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Review Article

The Role of Radiotherapy in Post-Operative Bone Metastases

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Abstract

Background: Bone metastases are when a cancer spread to the bones. It is estimated that they arise in 14 - 70% of all tumour patients, while it was reported that they occur in 70 - 85% patients in autopsy material. Bone metastases are mainly associated to an overstimulation of osteoclasts or osteoblasts causing a lytic or blastic lesion, respectively. Metastatic bone lesions prone for pathologic fracture leading to subsequent decrease the mobility, quality of life (QOL).

Results: A best result of post-operative RT requires a multidisciplinary approach and a close cooperation between radiation, surgical and clinical oncology. In order to ensure a precise diagnosis and proper integration of systematic and local treatments a well-experienced multidisciplinary team (orthopaedic surgeons, radiotherapist and general surgeon) required.

Conclusion: Patients with painful bone metastases usually receive RT as an acceptable local treatment. Radiation therapy (RT) is performed primarily to reduce tumor size, relieve pain.

***Keywords**: Bone metastases; RT; Quality of Life*

Abbreviations

RT: Radiotherapy; QOL: Quality of Life

Background

Solid tumors frequently metastasize to bone. Bone metastases around 15 - 69% of all tumors. In cancer metastasis cancer cells spread around from the primary tumor and place themselves at a site other than the primary one [1]. Cancer metastasis, not the primary tumor, causes the majority of deaths and is responsible for 90% of mortalities [2]. The bone is third most common site of metastasis after lung and liver. Incidence of bone metastatic lesion depending on primary tumor site, it varies extensively, with lung, breast or prostate cancer, accounting for over 80 - 85% [3].

In patients who suffer from higher stage metastatic disease, the relative incidence of bone metastasis by type of tumor is: 64 - 75% in prostate cancer; 60 - 74% in breast cancer; 50% in thyroid cancer; 35 - 45% in bladder cancer; 15 - 45% in melanoma; 40% in lung cancer; 20 - 30% in kidney cancer [4]. One of the greatest causes of morbidity is bone metastasis, which brings about difficulties in mobility, excruciating pain, pathologic fractures, spinal cord compression, bone marrow aplasia as well as hypercalcemia [5]. The pelvic, skull, ribs, and spine, lung bones are amongst the most commonplace areas for bone metastases because of multiple blood circulating channels [6]. The tumor cells may eat away areas of bone. This creates holes called osteolytic lesions therefore make bones fragile, weak and bones can break or fracture easily.

The most common type of pain in cancer patients has been reported to be pain from bone metastasis. Pathologic bone fractures resulting from metastatic disease are treated by fixation (internal or external) or removing existing bone. The main challenge for the orthopedic procedure is to achieve bone stability and reduce metastatic pain in the region of the lesion or fracture [7]. Postoperative RT can represent an effective palliative intervention in metastatic disease to maintain and improve patient's quality of life [8]. A best result (criteria for best result- Pain reduced by 50% and no any recurrence on radiograph) of post-operative RT requires a multidisciplinary approach and a close cooperation between radiation, surgical and clinical oncology [9].

Types of bone metastasis

Bone metastases are classified as osteolytic with bone resorption, osteoblastic with excessive bone formation or mixed phenotype of both [10]. Osteoblastic and osteolytic bone lesions usually metastasize to the axial skeleton, for example, pelvis and vertebrae, rib sternum, leading to skeletal-related events (SREs). This means spinal cord compression, pathologic fractures, severe pain requiring radiotherapy or surgery, and hypercalcemia are possible [11]. These are mainly associated to an overstimulation of osteoblasts or osteoclasts causing a blastic or lytic lesion, respectively. Both are cause the bone pain. Osteoclast activation contributes to painful lytic bone metastases due to higher incidence of pathologic bone fractures.

When cancer cells invade the bone compartment, there is usually an imbalance in their activities and this results mainly in, depending on the origin of the cancer, bone lysing or bone forming phenotypes. After the bony site is invaded, there is a disruption in the balance between osteoclastic and osteoblastic cells. In the most popular situation, bone destruction is mediated by tumor cells by stimulating osteoclastic activity; therefore, osteolytic metastases will happen [12].

Osteolytic, typically result from multiple myeloma, renal cell cancer, gastrointestinal tract cancer, melanoma, thyroid, lung and breast [13].

Osteoblastic/sclerotic metastasis, described as deposition of new bone, present in prostate cancer. If there are both osteoblastic and osteolytic lesions in a patient, or if the metastasis in a patient is in both osteoblastic and osteolytic components, they are called mixed. Both types lesions exist gastrointestinal cancers, squamous cancers and breast cancer. The women have around 15 - 20% of blastic or both types of bone lesions. however, osteolytic lesions take main origin from osteolytic lesions [14].

Osteoblastic metastases are described as the development of new bone after being colonized by the main tumor. Osteosclerotic metastatic lesions are normally considered to be developed by prostate cancer. In comparison with studies on osteolytic metastatic bone disease, the number of researches which have investigated the molecular mechanisms of osteoblastic bone metastases is notably lower [15]. It is worth mentioning that the majority of patients suffering from osteoblastic bone metastases have high markers of bone resorption. As a result, using antiresorptive agents is normally fruitful in the palliation of patients who suffer from osteoblastic bone metastases [16].

Postoperative radiation therapy for bone metastases

RT is performed to relieve pain, can reduce tumor size, and act protectively in the postoperative period by inducing bone. Radiation therapy can be giving in three forms of treatment: local-field wide-field and radionuclide therapy [17]. Preventing pathological bone fractures and induce mineralization as well as decrease recurrence risk of tumor [18]. Controlling pain is an important consideration for recommending radiation therapy, but it is only one component of improved quality of life (QOL). McDonald., *et al*. analyzed in 289 patients with radiotherapy the QOL improvement scores at 10 and 42 days. At 10 days, 41% of patients had an improvement in pain [19].

In combination of RT with bone stabilization it can sudden improves QOL. Townsend., *et al.* reported that radiotherapy after stabilization was superior to surgical intervention alone. He found that patients receiving postoperative radiation had significantly reduced bone pain levels and reached functional status at a rate of 53% compared to only 11.5% who were treated with surgery alone and 17% of the

surgery group required a another operation, while postoperative RT was protective out to one year with no patients requiring operation [20].

Surgical spinal cord decompression with stabilization with radiotherapy for selected single level spinal cord compression patients may increase the chances for maintaining or regaining ambulation when compared to radiotherapy alone in selected patients. Another Prospective randomized data from one trial resultant that there was a statistically significant improvement in overall duration of ambulation (122 days versus 13 days), ambulation rates (84% versus 57%), regaining lost ambulation (62% versus 19%), and survival (126 days versus 100 days) with surgery along post-operative RT compared to RT alone. Kyphoplasty and vertebroplasty may be useful for the treatment of lytic osteoclastic spine metastases or in cases of spinal instability where surgery is not feasible or indicated; they do not obviate the need for RT, and there are no result to suggest that the addition of kyphoplasty or vertebroplasty further improve symptoms or have a greater impact on clinically significant endpoints than RT alone [21].

A meta-analysis by Huisman and colleagues determined that of the 2,694 patients in seven studies in the beginning treated with single-fraction radiation therapy for bone metastasis, re-irradiation was done on 527 (20%) patients [22] and confirmed by Chow's meta-analysis that indicate that in single dose treatments re-irradiation is 2.5 times more than in multiple fraction RT arm patients [23]. Another meta- analysis studied 16 trials, 2482 and 2468 patients were treated with single fraction arm and with multiple fraction arm respectively. 497 patients were re-treated in single treatment arm (20%) and 192 patients re-treated in multiple fraction arm (8%) [24].

Radiation therapy dose

The optimal radiation dose for the treatment of localized bone metastasis with RT has been the subject of considerable research activity in the last 2 - 3 decades. Over this time over thousand patients have been listed into RCT comparing hypo-fractionation, typically a single fraction with multi fractionation schedules. These RCT trials have now been subject to 3 meta-analyses of which the recent included 12 trials with a total of 3508 patients. The results of the two previous meta-analyses and the individual trials themselves by showing no difference in either complete or partial response from treatment between any of the dose fractionation schedules used. The response rate was 55-65% and the complete response rate 33%. The recent of these studies from the RT has finally confirmed that even in a American setting, single dose radiotherapy is effective for metastatic bone pain, counteracting the results of the early RT study which proposed on the basis of a reanalysis of the data that multi fraction treatment was advantageous. The recent study in RT randomized 898 patients to receive either eight Gy or thirty Gy in 10 fractions. The overall response rate was 66%. Complete and partial response rates were 15% and 50%, respectively, in the 8-Gy arm compared with 18% and 48% in the 30-Gy arm [25,26].

Time for patients receive retreatment

Patients with persistent or recurrent pain more than 1 month following RT for symptomatic, peripheral bone metastases should be considered for retreatment while adhering to normal tissue dosing constraints described in the available literature. (High Quality Evidence, Strong Recommendation) [27]. A systematic review and meta-analysis of trials including patients receiving re-irradiation for painful bone metastases demonstrated moderate palliative efficacy, with overall pain response rate of 58% [28].

Toxicity of radiation therapy

Toxicity generally depends on the total dose of RT delivered to the normal tissues adjacent to the target volume. It is predictable and generally self-limiting. No major differences in gastrointestinal problems (including vomiting, nausea, loose motion), itching, skin rash and weakness were reported between single fraction or multiple fractions RT regimens [29].

Pain flare is described as a short term increase in bone pain at the treated metastatic lesion, during or shortly after RT given. Patients who treating a single eight Gy fraction are at on more risk for pain flare, whereas patients treated with steroids as part of their systemic therapy are less likely to pain flare. The use of NSAIDs can reduce the risk of pain flare [30].

Limitation or exclusion criteria of radiation therapy

RT avoids in children and pregnant and because mild risk of multiple visceral organ malignancy, we estimate the risk of a cancer forming from radiation therapy to be less than 0.2% per year and risk of teratogenic effects in pregnant.

Conclusion

Patients with painful bone metastases usually receive RT as an acceptable local treatment. In order to ensure a precise diagnosis and proper integration of systematic and local treatments a well-experienced multidisciplinary team (professionals with different skills and expertise together to solve a problem like orthopaedics surgeons, radiotherapist and general surgeon) is required. Although we can draw some considerations from the data which are available now, we need some large pooled analysis and prospective trials so as to make the best therapeutic algorithms individual to boost life quality as well as patients' survival.

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