DOse REduction of preoperative radiotherapy in MYxoid liposarcomas.

The “DOREMY” study

DSSG01

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1 Introduction and Rationale

Soft tissue sarcomas (STS) represent a heterogeneous group of approximately 50 histological subtypes. Although in general sarcomas are considered to be radioresistant, myxoid liposarcomas (MLS) have repeatedly been shown to display a marked volume decrease and necrosis induction after 25 x 2Gy preoperative radiotherapy (RT) (1-5). In addition, histological examination of the operated tumor specimens frequently reveals marked tumor necrosis after preoperative RT.

In the Canadian SR-2 phase III trial two conventional RT regimens were randomized: 25 x 2Gy preoperative versus 33 x 2Gy postoperative, irrespective of subtype. Both dose levels were chosen after decades of clinical experience, but without taking into account individual radiation sensitivity (6).

By daily cone beam CT setup verification, the MLS shrinkage can already be seen during RT, which is in sharp contrast with other STS subtypes where the volumes as a rule remain fairly constant (full paper in preparation). This observation is an argument against postmitotic cell death after RT. It is hypothesized that this remarkable clinicopathological response in MLS might be due to radiation induction vascular damage (3). MLS is known for its specific “crow-feet” pattern vasculature. After RT this pattern is completely lost with the induction of arteriole obliteration and necrosis. If it is true that the target of 25 x 2Gy RT in MLS is not so much the malignant sarcoma cell but the specific vasculature, than other (probably lower) dose levels may become relevant. It is already known from normal tissue radiobiology and extensive clinical experience that vascular damage can occur at much lower doses (7).

Recently we have treated 2 patients with a solitary metastasis of MLS to a dose of 18 x 2Gy. In these 2 patients there was overlap with prior RT fields. After multidisciplinary discussions on both patients it was decided that 25 x 2Gy would be too toxic, whereas 18 x 2Gy was considered feasible. The definitive surgical specimen revealed complete necrosis in both cases.

It is therefore worthwhile to investigate whether MLS can be effectively treated with lower doses of radiation in the preoperative setting. This will also very likely be associated with less acute and late radiation toxicity, such as fibrosis, arthrosis, edema and femoral fractures (8).

2 Objective

To study whether a dose reduction of preoperative radiotherapy in MLS from 50Gy to 36Gy is equally effective in inducing extensive pathological response (thus maintaining comparable clinicopathological responses). The dose reduction will be regarded as a success if at least 70% of thus treated patients show at least 50% pathological response in the definitive resection specimen (3).

3 Patient selection

3.1 Inclusion criteria

1. Age above or equal to 18 years.
2. Biopsy proven MLS (including the reciprocal chromosomal translocation t(12;16)(q13;p11);
   A the primary sarcoma in case of non-metastatic disease for management is with curative intent (regimen to be chosen = 18 x 2 Gy)
   B in case of oligometastatic patients, the metastasis may also be irradiated to a dose of 36 Gy in order to postpone the time interval to next systemic chemotherapy. These patients are usually not operated upon and the total dose may also be reached in 12 times 3 Gy, for convenience purposes (see paragraph 10 for radiobiological considerations).
3. ECOG PS 0-2
4. Patients must be able (physically, mentally and socially) to complete a series of RT, followed by an observation period of 4-6 weeks and undergo surgery.
5. Written informed consent

3.2 Exclusion criteria

1. Prior radiotherapy to the target area.
2. Anticoagulant medication of any kind; especially Ascal ® (and derivatives), coumarines (Sintrom ® and Marcoumar ®), all heparin and heparin-like formulations. (Note: this exclusion criterion only applies for patients consenting to the translational research part of the study; patients on anticoagulant medication as described above may take part in the dose reduction part of the study, but the repeat biopsies may not be taken.)
3. Pregnancy

4 Radiotherapy protocol.

Patients participating in this trial will be managed as previously performed. They will be staged and diagnosed as described in the Dutch Guidelines (9); MRI imaging of the sarcoma mass followed by (preferably ultrasound guided) biopsies, staging CT scans of chest and abdomen.

For the radiotherapy procedure all patients will be positioned in individually manufactured immobilization devices, in such a way, that the positioning is as comfortable as possible while, at the same time, allowing the setup of the most desirable beam-, gantry- and table geometries. Patients are CT scanned in their individual mould. Preferably the MRI scan is also performed in this treatment position to allow 3D image matching. Target volumes are delineated according to local guidelines (see appendix). Finally, treatment planning is performed using IMRT. The daily fraction size is 2Gy, prescribed conform the ICRU 50/62 guidelines, the number of fractions is 18, applied once daily, five fractions per week, for an overall treatment time of 3.5-4 weeks. The plan is multidisciplinary approved, signed and transferred to the linear accelerator. In summary, this procedure is in no aspect different from the standard of care for extremity sarcoma patients, except for the lower total dose.

5 Surgical and pathological management after RT.

After the last (18^{th}) fraction of 2Gy patients are followed for 4-6 weeks before they undergo the definitive surgical resection. Pre-, per- and postoperative care (thrombosis prophylaxis, antibiotics, wound dressings, reconstructive surgical techniques etc) is conform local guidelines and is no part of this study. The resection specimen is pathologically examined according to standards of care with respect to confirming MLS histology and resection margins. Special attention, however, will be given to the description of the pathological response (induction of (or absence of) necrosis, hyalinization, obliteration of tumor vasculature etc.).

All resection specimens are processed according to the same protocol. In brief: resection specimens are received, relevant resection margins are inked and the specimen is processed according to routine procedures. Specimens of vital tumor areas are taken for frozen tissue banking. After fixation in 4% buffered formalin for 12-24 hours, the specimen is sectioned at 1cm sections and specimen photographs including a ruler bar are taken. The extend and distribution of necrotic, degeneratively changed (edematous/myxoid) and vital areas are estimated and representative sections are taken for microscopy (1/cm of the largest diameter of the tumor with a minimum of 8 sections). The site of the sections is recorded on the

macro photographs according to routine procedures. The vital status of the tumor is checked by microscopic examination in relation to the macroscopic impression. Vascular alterations, including vessel wall necrosis and intravascular thrombosis are recorded. For examples of postradiotherapy pathological response estimation see reference 3.

6 Hypotheses, statistics and sample size.

A Bayesian approach is considered for the analysis of this trial. The aim is to provide a stopping rule for inefficacy of the new dose. The observed response is a binary variable indicating the presence of at least 50% of pathological response in the treated tumor (success, with probability p), or not (failure). The design requires a prior for p, typically a beta distribution with parameters a, b>0. The Jeffreys prior will be used, i.e. a=1/2 and b=1/2. The trial is stopped for inefficacy if the posterior probability that p is higher than a certain threshold (chosen as 0.7) is very low (specifically, below 0.05). See (10, 11) for details. The maximum sample size will be 100 subjects.

Sample size	No. of successes required to continue	Posterior probability P(p > 0.7)
1	0	0.077274
2	1	0.252316
3	1	0.088944
4	2	0.186967
5	2	0.077181
6	3	0.143053
7	3	0.064007
8	4	0.111434
9	4	0.052413
10	5	0.087826
11	6	0.132896
12	6	0.069798
13	7	0.104745
14	7	0.055819
15	8	0.083217
16	9	0.117062
17	9	0.06652

18	10	0.093653
19	10	0.053433
20	11	0.075267
21	12	0.101848
22	12	0.060717
23	13	0.082434
24	14	0.108333
25	14	0.066894
26	15	0.088328
27	15	0.054407
28	16	0.072134
29	17	0.093191
30	17	0.058994
31	18	0.076581
32	19	0.09721
33	19	0.062981
34	20	0.080359
35	20	0.051835
36	21	0.066445
37	22	0.083569
38	22	0.054955
39	23	0.069453
40	24	0.086294
41	24	0.057715
42	25	0.072063
43	26	0.088605
44	26	0.060152
45	27	0.074325
46	27	0.050193
47	28	0.062303
48	29	0.076282
49	29	0.052194
50	30	0.064198
51	31	0.0779718
52	31	0.05398459
53	32	0.06586397

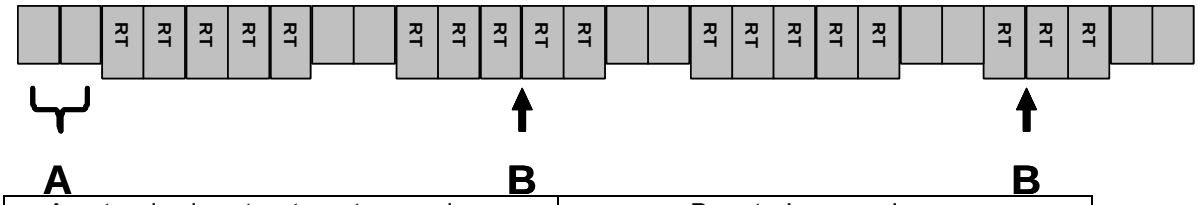
54	33	0.07942474
55	33	0.05558301
56	34	0.06732595
57	35	0.08066866
58	35	0.0570076
59	36	0.06860485
60	37	0.08172722
61	37	0.05827447
62	38	0.06971941
63	39	0.08262098
64	39	0.05939816
65	40	0.07068621
66	40	0.05054478
67	41	0.0603917
68	42	0.07151991
69	42	0.05153113
70	43	0.06126684
71	44	0.07223351
72	44	0.05241375
73	45	0.06203413
74	46	0.07283855
75	46	0.05320104
76	47	0.06270306
77	48	0.07334533
78	48	0.05390065
79	49	0.0632822
80	50	0.07376301
81	50	0.05451956
82	51	0.06377928
83	52	0.07409982
84	52	0.05506415
85	53	0.06420128
86	54	0.07436312
87	54	0.05554026
88	55	0.06455451
89	56	0.07455952

90	56	0.05595319
91	57	0.06484471
92	58	0.07469497
93	58	0.05630782
94	59	0.06507707
95	60	0.07477484
96	60	0.0566086
97	61	0.06525633
98	62	0.07480399
99	62	0.05685963
100	63	0.06538679

Each and every included patient will be discussed in the weekly sarcoma board meeting and recorded by Dr. R.L.M. Haas and Dr. A.N Scholten and/or by email with the participating centers outside the NKI-AVL. By gradually filling in this table, both doctors will decide upon further patient inclusion, keeping inclusion on-hold or closing the study.

7 Translational research.

Two aspects are important to elucidate the mechanism of this treatment: dynamic investigations of perfusion and vasculature. Apart from participation to the dose reduction paragraphs of this study, patients will be also asked to undergo, at clinically relevant dose points, dynamic contrast enhanced (DCE) MRI scans and separately tumor biopsies. (Figure and Table). This implies that patients will be asked for informed and signed consent to 3 distinct investigations. Of course, patients may take part in the dose reduction aspects without allowing to repeat the DCE MRI scans **and/or** the biopsies. (See the informed consent form and the Patient Information letter)



A= standard pretreatment procedures:	B = study procedures:
Ultrasound guided tumor biopsy	Ultrasound guided tumor biopsy
MRI scan of sarcoma mass	DCE-MRI
CT scan of chest and abdomen.	

DCE-MRI specifications:

- Protocol dynamic contrast enhanced MRI scan:
- Sequence for B1 mapping: 1 minute
- Sequence for T1 mapping: 3 minutes
- Dynamic sequence: 10 minutes after Gadolinium contrast injection.
- Sequence for T1 mapping 3 minutes

Total duration of the examination will be 20 minutes.

The repeated tumor biopsies will be used for pathological studies on sarcoma cell viability and on endothelial changes.

8 Serious Adverse Events (SAE's)

8.1 Introduction to a serious adverse event (SAE).

A serious adverse event (SAE) is any event that is fatal, life-threatening, requires or prolongs hospitalization, results in persistent or significant disability or incapacity, a congenital anomaly or birth defect or an important medical event.
Important medical events are those that may not be immediately life-threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes. A SAE is defined as:

- Results in death
- Is life threatening
- Requires hospitalization or prolongation of existing inpatients' hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

This DOREMY trial, however, uses standard radiotherapy schedules and unexpected serious adverse events are **very** unlikely to occur. Expected adverse events from radiotherapy include skin reactions leading to tenderness and itching. Skin reactions are usually mild and are seldom severe.
Nevertheless, all SAEs will be reported to the Principal Investigator and the Ethical Committee. Further notification will be forwarded to the authorities: (https://toetsingonline.ccmo.nl/)

8.2 Procedures for SAEs

All SAEs, deaths and life-threatening events irrespective of relationship to radiotherapy, must be reported within 1 working day to the safety desk of the NKI Data Center, preferably by email to drugsafety@nki.nl. In case of technical issues please phone: +31 (0) 20 512 2668 or fax+31 (0) 20 512 2679**.** All SAEs occurring during the treatment period must be reported. All deaths should be reported on the death report form section of the CRF regardless of cause. All SAEs will be recorded on the SAE form by the NKI Data Center.
The safety report should include:
- detailed information regarding the nature and severity of the event,
- patient initials and study number,
- date and time of treatment,
- start and stop date,

- maximum intensity of the event (CTCTCv3 grading),
- likelihood of its relationship to the study treatment,
- treatment administered as a result of the event,
- any concomitant medication taken before or as a result of the event.

All SAEs will be reported to the accredited METC that approved the protocol, according to the requirements of that METC.
All SAE reports will be filed in the Investigator Study File.

9 Follow-up.

Conform standard clinical practice MLS patients after recovery of surgery will be regularly invited for follow-up.

Year 1 and 2:	every 3 months
Year 3, 4 and 5:	every 6 months
Years 6 to 10:	annually.

Chest X-rays will be performed every 6 months up to 5 years and annually thereafter. While taking the medical history and performing the physical examination during follow-up care should be taken to the fact that the metastatic spread of MLS is not solely to the lungs. Appropriate imaging of a suspected metastatic site (e.g. abdomen) should be performed on indication.

Special attention will be given to:

- Functionality of the extremity
- Grade of fibrosis
- Grade of arthrosis
- Grade of edema
- Any radiation induced skin reaction like atrophy and teleangiactasia
- The occurrence of fractures

10 Radiobiological considerations.

	α/β 3 Gy	α/β 5 Gy	α/β 10 Gy
	Late responding normal tissues	Intermediate responding tissues (sarcoma cells; ref 12 and 13)	Late responding tissues (tumor control)
18 x 2 Gy	36 Gy	36 Gy	36 Gy
12 x 3 Gy	43.2 Gy	41.1 Gy	39 Gy

The biological equivalent dose to normal tissues is increased by 7.2 Gy in case of the 12 x 3 Gy regimen. This dose remains well below the tolerance level of small intestines (in case of frequently encountered intra-abdominal and/or retroperitoneal metastases) and spinal cord.

11 References

1 Pitson G, Robinson P, Wilke D, Kandel RA, White L, Griffin AM, Bell RS, Catton CN, Wunder JS, O'Sullivan B. Radiation response: an additional unique signature of myxoid liposarcoma. Int J Radiat Oncol Biol Phys. 2004; 60: 522-6.

2 Engström K, Bergh P, Cederlund CG, Hultborn R, Willen H, Åman P, Kindblom LG, Meis-Kindblom JM. Acta Oncologica 2007; 46: 838-845,

3 de Vreeze R, de Jong D, Haas R, 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: 1480-1487.

4 Chung PW, Deheshi BM, Ferguson PC, Wunder JS, Griffin AM, Catton CN, Bell RS, White LM, Kandel RA, O'Sullivan B. Radiosensitivity translates into excellent local control in extremity myxoid liposarcoma: a comparison with other soft tissue sarcomas. Cancer. 2009; 115: 3254-61.

5 Guadagnolo BA, Zagars GK, Ballo MT, Patel SR, Lewis VO, Benjamin RS, Pollock RE. 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: 760-5.

6 O'Sullivan B, Davis AM, Turcotte R, Bell R, Catton C, Chabot P, Wunder J, Kandel R, Goddard K, Sadura A, Pater J, Zee B. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. Lancet. 2002; 359: 2235-41.

7 E.C. Moser, E.M. Noordijk, F.E. van Leeuwen, S. le Cessie, J.W. Baars and J. Thomas et al., Long-term risk of cardiovascular disease after treatment for aggressive non-Hodgkin lymphoma, Blood 2006; 107: 2912–2919

8 Dickie CI, Parent AL, Griffin AM, Fung S, Chung PW, Catton CN, Ferguson PC, Wunder JS, Bell RS, Sharpe MB, O'Sullivan B. Bone fractures following external beam radiotherapy and limb-preservation surgery for lower extremity soft tissue sarcoma: relationship to irradiated bone length, volume, tumor location and dose. Int J Radiat Oncol Biol Phys. 2009; 75: 1119-24.

9 http://www.oncoline.nl/index.php?pagina=/richtlijn/item/pagina.php&richtlijn_id=249

10 Zohar, S., Teramukai, S. and Zhou, Y. (2008). Bayesian design and conduct of phase II single-arm clinical trials with binary outcomes: A tutorial. Contemporary Clinical Trials 2008; 29: 608—616.

11 Thall, P.F. and Simon, R. (1994). Practical Bayesian guidelines for phase IIB clinical trials. Biometrics 1994; 50: 337--349.

12 Fitzpatrick CL, Farese JP, Milner RJ, Salute ME, Rajon DA, Morris CG, Bova FJ, Lurie DM, Siemann DW. Intrinsic radiosensitivity and repair of sublethal radiation-induced damage in canine osteosarcoma cell lines. Am J Vet Res. 2008; 69: 1197-202.

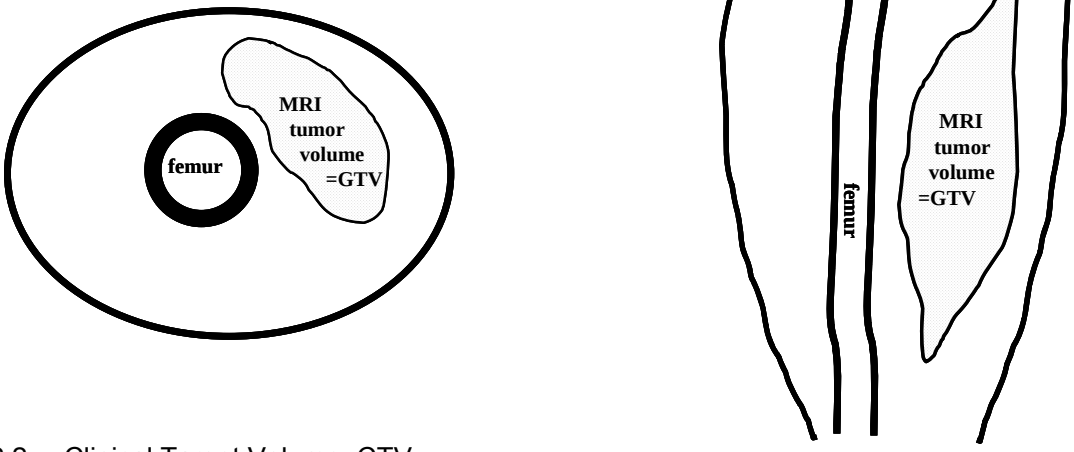
13 Abe Y, Urano M, Kenton LA, Kahn J, Willet CG. The accelerated repopulation of a murine fibrosarcoma, FSA-II, during the fractionated irradiation and the linear-quadratic model. Int J Radiat Oncol Biol Phys. 1991; 21:1529-34.

12 Appendix: Target volume guidelines

Guidelines in target volume delineation for soft tissue sarcomas of the extremity: DOREMY trial (N10DMY)

12.1 Gross Tumor Volume: GTV

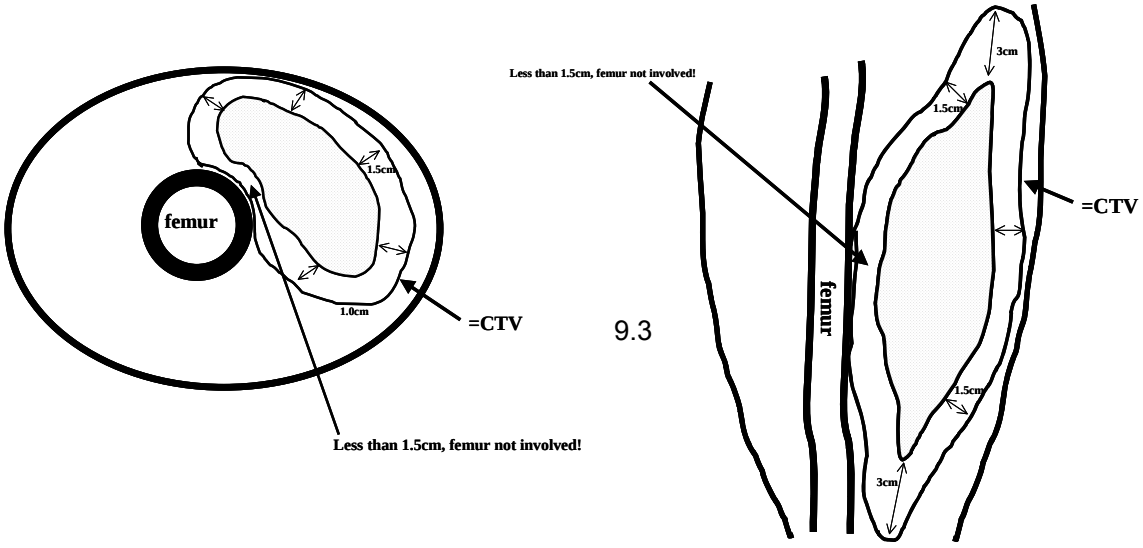
The GTV is defined by the volume of the tumor as visualized by contrast enhanced MRI, including the surrounding edema. Preferably the MRI and planning CT scans are matched with the patient in the same treatment position.



12.2 Clinical Target Volume: CTV

The CTV is constructed by expanding the GTV in all directions with 1.5 cm, except

- o longitudinally; the expansion is 3 cm in this direction
- o laterally in the directions of bones and fasciae, where the volume is expanded onto the surface on those bones and fasciae, unless these structures are involved.



12.3 Planning Target Volume: PTV

The PTV is produced by expanding the CTV with 1.0cm in all directions, without exceptions.