Perioperative fractionated high-dose rate brachytherapy in the treatment of soft tissue sarcomas

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The purpose of the study was to investigate the viability of perioperative fractionated high dose rate brachytherapy (HDR BT) for primary and reccurent soft tissue sarcomas (STS).

From February 1998 through June 2002, 21 adult patients, 11 females and 10 males with either low grade or high grade soft tissue sarcomas were treated by perioperative HDR BT. Surgical margin was negative in 10 cases, close in 4 and positive in 4 in cases. In 3 cases it was not described. BT was used as a part of primary treatment in 10 cases and for the treament of reccurent tumor in 11 cases.

The localisation of the tumor was the extremity in 16 patients and the trunk in 5 patients. Ten patients were treated with HDR BT alone (total mean dose 40 Gy) and 11 were treated with combination of external beam radiotherapy (EBRT) (40–50 Gy) and brachytherapy (total mean dose 24 Gy). Hyperfractionation 2.4–3 Gy twice daily at 10 mm from the source was used for BT. Follow-up periods were between 7–48 months (median: 20 months).

Local control in patients treated pro primary STS was 100%.The pulmonal metastases were a cause of death in one case, one patient was alive with dissemination and one patient was disease free after salvage surgery and chemotherapy for lung metastases. Local control was achieved only in 3 of 11 patients treated for reccurent tumor (27%). Six patiens were disease free after salvage surgery, 2 patients died of disease progression, one patient died of toxicity of chemotherapy without evidence of disease and 2 patients are alive with distant metastases. Local control was achieved in 5 of 11 (45%) patients with positive, close or not stated surgical margin and in 5 of 10 (50%) patients with negative margin. Local control was 100% in patients treated by EBRT + BT, but only 20% in patients treated by BT alone.

No infection or delayed wound healing has occurred after BT. Soft tissue necrosis was seen in 4 cases, subcutanous fistula in one case and peripheral nerve palsy in one case.

Despite small number of patients and short follow up our study suggest that perioperative HDR BT is easy and promissing when used as a part of primary treatment for STS. The treatment results for recurrence are poor and in a lot of cases radical surgical approach should have been considered for the salvage.

Key words: soft tissue sarcomas, high dose rate brachytherapy, local control, complications

Soft tissue sarcoma (STS) is a rare solid tumor with great heterogeneity in its anatomy, histological subtype, and degree of biologic aggressiveness. Amputation was previously a mainstay in treating extremity STS, being used in more than 40% of cases. In the 1970s, it became apparent that radiotherapy in combination with surgery could achieve an equivalent result. This shift has came about largely based on the results of a randomized, prospective trial, performed at the National Cancer Institute [5], in which no difference in disease-specific survival was appreciated between limb-sparing surgery and amputation.The results of series from numerous institutions have shown, that adjuvant radiation therapy improves local control over limb-sparing operations alone.

Brachytherapy (BT) has several advantages over conventional external beam radiotherapy (EBRT): capacity

of delivering a large dose to lesions with reduced irradiation of the surrounding healthy tissue, shorter overall treatment time (4 to 6 days vs 5–6.5 weeks), and treatment can be initiated sooner after surgery when tumor clonogen numbers are at minimum. The irradiated volume is also smaller, which may confer functional advantages. Brachytherapy may be used for the treatment of tumor recurrent event after previous EBR. Brachytherapy has been compared with surgery alone in a randomized trial [2]. The local recurrence rate in the group receiving adjuvant brachytherapy was 18% versus 33% in the group receiving no further therapy. After 5 years, there was no difference in rate of distant metastases or disease-specific survival.

No randomized data have compared EBRT and BRT directly. No apparent benefit for BRT over surgical excision alone is evident in low-grade lesions [6], and EBRT appears more effective for these tumors.

Most of the published experience is based on the use of manual afterloading and low dose (LDR) brachytherapy. In recent years, HRD BT with 192 Ir microsource was introduced clinically. HDR has a higher biological effect in comparison with LDR that is more profound for the normal late reacting tissues than for the tumor. The consequence is less beneficial therapeutic ratio. HDR implants must be fractionated and numerous small fractions are recommended to achieve biological equivalence with LDR brachytherapy. Preliminary data with HDR interstitial BRT for STS are scarce and further clinical data are needed to determine the specific role of HDR in the management of STS.

The aim of our retrospective study was evaluation of feasilibility, complications and local control of perioperative hyperfractionated HDR BRT in the management of STS.

Patients and methods

Patients. Between 2/1998 and 6/2002, 21 adult patients, 11 females and 10 males, with soft tisses sarcomas underwent perioperative HDR BRT at the Dept. of Oncology and Radiotherapy of University Hospital Hradec Králové and at Dept. of Radiation Oncology of Faculty Hospital, Bohunice, Brno. The mean age of the patients at the time of brachytherapy was 54 years (21–72). The perioperative BRT was used as a part of primary treatment in 10 cases and in 11 cases was combined with reoperation for local recurrence. The histology was epitheloid sarcoma (1x), leiomyosarcoma (2x), synovialosarcoma (3x), neurofibrosarcoma (1x), fibrosarcoma (3x), malignant fibrous histiocytoma (5x), extraosseal sarcoma (1x), liposarcoma (3x), chondorsarcoma (1x), malignant mesenchymal tumor (1x). Grade of differentiation was G1 (3x), G2 (5x), G3 (5x), G4 (3x) and in 5 cases it could not be assessed. The surgical margin was evaluated by the pathologist in 10 cases as negative, in 4 cases as close, in 4 cases as positive and in 3 cases the margin was not described. The localisation of the tumor was the extremity in 16 patients and the trunk in 5 patients. In 6 cases the diameter of the tumor was <5 cm, in 15 cases was >5 cm.

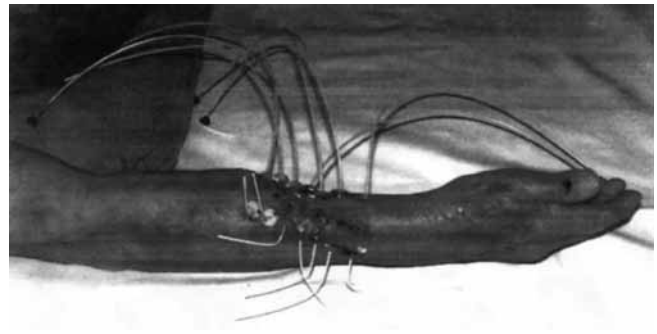

Figure 1. Brachytherapy implant.

Ten patients were treated with HDR BRT alone and the other 11 were treated with a combination of external beam radiotherapy (EBRT) and HDR BRT. Follow-up periods were between 7–48 months (median: 20 months).

Radiation treatment. The plastic tube technique was used for perioperative BRT. The afterloading catheters were placed intraoperatively in the tumor bed (Fig. 1). The tumor bed was evaluated simultaneously by the surgeon and radiation oncologist. A target region to be irradiated was determined by adding 2.0 cm to the superior and inferior dimensions of the tumor bed, with 1.5–2.0 cm added in the medial and lateral directions. Afterloading catheters were then implanted percutanously approximately 1 cm apart in the target area. The catheters were fixed in position in the target region using absorbable sutures and were secured to the skin at the catheter exit site with buttons and nonabsorbable sutures. The wound was closed in layers. Postoperatively, localization films were made and computed dosimetry was performed. Postoperative fractionated HDR brachytherapy was started on the 5th–11th day (mean 7th day) after surgery using a 192 Ir-HDR automatical afterloading system (Gammamed, MDS Nordion-Gammamed, Hahn, Germany). The single fractions 2.4–3 Gy at 5 or 10 mm from the source were delivered twice daily. The time interval between two treatments on the same day was at least 6 h. The mean total dose was 40 Gy (30–54), whith brachytherapy alone, and 24 Gy (18–24) in a combination with EBRT.

The dose from EBRT was 40–50 Gy. Linear accelerator and 3D technique were used for the treatment. Follow-up periods were between 7–48 months (median: 20 months).

Results

The outcomes in the group of patients treated with brachytherapy as a part of primary treatment and for the re-

Table 1. Perioperative HDR-brachytherapy for primary treatment

Case No	Surgical margin	EBRT	HDR	Follow-up state mo	Recurrence (mo)	Salvage	Distant metastases	Therapy	Complication
1	negative		18x3 Gy	NED 10					
2	negative	6 Gy	12x2.5 Gy	alive 40 with generaliz.			brain lung	CHT	soft tissue necrosis
3	negative	45 Gy	8x3 Gy	NED 11					
4	close	40 Gy	8x3 Gy	NED 17			lung	extirpation CHT	
5	NS	40 Gy	8x2.5 Gy	NED 17					
6	negative		8x3 Gy	NED 20					
7	close	50 Gy	10x3 Gy	NED 30					subcutaneous fistula
8	negative	40 Gy	8x3 Gy	NED 48					
9	negative	45 Gy	8x3 Gy	NED 29					
10	negative	50 Gy	6x3 Gy	DM 14			lung	CHT	

CHT – chemotherapy, EBRT – external beam radiotherapy, HDR – high dose rate brachytherapy, mo. – months, NED – no evidence of disease, DM – died of metastasis, NS – not stated.

Table 2. Perioperative HDR-brachytherapy for recurrence

Case No	Previous treatment	Surgical margin	HDR	EBRT	Follow-up state mo	Recurrence (mo)	Salvage	Distant metastases	Therapy	Complication
1.	resection i.a. CHT	close	17x3 Gy		NED 10	+4	amputation			skin necrosis
2.	8x resection CHT	NS	18x3 Gy		NED 21	+19	resection			
3.	resection, i.a. CHT	positiv	6x3 Gy	40 Gy	NED 36					paresthesia
4.	12x resection i.a. CHT	positiv	16x3 Gy		alive 37 generalization	+16	amputation	lung	extirpation CHT	subcutaneous necrosis
5.	resection, EBRT, CHT	NS	15x3 Gy		died of 14 toxicity of CHT	+13	resection CHT			
6.	resection	negative	6x3x Gy	44 Gy	NED 7					
7.	2x resection EBRT, i.a. CHT	negative	8x2.4 Gy		DTM 18	+16	EBRT	lung	CHT	
8.	repeated resections CHT, EBRT	negative	15x3 Gy		DT 39	+15	resection			soft tissue necrosis
9.	repeated resections EBRT	close	8x3 Gy		NED 19	+14	resection			
10.	2x resection	negative	6x3 Gy	50 Gy	NED 42	+41	resection			
11.	2x resection	close	10x3 Gy		alive 39 generalization			lung	CHT	

HDR – high dose rate brachytherapy, EBRT – external beam radiotherapy, CHT – chemotherapy, mo. – months, i.a. – intraarterial, NED – no evidence of disease, DTM – died of tumor and metastasis, DT – died of tumor, NS – not stated.

currence are shown in Tables 1 and 2. In the first group the local control was achieved in all 10 patients. The pulmonal metastasis was a cause of death in one case, one patient was alive with dissemination to the brain and lung, one patient underwent salvage surgery and chemotherapy for lung metastasis and was without evidence of disease. In the second group the local control was achieved with BRT in 3 cases of 11 (27%). After salvage surgery 6 patients were disease free, 2 patients died of disease progression, one patient died of toxicity of chemotherapy without evidence of the disease and 2 patients were alive with distant metastases.

Local control was achieved in 5 of 11 (45%) patients with positive, close or not described surgical margin and in 5 of 10 (50%) patients with negative margins.

Local control was 100% in all patients treated by EBRT and BT, but only 20% in the patients treated by BT alone.

No infection or delayed wound healing resulting from tubing or radiation occurred.

We observed serious toxicity of BRT in 5 cases (23%) – 4 cases of soft tissue necrosis, subcutanous fistula in one case, in one case peripheral nerve palsy of tretaed extremity was seen.

Discussion

Results of perioperative brachytherapy with LDR Iridium -192 and total doses of 45 Gy in 4–5 days have demonstrated local control of 82% in previously untreated soft tissues sarcomas. Patients who fail locally after surgery and particularly after surgery and adjuvant radiotherapy are the most difficult to retreat. Some reports suggest that combined re-treatment with limb-sparing surgery and irradiation can be an effective method of controlling disease and preserving a functional limb for these patients. Brachytherapy, in doses of 45 Gy or less, appears to be associated with the least toxicity [4].

Almost all the published experience with BRT for soft tissue sarcomas is based on the use of LDR BT. Based largely on patient convenience, cost, machine availability and improved radiation safety, there is a strong move towards the use of HDR (dose rate >12 Gy/hr) afterloading devices for brachytherapy. HDR BRT proved to be as good or better than LDR brachytherapy in a lot of situations (palliative intraluminal brachytherapy, intracavitary implants for cancer of uterine cervix). But, in general, a move from LDR to HDR involves a greater probability of toxic effects for a given level of tumor control, particularly in interstitial applications. There are sparse published data reporting the use of HDR in the treatment of patients with STS. Additionally, these series have small numbers of patients, short follow-up time and a variety of different fractionation regimens.

ALEKHTEYAR et al [1] achieved 77% (10 of 13 cases) local control rate for soft tissue tumors with perioperative HDR brachytherapy (40–48 Gy/12–14 fr) alone or with a combination of EBRT (30–50 Gy) and HDR brachytherapy (20–24 Gy /7–8 fr). KOIZUMI et al [3] treated 16 lesions in 14 patients with malignant bone and soft tissue tumors with HDR BRT. The total dose was 40–50 Gy/7–10 fr/4–7 day (bid). Follow-up periods were between 19 and 46 months (median: 30 months). Local control rates were 75% at 1 year and 48% in 2 years. Ultimate local control was achieved in 8 (50%) of 16 lesions. Of the 8 uncontrolled lesions, 5 (63%) had macroscopically positive resections margins. Peripheral nerve palsy was seen in one case after BRT.

In our study with median follow up of 20 months the local control was achieved in 100% of patients treated for primary sarcoma but only in 27% of patients treated for the recurrence. The reason may be biogical agressivity of relapsing tumors, poor oxygenation of regions heavily pretreated (repeated surgery, chemotherapy and radiotherapy) and difficulty to achieve microscopically negative resection margins. Several studies demonstrated adverese impact of positive margin of resection on local control [7]. In our limited number of patients the local control in patients with negative margins was not different from the patients with margins positive, close or not described.

Local control was achieved in all patients treated by tele- and brachytherapy and only in 2 from 10 patients treated by brachytherapy alone. Combination of brachytherapy as a boost to EBRT is now recommended for low-grade sarcomas and in the case of positive and uncertain margins.

The incidence of soft tissue complication after BRT was relatively high, but the soft tissue necrosis was encountered in 3 patients treated for relapse after previous repeated resections in fibrotic terrain and was combined with local recurrence. The treatment was amputation in 2 cases and resection in 1 case. One case of soft tissue necrosis and one case of subcutenous fistula in patients with primary HDR BT healed after conservative treatment.

Despite small number of patients and short follow up our retrospective study suggests, that perioperative fractionated HDR brachytherapy is easy and promissing when used as a part of primary treatment for STS. The treatment results for recurrence are very poor and in a lot of cases radical surgical approach should have been considered for the salvage.

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