

Radiotherapy in the Management of Kaposi's Sarcoma: Comparison of 8 Gy versus 6 Gy

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Objective: To evaluate prospectively the efficacy of a single fraction of high-dose radiotherapy in patients with Kaposi's sarcoma.

Patients: Between 1994 and 2004, 47 patients with Kaposi's sarcoma were treated at Hacettepe University, Department of Radiation Oncology. Thirteen (28%) patients received chemotherapy before radiotherapy and were referred due to recurrent or progressive disease or intolerance to chemotherapy.

All lesions were treated locally with a 2–3-cm safety margin with 4–6-MeV electron beams. Radiotherapy consisted of a single fraction of 8 Gy in the first four years and 6 Gy thereafter.

Results: The male:female ratio was 4:1. The median age was 61 years (range 18–87). Eight out of 47 patients (17%) had an underlying immunocompromised state, and one had a previous diagnosis of Hodgkin's disease. Of 203 fields treated, 51 and 152 fields were treated with 8 Gy and 6 Gy, respectively. Overall response rates (RR) at 12 months for 8- and 6 Gy were 93% and 86%, which were not statistically different. However, the difference between complete RRs at 12 months (93% and 60% for 8 Gy and 6 Gy respectively) was significant ($p < 0.0001$). Progression-free survival and reirradiation rates were not significantly different. Side effects were tolerable in all but three patients with grade 2–3 fibrosis and edema.

Conclusion: Radiotherapy is an effective mode of treatment for Kaposi's sarcoma, and a single dose of 8 Gy is more effective in terms of complete RR compared to 6 Gy, though overall response and progression-free survival rates were similar.

Key words: Kaposi's sarcoma ■ radiotherapy ■ single fraction

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INTRODUCTION

Kaposi's sarcoma is a multifocal neoplasm of endothelial cell origin. A recently discovered human herpes virus type 8 (HHV8) is accused to be the causative factor for all forms of the disease.¹ The classical form (CKS) occurs predominantly among elderly people of Mediterranean and Jewish ancestry and is mainly confined to the skin, predominantly that of lower limbs.² The course of CKS is usually indolent over many years and generally not life threatening, as opposed to the aggressive course associated with the African or the AIDS-related Kaposi's sarcoma.³ The incidence of Kaposi's sarcoma has been reported to increase due to HIV infection.^{4,5} While treatment consists of surgical excision or radiotherapy in localized disease, chemotherapy is administered in disseminated disease. In addition, observation alone is reasonable for elderly patients or cases with minimal symptoms since CKS has an indolent course and shows spontaneous regression occasionally.⁵⁻⁷

In 1997, we reported our preliminary results with 8-Gy single fraction of radiotherapy in patients with Kaposi's sarcoma with a median follow-up time of 17 months.⁹ Since the response rates and tumor control were satisfactory with 8 Gy, the dose was reduced to 6 Gy in 1998 in order to find the lowest effective dose. The aim of this manuscript is to report the treatment outcome and cosmetic results with local radiotherapy, mainly in CKS, since the majority of our patients were with classical form. To the best of our knowledge, there is no data in the literature regarding the efficacy of doses of <8 Gy. Herein, we report our long-term results with 8 Gy and also interim results with 6 Gy.

MATERIALS AND METHODS

Between 1994 and 2004, 47 consecutive patients with biopsy-confirmed Kaposi's sarcoma were treated with radiotherapy at the Department of Radiation Oncology, Hacettepe University. Patients were referred due to symptoms of pain, itching, bleeding, functional disabilities or cosmetic disfigurement. All patients underwent physical examination, hematological and

biochemical studies, serologic screening of HIV, chest radiography and histopathological examination.

Eight patients had an underlying immunocompromised state, and one had a previous diagnosis of Hodgkin's disease. There were no cases of AIDS-related Kaposi's sarcoma. Thirteen patients (28%) were administered systemic chemotherapy before radiotherapy and referred due to recurrent or progressive disease or intolerance to chemotherapy. These patients were mostly treated with single-agent chemotherapy, and the basic chemotherapeutic agents used were adriamycin, bleomycin or vinblastin.

Radiotherapy was performed with 4–6 MeV electron beams since the disease had limited depth of penetration. The lesions were irradiated with either 2-mm bolus material in order to increase the skin dose and 85% isodose depth was selected as a reference depth, or 80% of reference isodose depth was used without any bolus material. Local field radiotherapy was delivered to the tumor and its margins, usually consisting of a 2–3-cm normal tissue. Usually the size of the field was individually tailored to the extent of the lesions present. For patients with disseminated disease, radiotherapy portals were selected to cover all lesions.

All patients were evaluated by the same physicians before radiotherapy and during follow-up time. We planned to follow up our patients at the first and third months after radiotherapy and every three months thereafter. The response rates were reported as complete response (CR), partial response (PR), no response (NR) or progression (PR). CR was defined when the lesion had completely disappeared; PR was defined when there was ≥50% regression. NR was defined when there was <50% regression, and PR was defined when there was growth in the lesions or an increase in symptoms. Treatment-related toxicity was graded on the basis of the Radiation Therapy Oncology Group Grading System (RTOG).⁸

Statistical Analysis

Since the majority of the patients had CKS and due to the indolent nature of disease in these patients, we chose progression-free survival (PFS) as a main end point. PFS is defined as time from radiotherapy to the occurrence of new lesions or to the growth of the existing lesions in the irradiated area. A minimum follow-up of one month was required for inclusion of patients in the PFS analysis. The influence of radiation dose on the course of Kaposi's sarcoma was estimated by the Kaplan-Meier method. The significance of difference between response rates of the two groups was tested with Chi-squared test.

RESULTS

Patient characteristics are summarized in Table 1. The median age at the time of onset was 61 years (18–87 years) and the male:female ratio was 4:1. Disease was confined to extremities in 98% of cases, and lower limbs were the most frequent sites of the involvement (89%). The majority of patients presented with disseminated disease (77%), and only 11 cases (23%) had localized disease.

Median follow-up time was 48 months (1–130 months) for the whole population. It was 101 months for 8-Gy patients and 47 months for 6-Gy patients. Of 203 fields treated, 51 and 152 fields were treated with 8 Gy and 6 Gy, respectively. The majority of patients responded to radiation therapy. The overall response rates (complete and partial) for the whole population were 71%, 89%, 83% and 87% at one, three, six and 12 months, respectively. At 12 months, the overall response rates achieved with 8 Gy and 6 Gy were 93% and 86%, respectively (Table 2). The difference was not statistically significant. However, there was a significant difference between CR rates of the radiation fields treated with 8 Gy and 6 Gy at 12 months (p<0.0001). CR rates at one, three, six, 12 months were 43%, 73%, 77% and 93% for 8 Gy and 32%, 55%, 60% and 60% for 6 Gy.

In-field recurrences were 7% in both groups, and PFSs at one year were 80% and 88% for patients treated with 8 Gy and 6 Gy, respectively, without any statistical significant difference.

Eleven patients (23.4%)—nine in the 6-Gy group and two in the 8-Gy group—received systemic therapy either as interferon-α (five patients) or systemic chemotherapy (six patients) as single-agent vepesid®,

Table 1. Patient characteristics and distribution

Patient Characteristics	Number of Patients (%)
Gender	
Male	37 (79)
Female	10 (21)
Age Range (Years)	
<50	13 (28)
≥50	34 (72)
Immunocompromised State	
Organ transplantation	8 (17)
Location of Irradiated Lesions	
One limb	15 (32)
≥2 limbs ^a	31 (66)
Trunk	1 (2)

^a Includes two patients with trunk lesions

Table 2. Response rates for both radiotherapy regimens at 12 months

	8 Gy (%)	6 Gy (%)
Complete response	93	60
Partial response	–	26
No response	7	14

bleomycin, vinblastine or paclitaxel or combination of these agents due to disseminated or progressive disease following radiotherapy. The median follow-up time was 20 months after chemotherapy, and overall response rate after systemic treatment in these patients was 72% with 37% CR rate.

Cosmetic result was good or excellent in the majority of the patients. Forty-three patients developed grade-1 RTOG dermatitis as dry erythema, local hair loss, slight atrophy or hyperpigmentation. Only three patients developed grade 2–3 fibrosis and edema. There was no correlation between cosmetic results and the radiation dose.

DISCUSSION

Classical Kaposi's sarcoma is a rare neoplasm that comprises both an indolent course and occasional spontaneous regression. Treatment options include observation alone for immunocompetent asymptomatic patients, surgical excision for symptomatic resectable lesions and radiotherapy for unresectable or more advanced disease. Systemic chemotherapy is usually reserved for extensive disease or when other approaches fail.

Radiotherapy is an efficient, convenient treatment modality and associated with high response rates in all forms of Kaposi's sarcoma, including the classical one.¹⁰⁻¹⁸ It is reported to produce 85–95% overall response rates and 50–90% of CR rates.^{8,9,17,19-22} However there is no consensus on the optimal fractionation, total dose or field size selection as local or extended fields.²³⁻²⁵ Cohen's landmark analysis²⁶ indicated that Kaposi's sarcoma could be controlled with doses ranging from 1,000 cGy in single fraction to 2,500 cGy over one month. A single fraction of irradiation in the literature is mainly with 8–12 Gy, and it is reported that these high-dose single fractions produce equal response rates with more protracted fractionated regimens.^{21,22,26-28} In our prospective study, patients were irradiated with either 8 Gy or 6 Gy. Both doses produced high overall response rates at one year after radiotherapy as 93% and 86%, respectively, without any statistical difference. However, CR rates with 8 Gy are found to be significantly higher in long-term follow-up. The reirradiation rate due to in field progression or recurrence of the disease, on the other hand, was the same with both dose regimens. To our knowledge, there is no data in the literature regarding the efficacy of doses <8 Gy. Our report is the first result in this aspect. Though this study is not a randomized one and has some limitations, it gives an impression that 6 Gy is not sufficient in terms of CR rate, and there is no advantage of 6 Gy in terms of cosmetic result when compared to 8 Gy.

As Kaposi's sarcoma is a multifocal disease and can recur despite treatment, it is believed that extended field radiotherapy (EFRT) with megavoltage irradiation might be a more appropriate treatment approach. However, in a study by Hamilton et al.,²² the overall relapse rates of extended and local field irradiation were similar, though EFRT produced an increased rate of com-

plete remission. In our study, only local field irradiation with 4–6-MeV electron beams was used. The cosmetic outcome was excellent without extensive fibrosis. Patients were reirradiated when new lesions occurred. We think that using localized low-dose electron beam radiotherapy and reserving additional irradiations for recurrences could be a good option in order to avoid excessive radiation dose to uninvolved sites.

Patients with widespread mucocutaneous disease, lymphedema or visceral involvement are usually treated with systemic cytotoxic therapy or biologic agents such as interferon- α . The most active cytotoxic drugs are reported to be anthracyclins, paclitaxel, vinca alkaloids and bleomycin.¹⁹ Recently, a new agent—gemcitabine—has been shown to be effective in aggressive CKS resistant to other chemotherapeutic agents.²⁹ The response rates with these agents have been reported to be in the range of 50–80%.^{15,29} In a recent study, the patients with AIDS-associated Kaposi's sarcoma treated with etoposide have been reported to have a significantly better quality of life than the radiotherapy group.⁵ Eleven patients in our study received systemic treatment after radiotherapy due to disseminated or progressive disease. Among them, six patients received cytotoxic chemotherapy as a single agent of vepesid®, vinblastine, paclitaxel, adriamycin or a combination of them. In addition, five patients received interferon- α as the sole treatment. Overall response rate to systemic treatment was 72%, which is in accordance with the literature. There was no treatment-related toxicity in either of these patients.

In conclusion, single-dose radiotherapy is an effective treatment modality in the management of CKS, with acceptable morbidity. We have prospectively revealed that single dose of 8 Gy is more effective in terms of CR rates compared to 6 Gy without any significant adverse effect on cosmetic outcome in this single institutional study.

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