A dose-response analysis for classical Kaposi's sarcoma management by radiotherapy

Kaan Oysul, MD, Murat Beyzadeoglu, MD, Serdar Surenkok, MD, Gokhan Ozyigit, MD, Bahar Dirican, PhD.

ABSTRACT

الأهداف: تقييم علاقة الجرعة – والاستجابة في المرضى المصابين بورم كابوسي التقليدي (CKS) وتم علاجهم بحزمات العلاج الإشعاعي الخارجي.

الطريقة: تم تقييم المرضى المصابين بورم كابوسي التقليدي (CKS) في الفترة ما بين عام 1993م وحتى 2004م، والذين تلقوا العلاج في قسم العلاج الإشعاعي للأورام بمدرسة جولهان الطبية العسكري – تركيا. كان متوسط العمر عند الحضور المبدئي 60 عاماً. قمنا أولاً بتحليل معدلات الاستجابات الكلية لـ(NTD_{2Gy})، من (20Gy>)، و (20Gy) و(20Gy<). ثانياً تم البحث عن معدلات الاستجابة الأفضل التي يمكن استخدامها مع ($NTD2_{Gy}$) من (20Gy) مقارنة مع (NTD2Gy) من (20Gy<).

النتائج: تبين وجود 109 آفة قابلة للتقييم لدى 18 مريضاً. كان متوسط المتابعة 4 سنوات. كانت معدلات الاستجابة الكامل عند الشهر الثاني عشر بعد العلاج الإشعاعي 88% لـ(NTD_{2Gy}) من 97% ،(20Gy>) لـ(20Gy)، و 92% لـ(20Gy< NTD_{2Gy}) على التوالي لم تكن مختلفة إحصائياً. النتائج الجزئية والكاملة بعد 12 شهراً كانت كالتالي: 93% و 3.4% لـ(NTD_{2Gy}) من≥20Gy
64% و 24% لـ(NTD_{2Gy}) من (20Gy>) على التوالي وكانت مختلفة إحصائياً (p=0.001). كانت التأثيرات المتأخرة للعلاج الإشعاعي مقبولة في الجميع ولكن 4 من المرضي كان لديهم تليف ووذمة.

خاتمة: كشف هذا التحليل الوصفي إن جدول العلاج الإشعاعي مع (NTD_{2Gy}) من (20Gy) وأعلى باستخدام حقول الإشعاع الموضعية فعالاً في إكمال معدلات الاستجابة في علاج ورم كابوسي التقليدي (CKS) مقارنة مع (NTD_{2Gy}) لأقل من (20Gy).

Objectives: To evaluate the dose-response relationship in classical Kaposi's sarcoma (CKS) patients treated with external beam radiotherapy.

Methods: Between 1993 and 2004, patients with CKS treated at the Department of Radiation Oncology, Gulhane Military Medical School, Ankara, Turkey were evaluated in this retrospective study. The median age at initial presentation was 60 years. First, we analyzed the overall response rates for normalized total dose 2Gy (NTD_{2Gy}) of <20 Gy, 20 Gy, and >20 Gy. Secondly, we searched for whether better response rates could be obtained with the NTD_{2Gy} of ≥20 Gy compared to the NTD_{2Gy} of <20 Gy.

Results: There were 109 evaluable lesions in 18 patients. The median follow-up was 4 years. The overall response rates at the post-radiotherapy twelfth month were 88% for NTD_{2Gy} of <20 Gy, 97% for 20 Gy, and 96% for NTD_{2Gy}>20 Gy, which were not statistically different. The complete and partial response rates at 12 months were 93.2%, and 3.4% for NTD_{2Gy} of ≥20Gy, and 64% and 24% for NTD_{2Gy} of <20 Gy and these were statistically different (p=0.001). Late side effects of radiation therapy were acceptable in all but 4 patients with fibrosis and edema.

Conclusion: This retrospective analysis showed that radiotherapy schedules with an NTD_{2Gy} of 20 Gy and above by using local irradiation fields are effective in terms of complete response rates in the management of CKS compared to NTD_{2Gy} of <20 Gy.

Saudi Med J 2008; Vol. 29 (6): 837-840

From the Department of Radiation Oncology, Gulhane Military Medical School, Ankara, Turkey.

Received 23rd December 2007. Accepted 19th April 2008.

Address correspondence and reprint request to: Associate Professor Kaan Oysul, Department of Radiation Oncology, Gulhane Military Medical School, Ankara 06018, Turkey. Tel. +90 (312) 3044683. Fax. +90 (312) 3216066. E-mail: kaanoysul@yahoo.com

Disclosure: The authors declare no conflicts of interest relevant to the content of this study.

Classic Kaposi's sarcoma (CKS) is a rare form of Kaposi's sarcoma, which usually presents with asymptomatic purple, or brown patches, plaques, or nodular skin lesions. Classic Kaposi's sarcoma is usually confined to the skin predominantly in the lower limbs, and occurs predominantly among elderly people of Mediterranean and Eastern European Jewish ancestry.[1,2] The course of CKS is usually indolent for 10-15 years or more, with slow enlargement of the original tumors and the gradual development of additional lesions, and is generally not life-threatening unlike the aggressive course associated with the African or the acquired immunodeficiency syndrome (AIDS) related KS.[1-3] Treatment options include observation alone for non-immune-compromised asymptomatic patients, surgical excision for symptomatic resectable lesions and radiotherapy for unresectable or more advanced disease.[4] Radiotherapy is an effective treatment modality and associated with high response rates in all forms of KS, including the classical one.[5-7] It is reported to produce high overall and complete response rates.[4,5,8,9] Single fraction of irradiation in the literature is mainly with 8-12 Gy and it is reported that these high dose single fractions produce equaled response rates with more protracted fractionated regimens.[5,9-12] Although radiotherapy is an efficient and convenient treatment modality, this is yet an under-studied area with no consensus on the optimal fractionation and total dose with existing importance. In this study, we evaluated the radiation dose-response characteristics of CKS patients treated with different radiotherapy schedules by using biologically effective dose (BED) and normalized total dose (NTD) equations.

Methods. This retrospective study was conducted between 1993 and 2004, 109 lesions of 18 human immunodeficiency virus (HIV) negative consecutive patients with CKS were treated at the Department of Radiation Oncology, Gulhane Military Medical School, Ankara, Turkey. All patients underwent physical examination, hematological and biochemical studies, chest radiography and biopsy. Written informed consent was obtained from all patients. This study received ethical approval from the Ethics Committee of the Syrian Arab Republic, Damascus University. The median age at initial presentation was 60 years (range, 19-85 years), and the male to female ratio was 2:1. No patients had underlying immune-compromised state. There were no cases of AIDS-related KS. Disease was confined to extremities in 96% of cases and lower limbs were the most frequent sites of involvement (69%). Eight patients (44%) were given systemic chemotherapy before radiotherapy, and were irradiated for recurrent or progressive disease (**Table 1**). Four to six MeV electron beams (Linac SL-25, Philips, United Kingdom) were used in radiotherapy. The lesions were irradiated with either a bolus material in order to increase the skin dose, and 85% isodose depth was selected as reference depth or 80% of reference isodose depth was selected if no bolus materials were used. Local field radiotherapy was delivered to the tumor and its margins, usually consisting of a 3 cm normal tissue. The size of the field was individually customized to the extent of the lesions. Radiation-dose-response analysis was performed by using BED and NTD equations for the comparison of different radiotherapy schedules.[13] Biologically effective dose and NTD equations used in current study were as follows:[13]

$$BED_2 = D \times RE$$
$$RE = 1 + d/_{\alpha/\beta}$$
$$NTD_{2Gy} = BED_2/RE$$

Where D was the total radiation dose, d was the fraction dose, and RE was the relative effectiveness. The α/β ratio was assumed as 2 in current study. The RE of a regimen with 2 Gy daily fraction was equal to 2 with an α/β ratio of 2. For instance, the NTD_{2Gy} of 8 Gy in one fraction, which was the most frequent radiotherapy schedule used in this study, was equal to a BED_2 of 40 Gy and NTD_{2Gy} of 20 Gy, respectively by using the above equations. There is no an agreement on the optimal radiation doses and too many different radiation dose regimens were reported in the literature. Since we used 8 Gy (NTD_{2Gy} of 20 Gy) most frequently, we compared the differences between doses NTD_{2Gy} <20 Gy, 20 Gy, and >20 Gy. The follow-up of our patients were at the first and the third months after radiotherapy and every 3 months thereafter. A complete response (CR) was defined when the lesion had completely disappeared, partial response (PR) was defined if there was 50% or more regression. No response (NR) was defined when there was less than 50% regression, whilst progression (P) was defined when there is growth in the lesions.

Statistical analysis. Because of the indolent nature of CKS, we choose the objective response rate as the main end-point. A minimum follow-up of one year was required for inclusion of patients in the dose-response analysis. The significance of difference between response rates of the 2 groups was tested with Chi-square test. A *p*-value of less than 0.05 was accepted as statistically significant, and all tests were 2-sided. Statistical analyses were performed by SPSS 13.0 (SPSS Inc., Chicago, IL) software.

Results. Median follow-up was 4 years (range, 2-16 years) for the whole population. Patient and treatment characteristics are summarized in **Table 1**. The majority

Table 1- Patient and treatment characteristics.

Patient/treatment characteristics	n (%)
Gender	
Male	12 (67)
Female	6 (33)
Age	
<50 years	4 (78)
≥50 years	14 (22)
*Location of lesions**	
Leg and Foot	75 (69)
Face	2 (2)
Arm and Hand	27 (25)
Trunk	5 (4)
Extent of disease	
Disseminated	13 (72)
Localized	5 (28)
*Radiation dose (NTD_{2Gy})**	
<20 Gy	50 (42)
≥20 Gy	59 (58)
Chemotherapy	8 (44)

*Total number of lesions treated was 109 in 18 patients.
NTD_{2Gy} - normalized total dose 2 Gy

Table 2 - Normalized total doses of radiotherapy schedules used in the current study for the management of classical Kaposi's sarcoma.

Fraction dose (Gy)	n	Total Dose (Gy)	BED_2	NTD_{2Gy}
2	14	28	56	28
3	4	12	30	15
3	5	15	37.5	18.75
3	10	30	75	37.5
4	2	8	24	12
4	3	12	36	18
4	5	20	60	30
5	2	10	35	17.5
8	1	8	40	20
10	1	10	60	30

N - number of fractions, BED - biologically effective dose,
NTD_{2Gy} - normalized total dose 2 Gy

Table 3 - Response rates for NTD_{2Gy} <20 Gy, NTD_{2Gy} =20 Gy, and NTD_{2Gy} >20 Gy at 12 months.

Response rate	NTD_{2Gy} <20 Gy (N=50)	NTD_{2Gy} =20 Gy (N=35)	NTD_{2Gy} >20 Gy (N=24)	*P*-value
		%		
Overall	88	97	96	0.2
Complete	64	95	87	
Partial	24	2	9	
No response	12	3	4	

NTD_{2Gy} - normalized total dose 2 Gy
N = number of lesions treated

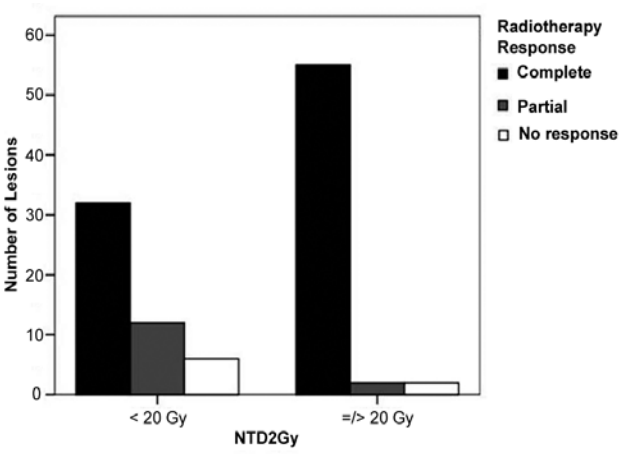

Figure 1 - Response rates at 12 months for NTD_{2Gy} of ≥20 Gy and for NTD_{2Gy} of <20 Gy (p=0.001).

of patients responded well to radiation therapy. The complete rate was 80% for the entire group and partial response rate was 13% at 12 months. Normalized total dose 2Gy of various radiotherapy schedules analyzed in the current study were summarized in **Table 2**. First, we analyzed the response rates for NTD_{2Gy} of <20 Gy, 20 Gy, and >20 Gy. The response rates are summarized in **Table 3**. Secondly, we searched for whether better response rates could be obtained with the NTD_{2Gy} of ≥20 Gy compared to NTD_{2Gy} of <20 Gy. The complete and partial response rates at 12 months were 93.2% and 3.4% for NTD_{2Gy} of ≥20 Gy; 64% and 24% for NTD_{2Gy} of <20 Gy, respectively that were statistically different (p=0.001) (**Figure 1**). Ten patients out of 18 (55%) developed dry erythema, slight skin atrophy, or hyperpigmentation. Side effects of radiation therapy were acceptable in all, however, 4 patients with fibrosis and edema.

Discussion. In this study, we performed a radiation dose-response analysis for CKS by using BED and NTD2Gy equations. A BED value can be calculated for any dose per fraction if the proper α/β ratio is assumed.[13] The ratio of α/β determines the sensitivity of a particular type of cell to alterations in fraction size. Unlike highly proliferating tumors, low proliferating tumor cells have low α/β ratios, and are very sensitive to increase in fraction size.[13] Comparative calculations are accomplished most easily as BED in Gy_2 or Gy_3 for slowly responding tumors to radiation. It is also common to convert a BED to the linear-quadratic equivalent dose in 2 Gy daily fractions called NTD_{2Gy}, which is the total dose in 2 Gy per fraction giving the same log cell kill for the schedule being analyzed.[13] The term NTD_{2Gy} was most useful for the comparison of hypofractionated regimens particularly delivered in one fraction similar to radiotherapy schedules

used in CKS. The course of CKS is usually indolent over many years.[1,2,11] Many series suggested that CKS behaves like late responding tissues due to its indolent course and reported that one year is usually needed for the observation of complete response.[1,2,9,11] Therefore, α/β ratio of 2 has been used in our current study, and we performed all dose-response analyses by using BED_2 and corresponding value of NTD_{2Gy} in order to compare various radiotherapy schedules.

Cohen's landmark study demonstrated that Kaposi's sarcoma could be controlled with doses ranging from 10 Gy in single fraction to 25 Gy over a month.[12] Moreover, several authors suggested that a single fraction of irradiation with 8-12 Gy in the management of CKS produced high overall response rates at one year.[3,5,6,9,11,12] Yildiz et al[9] performed a non-randomized prospective study, comparing a single fraction of 8 Gy-6 Gy. Both 8 Gy (93%) and 6 Gy (86%) single doses in their study produced high overall response rates at one year after radiotherapy without any statistical difference. However, they demonstrated that complete response rates with 8 Gy is significantly higher in the long-term follow-up. Similarly, we found that radiotherapy schedules with NTD_{2Gy} of 20 Gy and above (namely 8 Gy in one fraction or other equivalent schemes) were highly effective for CKS control. A major difference in the current series in comparison with the study of Yildiz et al,[9] was that we analyzed the response rates of various fractionation schemes, whereas they compared only 2 schedules, 6 Gy versus 8 Gy. However, one of the drawbacks of our current analysis is the fact that this study is not a randomized and has certain limitations due to its retrospective nature. However, it gives a sense that radiotherapy schedules with an NTD_{2Gy} of <20 Gy is not therapeutically sufficient of complete and partial response rates for CKS.

We used only local field irradiation, and patients were re-irradiated when new lesions occurred. However, it may also be argued whether the use of local radiotherapy fields is applicable, where the majority of our patients had disseminated lesions. Several authors suggested that modest doses of radiation applied to the lesions with a limited margin provided excellent control of disease in the treated area for solitary lesions.[4,9] However, some authors believe recurrences in adjacent, untreated skin is common if only involved-field radiation therapy is used and stated better cure rates when extended-field radiation therapy is used.[11,14] Nevertheless, Hamilton et al[11] reported that the overall relapse rates of extended and local field irradiation were similar. Furthermore, this treatment approach using localized radiotherapy and reserving additional irradiations for relapses may also be a good alternative in order to avoid excessive irradiation to uninvolved sites.

In summary, this retrospective analysis showed that radiotherapy schedules with an NTD_{2Gy} of 20 Gy and above by using local irradiation fields are effective in terms of complete therapeutic response rates in the management of CKS. Further studies will allow us to find the optimal fractionation, total dose, or field size selection in the management of this rare cutaneous disease.

References

1. Wahman A, Melnick SL, Rhame FS, Potter JD. The epidemiology of classic, African, and immunosuppressed Kaposi's sarcoma. ***Epidemiol Rev*** 1991; 13: 178-199.
2. Friedman-Kien AE, Saltzman BR. Clinical manifestations of classical, endemic African, and epidemic AIDS-associated Kaposi's sarcoma. ***J Am Acad Dermatol*** 1990; 22: 1237-1250.
3. Friedman-Birnbaum R, Weltfriend S, Katz I. Kaposi's sarcoma: retrospective study of 67 cases with the classical form. ***Dermatologica*** 1990; 180: 13-17.
4. Brenner B, Rakowsky E, Katz A, Gutman H, Sulkes A, Schacter J, et al. Tailoring treatment for classical Kaposi's sarcoma: comprehensive clinical guidelines. ***Int J Oncol*** 1999; 14: 1097-1102.
5. Yildiz F, Ozyar E, Uzal D, Sahin S, Atahan IL. Kaposi's sarcoma: the efficacy of a single fraction of 800 cGy. ***Dermatology*** 1997; 195: 142-144.
6. Chang LF, Reddy S, Shidnia H. Comparison of radiation therapy of classic and epidemic Kaposi's sarcoma. ***Am J Clin Oncol*** 1992; 15: 200-206.
7. Cooper JS, Steinfeld AD, Lerch I. Intentions and outcomes in the radiotherapeutic management of epidemic Kaposi's sarcoma. ***Int J Radiat Onco l Biol Phys*** 1991; 20: 419-422.
8. Piccinno R, Caccialanza M, Cusini M. Role of radiotherapy in the treatment of epidemic Kaposi's sarcoma: experience with sixty-five cases. ***J Am Acad Dermatol*** 1995; 32: 1000-1003.
9. Yildiz F, Genc M, Akyurek S, Cengiz M, Ozyar E, Selek U, et al. Radiotherapy in the management of Kaposi's sarcoma: comparison of 8 Gy versus 6 Gy. ***J Natl Med Assoc*** 2006; 98: 1136-1139.
10. Harrison M, Harrington KJ, Tomlinson DR, Stewart JS. Response and cosmetic outcome of two fractionation regimens for AIDS-related Kaposi's sarcoma. ***Radiother Oncol*** 1998; 46: 23-28.
11. Hamilton CR, Cummings BJ, Harwood AR. Radiotherapy of Kaposi's sarcoma. ***Int J Radiat Oncol Biol Phys*** 1986; 12: 1931-1935.
12. Cohen L, Palmer PE, Nickson JJ. Treatment of Kaposi's sarcoma by radiation. ***Acta Unio Int Contra Cancrum*** 1962; 18: 502-509.
13. Fowler JF. The radiobiology of prostate cancer including new aspects of fractionated radiotherapy. ***Acta Oncol*** 2005; 44: 265-276.
14. Nisce LZ, Safai B, Poussin-Rosillo H. Once weekly total and subtotal skin electron beam therapy for Kaposi's sarcoma. ***Cancer*** 1981; 47: 640-644.