

The Current Role of Radiation Therapy for Osteogenic Sarcoma

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Abstract

Osteosarcomas are known to be relatively radio-resistant, definitive radiotherapy has a role in cases that are unresectable or have poor prognostic factors. Neo-adjuvant Chemotherapy followed by local therapy (surgery alone and/or radiotherapy) and maintenance chemotherapy remain the current standard of care for treatment of non-metastatic high grade osteosarcoma. New technologies like particle beam therapy using proton and carbon ions and use of high precision radiation therapy techniques have further improved the results of definitive radiation therapy. Current review traces the advent of radiotherapy, its current role in management of osteosarcoma and future trends in the field.

Keywords: Osteogenic Sarcoma, Radiotherapy, Management

Introduction:

Osteosarcoma (OGS), an osteoid-producing malignant mesenchymal tumour, accounts for 20-45% of all skeletal malignancies. It has a bimodal age distribution with peak incidence at 10-19 years and over 60 years (secondary to prior radiotherapy exposure, Paget's disease etc). Male to female ratio is approximately 1.6:1. The most common sites of involvement are femur (50%), followed by tibia, humerus, pelvis, jaw, fibula and ribs. The major histological variants are conventional osteosarcoma (osteoblastic, fibroblastic or chondroblastic, according to the predominant type of matrix produced), teleangiectatic and small cell osteosarcoma. Patients commonly present with bony pain and local swelling. Patients may also present with symptoms of metastatic disease like dyspnoea, hemoptysis, or bone pain. Diagnostic investigations include Plain radiograph (characteristic 'Sun burst' appearance and 'Codman's triangle'), MRI

of local part, CT scan of chest, Bone scan (to look for skip lesions) and a histopathological examination. Tumors are staged according to either the AJCC or Enneking (MSTS) systems. Prognostic factors impacting survival [1] include presence of metastasis, response to Neoadjuvant chemotherapy (NACT), histologic type, age (each decade increases mortality rate by 7 fold), tumour location (tumours of tibia fare better than those of femur) and choice of therapy (post operative radiotherapy and amputation was associated with 92% and 76% increased relative risk of death respectively, may be confounded by advanced disease status). Prior to the extensive use of chemotherapy for treating patients with osteosarcoma, aggressive surgery was considered the treatment of choice, resulting in five year overall survival rate of 10-20% [2]. A meta-analysis by Kassir et al [3] on head and neck Osteosarcoma showed that surgical cut margin status was the sole prognostic factor

and there was no survival benefit by adding radiation therapy and/or chemotherapy. But subsequently there have been great leaps in the success of osteosarcoma management. Incorporation of highly active chemotherapeutic agents resulted in significant improvement in outcomes to the tune of 60-75% [4]. The MIOS trial [5] reporting 5% versus 65% overall survival rates in patients randomised to surgery versus surgery and chemotherapy respectively, formed the basis for multimodality therapy in these tumours.

Role of Radiotherapy in management of Osteosarcoma:

Osteosarcoma was always thought to be a radio-resistant tumour and hence radiotherapy was initially not included in the standard management regimens. Sir Stanford Cade a British surgeon radiotherapist in 1931 treated 133 patients with radiation therapy with an intention to avoid futile amputation in patients developing lung metastases in subsequent 6-9 months [6]. Following completion of therapy (60 Gy over six weeks) the resected specimen revealed 100% tumour necrosis in all patients.

1) Radiotherapy in definitive setting:

There are no randomized trials comparing surgery versus radiotherapy (RT) as primary local therapy for osteosarcoma and is unlikely to be one in future due to ethical issues. However there

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are a few single arm series showing encouraging results. Machak et al [7] treated 31 patients with extremity osteosarcomas with definitive radiotherapy to a median dose of 60 Gy (range, 40–68 Gy). The 5-year local control (LC), metastasis-free and overall survival (OS) rates were 56%, 62%, and 61%, respectively. Similarly, Caceres et al [8] also noted a complete pathological response in 80% patients with limb OGS treated by chemotherapy and 60 Gy of RT. Excellent functional outcomes was noted in 86% of the patients. In 13 patients treated with definitive RT to median dose of 60 Gy, at a median follow up of 161 months, 3 year LC and OS was 70% and 75% respectively [9]. Subsequently, in the COSS registry of 175 patients [10] treated from 1980 to 2007, at a median follow up of 1.5 years (0.2-23 years), the overall survival rates after RT for treatment of primary tumors, local recurrence, and metastases were 55%, 15%, and 0% respectively. Local control rates for combined surgery and RT were significantly better than those for RT alone (48% vs. 22%).

Feasibility of Stereotactic body radiotherapy (SBRT) for recurrent OGS lesions was evaluated by Brown et al [11]. Median dose delivered was 40 Gy in 5 fractions (range, 30-60 Gy in 3-10 fractions; total of 14 patients). Two grade 2 and 1 grade 3 late toxicities occurred (in the setting of concurrent chemotherapy and reirradiation); consisting of myonecrosis, avascular necrosis with pathologic fracture, and sacral plexopathy [11]. Efficacy and long term toxicity are yet to be determined. Gaitan-Yanguas showed a dose-response relationship with no lesion controlled at doses of 30 Gy, and all lesions controlled with doses of >90 Gy [12].

Approximately 25% of pelvic and 10% of head and neck osteosarcomas are not resectable and hence are candidates for definitive radiotherapy. In our institute, we prescribe 70.2 Gy in 39 fractions over 8 weeks.

2) Radiotherapy in preoperative setting: Preoperative radiotherapy is gradually evolving to facilitate function preserving less mutilating surgeries. Dincsbas et al [13] treated 44 patients with preoperative RT to a dose of 35 Gy in 10 fractions followed by

limb sparing surgery. The tumor necrosis rate was 90% in 87% of the patients. At a median follow-up of 44 months, the 5-year LC and OS were 97.5% and 48.4% respectively. They documented subcutaneous fibrosis in 16%, joint movement restriction in 20%, and osteo-radionecrosis and pathologic fracture in 4% patients. Chambers et al [14] reported an OS of 73% at 5 years of 33 patients treated with preoperative RT and resection for craniofacial OGS.

3) Radiotherapy in adjuvant setting:

Delaney et al [15] reported 41 patients with osteosarcoma involving various sites (primary, recurrent as well as metastatic) in different settings to a dose of 10 to 80 Gy (median 66 Gy) preceded by gross total tumor resection in 65.8%, subtotal resection in 21.9% and biopsy only in 12.2%. The local control rates according to the extent of resection were 78.4%, 77.8% and 40% respectively. The overall survival rates in corresponding groups were 74.45%, 74.1% and 25% respectively. The authors concluded that adjuvant RT can help provide local control of osteosarcoma for patients in whom surgical resection with widely negative margins is not possible. Dose response relationship was not found to be significant. Caveat of the study was that the patient population as well as the treatment parameters including dose and timing of radiation (some received preoperative followed by postoperative RT) was very heterogeneous.

Guadagnolo et al [16] reported that the addition of adjuvant RT in head and neck osteosarcoma definitely improves local control for those with positive or uncertain margins. Laskar et al reported the outcomes of patients with head and neck osteosarcomas treated at the Tata Memorial Hospital, Mumbai [17]. The authors highlighted the impact of post-operative adjuvant radiotherapy, even after R0 resection or in patients with adverse prognostic factors (large tumour size, lymphovascular invasion, soft tissue infiltration etc). The patients receiving adjuvant RT at TMH were prescribed a dose of 64.8 Gy in 36 fractions over 7 weeks. The authors reported local control rate of 36%.

High dose intra-operative EBRT with kV X rays or electrons is emerging as yet another experimental option. Hong et al reported outcome of extracorporeal irradiation (ECI) in the management of 16 pts with a variety of tumours (OGS being in 4 of them) to a dose of 50 Gy in single fraction. At a median follow-up of 19.5 months, there were no cases of local recurrence or graft failure. One patient required amputation due to chronic osteomyelitis [18]. Puri et al reported the outcomes of patients treated at the Tata Memorial Hospital, Mumbai, using extracorporeal irradiation [19]. Thirty-two patients (16 Ewing's sarcoma and 16 OGS) with a mean age of 15 years (2 to 35 years) underwent this procedure. There were three local recurrences. All were associated with disseminated disease and the recurrences were in soft-tissue remote from the irradiated graft. There were no local recurrences involving the irradiated bone. The OS for patients with osteosarcoma was 65% with excellent functional outcome.

4) Radiotherapy in palliative setting:

There is little data regarding dose fractionation and efficacy of radiotherapy for palliation of advanced osteosarcoma. Considering the similar mechanisms of pain and inflammation like bony metastases, data from the later are often extrapolated [20] and single fraction or protracted fractionation have both been equally used. Oligo-metastatic OGS is treated with curative intent. Metastatectomy is the gold standard as a component of the curative regimen with a documented 5 year OS of approx 22%. Stereotactic body radiotherapy (SBRT) to limited lung metastases is an equally efficacious emerging non invasive option. In a series of 46 patients with oligometastatic disease to lungs from sarcomas, at a median follow up of 22 months after median dose of 10-48 Gy in 1-5 fractions, 31% of patients survived for more than 3 years [21]. In a multicentric phase I/II trial treating 38 patients with oligometastases to a median dose of 38-60 Gy in 3 fractions, LC at two years was 96% and median survival was 19 months. Incidence of grade III-IV toxicity was 8% [22].

5) Particle therapy for osteosarcoma:

Ciernik et al, treated 55 patients (42% received definitive RT) with osteosarcoma of all sites [23] using combination of photons and protons to a mean dose of 68.4 Gy. With a median follow-up of 27 months, LC at 3 and 5 years were 82% and 72% respectively. The 5-year DFS and OS was 65% and 67% respectively. Prognostic factors found to have a significant impact on disease control were grade and bulk of the tumour. The extent of surgical resection did not correlate with outcome. Grade 3 to 4 late toxicity was seen in 30.1 % of patients. In another series of 30 patients with unresectable OGS of the trunk treated with definitive Carbon ion therapy to a dose of 52.8–73.6 Gy, the 3 and 5 year LC at a median follow up of 33 months was 62% and 49% respectively. The corresponding OS was 53% and 29%. Severe skin/soft tissue reaction was reported in 5 patients

[24]. With neutrons, local control rates of 55% were documented in patients with unresectable OGS of different sites [25]. A median prescribed dose of 66 Gy has been tried in a series to patients with paraspinal osteosarcomas with a resultant LC of 74%. There were no reported late toxicities [26].

6) Role of brachytherapy:

There is very limited role of brachytherapy in osteosarcomas. A new treatment strategy based on direct injections of 90Y-hydroxide into the tumor bed is under preclinical trial [27].

Conclusions

Neo-adjuvant Chemotherapy followed by local therapy (surgery alone and/or radiotherapy) and maintenance chemotherapy remain the current standard of care for treatment of non-metastatic high grade osteosarcoma. Although osteosarcomas are considered to be relatively radio-resistant, definitive radiation therapy results in significant long term disease control in patients with inoperable disease and postoperatively in patients with poor prognostic factors. The outcomes of definitive treatment using radiation therapy has further been improved by the use of particle beam therapy like protons & carbon ions & escalated doses of photon therapy using modern high precision radiation therapy techniques. Hence, Radiotherapy remains an important option for local treatment of unresectable tumors, following incomplete resection, or as an effective tool for palliation of symptomatic metastases

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