95%CI
<b>Age at diagnosis (years)</b>	18–49	500	1.00	(ref)
	50–64	518	0.85	0.60–1.19
	65–74	495	*0.55	0.38–0.79
	≥75	674	*0.52	0.37–0.74
<b>Tumour site</b>	Trunk	673	1.00	(ref)
	Head and neck	486	0.72	0.51–1.03
	Upper extremities	305	1.36	0.94–1.97
	Lower Extremities	723	1.17	0.85–1.62
<b>Clinical tumour size</b>	≤5 cm	1007	1.00	(ref)
	>5 cm	911	*0.45	0.32–0.63
	Unknown	269	1.09	0.78–1.51
<b>Preoperative imaging</b>	No	930	1.00	(ref)
	Yes	1257	*0.39	0.29–0.52
<b>Location of first surgery</b>	Sarcoma centre	862	1.00	(ref)
	Outside sarcoma centre	1325	*7.77	5.07–11.91

Area under the curve (AUC): 0.81.

\* Statistically significant (p < 0.05).

**Table 2B**  
Multivariable analysis of determinants of unplanned resections outside sarcoma centres.

		n	Odds ratio	95%CI
<b>Age at diagnosis (years)</b>	18–49	292	1.00	(ref)
	50–64	288	0.92	0.64–1.33
	65–74	264	*0.55	0.37–0.83
	≥75	481	*0.56	0.39–0.80
<b>Tumour site</b>	Trunk	432	1.00	(ref)
	Head and neck	374	0.71	0.49–1.02
	Upper extremities	183	1.45	0.98–2.14
	Lower Extremities	336	1.26	0.89–1.77
<b>Clinical tumour size</b>	≤5 cm	737	1.00	(ref)
	>5 cm	368	*0.48	0.33–0.69
	Unknown	220	1.12	0.80–1.57
<b>Preoperative imaging</b>	No	782	1.00	(ref)
	Yes	543	*0.38	0.28–0.52

AUC: 0.70.

\* Statistically significant (p < 0.05).

3.4. 'Potential' versus actual unplanned excisions

Application of the previously used proxy to determine 'potential' unplanned excisions [22,23], which was based on coinciding

dates of surgery and first histopathological confirmation, would have resulted in 926 procedures designated as unplanned excisions. This would have accounted for 42.3% of the total number of performed procedures, compared to the overall unplanned excision

**Table 3**  
Postsurgical management of planned and unplanned excisions.

	Total		R0		R1		R2		RX	
	n	%	n	% of total	n	% of total	n	% of total	n	% of total
<b>Planned excision</b>	1712	81.4%	1051	61.4%	495	28.9%	35	2.0%	131	7.7%
<b>Treatment following first surgery</b>										
None	1248	72.9%	922	73.9%	213	17.1%	20	1.6%	93	7.5%
Re-excision	286	16.7%	59	20.6%	198	69.2%	6	2.1%	23	8.0%
Re-excision + RTx	27	1.6%	1	3.7%	22	81.5%	0	0.0%	4	14.8%
RTx	151	8.8%	69	45.7%	62	41.1%	9	6.0%	11	7.3%
<b>Sarcoma centre involvement</b>										
First surgery in sarcoma centre	804	47.0%	566	70.4%	184	22.9%	16	2.0%	38	4.7%
Referral to/consultation with sarcoma centre	361	21.1%	147	40.7%	166	46.0%	9	2.5%	39	10.8%
Not referred to/consulted with sarcoma centre	547	32.0%	338	61.8%	145	26.5%	10	1.8%	54	9.9%
<b>Unplanned excision</b>	391	18.6%	79	20.2%	230	58.8%	25	6.4%	57	14.6%
<b>Treatment following first surgery</b>										
None	104	26.6%	51	47.2%	25	23.1%	4	3.7%	24	22.2%
Re-excision	215	55.0%	20	9.1%	156	71.2%	15	6.8%	24	11.0%
Re-excision + RTx	51	13.0%	0	0.0%	40	78.4%	4	7.8%	7	13.7%
RTx	21	5.4%	8	38.1%	9	42.9%	2	9.5%	2	9.5%
<b>Sarcoma centre involvement</b>										
First surgery in sarcoma centre	26	6.6%	12	46.2%	11	42.3%	2	7.7%	1	3.8%
Referral to/consultation with sarcoma centre	246	62.9%	31	12.6%	158	64.2%	17	6.9%	40	16.3%
Not referred to/consulted with sarcoma centre	119	30.4%	36	30.3%	61	51.3%	6	5.0%	16	13.4%

rate of 18.2% as established by this study—an overestimation with a factor of approximately 2.3.

#### 4. Discussion

Unplanned excisions represent a complex part of optimal STS management. According to this population-based study, they occur in almost one-fifth of first surgeries, and a quarter of them are performed outside hospitals. Although the overall rate appears to correspond with the lower estimates found by other studies [14,15], the present findings are assumedly much less affected by patient selection effects. To be sure, the low rates achieved by sarcoma centres may in part be explained by the diagnostic expertise of dedicated multidisciplinary teams, but should also be interpreted with reference to their specific patient populations. Firstly, given referral of cases suspected for STS to these centres, their *a priori* likelihood of malignancy is considerably higher, resulting in a more 'favourable' ratio of benign and malignant soft tissue tumours. At the same time, ratios depend on local referral patterns more directly as well. As has been demonstrated by this study, patients from other hospitals were more often referred to sarcoma centres after an unplanned excisions compared to a planned procedure.

Apparent discrepancies with other population-based studies may also be explained by differences in patient selection. Aside from the more elderly population and some differences in the inclusion of STS subtypes, Bateni et al. (unplanned excision rate: 36.9%) examined a comparatively earlier study period, namely 1992–2011 [17]. Their analyses could therefore not have accounted for advances in STS diagnostics and changes in referral patterns during the past decade. This also applies—albeit to a lesser extent—to the study conducted by Nakamura et al. [18], who reported on the time period 2006–2016. More importantly, it remains unclear whether their study included unplanned excisions that occurred outside hospitals. Indeed, our within-hospital rate of unplanned excisions comes closer to the rate reported by Nakamura et al. than our overall rate including unplanned excisions carried out by general practitioners and private practices.

The study findings confirm the main challenges in preventing unplanned excisions by means of care provider education on approaching potential STS [24,25]. Notwithstanding the trend towards centralisation of STS surgery that has taken place in the Netherlands and in other countries, not least because of the better outcomes achieved by sarcoma centres [22,26], soft tissue tumours will continue to be encountered in the average practice of general practitioners and general surgeons. With the vast majority of these eventually turning out to be benign lesions, a certain proportion of unplanned excisions cannot be prevented and should perhaps be considered 'all-in-the-game', particularly those of small, superficial lumps that lack any clinically suspicious signs of an STS.

On the other hand, some observations of this study do raise concern and emphasize education as a necessary means to standardise STS management, thereby stimulating better adherence to imaging and referral guidelines. The trend analyses suggest that the proportion of unplanned excisions in non-sarcoma centre hospitals is increasing over time. This need not be alarming in itself, and could even constitute a promising side effect of centralisation when more STS are timely recognized and referred to sarcoma centres. If so, unplanned excisions would increasingly concern small and superficial tumours. However, there was still a considerable number of large STS that had been excised without preoperative imaging or biopsy. Also, it seems that more than a quarter of patients who were left with residual disease after an unplanned excision outside a sarcoma centre was still not discussed with or referred to one the centres.

Fortunately, unplanned excisions do not necessarily entail an unfavourable prognosis for patients. The potential of salvage re-

excision has long been propagated [27], to the point that patients who underwent second surgery were considered to fare even better than those who only required one definitive radical operation [28]. Surely, re-excision remains warranted following an unplanned excision of a high-grade STS [5,7,29], possibly preceded by radiotherapy [30,31], potentially leading to higher morbidity. The debate has been raised, however, whether this invariably holds true for unplanned excisions of low-grade, smaller tumours [32,33], and those following a macroscopic complete result [3]. Although refraining from or delaying second surgery may elevate patients' risk of developing a local recurrence, this does not necessarily translate to poorer survival [3,16,34].

The observational design of the present study does call for some considerations in interpreting the results. The analyses substantially relied on data that had been routinely collected for the national cancer registry, with accuracy and completeness largely depending on the data quality of electronic records in hospitals. The study database therefore lacked more detailed information on patients' health status, surgical procedures and complications of treatment. For future evaluations on outcomes following unplanned excisions, the NCR has yet to register data on STS recurrence in the cohort studied here. Obviously, this first and foremost requires additional years of follow-up.

The NCR did start to collect more in-depth data on whether surgical procedures were planned or unplanned. The systematic and focused registry by specialised data managers resulted in a more precise estimate on the intent of STS surgery compared to previous studies [22,23]. The previously used proxy on the basis of overlapping dates of surgery and first histopathological confirmation of STS diagnosis would have led to a two- to threefold higher rate of unplanned excisions when applied to the current study cohort.

The above adds to the population-based coverage as the study's main strengths. As they could be performed on a complete STS population, the analyses accounted for a comprehensive assessment of unplanned excisions, not restricted to cases seen or treated by specialized centres. This may also prove pivotal in evaluating the follow-up of STS patients after an unplanned excision, in addition to, for example, research into more patient centred outcomes [35]. Information generated by comprehensive registries may thus contribute to more optimal management of STS following unplanned resections.

#### 5. Conclusion

Unplanned excisions occurred in approximately 18% of all first surgeries for STS and were mostly performed on small superficial tumours. A quarter of these procedures took place outside hospitals. These patients more often had residual disease after surgery and subsequently received a re-excision and radiotherapy more often. Potential improvement may be achieved by better compliance to preoperative imaging and referral guidelines, and by stimulating continuous awareness of STS among general surgeons, general practitioners and private practices.

#### CRediT authorship contribution statement

**Annemarie S. Melis:** Formal analysis, Software, Validation, Investigation, Writing – original draft. **Melissa Vos:** Conceptualization, Writing – review & editing. **Melinda S. Schuurman:** Formal analysis, Methodology, Software, Writing – review & editing. **Thijs van Dalen:** Writing – review & editing. **Winan J. van Houdt:** Writing – review & editing. **Jos A. van der Hage:** Writing – review & editing. **Yvonne M. Schrage:** Writing – review & editing. **Lukas B. Been:** Writing – review & editing. **Johannes B. Bonenkamp:**

Writing – review & editing. **Marc H.A. Bemelmans:** Writing – review & editing. **Dirk J. Grünhagen:** Writing – review & editing. **Cornelis Verhoef:** Writing – review & editing. **Vincent K.Y. Ho:** Supervision, Conceptualization, Methodology, Formal analysis, Software, Validation, Investigation, Data curation, Writing – original draft.

### 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.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejso.2021.11.123>.

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