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Case Report

Re-Irradiation after Radical Dose Radiotherapy: A Case Report Challenging an Established Dogma

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Abstract
Traditionally, external beam radiation therapy has a dogma pronouncing that re-irradiation of a region previously exposed to radical dose radiotherapy is contraindicated due to unacceptable risk to surrounding tissues. This edict is often zealously maintained to the detriment of certain, carefully selected patients that may benefit from re-irradiation. Liposarcoma is a high-grade malignancy with a poor prognosis and high rates of recurrence. A case is described of multiply recurrent liposarcoma that we treated with re-irradiation of an extended field encompassing the gross recurrent tumor mass and including the previously irradiated region. The patient had a very good cosmetic outcome and remained disease-free after 3 years of follow-up. The case demonstrates the potential to significantly improve patient care if established dogmas are challenged related to the re-irradiation of recurrent high-grade tumors. We propose that with careful patient selection, re-irradiation can be delivered safely to patients with recurrent tumors and contribute to improved clinical outcomes.

Introduction

Re-irradiation after radical dose of external beam radiotherapy (EBRT) to the same region has generally been regarded as contraindicated due to it posing unacceptable risk to normal surrounding tissue and it being ineffectual for achieving local disease control. A patient is

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described with a large, multiply recurrent dedifferentiated liposarcoma of the right trunk that was curatively salvaged with high-dose re-irradiation concurrently combined with radiosensitizing chemotherapy and reconstructive surgery. The case demonstrates a novel treatment approach that challenges established dogma, and we propose that re-irradiation in selected circumstances can form part of an effective and safe treatment plan. Patient consent was provided, and formal approval was granted from the Local Human Research Ethics Committee. The CARE Checklist has been completed by the authors for this case report and it is attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000534180).

Case Report

A 73-year-old man was diagnosed with a grade 2 well-differentiated liposarcoma of the right abdominal wall in 2013. Treatment was with surgical resection and reconstruction of the right abdominal wall. In 2015, he developed bulky local recurrence extending into the right flank, and an en bloc resection of the recurrent tumor showed recurrent liposarcoma with dedifferentiated components and involved margins. He had surgical reconstruction of the right abdominal wall and adjuvant radiotherapy given to the resected region with wide margins comprising 60 Gy in 30 fractions. In 2020, he presented to our institution with biopsy-proven second recurrence at the superior edge of the previous treatment area. CT scan showed significant local infiltration into the right chest wall with 9th and 10th rib erosion, and invasion into the right upper abdominal cavity and rectus sheath (shown in Fig. 1a, b). FDG PET CT did not show distant metastasis.

After discussion at a Sarcoma Multidisciplinary Tumor Board, salvage surgery was not considered feasible, and an individualized approach was taken utilizing radiosensitizing doxorubicin chemotherapy followed immediately by hyperfractionated radiotherapy. 30 Gy in 20 fractions of EBRT was delivered bi-daily over 2-week period to an extended field including the gross tumor recurrence. Anisotropic margins were delivered in the craniocaudal and anteromediolateral extent for the at-risk regions, while limiting the radiation dose posteriorly to the uninvolved tissues, especially the lung, liver, kidney, spinal cord, small and large bowel viscera. Simultaneous integrated boost of 40 Gy to the gross tumor volume was planned and delivered using sophisticated volumetric modulated arc therapy (VMAT) EBRT technique.

Progress FDG PET CT depicted significant metabolic regression, and MRI showed significant radiological regression. Surgery was performed 3 months later and involved wide excision of the recurrence site including resection of five right-sided ribs with Gore-Tex thoracoplasty and a left latissimus dorsi musculocutaneous free flap reconstruction (shown in Fig. 1c, d). Histopathology revealed complete pathologic response with no residual viable malignant cells. The patient has remained disease-free with 6 monthly FGD PET CT scans and close clinical surveillance for 3 years after salvage multimodality treatment. There was no progression of the existing soft-tissue fibrosis and telangiectasia that occurred following prior to EBRT. He has had excellent functional outcome with no ongoing analgesic requirement.

Discussion

The case presented was challenging due to the frequency, site, and extent of local recurrences and prior treatments. The patient was otherwise well without evidence of distant metastases, and salvage treatments were warranted because alternative management with palliative radiotherapy or chemotherapy alone would otherwise not confer a durable and

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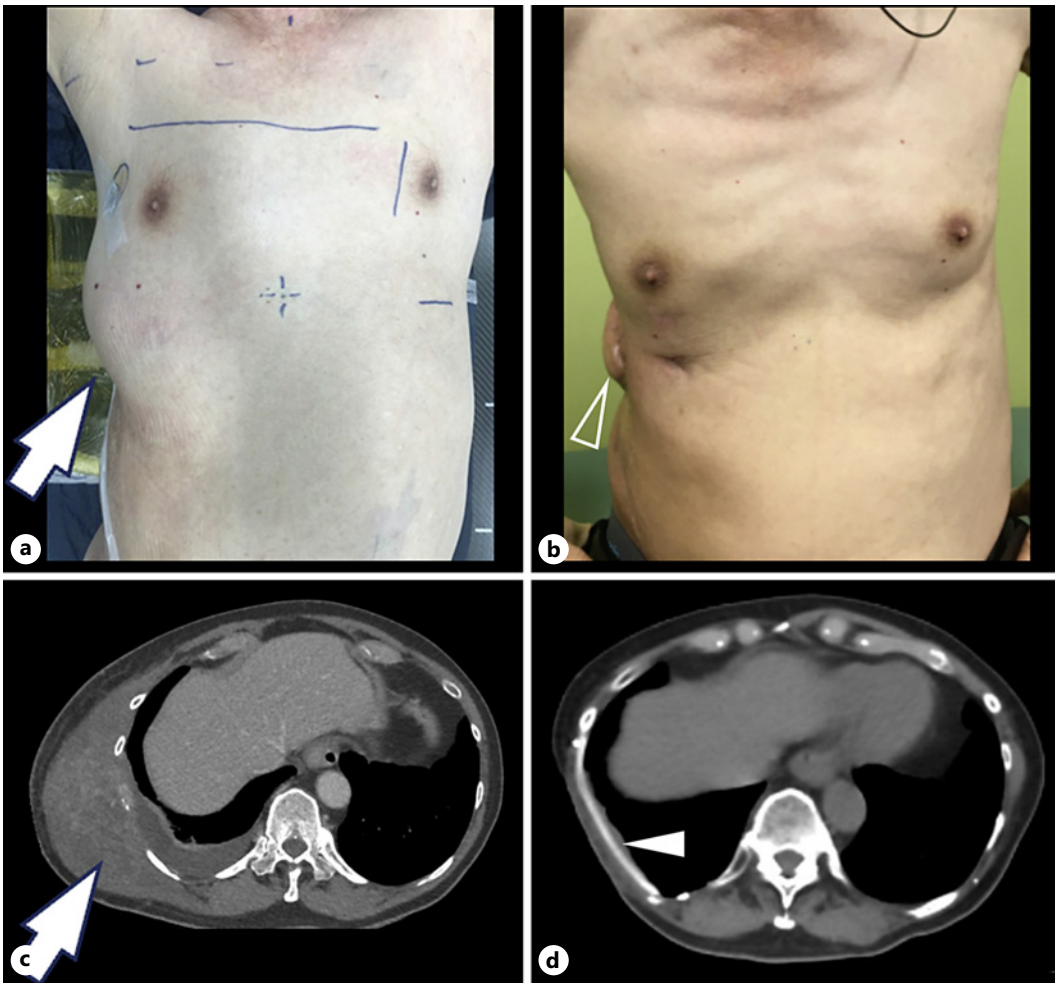

Fig. 1. **a**, **b** Tumor recurrence before re-irradiation. **a** Clinical photograph showing the recurrent liposarcoma in the right lateral chest wall (arrow). Radiotherapy set-up skin markers are seen on the patient's chest. **b** Representative axial CT through the lower thorax demonstrating the tumor recurrence at the right lateral chest wall involving the underlying ribs (arrow). **c**, **d** Three months after chemotherapy, re-irradiation, and surgical resection. **c** Photograph showing the post-therapy appearance with slight bulging of the tissue at the site of surgical flap repair but an otherwise very good cosmetic outcome. **d** Representative axial CT showing resolution of the recurrent right lateral chest wall mass and note the Gore-Tex chest wall implant forming part of the right lateral thoracic cage reconstructions.

meaningful local control. The patient understood the gravity of uncontrolled local recurrence and was willing to adopt the novel idea of combined modality approaches. At the time of this patient's salvage preoperative chemotherapy and subsequent re-irradiation, there were no published data to guide management. Coordinating his multimodality treatments with a dedicated team of pathologist, radiologist, radiation oncologist, medical and surgical oncologists including cardiothoracic and plastic surgeons with careful planning has contributed to the successful outcome for this patient, emphasizing the importance of management within the auspices of a multidisciplinary, experienced sarcoma team.

Re-irradiation for multiply recurrent sarcoma is one of several novel approaches to sarcoma treatment including adjuvant chemotherapy. Perhaps the most promising emerging therapeutic strategies involve tumor genomic analysis to enable the selective use of targeted molecular therapy and immune checkpoint inhibitors [1–3]. The challenge remains providing

access to patients for the required genetic tumor testing and funding of selected molecular therapy pharmaceuticals. There are studies that support the use of chemoradiotherapy in the neoadjuvant setting for high-risk soft-tissue sarcomas (STS) [4–7], but to date, the effectiveness of this treatment approach to local recurrences after prior definitive radiotherapy is unknown.

After initial diagnosis of STS, preoperative chemotherapy (i.e., modified Eilber protocol consisting of 3 days of doxorubicin (30 mg/day) and sequential hyperfractionated bi-daily radiation (3 Gy/day for 10 days) has been reported to provide maximum local control and minimal morbidity [6]. This protocol has provided similar rates of local control when compared with single modality adjuvant radiotherapy. Acute wound complication rates appear similar but there is less severe late toxicity in the Eilber group [5].

Recurrences tend to have worse local control, necessitating intensified therapy. The initial treatment course usually has already exploited much of the therapeutic window for radiotherapy with the treatment typically 50 Gy or 66 Gy if given in the neoadjuvant or adjuvant setting, respectively. The presented case study has demonstrated that in local recurrences after definitive EBRT, re-irradiation should be considered and can be delivered with minimal morbidity. This is relevant in patients with a long disease-free interval however requires meticulous assessment of the prior EBRT treatment plans regarding radiation doses to organs at risk.

Different EBRT dose constraints for organs at risk have been published [8–10] but these studies are markedly heterogeneous and suffer from variable delineation of the target volumes and the lack of multivariate approaches taking into account established factors contributing to radiation dose toxicity such as individual radiosensitivity, genomics, variable tumor microenvironment, or combined modality treatment approaches that include chemotherapy, immunotherapy, or biologic agents. Our opinion is that the dogmatic adherence to standardized EBRT dose limits may not always be in the patients' best interests. If re-irradiation is being considered, care is required to limit the re-irradiation volume and the cumulative doses to nontargeted organs at risk to the minimum to avoid major late complications. The use of modern EBRT techniques like intensity modulated radiotherapy, VMAT with image-guided radiotherapy, particle therapy, and alternative radiotherapy techniques like brachytherapy alone or in combination with EBRT, are all useful to limit nontargeted radiation and are of relevance to re-irradiation treatment approaches [11–16]. However, these published studies regarding re-irradiation are markedly heterogenous with different tumor locations and treatment combinations in comparably small cohorts.

The available comparative series mainly show increased local control by the addition of re-irradiation to conservative surgery at the cost of increased acute and late toxicity. Published re-irradiation data are confined mainly to extremity STS and little are reported in the trunk. For example, Catton [11] compared 11 patients treated by wide excision alone to 10 patients treated with wide excision followed by re-irradiation delivered by EBRT, brachytherapy, or both to a median cumulative dose of 100 Gy. They observed a significantly improved local control rate of 100% with re-irradiation compared to only 36% with surgery alone after a median follow-up of 24 months. Although 60% of the re-irradiation patients showed severe late complications, functional outcome was scored as good in 70% of them.

Brachytherapy has been proposed as optimal radiotherapy technique for re-irradiation with limited irradiated volume. Several series reported high local control rates with acceptable late toxicities [12, 14–16] with one study [13] indicating a higher risk for amputation due to complications if re-irradiation doses exceeded 60 Gy or cumulative doses exceeded 111 Gy. If EBRT is considered, preoperative radiotherapy is preferable to postoperative

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radiotherapy given the usually smaller irradiated volumes and the lower doses needed for equal efficacy based on the radiation experienced from treatment of the primary disease.

Particle therapy may also be considered because of its general ability to limit dose to surrounding tissues. A prospective series [17] of 23 patients (mainly non-extremity lesions) treated with perioperative or definitive re-irradiation with protons (50–74 Gy) observed a 3-year local failure rate of 41% with only 15% grade 3+ late toxicities.

With newer EBRT techniques such as VMAT, radiosensitizing chemotherapy, and a shortened overall treatment duration with hyperfractionated schedule, this case represents a novel and promising approach. By adapting Eilber protocol in the re-irradiation setting, an intensified local salvage approach is possible. The radiobiological principles of hyperfractionated radiotherapy and radiosensitization with chemotherapy can be exploited with maximal tumoricidal impact without exceeding tolerance radiotherapy dose limits to underlying organs at risk. There are additional advantage including the patient completing the entire course of treatment in shorter time and downsizing the recurrent tumor mass prior to resection, and in this case, converting unresectable recurrence to a complete resection with excellent functional outcome.

In conclusion, published guidelines for EBRT dose limits provide a clinically useful guide to radiotherapy planning but do not mention the potential benefits of exceeding dose limits in certain circumstances such as gaining disease control after recurrence within a previously definitively irradiated field. We believe that re-irradiation at sites of recurrence following definitive radiotherapy is a potentially overlooked treatment approach if the dogma of respecting widely adopted dose limits are accepted without consideration for individual patient factors. Re-irradiation in locally recurrent patients probably results in increased local control compared to conservative surgery alone but must be weighed against treatment-related late complications for the individual patient. Radiotherapy techniques with limited irradiation volumes like brachytherapy or particle therapy might be preferable options regarding functional outcome. Combining radiotherapy with chemotherapy, especially in the preoperative salvage surgical setting, offers an exciting alternative to traditional dogma. Treatment approaches depend strongly on tumor localization and prior treatment and should generally be assessed by a specialized multidisciplinary team for the individual patient.

Statement of Ethics

Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. The study protocol was reviewed and approved by the Adventist HealthCare Limited Human Research Ethics Committee, reference ID 2023-012.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

L.N.C. conceptualized the case report, obtained patient consent, obtained HREC approval, compiled the images, and wrote the draft of the manuscript. T.M.H. provided input to the conceptualization of the case report, provided clinical images, and contributed to the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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