

Preoperative Versus Postoperative Radiation Therapy in Patients with Soft Tissue Sarcomas

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Abstract

Purpose: To evaluate treatment outcome and to determine whether or not the timing of radiotherapy (RT) was associated with any difference in disease relapse, survival, or incidence of complications in patients with soft tissue sarcomas (STS). **Methods:** The medical files of 63 patients with a primary, nonmetastatic, STS, treated with surgery and irradiation were evaluated. Data regarding tumor stage, grade, site, dosage and timing of radiotherapy, treatment complications, disease relapse, and disease-free (DFS) and overall survival (OAS) rates were analyzed. **Results:** The median follow up was 47 months (range; 5-66 months). Four-year OAS and DFS rates were 82.6% and 78.8% respectively. There were significant higher 4-year OAS ($p = 0.024$) and DFS ($p = 0.011$) rates in patients with stage I and II diseases than those in patients with stage III disease. On the other hand, there were no significant differences in 4-year OAS ($p = 0.83$, HR: 0.743, 95% CI: 0.165 to 3.345) and DFS ($p = 0.64$, HR: 0.74, 95% CI: 0.21 to 2.61) rates between preoperative and postoperative RT patients. Disease relapse for preoperative versus postoperative RT patients was not statistically different ($p = 0.41$). Wound complications were more frequent in preoperative RT patients (25%) compared to postoperative RT patients (8%) ($p = 0.0566$ chi-square). **Conclusions:** Preoperative irradiation has not a positive impact on survival or disease relapse rates, but is associated with high wound complication rate.

Keywords: soft tissue sarcomas, adjuvant radiotherapy, survival

1. Introduction

Soft tissue sarcomas represent a large group of lesions that are often subtle in presentation and have wide variation in extent of aggressive or malignant behavior (Pisters et al., 2000; Weiss et al., 2001; Sondak & Chang, 2001).

The principal management of localized soft tissue sarcomas is surgery in order to achieve a negative margin. Local excision alone of soft tissue sarcoma resulted in local recurrence rate of 50-70% (Fuller, 2001). Therefore, adjuvant radiotherapy has a proven benefit in the treatment of soft tissue sarcoma, and results in a decrease in disease relapse. Radiation may be given either before or after surgery. However, there is lack of evidences regarding the relative effectiveness of preoperative in comparison with postoperative RT (Zagars et al., 2003).

The timing of adjuvant radiation therapy and surgery is often determined by institution preference. Pre-operative radiation therapy results in tumor shrinkage and reducing the risk of seeding at the time of surgery with facilitating surgical resection. On the other hand, postoperative radiotherapy has the advantages of no delay in definitive surgery, less wound complication and no interference with pathological analysis of the resection specimen (Fuller, 2001). Despite a low overall incidence, STS is a fairly common entity in radiation oncology clinics as level-one evidence from several randomized controlled trials supports a multidisciplinary approach (Yang et al., 1998; Prendergast et al., 2010).

This study was done to evaluate pathological and clinical patterns and treatment outcome of patients with soft tissue sarcomas as well as to determine whether or not the timing of radiotherapy was associated with any difference in disease relapse, survival, or incidence of surgical wound complications.

2. Methods

2.1. Study Subjects

This retrospective study was carried out by analyzing medical records of patients with the pathological diagnosis of soft tissue sarcomas (n=63), seen at the Surgical oncology and Radiotherapy Departments, SECI, Assiut University during the period from January 2006 until January 2012. Informed consent was obtained for all patients and the treatment decision was approved by the Institutional Review Board at our center.

Eligible patients had histologically confirmed, non metastatic soft tissue sarcomas, treated by wide local excision, with removal of a normal tissue margin from within the same muscle compartment, with negative surgical margins and radiation therapy. For patients with extremity lesions, limb sparing surgery was done. For patients with retroperitoneal sarcomas, removal of all gross disease was done, while sparing adjacent viscera not invaded by tumor. Abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic and periaortic selective lymphadenectomy was performed in 4 patients with leiomyosarcoma of uterus. In one patient with sarcoma of urinary bladder, partial cystectomy was performed as the lesion at the dome of the bladder less than 5 cm in diameter.

Data regarding age, sex, site, pathological type, tumor size, histologic grade, tumor stage, dosage and timing of radiotherapy, treatment complications, disease relapse, and disease-free interval, and last follow up were analyzed.

2.2 Radiotherapy Techniques Used

In the pre-operative setting, 3-D planning was done, with patients in supine position [except in patients with back lesions, where prone position was used]. Multiple CT cuts were taken throughout target volume at 0.5 cm intervals. At each CT slice, clinical target volume (CTV) [2 cm margin on tumor mass] and critical structures were defined. Tumor dose was 50 Gy, 2Gy/fraction, over 5 weeks, prescribed at the isocenter. In the postoperative setting, 2-D planning was done with CTV with a margin of 5cm length and 2 cm transverse on the tumor bed to tumor dose of 50 Gy, 2 Gy/fraction, then, conedown to 2cm margin on surgical scar was done to total dose of 64 Gy, using 6 MV photon beam. In patients with extremity lesions, a 1cm skin strip was preserved to avoid lymphedema.

2.3 After-Therapy Monitoring

Follow-up examinations were performed routinely monthly after treatment. MRI of the affected body site to detect local relapse and CT chest to scan for lung metastases were done annually.

2.4. Statistical Methods

The study cutoff point was January, 01, 2012. Overall survival was defined as the interval from enrollment to the date of death from any cause or last follow-up. Disease-free survival was defined as the interval from enrollment of patients, to the date of disease relapse, death from any cause or last follow-up. Disease free survival and OAS rates were estimated using Graphed prism program. The Log-rank test was used to examine differences in DFS and OAS rates. Chi-square test was used to compare percentages of wound complication and disease relapse rates in both RT groups.

3. Results

3.1 Patients' Characteristics

This retrospective study included 63 patients with soft tissue sarcomas. Median age was 40 years (range; 19-69 years). Forty one patients (65%) were males and 22 (35%) were females with male to female ratio of 1.9: 1. Twenty patients (32%) presented with lesions in lower extremities, 16 patients with lesions in trunk (25%) and in pelvis (25%), and 11 cases (18%) with lesions in upper extremities. The most common pathological type was MFH (18 patients; 28.6%), followed by FS, (17 patients; 27%), SS (12 patients; 19%), and RMS (8 patients; 13%). The majority of our patients had grade II disease (32 patients; 51%), tumor >5cm (53 patients; 84%), and stage II disease (34 patients; 54%). Preoperative radiation therapy was given in 24 patients (38%) [16 patients with pelvic lesions, 6 with abdominal lesions and 2 with thigh lesions], and postoperative radiation in 39 patients (62%) (Table 1).

Table 1. Patients' characteristics of 63 patients with soft tissue sarcomas

Patients' Characteristics	NO (%)
Age	
Median	40 years
range	19-69 years
Gender	
Male	41 (65.1%)
female	22 (34.9%)
Sites	
Upper extremities (shoulder, arm, forearm, axilla)	11 (17.5%)
Lower extremities (thigh, leg)	20 (31.7%)
Pelvis	16 (25.4%)
Trunk	16 (25.4%)
Histopathology	
Malignant fibrous histiocytoma (MFH)	18 (28.6%)
Fibrosarcoma/spindle cell sarcoma (FS)	17 (27%)
Synovial sarcoma (SS)	12 (19.1%)
Rhabdomyosarcoma (RMS)	8 (12.7%)
Liposarcoma (LS)	3(4.7%)
Leomyosarcoma of uterus	4(6.3%)
Sarcoma of urinary bladder	1(1.6%)
Histologic grade	
G1	9 (14.3 %)
G2	32 (50.8 %)
G3	22 (34.9 %)
Tumor size	
<5 cm	10 (15.9%)
≥5 cm	53 (84.1%)
Disease stage	
Stage I	9 (14.3%)
Stage IIa	7 (11.1%)
Stage IIb	27 (42.9%)
Stage III	20 (31.7%)
Radiotherapy given	
Preoperative RT	24 (38.1%)
Postoperative RT	39 (61.9%)
Total	63(100%)

G: grade; RT: radiotherapy

3.2 Survival Analysis

The median follow up was 47 months (range; 5-66 months). Four-year OAS and DFS rates were 82.6% and 78.8% respectively. Table 2 showed that, 4-year OAS and DFS rates did not significantly influenced by patients' age ($p=0.37$, HR: 1.89, 95% CI:0.47 to 7.61 and $p=0.27$, HR: 1.95, 95% CI:0.59 to 6.44, respectively), patients'

gender ($p = 0.71$, HR: 1.34, 95% CI: 0.299 to 6.024 and $p = 0.79$, HR: 1.187, 95% CI: 0.33 to 4.23, respectively), histopathological type ($p = 0.62$ and $p = 0.25$, respectively), and tumor size ($p=0.17$, HR: 3.5, 95% CI: 0.579 to 21.21 and $p= 0.116$, HR: 3.46, 95% CI: 0.737 to 16.23, respectively). Disease stage and grade were the only adverse prognostic factors. The 4-year OAS rates were 100%, 92.5% and 61% for patients with grade I, grade II, and grade III disease, respectively ($p = 0.0797$), while the 4-year DFS rates were 100%, 89.7%, and 55.5% respectively ($p=0.016$). The 4-year OAS rates were 100%, 100%, 91% and 54% for patients with stage I disease, stage IIa disease, stage IIb and stage III disease respectively ($p=0.024$), while the 4-year DFS rates were 100%, 100%, 87.8%, and 49% respectively ($p = 0.011$). Figures (1-4) illustrate both OAS and DFS rates in patients with STS according to adverse prognostic factors (i.e. disease stage and histologic grade). In the preoperative RT patients, 4-year OAS and DFS rates were 88%, and 86.5%, respectively compared to 80% ($p = 0.83$, HR: 0.743, 95% CI: 0.165 to 3.345) and 76% ($p= 0.64$, HR: 0.74, 95% CI: 0.21 to 2.61) respectively, for postoperative RT patients. Figures (5, 6) illustrate OAS and DFS rates for patients according to timing of adjuvant radiation therapy and surgery, with preoperative RT resulted in higher survival rates than postoperative RT, but the survival differences were not statistically significant ($p > 0.05$).

Table 2. Univariate analysis of prognostic factors that might affect 4 year OAS and DFS among 63 patients with soft tissue sarcomas

Variable	4-year OAS	P value	4-year DFS	P value
Age		P=0.37		P=0.27
≤40 years	81.4%	HR: 1.89, 95% CI: 0.47 to 7.61	76.2%	HR: 1.95, 95% CI: 0.59 to 6.44
>40 years	84.4%		81.7%	
Gender		P=0.71		P=0.79
Males	84.8 %	HR: 1.34, 95% CI: 0.299 to 6.024	81.2 %	HR: 1.187, 95% CI: 0.33 to 4.23
Females	76.8 %		71.8 %	
Histopathology				
MFH	81.8 %		75.6 %	
FS	76.7 %	P=0.62	76.7 %	P=0.25
SS	100 %		100 %	
RMS	72.9		60 %	
Others	85.7 %		85.7	
Tumor size		P=0.17		P=0.116
<5cm	100%	HR: 3.50, 95% CI: 0.579 to 21.210	100%	HR: 3.46, 95% CI: 0.74 to 16.23
≥5cm	79.6%		74.5%	
Histologic grade				
G I	100%	P=0.0797	100%	0.016
G II	92.5%		89.7%	
G III	60.8%		55.5%	
Disease stage				
Stage I	100 %		100 %	
Stage IIa	100 %	P=0.0236	100 %	P=0.011
Stage Iib	91 %		87.8 %	
Stage III	54.3%		49.3%	
Radiotherapy given		P=0.83		P=0.64
Preoperative RT	88.2%	HR: 0.743, 95% CI: 0.165 to 3.345	86.5%	HR: 0.74, 95% CI: 0.21 to 2.61
Postoperative RT	80.4%		75.8%	

G: grade; RT: radiotherapy

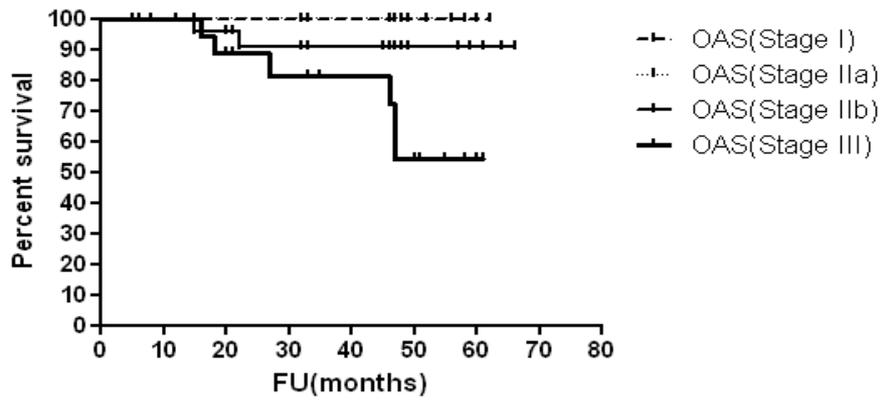


Figure 1. Overall survival curves for patients according to disease stage

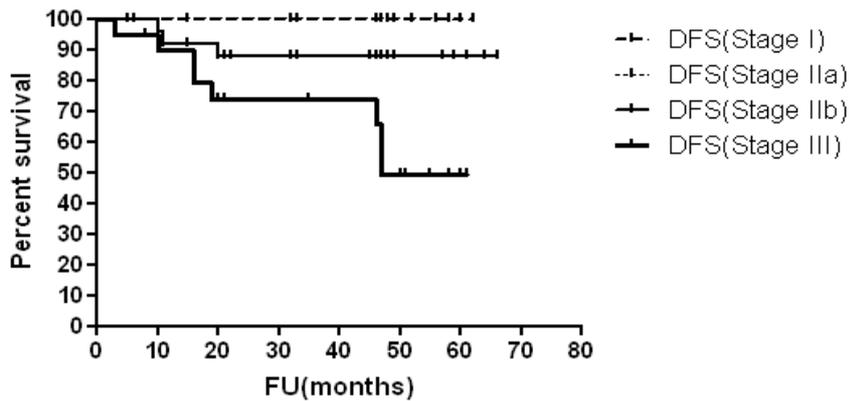


Figure 2. Disease free survival curves for patients according to disease stage

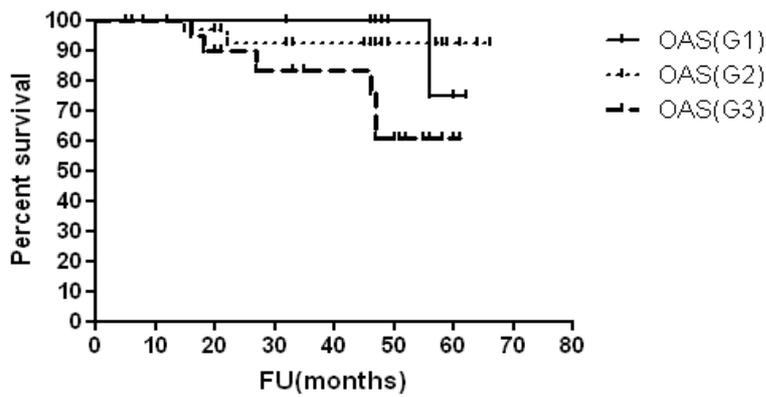


Figure 3. Overall survival curves for patients according to histologic grade

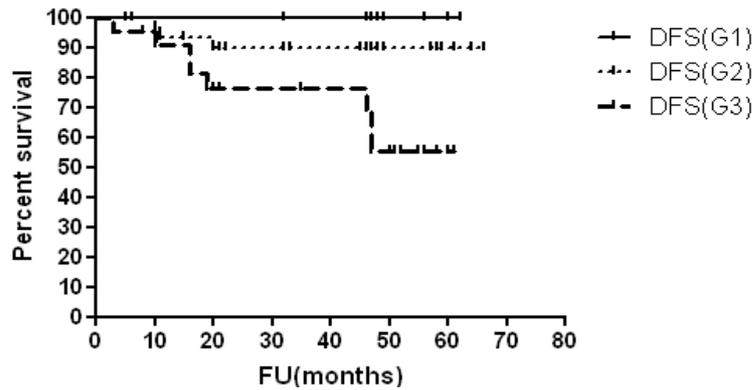


Figure 4. Disease free survival curves for patients according to histologic grade

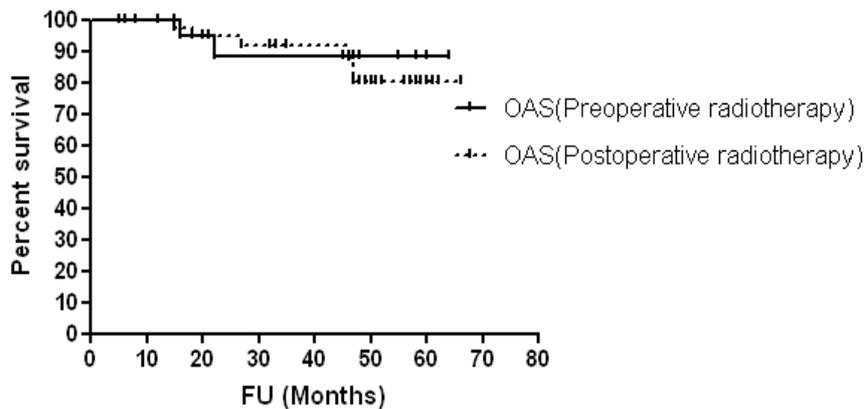


Figure 5. Overall survival curves for patients according to timing of radiotherapy

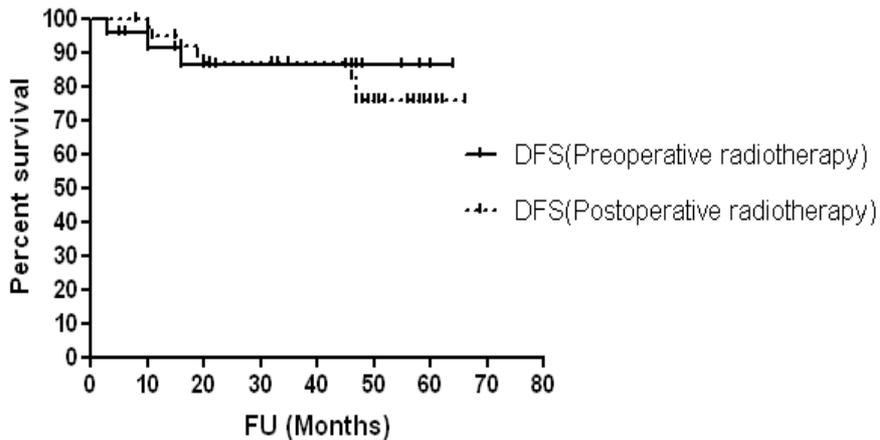


Figure 6. Disease free survival curves for patients according to timing of radiotherapy

3.3 Disease Relapses

The current study showed that disease relapse was found in 8 patients (12.7%). In the postoperative radiotherapy patients, there were 2 patients developed isolated LR, [underwent surgical excision] and 4 patients developed lung metastases [i.e. Six patients with disease relapses; 15.5%]. In the preoperative RT group, only 2 patients (8%) developed lung metastases. Patients with distant metastases (n=6), in both RT groups, were treated by salvage ifosfamide based chemotherapy. Although, disease relapse rate in the postoperative RT group was higher than that in preoperative group, there was no statistically significant difference (p=0.41) (Table 3).

Table 3. Disease relapses in soft tissue sarcoma patients who were given preoperative and postoperative radiotherapy

Variable	Preoperative radiotherapy	Postoperative radiotherapy	Total	P value
	NO (%)	NO (%)	NO (%)	
Disease relapse				
Yes	2 (8.3%)	6 (15.4%)	8(12.7%)	0.41
No	22 (91.7%)	33 (84.6%)	55(87.3%)	
Total	24	39	63(100%)	

3.4 Wound Complication Rate

Complications were defined as surgical interventions for wound repair with hospital admission for wound care. Acute wound complications were more frequent in preoperative RT patients (6 patients; 25%) compared to postoperative RT patients (3 patients; 8%) ($P = 0.0566$, chi-square) (Table 4).

Table 4. Wound complication rate in soft tissue sarcoma patients who were given preoperative and postoperative radiotherapy

Variable	Preoperative radiotherapy	Postoperative radiotherapy	Total	P value
	NO (%)	NO (%)	NO (%)	
Wound complications				
Yes	6 (25%)	3 (7.7%)	9(14.3%)	0.0566
No	18 (75%)	36 (92.3%)	54(85.7%)	
Total	24	39	63(100%)	

4. Discussion

Between 2006 and 2012, 63 patients with STS were treated at our institute, with median age of 40 years and male to female ratio of 1.9: 1. Most of the reported series showed that median age ranged between 44.5 (Kiatisevi et al., 2006), 59 years (Sternheim et al., 2011), with male predominance (van Geel et al., 2003). The most common pathological type was MFH (18 patients; 28.6%), and site was lower extremities (20 patients; 32%). In the reported series, although soft-tissue sarcomas can arise anywhere in the body, the lower extremities were the most common sites (Shmookler et al., 2001). The most common pathological type was the malignant fibrous histiocytoma (Mankin & Hornicek, 2005). The majority of our patients had grade II (32 patients; 51%), tumor >5cm (53 patients; 84%), and stage II diseases (34 patients; 54%). The reported studies showed that the most common disease grade was grade II (Van Geel et al., 2003), and tumor size was >5cm (Van Geel et al., 2003; Kiatisevi et al., 2006). A study conducted by Suit et al. (1985), showed that the most common disease stage was stage III. Regarding sequence of surgery and radiation therapy, the majority of our patients were treated by postoperative radiotherapy (62%), whereas preoperative radiotherapy was given in only 38% of patients. This is in agreement with O'Sullivan et al. (2002) where the majority of patients (55%) were treated with postoperative radiotherapy.

The present study showed that, with a median follow up of 47 months (range; 5-66 months), 4-year OAS and DFS rates were 82.6% and 78.8% respectively. This is comparable to reported survival rates as the 5-year survival rate was 74%±4% and the 10-year survival was 66%±5% (Sternheim et al., 2011).

The staging system devised by AJCC and UICC combines the most important determinants of survival in localized soft-tissue sarcomas: tumor grade, and size (Clark et al., 2005). In a univariate analysis of prognostic factors that might affect survival of patients with STS, the present study showed a trend of OAS advantage ($p=0.0797$) and significant DFS advantage ($p = 0.016$) in patients with grade I&II diseases when compared to patients with high grade disease. Regarding disease stage, the present study showed significant OAS ($p=0.024$) and DFS ($p=0.011$) advantages in patients with early disease stages when compared to patients with stage III disease. This is in agreement with reported series where high histological grade (Ramanathan et al., 1999;

Stojadinovic et al., 2002; Atalar et al., 2007) and advanced disease stage (Clark et al., 2005) were adverse prognostic factors for survival.

On the other hand, the present study showed no significant survival advantages according to patients' age and gender, histopathological type, and tumor size. Many trials have not been able to identify patients' age (Coindre et al., 1996; Cany et al., 1999), histologic type of sarcomas (Dahlberg et al., 1993; Yang et al., 1998), and tumor size (Atalar et al., 2007) as predictors of survival.

The current study showed that disease relapse was found in 8 patients (12.7%). This is confirmed by reported studies where disease relapse ranged between 9% (Prendergast et al., 2010) and 30.7% (Atalar et al., 2007).

The use of preoperative radiation has been popularized by Suit and co workers (Spiro & Suit, 1998). High rates (90 – 92%) of 10-year local control following preoperative radiation, have been reported (Brant et al., 1990). However, preparative radiation did not produce significant local control benefit when compared to postoperative radiation in the present study ($p = 0.41$) and in the reported study by investigators at the University of Minnesota (Cheng et al., 1996). Moreover, preparative radiation was associated with a significantly higher complication rate in the current study (25% versus 8%, $p = 0.0566$) and in the reported study ($p = 0.0014$) (Fuller, 2001). This is confirmed by other two studies (Cheng et al., 1996; O'Sullivan et al., 2002). The high rate of wound complication in the preoperative RT patients in the present study (25%) is comparable with complication rates (10% to 41%) found by reported studies (Eilber et al., 1995; O'Sullivan et al., 1999).

In the current study, preparative radiation did not produce significant OAS (88% versus 86%, $p=0.83$, HR: 0.743, 95% CI: 0.165 to 3.345) and DFS (80% versus 76%, $p = 0.64$, HR: 0.74, 95% CI: 0.21 to 2.61) advantages when compared to postoperative radiation. This is matched with reported studies which have revealed no significant difference in disease-free survival (Fuller, 2001), and in the overall survival ($75 \pm 15\%$ versus $79 \pm 11\%$, $p = 0.94$) (Cheng et al., 1996) between patients receiving RT preoperatively versus postoperatively.

5. Conclusion

In our retrospective study, high histological grade and advanced disease stage are found to be adverse prognostic factors for survival in patients with STS. The present study does not indicate that preoperative radiotherapy has a positive impact on survival or disease relapse rates. Moreover, it is associated with higher wound complication rates than postoperative irradiation. Prospective studies are recommended to identify subset of patients who may get benefit from preoperative irradiation.

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