# Adjuvant radiotherapy for dermatofibrosarcoma protuberans: a case report

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**Abstract:** Dermatofibrosarcoma protuberans (DFSP) is a rare and slowly growing tumor. Inadequate surgical resection is associated with a high recurrence rate. However, complete resection with wide margins in some cases may cause cosmetic or functional deficits. Previous studies suggest that adjuvant radiotherapy (RT) can effectively decrease the local recurrence rate. We report the case of a tumor in the right shoulder of a 25-year-old woman, in which the tumor was located adjacent to the skin and joint. She underwent wide excision of this tumor, and the pathologic findings of this tumor showed DFSP with close margins. She was subsequently administered intensity modulated radiation therapy (IMRT) of 46 Gy with 2 Gy per fraction for the tumor bed and wide margins followed by 14 Gy with 2 Gy per fraction for the tumor bed boost. She remained disease-free during the 3-year follow-up. This finding indicates that adjuvant RT is considered for patients with DFSP who have close margins or in whom wide surgical margins are not feasible.

Keywords: Dermatofibrosarcoma protuberans (DFSP); radiotherapy (RT)

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## Introduction

Dermatofibrosarcoma protuberans (DFSP) is an uncommon cutaneous sarcoma of fibroblast origin (1) DFSP constitutes approximately 1% of all sarcomas and <0.1% of all malignancies (2,3). These tumors tend to grow slowly and rarely metastasize (4,5). DFSP generally presents an asymptomatic, firm, protuberant swollen nodule or plaque (4,5). The typical presentation of DFSP is a long history (ranging from months to several years) of a slowly growing indurated dermal plaque or nodule with subsequent nodules appearing at later stages (5,6). Clinically, these are firm to hard lesions that are fixed to the skin and vary in color from brown to reddish-blue or violaceous (5,6).

The standard treatment for localized primary or recurrent DFSP is radical and wide local excision for achieving clear margins (7). The local recurrence rates after surgery have been reported to be 10–60% depending on the nature of the surgery and margin status of DFSP (7-12).

Mohs micrographic surgery (a technique of repeated surgery involving immediate microscopic examination of the tumor margin after excision until excision is complete) and wide surgical excision with 2–4 cm margins are recommended for DFSP (8,11,12). However, Mohs micrographic surgery is time-consuming and is not suitable for large tumors, whereas wide excision with resection margins  $\geq$ 3 cm may cause higher reconstruction rates (13).

For patients with DFSP in whom tumors cannot attain negative margins after surgery, adjuvant radiotherapy (RT) may be considered to improve local control and prevent undesired cosmetic or functional outcomes (14). Herein, we describe a rare case of DFSP in the right shoulder of a 25-year-old woman treated with excision and adjuvant RT.

## **Brief history**

A 25-year-old woman had a 2×2 cm-sized red-purple

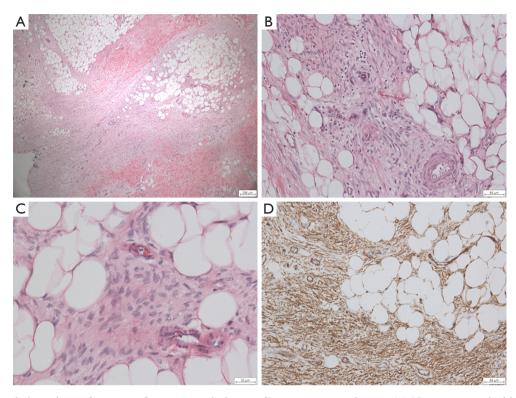


Figure 1 The histopathological manifestations of a patient with dermatofibrosarcoma protuberans. (A) Non-circumscribed hyper-cellular areas in scarring background, composed of thin spindle cells with scant cytoplasm, infiltrating into subcutaneous tissue and entrapping adipose tissue [hematoxylin eosin (H&E) staining, original magnification  $\times$  40]; (B) findings are similar to A, original magnification  $\times$ 200 (H&E); (C) findings are similar to A, original magnification  $\times$ 400 (H&E); (D) immunohistochemically, these tumor cells are diffusely positive for CD34, original magnification  $\times$ 200.

painless erosion in the right shoulder about 10 years ago. The skin lesion changed to a painless plaque 1 year ago. However, the plaque enlarged gradually. She then underwent excisional biopsy at a local hospital in November 2015. Histological evaluation revealed an ill-defined lesion throughout the thickness of the dermis and largely extending to the subcutis, comprising slender to plump spindle cells with low to high cellularity, mild nuclear atypia, and various amounts of collagenous matrix. Mitoses were occasionally found. DFSP was diagnosed based on the morphologic findings and immunohistochemical staining, which showed positivity for cluster of differentiation 34 (CD34) and negativity for S-100. The maximum dimension of the tumor was 1.7 cm. The basal cut margins were involved by tumor. She visited the physician at our hospital. Under the suspicion of positive margins of postoperative DFSP, she underwent wide excision in December 2015. The pathology report showed some non-circumscribed hyper-cellular areas in scarring in the background, composed of thin

spindle cells with scant cytoplasm, infiltrating subcutaneous tissue and entrapping adipose tissue (*Figure 1*). No conspicuous nuclear atypia or mitosis was observed. These tumor cells were diffusely positive for CD34 (*Figure 1*). In this case report, the expression of Ki-67 in tumor cells of this patient is around 3% to 5%. Foci of the section margins were close, but free. Because of the close section margins of DFSP, she then received adjuvant RT 1 month after reexcision. We administered intensity modulated radiation therapy (IMRT) to reduce the inhomogeneity and dose of the humeral head and improve the planned target volume dose coverage. The patient was immobilized with a prone pillow. A 0.5-cm bolus was placed on the skin to achieve adequate surface dose.

In this study, the gross tumor volume (GTV) [clinical target volume (CTV) boost] was defined as tumor bed (including surgical scar) according to post-operative MRI imaging and operation scar. To avoid anatomical boundaries (no penetrate deltoid muscle), the CTV was defined as

GTV (CTV boost) plus 3 cm margins in the superior and inferior directions and 1 to 1.5 cm margins in the medial and lateral directions. The planning target volume (PTV) was defined as CTV plus 5 mm margin, and the PTV boost was defined as CTV boost with 5 mm margin. The prescribed radiation dose for this patient was 46 Gy with 2 Gy per fraction to the CTV and PTV followed by 14 Gy with 2 Gy per fraction to the CTV boost and PTV boost. We used four fields (Figure 2A), 6 MV, coplanar, IMRT plans that were generated on the Eclipse Treatment Planning System, Version 13.0. Considering the target volumes of this patient were shoulder and upper extremity, dose constraints for organ at risk (OAR) in this patient were as follows: V20 (volume receiving at least 20 Gy) for lung <10%, V30 (volume receiving at least 30 Gy) for bone <50% (included humerus), and maximal doses for esophagus and spinal cord were  $\leq 15$  Gy.

As shown in *Figure 2B*, the proportion of CTV receiving 95% and PTV receiving 95% of the prescription dose of 46 Gy were 98% and 97.3%, respectively. The proportion of CTV boost receiving 95% and PTV boost receiving 95% of the prescription dose of 14 Gy were 100% and 98.6%, respectively (Figure 2C). As shown in Figure 3, the humerus of V30 was less than 35%. The patient experienced the greatest acute toxicity of grade 2 skin reaction at irradiated field. Fortunately, she had neither local recurrence nor grade 2 to 3 late adverse effects following the irradiation during the 3-year follow-up. The study protocol of retrospective analyses of the relationship between adjuvant RT and clinical outcomes of sarcoma was approved by the Research Ethics Committee of National Taiwan University Hospital. The patients' medical data were anonymized prior to the access and analysis.

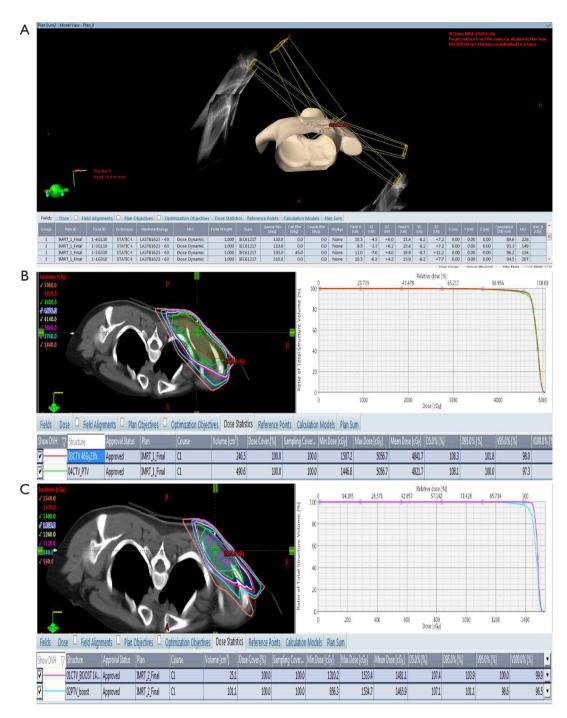
# Discussion

DFSP is a malignant fibroblastic tumor that most frequently arises in middle-aged individuals, with the peak age ranging from 25 to 45 years (4,5). The most common sites of DFSP are the trunk (40–50%), proximal extremities (30–40%), and head and neck (10–15%) (6,15). Morphologically, DFSP is characterized by a uniform population of small, slender to plump spindle cells with diffuse CD34 expression (6,15,16). However, the diagnosis for DFSP is frequently delayed because of many differential diagnoses (other spindle cell neoplasms) and the typically low clinical suspicion of malignancy in this slowly growing lesion (3,6,15). Despite frequent prolonged delays in the diagnosis of DFSP, metastasis to the lymph nodes or distant sites is very rare (<5%) (2,8); the most common site of metastasis for DFSP is the lungs (7).

DFSP consists of different histological subtypes, including conventional (classical) DFSP, sclerotic DFSP, giant cell fibroblastoma (a juvenile form of DFSP), pigmented DFSP (also known as Bednar tumor), myxoid DFSP, atrophic DFSP, and fibrosarcomatous DFSP (17,18). Among these subtypes, fibrosarcomatous DFSP is noticeable as the most aggressive subtype which has higher risks of local recurrences and distant metastases, whereas conventional DFSP is the most common subtypes and also has risk of local recurrence (around 20% to 50%) but rarely develops metastases (18-20). Pigmented DFSP, a rare neoplasm (around 5% of DFSP), presenting during early or middle adult life, is characterized by the histological manifestations of melanin-containing dendritic cells (most tumor cells are positive for CD34, like our case presented) within the tumor (21,22). Clinically, patients with pigmented DFSP have around 10% to 13% local recurrence rates and very rare distant metastases (21,22). Other subtypes of DFSP, such as sclerotic DFSP, giant cell fibroblastoma, myxoid DFSP, and atrophic DFSP were tremendously rare (17,18).

More than 90% of patients with DFSP harbor a specific reciprocal rearrangement of chromosomes 17 and 22: t(17;22)(q22;q13) (6,17,23). The rearrangement of t(17;22) (q22;q13) leads to the fusion of the platelet-derived growth factor beta (PDGF $\beta$ ) gene with the collagen type 1 alpha 1 (COL1A1) gene (3,6,24). The formation of the COL1A1–PDGF $\beta$  fusion gene results in the constitutive upregulation in the expression of PDGF $\beta$  (24). PDGF $\beta$  has been reported to stimulate cell growth, differentiation, and migration of tumor cells in DFSP (25,26). Several reports have described the usefulness of imatinib, a tyrosine-kinase inhibitor that inhibits PDGF receptors, in the treatment of metastatic and localized unresectable DFSP (4,6).

Considering that Ki-67 is a protein that involved in cell proliferation and severed as a reliable marker for detecting proliferation activities of tumor cells (27), several studies reported the association of Ki-67 with clinicopathological manifestations of DFSP (28-30). Zorlu *et al.* reported that the Ki-67 labeling index was different in the primary tumor (2%), in the recurrent tumor (15% to 20%), and in metastatic sites of lung (70%) of a 22-year-old woman with a classical cutaneous DFSP (28). Gu *et al.* also described a case of congenital DFSP with fibrosarcomatous and myxoid change, in which the Ki-67 labeling index was higher



**Figure 2** The beam arrangement and dose distribution of two-phase radiation treatment planning in a patient with dermatofibrosarcoma protuberans. (A) Four beam arrangement, 6 MV, coplanar, IMRT plans; (B) an isodose curve of adjuvant RT comprising the CTV and PTV is shown in an axial view (left panel) and cumulative DVH for this patient is shown in right panel. The proportion of CTV receiving 95% and PTV receiving 95% of the prescription dose of 46 Gy were 98% and 97.3%, respectively; (C) an isodose curve of adjuvant RT comprising the CTV boost and PTV boost is shown in an axial view (left panel) and cumulative (left panel) and cumulative DVH for this patient is shown in right panel. The proportion of CTV boost and PTV boost is shown in an axial view (left panel) and cumulative DVH for this patient is shown in right panel. The proportion of CTV boost receiving 95% and PTV boost receiving 95% of the prescription dose of 14 Gy were 100% and 98.6%, respectively. IMRT, intensity modulated radiation therapy; CTV, clinical target volume; PTV, planning target volume; DVH, dose-volume histogram; RT, radiotherapy.

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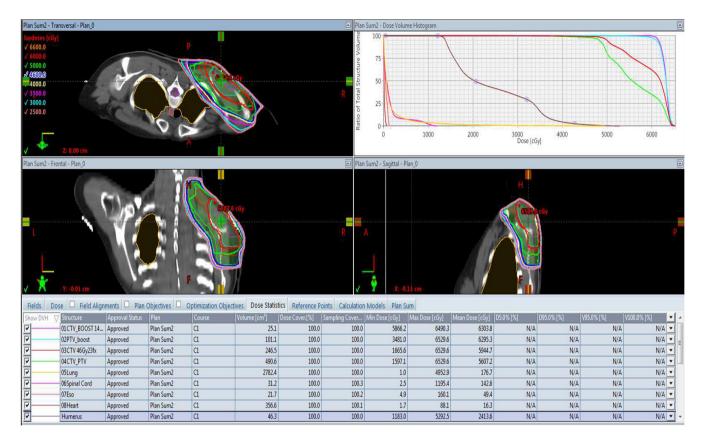


Figure 3 The summarized radiation field and treatment planning in a patient with dermatofibrosarcoma protuberans. (A) An isodose curve of adjuvant radiotherapy comprising the CTV, PTV, CTV boost, and PTV boost is shown in an axial view, in sagittal view, and in coronal view. A cumulative dose-volume histogram for CTV, PTV, CTV boost, and PTV boost, and for normal organ, such as esophagus, lung, spinal cord, and humerus for this patient is shown in right upper panel and lower panel. CTV, clinical target volume; PTV, planning target volume.

in components of fibrosarcomatous area (11.8%) and of myxoid areas (19.8%), but was lower in ordinary (plaquelike) area (2.2%) (29). In a recent analyses of relationship between Ki-67 labeling index and prognosis of 56 cases of DFSP, Du *et al.* reported that the Ki-67 expression ( $\geq$ 17%) was associated with age (<50 years old) (P=0.047) and fibrosarcomatous histological subtype (P=0.003) (30). Du also showed that patients with high expression of Ki-67 in tumor cells had a poor 5-year disease-free survival (DFS) than those with low Ki-67 expression in tumor cells (35.8% *vs.* 87.8%, P=0.002) (30). These results indicated that higher expression of Ki-67 may be closely associated with aggressive histology subtype, such as fibrosarcomatous DFSP, and higher risk of recurrence and distant metastases of DFSP.

Because DFSP is a rare tumor, there are no prospective

randomized trials evaluating adjuvant RT in decreasing local recurrence. Castle et al. retrospectively reviewed the outcomes of 53 patients with DFSP who were treated with preoperative RT (n=7; RT dose, 50-50.4 Gy) or postoperative RT (n=46; RT dose, 60-66 Gy) revealed an excellent local control rate of 93% after 10 years of implementing the combined modality approach (31). Williams et al. reported that 12 (92.3%) out of 13 patients with DFSP who underwent surgery followed by RT remained disease-free at a median follow-up of 10.5 years (32). Woo et al. also reported that the recurrence rate for patients with DFSP who underwent marginal excision was higher in the non-adjuvant RT group than that in the adjuvant RT group (60% vs. 0%) (13). A systemic review and metaanalysis of DFSP by Chen et al. demonstrated that surgery and adjuvant RT conferred a trend of lower recurrence

Authors, references Case number and margin status		Radiation dose	Local control	Interpretation
Woo <i>et al.</i> (13)	RT n=6 (negative margin n=2); no RT n=10 (negative margin n=4)	60 Gy	100% vs. 40% (median follow-up 65 months)	Adjuvant RT significantly reduced recurrence in the marginal excision cases
Du e <i>t al.</i> (30)	RT n=44; no RT n =140; propensity score matched cohort	50–66 Gy	5-year DFS 88.1% vs. 56.2%, P=0.044)	DFS was higher in the OP + RT group
Williams <i>et al.</i> (32)	n=13 (negative margin n=4	55.8–66 Gy	92.3% (median follow-up 10.5 years)	RT may improve local control in patients with DFSP
Chen <i>et al.</i> (33)	n=167 (positive/close margin n=92; meta-analysis)	57–65 Gy	88.26%	There was a trend that adjuvant RT had a lower recurrence rate than surgery alone (odds ratio 0.31, P=0.07)

Table 1 Selected studies and results of radiation for dermatofibrosarcoma protuberans

RT, radiotherapy; DFS, dermatofibrosarcoma protuberans; DFS, disease-free survival; OP, operation.

rates than those conferred by surgery alone (odds ratio 0.31, P=0.07), in which the pooled estimate of the recurrence rate for the surgery and adjuvant RT group was 11.74% (33). Du et al. used propensity score-matched analysis to minimize the selection bias and found that DFS was significantly higher in the surgery and RT group than in the surgery group (5-year DFS, 88.1% vs. 56.2%, P=0.044) (30). These findings suggest that adjuvant RT following surgery is considered as a treatment modality for DFSP (Table 1). The risk of radiation-related toxicity for DFSP should be considered. For example, Sun et al. reported that 6 (28.6%) out of 11 patients who received adjuvant RT ranging from 46 to 68 Gy had grade 2 fibrosis or telangiectasia (34). Castle et al. showed that 7 patients (13%) had radiationrelated complications at 5 and 10 years (31). Huber et al. reported 8 patients developed radiation-induced sarcoma, including DFSP, at their primary irradiated site after a median 7.35 years of RT (35). The prognosis of these patients was very poor, indicating that the possible cons of radiation-related sarcoma should be discussed with patients with DFSP who will receive adjuvant RT (35).

#### Conclusions

In summary, DFSP is a rare malignancy with a high recurrence rate, especially in patients with positive margin status. Adjuvant RT has the potential efficacy to reduce the local recurrence. Furthermore, for patients with large tumors, especially when wide excision with negative margins may cause undesired cosmetic or functional outcomes, postoperative RT is highly recommended. However, the dose-response relationship for adjuvant RT has not been established, and doses of 55–65 Gy have been used in most published studies, including our study. Recently, two studies evaluated the use of imatinib as a neoadjuvant therapy in decreasing the preoperative tumor size in DFSP (36,37). Further studies evaluating combined modalities including neoadjuvant imatinib treatment and reducing the need for wide resection margins followed by diminished RT fields to reduce late adverse effects in patients with DFSP, are warranted.

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#### Footnote

*Conflicts of Interest:* SHK serves as an Associate Editors-in-Chief of *Therapeutic Radiology and Oncology* from Oct 2017 to Sep 2019. MYH has no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this manuscript and any accompanying images.

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