Less is more: towards a tailored approach in myxoid liposarcoma

Lansu, J.T.P.

CHAPTER 7

"Moderate dose preoperative RT may render borderline or inoperable MLS resectable"

European Journal of Surgical Oncology, 2021 Oct;47(10):2633-2639

Jules Lansu, Pètra Braam, Erik van Werkhoven, Astrid Scholten, Yvonne Schrage, Winan van Houdt, *Kirsten van Langevelde, *Rick Haas

*equally contributing supervising authors

Abstract

Background

Histotype specific neoadjuvant therapy response data is scarce in soft tissue sarcomas. This study aimed to assess the impact of a moderate radiotherapy (RT) dose on resectability and to correlate MRI parameters to pathological treatment response in Myxoid Liposarcoma (MLS).

Methods

This prospective, multicenter, single-arm, phase 2 trial assessed the radiological effects of 36 Gy of preoperative radiotherapy in primary non-metastatic MLS. Distance of the tumor to the neurovascular bundle, tumor dimensions, fat fraction, enhancing fraction were determined on repeat MRI scans at baseline, 8 fractions, 16 fractions and preoperatively. Extensiveness of pathological response was established by central pathology review.

Results

Preoperative radiotherapy resulted in a median increase of 2 mm (IQR 0 – 6) of the distance of the tumor to the neurovascular bundle. As compared to baseline, the median change of the tumor volume, craniocaudal diameter and axial diameter at preoperative MRI were -60% (IQR -74 – -41), -19% (IQR -23– -7) and -20% (IQR -29 – -12), respectively. The median fat fraction of 0.1 (IQR 0.0 – 0.1) and enhancing fraction of 0.8 (IQR 0.6 – 0.9) at baseline, changed to 0.2 (IQR 0.1 – 0.5) and to 0.5 (IQR 0.4 – 0.9) preoperatively, respectively. Radiological signs of response in terms of volume, enhancing fraction and fat fraction were correlated with specific pathological expresses of response like hyalinization, necrosis and fatty maturation.

Conclusions

A moderate dose of preoperative radiotherapy may improve resectability in MLS and could facilitate achievement of clear margins and function preservation. MRI features which were predictive for signs of pathological response, can play a role in further personalization of neoadjuvant treatment strategies in order to improve outcome in MLS.

Introduction

Response evaluation is important in clinical trials investigating novel neoadjuvant treatment strategies. It is frequently used as a surrogate short-term endpoint to assess efficacy of neoadjuvant regimens in Soft Tissue Sarcoma (STS) including the myxoid liposarcoma (MLS) subtype.[43–46] The major limitation of pathological response is that it can only be assessed after surgery once neoadjuvant treatment already has been completed. In contrast, radiological response evaluations can be performed once or multiple times during neoadjuvant therapy. Provided clear correlations between radiological and histopathological parameters can be established, this could ultimately offer an opportunity to adapt neoadjuvant therapies on a personalized basis of actual treatment response.

Although the relationship between radiological and histopathological parameters in STS has been subject of previous investigations,[47–50] histotype specific data is scarce. For MLS, this would be particularly of interest given its distinctive clinical behavior. In sharp contrast to other STS subtypes, substantial volumetric reductions and even partial responses according to RECIST are frequently observed following preoperative radiotherapy in MLSs.[39,41,48,50–52] The reported association between tumor shrinkage and pathological response in a small and heterogeneous group of STS,[48] is likely to reflect at least partly the well-established high radiosensitivity of the MLS subtype in this series.[9,41,46,50] However, the question can be raised whether shrinkage is also predictive for pathological response in a cohort with only MLS patients. Furthermore, the clinical benefit of tumor shrinkage for the patient in terms of resectability, is currently unclear. Particularly for tumors in close proximity of the neurovascular bundle (NVB), function preservation could be facilitated by a radiotherapy induced increase of the distance from tumor to the NVB.

In addition to dimensional changes on Magnetic Resonance Imaging (MRI), other changes visible on MRI during and following preoperative radiotherapy may be interpreted as therapy effect in MLS.[53] Radiotherapy has been reported to potentially result in an increase of fat content on MRI in MLS,[47,50,54] with corresponding fatty maturation on histopathological examination of 13 MLS resection specimens.[50] Finally, MLSs frequently show radiotherapy associated decreases of enhancing fraction on MRI. However, this feature may not reliably predict pathological response in STS.[47,50]

The goal of the current study is (I) to determine the correlation of MRI parameters established during and after preoperative radiotherapy to pathological treatment response in MLS and (II) to assess the impact of a moderate radiotherapy dose on resectability.

Methods

Trial design and patients

In this study, the MRI data of MLS patients, included in the DOREMY (DOse REduction in MYxoid liposarcoma) trial (NCT02106312), were evaluated. This prospective, multicenter, single-arm, phase 2 trial was open for enrollment from 24 November, 2010, until 14 May, 2020. The study was designed to assess efficacy and morbidity of a reduced dose of 36 Gy of preoperative radiotherapy in 18 fractions in MLS.[46,52] Three trial centers participated in this complementary and voluntary part of the study investigating repeat MRI examinations before, during, and after preoperative radiotherapy. All patients provided a written informed consent. The protocol and all amendments thereon were approved by the ethics committee of the initiating center.

Eligible patients were adults (≥18 years) with a translocation confirmed MLS (either t(12;16)(q13;p11) or t(12;22)(q13q12) reciprocal translocation). Exclusion criteria were any other prior or concurrent malignancy, pregnancy, ECOG performance status >2, and prior radiotherapy to the target area.

Procedures

Staging consisted of MRI of the primary site followed by image guided biopsies and CT scans of the chest, abdomen, and pelvis.[27,28] Histopathological and molecular confirmation of the MLS diagnosis of the original primary tumor was mandatory. The comprehensive radiotherapy protocol has been published elsewhere and a summary is presented in the *Supplementary material*.[46] The interval between radiotherapy and resection was 4-8 weeks. Central pathology review of the resected specimen was performed and the percentage of vital tumor cells, hyalinization, fatty maturation, and necrosis were scored systematically,[55,56] together mounting to 100%. The cumulative percentage of hyalinization, fatty maturation, and necrosis, was considered as pathological treatment response. The cut-off value for an extensive pathological response was set at 90% (median % in this dataset).

Patients underwent MRI scans according to the study protocol within one week before the 1st fraction (baseline) and at the day of the 8th and 16th fraction. From 2015 onwards the study imaging protocol was also performed preoperatively. The study MRI protocol included conventional T1- and T2-weighted MRI sequences, followed by fat suppressed T1-weighted sequences pre- and post-gadolinium contrast administration. The tumors were imaged in at least two planes (axial and sagittal or axial and coronal). If the study MRI at baseline was missing, the same sequence of the diagnostic MRI (similar protocol) was used as a surrogate. If the MRI data at 8 fractions, 16 fractions or preoperative was missing, patients were excluded from the analysis at those respective time points.

MRI evaluation consisted of an estimation of the tumor's fat fraction on the T1-weighted sequence and enhancing fraction on post-contrast T1-weighted images. Both fat and enhancing fractions were graded visually for the complete tumor volume using all available scan planes (i.e. 0-9%, 10-19%, etcetera). Additionally, to express the impact of preoperative radiotherapy on resectability in a quantitative parameter, the shortest distance from the tumor to the NVB was measured on the axial T1-weighted images. The MRI evaluations were performed at all available time points by a musculoskeletal oncology radiologist (K.v.L.). Furthermore, the tumors were delineated and reviewed on post-contrast T1-weighted images by respectively a resident radiation oncology (J.L.) and sarcoma radiation oncologist (R.L.H.). Subsequently, tumor volumes and axial and craniocaudal tumor dimensions were automatically extracted.

Statistical analysis

Median values are presented with an interquartile range (IQR). For the analysis of the fat fractions and enhancing fractions, the lower boundary of the estimated range was used (i.e. 10% was used when the range was estimated to be 10-19%). Wilcoxon matched-pair signed rank tests were used to assess differences between measurements at different time points. Binary logistic regression and linear regression were used to test associations between MRI parameters and dichotomized and continuous pathology examination outcome measures, respectively. The standardized beta (β) ranges from 0 to 1 or 0 to -1, depending on the direction of the correlation. The closer the value is to 1 or -1, the stronger the correlation. Resection specimens not available for central pathology review were not taken into account for the pathology response analysis. P-values are considered

statistically significant when p≤0.05. Statistical analyses were conducted by using IBM SPSS statistics (version 25, Chicago, Illinois, Unites States).

Results

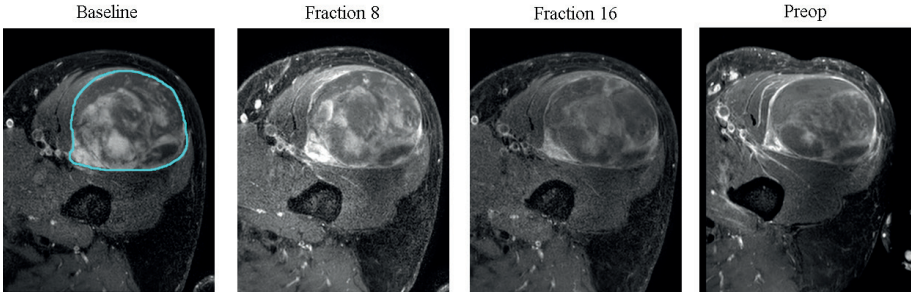
A total of 34 patients were included in the study population, consisting of 22 males (65%) and 12 females (35%). The median age was 45 years (IQR 37–52). Tumor locations included lower extremity (n=27), upper extremity (n=5), and the trunk (n=2). The Round Cell Component in diagnostic biopsies was estimated to be ≥5% in 4/34 (12%), <5% in 27/34 (79%), and unknown in 3/34 (9%) of the patients. At baseline MRI, the tumor was marginally resectable (≤2 mm distance of the tumor to the NVB) in 15/34 (44%) of the patients. The tumor was found in very close proximity (<1 mm) to the NVB in 11/34 (32%) of the patients. All patients underwent radiotherapy according to the protocol and subsequent surgery was with one exception performed in all patients. The reason for omitting surgery in this patient was development of intercurrent metastatic disease. Clear surgical margins were achieved in 32/33 (97%). One patient (3%) had microscopically positive resection margins. Neither major blood vessels nor nerves were sacrificed and function was preserved in all patients with a extremity tumor location.

Resection specimens were not available for central pathology review in four patients. The pathologic response percentages as determined in central pathology review were 25% in 1/29 (3%), 60% in 1/29 (3%), 75% in 1/29 (3%), 80% in 1/29 (3%), 85% in 6/29 (21%), 90% in 8/28 (28%), 95% in 9/29 (31%), and 99% in 2/29 (7%) of the patients.

MRI evaluation

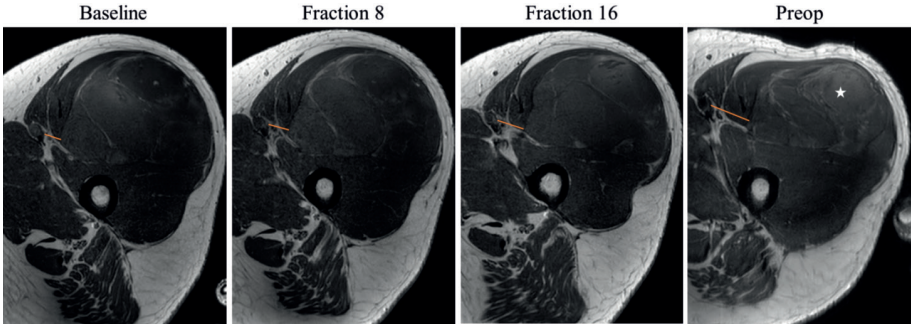
MRIs were available at baseline (n=34), after 8 fractions of radiotherapy (n=28), after 16 fractions of radiotherapy (n=30), and preoperatively (n=28). *Figure 1* shows an illustrative example of a tumor responding on radiotherapy. The boxplots in *Figure 2* depict change of MRI characteristics over time on a study population level. As compared to baseline MRI, the median change of the tumor volume, craniocaudal diameter, and axial diameter at preoperative MRI are -60% (IQR -74 – -41), -19% (IQR -23 – -7), and -20% (IQR -29 – -12), respectively. The median fat fraction of 0.1 (IQR 0.0–0.1) and enhancing fraction of 0.8 (IQR 0.6–0.9) at baseline MRI, increased to 0.2 (IQR 0.1–0.5) and decreased to 0.5 (IQR 0.4–0.9) preoperatively, respectively.

Figure 1A *T1-weigthed post contrast images of an illustrative example of a patient with a radiologically responding tumor*



Caption Figure 1A. Axial T1-weigthed post contrast images (above) of an example of a radiologically responding intramuscular tumor in the proximal lower extremity. The tumor is delineated with a blue line. In comparison to baseline (left), the decreases in enhancing fraction and tumor volume (modest decrease of tumor volume) observed at fraction 8 (middle) and fraction 16 (right).

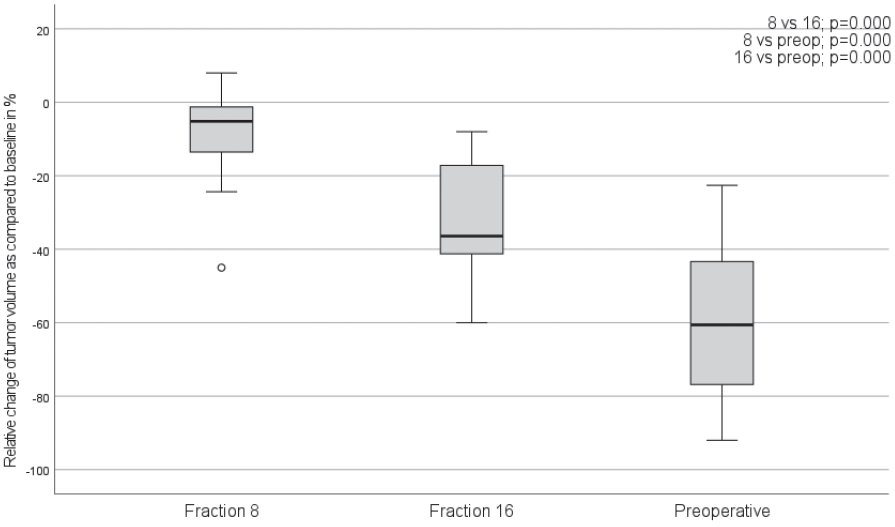
Figure 1B *T1-weigthed images of the same illustrative example of a patient with a radiologically responding tumor*



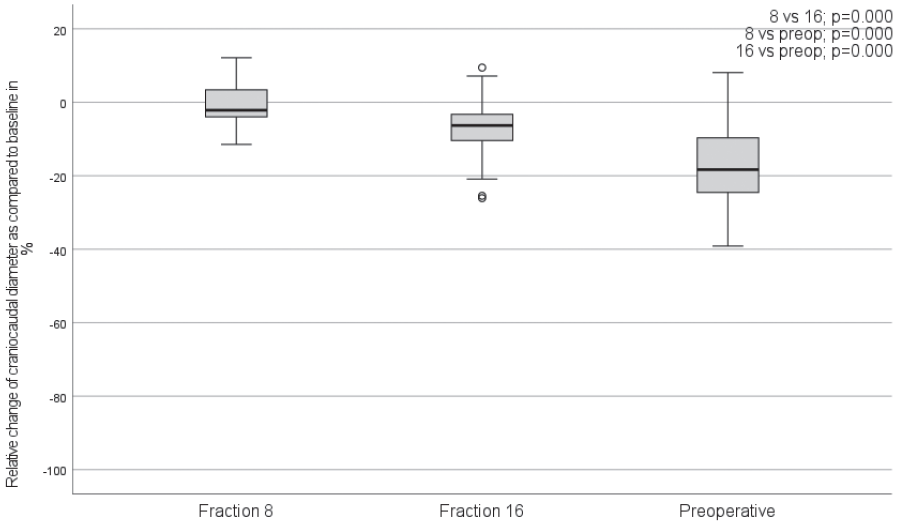
Caption Figure 1B. Axial T1-weigthed images of the same example as presented in Figure 1B. In comparison to baseline (left), tumor dimensions decrease and the distance of the tumor to the neurovascular bundle increases (in this example the distance from the tumor to the artery is marked with the orange line) over time. Furthermore, the fat fraction on MRI gradually increases between baseline and preoperative. The white star in the preoperative image (r ight) marks a new fat-containing area, as a sign of radiological response.

Figure 2. *Boxplots represent relative changes of tumor volume (A), craniocaudal tumor diameter (B) and axial tumor diameter (C), as compared with baseline. Other boxplots represent fat fraction (D), enhancing fraction (E) and distance of the tumor to the neurovascular bundle (F) over time.*

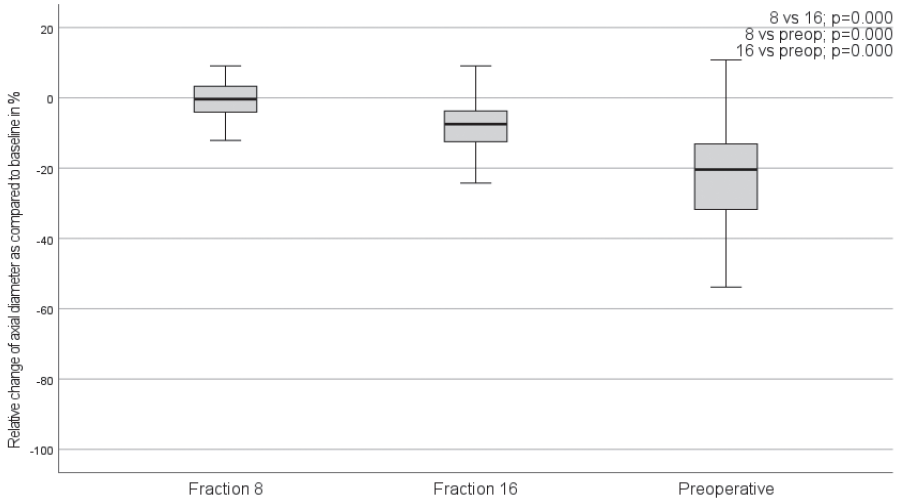
A *Tumor volume*



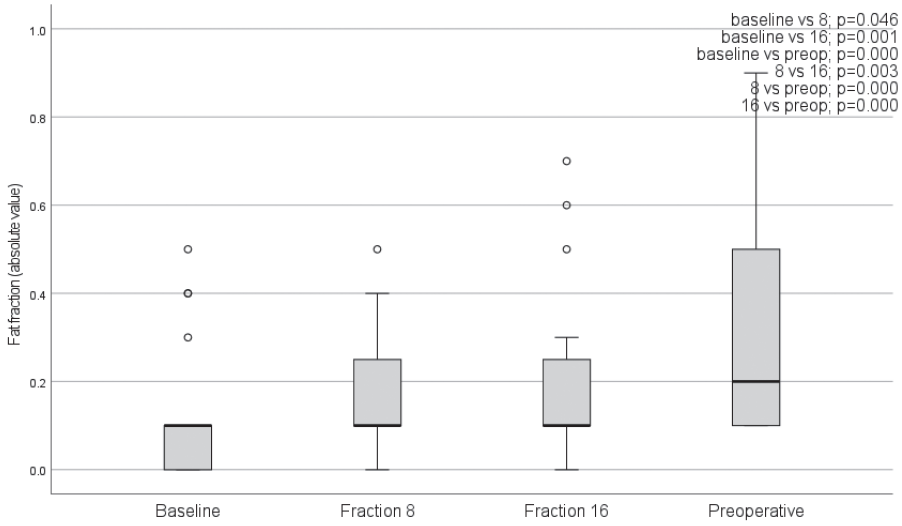
B *Craniocaudal tumor diameter*



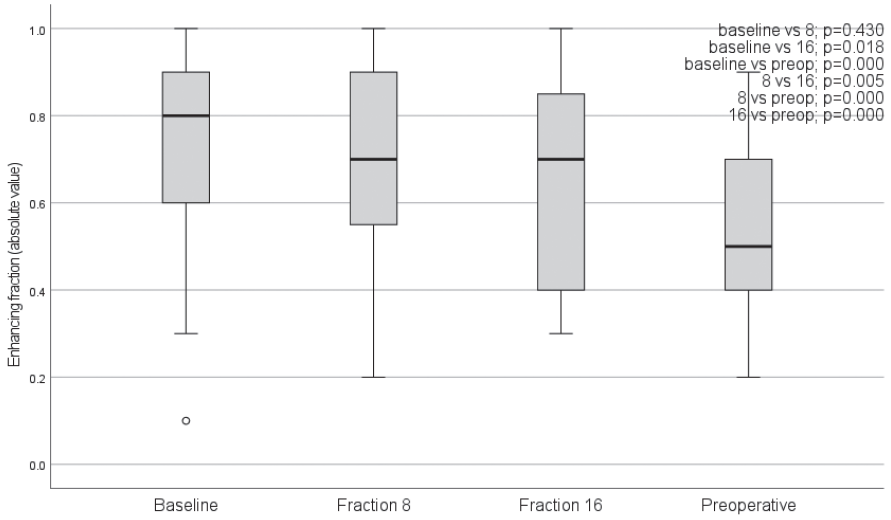
C *Axial tumor diameter*



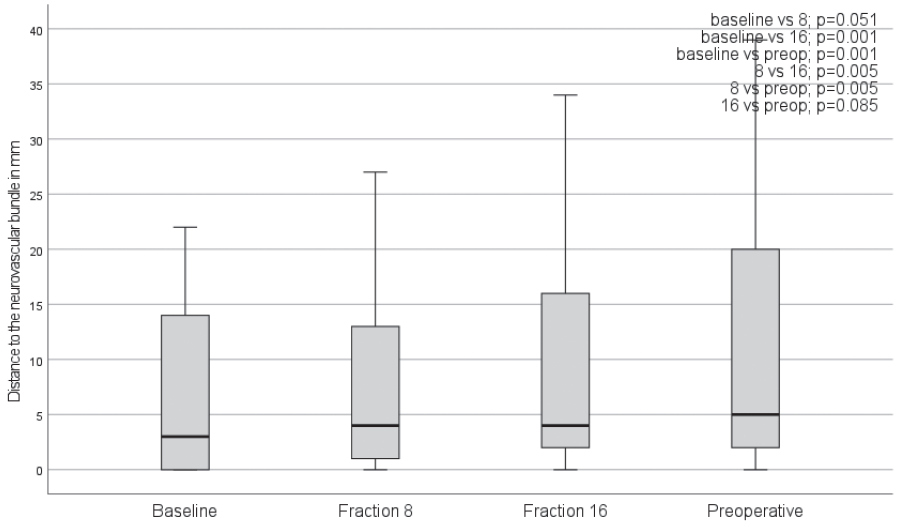
D *Fat fraction*



E *Enhancing fraction*



F *Distance of the tumor to neurovascular bundle*



Caption Figure 2. The horizontal black line in the gray box represents the median value. The gray box displays the interquartile range (IQR). Any value outside the whiskers is considered as an outlier and is represented with a circle.

An overview of individual distances between tumor and NVB as measured on MRI at the different time points, sorted by distance of the tumor to the NVB at the baseline measurement, is given in *Table 1*. The median difference in distance of the tumor to the NVB between the MRI at baseline and preoperative is +2mm (IQR 0–6). Although the large benefits in terms of increased distance of the tumor to the NVB are generally observed in patients who initially had resectable disease already, smaller but still relevant benefits are also observed in cases with preexistent smaller distances of the tumor to the NVB. At preoperative MRI, but not earlier, relative dimensional tumor changes as compared to baseline, are inversely associated with the distance of the tumor to the NVB (volume β =-.506, p=0.012; craniocaudal diameter β =-.457, p=0.021; axial diameter β =-.512, p=0.011). The "chart of benefit" in *Figure 3* visualizes the correlation between change in tumor volume and change in distance of the tumor to the NVB.

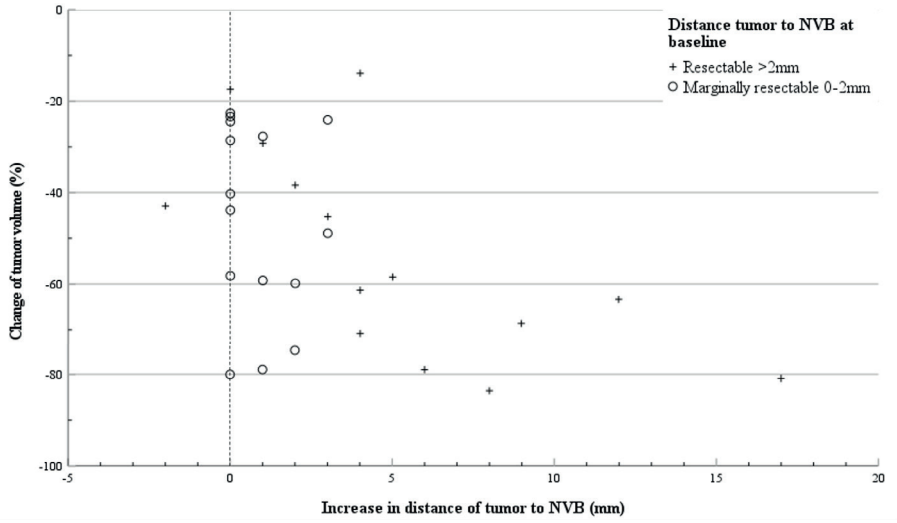
Table 1. *Distance on MRI from tumor to the neurovascular bundle before, during and after radiotherapy and the minimal margin at pathology examination, in millimeters assessed in 31 patients.*

MRI Baseline	MRI Fraction 8	MRI Fraction 16	MRI Preoperative	Pathology minimal margin	Radiological Difference
0	NA	1	NA	0	+1*
0	NA	NA	0	1	0
0	0	0	0	+	0
0	0	0	0	0	0
0	0	0	0	0	0
0	NA	NA	0	1	0
0	NA	0	0	1	0
0	0	0	0	0.1	0
0	0	0	1	1	+1
0	1	2	2	1	+2
0	3	3	3	2	+3
1	2	3	3	0.1	+2
2	2	2	NA	2	0*
2	2	3	3	1	+1
2	2	2	5	1	+3
3	5	7	NA	1	+4*
3	4	6	8	1	+5

MRI Baseline	MRI Fraction 8	MRI Fraction 16	MRI Preoperative	Pathology minimal margin	Radiological Difference
6	5	6	NA	4	0*
6	5	4	4	0.3	-2
7	7	8	NA	0.2	+1*
7	8	12	9	2	+2
7	7	7	10	2	+3
10	9	11	14	3	+4
11	NA	NA	22	3	+11
14	16	17	26	2	+12
15	20	16	24	3	+9
16	20	29	20	1	+4
16	16	19	22	1	+6
18	13	24	26	3	+8
22	27	34	39	3	+17
23	26	27	NA	3	+4*
3 (0-15)	**4 (1-15)**	**4 (1-17)**	**5 (2-21)**	**1 (0.28-2.25)**	**2 (0-6)**

*Caption Table 1. Tumors are sorted from small to large distance from the tumor to the neurovascular bundle (NVB) at baseline. The second, third and fourth column represent the distance of the tumor to the NVB after 8 fractions, 16 fractions and prior to surgery, respectively. The fifth column shows the minimal pathology margin in mm as reported by the pathologist at pathology examination and the sixth column represents the difference in distance of the tumor to the NVB between the measurement at baseline and the latest available MRI scan. The row below in bold represents the median value with the inter quartile range (IQR) between the parentheses. In cases with a thoracic wall localization (n=1) and subcutaneous mass (n=2) distance of the tumor to NVB were deemed irrelevant and excluded from this table. * = represents the difference in distance of the tumor to the NVB between baseline and fraction 16, because no preoperative MRI was performed in these patients. Given the possible underestimation of the difference in distance of the tumor to the NVB, these values are not taken into account for further descriptive analysis including the presented median difference at the bottom of the right column. + =this patient had microscopically positive surgical margins.*

Figure 3. *"Chart of benefit"*



Caption Figure 3. Scatterplot shows the correlation between change of tumor volume and change in distance of the tumor to the neurovacular bundle (NVB). Change is defined as the difference between the measured value at preoperative MRI, as compared to the MRI at baseline. Patients without preoperative MRI are excluded from this scatterplot. Each asterisk (*) represents a tumor deemed resectable at baseline, with a distance of the tumor to the NVB of >2mm. Each circle represent a tumor deemed marginally resecable at baseline, with a distance of the tumor to the NVB smaller or equal to 2mm.

MRI and pathological outcome

Associations were tested between clinical MRI parameters and pathological outcome. No associations were found between clinical MRI parameters and comprehensive pathological response at any of the time points; neither dichotomized with a 90% pathological response cut-off value, nor as a continuous variable. However, when the particular pathological treatment effects were tested separately, several associations were identified. Firstly, at all time points, fat fraction on MRI was associated with fatty maturation and inversely associated with hyalinization at pathology examination. In addition, relative volumetric change at 16 fractions and preoperatively, as compared to baseline, was associated with necrosis and inversely associated with hyalinization at pathology. Lastly, also from fraction 16 onwards, enhancing fraction was associated with hyalinization and inversely associated with necrosis at pathology examination. An overview of all tested associations is provided in the *Supplementary table 1.*

Discussion

This prospective study shows that preoperative radiotherapy, even after a relatively low dose of 36 Gy in 2 Gy fractions, increases the distance from tumor to NVB with a median of 2 mm. This may improve resectability in MLS and facilitate achievement of clear surgical margins and function preservation. Furthermore, radiological signs of response in terms of tumor volume, enhancing fraction and fat fraction were correlated with specific pathological signs of response like hyalinization, necrosis, and fatty maturation.

To the best of our knowledge, this investigation is the first to suggest an impact of preoperative radiotherapy on the resectability in the setting of MLS. Although the exceptional volumetric response on preoperative radiotherapy of MLS has been subject of several other investigations,[39,41,48,51] none of them addressed this surgically relevant question. We have attempted to parametrize this issue by measuring the shortest distances from tumor to NVB pre- and post-radiotherapy in 31 patients. Although the largest tumor to NVB distance increases were observed in patients with already resectable MLS, preoperative radiotherapy also appeared to be beneficial in terms of increased distance of the tumor to the NVB in roughly half of the patients with marginally resectable (≤2 mm distance to the NVB) or borderline resectable (<1 mm distance to the NVB) MLS. For 15 patients with a shortest distance from tumor to NVB of less than or equal to 2 mm before radiotherapy, this distance increased in 7 patients after radiotherapy (*Table 1*), implying improved resectability in these cases. Due to the lack of preoperative imaging in 2 of these 15 patients, this measurement was performed in these 2 cases on the MRI at 16 fractions of radiotherapy. Hence, this is a possible underestimation of the effect of preoperative radiotherapy on the distance from the tumor to the NVB, given the fact that a substantial part of the volumetric reduction takes place after 16 fractions (*Figure 2, A*). Moreover, the achievement of clear surgical margins in 97% of the patients supports the claim of a benefit in terms of resectability of preoperative radiotherapy.[57] Whether these data are also applicable in the setting of primary unresectable MLS remains to be established, as this study population consisted of patients with tumors considered formally resectable. However, we strictly cannot rule out that anticipated radiotherapy-induced responses have affected these initial decisions on resectability status.

Obviously, resectability is more complex than just this distance of the tumor to the NVB, as other parameters also affect resectability such as the location of the tumor and its relation to other adjacent anatomical structures. It should be acknowledged that preoperative radiotherapy can also has its downside, since radiotherapy can induce fibrotic changes to the tissue potentially hampering resections and moreover results in higher rates of wound complications.[34]

The volumetric changes in our MLS cohort are consistent with other reports.[39,41,48,50,51] In our study, volumetric change was inversely associated with hyalinization and necrosis from fraction 16 onwards, which is in line with the observations in 13 and 7 MLS patients as reported by Wortman and Roberge, respectively.[48,50] Similar to Wortman, we observed increases of fat fraction and decreases of enhancing fraction following radiotherapy. Most likely these observations are read-outs of therapy response. However, one should realize that an increase of enhancing fraction on MRI does not necessarily mean tumor progression, but can also reflect treatment induced vascular disruption.[53] The observed association between fat fraction, as visually graded on T1 weighted sequences, with fatty maturation at pathological examination, is in line with to the findings with respect to a cohort of 30 retroperitoneal STS using Dixon.[49] According to the authors, the radiological equivalent of hyalinization at pathology remains yet to be established in future research.

Importantly, the MRI at 8 fractions of radiotherapy did not yield additional predictive value above the MRI performed at baseline. However, the MRI at 16 fractions of radiotherapy predicted all three forms of pathological treatment response and therefore might play a role in the individualized adaptation of preoperative radiotherapy. Although in the currently used radiotherapy schedule the number of remaining fractions at this point is only two in the currently used radiotherapy schedule, this still provides opportunity to remit these last two fractions in case of an excellent MRI response. Contrarily, if a tumor does not show any radiological signs of response in terms of volume, enhancing fraction, and fat fraction, a prolongation of the schedule to for instance the conventional 25 fractions realizing 50 Gy might be considered.

With respect to the limitations of the association of MRI parameters with pathological response, visual grading of fat fraction and enhancing fraction is subject to a certain

extent of subjectivity. Previous reports suggest that quantitative Dixon techniques to be preferable in fat content estimation and indicate that radiologists tend to overestimate fat fractions above 50%,[54,58] and albeit this was the case in only eight patients, this possibly could have biased our findings. Another potential limitation of the study is the uncertainty regarding the predictive value of the pathological response for outcome in STS. Although the correlation of pathological treatment response with oncological survival outcomes in STS is well-established,[22,56,59–62] the evidence for the correlation of pathological treatment response with local control is less solid. Of note, given the demonstrated benefit of perioperative radiotherapy in terms of local control,[24,25] local control is in the end the most important outcome in radiotherapy trials regarding STS. Whereas associations between pathological response and local control were shown in the three largest series reporting on this topic,[22,59,62], others failed to establish this correlation in smaller study samples.[56,63,64] Sample size appears to play an important role in this controversy. As a consequence of the low local recurrence rates in recent years, very large sample sizes are required to reach sufficient numbers of events and therewith statistical power to possibly demonstrate a possible correlation. Single institution series hardly ever meet these patient numbers in the setting of rare cancers such as STS. Hence, it is expected that – in line with other malignancies –[65–68] treatment induced pathological response is an independent prognostic marker for local control in STS.

In conclusion, this cohort suggests that preoperative radiotherapy is beneficial in terms of resectability in approximately half of the at best marginally resectable tumors and that the distance from the tumor to the NVB on MRI increases in two-thirds of MLS patients. Tumor shrinkage following a modest dose of preoperative radiotherapy in MLS results in a 2 mm median increase of the distance between the tumor and the NVB. Both volumetric change and enhancing fraction were correlated with hyalinization and necrosis at pathology examination. Furthermore, fat fraction on MRI was associated with the pathological response parameters fatty maturation and hyalinization. Given the negligible predictive value of the MRI at 8 fractions, we do not recommend to routinely perform MRI response assessments before the end of the second week of preoperative radiotherapy outside clinical trials in MLS.

References

1. Jones RL, Lee ATJ, Thway K, Huang PH. Clinical and molecular spectrum of liposarcoma. *J Clin Oncol*. 2018;36(2):151-159. doi:10.1200/JCO.2017.74.9598
2. Aman P, Ron D, Mandahl N. Rearrangement of the transcription factor gene CHOP in myxoid liposarcomas with t(12;16)(q13;p11). *Genes Chromosom Cancer*. 1992.
3. Crozat A, Åman P, Mandahl N, Ron D. Fusion of CHOP to a novel RNA-binding protein in human myxoid liposarcoma. *Nature*. 1993. doi:10.1038/363640a0
4. Panagopoulos I, Höglund M, Mertens F, Mandahl N, Mitelman F, Åman P. Fusion of the EWS and CHOP genes in myxoid liposarcoma. *Oncogene*. 1996. doi:10.1016/s0165-4608(97)82589-7
5. Powers MP, Wang WL, Hernandez VS, et al. Detection of myxoid liposarcoma-associated FUS-DDIT3 rearrangement variants including a newly identified breakpoint using an optimized RT-PCR assay. *Mod Pathol*. 2010. doi:10.1038/modpathol.2010.118
6. Antonescu CR, Ladanyi M. Myxoid liposarcoma. In: *WHO Classification of Tumours of Soft Tissue and Bone*. ; 2013:39-41.
7. Fiore M, Grosso F, Lo Vullo S, et al. Myxoid/round cell and pleomorphic liposarcomas: Prognostic factors and survival in a series of patients treated at a single institution. *Cancer*. 2007;109(12):2522-2531. doi:10.1002/cncr.22720
8. Moreau LC, Turcotte R, Ferguson P, et al. Myxoid\round cell liposarcoma (MRCLS) revisited: An analysis of 418 primarily managed cases. *Ann Surg Oncol*. 2012;19(4):1081-1088. doi:10.1245/s10434-011-2127-z
9. Chung PWM, Deheshi BM, Ferguson PC, et al. Radiosensitivity translates into excellent local control in extremity myxoid liposarcoma: A comparison with other soft tissue sarcomas. *Cancer*. 2009;115(14):3254-3261. doi:10.1002/cncr.24375
10. De Vreeze RSA, De Jong D, Tielen IHG, et al. Primary retroperitoneal myxoid/round cell liposarcoma is a nonexisting disease: An immunohistochemical and molecular biological analysis. *Mod Pathol*. 2009;22(2):223-231. doi:10.1038/modpathol.2008.164
11. Guadagnolo BA, Zagars GK, Ballo MT, et al. Excellent Local Control Rates and Distinctive Patterns of Failure in Myxoid Liposarcoma Treated With Conservation Surgery and Radiotherapy. *Int J Radiat Oncol Biol Phys*. 2008;70(3):760-765. doi:10.1016/j.ijrobp.2007.07.2337
12. Asano N, Susa M, Hosaka S, et al. Metastatic patterns of myxoid/round cell liposarcoma: A review of a 25-year experience. *Sarcoma*. 2012;2012. doi:10.1155/2012/345161
13. Estourgie SH, Nielsen GP, Ott MJ. Metastatic patterns of extremity myxoid liposarcoma and their outcome. *J Surg Oncol*. 2002. doi:10.1002/jso.10093
14. Fuglø HM, Maretty-Nielsen K, Hovgaard D, Keller J, Safwat AA, Petersen MM. Metastatic pattern, local relapse, and survival of patients with myxoid liposarcoma: A retrospective study of 45 patients. *Sarcoma*. 2013. doi:10.1155/2013/548628
15. Gouin F, Renault A, Bertrand-Vasseur A, et al. Early detection of multiple bone and extra-skeletal metastases by body magnetic resonance imaging (BMRI) after treatment of Myxoid/Round-Cell Liposarcoma (MRCLS). *Eur J Surg Oncol*. 2019. doi:10.1016/j.ejso.2019.08.014
16. Schwab JH, Boland P, Guo T, et al. Skeletal metastases in myxoid liposarcoma: An unusual pattern of distant spread. *Ann Surg Oncol*. 2007;14(4):1507-1514. doi:10.1245/s10434-006-9306-3

17. Muratori F, Bettini L, Frenos F, et al. Myxoid Liposarcoma: Prognostic Factors and Metastatic Pattern in a Series of 148 Patients Treated at a Single Institution. *Int J Surg Oncol*. 2018;2018. doi:10.1155/2018/8928706

18. Dürr HR, Rauh J, Baur-Melnyk A, et al. Myxoid liposarcoma: Local relapse and metastatic pattern in 43 patients. *BMC Cancer*. 2018;18(1):1-7. doi:10.1186/s12885-018-4226-8

19. Antonescu CR, Tschernyavsky SJ, Decuseara R, et al. Prognostic impact of P53 status, TLS-CHOP fusion transcript structure, and histological grade in myxoid liposarcoma: A molecular and clinicopathologic study of 82 cases. *Clin Cancer Res*. 2001;7(12):3977-3987.

20. Haniball J, Sumathi VP, Kindblom LG, et al. Prognostic factors and metastatic patterns in primary myxoid/round-cell liposarcoma. *Sarcoma*. 2011;2011. doi:10.1155/2011/538085

21. Ten Heuvel SE, Hoekstra HJ, Van Ginkel RJ, Bastiaannet E, Suurmeijer AJH. Clinicopathologic prognostic factors in myxoid liposarcoma: A retrospective study of 49 patients with long-term follow-up. *Ann Surg Oncol*. 2007;14(1):222-229. doi:10.1245/s10434-006-9043-7

22. Eilber FC, Rosen G, Eckardt J, et al. Treatment-induced pathologic necrosis: A predictor of local recurrence and survival in patients receiving neoadjuvant therapy for high-grade extremity soft tissue sarcomas. *J Clin Oncol*. 2001;19(13):3203-3209. doi:10.1200/JCO.2001.19.13.3203

23. Rosenberg SA, Tepper J, Glatstein E, et al. The treatment of soft-tissue sarcomas of the extremities. Prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. *Ann Surg*. 1982. doi:10.1097/00000658-198209000-00009

24. Pisters PW, Harrison LB, Leung DH, Woodruff JM, Casper ES, Brennan MF. Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. *J Clin Oncol*. 1996;14(3):859-868. doi:10.1200/JCO.1996.14.3.859

25. Yang JC, Chang AE, Baker AR, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. *J Clin Oncol*. 1998;16(1):197-203. doi:10.1200/JCO.1998.16.1.197

26. Werkgroep NWWDT. Landelijke Richtlijn Wekedelentumoren versie 2.0. 2011:25.

27. Casali PG, Abecassis N, Bauer S, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(October):iv51-iv67. doi:10.1093/annonc/mdy096

28. Soft Tissue Sarcoma, Version 1.2020, NCCN Clinical Practice Guidelines in Oncology. 2020. https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf.

29. Collaboration SM-A. Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. *Lancet*. 1997.

30. Pervaiz N, Colterjohn N, Farrokhyar F, Tozer R, Figueredo A, Ghert M. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. *Cancer*. 2008;113(3):573-581. doi:10.1002/cncr.23592

31. Le Cesne A, Ouali M, Leahy MG, et al. Doxorubicin-based adjuvant chemotherapy in soft tissue sarcoma: Pooled analysis of two STBSG-EORTC phase III clinical trials. *Ann Oncol*. 2014. doi:10.1093/annonc/mdu460

32. Loehmer P, Gronchi A, Brodowicz T, et al. Adjuvant chemotherapy in high-risk liposarcomas. *J Clin Oncol*. 2016. doi:10.1200/jco.2016.34.15_suppl.11036

33. Gronchi A, Ferrari S, Quagliuolo V, et al. Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial. *Lancet Oncol*. 2017;18(6):812-822. doi:10.1016/S1470-2045(17)30334-0
34. Sullivan BO, Davis AM, Turcotte R, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. *Lancet*. 2002;359:2235-2241. doi:10.1016/S0140-6736(02)09292-9
35. Davis AM, O'Sullivan B, Turcotte R, et al. Late radiation morbidity following randomization to preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma. *Radiother Oncol*. 2005;75(1):48-53. doi:10.1016/j.radonc.2004.12.020
36. Davis AM, O'Sullivan B, Bell RS, et al. Function and health status outcomes in a randomized trial comparing preoperative and postoperative radiotherapy in extremity soft tissue sarcoma. *J Clin Oncol*. 2002;20(22):4472-4477. doi:10.1200/JCO.2002.03.084
37. Haas RL, Gronchi A, van de Sande MAJ, et al. Perioperative management of extremity soft tissue sarcomas. *J Clin Oncol*. 2018;36(2):118-124. doi:10.1200/JCO.2017.74.7527
38. Qu XM, Louie A V., Ashman J, Wasif N. Cost-Effectiveness Analysis of Preoperative Versus Postoperative Radiation Therapy in Extremity Soft Tissue Sarcoma. In: *International Journal of Radiation Oncology Biology Physics*. ; 2017. doi:10.1016/j.ijrobp.2016.10.009
39. Betgen A, Haas RLM, Sonke J-J. Volume changes in soft tissue sarcomas during preoperative radiotherapy of extremities evaluated using cone-beam CT. *J Radiat Oncol*. 2013;2(1):55-62. doi:10.1007/s13566-012-0085-0
40. Engström K, Bergh P, Cederlund CG, et al. Irradiation of myxoid/round cell liposarcoma induces volume reduction and lipoma-like morphology. *Acta Oncol (Madr)*. 2007;46(6):838-845. doi:10.1080/02841860601080415
41. Pitson G, Robinson P, Wilke D, et al. Radiation response: An additional unique signature of myxoid liposarcoma. *Int J Radiat Oncol Biol Phys*. 2004;60(2):522-526. doi:10.1016/j.ijrobp.2004.03.009
42. de Vreeze RSA, de Jong D, Haas RL, Stewart F, van Coevorden F. Effectiveness of Radiotherapy in Myxoid Sarcomas Is Associated With a Dense Vascular Pattern. *Int J Radiat Oncol Biol Phys*. 2008;72(5):1480-1487. doi:10.1016/j.ijrobp.2008.03.008
43. Chen Y-L, Weiss AR, Scharschmidt T, et al. Results of the dose-finding phase of ARST 1321 from the Children's Oncology Group and NRG Oncology: Neoadjuvant chemoradiation or radiation therapy +/- pazopanib in non-rhabdomyosarcoma soft tissue sarcomas. *J Clin Oncol*. 2019. doi:10.1200/jco.2019.37.15_suppl.11070
44. Bonvalot S, Rutkowski PL, Thariat J, et al. NBTXR3, a first-in-class radioenhancer hafnium oxide nanoparticle, plus radiotherapy versus radiotherapy alone in patients with locally advanced soft-tissue sarcoma (Act.In.Sarc): a multicentre, phase 2–3, randomised, controlled trial. *Lancet Oncol*. 2019. doi:10.1016/S1470-2045(19)30326-2
45. Gronchi A, Bui BN, Bonvalot S, et al. Phase II clinical trial of neoadjuvant trabectedin in patients with advanced localized myxoid liposarcoma. *Ann Oncol*. 2012;23(3):771-776. doi:10.1093/annonc/mdr265
46. Lansu J, Bovée JVMG, Braam P, et al. Dose Reduction of Preoperative Radiotherapy in Myxoid Liposarcoma A Nonrandomized Controlled Trial. *JAMA Oncol*. 2021;7(1):1-8. doi:10.1001/Jamaoncol.20205865

47. Einarsdottir H, Wejde J, Bauer HC. Pre-operative radiotherapy in soft tissue tumors. Assessment of response by static post-contrast MR imaging compared to histopathology. *Acta Radiol*. 2001;42(1):1-5.

48. Roberge D, Skamene T, Nahal A, Turcotte RE, Powell T, Freeman C. Radiological and pathological response following pre-operative radiotherapy for soft-tissue sarcoma. *Radiother Oncol*. 2010;97(3):404-407. doi:10.1016/j.radonc.2010.10.007

49. Winfield M. J, Miah AB, Dirk S, et al. Utility of Multi-Parametric Quantitative Magnetic Resonance Imaging for Characterization and Radiotherapy Response Assessment in Soft-Tissue Sarcomas and Correlation With Histopathology. *Front Oncol*. 2019;9(April). doi:10.3389/fonc.2019.00280

50. Wortman JR, Tirumani SH, Tirumani H, et al. Neoadjuvant radiation in primary extremity liposarcoma: correlation of MRI features with histopathology. *Eur Radiol*. 2016. doi:10.1007/s00330-015-3953-3

51. le Grange F, Cassoni AM, Seddon BM. Tumour volume changes following pre-operative radiotherapy in borderline resectable limb and trunk soft tissue sarcoma. *Eur J Surg Oncol J Eur Soc Surg Oncol Br Assoc Surg Oncol*. 2014;40(4):394-401. doi:10.1016/j.ejso.2014.01.011

52. Lansu J, Van Houdt WJ, van Langevelde K, et al. Local control and postponement of systemictherapy after modest dose radiotherapy in oligometastatic myxoid liposarcomas. *Radiother Oncol*. 2021.

53. Messiou C, Bonvalot S, Gronchi A, Vanel D, Meyer M, Haas RL. Evaluation of response after pre-operative radiotherapy in soft tissue sarcomas ; the European Organisation for Research and Treatment of Cancer e Soft Tissue and Bone Sarcoma Group (EORTC e STBSG) and Imaging Group recommendations for radiological exam. *Eur J Cancer*. 2016;56:37-44. doi:10.1016/j.ejca.2015.12.008

54. Skorpil M, Rydén H, Wejde J, Lidbrink E, Brosjö O, Berglund J. The effect of radiotherapy on fat content and fatty acids in myxoid liposarcomas quanti fi ed by MRI. 2017;43(1):37-41.

55. Wardelmann E, Haas RL, Bovée JVMG, et al. Evaluation of response after neoadjuvant treatment in soft tissue sarcomas; The European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) recommendations for pathological examination and reporting. *Eur J Cancer*. 2016;53:84-95. doi:10.1016/j.ejca.2015.09.021

56. Schaefer IM, Hornick JL, Barysauskas CM, et al. Histologic Appearance After Preoperative Radiation Therapy for Soft Tissue Sarcoma: Assessment of the European Organization for Research and Treatment of Cancer–Soft Tissue and Bone Sarcoma Group Response Score. *Int J Radiat Oncol Biol Phys*. 2017;98(2):375-383. doi:10.1016/j.ijrobp.2017.02.087

57. Lansu J, Van Houdt WJ, Schaapveld M, et al. Time Trends and Prognostic Factors for Overall Survival in Myxoid Liposarcomas: A Population-Based Study. *Sarcoma*. 2020;2020. doi:10.1155/2020/2437850

58. Kuyumcu G, Rubin BP, Bullen J, Ilaslan H. Quantification of fat content in lipid-rich myxoid liposarcomas with MRI : a single-center experience with survival analysis. 2018.

59. Vaynrub M, Taheri N, Ahlmann ER, et al. Prognostic value of necrosis after neoadjuvant therapy for soft tissue sarcoma. *J Surg Oncol*. 2015;111(2):152-157. doi:10.1002/jso.23775

60. Salah S, Lewin J, Amir E, Abdul Razak A. Tumor necrosis and clinical outcomes following neoadjuvant therapy in soft tissue sarcoma: A systematic review and meta-analysis. *Cancer Treat Rev*. 2018;69(May):1-10. doi:10.1016/j.ctrv.2018.05.007

61. Andreou D, Werner M, Pink D, et al. Prognostic relevance of the mitotic count and the amount of viable tumour after neoadjuvant chemotherapy for primary, localised, high-grade soft tissue sarcoma. *Br J Cancer*. 2015. doi:10.1038/bjc.2014.635

62. Bonvalot S, Wunder J, Gronchi A, et al. Complete pathological response to neoadjuvant treatment is associated with better survival outcomes in patients with soft tissue sarcoma: Results of a retrospective multicenter study. *Eur J Surg Oncol*. 2021. doi:10.1016/j.ejso.2021.02.024

63. Menendez LR, Ahlmann ER, Savage K, Cluck M, Fedenko AN. Tumor necrosis has no prognostic value in neoadjuvant chemotherapy for soft tissue sarcoma. *Clin Orthop Relat Res*. 2007. doi:10.1097/01.blo.0000238864.69486.59

64. Mullen JT, Hornicek FJ, Harmon DC, et al. Prognostic significance of treatment-induced pathologic necrosis in extremity and truncal soft tissue sarcoma after neoadjuvant chemoradiotherapy. *Cancer*. 2014. doi:10.1002/cncr.28945

65. Lin PP, Jaffe N, Herzog CE, et al. Chemotherapy response is an important predictor of local recurrence in Ewing sarcoma. *Cancer*. 2007. doi:10.1002/cncr.22412

66. Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: A pooled analysis of individual patient data. *Lancet Oncol*. 2010. doi:10.1016/S1470-2045(10)70172-8

67. Chen VE, Gillespie EF, Zakeri K, et al. Pathologic response after neoadjuvant chemotherapy predicts locoregional control in patients with triple negative breast cancer. *Adv Radiat Oncol*. 2017. doi:10.1016/j.adro.2017.01.012

68. Blaauwgeers JL, Kappers I, Klomp HM, et al. Complete pathological response is predictive for clinical outcome after tri-modality therapy for carcinomas of the superior pulmonary sulcus. *Virchows Arch*. 2013;462(5):547-556. doi:10.1007/s00428-013-1404-6

69. Kilpatrick SE, Doyon J, Choong PFM, Sim FH, Nascimento AG. The clinicopathologic spectrum of myxoid and round cell liposarcoma: A study of 95 cases. *Cancer*. 1996;77(8):1450-1458. doi:10.1002/(SICI)1097-0142(19960415)77:8<1450::AID-CNCR5>3.0.CO;2-G

70. Hoffman A, Ghadimi MPH, Demicco EG, et al. Localized and metastatic myxoid/round cell liposarcoma: Clinical and molecular observations. *Cancer*. 2013;119(10):1868-1877. doi:10.1002/cncr.27847

71. Wu J, Qian S, Jin L. Prognostic factors of patients with extremity myxoid liposarcomas after surgery. *J Orthop Surg Res*. 2019;14(1):1-8. doi:10.1186/s13018-019-1120-2

72. Pisters PW, Leung DH, Woodruff J, Shi W, Brennan MF. Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcomas of the extremities. *J Clin Oncol*. 1996;14(5):1679-1689. doi:10.1200/JCO.1996.14.5.1679

73. Lemeur M, Mattei JC, Souteyrand P, Chagnaud C, Curvale G, Rochwerger A. Prognostic factors for the recurrence of myxoid liposarcoma: 20 cases with up to 8 years follow-up. *Orthop Traumatol Surg Res*. 2015;101(1):103-107. doi:10.1016/j.otsr.2014.09.024

74. Smith TA, Easley KA, Goldblum JR. Myxoid/round cell liposarcoma of the extremities: A clinicopathologic study of 29 cases with particular attention to extent of round cell liposarcoma. *Am J Surg Pathol*. 1996. doi:10.1097/00000478-199602000-00005

75. Lansu J, Bovée JVMG, Braam P, et al. Dose Reduction of Preoperative Radiotherapy in Myxoid Liposarcoma: A Nonrandomized Controlled Trial. *JAMA Oncol*. 2021;7(1):1-8. doi:10.1001/jamaoncol.2020.5865

76. Chowdhry V, Goldberg S, DeLaney TF, et al. Myxoid liposarcoma: Treatment outcomes from chemotherapy and radiation therapy. *Sarcoma*. 2018;2018. doi:10.1155/2018/8029157

77. Wu J, Qian S, Jin L. Prognostic factors of patients with extremity myxoid liposarcomas after surgery. *J Orthop Surg Res*. 2019;14(1):90. doi:10.1186/s13018-019-1120-2

78. Kollár A, Rothermundt C, Klenke F, et al. Incidence, mortality, and survival trends of soft tissue and bone sarcoma in Switzerland between 1996 and 2015. *Cancer Epidemiol*. 2019;63(September). doi:10.1016/j.canep.2019.101596

79. Lazarev S, McGee H, Moshier E, Ru M, Demicco EG, Gupta V. Preoperative vs postoperative radiation therapy in localized soft tissue sarcoma: Nationwide patterns of care and trends in utilization. *Pract Radiat Oncol*. 2017;7(6):e507-e516. doi:10.1016/j.prro.2017.04.010

80. Assi T, Kattan J, El Rassy E, et al. A comprehensive review of the current evidence for trabectedin in advanced myxoid liposarcoma. *Cancer Treat Rev*. 2019;72(November 2018):37-44. doi:10.1016/j.ctrv.2018.11.003

81. Demetri GD, Schöffski P, Grignani G, et al. Activity of eribulin in patients with advanced liposarcoma demonstrated in a subgroup analysis from a randomized phase III study of eribulin versus dacarbazine. *J Clin Oncol*. 2017;35(30):3433-3439. doi:10.1200/JCO.2016.71.6605

82. Korah MP, Deyrup AT, Monson DK, et al. Anatomic tumor location influences the success of contemporary limb-sparing surgery and radiation among adults with soft tissue sarcomas of the extremities. *Int J Radiat Oncol Biol Phys*. 2012;82(2):933-939. doi:10.1016/j.ijrobp.2010.11.020

83. Baldini EH, Lapidus MR, Wang Q, et al. Predictors for major wound complications following preoperative radiotherapy and surgery for soft-tissue sarcoma of the extremities and trunk: Importance of tumor proximity to skin surface. *Ann Surg Oncol*. 2013. doi:10.1245/s10434-012-2797-1

84. Tseng JF, Ballo MT, Langstein HN, et al. The effect of preoperative radiotherapy and reconstructive surgery on wound complications after resection of extremity soft-tissue sarcomas. *Ann Surg Oncol*. 2006;13(9):1209-1215. doi:10.1245/s10434-006-9028-6

85. Rosenberg LA, Esther RJ, Erfanian K, et al. Wound complications in preoperatively irradiated soft-tissue sarcomas of the extremities. *Int J Radiat Oncol Biol Phys*. 2013. doi:10.1016/j.ijrobp.2012.04.037

86. Bedi M, King DM, Hackbarth DA, Charlson JA, Baynes K, Neilson JC. Biopsies in the community lead to postoperative complications in soft tissue sarcomas. *Orthopedics*. 2015. doi:10.3928/01477447-20150902-51

87. Saeed H, Johnstone C, King DM, et al. The impact of 3D conformal radiotherapy versus intensity-modulated radiotherapy on post-operative wound complications in soft tissue sarcomas of the extremity and chest-wall. *J Radiat Oncol*. 2016. doi:10.1007/s13566-016-0277-0

88. Slump J, Bastiaannet E, Halka A, et al. Risk factors for postoperative wound complications after extremity soft tissue sarcoma resection: A systematic review and meta-analyses. *J Plast Reconstr Aesthetic Surg*. 2019;72(9):1449-1464. doi:10.1016/j.bjps.2019.05.041

89. Chen Y, Guo Q, Pan X, Qin L, Zhang P. Smoking and impaired bone healing: Will activation of cholinergic anti-inflammatory pathway be the bridge? *Int Orthop*. 2011. doi:10.1007/s00264-011-1243-5

90. Rahman M, Laher I. Structural and Functional Alteration of Blood Vessels Caused by Cigarette Smoking: An Overview of Molecular Mechanisms. *Curr Vasc Pharmacol*. 2007. doi:10.2174/157016107782023406

91. Wang D, Harris J, Kraybill WG, et al. Pathologic complete response and survival outcomes in patients with localized soft tissue sarcoma treated with neoadjuvant chemoradiotherapy or radiotherapy: Long-term update of NRG Oncology RTOG 9514 and 0630. *J Clin Oncol*. 2017. doi:10.1200/jco.2017.35.15_suppl.11012

92. Koseła-Paterczyk H, Spałek M, Borkowska A, et al. Hypofractionated Radiotherapy in Locally Advanced Myxoid Liposarcomas of Extremities or Trunk Wall: Results of a Single-Arm Prospective Clinical Trial. *J Clin Med*. 2020;9(8):2471. doi:10.3390/jcm9082471

93. Haas RL, Floot B, Scholten AN, et al. Soft tissue sarcoma radiobiology in vitro and in vivo. *Radiat Res Res*. 2021;In press.

94. O'Sullivan B, Griffin AM, Dickie CI, et al. Phase 2 study of preoperative image-guided intensity-modulated radiation therapy to reduce wound and combined modality morbidities in lower extremity soft tissue sarcoma. *Cancer*. 2013;119(10):1878-1884. doi:10.1002/cncr.27951

95. Wang D, Zhang Q, Eisenberg BL, et al. Significant reduction of late toxicities in patients with extremity sarcoma treated with image-guided radiation therapy to a reduced target volume: Results of radiation therapy oncology group RTOG-0630 trial. *J Clin Oncol*. 2015. doi:10.1200/JCO.2014.58.5828

96. Koseła-Paterczyk H, Szacht M, Morysiński T, et al. Preoperative hypofractionated radiotherapy in the treatment of localized soft tissue sarcomas. *Eur J Surg Oncol*. 2014. doi:10.1016/j.ejso.2014.05.016

97. Navarria P, Ascolese AM, Cozzi L, et al. Stereotactic body radiation therapy for lung metastases from soft tissue sarcoma. *Eur J Cancer*. 2015;51(5):668-674. doi:10.1016/j.ejca.2015.01.061

98. Dhakal S, Corbin KS, Milano MT, et al. Stereotactic body radiotherapy for pulmonary metastases from soft-tissue sarcomas: Excellent local lesion control and improved patient survival. *Int J Radiat Oncol Biol Phys*. 2012;82(2):940-945. doi:10.1016/j.ijrobp.2010.11.052

99. Demetri GD, Von Mehren M, Jones RL, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: Results of a phase III randomized multicenter clinical trial. *J Clin Oncol*. 2016;34(8):786-793. doi:10.1200/JCO.2015.62.4734

100. Kawai A, Araki N, Sugiura H, et al. Trabectedin monotherapy after standard chemotherapy versus best supportive care in patients with advanced, translocation-related sarcoma: A randomised, open-label, phase 2 study. *Lancet Oncol*. 2015;16(4):406-416. doi:10.1016/S1470-2045(15)70098-7

101. Schöffski P, Chawla S, Maki RG, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: A randomised, open-label, multicentre, phase 3 trial. *Lancet*. 2016;387(10028):1629-1637. doi:10.1016/S0140-6736(15)01283-0

102. Judson I, Verweij J, Gelderblom H, et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: A randomised controlled phase 3 trial. *Lancet Oncol*. 2014;15(4):415-423. doi:10.1016/S1470-2045(14)70063-4

103. Blay JY, Leahy MG, Nguyen BB, et al. Randomised phase III trial of trabectedin versus doxorubicin-based chemotherapy as first-line therapy in translocation-related sarcomas. *Eur J Cancer*. 2014:1137-1147. doi:10.1016/j.ejca.2014.01.012

104. Pisters PW, Harrison LB, Leung DH, Woodruff JM, Casper ES, Brennan MF. Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. *J Clin Oncol*. 1996;14(3):859-868. doi:10.1200/JCO.1996.14.3.859

105. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011. doi:10.1007/s11136-011-9903-x

106. Aaronson NK, Ahmedzai S, Bergman B, et al. The European organization for research and treatment of cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993. doi:10.1093/jnci/85.5.365

107. https://healthcaredelivery.cancer.gov/pro-ctcae/.

108. Bouwmans C, Krol M, Severens H, Koopmanschap M, Brouwer W, Roijen LH Van. The iMTA Productivity Cost Questionnaire: A Standardized Instrument for Measuring and Valuing Health-Related Productivity Losses. *Value Heal*. 2015. doi:10.1016/j.jval.2015.05.009

109. Haas RLM, Miah AB, LePechoux C, et al. Preoperative radiotherapy for extremity soft tissue sarcoma; Past, present and future perspectives on dose fractionation regimens and combined modality strategies. *Radiother Oncol*. 2016;119(1):14-21. doi:10.1016/j.radonc.2015.12.002

Supplementary material

Radiotherapy protocol

The RT protocol, conform to the ICRU 50/62 guidelines, required standardized target volume delineation. Mirada DBx 1.2.0. delineation software (Mirada Medical, Oxford, United Kingdom) was used for target volume delineation. The gross tumor volume (GTV) was defined on the gadolinium-enhanced, T1-weighted MRI. The clinical target volume (CTV) was constructed by expanding the GTV with 3 cm in the longitudinal axis, and 1.5 cm in all other directions. Subsequently, if applicable, the GTV was manually edited to encompass any on T2-weighted MRI identified peritumoral edema in order to construct the CTV. The planning target volume was produced by expanding the CTV by 1 cm isotropically in all directions. The total prescribed dose was 36Gy, given in once-daily 2Gy fractions in a total treatment time of 24 days. IMRT or VMAT planning techniques were used. Dose distributions were calculated using Pinnacle with collapsed cone algorithm and inhomogeneity corrections (Pinnacle versions 9.2–9.10, Philips, Best, The Netherlands). The dose inhomogeneity within the PTV was between the 90% and 107%. Position verification at treatment was performed prior to every fraction with an online cone beam CT scan set-up correction protocol.

Supplementary Table

***Supplementary Table 1**. Overview of tested correlations between clinical MRI parameters and specific pathology treatment response effects*

MRI parameter	Pathology outcome	Baseline	Fraction 8	Fraction 16	Preoperative
Volumetric change*	Hyalinization	NA	NS	β =-.663, p=.000	β =-.588,p=.003
Enhancing fraction		β =.376, p=.044	NS	β =.578, p=.002	β =.622, p=.001
Fat fraction		β =-.584, p=.001	β =-.557, p=.009	β =-.588, p=.005	β =-.775, p=.000
Volumetric change*	Necrosis	NA	NS	β =.514, p=.009	β =.570, p=.005
Enhancing fraction		NS	NS	β =-.565, p=.003	β =-.536, p=.007
Fat fraction		NS	NS	NS	NS
Volumetric change*	Fatty maturation	NA	NS	NS	NS
Enhancing fraction		NS	NS	NS	NS
Fat fraction		β =.664, p=.000	β =.526, p=.014	β =.632, p=.002	β =.672, p=.000

Caption Supplementary Table 1. Correlations between MRI parameters and pathology treatment response effects are tested by logistic regression. A significant correlation exists between the MRI parameter and the pathology treatment response effect if the presented p-value meets the predefined level of statistical significance of p≤0.05. β *-values below and above zero represent negative and positive correlations for high pathology treatment response effects, respectively. *= As this parameter is a relative value (as compared to the baseline measurement) and therefore only tested at fraction 8, fraction 16 and preoperative. Abbreviations: NA= not assessed, NS= not significant,* β *= standardized coefficient Beta, p= level of significance*