RESEARCH ARTICLE

Neoadjuvant Treatment with Preoperative Radiotherapy for Extremity Soft Tissue Sarcomas: Long-Term Results from a Single Institution in Turkey

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Abstract

Background: To assess the long term clinical outcome of preoperative radiotherapy with or without chemotherapy followed by limb sparing surgery in patients with non-metastatic soft tissue sarcomas (STS) of the extremities. Materials and Methods: Sixty patients with locally advanced STS were retrospectively analyzed. The median tumor diameter was 12 cm. All patients were treated with preoperative radiotherapy delivered with two different fractionation schedules (35Gy/10fr or 46-50Gy/23-25fr). Neoadjuvant chemotherapy was added to 44 patients with large and/or high grade tumors. Surgery was performed 2-6 weeks after radiotherapy. Chemotherapy was completed up to 6 courses after surgery in patients who had good responses. Results: Median follow-up time was 67 months (8-268 months). All of the patients had limb sparing surgery. The 5-year local control (LC), disease free (DFS) and overall survival (OSS) rates for all of the patients were 81%, 48.1% and 68.3% respectively. 5-year LC, DFS and cause specific survival (CSS) were 81.7%, 47%, 69.8%, and 80%, 60%, 60% in the chemoradiotherapy and radiotherapy groups, respectively. On univariate analysis, patients who were treated with hypofractionation experienced significantly superior LC, DFS and CSS rates with similar rates of late toxicity when compared with patients who were treated with conventional fractionation and statistical significance was retained on multivariate analysis. Conclusions: Treatment results are consistent with the literature. As neoadjuvant chemoradiotherapy provides effective LC and CSS with acceptable morbidity, it should be preferred for patients with large and borderline resectable STS.

Keywords: Soft-tissue sarcomas - preoperative radiotherapy/chemotherapy - limb-sparing surgery

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Introduction

The major therapeutic goals of the treatment of extremity STS are long-term local control and survival, while preserving limb function. Local recurrence rate differed between 60-90% with marginal excision (Delaney, 2004). Radical resection or amputation improves LC but may result in significant functional disability and reduced quality of life for patients (Suit et al., 1985). Randomized trials have showed that, limb-sparing surgery with adjuvant radiotherapy yields equivalent local control rates with improved functional and psychological outcome compared to amputation alone (Rosenberg et al., 1982 ; Yang et al., 1998). Recent SEER database demonstrated a survival benefit for the addition of radiotherapy to surgery in large, high-grade tumors (Koshy et al., 2010).

A considerable proportion of the patients are presenting with locally advanced tumors not safely amenable to a limb salvage procedure due to the bulk and extent of the tumor or proximity to critical tissues. Preoperative radiotherapy combined with or without chemotherapy is preferred for these patients. Preoperative treatment modalities yield tumor cytoreduction that potentially allows more conservative surgery with safe margins. Besides, we use lower total dose to a smaller irradiation volume as well as the surrounding normal tissue, which will improve limb function. Easier tumor delineation and eradication of microscopic tumor seeding are the other advantageous of preoperative radiotherapy. Although wound complications are reported more in the patients treated by means of preoperative treatment than the patients treated by postoperative radiotherapy,

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less late toxicity were seen compared with postoperative radiotherapy in the long-term follow-up analysis (Suit et al., 1985; Nielsen et al., 1991; Sadoski et al., 1993; O'Sullivan et al., 2002; Davis et al., 2005). Furthermore, delay of adjuvant radiotherapy due to wound healing after surgery is prevented by using radiotherapy in the preoperative setting.

Besides local recurrence risk, patients with high-grade sarcomas larger than 5 cm are confronted with a significant risk of distal failure. Even the role of adjuvant chemotherapy remains controversial; the updated meta-analysis from the Sarcoma Meta-Analysis Collaboration suggested that, adequately dosed anthracycline/ifosfamide-containing regimen significantly prolongs survival in patients with high-grade, large tumors arising in the extremities (Pervaiz, 2008; Schuetze et al., 2009). Nowadays, neoadjuvant chemotherapy are used with preoperative radiotherapy in order to get better tumor response and local control due to the synergistic effect of both modality and to prevent the potential micrometastases earlier especially in large and high grade lesions.

In this study, the long term outcome of the patients treated with neoadjuvant protocol in our institution, were retrospectively evaluated. All the cases with soft tissue sarcoma are discussed weekly at our instutional sarcoma board and the optimal treatment schedule for the patients were decided there.

Materials and Methods

Between the years 1989 and 2007, 60 patients with non-metastatic extremity STS were treated by preoperative radiotherapy with or without chemotherapy at Cerrahpasa Medical Faculty which is a reference center for sarcomas, were retrospectively evaluated. Pathologic diagnosis was established by open biopsy or computed tomography-guided core biopsy at our institution or by excision at another center in the case of recurrent tumors. All pathology specimens were reviewed by the same pathologist at our hospital before the treatment. The French Federation of Cancer Centers Sarcoma Group (FNCLCC) system was used for grading the tumor. Patients who received prior chemotherapy, prior radiotherapy to the local site or who had previous or concurrent malignancy and patients with distant metastasis, specific histologic subgroups, including, rhabdomyosarcoma, extraosseaus Ewing, primitive neuroectodermal tumor or aggressive fibromatosis were not included in this study. Baseline evaluation consisted of a medical history and physical examination, complete blood count, serum chemistries, urinalysis, pregnancy test, electrocardiogram, echocardiogram, computed tomography (CT) of the thorax, and magnetic resonance imaging (MRI) or CT scan of the involved extremity. The disease was restaged according to the 2002 classification of the American Joint Committee on Cancer Staging.

Treatment

Patients with large tumor and whose limb-sparing surgery would have been difficult because of borderline resectability were treated according to neoadjuvant schedule. In addition, the patients who were suggested to be treated by amputation but who refused it were treated by the same way, in order to acquire the chance of the limb sparing surgery. All of the patients had preoperative radiotherapy. Three cycles of neoadjuvant chemotherapy was administered to patients with high grade, large tumors. Each chemotherapy cycle consisted of 75mg/m^2 doxorubicin on D1, 2 gr/m^2 ifosfamide with 2gr/m^2 mesna on 3 consecutive days (D1-3) every 3 weeks. Prophylactic granulocyte colony-stimulating factor (G-CSF) was routinely used. Preoperative external radiotherapy was applied usually between the second and third cycle of chemotherapy. Adjuvant chemotherapy was continued up to 6 courses to complete the schedule in patients who had good response to neoadjuvant treatment.

Preoperative radiotherapy was delivered with Co^{60} or 4-6 MV linear accelerators. Hypofractionated radiotherapy to a dose of 35Gy in 3.5 Gy daily fractions was generally preferred. If the radiotherapy field was too large, 46-50Gy with conventional fractionation schedule was used. Biologic effective dose (BED) was 70 (α/β=3.5Gy), 47.3(α/β=10Gy), and 72.3(α/β=3.5Gy), 55.2 (α/β=10Gy), for hypo fractionated and conventional treatment, respectively. Before 2000 most of the patients were irradiated by 2D plans with two parallel-opposed or tangential beams. The treatment volume included all the mass including the surrounding edematous part with a margin to 2 cm radial and 5 cm longitudinal directions, and was adapted to anatomic barriers including the biopsy tract. A strip of skin (1.5-2 cm when possible) was spared along the irradiated limb to limit distal-extremity edema and constrictive fibrosis. Epiphysis and joints were excluded whenever possible. After 2000, 3D conformal planning was used. The clinical target volume was created by giving a margin 2 cm for the radial and 3-5 cm to upper and lower directions from the gross tumor volume seen in the planning CT and also we took into account the edema and extension of the tumor seen on MRI images. The planning target volume included the clinical target volume with a 1 cm margin. Definitive surgery was planned 2-3 weeks after hypofractionated radiotherapy, while 4-6 weeks after conventional irradiation. A limb sparing approach was undertaken in all patients by the same orthopedic surgeon. If the surgical margin was positive, another 10-20 Gy was delivered to postoperatively to tumor bed.

Follow-up

All patients were followed by a multidisciplinary team. Treatment details and outcomes were recorded prospectively. All patients were followed regularly with a physical examination every 3 months for 2 years, then every 6 months up to 5 years and yearly thereafter. Thorax CT, CT or MRI of the involved extremity, routine blood biochemistry profiles were repeated every 6-12 months. Further investigative studies were done according to the patients' complaints. Local recurrences were confirmed by a biopsy sample.

Statistical methods

Survival was calculated from the date of histological

diagnosis. Local control time was defined as the time from the date of diagnosis to date of local relapse. For distant metastases-free survival (DMFS), first recurrence at distant site was taken as an event. Cause-specific survival (CSS) events were defined as death from cancer or treatment complications. Death from any cause was used to determine overall survival (OS). Kaplan-Meier analysis with a log-rank test was used for survival analysis. The Cox proportional hazards regression model was used for multivariate survival analyses. A p value < 0.05 value was accepted as statistically significant. Toxicities for chemotherapy were recorded and graded from 1-4 according to the NCI Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Late side effects of radiotherapy were scored according to the Radiation Therapy Oncology Group morbidity scoring criteria. Since this was a retrospective analysis; our institutional board was informed before the analysis which was conducted in accordance with the principles of the Declaration of Helsinki and the rules of Good Clinical Practice. National rules do not require obtaining ethical committee approvals for retrospective studies.

Results

Thirty-seven patients were male. The patients' ages varied between 13 to 72 years, with a median of 44 years. Tumors were mostly localized in the lower extremity (88.3%). The median tumor size was 12 cm (3-33 cm). Most common histology was synovial sarcoma (35%). Forty-four patients (73.3%) were treated with neoadjuvant chemoradiotherapy protocol and 16 (26.7%) patients were treated with sole preoperative radiotherapy followed by surgery. Twenty-four patients were treated with hypofractionated radiotherapy, 36 patients were treated with conventional fractionated radiotherapy. Conventional radiotherapy dose was 46 Gy except 4 patients. Patient characteristics are summarized in Table 1.

Definitive surgery was performed within median of 42 days (7-438 days) after radiotherapy. Only three patients did not have an operation on planned time since they refused operation after the termination of neoadjuvant treatment protocol. However, subsequently they accepted operation due to tumor progression. All the patients underwent limb-sparing surgery. Thirty one (51.7%) patients had a marginal resection, 24 (40%) patients had wide local excision. Radical excision was performed to 5 patients. Nineteen patients (31.7%) had microscopically positive surgical margins and 11 of them received postoperative boost radiotherapy.

Median follow-up was 67 months (8- 268 months). Eleven patients (18.3%) had local recurrence. Two of them had isolated local recurrence and they were treated with salvage surgery. Distant metastases were seen in 30 patients. The median time of metastases was 22 months (5-90 months). The most common site of distant metastases was lung in 24 patients and bone in 4 patients. Thirteen patients with lung metastases had metastatectomy. The metastasis-free survival rate at 5 years was 51.8%. Twenty-four patients died due to their disease and 1 patient died of colon cancer. 5-year LC, DFS and OSS rates were 81%, 48.1%, 68.3%, respectively in all patients. In the preoperative chemoradiotherapy group the 5-year LC, DFS and CSS rates were 81.7%, 47% and 69.8%, respectively. In sole preoperative radiotherapy group the 5-year LC, DFS and CSS rates were 80%, 60% and 60%, respectively (Figure 1).

On univariate analysis; the CSS rate was significantly higher in male patients than female patients (p=0.04). Surgical margin status had no significant impact on LC, DFS and CSS. Although there was no significant difference for 5-year LC and DFS within the subgroups of marginal, wide or radical excision; there was a trend favoring wide or radical excision compared to marginal excision for CSS (p=0.08) The 5-year LC, DFS and CSS

Table 1. Characteristics of Patients

		N (%)
Gender	Female	23(38.3%)
	Male	37(61.7%)
Age	<50 years	35 (58.3%)
	≥50 years	25 (41.7%)
Location	Upper extremity	7 (11.7%)
	Lower extremity	53 (88.3%)
Tumor size	<12 cm	23 (38.3%)
	≥12 cm	37 (61.7%)
Stage	I	18 (30%)
	II	14 (23.3%)
	III	28 (46.7%)
Histopathological diagnosis		
Synovial cell sarcoma		21 (35%)
Undifferentiated pleomorphic sarcom		13 (21.7%)
Liposarcoma		14 (23.3%)
Leiomyosarcoma		4 (6.7%)
Others		8 (13.3%)
Radiotherapy fractionation type		
Conventional fractionation		36 (60%)
Hypofractionation		24 (40%)
Operation type	Marginal resection	31 (%)
	Wide local resection	24 (%)
	Radical excision	5 (%)

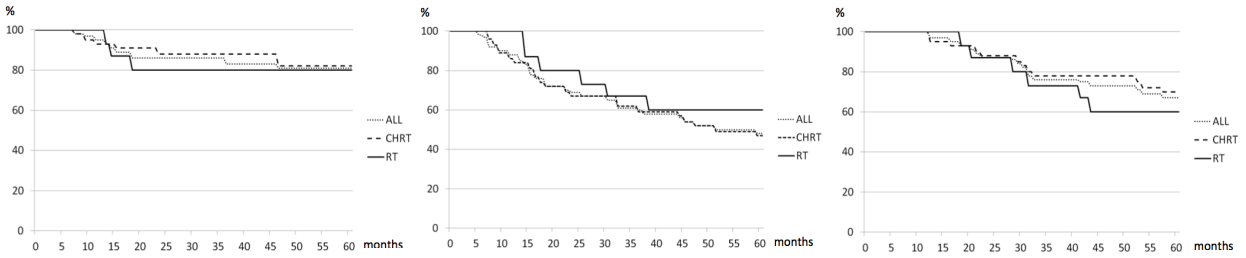

Figure 1. A) Local Control; B) Disease Free Survival and; C) Cause Specific Survival for All Patients, Chemoradiotherapy (CHRT) and Radiotherapy (RT) Groups

Table 2. Univariate Analysis for Local Control, Disease free Survival and Cause Specific Survival Rates

		N	5 year (%)	p	5 year (%)	p	5 year (%)	p
Gender	Female	23	80	0.9	40	0.2	55	0.04
	Male	37	82		53		70	
Tumor size	<12 cm	23	86	0.7	64	0.1	77	0.2
	≥12 cm	37	79		38		60	
Treatment type	Radiotherapy alone	16	80	0.9	60	0.5	60	0.9
	Chemoradiotherapy	44	82		47		70	
Radiotherapy fractionation type	Hypofractionation	24	95	0.006	66	0.04	88	0.05
	Conventional fractionation	36	70		35		51	
Operation type	Marginal excision	31	83	0.9	45.2	0.6	58.1	0.08
	Wide local excision/radical excision	29	78.9		52.5		79.3	
Surgical margin	Negative	41	79	0.6	54	0.9	77	0.8
	Positive	19	84		43		58	

Table 3. Multivariate Analysis of Prognostic Factors for Local Control (LC), Disease-free Survival (DFS) and Cause-Specific Survival (CSS)

		LC		DFS		CSS	
		p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)
Gender	Female	0.833	0.856(0.203-3.605)	0.109	1.907 (0.866-4.201)	0.024	2.761 (1.143-6.669)
	Male		1		1		1
Tumor size	<12 cm	0.452	0.612(0.17-2.203)	0.056	0.466 (0.213-1.018)	0.115	0.477 (0.19-1.198)
	≥12 cm		1		1		1
Treatment type	Radiotherapy alone	0.464	1	0.519	1	0.982	1
	Chemoradiotherapy		0.551(0.112-2.711)		1.369(0.527-3.559)		1.012 (0.357-2.865)
Radiotherapy fractionation type							
	Hypofractionation	0.019	1	0.002	1	0.017	1
	Conventional fractionation		12.327(1.510-100.643)		3.725(1.621-8.559)		3.155(1.232-8.08)
Operation type	Marginal excision	0.621	1.373(0.39-4.83)	0.253	1.547(0.732-3.273)	0.018	3.207(1.218-8.441)
	Wide local/ Radical excision		1		1		1
Surgical margin	Negative	0.467	1	0.610	1	0.514	1
	Positive		0.624 (0.175-2.26)		0.825 (0.393-1.730)		0.744(0.306-1.808)

Table 4. Incidence of Grade 2-4 Late Complications According to RTOG Toxicity Scale

Late complications	Grade 2	Grade 3	Grade 4
Subcutaneous tissue	15	4	-
Joint	2	4	1
Bone	-	-	2

rate was significantly better for the patients irradiated with hypofractionation compared with conventional fractionation ($p<0.05$). Although CSS rate was better in the chemoradiotherapy group than the radiotherapy group, the difference was not significant (Table 2). Variables evaluated by multivariate analysis included gender, tumor size, treatment type, radiotherapy fractionation type, surgical margin status and operation type. Fractionation schedule was found to be a significant independent factor affecting LC, DFS and CSS rates ($p=0.019$, $p=0.002$ and $p=0.01$). Gender and operation type were also an independent prognostic factors for CSS rate ($p=0.02$ and $p=0.01$) (Table 3).

All patients in the chemoradiotherapy group completed all cycles of chemotherapy. Gastrointestinal bleeding was observed in one patient and one patient developed pulmonary embolism. None of the patients experienced grade 4 toxicity other than hematologic toxicities and no treatment-related deaths were observed. All patients experienced, grade 1 and 2 mucositis. Grade 2 hematological toxicity was seen in 48% of patients and 5 patients had a neutropenic fever.

Grade 1-2 early skin reactions were reported after radiotherapy. There was delayed wound healing in 10 patients in chemoradiotherapy group, 2 patients in preoperative radiotherapy group after surgery. Postoperative wound complications requiring surgical intervention occurred in 5 patients in chemoradiotherapy group, 2 patients in radiotherapy group. Most common reasons for secondary surgery were infections around the wound area and greft related complications. One patient required a finger amputation due to a local infection. Deep vein thrombosis was occurred in one patient in each group. The incidence of late morbidity was as follows: soft tissue fibrosis in 14 patients in the chemoradiotherapy group and 5 patients in the radiotherapy group; chronic edema in 6 patients in chemoradiotherapy group, 2 patients in radiotherapy group. Osteoradionecrosis was detected in 2 patients in chemoradiotherapy group and all needed prosthesis replacement. Two patients were reoperated due to prostheses-related problems at a later date. There was no difference in the incidence of late side effects between fractionation schedules. The incidence of Grade 2-4 late complications according to RTOG toxicity scale are summarized in Table 4.

Discussion

The management of localized adult extremity STS is limb sparing surgical resection combined with radiotherapy. The optimal timing of radiotherapy in relation to surgery remains controversial. In Sampath et. al.' multiinstitutional retrospective analysis of 821 patients from National Oncology database with a median follow-up time of 63 months, comparing preoperative and

postoperative radiotherapy, preoperative radiation was associated with significantly better CSS. These results can be attributed to the better local control and DMFS achieved by means of preoperative irradiation, eradicating the tumor cells with the potential of distant spread (Sampath et al., 2011). The only phase III clinical trial was conducted by the NCI Canada Clinical Trial Group and randomized patients treated with either preoperative or postoperative irradiation (O'Sullivan et al., 2002). The trial was terminated when significantly higher rate of acute wound healing complications (35%) in preoperatively treated patients were obtained at the time of a planned interim analysis. Updated data with a median follow-up of 6.9 years showed that the local control, distant metastasis, progression-free and overall survival rates were comparable in the two arms of the study (O'Sullivan et al., 2004). Although, the wound complications were reported to be more in the preoperative group, the incidence of late toxicity especially grade 3 subcutaneous fibrosis was significantly higher in the postoperative group (Davis et al., 2005). A meta-analysis also including four retrospective cohort studies concluded that LC is better after preoperative radiotherapy (Al-Absi, 2010).

Distant metastasis is still a problem for the survival for the patients with soft tissue survival. Adjuvant chemotherapy is administered for some subgroup of patients with high grade tumors showing better results however, there is no compelling evidence on the benefit of neoadjuvant chemotherapy alone since randomized phase III trials with sufficient statistical significance are not available. A retrospective study from the Dana-Farber Cancer Institute and Memorial Sloan-Kettering Cancer Center demonstrated a significant improvement in disease specific survival rate especially in patients with tumors larger than 10 cm with neoadjuvant chemotherapy (Grobmyer et al., 2004). A randomized phase II EORTC STBSG-62874 trial in which patients with high risk STS were randomized between surgery alone or three cycles of neoadjuvant doxorubicin and ifosfamide failed to show better survival in the chemotherapy arm (Gortzak et al., 2001).

Theoretically, there is belief that combining preoperative with chemotherapy may both improve the results for large and high grade tumors and enables limb sparing surgery to be performed with adequate margins. This was first introduced by Eilber et al. with a protocol by preoperative intra-arterial doxorubicin with sequential hypofractionated radiotherapy (35 Gy in 10 fractions) followed by limb salvage surgery in patients with high-grade extremity STS. They reported a high rate of primary limb salvage with good LC and long-term survival (Eilber et al., 1984). Due to high rates of complications related with intravenous administration of doxorubicin instead of intra-arterial administration has been used in the subsequent chemoradiotherapy protocols. More recent efforts have explored the use of interdigitated radiotherapy with doxorubicin-containing chemotherapy regimens such as MAID (mesna, doxorubicin, ifosfamide, and dacarbazine). Favorable outcome with this schedule, though substantially greater short-term toxicities has been reported (Kraybill et al., 2010). We prefer to use doxorubicin, ifosfamide with mesna (AIM) rather than MAID regimen while there are several published data showing good results with high dose adriamycin and ifosfamide with G-CSF (Le Cesne et al., 2000; Pervaiz, 2008). This allows the administration of effective doses of doxorubicin and ifosfamide, rather than adding myelotoxicity with dacarbazine. In the current study, this regimen used in the neoadjuvant setting is well tolerated and our treatment results are comparable with the others although the majority of our patients have inferior prognostic characteristics.

Preoperative radiotherapy is mostly used with conventional fractions up to 45-50Gy with 1.8-2.0 Gy/fraction. However, the preclinical speculation about the potential radioresistance of sarcoma led to pilot studies with short-course, high-dose per fraction radiation with concurrent antracycline based chemotherapy (Eilber et al., 1984; Wanebo et al., 1995). While sarcoma cells are considered to have low α/β values, using relatively large fraction doses may improve the results when we look at the radiobiological era. There are some reports showing good LC and DM control for the selected patients with high risk STS treated by hypofractionated radiotherapy between the chemotherapy cycles with acceptable treatment related morbidity (Mack et al., 2005). In the current series, both the univariate and multivariate analysis showed that hypofractionated radiotherapy protocol yielded significantly better LC, DFS and CSS rates with similar late complication rates compared to conventional fractionation. While the BED 3.5 were similar for the two fractionation types, the advantage might be due to early surgery or continuation of chemotherapy since radiotherapy was administered in a shorter period, between two cycles of chemotherapy not allowing time to developing side effects due to radiotherapy or preventing the interruption of radiotherapy because of neutropenia of chemotherapy. Nevertheless, small sample size of patients and heterogeneity of the groups inhibits us to make definitive conclusions on the analysis.

Treatment results are influenced by a variety of factors, including gender, tumor size, tumor site, histologic grade and subtype, operation type. Pisters et al. found that tumor size >10 cm was an adverse factor for CSS (Pisters et al., 1996). Although we didn't find any significance for tumor size within the range of 5 cm multiples, it seems to be an independent prognostic factor for DFS when we reanalyze it regarding the median size. Positive surgical margin increases the local recurrence rate even in patients with combined surgery and radiotherapy (Rosenberg et al., 1982; Sadoski et al., 1993; Pisters et al., 1996; Zagars et al., 2003). In our series, there were 19 patients with positive margin after resection. This rate might be higher than the other series. However, we should not forget that most of our tumors were big tumors (median 12 cm) and it was not easy to make adequate wide or radical dissections due to the size and the proximity to the vascular structures or nerve bundles and joints. Only three of the patients with positive surgical margin had local recurrence. It seems that, radiotherapy enables to control local recurrence even in margin positive tumors. This finding may be related to radiosterilization of tumor cells within the reactive zone

following preoperative radiotherapy as noted in the study of Dagan et al (2012).

It is obvious that the major disadvantage of preoperative radiotherapy is an increased risk of wound healing complications. However, they can usually be managed with careful care and multidisciplinary team work and nursing in the long run. It is not easy to distinguish which of the side effects are related to surgery, radiotherapy or chemotherapy. Various rates of major wound complications have been reported since many factors such as; size and anatomic location of the tumor, wound closure, radiotherapy dose and volume, prior surgery, medical status and age of the patient might affect the outcome (Nielsen et al., 1991; Le Cesne et al., 2000; Kunisada et al., 2002; O'Sullivan et al., 2002; Davis et al.2005; Mack et al., 2005; Kraybill et al., 2010). O'Sullivan et al reported that, acute wound complications were significantly more common with preoperative treatment compared with postoperative treatment (35 versus 17 %) (O'Sullivan et al., 2002). In our study, delay in wound healing rate was 20% and was greater in the chemoradiotherapy group as expected. However, the reoperation rates were within the range of other studies. Finger amputation was performed to one patient due to uncontrolled local infection during the follow-up which was outside the irradiation field. Contrarily, late effects due to preoperative radiotherapy were reported to be significantly less than postoperative radiotherapy in O'Sullivan et al's long term follow-up (Davis et al., 2005). The incidence of grade 2-4 fibrosis was reported to be 48% for postoperative and 31.5 % for preoperative radiotherapy. Although not statistically significant, limb edema (23 versus 16 %) and joint stiffness (23 versus 18 %) were both more common in the postoperative treatment group (Davis et al., 2005). Sampath et al. reported a modified analysis from a retrospective study comparing preoperative and postoperative radiotherapy and found that grade >2 skin toxicity was 52%, 72% and subcutaneous tissue toxicity was 60%, 74% for preoperative and postoperative radiotherapy respectively, confirming the findings above (Sampath et al., 2011). Grade 2-4 subcutaneous tissue side effect including fibrosis and edema rate was 45% in our series. Fibrosis rates were similar in 7/24(29%) the patients treated by hypofractionated radiotherapy and 12/36 (33%) in the patients treated by conventional fractionation group. The late effects were seen usually in the patients whose tumor location was lower extremity as reported by the other centers. Although extremity edema resulted in joint stiffness in some of the patients, all of the patients were ambulatory mostly without external support and able to maintain their daily life.

The optimal regimen and sequencing of chemotherapy, radiation with surgery in the management of high-risk patients remains controversial and usually depends on the institutional expertise, experience and preferences. Our institution's policy is to use the preoperative radiotherapy with or without chemotherapy (AIM regimen) to patients who have large or high grade tumors and those for whom limb-sparing surgery is difficult due to tumor localization. Although most of our patients had big tumors with the probability of marginal resection, local control and survival rates were comparable to literature with this neoadjuvant protocol in our series. We believe that multidisciplinary team work and close follow-up and management of side effects properly during and after the treatment improve the clinical outcomes.

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