J BUON 2013; 18(1): 268-273
ISSN: 1107-0625 www.bu-on.org/jbuon
E-mail: jbuon@ath.forthnet.gr

ORIGINAL ARTICLE

Evaluation of the role of radiotherapy in the management of dermatofibrosarcoma protuberans

B. Uysal[1], O. Sager[1], H. Gamsiz[1], A. Cicek[2], S. Demiral[1], F. Dincoglan[1], S. Surenkok[1], M. Demiriz[2], M. Beyzadeoglu[1]

[1]Department of Radiation Oncology, [2]Department of Pathology, Gulhane Military Medical Academy, Ankara, Turkey

Summary

Purpose: The aim of this study was to evaluate the role of radiotherapy (RT) in the management of dermatofibrosarcoma protuberans (DFSP).

Methods: Twenty-eight patients treated with RT for DFSP between 1974 and 2012 at Gulhane Military Medical Academy (GMMA) Radiation Oncology Department were retrospectively evaluated. Twenty-five out of 28 patients (89%) received postoperative RT and 3 received definitive RT alone. In the 25 patients receiving postoperative RT, the type of surgical excision was limited excision in 5 patients and wide excision in the remaining 20. Median RT dose was 63.21±3.7 Gy (range 50-70).

Results: At a median follow-up of 5 years, 5-year overall survival (OS) for the whole patient group was 93%. No relationship was determined between the total delivered RT dose and OS. The 5-year OS of the 10 female patients was 90% whereas it was 94% for the 18 male patients ($p>0.05$). Five-year disease-free survival (DFS) for the patients undergoing wide excision with RT vs. those undergoing limited excision with RT was significantly superior ($p <0.05$) in patients treated with wide excision and RT.

Conclusion: RT is an effective treatment option for DFSP patients with positive postoperative margins, recurrent disease and selected inoperable cases.

Key words: dermatofibrosarcoma protuberans, limited excision, radiotherapy, wide excision

Correspondence to: Bora Uysal, MD.
Gulhane Military Medical Academy, Department of Radiation Oncology, Gn. Tevfik Saglam Cad. 06018, Etlik, Kecioren, Ankara, Turkey.
Tel: +90 312 304 46 85, Fax:+90 312 304 46 80, E-mail: drborauysal@windowslive.com
Received: 01/12/2012; Accepted: 04/01/2013

Introduction

DFSP is a soft tissue neoplasm with a very limited metastatic potential, however, it has a high propensity for local invasion and recurrence.

This monoclonal dermal fibroblast-originated sarcoma, mostly arising within the dermis, has an incidence of 0.8 cases per million people per year [1]. Lesions are mostly low-grade with indolent growth, rarely metastasizing through lymphatic or hematogeneous routes but frequently recurring locally [1,2]. Lesions with high-grade fibrosarcoma components tend to behave more aggressively [3,4]. Diagnosis is often delayed until the lesions reach a large size. Trunk, head and neck, and proximal extremities comprise the most common locations for DFSP, presenting with red or pink dermal painless plaques. DFSP occurs more commonly in men, typically manifesting in the fourth decade of life. Horizontal dermal persisting growth pattern is typical prior to deep extention and fixation to the subcutaneous tissue with nodular growth. Core needle or incisional biopsy along with magnetic resonance imaging (MRI) to assess invasion depth are important steps of the work-up. DFSP is staged according to the guidelines of American Musculoskeletal Tumor Society as IA or IB, low-grade IA not extending beyond the subcutaneal compartment and low-grade IB involving fascia or muscle [4]. Surgery with clear margins constitutes the mainstay of treatment for DFSP. RT may be used either before or after surgery with regard to certain characteristics. Patients with large or unresectable tumors often receive preoperative RT, whereas postoperative RT is usually reserved for close or positive margins after surgery since local recurrence is very common in this setting. Late recurrences may occur within the postoperative period, thus close follow-up of at least 5 years is recommended. Microscopically, spindle-shaped fibroblasts surrounded by rich fibrous stroma lacking mitotic figures are the prominent histopathological features of DFSP (Figure 1). DFSP commonly arises in hairy skin, face and neck, however it may also be seen in different localizations throughout the body. Insidious tumor growth may preclude prompt detection and diagnosis of DFSP. CD34 (Figure 2) and apolipoprotein-D are highly expressed in DFSP with ambiguous prognostic significance [5]. Differential diagnosis of DFSP includes epidermal inclusion cyst, keloid, hypertrophic scar, malignant melanoma and metastatic carcinoma [6]. The incidence of DFSP is increasing in women and decreasing in men albeit with male predominance. Typical disease presentation is at the fourth decade. Although histologically low-grade and borderline, DFSP has a high propensity for local recurrence after simple excision. Fibrosarcomatous changes and multiple recurrences may be seen throughout the life span of DFSP patients. To minimize the risk of local and distant failure, optimal tumor control should be achieved with rigorous treatment notwithstanding cosmetic considerations. In the management of DFSP, excellent outcomes may be achieved with a multidisciplinary treatment approach [7]. Surgery is a *sine-quanon* for cure, and resection with wide clear surgical margins provide high local control rates of over 90%. Mohs micrographic surgery, an emerging surgical technique, provides superior local control rates compared to wide local excision [8,9]. However, complete surgical removal of the tumor may not be achieved in some circumstances and development of local recurrence remains a major problem in the setting of positive or close surgical margins. Definitive RT is a viable therapeutic option in the management of patients with unresectable tumors or in the presence of positive surgical margins [10]. Distant metastasis develops in 5% of DFSP patients despite surgery. Imatinib, a molecular-targeted agent, is currently used as another therapeutic option in the management of patients with unresectable, metastatic DFSP [11]. In this study, we evaluated the role of RT in the management of DFSP, making also a literature review.

Methods

Twenty-eight patients with DFSP, treated at GMMA, Department of Radiation Oncology, between 1974 and 2012 were studied. Parameters including age, gender, surgical method, RT dose, DFS, tumor localization and lesion size were assessed. Twenty-five out of 28 patients (89%) received postoperative RT and 3 patients received definitive RT alone. The 3 patients treated with definitive RT were not amenable to surgery due to critical tumor localization and comor-

Table 1. Patient, disease and radiotherapy characteristics

Patient number	*Age (years)*	*Gender M/F*	*Location*	*Stage*	*RT dose (Gy)*	*Follow-up (months)*
1	88	M	H/N	IA	60	120
2	43	F	T	IA	60	60
3	30	F	E.	IB	66	60
4	21	M	T	IB	66	120
5	28	M	E	IB	60	60
6	30	M	E	IA	70	120
7	29	M	E	IA	60	120
8	22	F	T	IA	60	60
9	23	M	E	IB	60	60
10	20	F	E	IA	66	24
11	26	M	E	IB	60	24
12	35	M	E	IB	60	60
13	23	M	E	IA	60	60
14	36	M	H/N	IB	60	120
15	20	F	T	IB	66	60
16	25	F	E	IA	60	60
17	26	M	E	IB	66	24
18	21	M	T	IA	60	24
19	38	M	H/N	IA	70	60
20	24	F	E	IA	66	120
21	27	F	E	IA	60	60
22	29	M	E	IA	66	120
23	22	M	E	IA	60	120
24	21	M	T	IA	70	60
25	24	M	H/N	IA	60	120
26	27	M	E	IA	66	120
27	31	F	E	IA	66	120
28	23	F	E	IA	66	120

M: male, F: female, H/N: head/neck, E: extremity, T: trunk

bidities. Eleven patients in the postoperative RT group were delivered RT because of recurrent disease after surgery and the other 14 patients were irradiated owing to postoperative surgical margin positivity. In the postoperative group of 25 patients, the types of surgical excision were limited excision in 5 patients and wide excision in 20 patients. Three patients treated with definitive RT were diagnosed by incisional biopsy only.

Radiotherapy

Median RT dose was 63.21±3.7 Gy (range 50-70) in 25-35 fractions. RT was delivered using a Linear Accelerator (LINAC) (Elekta Synergy, UK) or Co-60 Teletherapy Device at GMMA Radiation Oncology Department. Co-60 was used between 1974 and 1996, and from 1996 till 2012 LINAC-based therapies were introduced. Scar tissue was marked with flexible wire during RT simulation. Intravenous contrast was used in the simulation process to improve tumor localization. The planning computed tomography (CT) images with 2.5 mm slice spacing were acquired using CT-simulator (GE Lightspeed RT, GE Healthcare, Chalfont St. Giles, UK) and were sent to Sim MD simulation and localization software (Advantage SimMD, GE, UK) for contouring treatment volumes and organs-at-risk. Planning Target Volume

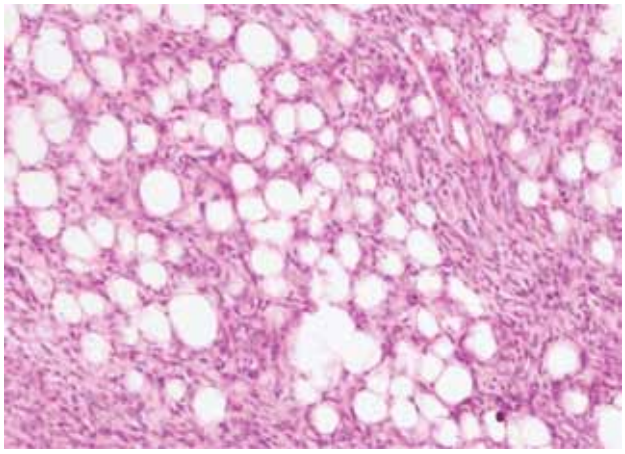

Figure 1. Tumor infiltrating the deeper dermis and subcutaneous adipose tissue. Characteristic honeycomb pattern with neoplastic cell infiltration between adipocytes in adipose tissue (H&E, x40).

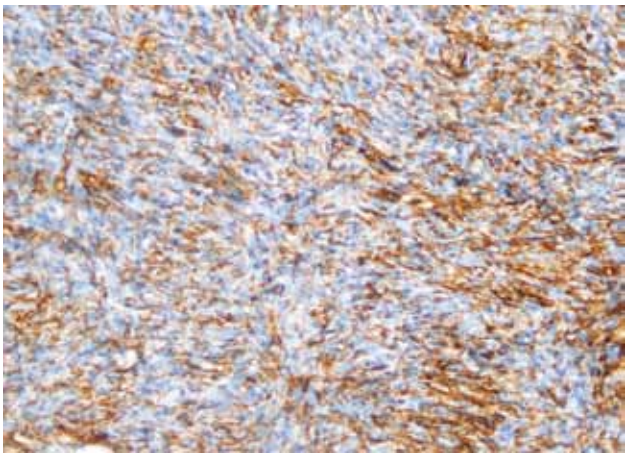

Figure 2. Cytoplasmic and membranous diffuse CD34 positivity (immunohistochemistry, x40).

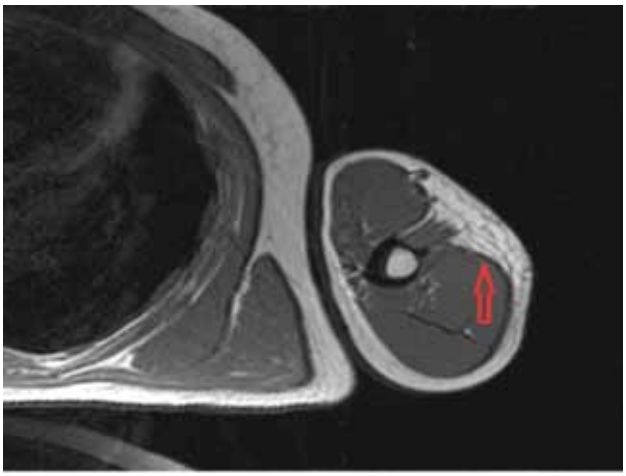

Figure 3a. Preoperative CT of a DFSP patient. Arrow shows the subcutaneous tumor.

(PTV) was generated by adding 2-3 cm mediolateral and 5-8 cm craniocaudal margins to the Clinical Target Volume (CTV). Two cm normal tissue was spared for lymphatic drainage mediolaterally. After treatment planning, RT was delivered under image guidance for set-up verification. Preoperative and posttreatment CT of a patient is shown in Figure 3a and 3b.

Statistics

The Statistical Package for Social Sciences, version 16.0 (SPSS Inc., Chicago, IL) software was used for statistical analyses. Student's-t test was used to assess the relationship between RT dose and survival whereas Fischer's exact test was used to determine the relationship between gender and survival. Five-year DFS of the patients receiving RT after wide excision or limited excision were comparatively evaluated; 5-year OS survival was also determined. The level of significance was set at $p < 0.05$.

Results

Age, gender, surgical method, RT dose, tumor localization and lesion size were evaluated statistically. Patient characteristics are shown in Table 1. Median age was 26 years (range 20-88). Eighteen out of 28 DFSP patients (64.3%) were male and 10 (35.7%) female. The DFSP localization was 64% in the extremities, 22% in the trunk and 14% in the head and neck region. Eighty percent of the surgically treated patients (N=20) had

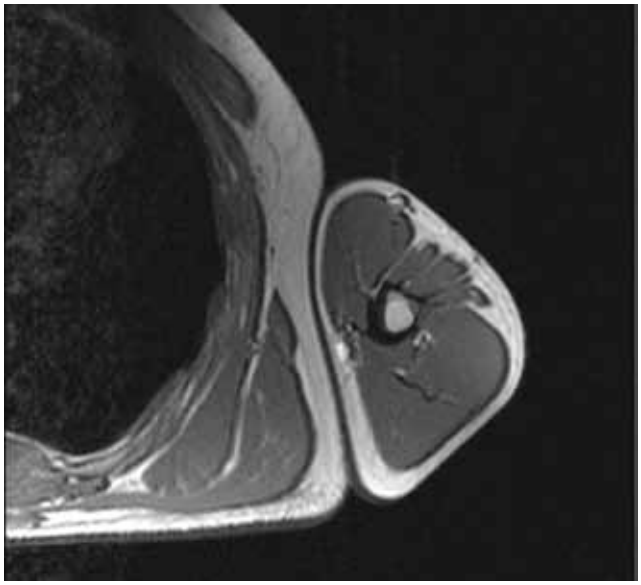

Figure 3b. Posttreatment CT of the DFSP patient in Figure 3a.

excisional biopsy and 20% (N=5) had limited excision. Diagnostic incisional biopsy was performed in 3 patients receiving definitive RT. These 3 patients treated with definitive RT were not amenable to surgery due to tumor localization in close proximity to nerves and vessels or had severe comorbidities precluding surgical resection. The median lesion size according to the examination of the postsurgery or biopsy pathological material was 5.2 cm (range 2.1-8.4). The median RT dose delivered was 63.21±3.7 Gy (range 50-70). The RT doses varied according to postoperative or definitive treatment intent along with improvements in the planning systems in years. All patients were followed up for a median of 80.57 months (range 24-120). The 5-year OS of the whole study group was 93%. Local recurrence occurred in 3 of the 5 locally excised patients with limited surgery and 2 patients with recurrence died of pulmonary metastases. Student's-t test was used to assess the relationship between RT dose and OS, revealing no statistically significant effect of RT dose on OS ($p>0.05$). Fischer's exact test was used to determine the relationship between gender and survival and showed statistical significance in favor of women compared to men ($p<0.05$). Five-year RFS of the 20 patients receiving RT after wide excision was 89.6% and 5-year RFS of the 5 patients who were treated with adjuvant RT after limited excision was 74%, revealing statistically significant difference between limited excision+RT vs. wide excision+RT groups ($p<0.05$).

Discussion

DFSP is a highly recurring but rarely metastasizing cutaneous low-grade malignancy. DFSP is geneticall related with Col1A1 gene in chromosome 17 and PDGFB (platelet derived growth factor B) in chromosome 22 [12]. Surgery is the cornerstone of treatment and definitive surgery may be performed as wide excision or as Mohs micrographic surgery [13,14]. In our study, 25 out of 28 patients underwent definitive surgery, however, Mohs micrographic surgery was not used in any patient. Systemic chemotherapeutic agents were used for many years in high-grade DFSP with limited success, whereas molecular-targeted therapy agents are expected to introduce encouraging results as the molecular biology of the disease becomes more clearly understood. During follow-up, 2 out of 28 patients had local recurrences and underwent repeated limited excisions. These 2 patients died of distant failure and none of them received imatinib. In case of complete resection but with close surgical margins, some authors favor no adjuvant RT, considering the chance of reexcision in a future recurrence, surgical margin positivity, large tumor size along with unresectable tumor sites requiring postoperative RT with minimal morbidity. However, optimal tumor control is required to minimize the risk of local and distant failure, and incorporating RT to the management of these patients with close surgical margins may improve treatment outcomes. Clearly, recent technological advances have substantially improved the toxicity profile of radiation delivery, thus making RT a viable therapeutic option. Dose-response relationship is not clear for postoperative RT and doses of 50-55 Gy are used for either subclinical or gross disease. Achieving tumor response may take 6 months, but it may also take longer, about 1-2 years in the course of follow-up [15]. DFSP is a rare soft tissue tumor. It is locally aggressive and has a high propensity for recurrence after excision. In a study by Marks et al. with 10 patients, 3 DFSP patients received definitive RT of 66.7-75 Gy and 7 of them received adjuvant RT at a dose of 60-67 Gy to eradicate microscopic residual disease [16].

The definitive and postoperative RT doses we used in our study are consistent with the literature. In a study by Dagan et al., 10 DFSP patients were delivered postoperative RT and 9 of them had a significantly long DFS after the completion of therapy. One patient out of 10 had recurred early and died of the disease. No acute or late complications were noted [17]. In another study by Mendenhall et al. , local control rate was over 85% with postoperative RT in cases with surgical margin positivity or close surgical margins. The experience in usage of RT was evaluated in unresectable macroscopic DFSP patients [4]. DFSP is a moderately radioresponsive tumor. Ballo et al. recommended adjuvant RT doses of 50-60 Gy in case of postoperative surgical margin positivity [2]. Ni et al. reported 28 DFSP patients in the head and neck region; local recurrence significantly decreased with wide excision and adjuvant RT essential in

the setting of close surgical margins and surgical margin positivity recommending immediate reconstruction for large defects [18]. Recently, imatinib, a tyrosine kinase inhibitor, is used as an effective treatment option [19].

RT can be used alone or after surgery in cases with positive surgical margins and can increase local control and DFS rates. Multidisciplinary approach may increase local control rates in the management of DFSP [20,21]. Studies on the role of RT in the treatment of DFSP are limited and this study is upholding the use of adjuvant and definitive RT in the management of DFSP where surgery is a *sine-qua-non* for cure. In conclusion, DFSP is a rare disease benefiting from the combination of conservative surgery with adjuvant RT, resulting in high local control rates. This retrospective study with a limited number of patients suggests that RT is an effective treatment modality in DFSP management that can be used after surgery in cases with positive surgical margins, postoperative recurrences and as the sole definitive therapy for patients with unresectable disease.

References

1. Miller S, Alam M, Andersen J et al. Dermatofibrosarcoma protuberans. J Natl Compr Cancer Netw 2012; 10:312-318.
2. Ballo MT, Zagars GK, Pisters P et al. The role of radiation therapy in the management of dermatofibrosarcoma protuberans. Int J Radiat Oncol Biol Phys 1998; 40: 823-827.
3. Dogan R, Morris C, Zlotecki et al. Radiotherapy in the treatment of dermatofibrosarcoma protuberans. Am J Clin Oncol 2005; 28: 537-539.
4. Mendenhall WM, Ziotecki RA, Scarborough MT. Dermatofibrosarcoma protuberans. Cancer 2004; 101: 2503-2508.
5. Palmerini E, Gambarotti M, Staals EL, Zanella L, Sieberova G, Longhi A. Fibrosarcomatous changes and expression of CD34+ and apolipoprotein-D in dermatofibrosarcoma protuberans. Clin Sarcoma Res 2012; 2: 4-9.
6. Rahman GA, Adigun IA, Buhari MO, Ogundipe KO, Omotayo JA. Dermatofibrosarcoma Protuberans: Experience with Management of Eighteen Cases. Eur J Sci Res 2009; 25: 145-150.
7. Matrai Z, Liszkay G, Plotar V, Orosz Z, Szekely J, Hitre E. Long-term experience with multidisciplinary therapy of twenty-six patients with dermatofibrosarcoma protuberans. Orv Hetil 2009; 150: 1894-1902.
8. Gunderson L. Dermatofibrosarcoma protuberans. In: Tepper J (Ed): Clinical Radiation Oncology (3rd Edn). Oxford: Elsevier, 2011, pp 1362-1363.
9. Bogucki B, Neuhaus I, Hurst EA. Dermatofibrosarcoma protuberans: A review of the literature. Dermatol Surg 2012; 38: 537-551.
10. Suit H, Spiro I, Mankin HJ, Efird J, Rosenberg AE. Radiation in management of patients with dermatofibrosarcoma protuberans. J Clin Oncol 1996; 14: 2365-2369.
11. Malhotra B, Schuetze SM. Dermatofibrosarcoma protuberans treatment with platelet-derived growth factor receptor inhibitor: a review of clinical trial results. Curr Opin Oncol 2012; 24: 419-424.
12. Fattoruso SI, Visca P, Lopez M. Molecular approach in the treatment of dermatofibrosarcoma protuberans. Clin Ther 2008; 159: 361-367.
13. Angouridakis N, Kafas P, Jerjes W, Triaridis S, Upile T, Karkavelas G. Dermatofibrosarcoma protuberans with fibrosarcomatous transformation of the head and neck. Head Neck Oncol 2011; 3:5-11.
14. Xiang Q, Lu W, He X, Li H. Surgical treatment of dermatofibrosarcoma protuberans using wide local excision combined with Mohs micrographic surgery. Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi 2011; 25: 1350-1353.
15. Ballo MT, Zagars GK, Pollack A et al. Desmoid tumor: Prognostic factors and outcome after surgery, radiation therapy, or combined surgery and radiation therapy. J Clin Oncol 1999; 17: 158-167.
16. Marks LB, Suit HD, Rosenborg AE, Wood WC. Dermatofibrosarcoma protuberans treated with radiation therapy. Int J Radiat Oncol Biol Phys 1989; 17: 379-384.
17. Dagan R, Morris CG, Zlotecki RA, Scarborough MT, Mendenhall WM. Radiotherapy in the treatment of dermatofibrosarcoma protuberans. Am J Clin Oncol 2005; 28: 537-539.
18. Ni S, Xu ZG, Wang XL, Liu SY, Lu N, Xue LY. Clinical analysis of dermatofibrosarcoma protuberans in head and neck. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2007; 42: 404-407.
19. Llombart B, Serra-Guillen C, Monteagudo C, Lopez Guerrero JA, Sanmartin O. Dermatofibrosarcoma protuberans: A comprehensive review and update on diagnosis and management. Semin Diagn Pathol 2013; 30: 13-28.
20. Xiushen W, Mengzhong L, Hui L, Nianji C. The role of radiotherapy in 74 patients with dermatofibrosarcoma protuberans. The Chin-German J Clin Oncol 2006; 5: 454-457.
21. Derek D, Vincent C, Lori L, Timothy MJ, Vernon KS. Low recurrence rate after surgery for dermatofibrosarcoma protuberans. Cancer 2004; 100: 1008-1016.