Postoperative Radiotherapy in the Treatment of Soft Tissue Sarcomas

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= Abstract =

Seventy four patients with soft tissue sarcomas treated by postoperative radiotherapy in the Department of Therapeutic Radiology, Seoul National University Hospital between August 1979 and September 1990 were analyzed. The follow-up period ranged from 3 to 145 months with a median of 51 months. Liposarcoma and malignant fibrous histiocytoma(MFH) constituted 54% of the cases and the histologic grades of tumors are as follows: grade I, 23 cases; grade II, 17 cases; grade III, 24 cases; unknown grade, 10 cases. The patients were treated by marginal(17 cases), wide(55 cases) or compartmental(2 cases) excision followed by postoperative radiotherapy. The total radiation doses were 4200-8820 cGy(median 6000 cGy), 180-200 cGy daily, 5 times per week.

Of 74 patients, 35 ultimately failed. The local control was 62.2% at 5 years and cumulative risk of distant metastasis was 22.3% at 5 years. The overall survival and disease free survival were 72.3% and 53.3% at 5 years, respectively. Survival after appearance of metastasis was 15.1% at 3 years.

Patients with liposarcoma experienced better local control than those with other histologic type and tumor grade and surgical resection margin significantly correlated with local recurrence, distant metastasis and overall survival on univariate analysis.

In conclusion, re-excision is needed for patients with positive surgical resection margin to improve local control and further therapeutic measures using effective chemotherapy should be explored in the hope of improving overall survival.

Key Words : Soft tissue sarcoma, Postoperative radiotherapy, Local control, Survival

INTRODUCTION

Soft tissue sarcomas are uncommon cancers that represent only 1% of all malignant neoplasms(excluding skin) in adults and arise from mesenchymal structures at any site in the body, even within visceral stroma and neurovascular bundles[1]. They are characterized by diversity, not only in histologic appearance but also in biologic behavior depending on grade and the putative cell of origin but can be considered as a single entity in evaluating proper therapy[2]. They usually spread via direct invasion into surrounding soft tissues or hematogenous seeding to the lung. The degree of

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differentiation(histologic grade) is known as the major prognostic factor[3].

The standard treatment of soft tissue sarcoma was radical excision of the involved area. For extremity lesions, this often required amputation. Despite this vigorous surgical approach, local recurrence rates are still high, varying from 20% to 80% depending on the extent of the surgery, and the survival is poor[4].

Since the first report of National Cancer Institute's(NCI) randomized prospective study[5,6] comparing amputation with limb-sparing surgery and postoperative radiotherapy for soft tissue sarcomas of the extremities was published, radiotherpy has established a role in the multidisciplinary management of soft tissue sarcoma. This combined approach can achieve local control rate comparable to radical surgery while offering the benefit of functional limb preservation[7]. However, the magnititude of the surgical procedure, the dose and volume of radiotherapy and related various surgical and pathological factors have been difficult to define clearly in the multidisciplinary management of these tumors.

Thus we have retrospectively reviewed our cases to evaluate treatment result of postoperative radiotherpy and to analyze various clinical, surgical and pathological factors that affect prognosis.

MATERIALS AND METHODS

Clinical records of 74 consecutive patients with stage M0 soft tissue sarcoma treated by surgery and postoperative radiotherapy in Seoul National University Hospital between August 1979 and September 1990 were analyzed. Exclusions from this analysis are patients with Kaposi's sarcoma, rhabdomyosarcoma, Ewing's sarcoma and patients whose radiation dose was less than 4000 cGy. The age of patients ranged from 20 to 67 years with a median of 49 years. Sex distribution was equal-37 men to 37 women. Follow-up period from the day of operation was from 3 to 145 months with a median of 51 months.

The distribution by histology, grade, size is shown in Table 1 and 2. The most commom histology was liposarcoma(22 cases) followed by malignant fibrous histiocytoma(18 cases), the sum of these two representing 54% of the total. Five cases could not be specified histologically and were designated as 'unclassified'. Tumors were retrospectively re-graded on the basis of differentiation, number of mitosis(per 10 HPF), and necrosis(Coindre's classification[8]) and scored as grade I, II, or III(grade I, 23 cases; grade II, 17 cases; grade III, 24 cases). Ten cases were classified as 'unknown grade' due to unavailability of histologic slides. While 68%(15/22) of liposarcoma belonged to grade I, 50%(9/18) of MFH belonged to grade III.

Table 3 shows the distribution by anatomic site and stage. Forty one tumors arose in ex-

Table 1. Histologic Type and Grade

Type	Grade				
	I	II	III	Unknown	Total
Liposarcoma	15	4	2	1	22
MFH	1	3	9	5	18
Mal. schwannoma	2	4	1	1	8
Synovial sarcoma	1	3	2	2	8
Leiomyosarcoma	0	3	4	0	7
Angiosarcoma	1	0	3	0	4
Epithelioid sarcoma	0	0	1	0	1
Fibrosarcoma	0	0	0	1	1
Unclassified	3	0	2	0	5
Total	23	17	24	10	74

Table 2. Tumor Size and Grade

Grade	Maximum diameter(D ; cm)			
	D≤5	5<D≤10	D>10	Total
I	4	8	11	23
II	2	11	4	17
III	7	11	6	24
Unknown	4	5	1	10
Total	17	35	22	74

tremity(8 in upper extremity, 33 in lower extremity, especially in thigh), 26 in the trunk(15 in the retroperitoneum), and 7 in head and neck. Patients could be retrospectively re-staged according to the American Joint Committee on Cancer(AJCC) system[9]. This system uses histologic grade as the major parameter with tumor size considered secondarily. The stage of our cases were: stage I, 22 cases; stage II, 16 cases; stage III, 20 cases; stage IVA, 6 cases. Ten cases could not be staged beacuse of 'unknown grade'.

The patients were treated by marginal (17cases), wide(55 cases) or compartmental(2 cases) excision(Table 4) and all of the patients received external beam postoperative radiotherapy using ^{60}Co teletherapy unit or LINAC(6X, 10X, electron). Daily treatment was given at 180 to 200 cGy per fraction to a dose of 4500 to 5000 cGy. Boost dose was delivered to the tumor bed through reduced field. Total radiation doses were 4200-8820 cGy with a median of 6000 cGy. Wedge and bolus were used when applicable. The radiation fields were designed to cover the entire surgical bed. Treatment of the entire circumference of the extremity was avoided to prevent the development of lymphedema. Eleven patients received chemotherapy of adriamycin containing regimens, as a part of their care at the discretion of their physicians.

Local control, cumulative risk of distant metastasis, disease free survival, and overall survival were calculated on an actuarial basis(life table method[10]) from the date of surgery until local recurrence, distant metastasis, or death, respectively. Clinical, surgical and pathological factors were analyzed univariately to determine their effect on local control, freedom from distant metastasis, and survival. Comparison of results was performed using the Logrank test[11].

Table 3. Site and Stage

Site	AJCC Stage					
	I	II	III	IVA	Unknown	Total
Head & neck	1	0	2	4	0	7
Trunk	7	9	6	1	3	26
Upper extremity	4	0	2	0	2	8
Lower extremity	10	7	10	1	5	33
Total	22	16	20	6	10	74

Table 4. Type of Combined Treatment Modalities

Type	No(%)
Marginal exision	13(18)
Marginal excision+chemotherapy	4(5)
Wide excision	48(65)
Wide excision+chemotherapy	7(9)
Compartmental excision	2(3)

RESULTS

Twenty seven patients(36%) experienced local recurrences. The local contol rate for all patients was 62.2% at 5 years and 60.0% at 8 years. Distant metastasis developed in 17 patients(23%) and the cumulative risk of distant metastasis was 22.3% at 5 years. The overall survival rate was 72.3% at 5 years and 58.5% at 8 years. The disease free survival rate was 53.3% at 5 years and 48.3% at 8 years(Fig. 1). Survival after appearance of distant metastasis was 15.1% at 3 years.

Among 74 patients, 35(47 %) ultimately

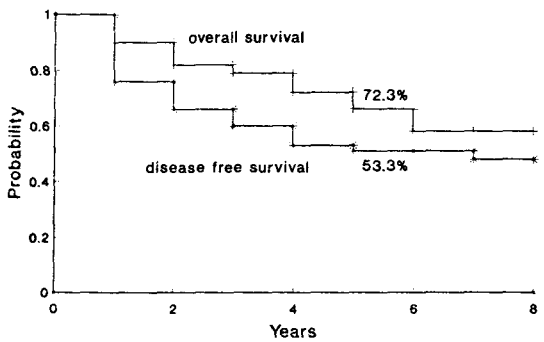

Fig. 1. Survival in 74 patients with soft tissue sarcoma.

Table 5. Prognostic Factors Affecting Local Control

Factors	No	5 year local control(%)	P
Case			
primary	41	72.0	
recurrent	33	50.7	0.1712
Site			
head & neck, trunk	33	58.1	
extremity	41	65.6	0.3346
Size(cm)			
D≤5	17	50.4	
D>5	57	66.2	0.3291
Grade			
I	23	86.8	
II	17	59.6	0.0175
III	24	42.1	
Histology			
liposa	22	81.0	
MFH	18	41.9	
mal schwannoma	8	35.7	0.0244
synovial sa	8	50.0	
Operation			
marginal	17	62.3	
wide	55	61.1	0.7182
compartmental	2	100	
Resection margin			
positive	17	44.1	
close(≤2cm)	5	40.0	0.0271
negative	52	71.0	
Lymph node			
negative	68	60.9	
positive	6	77.8	0.2992
Chemotherapy			
yes	11	54.5	
no	63	63.5	0.6715
Interval(wks)*			
≤6	53	62.2	
>6	21	62.1	0.9674
Dose(cGy)			
<6000	35	64.9	
≥6000	39	59.8	0.6295

*interval between surgery and radiotherapy

failed. Local recurrences were documented as the first evidence of recurrence in 27 patients. Of those, 23 had a local failure only and the remaining 4 patients had a concurrent distant metastasis, too. Though regional lymph node involvement was found in 6 patients at presentation, lymph node failure occurred only in two cases. One was an isolated nodal failure (leiomyosarcoma) and the other was combined with primary site failure(MFH). Distant metastasis occurred as the first site of failure in 12 patients(8 as the only failure, 4 with local recurrence) and 5 additional patients developed such metastasis after local or nodal relapse. The most common sites for distant metastasis include the lung(59%), bone(18%), and liver(12 %).

Case(primary, recurrent), site of tumor, size of tumor, tumor grade, histologic type, type of operation, surgical resection margin, initial lymph node involvement, use of chemotherapy, interval between surgery and radiotherapy, radiation dose were analyzed to determine their effect on local control, freedom from distant metastasis and survival. Because regional lymph node involvement was observed in only two patients, the factor was not included in the analysis.

The tumor grade correlated well with local disease recurrence. The 5 year local control was 86.8% for grade I, 59.6% for grade II, 42.1% for grade III(p=0.0175). Local control also was predicted by histologic type. Of the 22 patients with liposarcoma, 17 patients experienced local control(81.0% at 5 years), whereas 5 year local control was only 41.9% for patients with MFH, 35.7% for malignant schwannoma, 50.0% for synovial sarcoma(p= 0.0244). The status of surgical margin also had a significant effect on local recurrence. Five year local control was 71.0% for patients with negative margin, whereas local control was 40.0% for patients with close margin and 44.1% for patients with positive margin(p = 0.0271). None of the other variables analyzed achieved statistical significance with an endpoint of local control(Table 5). Especially it is not possible to relate the radiation dose de-

livered to local control. But in subgroup analysis, among the 52 patients who had a negative resection margin, fourteen patients(14/46, 30%) who received less than 6500 cGy failed locally versus none (0/6) who received 6500 cGy or more(p=0.1680)(Table 6).

Tumor grade and surgical margin also significantly correlated with distant metastasis. Five year distant metastasis free rate was 95.7% of lesions with grade I, 86.7% of lesions with grade II, 54.8% of lesions with grade III (p=0.0043) and was 86.5% for patients with negative margin as compared to 60.0% for patients with close margin, 55.1% for patients with positive margin(p=0.0331). Recurrent cases also have a trend toward a higher incidence of metastasis(p=0.0255). No other variable was found to significantly correlate with distant metastasis(Table 7).

Tumor grade and surgical margin affected overall survival significantly. 5 year survival was 95.7% for patients with grade I, 73.0% for those with grade II, and 53.7% for those with grade III(p=0.0015). For patients with positive, close, and negative surgical margin, 5 year survival was 41.2%, 60.0%, and 86.3%, respectively(p=0.0001). Tumor site has a borderline significance on the survival. The patients with head & neck or truncal sarcoma had a lower survival rate than patients with extremity lesion(58.5% vs 82.9% p=0.0510). No survival benefit was associated with use of chemotherapy. All other factors analyzed had no effect on overall survival(Table 8).

Table 6. Local Failure according to Dose and Resection Margin

Dose(cGy)	No. of local failure/No. treated		
	Positive or close RM*	Negative RM*	Total
D<6000	5/10	7/25	12/35
6000≤D<6500	5/ 7	7/21	12/28
6500≤D<7000	2/ 4	0/ 2	2/ 6
D≥7000	1/ 1	0/ 4	1/ 5
Total	13/22	14/52	27/74

*resecton margin

DISCUSSION

In this study, 5 year disease free and overall

Table 7. Prognostic Factors Affecting Freedom From Distant Metastasis

Factors	No	5 year freedom from distant metastasis(%)	P
Case			
primary	41	84.2	
recurrent	33	70.6	0.0255
Site			
head & neck, trunk	33	81.9	
extremity	41	75.7	0.7518
Size(cm)			
D≤5	17	80.1	
D>5	57	77.1	0.8913
Grade			
I	23	95.7	
II	17	86.7	0.0043
III	24	54.8	
Histology			
liposa	22	90.2	
MFH	18	56.5	
mal schwannoma	8	81.8	0.2154
synovial sa	8	72.2	
Operation			
marginal	17	79.6	
wide	55	76.4	0.6036
compartmental	2	100	
Resection margin			
positive	17	55.1	
close(≤2cm)	5	60.0	0.0331
negative	52	86.5	
Lymph node			
negative	68	78.6	
positive	6	66.7	0.1842
Chemotherapy			
yes	11	70.1	
no	63	79.3	0.3607
Interval(wks)*			
≤6	53	77.6	
>6	21	77.6	0.9550
Dose(cGy)			
<6000	35	87.1	
≥6000	39	69.1	0.0841

*interval between surgery and radiotherapy

survival rate of all patients were 53.3% and 72.3% respectively. Although the reported survivals are difficult to compare because of potential differences in histologic grade, tumor site, pathologic type, this results of relatively heterogenous population of patients parallels the finding of others. For example, about the 5 year survival rate, Lindberg et al[12] reported 33% for a trunk lesions and NCI randomized trial[6] and Herbert et al[13] reported 83% and 70 %, respectively for the extremity lesions. In our study, among 74 patients, 27 patients experienced local recurrences and 17 patients developed distant metastasis. The most common site of distant metastasis was the lung (59%). Survival after appearance of distant metastasis dropped abruptly to 15.1% at 3 years. Thus the factor which most strongly determines the survival time is the advent of distant metastasis.

Table 8. Prognostic Factors Affecting Survival

Factors	No	5 year survival(%)	P
Case			
primary	41	77.0	
recurrent	33	67.2	0.1801
Site			
head & neck, trunk	33	58.5	
extremity	41	82.9	0.0510
Size(cm)			
D≤5	17	85.0	
D>5	57	68.5	0.4025
Grade			
I	23	95.7	
II	17	73.0	0.0015
III	24	53.7	
Histology			
liposa	22	90.6	
MFH	18	51.0	
mal schwannoma	8	58.3	0.1769
synovial sa	8	75.0	
Operation			
marginal	17	81.0	
wide	55	68.9	0.4549
compartmental	2	100	
Resection margin			
positive	17	41.2	
close(≤2cm)	5	60.0	0.0001
negative	52	86.3	
Lymph node			
negative	68	72.8	
positive	6	66.7	0.6255
Chemotherapy			
yes	11	71.8	
no	63	72.3	0.5131
Interval(wks)*			
≤6	53	55.7	
>6	21	66.4	0.4203
Dose(cGy)			
<6000	35	72.1	
≥6000	39	72.0	0.6722

*interval between surgery and radiotherapy

The incidence of nodal involvement at presentation in our series(8%, 6/74) is slightly higher than that(1.3%) reported by Suit et al[14] but consistent with that(10%) reported by Pao et al[15]. We are in agreement with other authors that elective lymph node dissection or prophylactic irradiation to the lymph node drainage area is not generally warranted[16].

This our analysis found the tumor grade, histologic type, and the status of the surgical resection margin to be prognostic factors for local control. Lindberg et al[12] reported that the difference in local failures between grade I and grade III(6.3% and 31.6% respectively) was significant($p<0.025$) in lesions less than 5cm. But Pao et al[15]demonstrated no such correlation. In this study, a histologic diagnosis of liposarcoma was less commonly associated with local recurrence probably due to high proportion(15/22) of a low grade lesions. Collin et al[17] found liposarcoma to be associated with the best local control and same difference has been noticed in the lower extremity lesions by Lindberg et al[12] (i.e. local recurrence rate for liposarcoma was 3.6%(1/28) in contrast to 50%(12/24) for neurofibrosarcoma). Suit et al's report[14] of the MGH experience for patients with stages IIB, IIIB, IVA showed that

local control rate was 79% with negative margin and only 57% with positive margin and a recent review of patients with MFH treated with surgery and postoperative radiotherapy also found high local recurrence among patients with positive or close margin[18]. But the review by Potter et al[19] of 211 patients with high grade soft tissue sarcomas treated at the NCI showed that the status of microscopic margin in the definitive resection specimen was not a significant prognostic variable in determining local control. Other factors analyzed in the current analysis for local control were not found to be statistically significant. Especially about the radiation dose, although the range of radiation doses in the current experience was wide(4400-8820cGy), we did not identify any dose response relationship with regard to local control. This result could be explained by the uneven distribution of doses (i.e. the only 3 patients received more than 7000cGy). But in subgroup analysis of negative resection margin group, we found a trend toward favoring dose more than 6500cGy($p=0.1680$). According to Pao et al[15] among the 35 patients who did not have gross residual tumor or limited treatment volume, all of two patients who received less than 5000cGy failed locally versus 1/18 patients who received between 5000-6000cGy and 2/15 patients who received more than 6000cGy. In Herbert's analysis[13] there was a trend toward improved local control with higher dose by univariate analysis($p=0.09$). Now the majority of the larger modern series reported their results with postoperative doses of 6000cGy or more to the tumor bed.

In our analysis, tumor grade and status of surgical margin predicted distant metastasis. Leibel et al[20] showed that the development of distant metastasis was significantly influenced by the grade. Fifty three percent of the patients with grade III tumors developed distant metastasis while only 7% of patients with grade I or grade II diseases developed distant spread. Our patients have a similar 5 year cumulative risk of distant metastasis according to grade. The finding of an association between surgical margin and distant metastasis had been reported by the Herbert et al[13] and may represent a extensive residual disease which provide focus of hematogenous seeding. Some authors suggest tumor size as a prognostic factor of distant metastasis. Among patients with grade II or III sarcomas, Suit et al [14] found that there is a relentless and progressive increase in the frequency of distant metastasis with size of the primary lesion, namely 6% at ≤ 2.5cm, 60% at 15 to 20cm, and 80% at >20cm.

Our analysis also found that tumor grade and surgical margin have a great effect on survival. The tumor grade is well known prognostic factor of survival and numerous study confirmed this correlation[12,15,19]. Recent report of Ueda et al[21] also showed the difference in survival between the patients with low grade and high grade($p=0.05$). Thus the current American Joint Committee on Cancer(AJCC) handled tumor grade as a most important component of staging system. As like our study, Rosenberg[6] and Herbert[13] showed that patients with negative margin had significantly superior survival rates compared with patients with inadequate(grossly or microscopically positive) margin. However in Pao and Potter's analyses[15,19] microscopic margin status showed no effect on overall survival. This analysis also revealed tumor site as an adverse prognostic factor. Like Lawrence and Lindberg's experiences[1,12], anatomic site of head & neck, retroperitoneum was related with poor prognosis in terms of 5 year survival. But Ueda et al [21] did not find such relationship. Tumor size has been found to be associated with survival in other study[22] and now is a component of the AJCC staging system.

Conclusively, our data showed that status of surgical margin in the resection specimen is a very significant prognostic variable in deter-

mining disease free and overall survival. The best treatment of patients with positive surgical margin has not yet been established. Generally patients undergoing a limited surgical procedure should undergo a definitive sarcoma operation and operating surgeon should be eager to get adequate resection margins. Giuliano and Eilber[23] reported a 49% incidence of macroscopic residual tumor at the time of re-excision. In addition to re-excision, afterloading brachytherapy catheters can be placed at the time of second excision and this approach has been selectively and successfully utilized by some authors[24-26]. In spite of re-excision or radiotherapy, the patients may continuously suffer from distant metastases seen frequently among patients with inadequate surgical margin. However, a recent article by Leibel et al[27] suggested that locoregional control was the most significant variable affecting the development of distant metastasis. Thus more effective local therapy(re-excision, intraarterial chemotherapy with hyperthermia, high LET radiotherapy) for patients with positive surgical margin may affect local control and perhaps distant metastasis and survival for some patients. But unsolved remaining problem of distant metastasis demands more effective chemotherapy for the purpose of improving survival definitely.

CONCLUSION

Seventy four cases of soft tissue sarcoma which had been treated with surgery and postoperative radiotherapy were analyzed and the following results were obtained.

1) Combined conservative surgery and postoperative radiotherapy for soft tissue sarcoma can obtain good local control and overall survival.

2) High histologic grade and involvement of the surgical resection margin are adverse prognostic factors for local disease control, distant metastasis free and overall survival.

3) The operating surgeon should do his best to get negative resection margin. In cases where margins are close or positive, re-excision should be performed.

4) Further therapeutic measures using effective chemotherapy should be explored in the hope of improving overall survival.

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=국문초록=

연조직육종에서의 수술후 방사선치료

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연조직육종의 치료는 고전적으로 근치적 절제술이 사용되어 왔으나 최근에는 보존적 치료로 대치되고 있으며 이때 방사선치료의 역할도 입증되어 있다. 저자들은 1979년부터 1990년까지 11년 동안 서울대학교병원 치료방사선과에서 수술후 방사선치료를 시행한 연조직육종 환자 74명을 대상으로 후향 분석을 시행하여 방사선치료의 효과와 환자의 재발 및 생존에 영향을 미치는 예후인자를 알아보고자 하였다. 모든 환자의 병리조직학적 소견을 재판독하였으며 지방육종 및 악성섬유조직구종이 제일 많았다. 17예에서 국소절제, 55예에서 광범위 절제 그리고 2예에서 근치적 구획절제가 시행되었으며 11예에서는 항암화학요법이 병행되었다. 방사선치료선량의 중앙값은 6000cGy(범위 4200-8820cGy)였으며 환자들의 중앙추적기간은 51개월(범위 3-145개월)이었다. 국소치유율은 5년에 62.2%, 8년에 60.0%이었다. 조직학적 등급, 절제변연의 침윤여부가 국소치유율에 영향을 미치는 유의한 예후인자였으며 조직학적 유형중에서는 지방육종의 경우가 높은 국소치유율을 나타내었다. 전체 생존율은 5년에 72.3%, 8년에 58.5%이었으며, 무병생존율은 5년에 53.3%, 8년에 48.3%이었다. 생존 및 원격전이에 영향을 주는 예후인자로는 역시 조직학적 등급, 절제변연의 침윤여부가 중요하였으며 육종의 발생부위도 생존율에 영향을 주었다. 대부분의 재발은 국소에서 일어났으나 17명의 환자에서는 원격전이가 일어났으며 주로 폐를 침범하였다. 원격전이후의 생존율은 3년에 15.1%로서 원격전이가 생존율을 결정하는 중요한 요인임을 알 수 있었다.

따라서 연조직육종 환자의 수술시 충분한 절제변연을 얻는 것이 매우 중요하며 절제변연이 침범된 경우에는 재수술을 시행함으로써 국소치유율을 향상시킬 필요가 있는 것으로 판단된다. 또한 궁극적인 생존율의 향상을 위하여는 효과적인 항암제의 개발이 시급하다 하겠다.