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Irradiation of myxoid/round cell liposarcoma induces volume reduction and lipoma-like morphology

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Abstract

The aim of the study was to investigate the clinical and morphological effects of radiotherapy in the treatment of myxoid/round cell liposarcoma (MLS/RCLS). Thirty-three primary and metastatic MLS/RCLS tumours in 15 patients were treated with radiation therapy. Twenty-seven of the 33 tumours were surgically removed after preoperative radiation (34–46 Gy) while six tumours were treated with radiotherapy alone (44–60 Gy). The pretreatment diagnosis was established in all 15 patients based on fine needle aspirates or histological findings. Tumour size was measured by CT or MRI before and after radiotherapy in 30 tumours. Thirteen tumours from 11 patients were genetically characterised before and/or after radiation therapy. Twenty-three of 30 irradiated tumours showed a median reduction in tumour volume of 52% and seven lesions a median progression of 36%. All 27 surgically removed tumours revealed histological features of radiation response. The most striking morphological changes were lipoma-like appearance, paucicellularity and hyalinisation. Twelve of 13 tumours analysed before and/or after radiation therapy showed the FUS-DDIT3 translocation. Radiation therapy of MLS/RCLS induces histopathologic accumulation of mature lipoma-like areas and tumour volume reduction that may facilitate resectability.

Liposarcoma, one of the most common soft tissue sarcomas in adults, has a wide clinical and morphological spectrum as well as type specific genetic rearrangements. Myxoid/round cell liposarcoma (MLS/RCLS) is a distinctive subgroup of liposarcoma with unique histological and cytogenetic features [1,2]. More than 95% of MLS/RCLS cases carry the *FUS-DDIT3* fusion oncogene [3]. A continuum of cellularity ranges from low or moderately cellular MLS to highly cellular RCLS, which correlates with the clinical behaviour. While classical MLS has a good prognosis with a low metastatic rate, the round cell type represents a high-grade malignancy with a high propensity for local recurrences, metastases and tumour-related death [4–9].

Experience with radiation therapy as the sole modality or as a preoperative adjunct in the treatment of liposarcoma is limited. Many older studies are difficult to evaluate since different subtypes of liposarcomas have not been distinguished clearly and diagnostic criteria have changed over time. Moreover, radiation techniques have varied considerably and also changed over time [6,10–14]. Little has been published regarding the effect of radiotherapy in MLS/RCLS, with only a few case reports or small series [4,5,10–12,15,16]. Despite the general belief that radiation therapy is of limited value in low-grade sarcomas a few reports of MLS illustrate its remarkable response to radiation therapy with dramatic reduction in tumour size [10,11,14–16].

The aim of this study was to analyse the effects of preoperative radiation in MLS/RCLS with regard to morphology and changes in tumour volume. The present study of 33 MLS/RCLS tumours in 15 patients, treated with preoperative radiotherapy (27 tumours) or radiotherapy as the sole treatment (6 tumours), illustrates a striking response radiographically and histologically.

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Material and methods

Patients

During the period 1994–2004, 15 patients with 33 primary or metastatic MLS/RCLS tumours received radiation therapy. All patients referred to the Department of Orthopaedics at the Sahlgrenska University Hospital, Göteborg, Sweden were included consecutively.

The primary diagnosis was made by fine needle aspiration (FNA) cytology in 12 patients, by FNA and core needle biopsy in one patient and by core needle biopsy in another patient. The remaining patient underwent surgical resection of abdominal tumours without a preoperative diagnosis. Complete follow-up information was obtained in all cases (August 2005) (Table I).

The median age was 45 years (28–76 years) and included ten males and five females. The median follow-up time was 44 months (24–99 months). At primary diagnosis 13 patients had a solitary tumour while two patients presented with multiple tumours (5 in patient no. 1 and 2 in patient no. 2). Twelve of 20 tumours detected at primary diagnosis were located in the thigh, one in the lower leg, five in the abdomen, one in the thoracic cavity and one in the upper trunk. During follow-up four patients (patient no. 1–4) developed multiple metastases, a total of 47 tumours were treated in various ways (Table II).

The four patients with multiple metastases also received palliative chemotherapy during the course of treatment.

The largest pretherapy diameter of the 33 irradiated tumours exceeded 10 cm in 14 tumours, followed by 5–10 cm in eight tumours and <5 cm in 11 tumours. Altogether 62 tumours were surgically removed, 27 tumours after preoperative radiotherapy, one tumour 16 months after irradiation and 34 tumours without preoperative radiotherapy.

Diagnostic radiology

All 33 tumours in 15 patients were investigated with contrast-enhanced MRI and/or CT at referring hospitals or at the Department of Radiology at Sahlgrenska University Hospital before radiotherapy. Tumour response was assessed using MRI and/or CT in 30 tumours. All radiological examinations were reviewed for the study. The largest tumour diameter was measured in three planes. The volume response to radiotherapy was calculated according to the formula ($\Pi \times d_1 \times d_2 \times d_3/6$) expressing the outcome as the per cent volume change from the initial volume.

Cytology

Before irradiation FNA cytology was performed on 17 tumours, (needles 0.7 mm diameter). FNA and core needle biopsy (Bard®Magnum® 14g) were performed on one tumour and only core needle biopsy on another tumour. The other 14 tumours were irradiated without morphologic diagnosis, since the patients' diagnoses had already been established. Wet smears and core biopsy material were stained by hematoxylin and eosin.

Molecular genetics

Reverse transcription PCR was performed on 13 tumours from 11 patients to detect the fusion gene *FUS-DDIT3* with *FUS-DDIT3* specific primers as described by Panagopoulos et al. [17] but with the following primers: *FUS* 431F 5′CAGCCAGCAGCCTAGCTATG, and *DDIT3* 157L23 5′GCCATCTCTGCAGTTGGATCAGT. The analysis was performed by FNA in four patients, on frozen irradiated tumour tissue in five patients and on both non-irradiated and irradiated frozen tumour tissue in two patients (Table I).

Radiotherapy

Thirteen primary tumours and two metastases present at primary diagnosis were irradiated preoperatively. Eighteen metastatic tumours occurring in four patients during the follow-up time were also irradiated. External radiotherapy was planned using computed tomography-based, three-dimensional technique in all patients. Planning CTs were performed in treatment position for delineation of gross tumour volume (GTV). The clinical target volume (CTV) consisted of GTV with a margin of 3–5 cm. All prescribed doses were at the isocenter in the middle of the CTV, according to the International Commission on Radiation Units and Measurement (ICRU-50/62) recommendation. The 95% isodose of the prescribed dose surrounded the planning target volume (PTV). A portion of the circumference of a limb was excluded from the irradiated volume to avoid radiation-related edema and the dose to kidney was not allowed to exceed 20 Gy. The radiotherapy was administered by a linear accelerator with photon energies 4–15 MV in multiple fields, 1.75–2.0 Gy per fraction five times weekly to 34–46 Gy. One inoperable lesion was irradiated to 60 Gy. Preoperative radiotherapy in soft tissue sarcoma is not a standard treatment strategy in Göteborg and therefore the radiation dose was low, 40 Gy at the beginning of this study but was gradually increased to 46 Gy when no postoperative complications were seen after the lower doses. One patient was treated

with 34 Gy due to overlapping radiation fields of previously irradiated tumour.

Results

Patients

Clinical data and outcomes are summarised in Tables I, II and III.

Altogether 62 tumours were surgically removed, 27 tumours after preoperative radiotherapy, one tumour 16 months after irradiation and 34 tumours without preoperative radiotherapy. The surgical margins were wide or marginal in all cases. Two patients needed an amputation (one transfemoral and one hemipelvectomy), the other tumours were removed by local excision. No serious wound complications were seen after preoperative radiotherapy. None of the patients developed a local recurrence.

Four of the six patients with round cell areas developed multiple metastases (patients no. 1–4). The metastases were treated with different approaches; surgery only, preoperative radiotherapy and surgery or radiotherapy only. Chemotherapy (ifosfamide, doxorubicin and pegylated liposomal doxorubicin) was used with transient responses. These patients died from tumour progression after 39, 62, 62 and 99 months, respectively. The other 11 patients continued to be disease-free throughout the observation period (Table I).

FNA cytology

The fine needle aspiration (FNA) material was adequate in all cases and included tissue microbiopsies in most cases. Univacuolated or multivacuolated lipoblasts were dispersed in the rich myxoid matrix. Nuclear atypia and cellularity were more pronounced in the RCLS that also contained a less prominent myxoid matrix. A delicate ramifying capillary network was noticed in all cases, although less prominent in the RCLS.

Diagnostic radiology

The radiation-induced change in tumour volume was analysed before and after treatment with MRI in 18 tumours, with CT in 11 and MRI and CT in one tumour. The median pre-irradiation tumour volume was 128 cm^3 (1–2 720 cm^3). Median time period between radiological examination and initiation of radiotherapy was 48 days (12–121 days), between termination of radiotherapy and radiological reexamination 13 days (0–62 days), and between termination of radiotherapy and surgery 21 days (12–81 days). There was no systematic change in enhancement pattern.

After radiotherapy four small tumours (1–12 cm^3) had complete remissions, eight tumours (6–707 cm^3) showed a more than 50% reduction in volume (Figure 1), 11 tumours (6–2 720 cm^3) showed a less than 50% reduction in volume and seven tumours (4.4–1 140 cm^3) showed an increase in volume. No clear correlation between initial tumour size and volume change was seen. There was a non-significant tendency for less volume reduction at longer time lapse between MRI and radiotherapy.

Histopathology

A total of 62 surgically removed tumours were examined histologically, 27 after preoperative radiotherapy, one removed 16 months after irradiation and 34 without irradiation in patients no. 1, 2 and 4.

Surgical specimens from irradiated and non-irradiated lesions from the same individuals could be compared in three patients with a striking difference. While the non-irradiated tumours had the typical features of purely myxoid or mixed MLS/RCLS (Figure 2) the irradiated tumours showed paucicellularity, fibrosis, hyalinisation and in 21/27 lesions lipomatous appearance with mostly univacuolated adipocyte-like cells that varied in size (Figure 3 a–c). Occasionally minimal microscopic foci of characteristic MLS were seen in a lipoma-like or fibrous paucicellular background.

All tumours were irradiated in the remaining 12 patients and showed similar findings of hyalinisation, paucicellularity and lipoma-like morphology.

There was no correlation between radiological response and histopathological appearance.

The presence of round cells did not correlate to either radiological response or to the post- irradiation morphology.

FUS-DDIT3 fusion gene detection

Reverse transcription PCR analysis performed in 11 patients detected the fusion gene *FUS-DDIT3* in ten patients. A total of 13 tumours, seven irradiated and six non-irradiated, were analysed in these 11 patients. All six non-irradiated and six of the seven irradiated tumours disclosed the fusion gene (Table I).

Discussion

The present study originated from the observation that irradiation led to a considerable tumour volume reduction and change in morphology in a MLS/RCLS metastasis in the thoracic cavity, which made

Table I. Clinical data on patients.

Patient (no.)	Age / Sex	Primary tumour site	Pre-treatment diagnosis	Presence of FUS-DDIT3 (RT-PCR)	Treatment of primary tumour	Interval to metastases (mos.) / Sites	Follow-up* (mos.) / Status
1.	33/F	Abdomen	MLS/RCLS	+[1]	Surgery	At diagnosis / Multiple	99 / TRD
		Thorax			Preop R		
2.	28/M	Thigh	MLS/RCLS	+[2]	Preop R	At diagnosis / Multiple	62 / TRD
		Upper trunk			Preop R		
3.	38/M	Abdomen	MLS/RCLS	−[2]	Preop R	16 / Multiple	62 / TRD
4.	36/M	Thigh	MLS/RCLS	+[1]	Surgery	26 / Multiple	39 / TRD
5.	38/M	Thigh	MLS/RCLS	+[3]	Preop R	—	42 / CDF
6.	59/M	Thigh	MLS/RCLS	+[3]	Preop R	—	41 / CDF
7.	59/F	Thigh	MLS	+[2]	Preop R	—	95 / CDF
8.	52/M	Thigh	MLS	ND	Preop R	—	95 / CDF
9.	76/M	Thigh	MLS	ND	Preop R	—	77 / CDF
10.	48/F	Thigh	MLS	+[3]	Preop R	—	52 / CDF
11.	45/M	Thigh	MLS	+[2]	Preop R	—	44 / CDF
12.	64/M	Thigh	MLS	+[3]	Preop R	—	37 / CDF
13.	47/M	Thigh	MLS	+[2]	Preop R	—	36 / CDF
14.	38/F	Thigh	MLS	ND	Preop R	—	25 / CDF
15.	36/F	Lower leg	MLS	ND	Preop R	—	24 / CDF

*from date of surgery of primary tumour, R-radiation, TRD-tumour related death, CDF-continuously disease free, RT-PCR-reverse transcription PCR, ND-not done.
[1] irradiated and non-irradiated specimens.
[2] irradiated specimens.
[3] fine needle aspiration cytology, non-irradiated.

surgery possible (patient no.1). Review of the literature revealed occasional case reports and a recent retrospective study [16] of MLS with dramatic tumour reduction after radiotherapy.

Fifteen consecutive patients with MLS/RCLS referred to the Department of Orthopaedics at the Sahlgrenska University Hospital were selected for the present study of irradiation treatment.

The preoperative diagnosis of MLS with or without an RCLS component was based on FNA cytology alone in 12 patients because the FNA cytology findings of MLS are characteristic [18–20]. The accuracy of the preoperative diagnosis was further supported by the findings in the post-treatment surgical specimens, which sometimes showed diagnostic residual tumour foci as well as demonstration of the FUS-DDIT3 transcript with PCR technique in ten of 11 studied patients.

The notable finding of this study was a reduced tumour volume in the majority of tumours (23/30). In the majority, the reduction in tumour volume was likely underestimated because a long period often elapsed between the pretreatment radiological evaluation of tumour size and initiation of radiotherapy.

Table II. Summary of treatment in 4 patients with metastases (patient no. 1–4).

Patient (no.)	Primary presentation	Primary treatment	Treatment of metastases during follow–up		
			XRT only (no. of met.)	Preop. XRT and surgery (no. of met,)	Surgery only (no. of met)
1.	4 tumours in abdomen 1 tumour in thorax	Surgery High dose ifosfamide without response preop. XRT and surgery	5 (1 tumour was surgically removed 16 mos. after XRT)	2	24
2.	1 tumour in thigh 1 tumour in upper trunk	Preop. XRT and surgery of both	1	4	1
3.	1 tumour in abdomen	preop. XRT and surgery	0	4	0
4.	thigh	surgery	0	2	4

XRT external radiation therapy.

Table III. Radiological response to radiation therapy.

Pt. (no.)	Tumour	XRT (Gy)	Tumour volume before XRT (cm^3)	Tumour volume change (%) regression(−) / progression(+)
1.	thorax	40	47	−60
	thigh	40	387	−33
	thorax	46	1	−100
	abdomen	44	3	−100
	abdomen	44	1	−100
	abdomen	44	6	−88
	abdomen	44	12	−100
	sacrum	34	6	−42
2.	thigh	40	363	−23
	upper trunk	40	521	+24
	abdomen	40	1	—
	abdomen	46	22	+36
	sacrum	60	157	+25
	upper trunk			
	left	46	308	−31
	right	40	30	−53
3.	abdomen.	42	849	−9
	upper trunk	44	4.4	0
	upper trunk	44	163	−15
	upper trunk	44	25	+40
	upper trunk	44	122	−21
4.	abdomen	46	2720	−14
	thorax	44	17	+100
5.	thigh	46	250	−44
6.	thigh	46	390	−76
7.	thigh	46	186	−81
8.	thigh	46	27	—
9.	thigh	46	205	—
10.	thigh	46	128	−52
11.	thigh	44	1140	+44
12.	thigh	46	150	−23
13.	thigh	46	225	−46
14.	thigh	46	707	−71
15.	lower leg	46	75	−64

XRT-external radiation therapy.

In fact in 24 of 30 evaluated tumours more than 30 days had elapsed, thus exceeding the RECIST criteria of <30 days [21]. Even the tumours with radiological progression might have responded with a volume reduction not revealed due to the long time interval (median 63 days) between initial MRI and radiotherapy.

Most studies, from different sarcoma centers, report preoperative radiation dose of 50 Gy but optimal radiation dose in this setting has not been established [22]. Friedman [10] reported that a radiation dose of 30 Gy resulted in 75–90% tumour size reduction and Perry and Chu [11] found tumour response after as low dose as 10 Gy in liposarcomas.

Our data suggest that a considerable tumour volume response was achieved with doses between 40–46 Gy which indicates that MLS/RCLS is a more radiation-responding entity than other soft tissue sarcomas. More wound complications are reported in preoperative radiation therapy of soft tissue sarcomas in comparison with postoperative treatment [23]. The lower doses in our study could contribute to the lack of serious wound complications.

Previous research has suggested that RCLS tumours are fairly resistant to radiation treatment [10]. None of the tumours in our series were entirely of the round cell type, but six tumours had mixed myxoid/round cell features. There were no obvious differences in volume reduction or degree or type of morphologic response in this subset.

Besides the reduction in tumour volume the radiation induced a particular type of morphological changes including lipoma-like areas, paucicellularity and hyalinised sclerotic areas, which only occasionally contained minimal residuals of unaffected MLS/RCLS. Striking features were small and often variable sized adipocyte-like cells in the lipoma-like areas and a delicate capillary network that often remained. The histopathological findings can either be interpreted as a radiation induced elimination of the most

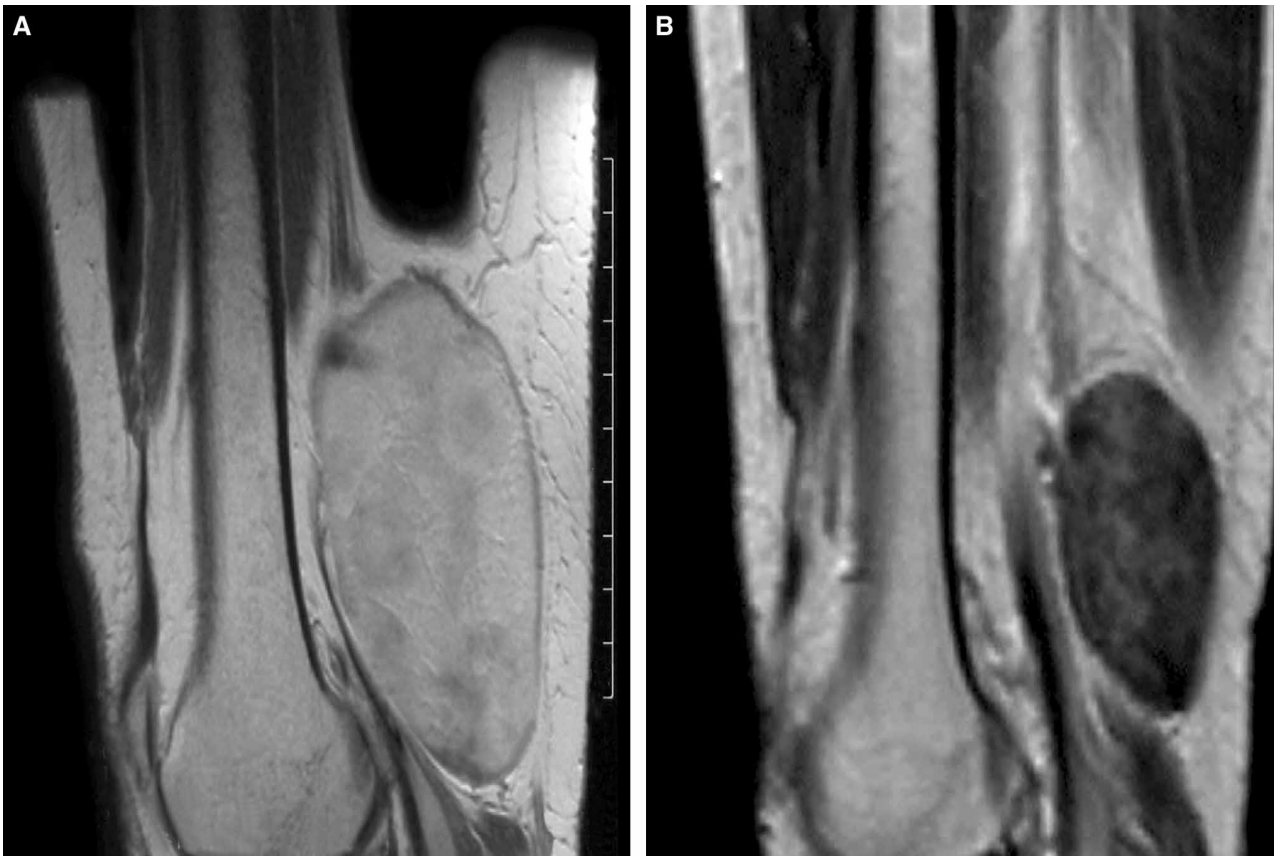

Figure 1. MRI of patient no. 7 with intramuscular MLS in the distal thigh. A: Pre-irradiation: T1 weighted sagittal image after Gd-DTPA contrast shows well-defined tumour with rather homogenous and intense enhancement. B: Post-irradiation: Considerable reduction in tumour volume (81%) as well as in enhancement intensity.

rapidly proliferating cells leaving the more mature, presumably less radiosensitive, adipocyte-like cells unaffected or as a radiation induced cell-cycle arrest leading to differentiation and maturation of tumour cells [24].

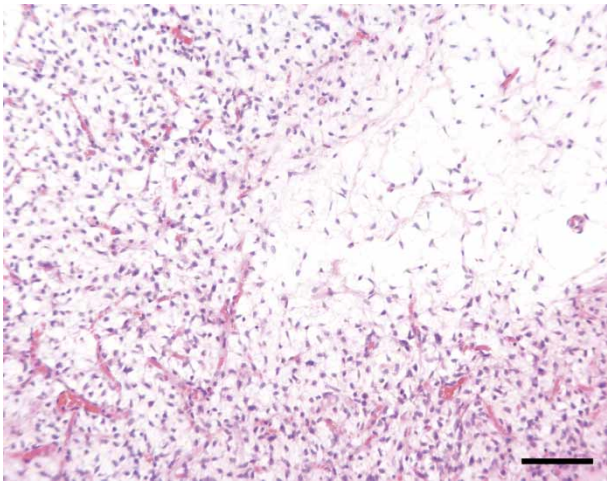

Figure 2. Non-irradiated MLS/RCLS (patient no. 1) with myxoid matrix, delicate capillary network and round cells (10 ×). Bar denote 100 micrometres.

There is a report of one non-irradiated MLS with two components, one classic myxoid liposarcoma and one lipoma-like and both parts revealed FUS/DDIT3 fusion gene transcript [25]. This type of mixed histopathology with lipoma-like areas juxtaposed to typical MLS areas is however rare in MLS/RCLS [26]. This supports the hypothesis that radiation induces adipocyte-like maturation of MLS/RCLS. It has been suggested that inhibition of amplification division triggers many cells to enter terminal differentiation [24]. Induction of differentiation in erythroleukemic cells by increase of cytoplasmic constituents during radiation-induced mitotic delay was described by Schwenke et al. [27] and Nicoletti et al. [28] reported induction of myogenic differentiation in human rhabdomyosarcoma cells.

Morphological response and induction of differentiation markers in MLS cells treated with troglitazone, a proliferator-activated receptor-gamma ligand was reported by Tontonoz et al. [29]. Thus there are indications that MLS/RCLS cells may differentiate to adipocyte-like cells. The morphological changes in our material may be in part due to radiation-induced elimination but also due to en-

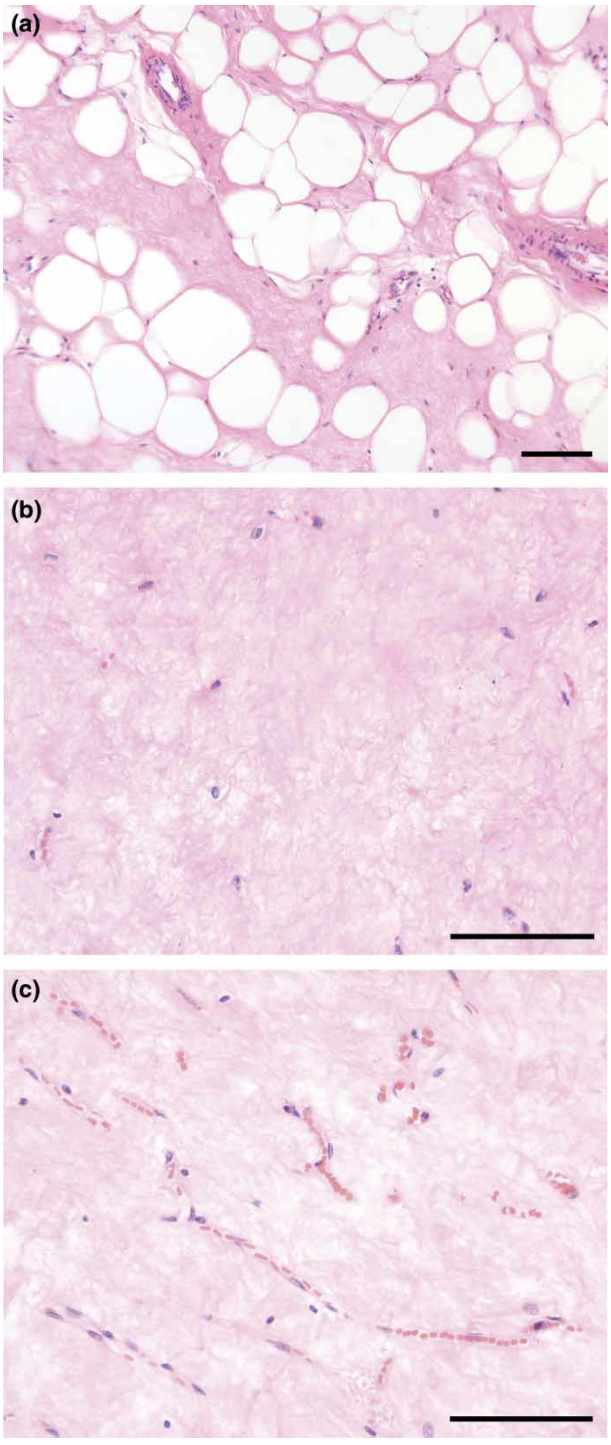

Figure 3. Irradiated MLS/RCLS (patient no. 1) with lipogenic maturation with mostly univacuolated adipocyte-like cells, (10 ×) (a), hyalinisation and paucicellularity, (20 ×) (b) and preserved delicate capillary network, (20 ×) (c). Bar denote 100 micrometres.

hancement of differentiation of the lipoblasts. In support of this view, our preliminary results show that irradiation induces P21 expression in cultured MLS/RCLS cells. P21 expression is known to cause a G1 cell cycle retardation and this could provide an explanation why the more mature tumor cells i.e. lipoblasts, differentiate to adipocyte-like cells. Further studies are needed to investigate the molecular mechanism behind this phenomenon.

In conclusion, the present study illustrates that radiation treatment often leads to significant volume reduction and dramatic morphologic response in MLS/RCLS. Radiation treatment may be a useful preoperative option to increase resectability and could be used as a sole treatment in inoperable patients. Further studies are needed to explain the lipoma-like morphology that is observed after radiation therapy in MLS/RCLS patients.

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