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PII: S0959-8049(23)00301-5

DOI: https://doi.org/10.1016/j.ejca.2023.112949

Reference: EJC112949

To appear in: *European Journal of Cancer*

Received date: 29 March 2023
Revised date: 11 May 2023
Accepted date: 13 June 2023

AN INTERNATIONAL MULTI-CENTER STUDY, *European Journal of Cancer,* (2023) doi:https://doi.org/10.1016/j.ejca.2023.112949

VARIATION IN RESPONSE RATES TO ISOLATED LIMB PERFUSION IN DIFFERENT SOFT TISSUE TUMOR SUBTYPES – AN INTERNATIONAL MULTI-CENTER STUDY

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Key words: soft tissue sarcoma, response evaluation, isolated limb perfusion, ILP

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Abstract

Objective: The aim of this study was to investigate response rates of different extremity soft tissue sarcoma subtypes (eSTS) after isolated limb perfusion (ILP), based on an international multicenter study.

Methods: The retrospective cohort comprised eSTS patients from 17 specialized ILP centers that underwent melphalan based ILP, with or without recombinant human (rh)TNFα (respectively TM-ILP and M-ILP). Response was measured on imaging (MRI) and/or clinical response, for which M-ILPs were excluded.

Results: A total of 1109 eSTS patients were included. The three most common histological subtypes were undifferentiated pleomorphic sarcoma (17%, n=184), synovial sarcoma (16%, n=175) and myxofibrosarcoma (8%, n=87). rhTNFα was used in 93% (TM-ILP) and resulted in a significantly better overall response rate (ORR, p=0.031) and complete responses (CR, p<0.001) in comparison to M-ILP, without significant differences among histological subgroups. The ORR of TM-ILP was 68%, including 17% CR. Eight percent showed progressive disease. Significantly higher response rates were shown for Kaposi sarcoma (KS) with 42% CR and 96% ORR (both p<0.001), and significantly higher CR rates for angiosarcoma (AS, 45%, p<0.001) and clear cell sarcoma (CCS, 31%, p=0.049). ILP was followed by resection ≤6 months in 80% of the patients. The overall limb salvage rate (LSR) was 88%, without significant differences among histological subgroups, but was significantly higher for ILP responders compared to non-responders (93% versus 76%, p<0.001).

Conclusion: ILP resulted in high response and LRS among all eSTS subtypes, however with significant differences between subtypes with most promising results for KS, AS and CCS.

Introduction

Soft tissue sarcomas (STS) represent 1% of all malignant tumors in adults with more than 70 histological subtypes[1]. These subtypes vary widely in genotype, clinical presentation and treatment response. STS can occur anywhere in the body, but 75% is located in the extremities (eSTS)[1]. Surgery remains the primary curative strategy for localized eSTS. However if the primary tumor is locally advanced or in case of multifocal/ recurrent sarcoma, curative surgery may result in major functional morbidity or necessitate amputation. Isolated limb perfusion (ILP) involves isolation of the vasculature of an extremity by means of a tourniquet, and cannulas are surgically inserted facilitating the local administration of high dosed melphalan, mostly combined with recombinant human tumor necrosis factor alpha (rhTNFα).

ILP can be used to achieve a complete response in some selected cases, but is more often used to downsize an advanced primary sarcoma to allow marginal function preserving operation that without an ILP would require an amputation. For multifocal or locally recurrent disease within a limb in patients with or without metastases, ILP can be used as a stand-alone procedure to avoid the need for a salvage amputation.

Already since the first ILP publication in 1957 by Creech et al., this procedure has been a part of the treatment options in eSTS[2]. ILP for eSTS has shown to be effective: the procedure leads to a high overall response rates (ORR, 61-83%) and limb salvage rates (LSR, 67%-87%)[3-7]. Many further studies aimed to optimize this procedure, however sarcoma subtype specific response data is limited to date due to the rarity of eSTS in general, and the relatively limited number of ILPs per center. It is established that vascular tumors respond well to ILP[8, 9], but it is quite unclear what the response rate is for other

eSTS subtypes. Therefore, the aim of this international multi-center collaboration was to investigate the subtype-related response rate after ILP, providing valuable information clinical decision-making process of eSTS treatment.

Material and methods

Patients

A multi-center database was set up using Castor EDC[10], after which 17 specialized ILP centers worldwide identified and included data of patients treated with ILP between March 1987 and July 2021. The 17 centers were: Netherland Cancer Institute [Amsterdam, the Netherlands], Royal Marsden Hospital [London, United Kingdom], Erasmus Medical Center [Rotterdam, the Netherlands], Fondazione IRCCS Istituto Nazionale dei Tumori [Milan, Italy], Gustave Roussy Cancer Campus [Villejuif, France], Istituto Oncologico Veneto - IOV [Padua, Italy], Mannheim University Medical Center [Mannheim, Germany], Essen University Hospital [Essen, Germany], Helios Klinikum Berlin-Buch [Berlin, Germany], Institute of Oncology Ljubljana [Ljubljana, Slovenia], Instituto Nacional de Cancerología [Bogota, Colombia], Universitair Ziekenhuis Leuven [Leuven, Belgium], Peter MacCallum Cancer Centre [Melbourne, Australia], Clínica Universidad de Navarra [Pamplona, Spain], National Cancer Institute Mexico [Mexico-City, Mexico], Centre Hospitalier Universitaire Vaudois [Lausanne, Switserland], and Sahlgrenska University Hospital [Gothenburg, Sweden]. Inclusion criteria were eSTS tumors and melphalan based ILP's, with or without rhTNFα (respectively TM-ILP and M-ILP). All ILPs were first time procedures and repeat perfusions were excluded from the study. Patient characteristics and clinical data was obtained from institutional databases or patient files. A total of 1343 patients were identified of which data on ILP response was not available in 212 patients, resulting in a total of 1109 included patients. Although desmoid fibromatosis is not a soft tissue sarcoma, it is considered a borderline soft tissue tumor with locally aggressive behavior which can also be treated with ILP and is

therefore included in this analysis as well. Histological subtype categories were created when ≥10 patients were available per subtype, remainders were classified under 'other'.

Isolated limb perfusion (ILP)

Although specifications of the technique may vary, the procedure has been described extensively elsewhere[11, 12]. In short, the procedure is performed under general anesthesia, the vascularization of the limb is isolated with a tourniquet and cannulas are surgically inserted in both artery and vein. When a stable circuit is formed with minimal to no leakage (monitored by a radioactive label tracer), the limb is perfused with high doses of cytostatics (melphalan, with or without rhTNFα). Local toxicity is assed using the Wieberdink classification[13].

Response evaluation and limb salvage

The primary endpoint of this study was response to ILP. For the response rates and limb salvage rate (LSR) M-ILP's were excluded in order to present data as uniformly as possible. Response was measured by means of imaging (MRI) using the RECIST criteria[14], or when RECIST was not available, by the WHO clinical response criteria[15]. Response is established ±3 months after ILP. The ORR is complete response (CR) and partial response (PR) rate combined.

If performed, subsequent resection in addition to ILP was performed ≤6 months after ILP. Surgical CR by means of subsequent resection after ILP is not included in the response rate. For resection rates and LSR, unknown data was excluded from percentage calculations. LSR is the percentage of patients in in whom the limb can be preserved after ILP and potential subsequential surgery. However if an amputation was needed for a later local recurrence this was considered a new situation, and the patient would be classified as limb salvage for the ILP.

Statistical analysis

All analyses were performed in IBM SPSS version 29.0 for Windows with a significance level of α=0.05. Continuous variables are presented with median and corresponding interquartile range (IQR). Chi square tests were used in case of nominal variables, Mann Whitney-U test for continuous variables in two unpaired groups and Kruskal-Wallis test for continuous variables in more than two unpaired groups. Local progression-free survival (LPFS) included progression after ILP as stand-alone procedure (without subsequent resection) and is calculated from ILP to progression. Local recurrence-free survival (LRFS) included recurrence after subsequent resection of the tumor after ILP and is calculated from resection to recurrence.

Results

Patient, tumor and treatment characteristics

Baseline characteristics are presented in Table 1. The distribution of patients is equal between male and female and the median age at ILP of the total group was 56 years (IQR 40-70). The overall three most common histological subtypes were (1) undifferentiated pleomorphic sarcoma (UPS, 17%, n=184), (2) synovial sarcoma (SS, 16%, n=175), (3) myxofibrosarcoma (MFS, 8%, n=87). The median tumor size for all patients at ILP was 8.7 cm (IQR 5.0-14.0), however unknown in n=338 (30%). Tumors were categorized high grade (FNCLCC II & III) in the majority of the patients (69%, n=765), but the grade was unknown in n=253.

For all ILP treatment specifications see Table 2. Most ILP's were performed for the lower extremity (62%, n=689), and the most commonly used perfusion level was femoral (36%, n=399). All ILP's were melphalan based with a median dose of 70 mg (IQR 50-100). The majority of the ILP's also used rhTNFα (93%) with a median dose of 1 mg (IQR 1-2) for upper extremities, and 2 mg (IQR 1-3) for lower extremities.

Response evaluation

The addition of rhTNFα resulted in a significantly better ORR (p=0.031) and a significantly better CR rate (p<0.001) (Figure 1). No significant difference in response between TM-ILP and M-ILP was observed within the histological subgroups.

For TM-ILP (n=1035), the ORR was 68% with 17% of the patients having a CR (n=180) and 50% a PR (n=520). In 24% (n=251) of the patients stable disease (SD) was observed and 8% (n=84) of the patients had progressive disease (PD). The ORR and CR of the three most common subtypes were respectively (1) UPS: 65% and 12%, (2) SS: 68% and 16%, (3) MFS: 50% and 18%, see Figure 2 and Table A of the supplementary material. Kaposi sarcoma (KS) showed a significantly higher ORR (96%, p<0.001) and CR rate (42%, p<0.001). Angiosarcoma (AS) and clear cell sarcoma (CCS) showed a significantly higher CR rate (45%, p<0.001 and 31%, p=0.049). Significantly lower CR rates were seen in dedifferentiated liposarcoma (DDLPS, 6%, p=0.009) and sarcoma NOS (NOS, 8%, p=0.039). Of the patients that showed PD, significantly higher PD rates were observed for undifferentiated pleomorphic sarcoma with (UPS, 13%, p=0.012).

Surgery and limb salvage

Of all TM-ILP's, in 345 patients information regarding resection was unknown. Of all patients were information regarding resection after ILP was available (n=690), was 20% (n=137) a stand-alone TM-ILP procedure (without subsequent resection) and received 80% (n=553) of the patients ILP with subsequent resection within 6 months. The median time between ILP and resection was two months (IQR 2-3). The indications for subsequent resection after ILP could not be retrieved in most cases.

Information regarding limb salvage rate (LSR) was unknown in 322 (31%) patients, which were excluded for the LSR analysis, leaving 713 evaluable candidates. Of these patients, the overall LSR was

88% (n=624) and 12% (n=89) ultimately received an amputation. There were no significant differences in LSR between the different subtypes, however there was a significantly better LSR in patients responding to ILP compared to non-responders (93% versus 76%, p<0.001).

Local progression or recurrence

Median follow-up (FU) was 27 months (IQR 12-62). Information regarding local progression (after stand-alone TM-ILP, n=137) was unknown in 19 patients. Of all patients were information was available (n=118), 59% (n=70) showed local progression. Of these 70 patients, 14 already showed progression at response evaluation after TM-ILP. The median local progression free interval was 9 months (IQR 5-19).

Information regarding local recurrence (after TM-ILP with subsequent resection, n=553) was unknown in 60 patients. Of all patients were information was available (n=493), 25% (n=125) showed local recurrence. The median local recurrence free interval was 11 months (IQR 4-30).

Discussion

In this study, we report the largest retrospective international multi-center cohort of patients treated with ILP for eSTS, analyzing response rates per histological eSTS subtype. The ORR in our study was 68% with a LSR of 88%, and although there were differences in response rates between the subtypes, this study confirmed that ILP is a valuable and general applicable procedure in eSTS.

This study was designed to illuminate differences in response rates and LSR between the different eSTS subtypes, in order to be able to better tailor the use of ILP for eSTS subtypes. The effectiveness of ILP for all eSTS combined has been proven in multiple studies, and when comparing the overall eSTS results in this study with the ORR and CR rates of other TM-ILP studies, the results are more or less comparable[3-7, 16-24]. The variability in response rate is wide with ORR ranging from 22% to 88%

and CR rates ranging from 5% to 42%[3-8, 16, 17, 19, 21-25]. This wide variation can be explained by the various response evaluation methods that were used, the technical ILP differences between the studies such as different rhTNF doses, by not including non-evaluable patients in the total response rate calculation, or selection biases in patient inclusions. Neuwirth et al. published the most recent (2017) and largest meta-analysis of 19 studies including 1288 eSTS patients[26]. However, they also included ILI procedures and non-melphalan based chemotherapeutic regimens. The merged response rates in this study showed an ORR of 73%, a CR of 26% and a LSR of 74%, more or less comparable to our results. Given that the individual response data linked to subtype was not available in most studies, they were unable to perform subgroup analysis based on histological subtype.

Although our study confirms that all eSTS subtypes show a relatively high response rate to ILP, especially Kaposi sarcoma, angiosarcoma and clear cell sarcoma have significantly better (complete) responses than other subtypes, while dedifferentiated liposarcoma and sarcoma NOS have significantly worse CR rates. The excellent CR rates in angiosarcoma (45%) and Kaposi sarcoma (42%) have been reported before[8, 9]. However, the excellent CR rate of clear cell sarcoma (31%) is a novel finding. At the other end of the spectrum, the dismal CR rates of dedifferentiated liposarcoma (6%) and sarcoma NOS (8%), and of note also the significantly higher PD rate of undifferentiated pleomorphic sarcoma (13%), have also not been reported before. However, these last results did not translate into a difference in ORR or LSR and therefore these histological subtypes are not necessarily a contra-indication for ILP. Other studies have analyzed responses after ILP separately for specific subtypes before, such as for liposarcoma (MLS and PLS, no DDLPS), synovial sarcoma, epithelioid sarcoma and desmoid fibromatosis[27-32]. The response rates in these studies were all comparable with the results from our study.

In our cohort, melphalan was complemented by rhTNFα in 93% of all procedures (TM-ILP), which led to a significantly better response rates (both CR and ORR) compared to M-ILP, reaffirming the value of rhTNFα. rhTNFα was approved in Europe in 1998 after multiple multicenter trials showed superior

response rates of eSTS after the addition of rhTNFα to melphalan for ILPs. Since that moment, TM-ILP has been the standard of care treatment and is recommended by all guidelines. With all evidence over the years, M-ILP should therefore no longer be applied for eSTS.

Despite the high response rates and limb salvation rates, progression and recurrence after ILP (with or without additional surgery) was still seen in 32% of all patients, which indicates that the response is not always durable. Even some patients with a CR who received an additional resection of the tumor area, still recurred. However we still observed a significantly better LSR in patients responding to ILP compared to non-responders (93% versus 76%, $p<0.001$). Also, in addition to the oncological outcome, an important health related quality of life benefit can be achieved due to the sparing of the limb with ILP[33]. Despite the relatively high cost of this procedure, it is still cheaper than either multiple cycles of systemic therapy or an amputation with the necessary rehabilitation and supporting material.

There are several limitations to our study. First of all, since this is a retrospective study, some data are missing and several patients had to be excluded due to missing data on response. In addition, the criteria for response could have been better defined and assessed in a prospective manner. A third limitation is that there was no central review of pathology in this study, and some diagnoses have changed over time, which might influence the subtype categories. However; in some hospitals, pathology is revisited over time with expansion of translocation panel or specific genomic alterations. Last limitation is that the exact indication for ILP is not always clearly recorded in the patient's file and are therefore difficult to retrieve in retrospective data. To overcome these limitations, a next step would be to continue our collaboration by means of a prospective database with standardized radiological and histopathological response measurements.

Conclusion

Isolated limb perfusion (ILP) resulted in a high overall response rate (ORR) of 68%, with a complete response (CR) rate of 17% and durable locoregional control with limb salvage (88%) in patients with

extremity soft tissue sarcomas (eSTS.. Kaposi sarcoma, angiosarcoma and clear cell sarcoma had significantly higher response rates, while undifferentiated pleomorphic sarcoma, dedifferentiated liposarcoma and sarcoma NOS had significantly lower response rates.

Funding statement:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Declaration of interest:

The authors declare that there is no conflict of interest.

Figure 1. Complete and overall response rates of ILP with and without TNFα

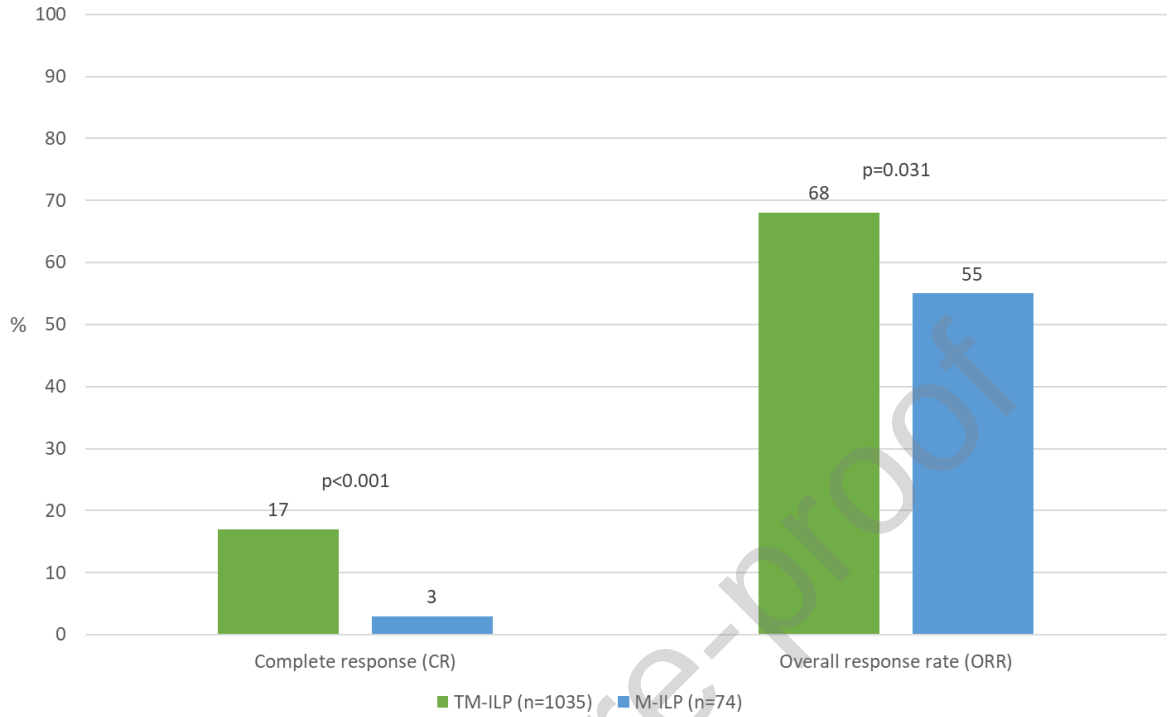
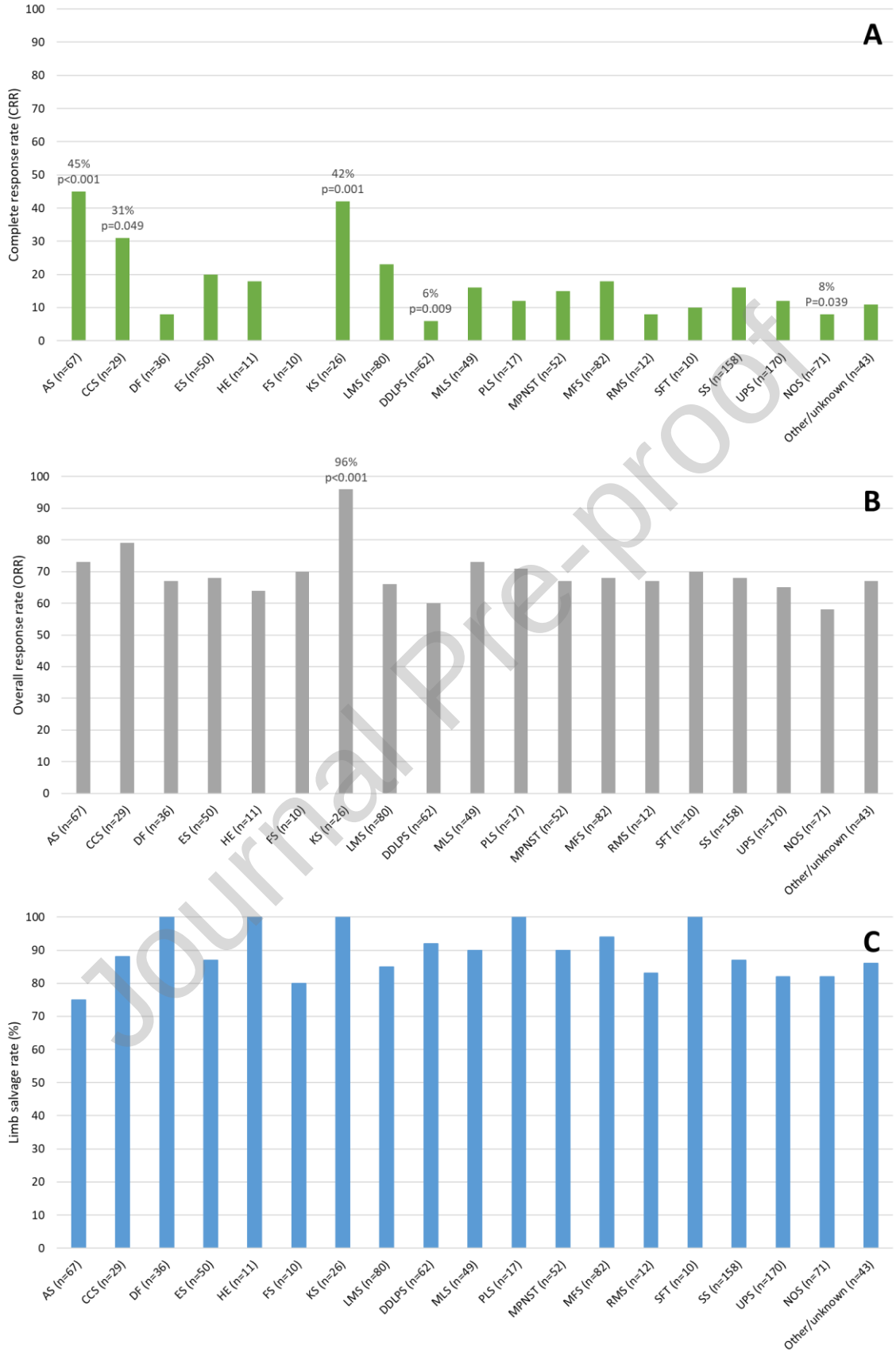


Figure 2. Response rates and limb salvage rate (LSR) per histological subtype, TM-ILP only (n=1035)



A. Complete response rate (CRR), B. Overall response rate (ORR) and C. Limb salvage rate (LSR). Significant differences are indicated by corresponding p-value.

Table 1. Baseline characteristics

	TM-ILP (n=1035)	M-ILP (n=74)	Total (n=1109)
Gender			
Male	539 (52)	36 (49)	575 (52)
Female	496 (48)	38 (51)	534 (48)
Age at ILP (years)	55 (41-71)	44 (28-59)	56 (40-70)
Unknown	2 (<1)	-	2 (<1)
Tumor type			
Advanced primary disease	328 (32)	13 (18)	341 (31)
Residual disease	132 (13)	4 (5)	136 (12)
Recurrent disease	208 (20)	10 (13)	218 (20)
Metastatic disease	14 (1)	2 (3)	16 (1)
Unknown	353 (34)	45 (61)	398 (36)
Histological subtype			
Angiosarcoma (AS)	67 (6)	-	67 (6)
Clear cell sarcoma (CCS)	29 (3)	3 (4)	32 (3)
Desmoid fibromatosis (DF)	36 (3)	5 (7)	41 (4)
Epithelioid sarcoma (ES)	50 (5)	1 (1)	51 (5)
Hemangioendothelioma (HE)	11 (1)	1 (1)	12 (1)
Fibrosarcoma NOS (FS)	10 (<1)	1 (1)	11 (<1)
Kaposi sarcoma (KS)	26 (3)	-	26 (2)
Leiomyosarcoma (LMS)	80 (8)	5 (7)	85 (8)
Liposarcoma (LPS)			
Dedifferentiated liposarcoma (DDLPS)	62 (6)	1 (1)	63 (6)
Myxoid liposarcoma (MLS)	49 (5)	8 (11)	57 (5)
Pleomorphic liposarcoma (PLS)	17 (2)	-	17 (2)
Malignant peripheral nerve sheet tumor (MPNST)	52 (5)	7 (9)	59 (5)
Myxofibrosarcoma (MFS)	82 (8)	5 (7)	87 (8)
Rhabdomyosarcoma (RMS)	12 (1)	-	12 (1)
Solitary fibrous tumor (SFT)	10 (<1)	-	10 (<1)
Synovial sarcoma (SS)	158 (15)	17 (23)	175 (16)
Undifferentiated pleomorphic sarcoma (UPS)	170 (16)	14 (19)	184 (17)
Sarcoma NOS/ spindle cell sarcoma (NOS)	71 (7)	-	71 (6)
Other/unknown	43 (4)	6 (8)	49 (4)
Tumor size at ILP (cm)	8.0 (5.0-14.0)	10.0 (7.0-16.5)	8.7 (5.0-14.0)
Unknown	336 (32)	2 (3)	338 (30)
Multifocality/ anatomical site			
Unifocal	601 (58)	30 (41)	631 (57)
Upper arm	50 (5)	3 (4)	53 (5)
Forearm	106 (10)	6 (8)	112 (10)
Upper leg	207 (20)	7 (9)	214 (19)
Lower leg	182 (18)	14 (19)	196 (18)
Unknown	56 (5)	-	56 (5)
Multifocal	169 (16)	3 (4)	172 (16)
Upper extremity	38 (4)	1 (1)	39 (4)
Lower extremity	113 (11)	2 (3)	115 (10)
Unknown	18 (2)	-	18 (2)
Unknown	265 (26)	41 (55)	306 (28)
Grading (FNCLCC)			
Low (grade I)	89 (9)	2 (3)	91 (8)
High (grade II & III)	717 (69)	48 (65)	765 (69)

Unknown	229 (22)	24 (32)	253 (23)

All variables are n (%) or median (IQR)

Table 2. ILP characteristics

	TM-ILP (n=1035)	M-ILP (n=74)	Total (n=1109)
Level of perfusion			
Supraclavicular	33 (3)	-	33 (3)
Axillary	116 (11)	7 (9)	123 (11)
Brachial	131 (13)	3 (4)	134 (12)
Iliac	219 (21)	2 (3)	221 (20)
Inguinal	37 (4)	1 (1)	38 (3)
Femoral	379 (37)	20 (27)	399 (36)
Popliteal	31 (3)	-	31 (3)
Unknown	89 (9)	41 (55)	130 (12)
Dosage rhTNFα			
Upper extremity (mg)	1 (1-2)	n/a	1 (1-2)
Lower extremity (mg)	2 (1-3)	n/a	2 (1-3)
Unknown	17 (2)	n/a	17 (2)
Dosage Melphalan (mg	70 (50-100)	80 (58-93)	70 (50-100)
Unknown	36 (3)	48 (65)	84 (8)
Dose calculation			
Total body weight	66 (6)	-	66 (11)
Limb volume	535 (52)	7 (9)	542 (88)
Other/ unknown	426 (42)	67 (91)	523 (47)
Toxicity (Wieberdink)			
Grade I-II	621 (60)	67 (91)	688 (62)
Grading III	106 (10)	6 (8)	112 (10)
Grade IV	15 (1)	-	15 (1)
Grade V	2 (<1)	-	2 (<1)
Unknown	291 (28)	1 (<1)	292 (26)

All variables are n (%) or median (IQR)

Highlights

- ILP shows high response rates with an ORR of 68% and a CR of 17%
- With a LSR of 88%, is ILP a valuable limb salvage treatment for patients with eSTS
- ILP is a generic eSTS treatment with responses in every subtype