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Radiotherapy in the management of classic Kaposi's sarcoma: A single institution experience from Northeast Turkey

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Abstract

Kaposi sarcoma is a rare adult neoplasm and there has been no certain consensus on standard treatment, either local or systemic. Radiotherapy is an effective, suitable treatment modality. Between 1996 and 2016, patients who were diagnosed with Kaposi sarcoma and referred to our clinic for radiotherapy were included in this retrospective study. Ninety-two patients were examined in total and it was diagnosed that all the patients had non-HIV associated Kaposi's sarcoma. There were 36 (39%) females and 56 (61%) males and female to male ratio was 2/3. Median age at presentation was 72 (30–93) years. Sixty-eight patients (77%) were treated with 8 Gy (1 fraction), 15 patients (16%) were treated with 20 Gy (2 Gy/fraction), four patients (4%) were treated 25 Gy (2.5 Gy/fraction), and five patients (6%) were treated 30 Gy (3 Gy/fraction). The median follow-up time was 72 (5–192) months. The complete response at 5 years was 91.6% with >20 Gy and 89.6% with 8 Gy. Radiotherapy is an effective, suitable treatment modality of Classic Kaposi sarcoma and usually, radiotherapy is well tolerated with minimal side effects.

KEYWORDS

classic Kaposi sarcoma, radiotherapy

1 | INTRODUCTION

Kaposi sarcoma (KS) is a lymphoangioproliferative disease often caused by human herpes virus 8 (HHV8) (Chang et al., 1994). It can be classified into four categories by the region, race, immunosuppression, and human immunodeficiency virus (HIV) infection. These are epidemic (HIV-associated), endemic (African KS), iatrogenic or post-transplantation KS, and the Mediterranean or classic KS (CKS) (Schwartz, 2004). Median survival varies from several weeks to years according to the classification (Mitsuyasu & Groopman, 1984).

There appear to be four clinically distinct forms of KS: Stage I: Localized nodular KS, Stage II: Localized, invasive, and aggressive KS, Stage III: Disseminated mucocutaneous KS, Stage IV: Stage III with visceral involvement (Mitsuyasu & Groopman, 1984).

CKS is usually chronic, persisting over many years, but is not life-threatening. For localized forms, the available options are radiotherapy (RT), surgery, cytotoxic therapies, cidofovir, and interferon alfa, as well as topical and systemic retinoids and observation (Vander Straten, Carrasco, & Tyring, 2000). The main treatment for single lesions usually consists of local therapies while systemic therapies could be used for disseminated disease. CKS usually arises on the skin of extremities and may involve mucosa and visceral organs. The CKS typically follows an indolent course and rarely affects viscera or mucosa and primarily affect elderly men of Mediterranean or Eastern European origin (Antman & Chang, 2000).

Radiation therapy (RT), as local treatment, is commonly used in patients with CKS who does not have disseminated disease. Optimal dose and fractionation varies among centers. In addition to that, an RT technique and energy source also varies according to patients. It is technically difficult to deliver a homogeneous dose distribution over the lesion with the irregular contour. Nevertheless, RT provides sufficient symptom relief and effective tumor control in more than 80% of CKS patients (Cooper, 1988; Stein et al., 1994).

In this retrospective analysis, we sought to determine the clinical characteristics of CKS patients and identify the prognostic factors that influence the clinical outcome in CKS patients treated with RT.

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2 | PATIENTS AND METHODS

Between 1996 and 2016, patients who were diagnosed with KS and referred to our clinic for RT were included in this retrospective study, HIV (+) patients were excluded from the study. No patients had transplantation or immunosuppressive therapy. Patients were applying due to usually symptoms of pain, itching or cosmetic disfigurement. The diagnosis was confirmed in all cases by histopathologic examination. Demographic information (age, sex, anatomic distribution) were retrieved. All patients underwent the physical examination and routine hematologic and biochemical analysis and chest radiography. Lesion site, field numbers, radiation dose, and fractionation were evaluated. Complete response (CR) and partial response (PR) were defined as no clinically detectable tumor and regression of 50% or more in tumor size or fading of the typical color of the lesion, respectively.

RT was performed with 6 MeV electron or 6 MV photon beams since the disease had limited depth of penetration. Eighty-five percent iso-dose depth was selected as a reference depth. Planned target volume was defined as 1.5–2 cm additional margin to the gross lesions. Usually, the size of the field was individually made to measure the extent of the lesions present.

2.1 | Follow-up

Visits for follow-up was arranged as a control visit at the first month after completion of RT and then once every 3 months, after this procedure the follow-up visits were applied at six months intervals. Physical examination, a complete blood count, liver function tests were repeated in each visit and thoracic and abdominal computed tomography scanning were administrated when clinically indicated. The responses were recorded as CR, PR, stable disease, no response (NR), or progression (PR).

2.2 | Endpoints

Follow-up visits continued from the initial diagnosis to the last follow-up or date of death.

2.3 | Statistical methods

Statistical analysis of the data was done with SPSS Software (version 13.0 for Windows). For interaction analysis, Repeated Measures test was used.

3 | RESULTS

3.1 | Patients characteristics

Ninety-two patients were examined in total and it was diagnosed that all the patients had non-HIV associated KS. There were 36 (39%) females and 56 (61%) males and female to male ratio was 2/3. Median age at presentation was 72 (30–93) years. ≤50 years and >50 is allocated as the 10 (11%) and 82 (89%) respectively. Of those KS, 7 (8%) were located in the upper extremity, 2 (2%) in the body, 55 (60%) in the lower extremity, and 28 (30%) in the upper and lower extremity. In terms of the number of lesions: 21 (23%) patients were diagnosed as a single lesion, 5 (5%) patients as two lesions, 9 (10%) patients as three lesions, 2 (2%) patients as four lesions, and 55 (60%) patients as ≥5 lesions. Fifteen patients (16%) had disseminated disease at the time of diagnosis while 2 (2%) patients experienced disseminated disease during follow-up. In terms of stage: 47 (51%) patients were diagnosed as Stage I, 25 (27%) patients as Stage II, 5 (5%) patients as Stage III, and 15 (17%) patients as Stage IV. Patient characteristics are summarized in Table 1.

TABLE 1 Patient characteristic

	n (%)
General	92
Age	68.78 ± 13.55 (30–93)
≤50	10 (11%)
>51	82 (89%)
Gender	
Female	36 (39%)
Male	56 (61%)
Primer site	
upper extremity	7 (8%)
body	2 (2%)
lower extremity	55 (60%)
upper and lower extremity	28 (30%)
Number of lesions	
A single lesion	21 (23%)
two lesion	5 (5%)
three lesion	9 (10%)
four lesion	2 (2%)
≥five lesions	55 (60%)
Stage	
Stage I	47 (51%)
Stage II	25 (27%)
Stage III	5 (5%)
Stage IV	15 (17%)

3.2 | Treatment

Patients were referred to RT due to the pain, itching, cosmetic disfigurement, or the impairment of life quality. Sixty-eight patients (77%) were treated with 8 Gy (1 fraction), 15 patients (16%) were treated with 20 Gy (2 Gy/fraction), 4 patients (4%) were treated 25 Gy (2.5 Gy/fraction), and 5 patients (6%) were treated 30 Gy (3 Gy/fraction). Fifteen patients (22%) who received 8 Gy RT developed the persistent disease (median 3, range: 2–13 months). Reirradiation was performed on these patients (8 Gy in ten patients, 20 Gy in five patients). Seven (10%) patients experienced new lesion outside of the RT portal and 20 Gy RT was administered to these lesions. Four patients (16%) who received ≥ 20 Gy RT developed the persistent disease (median 8, range: 4–11 months). Eight Gy reirradiation performed to these patients. Three (13%) patients experienced new lesion outside of the RT portal and 20 Gy RT was administered to these lesions. RT energy was selected by the site and depth of the tumor; 75 (82%) patients received electron beam RT, 4 (4%) patients received photon beam RT,

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and 13 (13%) patients received both electron and photon beam RT. Treatment portal for patients: single RT field for 21 patients, two RT fields for five patients, three RT fields for nine patients, four RT fields for 10 patients, five RT field for six patients, six RT fields for 10 patients, and 10–21 RT fields for 31 patients.

3.3 | Tumor response

The median follow-up time was 72 (5–192) months. Among the patients who received 8 Gy, CR was obtained in 53 (77.9%), PR was obtained in 15 (22.1%) at three months. Patients with PR were treated with reirradiation. At 6 months, CR was obtained in 8 (11.7%) and stable disease was obtained in 7 (10.2%) of PR patients. Seven patients (10.2%) developed new lesions (median 36, range 11–91 months) outside RT fields. They subsequently received another session of RT. Among the patients who received $\geq$20 Gy, CR was obtained in 20 (83.3%), PR was obtained in 4 (16.7%) at three months. At 6 months, CR was obtained in 2 (8.3%) and stable disease was obtained in 2 (8.3%) of PR patients. Three patients (13.6%) developed new lesions (median 24, range 4–41 months) outside RT fields. They subsequently received another session of RT. The CR at 5 years was 91.6% with >20 Gy and 89.6% with 8 Gy.

Until April 30, 2017, with a median follow-up of 72 months, 68 (74%) patients were alive and 24 (26%) patients have died. Nine patients died of disseminated disease and fifteen died of his underlying medical illnesses.

3.4 | Toxicity evaluation

The acute complication was observed in 57 therapy areas (61.9%) with Grades 1 and 2 toxicity. The most common side effects were infection and pain, dry desquamation, wet desquamation, both wet and dry desquamation, hyperpigmentation, swelling, and edema. There were swelling and edema resulting from RT 13% (12 patients) and 11% (10 patients), respectively. All adverse effects developed due to the RT were controlled with supportive therapy and during follow-up, no chronic and fatal toxicities occurred.

4 | DISCUSSION

KS was first described in 1872 by Moritz Kaposi. KS is a rare neoplasm and occasional spontaneous regression (Van Kessel & Quint, 2011). RT is an effective and definite treatment modality for KS. The other treatment methods such as chemotherapy, cryotherapy, immunotherapy, and surgery are of limited efficacy.

KS is seen more in men at worldwide. The literature is notified that a rate of women/men is 1/2.3 (Iscovich, Boffetta, Franceschi, Azizi, & Sarid, 2000; Wahman, Melnick, Rhame, & Potter, 1991). In this study, women/men rate was found to be 2/3. The patients presented with KS in the seventh and eighth decades of their lives (Brenner et al., 2002; Fenig et al., 1998; Weissmann, Linn, Weltfriend, & Friedman-Birnbaum, 2000). The average age was found 68 in this study. Our study, all patients had the commonly reported clinical characteristics, such as old age in presentation and the male predominance.

Treatment modalities include only observation in asymptomatic patients with normal immunocompetent, surgical excision for symptomatic resectable lesions, RT for unresectable, or more advanced disease and systemic chemotherapy for usually reserved for extensive disease or when other treatments fail.

RT is an effective, suitable treatment modality of KS. The literature is reported to produce more than 90% overall response rates and 50–90% of CR rates (Akmansu, Göksel, & Erpolat, 2011; Antman & Chang, 2000; Yıldız, Genç, & Akyürek, 2006). There is also no consensus on the optimal dose and fractionation of RT of CKS. The various studies were available in the literature and the studies have reported that the total dose of radiation, ranging from 8 to 12 Gy in one fraction to 20–30 Gy fractionated over 2 to 3 weeks, can achieve significant palliation in KS lesions (Antman & Chang, 2000; Nisce, Safai, & Poussin-Rosillo, 1981; Yıldız et al., 2006). This study, we used 8 Gy in one fraction, 20 Gy, 25 Gy, and 30 Gy in ten fractions. As known, there is no study in the literature regarding the efficacy of doses <8 Gy. The Yıldız et al. reported that CR at 12 months was 93% with 8 Gy and 60% with 6 Gy (Yıldız et al., 2006). In Caccialanza et al, study, the CR rate was 98.59% for lesions in all localizations with a total dose of 10–40 Gy; mean dose 29.24 Gy (Caccialanza, Marca, Piccinno, & Eulisse, 2008). Singh et al. compared 24 Gy in 12 fractions versus 20 Gy in five fractions. The authors concluded that CR and local control rates were not statistically different between the two arms (Singh, Lakier, & Donde, 2008). In our study, the CR at 5 years was 92% with $\geq$ 20 Gy and 86.6% with 8 Gy. In our patients had high response rates after RT similar in the literature.

Usually, RT is well tolerated with minimum toxicity. The most common side effects were infection, pain, dry desquamation, wet desquamation, both wet and dry desquamation, hyperpigmentation, swelling, and edema. In Akmansu et al. study, the ratio of acute complications was 54.8% and it was seen that a complete improvement occurred with convenient support therapy and normal foot movements were provided within 2–3 weeks after completion of RT (Akmansu et al., 2011). In Singh et al, study, acute and late skin toxicity was also not statistically different between the two arms (Singh et al., 2008). In our study, the ratio of acute complications was similar to the literature. There was no severe acute reaction to discontinue the treatment. No chronic and fatal side effects occurred.

Surgical excision, cryotherapy, intralesional (vinblastine, bleomycin, vincristine, and doxorubicin) injection, topical therapy (alitretinoin, imiquimod, timolol, and propranolol), laser therapy, electrochemotherapy or RT is used for local treatment. The choice of modality depends on a number of factors, including the site and extent of the disease involvement, as well as clinician and patient preference. Systemic treatment modality as, doxorubicin, vinblastine, bleomycin, paclitaxel, etoposide, vinorelbine, or gemcitabine are used for systemic control.

The restrictions of this study include the retrospective nature of the analysis and difference on scheduled RT dose fractionation.

5 | CONCLUSION

RT is an effective, suitable treatment modality of CKS and RT is usually well tolerated with minimal side effects. However, the prospective

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studies are warranted to determine the true benefit and toxicity of radiotherapy in the treatment of CKS patients.

ETHICAL ASPECTS

This work was in accordance with the Declaration of Helsinki, respecting the ethical and legal aspects, and was approved by the Committees for Research Ethics in the reference Institutions (Karadeniz Technical University, Faculty of Medicine, Clinical Trial Protocol number:2017-77)

CONFLICT OF INTEREST

None

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