Local control and postponement of systemic therapy after modest dose radiotherapy in oligometastatic myxoid liposarcomas

Lansu, J.; Houdt, W.J. van; Langevelde, K. van; Ende, P.L.A. van den; Graaf, W.T.A. van der; Schrage, Y.; ... ; Haas, R.L.

Radiotherapy and Oncology 158 (2021) 33–39

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Local control and postponement of systemic therapy after modest dose radiotherapy in oligometastatic myxoid liposarcomas

Jules Lansu [a], Winan J. van Houdt [b], Kirsten van Langevelde [c], Piet L.A. van den Ende [d], Winette T.A. van der Graaf [e], Yvonne Schrage [b], Hester van Boven [f], Astrid N. Scholten [a], Rick L. Haas [a,g,*]

[a] Department of Radiotherapy, the Netherlands Cancer Institute; [b] Department of Surgical Oncology, the Netherlands Cancer Institute, Amsterdam, The Netherlands; [c] Department of Radiology, Leiden University Medical Center, Leiden; [d] Department of Radiotherapy, Maastricht University Medical Center; [e] Department of Medical Oncology, the Netherlands Cancer Institute; [f] Department of Pathology, the Netherlands Cancer Institute, Amsterdam; and [g] Department of Radiotherapy, Leiden University Medical Center

ARTICLE INFO

Article history:
Received 2 January 2021
Received in revised form 27 January 2021
Accepted 8 February 2021
Available online 19 February 2021

Keywords:
Myxoid liposarcoma
Myxoid liposarcomas
Soft tissue sarcoma, soft tissue sarcomas
Metastatic
Palliative therapy
Adjuvant radiotherapy

ABSTRACT

Introduction: Oligometastatic disease and/or oligoprogression in myxoid liposarcoma(oMLS) triggers discussions on local treatment options and delay of systemic treatments. We hypothesized that satisfactory local control and postponement of systemic therapy could be achieved with a modest radiotherapy(RT) dose in oMLS.

Methods: The DOREMY trial is a multicenter, phase 2 trial evaluating efficacy and toxicity of a modest RT dose in both localized and oMLS; this report presents the data of the oMLS cohort treated with 36 Gy in 12–18 fractions with optional subsequent metastasectomy. The primary endpoint was local progression free survival(LPFS). Secondary endpoints included postponement of systemic therapy, symptom reduction, radiological objective response, and toxicity.

Results: Nine patients with a total of 25 lesions were included, with a median follow-up of 23 months. The median number of lesions per patient was three and the trunk wall and bone were the most frequently affected sites. In lesions treated with definitive RT(n = 21), LPFS rates at 1, 2, and 3 years were respectively 73%, 61%, and 40%. Radiological objective response and clinical symptom reduction were achieved in 8/15(53%) and 9/10(90%) of the evaluable lesions, respectively. No local recurrences occurred in lesions treated with RT and metastasectomy(n = 4). For the entire study population, the median postponement of systemic therapy was 10 months. Grade $\geq$ 2 toxicity was observed in 2/9(22%) of patients.

Conclusions: This trial suggests that 36 Gy could possibly be effective to achieve local control, postpone systemic therapy and reduce symptoms in oMLS. Given the minimal toxicity this treatment could be reasonably considered in oMLS.

Myxoid liposarcoma(MLS) is a rare malignancy with an estimated incidence of 2 per million person years and belongs to the heterogeneous group of Soft Tissue Sarcomas(STS) [1]. The standard treatment of primary MLS consists of surgery and RT [2,3]. The 5-year local control rates of 96–98% are to an important extent a result of the well-established exceptional clinical radiosensitivity of MLS [4–10]. However, notwithstanding the excellent local control, disease specific mortality is predominantly determined by the 14–33% of patients who eventually develop distant metastases [8–11]. As major morbidity can be induced when distant metastases become symptomatic, effective strategies to achieve local control of metastatic lesions are desired. Treatment options for metastatic MLS are traditionally systemic and include anthracycline-based regimens, trabectedin, and eribulin. Objective response rates of these agents do not exceed 33% in prospective trials with median progression free intervals of 2.9–18.8 months [12–19]. Associated toxicities are nausea, vomiting, alopecia and hematological and liver toxicity. Metastatic disease of MLS is not always widespread at first presentation, sometimes presenting in an oligometastatic state. Likewise, patients may become oligo progressive when only one or two lesions progress while others remain stable with or without systemic therapy. Given the limited efficacy and frequently substantial toxicity of systemic treatment, exploration of the role of local treatment for oligometastatic disease and/or oligoprogression in MLS(oMLS) metastases is important.

Local treatment of STS metastases is recommended in selected cases and has been associated with long-term survival in several retrospective series [2,20–26]. Doubling time, number of metastatic lesions and disease-free interval are mostly used as selection criteria.[21] The only prospective phase II trial(NCT01986829)

* Corresponding author at: Department of Radiation Oncology, Netherlands Cancer Institute, Plesmanlaan 121, 1006 BE Amsterdam, The Netherlands.
E-mail address: r.haas@nki.nl (R.L. Haas).

https://doi.org/10.1016/j.radonc.2021.02.013
0167-8140/

showed promising results for tumor ablation in metastatic STS patients stable on chemotherapy, although it was terminated early due to low accrual.[27] Of note, these studies are predominantly focused on pulmonary metastases, while metastatic MLS has a tendency to metastasize to extra-pulmonary sites such as the retroperitoneum, soft tissues or bone even before spreading to the lungs.[11] At these locations, metastasectomies or tumor ablation are not always feasible due to comorbidity or technical considerations. Although stereotactic body radiotherapy(SBRT) has been shown to be an effective treatment for pulmonary STS metastases [25,28], target volume restrictions frequently preclude SBRT as a treatment option in large MLS metastases. Therefore, conventionally fractionated to mildly hypofractionated RT could prove a reasonable alternative, particularly given the well-established radiosensitivity of MLS in the primary tumor setting [4–10]. A standard dose fractionation scheme has not yet been determined in the setting of oMLS.

We hypothesized that a modest radiation dose could (i) provide satisfactory local progression free survival(LPFS) and (ii) postpone systemic treatment with a (iii) reasonable toxicity profile. Hereto, the DOREMY trial(NCT02106312) design included an arm to assess efficacy and toxicity of a radiation dose of 36 Gy of oMLS.

Methods

Trial design and patients

This paper reports on the clinical outcome of the patients in the oMLS cohort in the DOREMY(DOse REduction in Myxoid liposarcoma) trial. The complete trial design has been published previously along with the data of the patients in the primary non-metastatic MLS cohort.[29] In brief, the DOREMY trial is a prospective, multicenter, single-arm, phase 2 trial and opened to accrual November 24th of 2010. Two centers were open for recruitment of patients with oMLS. Eligible patients were adults ($\geq$18 years) with a limited number of MLS metastases. The maximum number of target lesions per patient was left to the discretion of the treating multidisciplinary sarcoma board, in consideration of the disease/progression-free interval, anatomical sites of the metastatic lesions (and their relation to prior RT areas), alternative treatment options, and patient performance and preferences. Not all MLS metastases were necessarily irradiated, as in case of oligo progressive MLS only progressive or symptomatic lesions were treated. Exclusion criteria were any other prior or concurrent malignancy, pregnancy and ECOG performance status > 2.

All patients provided written informed consent prior to enrolment, and conduct of the trial was in compliance with the Declaration of Helsinki and all applicable laws. The protocol and all amendments thereon were approved by the ethics committee of the initiating center.

Procedures

Besides history review and physical examination, the staging procedure consisted of Magnetic Resonance Imaging(MRI) of the target lesion, or computed tomography(CT) for pulmonary target lesions without thoracic wall invasion. Recent(<2 months) CT imaging of the chest, abdomen, and pelvis was required for evaluation of the metastatic status.[2,3] Histopathological and molecular confirmation of the MLS diagnosis of the original primary tumor or at least one of its metastases, if not already previously performed, was mandatory. When metastatic MLS was proven previously in another lesion, CT and/or MRI was deemed sufficient for confirmation of a new or progressive MLS lesion.

In the oMLS cohort of the study, RT could be provided with two distinct treatment options; as definitive RT or as preoperative RT before metastasectomy. The RT protocol, conform to the ICRU 50/62 guidelines, required standardized target volume delineation. The gross tumor volume(GTV) was defined using the gadolinium-enhanced, T1-weighted MRI. In case of a pulmonary lesion, a respiratory-correlated 4-dimensional planning CT scan was performed, of which the CT lung window of the mid ventilation phase (time-weighted mean tumor position) was used for tumor delineation of the GTV. Subsequently, if applicable, the GTV was manually edited to encompass any on T2-weighted MRI identified peritumoral edema in order to construct the clinical target volume(CTV). Eventually, the CTV was expanded by tumor site specific planning target volume(PTV) margins, which are presented in Supplementary Table 1. The total prescribed dose was 36 Gy, given in fractions of either 2 Gy or 3 Gy. The 2 Gy fraction schedule was administered once-daily for five consecutive days per week in a total treatment time of 24 days. The 3 Gy regimen consisted of 4–5 once-daily fractions per week, with a total treatment time of 16–19 days. IMRT or VMAT planning techniques were used. Dose distributions were calculated using collapsed cone inhomogeneity corrections (Pinnacle versions 9.2–9.10, Philips, Best, The Netherlands). The dose inhomogeneity within the PTV ranged between 90% and 107%. Treatment verification was performed daily with an online cone beam CT scan set-up correction protocol.

Eligibility of subsequent metastasectomy was assessed prior to RT by the multidisciplinary sarcoma board, predominantly determined by the number of metastases, doubling time, disease-free-interval, resectability, anticipated surgically induced morbidity as well as patient preferences. In case of a metastasectomy, it was performed at least 4 weeks after completion of the RT course, preferably after repeated preoperative MRI. The resection specimens were processed in accordance with local routines, including the quantification of all pathological treatment effects such as hyalinization, fatty maturation and necrosis [29]. Follow-up visits were scheduled two- to three-monthly, including physical examination and appropriate imaging to detect new metastases and to repeat the CT and/or MRI of the treated lesion site.

Endpoints

The primary endpoint in the oMLS cohort was LPFS, defined as the interval between baseline visit and the date of the first clinical or any radiological local progression of the target lesion. Secondary endpoints included the time to (the next line of) systemic therapy, LPFS censored at the date of the first cycle of (the next line of) systemic therapy, progression free survival(PFS), disease specific survival(DSS), overall survival(OS), and toxicity. Of note, the indication for systemic therapy was set at the discretion of the treating clinicians in the multidisciplinary sarcoma board. Acute(<3 months) and late($\geq$3 months) toxicities were scored during the on-treatment check-ups and follow-up visits, respectively [30]. Furthermore, if target lesions were symptomatic at baseline visit, clinical symptom reduction was evaluated at the first follow-up visit. In case of definitive RT of (predominantly) non-bone metastases, the best achieved radiological response of the target lesion was an additional secondary endpoint, with an objective radiological response defined as either complete (disappearance) or partial (maximum diameter $\leq$ -30%) response [31]. Other secondary endpoints for patients with metastasectomy were wound complications and extensive treatment response, defined as $\geq$50% of any treatment effect in the resection specimen during pathological examination.

Statistical analysis

Descriptive statistics were used to analyze the data. Radiological response, pathological response, symptom reduction, and LPFS,

Table 1
Baseline characteristics, treatment details and outcome per patient and lesion.

Pt #	Age	Sex	Lesion	Lesion site	Tumor size (cm)	RCC > 5%	PS	Progression free interval‘‘ (months)	RT schedule (Gy)	Resection	Target Lesion response	Symptom reduction	Time to local progression (months)	Time to distant progression (months)	Time to next systemic line (months)	Cause of death	FU (months)
1	37	f	A	Trunk wall	2	No	0	12	18 × 2	yes	NA	NA	–	22	50	PD	71
2	33	m	A	Lung	10	No	0	26	18 × 2	no	SD○	Yes	14	2	2	PD	24
			B	Bone	9				12 × 3	no	NA	NA	–				24
			C	Bone	10				12 × 3	no	NA	NA	–				24
3	49	f	A	Trunk wall	8	No	0	68	18 × 2	yes	NA	NA	–	–	–*	Second primary	14
			B	Lung	3				18 × 2	yes	NA	NA	–				14
4	62	f	A	Trunk wall, lung	10	No	0	31	12 × 3	no	PR○	Yes	–	2	2	PD	68
			B	Neck	5		1	38	12 × 3	no	SD	Yes	–	10	–		28
			C	Trunk wall	5		1	10	18 × 2	no	PR	Yes	–	–	–		18
5	47	m	A	Retro–peritoneum	12	Yes	0	63	18 × 2	yes	NA	Yes	–	18	18	PD	39
6	57	m	A	Intra–abdominal	2	Yes	0	18	18 × 2	no	PR	NA	56	10	56	–	60
			B	Trunk wall	4		0	10	12 × 3	no	PR	NA	28	–	45		50
			B	Trunk wall	7		0	28	20x1.8 (reirradiation)	no	SD	Yes	18	7	18		22
7	30	m	A	Bone, Trunk wall	9	No	0	10	12 × 3	no	PR	Yes	9	4	10	PD	39
			B	Bone	3		0	4	12 × 3	no	NA	Yes	–	6	6		35
			C	Trunk wall	16		0	17	12 × 3	no	PR	Yes	8	2	–		12
			D	Bone	5				18 × 2	no	NA	No	7				12
			E	Lung	3		1	2	18 × 2	no	SD	NA	–	5	–		10
			F	Intra–abdominal	4				18 × 2	no	PR	NA	–				10
8	58	f	A	Trunk wall	5	Yes	0	12	12 × 3	no	SD	NA	–	5	6	–	23
			B	Para–rectal	6				12 × 3	no	SD	NA	20^				23
			C	Intra–abdominal	7		0	12	12 × 3	no	SD	NA	–	–	–		5
9	48	m	A	Bone	6	Yes	0	43	12 × 3	no	NA	Yes	–	4	6	–	11
			B	Bone	2				12 × 3	no	NA	Yes	-				11
			C	Trunk wall	8		0	4	12 × 3	no	PR	Yes	–	2	2		6

‘‘ The progression-free interval prior to radiotherapy of the target lesion(s).
* This patient received a different chemotherapy regimen for another indication.
^ This patient was treated with a metastasectomy because of local tumor progression 20 months after RT of this lesion.
○ The radiological responses in these lesions have been observed when the next line of systemic was already started. Of note, none of these two patients achieved an objective response in any of the non-irradiated lesions at the time of these radiology assessments.
Abbreviations:Pt = patient, cm = centimeter, PS = WHO performance score, RT = radiotherapy, Gy = Gray, FU = follow-up, f = female, m = male, NA = not assessed, PR = partial response, SD = stable disease, PD = progressive disease.

were analyzed per-lesion. Postponement of systemic therapy, PFS, DSS, OS, and toxicity, were analyzed per-patient. Survival endpoints were measured from the date of baseline visit and analyzed per-protocol, using the Kaplan-Meier approach. A cox-regression model was constructed to test whether radiological objective response and/or tumor size of the target lesion were correlated with LPFS, using a level of significance of $p \leq 0.05$. Statistical analyses were conducted by using IBM SPSS V25, with a follow-up until September 15, 2020.

Results

On April 1st, 2020, the predefined accrual of 100 patients in the comprehensive DOREMY trial was reached and the trial was closed. A total of 9 eligible patients were enrolled in the oMLS cohort of the trial. Together these patients had 25 MLS target lesions, of which 11 were symptomatic lesions with the majority consisting of pain. At baseline visit of the first lesion, the median age was 48 years and the WHO performance status was 0 in all of the patients. The patient population consisted of 4 females and 5 males. All patients had metachronous metastatic disease, with a median interval of 26 months between previous disease manifestation and the first target lesion in this trial(range 10–68 months). The site of the primary tumor location was controlled in all of the patients at first baseline visit. The median number of MLS target lesions per patient was 3 lesions(range 1–6), which were treated all in once($n = 4$), partly simultaneously($n = 3$), or consecutively with progression free intervals($n = 2$). Most frequent lesion sites were the trunk wall($n = 10$), (involvement of) bone($n = 7$), and the lung($n = 4$). An overview of baseline characteristics, treatment characteristics and outcome is presented in Table 1.

Treatment comprises definitive RT in 6 patients with 21 lesions and preoperative RT with metastasectomy in 3 patients with 4 lesions. RT was performed according to the RT protocol in 2 Gy fractions($n = 10$) and 3 Gy fractions($n = 14$). Because of surrounding normal tissue concerns, one further lesion was irradiated in 1.8 Gy fractions to 36 Gy. Fig. 1 provides individual patient treatment timelines, with T = 0 representing the treatment of the first target lesion in this trial. An overview of lesion specific timelines is presented in Fig. 2.

Objective radiological response was achieved in 8/15(53%) for this endpoint evaluable lesions, consisting of 8 partial responses (PR). The 7 remaining evaluable lesions exhibited stable disease (SD), and there were no patients with progressive disease. Two of the patients(one SD lesion and one PR lesion) had started with systemic therapy at the moment of radiological assessment of the target lesion, although without an objective response in non-irradiated lesions. Clinical symptom reduction was achieved in 9/10(90%) of the symptomatic lesions, with the first improvement already observed before the end of RT course in the majority of cases.

Following definitive RT, local progression was observed in 8/21 (38%) lesions after a median follow-up of 23 months(IQR 11–31). Rates of LPFS at 1, 2 and 3 years were 84%, 62% and 47%, respectively (Fig. 3). For those lesions with local progression, the median interval to local progression was 16 months. LPFS was neither correlated with radiological objective response(Hazard Ratio(HR) 0.68; 95% Confidence Interval(CI)0.11–4.05, $p = 0.67$), nor with tumor size of the target lesion (HR1.11; 95%CI0.92–1.36, $p = 0.27$). Systemic therapy following local or distant progression was given to 6/6 patients, with a median interval of 6 months between baseline visit of the RT of the first lesion and the first cycle of systemic therapy. LPFS censored at the start date of the (next line of) systemic therapy following RT of the target lesion at 1, 2 and 3 years are 73%, 61% and 40%, respectively. Median PFS, DSS, and OS, were 5, 39, and 39 months, respectively.

In patients treated with preoperative RT followed by metastasectomy, none of the four lesions recurred locally after a median follow-up of 26 months(IQR 14–63). Due to development of distant metastases, systemic treatment was started in 2/3 patients at 18 and 50 months after baseline visit. The third patient, which had two simultaneous metastasectomies, did not have a systemic therapy indication for MLS, however, chemotherapy for gastric cancer with peritoneal metastases consisting of Capecitabine monotherapy, was started at 7 months follow-up. Pathology examination showed extensive treatment response (≥50%) in 3/4 resection specimens, with estimated treatment effects in 100%, 100% and 90% of the resection volumes. The fourth resection specimen contained just 1% of necrosis. Surgical margins were negative in all four resected lesions. Median PFS, DSS, and OS, were 18, 39, and 39 months, respectively.

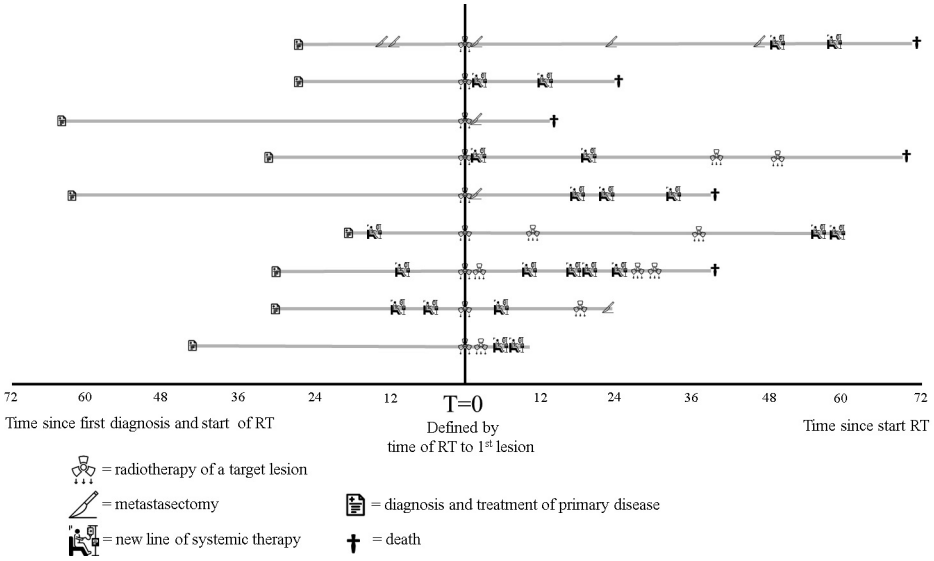

Fig. 1. Patient specific timelines with an overview of therapeutic interventions. For each patient an individual timeline is provided starting from the diagnosis of the primary MLS until death or the end of follow-up. All relevant therapeutic interventions for metastatic lesions are included in this overview, but not the initial treatment of the primary MLS manifestation as this falls out of the scope of this trial. The y-axis ($T = 0$) represents the treatment of the first oligometastatic or oligoprogressive lesion of each patient in this study.

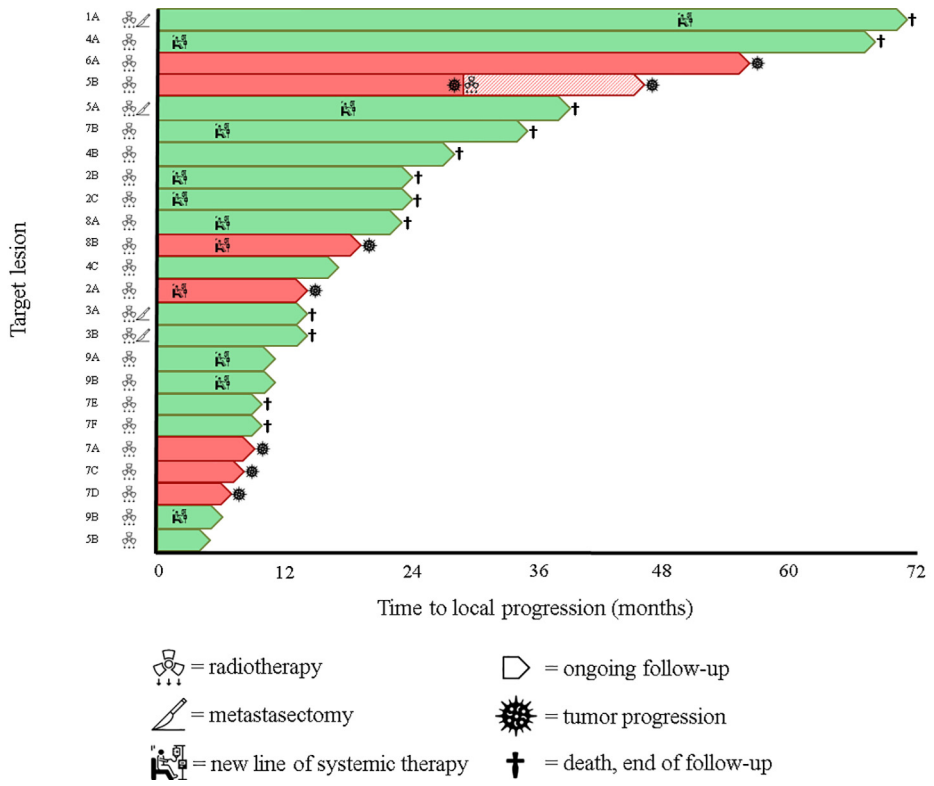

Fig. 2. Lesion specific timelines with an overview of therapeutic interventions. Each bar represents an oligometastatic/oligoprogressive target lesion in this trial, sorted by local progression free survival. Lesions with and without progression are displayed in red and green, respectively. On the left side of the y-axis, the patient number ("Pt #" in Table 1) and lesion letter ("Lesion" in Table 1) are presented together with the study intervention consisting of definitive radiotherapy or preoperative radiotherapy with subsequent metastasectomy. If systemic therapy was given for progressive other lesions, which could possibly have impacted local progression free survival of the target lesion, it is displayed in the bars at the time of administration of the first cycle. Lesion 5B showed local progression at 28 months after initial radiotherapy of the target lesion, therefore, the lesion was reirradiated to 36 Gy in 1.8 Gy fractions, on which the lesion remained stable for another 20 months.

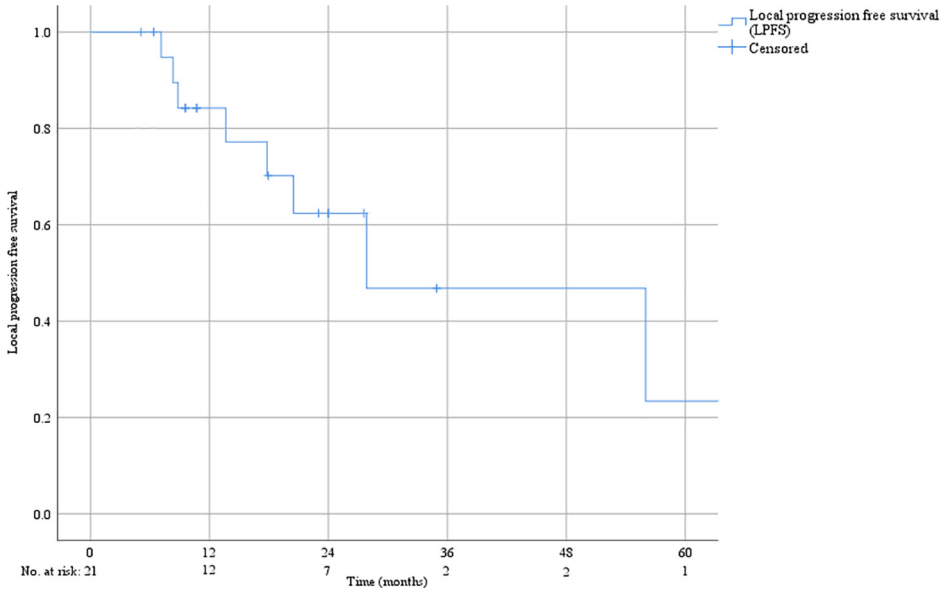

Fig. 3. Local progression free survival (primary endpoint) after definitive radiotherapy**.** Local progression free survival following definitive radiotherapy presented by a Kaplan Meier curve.

Acute and late toxicity of any grade was observed in 7/9 and 0/9 patients, respectively. Acute toxicity consisted of grade 2 dysphagia(n = 1), grade 1 fatigue(n = 3), grade 1 xerostomia(n = 1) and grade 1 proctitis(n = 1). Furthermore, one patient developed grade 2 thoracic pain, which was most likely not radiation-induced, but caused by the subsequent pulmonary metastasectomy. None of the patients who underwent subsequent metastasectomy developed wound complications requiring intervention.

Discussion

This prospective trial suggests that RT to a dose of 3 Gy in 12 or 18 fractions could be an effective and minimally toxic treatment in oMLS. Definitive RT provided local control in 62% of the irradiated lesions at two years and for those lesions with local progression, the median interval to progression was 16 months. It could be considered to perform a subsequent surgical resection to further increase local control, if this is justified by the anticipated surgery induced morbidity and the prognosis of the patient. Systemic therapy was postponed with a median interval of 6 months. Symptom reduction was achieved in 90% of the symptomatic lesions and the objective radiological response rate was 53% in definitively irradiated lesions with no patients having progressive disease. However, no correlation was found between objective radiological response and LPFS.

To the best of our knowledge, this is the first prospective trial assessing LPFS following definitive RT in (oligo)metastatic MLS. There is one retrospective study of 112 unresectable STS cases reporting on LPFS by Kepka et al., although unfortunately without histological subtype stratification [32]. Following a median radiation dose of 64 Gy of definitive RT, the reported two-year actuarial LPFS rate of 52% in that study was slightly lower than the 62% in the current trial. The at least comparable LPFS in the current trial achieved by delivering just over half of that radiation dose obviously reflects the variety of STS subtypes included by Kepka, while our cohort was purely MLS. Yet, it underscores the vast difference in clinical radiosensitivity between MLS and other STS subtypes, apparently also for metastatic disease. To further put our findings into perspective, our results are non-inferior to the previously mentioned trial investigating tumor ablation of up to three metastases in STS patients stable after six cycles of chemotherapy [27]. The primary endpoint in that trial consisting of the 3-month progression free survival rate was 75% versus 78% in our unselected patient population. Lastly, when comparing our findings with reports on SBRT in STS [25,28], SBRT is still associated with superior local control and a lower patient burden as compared to our regimen. Therefore, if SBRT is deemed feasible such as in small pulmonary and bone lesions, this obviously remains the RT treatment of choice in oMLS. In line with retrospective RT MLS data [4,5,7,33,34], we observed superior radiological responses of the target lesions, as compared to the 4–34% objective response rates we know from systemic agents [12,14–17]. Our radiological objective response rate of 53% according to RECIST is similar to the 58% in a recently reported phase II trial by Koseła-Paterczyk et al., exploring 25 Gy in 5 fractions followed by delayed surgery in MLS [35]. This could be expected, as the RT regimens in Koseła-Paterczyk's and our trial are biologically practically equivalent for MLS cells. Of note, with respect to the late responding normal tissues, the large fraction size in the Polish trial implicates theoretically increased late toxicity on the long-term, although this was not observed yet after 27 months median follow-up. In a phase I trial investigating 45 Gy of neoadjuvant RT with concurrent Trabectedin (1.1–1.5 mg/m^2) in locally advanced MLS a 36% of objective response rate according to RECIST was reported [36]. Despite the higher dose and the addition of a potential radiosensitizer, this is remarkably lower than Koseła-Paterczyk's and our rates.

Although the proportion of RECIST objective responses we observed was high, no correlation was found with LPFR in this modest dataset of 15 for this endpoint evaluable lesions. This is in line with previous reports suggesting that the predictive value of RECIST response assessment in STS is low [37–40]. Radiological responses were unfortunately not assessable according to modified Choi criteria, which are possibly more appropriate than RECIST in this setting. The required contrast enhanced CT imaging was not routinely-based performed during the follow-up, in order to limit the standard-of-care exceeding patient burden in this trial to a minimum.

Other limitations of this trial include the above mentioned small sample size and the lack of a control arm. Inherent to the rarity with yearly approximately 30–40 new primary MLS cases in the Netherlands, of which only a few develop metastatic disease [1], the number of eligible oMLS cases presenting in the two trial centers within a reasonable timeframe is very limited. For that reason, a single-arm study design was pragmatically chosen in order to maximize the body of the prospective data on the new regimen. An additional limitation is the lack of quality of life(QOL) assessments. This precludes objectification of a potential QOL benefit as compared to systemic regimens or wait and see, which could fairly be expected based on the high symptom reduction rate and the very mild toxicity profile observed in this trial.

In summary, the DOREMY trial suggests that a 36 Gy radiation dose could be effective to achieve local control, postponement of systemic therapy and symptom reduction in oMLS. Given the minimal associated toxicity and the convenience of the – particularly 12 $\times$ 3 Gy – schedule, this treatment could be reasonably considered in oligometastatic MLS, particularly when SBRT is deemed unfeasible. Whether this strategy also translates into improved quality of life and prolonged survival is yet to be determined in future research. The first step will be the recently initiated international prospective registration study(NCT04699292) for MLS.

Data sharing statement

The data will be shared on request, if this request is considered scientifically valid by the authors.

Declaration of Competing Interest

W.vd.G: advisory Bayer and GSK, consultant Spingworks, research grant Novartis. The other authors have nothing to disclose.

Acknowledgements

We thank Henk Botma, Pietje Muller and Rody Zuidema for their support regarding the data management in the study.

This research was supported by grants of KWF (8069/KaWeFis Batch7), Nanobiotix Company, foundation "Honderdduizend Keer een Tientje", and the European Organization for Research and Treatment of Cancer - Soft Tissue and Bone Sarcoma Group.

The funding sources had no role in the trial design, data collection, data analysis, data interpretation, or writing of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.02.013.

References

[1] Lansu J, Van HWJ, Schaapveld M, et al. Time trends and prognostic factors for overall survival in myxoid liposarcomas: A population-based study. Sarcoma 2020;2020:2437850. https://doi.org/10.1155/2020/2437850.

[2] Casali PG, Abecassis N, Bauer S, Biagini R, Bielack S, Bonvalot S, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29:iv51–67. https://doi.org/10.1093/annonc/mdy096.

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

[4] Pitson G, Robinson P, Wilke D, Kandel RA, White L, Griffin AM, et al. Radiation response: An additional unique signature of myxoid liposarcoma. Int J Radiat Oncol Biol Phys 2004;60(2):522–6. https://doi.org/10.1016/j.ijrobp.2004.03.009.
[5] Engström K, Bergh P, Cederlund C-G, Hultborn R, Willen H, Åman P, et al. Irradiation of myxoid/round cell liposarcoma induces volume reduction and lipoma-like morphology. Acta Oncol (Madr) 2007;46(6):838–45. https://doi.org/10.1080/02841860601080415.
[6] 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):1480–7. https://doi.org/10.1016/j.ijrobp.2008.03.008.
[7] 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. https://doi.org/10.1007/s13566-012-0085-0.
[8] Chung PWM, Deheshi BM, Ferguson PC, Wunder JS, Griffin AM, Catton CN, et al. Radiosensitivity translates into excellent local control in extremity myxoid liposarcoma: A comparison with other soft tissue sarcomas. Cancer 2009;115(14):3254–61. https://doi.org/10.1002/cncr.v115:1410.1002/cncr.24375.
[9] Guadagnolo BA, Zagars GK, Ballo MT, Patel SR, Lewis VO, Benjamin RS, 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):760–5. https://doi.org/10.1016/j.ijrobp.2007.07.2337.
[10] Moreau L-C, Turcotte R, Ferguson P, Wunder J, Clarkson P, Masri B, et al. Myxoid\round cell liposarcoma (MRCLS) revisited: An analysis of 418 primarily managed cases. Ann Surg Oncol 2012;19(4):1081–8. https://doi.org/10.1245/s10434-011-2127-z.
[11] Antonescu CR, Ladanyi M. Myxoid liposarcoma. In: WHO classification of tumours of soft tissue and bone. p. 39–41.
[12] Blay J-Y, Leahy MG, Nguyen BB, Patel SR, Hohenberger P, Santoro A, et al. Randomised phase III trial of trabectedin versus doxorubicin-based chemotherapy as first-line therapy in translocation-related sarcomas. Eur J Cancer 2014;50(6):1137–47. https://doi.org/10.1016/j.ejca.2014.01.012.
[13] Demetri GD, von Mehren M, Jones RL, Hensley ML, Schuetze SM, Staddon A, 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):786–93. https://doi.org/10.1200/JCO.2015.62.4734.
[14] Kawai A, Araki N, Sugiura H, Ueda T, Yonemoto T, Takahashi M, 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):406–16. https://doi.org/10.1016/S1470-2045(15)70098-7.
[15] Schöffski P, Chawla S, Maki RG, Italiano A, Gelderblom H, Choy E, 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):1629–37. https://doi.org/10.1016/S0140-6736(15)01283-0.
[16] Demetri GD, Schöffski P, Grignani G, Blay J-Y, Maki RG, Van Tine BA, 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):3433–9. https://doi.org/10.1200/JCO.2016.71.6605.
[17] Judson I, Verweij J, Gelderblom H, Hartmann JT, Schöffski P, Blay J-Y, 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):415–23. https://doi.org/10.1016/S1470-2045(14)70063-4.
[18] Assi T, Kattan J, El Rassy E, Honore C, Dumont S, Mir O, et al. A comprehensive review of the current evidence for trabectedin in advanced myxoid liposarcoma. Cancer Treat Rev 2019;72:37–44. https://doi.org/10.1016/j.ctrv.2018.11.003.
[19] Smrke A, Wang Y, Simmons C. Update on systemic therapy for advanced soft-tissue sarcoma. Curr Oncol 2020;27(February):25–33. https://doi.org/10.3747/co.27.5475.
[20] Blackmon SH, Shah N, Roth JA, Correa AM, Vaporciyan AA, Rice DC, et al. Resection of Pulmonary and Extrapulmonary Sarcomatous Metastases Is Associated With Long-Term Survival. Ann Thorac Surg 2009;88(3):877–85. https://doi.org/10.1016/j.athoracsur.2009.04.144.
[21] Rehders A, Hosch SB, Scheunemann P, Stoecklein NH, Knoefel WT, Peiper M. Benefit of surgical treatment of lung metastasis in soft tissue sarcoma. Arch Surg 2007;142(1):70–5. https://doi.org/10.1001/archsurg.142.1.70.
[22] Cariboni U, De Sanctis R, Giaretta M, et al. Survival outcome and prognostic factors after pulmonary metastasectomy in sarcoma patients. Am J Clin Oncol Cancer Clin Trials 2019;42:6–11. https://doi.org/10.1097/COC.0000000000000476.
[23] García Franco CE, Algarra SM, Ezcurra AT, et al. Long-term results after resection for soft tissue sarcoma pulmonary metastases. Interact Cardiovasc Thorac Surg 2009;9:223–6. https://doi.org/10.1510/icvts.2009.204818.
[24] Nakamura T, Matsumine A, Yamakado K, Matsubara T, Takaki H, Nakatsuka A, et al. Lung radiofrequency ablation in patients with pulmonary metastases from musculoskeletal sarcomas: An initial experience (R#2). Cancer 2009;115(16):3774–81. https://doi.org/10.1002/cncr.v115:1610.1002/cncr.24420.
[25] Navarria P, Ascolese AM, Cozzi L, Tomatis S, D'Agostino GR, De Rose F, et al. Stereotactic body radiation therapy for lung metastases from soft tissue sarcoma. Eur J Cancer 2015;51(5):668–74. https://doi.org/10.1016/j.ejca.2015.01.061.
[26] Gamboa AC, Gronchi A, Cardona K. Soft-tissue sarcoma in adults: An update on the current state of histiotype-specific management in an era of personalized medicine. CA Cancer J Clin 2020;70(3):200–29. https://doi.org/10.3322/caac.v70.310.3322/caac.21605.
[27] Hirbe AC, Jennings J, Saad N, Giardina JD, Tao Yu, Luo J, et al. A phase II study of tumor ablation in patients with metastatic sarcoma stable on chemotherapy. Oncologist 2018;23(7):760. https://doi.org/10.1634/theoncologist.2017-0536.
[28] Dhakal S, Corbin KS, Milano MT, Philip A, Sahasrabudhe D, Jones C, 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):940–5. https://doi.org/10.1016/j.ijrobp.2010.11.052.
[29] 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. https://doi.org/10.1001/jamaoncol.20205865.
[30] Cox JD, Stetz JoAnn, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European organization for research and treatment of cancer (EORTC). Int J Radiat Oncol Biol Phys 1995;31(5):1341–6. https://doi.org/10.1016/0360-3016(95)00060-C.
[31] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228–47. https://doi.org/10.1016/j.ejca.2008.10.026.
[32] Kepka L, DeLaney TF, Suit HD, Goldberg SI. Results of radiation therapy for unresected soft-tissue sarcomas. Int J Radiat Oncol Biol Phys 2005;63(3):852–9. https://doi.org/10.1016/j.ijrobp.2005.03.004.
[33] Wang W-L, Katz D, Araujo DM, et al. Extensive adipocytic maturation can be seen in myxoid liposarcomas treated with neoadjuvant doxorubicin and ifosfamide and pre-operative radiation therapy. Clin Sarcoma Res 2012;2(1):25. https://doi.org/10.1186/2045-3329-2-25.
[34] 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):404–7. https://doi.org/10.1016/j.radonc.2010.10.007.
[35] 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. https://doi.org/10.3390/jcm9082471.
[36] Gronchi A, Hindi N, Cruz J, et al. Trabectedin and RAdiotherapy in Soft Tissue Sarcoma (TRASTS): Results of a phase I study in myxoid liposarcoma from spanish (GEIS), Italian (ISG), French (FSG) Sarcoma Groups. EClinicalMedicine 2019;9:35–43. https://doi.org/10.1016/j.eclinm.2019.03.007.
[37] Stacchiotti S, Collini P, Messina A, Morosi C, Barisella M, Gronchi A. Sarcomas: tumor response assessment — pilot study to assess the correlation between radiologic and pathologic response by using methods : results : conclusion. Radiology 2009;251(2):447–56.
[38] Stacchiotti S, Verderio P, Messina A, et al. Tumor response assessment by Choi criteria in localized high-risk soft tissue sarcoma (STS) treated with chemotherapy (CT): Update at 10-year follow-up of an exploratory analysis on a phase III trial. J Clin Oncol 2016;34:11044. https://doi.org/10.1200/JCO.2016.34.15_suppl.11044.
[39] Hong NJL, Hornicek FJ, Harmon DC, et al. Neoadjuvant chemoradiotherapy for patients with high-risk extremity and truncal sarcomas: A 10-year single institution retrospective study. Eur J Cancer 2013;49(4):875–83. https://doi.org/10.1016/j.ejca.2012.10.002.
[40] Stacchiotti S, Verderio P, Messina A, et al. Tumor response assessment by modified Choi criteria in localized high-risk soft tissue sarcoma treated with chemotherapy. Cancer 2012;118(23):5857–66. https://doi.org/10.1002/cncr.27624.