

Postoperative External Beam Radiotherapy for Retroperitoneal Soft Tissue Sarcoma

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Purpose: To evaluate the clinical outcomes and prognostic factors in retroperitoneal soft tissue sarcomas treated by postoperative radiotherapy.

Materials and Methods: The records of 23 patients with retroperitoneal soft tissue sarcomas, who underwent postoperative radiotherapy between 1985 and 2003, were analyzed. The median follow-up period was 77 months (range, 8~240 months). A total of 21 patients presented with primary disease, and two patients presented with recurrent disease. Liposarcomas and leiomyosarcomas represented 78% of the diagnosed tumor cases. Moreover, 17 cases were of high grade (grade 2 or 3). The median tumor size was 13 cm (range, 3~50 cm). Complete excision was achieved in 65% of patients. The median radiation dose was 50.4 Gy (range, 45.0 to 59.4 Gy), with conventional fractionation.

Results: The 5-year overall, local recurrence-free, and distant metastasis-free survival rates were 68%, 58%, and 71%, respectively. Eleven patients experienced local recurrence, while 9 patients experienced distant metastasis. The most common site for distant metastasis was the liver. A univariate analysis revealed that adjacent organ invasion and age (>60 years) as the significant risk factors contributing to the prediction of poor overall survival. Moreover, multivariate analyses indicated that adjacent organ invasion remained significantly associated with a higher risk of death. In addition, patient age (>60 years) was the other identified risk factor for local recurrence by univariate and multivariate analyses. Except for one case of grade 3 diarrhea, no patient suffered grade 3 or higher complications.

Conclusion: Our results were comparable to previous reports in that adjacent organ invasion and patient age (>60 years) were significant predictors of poor survival and tumor recurrence, respectively.

Key Words: Retroperitoneal, Soft tissue sarcoma, Radiotherapy

Introduction

Retroperitoneal soft tissue sarcomas (RPS) are relatively uncommon, accounting for 15% of all soft tissue sarcomas.¹⁾ Historically, patients have had a poor prognosis, with 5-year survival rates ranging from 10 to 65%.^{1~7)} Surgery is the mainstay of treatment. However, anatomic location and frequent invasion of contiguous retroperitoneal organs often make surgical resection difficult.^{3~5,7)} Consequently, local recurrence remains the most common cause of failure.

Radiotherapy has been widely used as adjuvant treatment, but its role still remains controversial. Several retrospective studies have suggested that adjuvant radiotherapy may improve treatment outcomes, whereas other studies have found limited benefit.^{1,2,8~10)} To address this issue, we report our institutional experience in the use of postoperative radiotherapy as an adjuvant to surgical resection in patients with RPS.

Materials and Methods

Between July 1985 and October 2003, 32 patients with pathologically confirmed RPS were treated with surgery and postoperative radiotherapy at the Seoul National University Hospital. Four patients treated with palliative intent, 3 patients with incomplete treatment, and 2 patients who were never

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followed up after completion of radiotherapy were excluded from the analysis, and therefore a total of 23 patients were ultimately analyzed.

Performance status was graded using Eastern Cooperative Oncology Group (ECOG) performance status.¹¹⁾ Tumors were graded according to the French Federation of Cancer Centres system (the French system),¹²⁾ then divided into 2 groups: low (grade 1) and high (grades 2 and 3) grade. Positivity of adjacent organ invasion was decided based on radiologic images, operative records, and pathologic results. Gross residual disease was defined by a description of residual tumor in the operative record or definite evidence of residual tumor on immediate postoperative imaging.

Toxicities were graded using toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC).¹³⁾ The follow-up period was measured from the date of surgery. Survival rates were calculated using the Kaplan-Meier method. Univariate and multivariate analyses were performed using log-rank test and Cox regression, respectively.

Results

1. Patients, tumors, and treatment characteristics (Table 1)

Patient ages ranged from 33 to 72 years (median, 54 years). There were 14 female and 9 male patients. Nineteen patients had ECOG performance status 1.

There were 21 primary and 2 recurrent RPSs. The most common histology was liposarcoma. Records concerning tumor grade were available in 18 patients, and there was only one case of a low-grade tumor. Tumor sizes ranged from 3 to 50 cm (median 13 cm), and 65% of them were larger than 10 cm. There were 5 tumors invading adjacent organs.

Ten patients underwent tumor excision only, and 13 patients underwent continuous adjacent organ resection together. Gross total resection was performed in 15 patients, gross residual disease was found in 6 patients, and there was no information about quality of resection in 2 patients.

External beam radiotherapy was delivered to the tumor bed (plus gross residual tumor if present) using 6 or 10 megavoltage photon beam. Median dose was 50.4 Gy (range, 45 to 59.4 Gy). Radiotherapy dose was not related to quality of resection.

Table 1. Patients, Tumor, and Treatment Characteristics

Characteristics		Number of patients
Patient	Age (years)	
	Median	54
	Range	33~72
	Sex	
	Male	9
	Female	14
	Performance status	
	ECOG 0	1
	ECOG 1	19
	ECOG 2	3
Tumor	Initial presentation	
	Primary	21
	Recurrent	2
	Histology	
	Liposarcoma	10
	Conventional	2
	Dedifferentiated	4
	Myxoid	3
	Round cell type	1
	Leiomyosarcoma	8
	Conventional	7
	Myxoid	1
	Malignant fibrous histiocytoma	1
	Malignant peripheral nerve sheath tumor	1
	Malignant schwannoma	1
	Myxoid chondrosarcoma	1
	Malignant spindle cell tumor	1
	Grade	
	Low	1
	High	17
	Size	
	Median (cm)	13
Range (cm)	3~50	
≤10 cm	8	
10~20 cm	7	
>20 cm	8	
Adjacent organ invasion		
No	18	
Yes	5	
Treatment	Type of surgery	
	Tumor excision only	10
	Continuous adjacent organ resection	13
	Quality of surgery	
	Complete resection	15
	Incomplete resection (gross residual disease)	6
	Interval between surgery and start of radiotherapy (days)	
	Median	33
	Range	19~57
	Radiotherapy dose (Gy)	
Median	50.4	
Range	45~59.4	
Radiotherapy technique		
Conventional/2-dimensional	20	
3-dimensional conformal	3	

Twenty patients received conventional or 2-dimensional (2D) radiotherapy, and 3 patients received 3-dimensional (3D) conformal radiotherapy. The interval between surgery and start of radiotherapy ranged from 19 to 57 days (median, 33 days). Only 1 patient received adjuvant chemotherapy.

2. Treatment outcomes

At a median follow-up time of 77 months (range, 8~240 months), 10 patients were dead, and 15 patients had experienced recurrence. Nine patients had died from tumor recurrence, and 1 patient had died from hepatocellular carcinoma. The 5-/10-year overall and cause-specific survival rates were 68%/53% (Fig. 1) and 72%/55%, respectively. Of the 15 recurrences, the numbers of local only, distant only, and local and distant recurrences were 6, 4, and 5, respectively. Sites of metastasis were the liver in 7 patients,

lung in 4 patients, and peritoneal seeding, pleura, kidney, bone, and brain in 1 patient each. The 5-/10-year local recurrence-free and distant metastasis-free survival rates were 58%/35% and 71%/51%, respectively (Fig. 1).

Thirteen patients received salvage treatment, but only 2 patients were successfully salvaged (Table 2). Isolated local recurrence followed a different course. Of the 6 patients, 5 patients underwent salvage surgery. Two patients were alive without disease after one or two surgeries, with the interval between first recurrence and last follow-up being 57 and 56 months, respectively. A third patient underwent 5 salvage surgeries, 1 course of radiotherapy, and 6 cycles of chemotherapy, and he was alive with local disease at the last follow-up date, 111 months after the first local failure. A fourth patient underwent 4 salvage surgeries and was alive with local disease 35 months after first failure. Another patient who

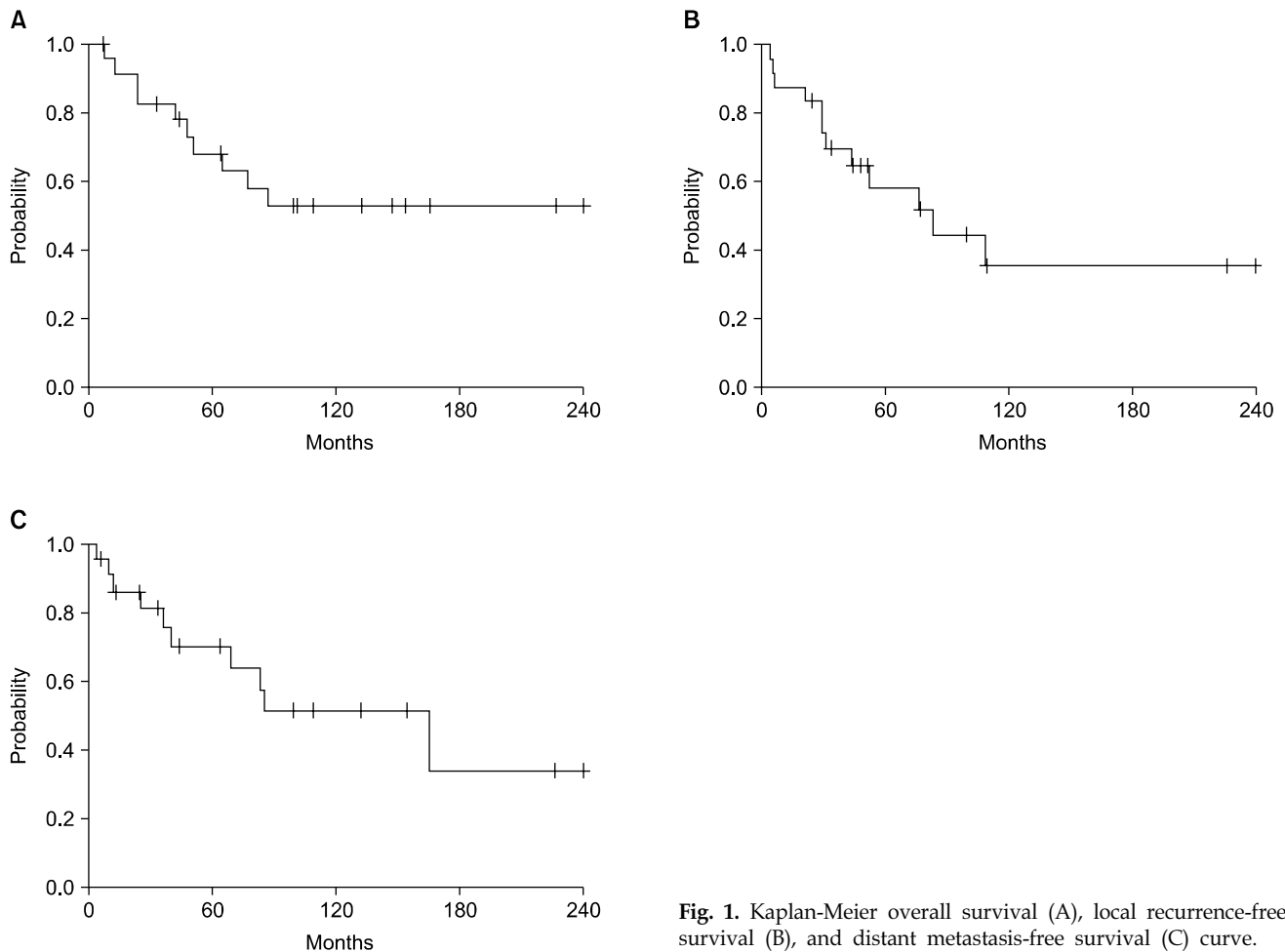


Fig. 1. Kaplan-Meier overall survival (A), local recurrence-free survival (B), and distant metastasis-free survival (C) curve.

Table 2. Salvage Treatment

Site of failure	BFU*-failure (mo) [†]	OP [‡]	RT [§]	CT	Failure-LFU [¶] (mo) [#]	LFU status
Local only	76	×2	—	—	56	NED**
	108	×1	—	—	57	NED
	29	×4	—	—	35	AWD ^{††}
	43	×5	+	+	111	AWD
	31	×2	+	—	55	DWD ^{‡‡}
	4	—	—	+	10	DWD
Distant only	4	—	—	+	44	DWD
	10	—	—	+	14	DWD
	12	—	—	+	39	DWD
	36	—	—	+	40	DWD
Local+distant	29	×3	—	+	118	AWD
	83	—	—	—	18	AWD
	6	—	—	—	3	DWD
	21	×1	+	—	20	DWD
	25	×1	—	+	40	DWD

*base of follow-up, [†]interval between base of follow-up and first failure (months), [‡]operation, [§]radiotherapy, ^{||}chemotherapy, [¶]last follow-up, [#]interval between first failure and last follow-up (months), **no evidence of disease, ^{††}alive with disease, ^{‡‡}dead with disease

underwent 2 surgeries and 1 course of radiotherapy died of progressive disease 55 months after failure. One patient who received only chemotherapy was dead at 10 months.

We performed univariate and multivariate analyses for sex, age, tumor grade, tumor size, adjacent organ invasion, quality of surgery, radiotherapy dose, and interval between surgery and the start of radiotherapy, to determine prognostic factors for overall survival and local control. Age greater than 60 years (p=0.045) and adjacent organ invasion (p=0.001) were adverse prognostic factors of overall survival on univariate analysis, with adjacent organ invasion retaining its significance on multivariate analysis (p=0.009). Age greater than 60 years was the only variable to show a significant effect on local control on both univariate (p=0.001) and multivariate analyses (p=0.014).

3. Toxicity

The majority of treatment-related toxicities were grade 1~2 gastrointestinal toxicities, including abdominal pain, nausea, diarrhea, anorexia, and vomiting, in order by frequency. There was 1 case of grade 3 diarrhea. The patient was 65 years old and underwent surgery at an outside hospital. Radiotherapy was delayed due to fever and diarrhea. During radiotherapy, severe diarrhea developed, and the patient was diagnosed with pseudomembranous colitis.

Discussion and Conclusion

In RPS, advanced stage at diagnosis and anatomic complexity of surrounding structures make complete resection difficult. High local recurrence rates, despite complete resection, suggest the need for adjuvant treatment. Radiotherapy has been used in many institutions as an adjuvant treatment.

Several retrospective studies for RPS have reported improved 5-year local control rates of more than 50% with radiotherapy, whereas local control rates with surgery alone have remained at less than 50%.^{2,3,14~16)} There are randomized trials supporting the routine use of radiotherapy in extremity or superficial trunk soft tissue sarcomas.^{17,18)}

Many studies have demonstrated the importance of tumor grade and completeness of surgery as independent prognostic factors for predicting survival and local recurrence.^{6,7,15,19~22)} The current American Joint Committee on Cancer staging system has been designed and validated for extremity soft tissue sarcomas and is therefore of limited value for determining prognosis in patients with RPS.²³⁾ Thus, the Dutch Soft Tissue Sarcoma Group and Memorial-Sloan Kettering Cancer Center developed a postsurgical classification system for primary RPS based on tumor grade, completeness of surgery, and metastasis.²⁴⁾

In the current analysis, reports of tumor grade were available in 18 patients, and 17 of these patients had high-grade tumors. Concerning quality of resection, 6 of 21 patients (2 patients, no information) had gross residual tumors after surgery. Although most patients had high-grade tumors and one-fourth of patients underwent incomplete surgery, 5-year overall (68%) and local recurrence-free (58%) survival rates were comparable with available literature. Despite the small number of patients, adjacent organ invasion and age >60 years were determined to be significant adverse prognostic factors for survival and local control, respectively. Confirmative analysis in a large number of patients may be needed.

Consistent with other studies concerning RPS or studies concerning soft tissue sarcomas arising at other sites, the most common pattern of failure in our study was local recurrence. However, distant metastasis developed in 9 patients, and isolated distant metastasis was discovered in 4 patients. This is quite different from the pattern seen in extremity soft tissue sarcoma, and chemotherapy or targeted therapy may be used for preventing systemic recurrence in RPS. Of the 9 distant metastatic patients, 6 patients received salvage chemotherapy. No one was successfully salvaged, and only one patient was alive at the time of analysis. However, in cases of isolated local recurrence, repeated salvage surgery was performed in 5 patients, and 4 patients were still alive at the last follow-up visit. In cases of isolated local recurrence, repeat surgery may improve survival.

In this analysis, we used postoperative external beam radiotherapy. Some institutions use preoperative external beam radiotherapy or intraoperative radiotherapy (IORT) or brachytherapy.^{2,10,16,20,25,26)} Preoperative radiotherapy has been proposed for several situations: readily definable tumor, displacement of radiosensitive organ outside the treatment field, and decreasing the risk of tumor implantation at the time of resection by sterilizing the operative field of microscopic tumor emboli. In a past study, intermediate-or high-grade RPS patients treated with preoperative external beam radiotherapy plus complete resection had a median survival >60 months, which is better than that of historical controls.²⁶⁾ In a recently activated American College of Surgeons Oncology group phase III trial (ACOSOG Z9031), patients with RPS are being randomized to receive either surgery alone or preoperative radiation followed by resection.

In postoperative therapy of extremity soft tissue sarcomas, initial volume is usually treated to 34 to 50 Gy, with subsequent cone downs to a final dose of 60 to 66 Gy and postoperative radiotherapy lowers local recurrence rates from approximately 30% to less than 10%.^{18,27)} Concerning RPS, postoperative radiotherapy is limited by the tolerance of the surrounding healthy tissues and external beam radiotherapy doses exceeding 45~50 Gy have been rarely performed.^{2,10)} Fein et al. found that a dose of >55 Gy improved the likelihood of local control.⁸⁾ In the current analysis, problems with small sample size and patient selection make it difficult to define the benefit of dose escalation. However, there is sufficient literature on the safety of dose escalation with IORT or brachytherapy or intensity-modulated radiotherapy (IM-RT).^{2,10,16,20,28,29)} Therefore, investigation of dose escalation using various modalities, as above, or proton therapy may be undertaken.

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후복막 연조직 육종의 수술 후 외부 방사선 치료

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목적: 수술 후 방사선 치료를 받은 후복막 연조직 육종 환자들의 치료 성과와 예후 인자를 분석해 보고자 하였다.

대상 및 방법: 1985년부터 2003년까지 수술 후 방사선 치료를 받은 후복막 연조직 육종 환자 23명의 자료를 분석하였다. 추적 관찰 기간은 8개월에서 240개월까지로 중앙값은 77개월이었다. 전체 환자 중 21명이 원발성 종양이었고, 두 명은 재발성 이었다. 지방육종과 평활근육종이 전체 종양의 78%를 차지하였고 17명의 환자가 조직학적으로 고등급(2 또는 3등급)이었다. 종양의 크기는 3에서 50 cm까지 분포하였으며 중앙값은 13 cm이었다. 65%의 환자에서 종양의 완전절제가 이루어졌다. 방사선치료는 일일 1.8에서 2.0 Gy를 주 5회 조사하여 총 45에서 59.4 Gy를 조사하였으며 중앙값은 50.4 Gy였다.

결과: 환자들의 5년 전체생존율, 국소무재발생존율, 무전이생존율은 각각 68%, 58%, 71%였다. 11명의 환자에서 국소 재발이 일어났으며, 9명에서는 원격전이가 발생했다. 원격전이는 간에서 가장 많이 발생했다. 예후인자 분석 중 일변량 분석에서는 주변장기를 침윤한 경우와 60세를 초과한 나이가 생존율에 나쁜 영향을 주는 인자로 분석되었고 이중 주변장기를 침윤한 것은 다변량 분석에서도 유의한 인자로 분석되었다. 60세를 초과한 경우는 일변량과 다변량 분석 모두에서 국소재발에 유의한 영향을 미치는 인자였다. 한 명의 3등급의 설사를 제외하고는 3등급 이상의 치료에 의한 부작용은 보고되지 않았다.

결론: 본 연구 결과 이전에 보고 되었던 다른 연구들의 결과와 비슷한 정도의 치료성적이 분석되었으며 주변 장기를 침범한 경우와 60세를 초과한 경우가 환자의 생존과 재발에 나쁜 영향을 미치는 유의한 인자였다.

핵심용어: 후복막, 연조직 육종, 방사선치료