

Research Article

Neoadjuvant Radiotherapy Is Associated with Fewer Acute Adverse Skin Reactions Without Increased Risk of Postoperative Wound Complications in High-Grade Extremity Soft Tissue Sarcoma - A Retrospective Comparative Study with A Mean Follow-Up of 7 Years

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Abstract

Aim: In this study, we aim to compare the adverse effects and oncological outcomes of patients with high-grade extremity soft tissue sarcoma receiving neoadjuvant or adjuvant RT.

Methods: From 2008 to 2022, Sixty-four patients underwent limb-preserving surgery in our institute for localized high-grade extremity soft tissue sarcoma were included. Thirty-nine patients received adjuvant radiotherapy while twenty-five patients received neoadjuvant RT before surgery if the soft tissue sarcomas were close to the neurovascular bundles, bones or histological types of myxoid liposarcoma or rhabdomyosarcoma. Primary outcomes were acute RT-related skin adverse reactions and significant side effects comprising postoperative wound complications, pathological fractures and RT-induced sarcoma. Secondary outcomes included surgical margin quality, Local-Recurrence (LR)-free survival, metastasis-free survival and overall survivorship.

Results and Discussion: Patients in the neoadjuvant RT group had significantly fewer acute RT-induced adverse skin reactions than the adjuvant RT group ($p=0.044$, Table 2). None in the neoadjuvant RT group suffered severe acute skin reaction (RTOG grade 3-4). Wound infection ($n=2$) and pathological fracture ($n=1$) were rare in both adjuvant and neoadjuvant RT groups ($P=0.640$ & 1.000 respectively). Survival curves for local-recurrence-free survival, metastasis-free survival and overall survivorship of both neoadjuvant and adjuvant groups were analyzed via Kaplan-Meier Curve. All results are statistically insignificant, with $p=0.835$, 0.948 and 0.540 , respectively. Presence of metastasis was the only statistically significant predictor of the overall survival-adjusted hazard ratio of 8.7 (95%CI $2.7-28$), $p<0.001$.

Conclusion: Patients with neoadjuvant RT had lower cumulative radiation doses and fewer acute adverse skin reactions. There was no increased risk of postoperative wound complication compared to adjuvant RT. The LR-free survival, metastasis-free survival and overall survival were comparable in both groups. Our results suggested that postponing surgery to eight weeks after neoadjuvant RT and primary wound closure were associated with fewer wound complications, but further studies were warranted.

Keywords: Tumours; Sarcoma; Wound Complications; Radiotherapy

Introduction

Soft Tissue Sarcomas (STS) contain a heterogeneous group of tumours of mesenchymal origin, which are rare accounting for less than 1% of all solid tumor in adult. Most STS have no identifiable etiology. STS commonly presents as an asymptomatic, painless

mass that are progressively increase in size¹. STS most commonly occur in extremities and metastasize to the lung via hematogenous spread. Local and systemic imaging, together with ultrasound guided tissue biopsy are essential to establish the diagnosis. It is recommended STS should be referred to sarcoma center and managed by multidisciplinary team [1].

The overall aim of treatment of patient with STS is to achieve local control of the tumor with no distant metastasis and good overall long-term survival. Wide local resection and radiation therapy (RT) form the standard of treatment for high-grade STS [2]. There is controversy on the neoadjuvant (preoperative) versus adjuvant (postoperative) radiotherapy in high-grade STS. The neoadjuvant RT is given at a lower dose (50Gy) and to a smaller-sized field, compared to adjuvant RT (66Gy) [3]. However, neoadjuvant RT is not routinely used in soft tissue sarcoma of extremities as postoperative wound complication remains a concern that may require multiple or flap surgeries [4].

The time interval between the neoadjuvant RT and surgical resection is of great importance in management of STS. Early sarcoma resection at three to six weeks following neoadjuvant RT is suggested to avoid wound complication and tumor progression [5]. In this study, we aim to compare the adverse effects and oncological outcomes of patients with high-grade extremity soft tissue sarcoma receiving neoadjuvant or adjuvant RT. Primary outcomes were acute RT-related skin adverse reactions and significant side effects comprising postoperative wound complications, pathological fractures and RT-induced sarcoma. Secondary outcomes included surgical margin quality, Local-Recurrence (LR)-free survival, metastasis-free survival and overall survivorship.

Methodology

The study was performed in accordance with the ethical standards of our institute's Clinical Research Ethics Committee (reference no. 2023.213). This is a retrospective comparative study for patients received either neoadjuvant or adjuvant RT, with dosage of 50Gy and 66 Gy respectively. All patients received external beam RT and none received brachytherapy. From May 2008 to May 2022, sixty-four patients underwent limb-preserving surgery in our institute for localized high-grade extremity soft tissue sarcoma were included (Fig. 1). The diagnosis was confirmed histologically by ultrasound-guided biopsy. Thirty-nine patients received postoperative radiotherapy. Since 2015, twenty-five patients received neoadjuvant RT before surgery if the soft tissue sarcomas were close to the neurovascular bundles (Fig. 2), bones or histological types of myxoid liposarcoma or rhabdomyosarcoma. Patients with less than six months of Follow-Ups (FU), underwent amputation or received incomplete RT were excluded. Primary outcomes were acute RT-related skin adverse reactions and significant side effects comprising postoperative wound complications, pathological fractures and RT-induced sarcoma. The acute RT-related skin adverse reaction was referred to the acute toxic effects occurred on the skin after RT which were assessed by the scoring criteria of Radiation Therapy Oncology Group (RTOG) and the European Organization for Research [6].

In the study, RTOG grade 0-1 were classified as mild, RTOG grade 2 as moderate and RTOG grade 3-4 as severe. Secondary outcomes included surgical margin quality, Local-Recurrence (LR)-free survival, metastasis-free survival and overall survivorship. The surgical margin quality was divided into R0, R1 and R2 resection. R0 resection indicated a complete tumor resection. R1 referred to positive resection margin microscopically and R2 revealed macroscopic residual tumor. Statistical analysis was performed using SPSS version 27. The cumulative RT dose and the time from RT completion to operation were expressed as median and interquartile range. The patient age, as well as follow-up times, tumor size and volume were depicted as mean and standard deviation with the minimum and maximum.

The data of neoadjuvant and adjuvant group were compared by Mann-Whitney U test and t-test. Kaplan-Meier method was used to calculate the survival curves for local-recurrence-free (LR-free) survival, metastasis-free survival and overall survivorship. Multivariable analysis using cox proportional hazard model were used to determine the relationship between LR-free survival and neoadjuvant vs adjuvant RT, adjusting for age, gender, tumor size, pathology, tumor location, surgical margin quality and type of RT.

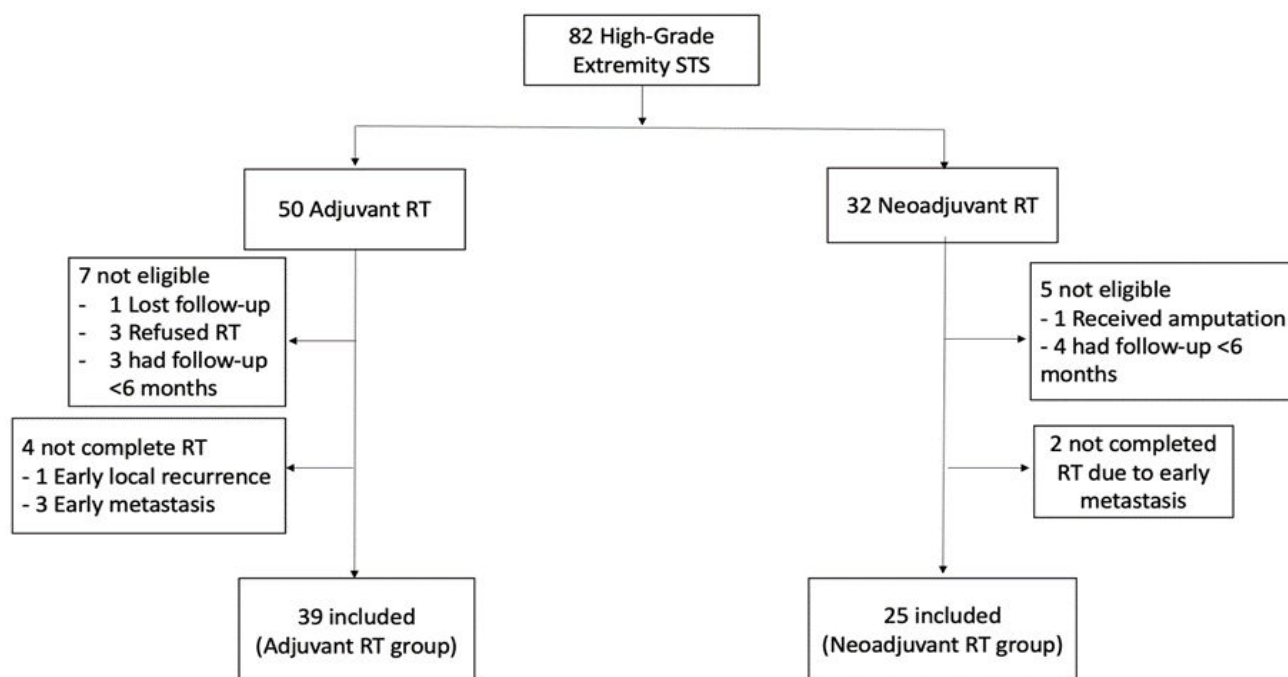


Figure 1: 64 patients were included for assessment and data analysis in the study.

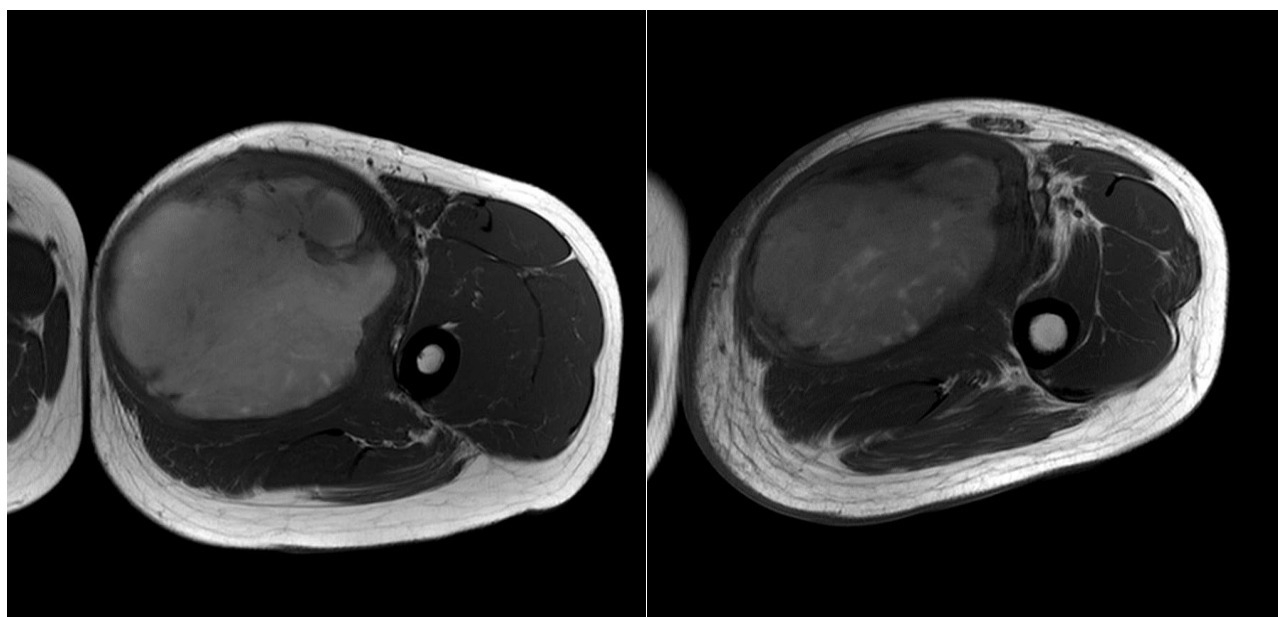


Figure 2: (Left): A large soft tissue tumor located in the adductor compartment of left medial thigh, which is close to the superficial femoral artery and deep femoral artery; (Right): There was reduction in size of the soft tissue tumor after neoadjuvant RT, which facilitate subsequent surgical resection.

Results

The patient and tumor characteristics of neoadjuvant RT group and adjuvant RT group were listed in Table 1. Patients in the neoadjuvant RT group received significantly fewer cumulative radiation doses than those in the adjuvant RT group (50Gy vs. 66 Gy, $p < 0.001$). The average tumor length and volume were also larger in the neoadjuvant RT group ($P < 0.05$). The mean follow-up time for all patients was 85 months (7.1 years). Patients in the adjuvant RT group had a significantly longer follow-up duration ($P < 0.001$). Patients underwent surgery at a median of 8.3 weeks following neoadjuvant RT (Table 2). The tumor response to neoadjuvant RT was assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines [7]. 80% of patients in the neoadjuvant RT group were classified into either Partial Response (PR) or Stable Disease (SD) according to RECIST guideline

while only 20% were found to have Progressive Disease (PD) in our study. All wounds could be closed primarily. Skin graft and flap surgery were not required.

Patients in the neoadjuvant RT group had significantly fewer acute RT-induced adverse skin reactions than the adjuvant RT group ($p=0.044$, Table 3). None in the neoadjuvant RT group suffered from severe acute skin reaction (RTOG grade 3 or 4), but 18% of patients in adjuvant RT group had. Wound infection ($n=2$) and pathological fracture ($n=1$) were rare in both adjuvant and neoadjuvant RT groups, with insignificant p -value of 0.640 and 1.000 respectively. No patient suffered from RT-induced sarcoma in both adjuvant and neoadjuvant RT groups in the study. Neoadjuvant RT could improve the surgical margin by consolidating the tumor, but the difference was insignificant in the study ($p=0.363$). Complete tumor removal (R0 Resection) was achieved in 84% patients in neoadjuvant RT group, compared to 74% in adjuvant RT group.

Survival curves (Fig. 3) for local-recurrence-free survival, metastasis-free survival and overall survivorship of both neoadjuvant and adjuvant RT groups were analyzed via Kaplan-Meier Curve. All results are statistically insignificant, with $p=0.835$, 0.948 and 0.540, respectively.

Multivariable analysis using Cox proportional hazards model was performed for LR risk (Table 4), adjusting for types of RT, age, gender, tumor volume and length, tumor pathology, location (upper limb vs lower limb) and surgical margin quality. None was found to be statistically significant with $p>0.05$. Subgroup analysis in the neoadjuvant RT group did not reveal a significant association between LR-free survival and time from the neoadjuvant RT completion to surgery ($p=0.817$) and response to RT ($p=0.964$).

Multivariable analysis using Cox proportional hazards model was also performed for overall survival (Table 5), including types of RT, patient age, gender, tumor length and volume, tumor pathology, location (upper limb vs lower limb), surgical margin quality, presence of local recurrence and metastasis. Presence of distant metastasis was the only statistically significant predictor of the overall survival –adjusted hazard ratio of 8.7 (95%CI 2.667-28.571), $p<0.001$.

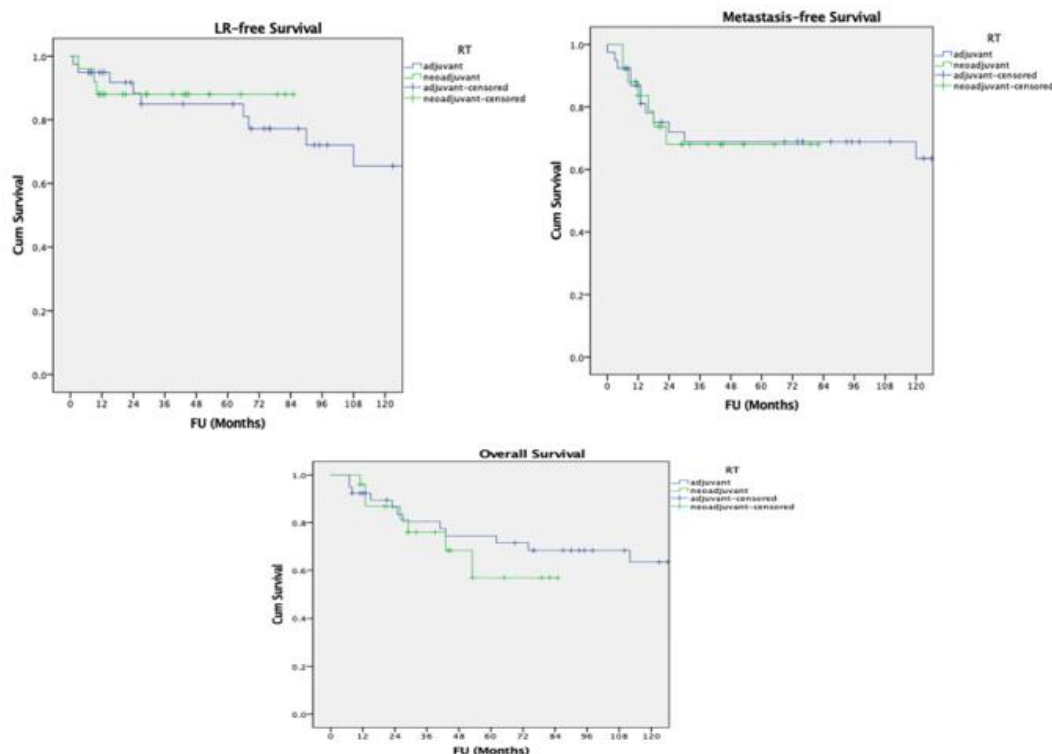


Figure 3: (Left): Kaplan-Meier Curve for local-recurrence-free survival with $p=0.835$; (Right): Kaplan-Meier Curve for metastasis-free survival with $p=0.948$; (Centre): Kaplan-Meier Curve for overall survival with $p=0.540$.

Total Patient (n=64)	Adjuvant (n=39)		Neoadjuvant (n=25)		
Gender					P=0.087
• Male	18	46%	17	68%	
• Female	21	54%	8	32%	
Age (mean +/- SD) Years	60.2 +/- 11.8		53.1 +/- 13.7		P= 0.033
Location					P= 0.537
• Upper Limb	10	26%	4	16%	
• Lower Limb	29	74%	21	84%	
Subtypes					P= 0.142
• Undifferentiated Pleomorphic Sarcoma	24	62%	8	32%	
• Liposarcoma	4	10%	5	20%	
• Synovial Sarcoma	3	8%	4	16%	
• Others	8	20%	8	32%	
Cumulative RT Dose (Gy)					P< 0.001
- Median	66		50		
- Interquartile Range	6		0		
Size	8.5501 +/- 4.46		13.46 +/- 6.42		P= 0.036
- Tumor Length (cm) (mean +/- SD)	(1.5-21)		(6-32)		
- Mean Tumor Volume +/- SD (cm ³) (Mean +/- SD)	450 (2-2520)		1580 (54-10944)		P= 0.001
FU Period: Mean +/-SD (Range)	111 +/- 50 Months		44 +/- 23 Months		P< 0.001
- 85 +/- 53 (8-178) Months	(8-178)		(11-88)		
Neoadjuvant Chemotherapy			16/25 (64%)		

Table 1: Patient and tumor characteristics.

Time from RT Completion to Operation	Median: 8.3 Week Interquartile Range: 2.9 Week (6.0-8.9)
RECIST Response Criteria	- CR: Disappearance of all lesions with no new lesion
- Complete Response (CR)	- PR: greater than or equal to 30% decrease in the sum of greatest diameter with no new lesions
- Partial Response (PR)	- SD: does not meet criteria for CR, PR or PD
- Stable Disease (SD)	- PD: greater than or equal to 20% increase in the sum of the greatest diameter or the presence of a new lesion
- Progressive Disease (PD)	
Tumor Response to Neoadjuvant RT by RECIST Response Criteria	- CR 0%
	- PR 44% (11/25)
	- SD 36% (9/25)
	- PD 20% (5/25)
Neoadjuvant Chemotherapy + RT	- 64% (16/25)

Table 2: Neoadjuvant RT group.

Total Patient (n=64)	Adjuvant (n=39)		Neoadjuvant (n=25)		
Acute RT-Induced Adverse Skin Reaction	Mild	24 (61%)	Mild	21 (84%)	P=0.044
RTOG Toxicity Grading	Mod.	8 (21%)	Mod.	4 (16%)	
- Mild: Grade 0-1	Severe	7(18%)	Severe	0	
- Moderate: Grade 2					
- Severe: Grade 3-4					

(RTOG-Radiation Therapy Oncology Group)					
Significant Adverse Effects					
- Wound Infection	2	5%	2	8%	P=0.640
- Pathological Fracture	1	2.5%	1	4%	P=1.000
- RT-Induced Sarcoma	0	0%	0	0%	P=1.000
Surgical Margin	R0	29 (74%)	R0	21 (84%)	P =0.363
	R1	10 (26%)	R1	4 (16%)	
	R2	0	R2	0	

Table 3: Study outcomes.

	Hazard Ratio	95% CI	P-value
Radiotherapy			0.228
- Neoadjuvant	1.000		
- Adjuvant	2.849	0.519-15.625	
Age	0.978	0.914-1.047	0.527
Gender			0.483
- Female	1.000		
- Male	1.647	0.408-6.667	
Tumor Volume	0.998	0.995-1.002	0.348
Tumor Length	1.102	0.760-1.598	0.607
Pathology			
- MFH/UPS	1.000		0.999
- SS	N/A*	N/A*	
- LPS	2.137	0.314-5.152	0.736
- Others	N/A*	N/A*	0.999
Location			0.694
- Lower Limb	1.000		
- Upper Limb	1.404	0.259-7.634	
Margin			0.066
- R0	1.000		
- R1	3.247	0.927-11.364	
- *Small sample size			

Table 4: Result of Cox regression analysis on Local Recurrence (LR).

	Hazard Ratio	95% CI	P-value
Radiotherapy			0.525
- Adjuvant	1.000		
- Neoadjuvant	1.707	0.328-8.898	
Age	1.009	0.953-1.068	0.761
Gender			0.294
- Male	1.000		
- Female	1.783	0.606-5.242	
Tumor Volume	1.000	0.999-1.001	0.989
Tumor Length	1.126	0.945-1.341	0.184
Pathology			
- MFH/UPS	1.000		0.272
- SS	0.287	0.031-2.661	
- LPS	0.756	0.197-2.904	0.683

- Others	0.398	0.0334-4.657	0.463
Location			0.814
- Lower Limb	1.000		
- Upper Limb	1.230	0.221-6.849	
Margin			0.919
- R0	1.000		
- R1	0.916	0.169-4.963	
Local Recurrence			0.929
- no	1.000		
- yes	1.057	0.308-3.627	
Distant Metastasis			0.000
- No	1.000		
- Yes	8.670	02.667-28.571	

Table 5: Result of Cox regression analysis on overall survival.

Discussion

Our study provides a new insight on the acute skin adverse reaction and wound complications of neoadjuvant RT in management of localized high-grade extremity STS. With a mean FU of 7 years, neoadjuvant RT is associated with fewer acute adverse skin reactions ($P=0.044$) without increased risk of postoperative wound complications in high-grade soft tissue sarcoma of the extremity. The LR risk, metastatic risk and overall survival were comparable in both the neoadjuvant RT and adjuvant RT group. A multicentered randomized trial also showed neoadjuvant RT is associated lower rate of late RT-induced morbidities, including subcutaneous fibrosis, joint stiffness and lymphedema, at 2 years after RT [8]. Therefore, neoadjuvant RT is considered as safe and effective treatment with less acute and late radiation morbidity compared to adjuvant RT.

Wide local resection and radiotherapy are the mainstay of management of high-grade soft tissue sarcoma. The addition of RT provides a local control benefit. A randomized prospective study of ninety-one patients with median FU of 9.6 years showed that adjuvant RT could effectively prevent LR in high grade STS in extremity [9]. A more recent publication with median FU of 17.9 years by the same institute showed that adjuvant RT could provide excellent local control with no statistically significant improvement in overall survival [10]. Nevertheless, RT was reported to have positive effect on overall survival in high grade STS in other literature. In a series of 6960 patients, RT was associated with improved overall survival in patients with high grade STS undergoing limb-sparing surgery. Moreover, neoadjuvant RT appeared equivalent to adjuvant RT in terms of survival outcomes in patients with large high-grade STS [11].

However, there is controversy on the timing of radiotherapy in radical treatment of STS of the extremities [3]. There are arguments favor the use of the neoadjuvant RT over adjuvant RT. Patients with neoadjuvant RT received lower cumulative doses of radiation (50 vs 60-66Gy) over a smaller field and volume. With neoadjuvant RT, it would be easier for oncologist to define the radiotherapy target volume due to the presence of the tumor. Neoadjuvant RT could also consolidate the tumor and reduce the tumor burden, which could facilitate the resection by orthopedic surgeons and potentially allow a more conservative surgery.

However, there are reservation on the use of neoadjuvant RT. The major concern of neoadjuvant RT is acute wound complications. A randomized controlled trial of 190 patients performed by O'Sullivan et al showed the number of severe wound complication was related to timing of external beam RT [4]. With a mean FU of 3.3 years, acute wound complications were significantly higher in the neoadjuvant RT arm compared to adjuvant RT group (35 vs 17%, $p=0.01$).

Neoadjuvant RT could consolidate the tumor and facilitate tumor resection with negative margins. However, contrary to the literature reported by O'Sullivan, et al., acute wound complication was uncommon in the neoadjuvant RT group in our series [4]. Wound complication rates were only 8% and 5% in neoadjuvant RT and adjuvant RT group respectively ($p=0.640$). The time from the neoadjuvant RT to surgery might play an important role in the low wound complication rate. Griffin et al. suggested four-to-five-week intervals between neoadjuvant RT and surgical resection could be an optimal interval to reduce the potential

wound complication in patients with STS of extremity. However, in our study, surgery was performed at a median time of eight weeks after neoadjuvant RT instead of traditionally within 4-5 weeks. Moreover, all wounds in our series could be closed primarily.

Clinical Implication

Neoadjuvant RT would be considered in selected case of high-grade STS of the extremity in our institute. Since 2015, twenty-five patients received neoadjuvant RT before surgery if the soft tissue sarcomas were close to the neurovascular bundles, bones or histological types of myxoid liposarcoma or rhabdomyosarcoma. Our team considered the optimal time interval between neoadjuvant radiation and surgical resection is between eight to ten weeks. It is postulated that wound complications rate would be higher if the surgery was performed too early (<8 weeks) or flap surgery performed. If the surgery was performed too late (>10 week), surgical resection would be more difficult due to presence of excessive scarring and tumor progression.

The role of chemotherapy and the significance of concomitant chemotherapy added to neoadjuvant RT in soft tissue sarcoma remain unclear. In theory, combined neoadjuvant chemoradiotherapy could provide control of potential micro-metastasis and increase the local effect of RT through radio-sensitization. A 10-year retrospective study revealed neoadjuvant chemoradiotherapy and surgery resulted in high rates of survival with tolerable short- and long-term toxicity for patients with high grade extremity and truncal STS [12]. The retrospective study conducted by Kobus et al. also revealed similar findings [13]. Patients with localized high-grade STS underwent neoadjuvant radio chemotherapy had significantly lower local recurrence and distant metastasis risk, but at the expense of higher risk of acute toxicity including hematological toxicity, fatigue and wound complications. In our series, 60% (16/25) in neoadjuvant RT group received upfront chemotherapy as well. However, the patient number in this sub-group was too small and the results of it were out of scope of this study.

Limitation

The current study findings should be analyzed with the following limitations. Firstly, STS comprise a highly heterogenous group of malignant tumours of mesenchymal origin. This was a retrospective study conducted at a single institute, which was prone to selection and sampling bias. Secondly, the sample size of neoadjuvant RT group was relatively small (n=25), which account for 39% of the entire study. Furthermore, the mean follow-up time in neoadjuvant RT group was 44 months (3.7 years), which was significantly shorter than the adjuvant RT group (9.3 years).

Conclusion

Patients with neoadjuvant RT had lower cumulative radiation doses and fewer acute adverse skin reactions. There was no increased risk of postoperative wound complication compared to adjuvant RT. The LR-free survival and overall survival were comparable in both groups. Our results suggested that postponing surgery to eight weeks after neoadjuvant RT and primary wound closure were associated with fewer wound complications, but further studies were warranted.

Conflict of Interest

The authors have no conflict of interest to declare.

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