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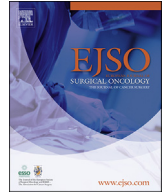
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## The oncological outcomes of isolated limb perfusion and neo-adjuvant radiotherapy in soft tissue sarcoma patients - A nationwide multicenter study

V.M. van Praag<sup>a, \*</sup>, M. Fiocco<sup>b, c</sup>, R.F. Bleckman<sup>d</sup>, W.J. van Houdt<sup>e</sup>, R.L.M. Haas<sup>f</sup>,  
C. Verhoef<sup>g</sup>, D.J. Grunhagen<sup>g</sup>, R.J. van Ginkel<sup>d</sup>, J.J. Bonenkamp<sup>h</sup>, M.A.J. van de Sande<sup>a</sup>

<sup>a</sup> Department of Orthopaedic Surgery, Leiden University Medical Centre, Albinusdreef 2, 2333 ZA, Leiden, the Netherlands

<sup>b</sup> Mathematical Institute, Leiden University, Niels Bohrweg 1, 2333 CA, Leiden, the Netherlands

<sup>c</sup> Department of Biomedical Data Science, Section Medical Statistics, Leiden University Medical Centre, Albinusdreef 2, 2333 ZA, Leiden, the Netherlands

<sup>d</sup> Department of Surgical Oncology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

<sup>e</sup> Department of Surgical Oncology, Netherlands Cancer Institute, Amsterdam, the Netherlands

<sup>f</sup> Department of Radiotherapy, Netherlands Cancer Institute, Amsterdam, and the LUMC, Leiden, the Netherlands

<sup>g</sup> Erasmus MC-Cancer Institute, Department of Surgical Oncology, 's Gravendijkwal 230, 3015 CE, Rotterdam, the Netherlands

<sup>h</sup> Radboud University Medical Center, Department of Surgical Oncology, P.O. Box 9101, 6500 HB, Nijmegen, the Netherlands

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### ABSTRACT

**Introduction:** Patients with locally extensive high-grade extremity soft tissue sarcomas (eSTS) are often presented in multidisciplinary teams to decide between ablative surgery (amputation) or limb-salvage surgery supplemented with either neo-adjuvant radiotherapy (RT) or induction isolated limb perfusion (ILP).

In The Netherlands, ILP typically aims to reduce the size of tumors that would otherwise be considered irresectable, whereas neo-adjuvant RT aims mainly at improving local control and reducing morbidity of required marginal margins.

This study presents a 15-year nationwide cohort to describe the oncological outcomes of both pre-operative treatment strategies.

**Methods:** All consecutive patients with locally extensive primary high-grade eSTS surgically treated between 2000 and 2015 at five tertiary sarcoma centers that received neo-adjuvant ILP or RT were included. 169 patients met the inclusion criteria (89 ILP, 80 RT). Median follow-up was 7.3 years.

**Results:** Limb salvage was achieved in 84% of cases in the ILP group (80% for patients with amputation indication) and 96% of cases in the RT group. 5-Year overall survival was 47% in the ILP group, 69% in the RT group. 5-Year local recurrence rate was 14% in the ILP group, 10% in the RT group. Distant metastasis rate was 55% in the ILP group, 36% in the RT group.

**Conclusion:** We find oncological outcomes and limb salvage rates in line with existing literature for both treatment modalities. Whether the tumor was locally advanced with an indication for induction therapy to prevent amputation or morbid surgery appeared to be the main determinant in choosing between neo-adjuvant ILP or RT.

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## 1. Introduction

In soft tissue sarcomas of the extremities (eSTS) surgical resection is mainstay of treatment. Treatment is aimed at optimizing

local control and overall survival rates while salvaging the limb if possible. The standard procedure is to supplement surgery with neo-adjuvant or adjuvant radiotherapy to improve local control.

In randomized trials comparing surgery with radiotherapy and without, radiotherapy shows a protective effect on local recurrences; however no clear association with distant metastases, disease-specific- or overall survival has been found [1,2]. To our knowledge, local control is not influenced by the timing of

\* Corresponding author.

E-mail address: [v.v.praag@gmail.com](mailto:v.v.praag@gmail.com) (V.M. van Praag).

**Table 1**  
Baseline study population characteristics. Overall distribution and by treatment group.

Characteristic	Overall (n = 169)	RT and surgery (n = 80)	ILP and surgery (n = 89)	p-value
Age (mean [SD])	58.28 (19.39)	60.9 (16.9)	54.3 (16.1)	0.012*
Male (N [%])	50.9% (86)	50.0% (40)	51.7% (46)	0.827
Tumor depth (N [%]) <sup>a</sup>				0.001*
<b>Deep</b>	83.8% (140)	73.8% (59)	93.1% (81)	
<b>Superficial</b>	16.2% (27)	26.3% (21)	6.9% (6)	
<b>Missing</b>	2	—	2	
Tumor size in cm (mean [SD])	9.9 (5.7)	9.6 (5.7)	10.1 (5.7)	0.522
Tumor location (N [%])				0.020*
<b>Arm, proximal incl. Shoulder or Leg, proximal incl. Hip</b>	55.6% (94)	65.0% (52)	47.2% (42)	
<b>Arm, distal incl. Hand or Leg, distal incl. Knee</b>	44.4% (75)	35.0% (28)	52.8% (47)	
<b>Missing</b>	—	—	—	
Tumor histology (N [%])				0.039*
<b>MFH/UPS and NOS</b>	33.7% (57)	35.0% (28)	32.6% (29)	
<b>Myxofibrosarcoma</b>	16.0% (27)	17.5% (14)	14.6% (13)	
<b>Other</b>	18.9% (32)	16.3% (13)	21.3% (19)	
<b>SS</b>	13.6% (23)	7.5% (6)	19.1% (17)	
<b>LMS</b>	6.5% (11)	6.3% (5)	6.7% (6)	
<b>LPS</b>	11.2% (19)	17.5% (14)	5.6% (5)	
<b>Missing</b>	—	—	—	
Tumor grade in FNCLCC (N [%])				0.183
<b>II</b>	13.6% (23)	17.5% (14)	10.1% (9)	
<b>III</b>	86.4% (146)	82.5% (66)	89.9% (80)	
<b>Missing</b>	—	—	—	
Neurovascular bundle (N [%])				<0.001*
<b>Ingrowth</b>	0.7% (1)	—	1.5% (1)	
<b>Adjacent</b>	26.9% (36)	13.0% (9)	41.5% (27)	
<b>No contact</b>	72.4% (97)	87.0% (60)	56.9% (37)	
<b>Missing</b>	35	11	33	
Ingrowth into joint (N [%])				0.038*
<b>Yes</b>	16.6% (28)	10.0% (8)	22.5% (20)	
<b>No</b>	83.4% (141)	90.0% (72)	77.5% (69)	
<b>Missing</b>	—	—	—	
Bone (N [%])				0.011*
<b>Infiltration marrow</b>	0.7% (1)	—	1.5% (1)	
<b>Infiltration cortex</b>	9.0% (12)	4.5% (3)	13.2% (9)	
<b>Dubious whether involvement</b>	20.1% (27)	12.1% (8)	27.9% (19)	
<b>No involvement</b>	70.1% (94)	83.3% (55)	57.4% (39)	
<b>Missing</b>	35	12	21	
Amputation indication (N [%])				<0.001*
<b>Yes</b>	37.9% (65)	6.3% (5)	66.3% (59)	
<b>No</b>	62.1% (105)	93.8% (75)	33.7% (30)	
<b>Missing</b>	—	—	—	

-Note: abbreviations: N, number of patients; SD, standard deviation; IQR, interquartile range; RT, radiotherapy; ILP, isolated limb perfusion; MFH/UPS, malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma; MPNST, malignant peripheral nerve sheath tumour; n/a, not applicable.

<sup>a</sup> Depth: relative to the investing fascia.

radiotherapy [3]. However, the incidence and type of complications do differ for neo-adjuvant vs. adjuvant radiotherapy. The risk of developing wound complications is higher for neo-adjuvant radiotherapy administration than adjuvant [4]. Risk factors for developing wound complications are adipose, tobacco use (during treatment), superficial tumors and locations in the lower extremity [5]. One year postoperative, functional mean scores do not differ significantly [6]. In the long-term, patients that received adjuvant radiotherapy are more likely to develop fibrosis, stiff joints and edema, causing a lower functional outcome [7]. If both radiotherapy timings are possible for a given patient, current clinical guidelines therefore prescribe neo-adjuvant rather than adjuvant radiotherapy if wound complications are considered to be a manageable problem [3].

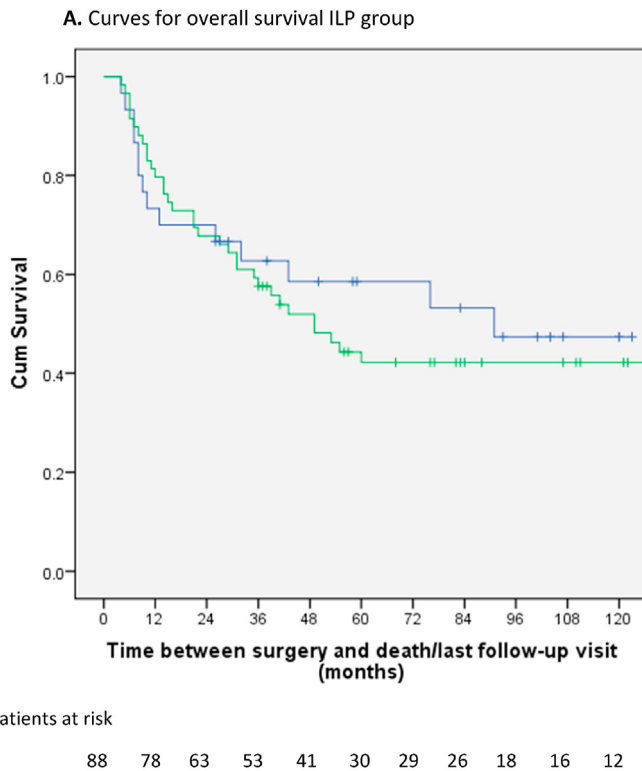
As eSTS are mostly asymptomatic, this often allows the tumor to grow undisturbed and results in generally large (>5 cm) tumors (especially in the upper leg and pelvis) that are locally advanced, meaning the tumor involves or attaches to nearby tissues or organs [8]. These tumors often require mutilating surgery with impaired limb function or an amputation of the affected extremity as result, especially when the tumor has grown close to important structures such as joints, nerves or blood vessels [8]. In these cases, neo-

adjuvant treatment is a strategy to avoid mutilating surgery or amputation, often allowing for marginal surgical excision and limb salvage [9].

If neo-adjuvant RT is not expected/considered to be helpful in providing limb salvage surgery, isolated limb perfusion (ILP), where a combination of Melphalan (M) and tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) are administered in high dosage, is an alternative treatment strategy. Several studies have shown promising results of ILP as neoadjuvant treatment in locally advanced STS [9–11] with high complete pathological response rates [12]. ILP (with or without adjuvant RT) was shown to have similar oncological outcomes to only adjuvant RT [13]. In eSTS, both neoadjuvant RT and ILP show high limb salvage rates and excellent local control. For neoadjuvant radiotherapy, limb salvage rates of 89%–99% were found. For ILP limb salvage rates of 80–88% were reported [9,14,15].

In The Netherlands, the primary aim of the optional neo-adjuvant treatment strategies differs. ILP typically aims to reduce the size of tumors that would otherwise be considered irresectable, whereas neo-adjuvant RT is the common treatment choice in limb-salvageable cases and aims mainly at improving local control and reducing required surgical margins.

Here we present the results of five tertiary sarcoma centers in



-Note: **Green** amputation indication. **Blue** no amputation indication.

**Fig. 1A.** Curves for overall survival ILP group.

-Note: **Green** amputation indication. **Blue** no amputation indication.

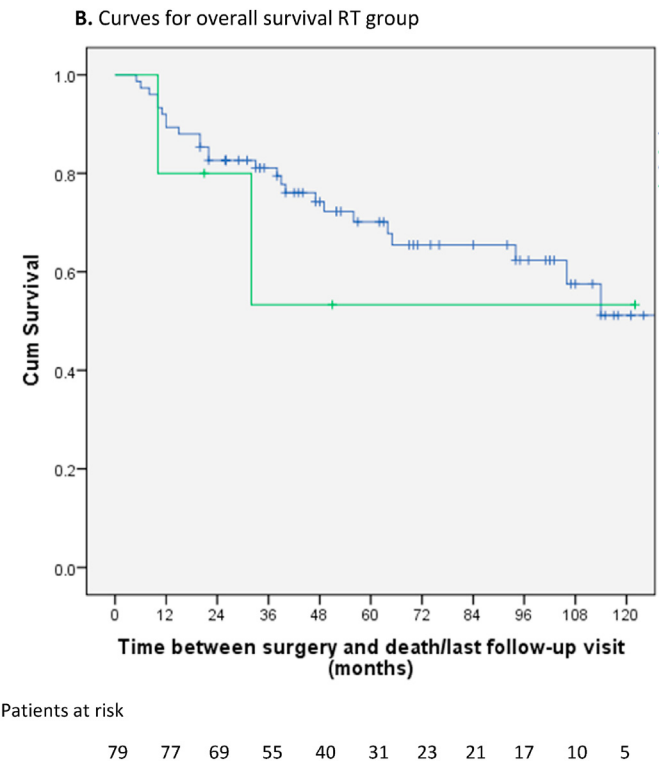
the Netherlands that participated in this study on multi-modality treatment of high-grade eSTS. This allowed for the primary aim of this nationwide multicenter study: to describe oncological outcome and limb salvage rates for both treatment modalities in eSTS.

## 2. Patients and methods

### 2.1. Patients

For this study all consecutive patients with locally advanced primary high-grade extremity STS without distant metastasis (DM) or local recurrence (LR) at presentation, treated at one of the five tertiary sarcoma centers in the Netherlands between 2000 and 2015, were evaluated. All included patients had a follow-up of at least two years or experienced an event before that date, were planned for surgical treatment with curative intent and received either neo-adjuvant induction ILP or neo-adjuvant radiotherapy to facilitate limb-salvage. Patients who received neo-adjuvant systemic chemotherapy or intraoperative RT were excluded, as well as patients who received both ILP and neo-adjuvant RT. Median follow-up was calculated by reverse Kaplan Meier and was equal to 7.3 years (95% CI 6.0–8.7 years) [16].

A total of 169 patients met the inclusion criteria (Fig. 3). Eighty-nine patients were treated with induction ILP and surgery (74% received additional adjuvant radiotherapy), while 80 received neo-adjuvant RT and surgery.



-Note: **Green** amputation indication. **Blue** no amputation indication.

**Fig. 1B.** Curves for overall survival RT group.

-Note: **Green** amputation indication. **Blue** no amputation indication.

### 2.2. Treatment indications

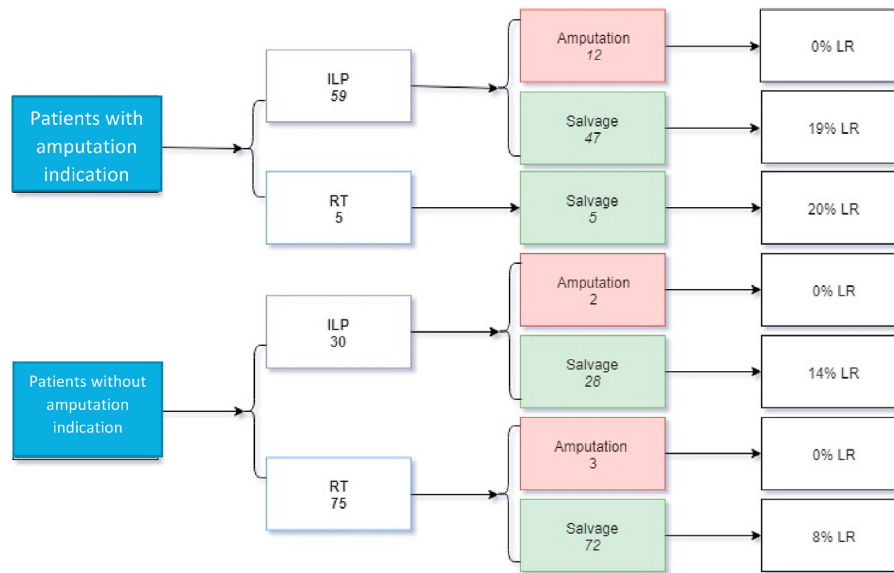
In the centers covered by this study, ILP is indicated for patients with an amputation indication where the tumor is believed to be resectable after ILP with oncological acceptable margins and functional outcomes comparable to or better than amputation. Neo-adjuvant RT is indicated for high-grade tumors where a narrow surgical margin is expected due to the anatomic relation with surrounding structures and based on the expected impact on limb functionality of resection vs. resection with a narrower margin supplemented with neo-adjuvant RT.

### 2.3. Histological types

The different histological types of STS were classified according to the WHO Tumors of Soft tissue and Bone classification. This classification has been updated in 2013 resulting in an elimination of the category Malignant Fibrous Histiocytoma and an addition of the new category Undifferentiated Pleomorphic Sarcoma. The histological types have not been reviewed by a central pathologist but to avoid misclassification between the old and the new WHO classification these two categories have been classified together under sarcoma-NOS.

### 2.4. Data collection

All data were collected by the same person, and reviewed by a second person, from five sarcoma centers patients' files in the



- Note: Abbreviations: ILP, isolated limb perfusion; RT, radiotherapy.

**Fig. 2.** Success rates for limb salvage per indicated treatment group.

- Note: Abbreviations: ILP, isolated limb perfusion; RT, radiotherapy.

**Table 2**

Treatment per neo-adjuvant group.

Characteristic	Overall (n = 169)	RT and surgery (n = 80)	ILP and surgery (n = 89)	p-value
Margin (N [%])				<0.001*
<b>Wide (&gt;2 mm)</b>	24.3% (35)	32.9% (24)	15.5% (11)	
<b>Marginal (0.1-2 mm)</b>	49.3% (71)	53.4% (39)	45.1% (32)	
<b>Intralesional (&lt;0.1 mm)</b>	26.4% (38)	13.7% (10)	39.5% (28)	
<b>Missing</b>	25	7	18	
Amputation (N [%])				0.011*
<b>No</b>	89.9% (152)	96.3% (77)	84.3% (75)	
<b>Yes</b>	10.1% (17)	3.8% (3)	15.7% (14)	
<b>Missing</b>	—	—	—	
Additional RT (N [%])				
<b>Neo-adjuvant</b>	47.3% (80)	100% (80)	—	
<b>Adjuvant</b>	39.1% (66)	—	74.2% (66)	
<b>No RT</b>	13.6% (23)	—	25.8% (23)	
<b>Missing</b>	—	—	—	
Time diagnosis to surgery in months (median [IQR])		3.5 (3.1–4.2)	3.5 (2.7–4.5)	0.713

-Note: abbreviations: N, number of patients; SD, standard deviation; IQR, interquartile range; RT, radiotherapy; ILP, isolated limb perfusion.

Netherlands to avoid difference in interpretation of the collected variables. Characteristics such as patients age, gender, tumor grade and histological type were similar to those found in other studies of high-grade eSTS (Table 1).

### 2.5. Amputation indication

Sarcomas that were considered irresectable or only resectable at the cost of major functional morbidity were identified at the local multidisciplinary team meeting. At least one of the following tumor-associated criteria was observed: multifocal and large tumors; single tumors with fixation to or invasion into the neurovascular bundle and/or bone; tumors located in the ankle, wrist, hand or foot with no possibility for a resection with free margins. Marginal curative resections, i.e. resections with a free margin, preserving limb function, based on clinical examination, computed tomography and magnetic resonance imaging scans, were

considered impossible in these patients without extensive (neo-) adjuvant therapy.

### 2.6. Statistical analysis

The primary outcomes for this study were: five-year cumulative incidence for local recurrence (LR), five-year overall survival (OS), distant metastasis (DM) percentage, limb salvage and percentage of limb salvage for patients with an amputation indication. Five-year survival was estimated using Kaplan-Meier's methodology. To estimate the cumulative incidence of LR a competing risk model with death as competing event was used [17]. Baseline characteristics for the population are reported. Continuous variables are reported as mean and standard deviation while categorical variables are presented as counts and proportion. Difference between the two groups at baseline are assessed by using the independent *t*-test and the chi-square test for continuous and categorical variables

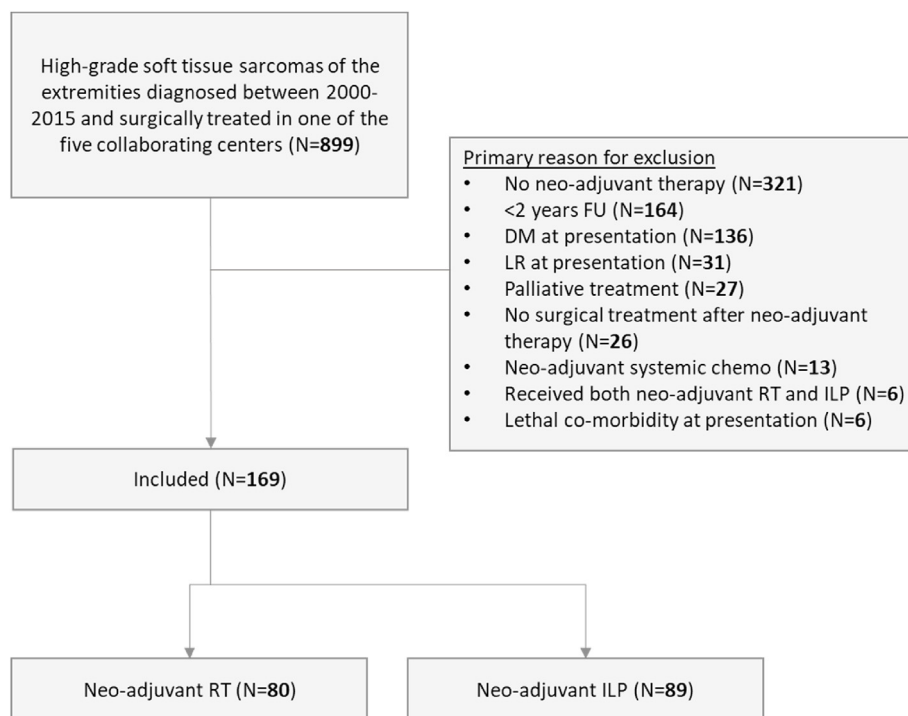


Fig. 3. Flowchart detailing patient inclusion.

respectively. All analysis concerning the competing risk model has been performed with the `mstate` library [18] in R environment [19].

### 3. Results

#### 3.1. Study population characteristics

The mean age of the study population was 58 years (SD 19) (Table 1). At last follow-up time 44% (74) patients had died. The median time between diagnosis and surgery in both the ILP and RT group was 3.5 months (IQR 2.7–4.5 and 3.1–4.2, respectively).

Both treatment groups did not differ statistically on gender, tumor size, tumor grade and time between diagnosis and surgery. Patients in the ILP group were significantly younger and the tumors were more often deeply seated, had a different spread of histological subtypes (e.g. more synovial sarcoma in the ILP group and more liposarcomas in the RT group) and had more often grown into or were adjacent to the neurovascular bundle, joint or bone (Table 1). Patients in the ILP group were also more likely to have been indicated for amputation (66%) when compared to patients in the RT group (6%) and were more likely to have a distally located tumor (53% vs. 35%) (Table 1).

#### 3.2. Outcomes

The limb salvage percentage at final follow-up was 84% in the ILP group (80% for patients with amputation indication) and 96% in the RT group (100% for patients with amputation indication) (Table 2 and Fig. 2). Five-year OS was 47% in the ILP group and 69% in the RT group (Fig. 1). Five-year LR rate was 14% in the ILP group and 10% in the RT group. DM rate was 55% in the ILP group and 36% in the RT group.

### 4. Discussion

Given the difference in indication for neo-adjuvant ILP vs. RT

and the resulting difference in patient populations, no direct comparison can be made between the groups in terms of outcomes. Rather, this study was able to detail the oncological outcomes and limb salvage rates of the two neo-adjuvant treatment modalities, independent of each other, using a relatively large nationwide sample.

Overall limb salvage percentage and limb salvage percentage for patients with amputation indication are very acceptable in both groups. Limb salvage percentages found for both neo-adjuvant RT and induction ILP are in line with existing literature [2,5].

Patients in this ILP group more often had synovial sarcomas and were younger than in the RT group. The tumors had more often grown into their surroundings (bone, joint and neurovascular structures) and were more often deeply seated in the ILP group (Table 1). This is as expected based on the previously described indications for ILP. Tumors in the ILP group were also more often distally located, which is likely due to the technical impossibility of isolating the limb in some cases of a rather proximally located tumor.

It is notable that tumor size is similar in the two groups in our study (Table 1). Whether the tumor is locally advanced and whether the tumor is located proximally or distally made the difference in determining treatment modality, not size.

The 5-year OS in the ILP group (47%) is in line with existing literature (42–59%) [11,20–22]. The 5-year OS in the RT group (69%) is at the higher end of the outcomes reported in literature (59–72%) [4,23–26]. This range of outcomes is based on studies looking at both adjuvant and neo-adjuvant RT, as the timing of RT appears not to impact survival [3].

LR in the ILP group is the same as the rate (14%) found in a Dutch study looking at patients treated at a single institution between 1991 and 2011 [20]. A higher LR rate is reported in an Italian study looking at patients treated between 1982 and 2005 at a single institution (25% for the group receiving TNF-ILP) [22]. This may be explained by slight differences in indication for ILP, or by the fact that all our patients are treated in the past two decades. For RT,

studies have tended to find an LR rate below 15% is achievable [1,27], in line with our outcome (10%). Rates of DM in our ILP group (55%) are above those reported in existing literature (36–43%) [20,22]. The rate found in the RT group (36%) is in line with previous findings (27–40%) [23,28].

Partly through the retrospective design, there are a couple of limitations to this study. This study includes all patients diagnosed in 2000–2015, with decreasing doses of TNF $\alpha$  being given over time. In theory this could impact oncological outcomes. However, Deroose et al. have evaluated the treatment results of two periods, 1991–2003 and 2003–2012, with high-dose and reduced-dose of TNF $\alpha$ , respectively. No statistical differences were observed in recurrence and overall survival between the two study periods [10]. Secondly, it would have been preferable for this study to have stratified or made subgroups for tumor histology, as some types are considered more sensitive to chemo- or radiotherapy.

### Author contribution statement

VM van Praag: Conceptualization; Data curation; Formal analysis; Project administration; Writing original draft; Writing review & editing. M Fiocco: Funding acquisition; Methodology; Formal analysis; Visualization; Writing review & editing. RF Bleckman: Data curation; Roles/Writing original draft. WJ van Houdt: Conceptualization; Data curation; Writing review & editing. RLM Haas: Conceptualization; Data curation; Writing review & editing. C Verhoef: Conceptualization; Data curation; Writing review & editing. DJ Grunhagen: Conceptualization; Data curation; Writing review & editing. RJ van Ginkel: Conceptualization; Data curation; Writing review & editing. JJ Bonenkamp: Conceptualization; Data curation; Writing review & editing. MAJ van de Sande: Funding acquisition; Conceptualization; Data curation; Project administration; Writing original draft; Writing review & editing.

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### Ethical approval

The ethics committee of the Leiden University Medical Center issued a “Declaration of no objection” (G16.022) as no persons were subjected to a treatment or were required to behave in a certain manner for this study.

### Declaration of competing interest

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

### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejso.2022.08.018>.

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