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Original article

Local control and fracture risk following stereotactic body radiation therapy for non-spine bone metastases

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ABSTRACT

Aims: To report local control and toxicity rates for patients treated with stereotactic body radiotherapy (SBRT) for non-spine bone metastases.

Methods and materials: Eighty-one patients with 106 non-spine bone metastases were treated between 2011 and 2014 and retrospectively reviewed. Indications included: oligometastases (63%), oligoprogression (17.3%), retreatment (2.4%) or other (17.3%). Cumulative incidence function was used to assess local recurrence and fracture probability. Bivariate relationships were investigated based on selected patient, tumour and dose–volume factors.

Results: Mean follow-up was 13 months (range, 0.25–45.6) and the median patient age was 66.4 years (range, 36–86). Most patients were male (60.5%) and the predominant histology prostate cancer (32%). Bone metastases were most commonly located in the pelvis (41.5%) and almost half sclerotic. The most common prescriptions were 30 Gy/5 (30.2%) and 35 Gy/5 (42.5%). The cumulative incidence of local recurrence at 6,18 and 24 months respectively was 4.7%, 8.3% and 13.3% with a mean time to local recurrence of 11.8 months (range, 3.9–23.4). A significant association was found between local recurrence and volume of the PTV ($p = 0.02$), with larger PTVs having a greater risk of local failure. Fracture was observed radiographically in the treatment volume in 9/106 (8.5%) of treated lesions and the mean time to fracture was 8.4 months (range, 0.7–32.5 months). With respect to predictors, a trend was observed for lytic lesions ($p = 0.11$) and female gender ($p = 0.09$).

Conclusions: The results of this study confirm that SBRT yields high rates of long-term local control for non-spine bone metastases with a low fracture risk.

Bone is one of the most common sites of metastatic disease in cancer patients and can cause debilitating effects including pain, hypercalcemia and pathological fracture. Bone metastases can be treated medically (analgesics and bisphosphonates), surgically, or with less invasive techniques (radiofrequency ablation or radiation therapy). Typically, conventional external beam radiotherapy (cEBRT) with low dose palliative treatments has been the mainstay treatment modality with regimens such as 8 Gy/1, 20 Gy/5 and 30 Gy/10. These doses are safe for adjacent normal tissues and convenient in terms of minimizing delays and interruptions in systemic therapy. These low palliative doses, however, have proven to yield predominantly partial relief as opposed to complete pain relief and durable long-term local control [1].

Over the last decade, stereotactic body radiation therapy (SBRT) [2] has been developed for numerous sites of primary cancers including metastatic disease. The intent is fundamentally different as SBRT delivers a far greater biologically effective dose (BED), as compared to palliative conventional radiation, in order to maximize local control and pain response. In terms of bone metastases, SBRT has been more commonly adopted for the treatment of spinal metastases. Few data have been reported specific to non-spine bone metastases and large series are lacking with respect to reporting imaging-based local control rates and adverse effects. The purpose of this study is to report our institutional experience with SBRT for non-spine bone metastases, specifically local control and toxicity rates.

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Materials and methods

Patients

Between 2011 and 2014, 81 patients with 106 non-spine bone metastases were treated with SBRT. Metastases were considered non-spine if they were located outside of the vertebral column or sacrum. This retrospective review was approved by our local Institutional Research Ethics Board. Information was collected on patient characteristics, tumour characteristics, previous treatment and dose–volume parameters. BED was calculated using the equation BED = $D \times (1 + (D/d)/(\alpha/\beta)$, where D is the total dose, d is the dose per fraction and assuming $\alpha/\beta = 10$ for all tumours regardless of histology, acknowledging that this likely underestimates the true biological dose for histologies such as prostate where the α/β is thought to be significantly lower than 10. To evaluate potential dose association with fracture, BED was calculated using $\alpha/\beta = 3$. Patients were retrospectively categorized as oligometastatic if $\leq$5 sites of metastases, oligo progressive if <5 sites of metastatic disease progressed while other sites including the primary disease remained stable on systemic treatment or observation, retreatment if radiologic progression was observed following a course of cEBRT and other, for situations where durable long term control was the rationale. For the latter, these patients typically were those with large metastases and/or radioresistant histologies such as renal cell carcinoma and melanoma.

Radiotherapy technique

The SBRT technique depended on the location of the bone metastasis. Patients were immobilized using one of four techniques: a thermoplastic head and shoulder mask for metastases located cranial to T5, a Blue-BAG vacuum cushion (Elekta AB, Stockholm, Sweden) for bone metastases in the pelvis, a Blue-BAG vacuum cushion (Elekta AB, Stockholm, Sweden) with an abdominal compression plate for rib metastases, or the complete BodyFIX dual vacuum system based on physician preference [3,4]. 4DCT was used for rib and sternal lesions to account for respiratory motion and all treatment planning CT scan was acquired using thin slices (1–3 mm). A volumetric MRI was obtained and co-registered with planning CT to facilitate gross tumour volume (GTV) delineation at the discretion of the radiation oncologist. The GTV was defined as radiologically evident disease based on CT and/or MRI. A clinical target volume (CTV) was electively applied to regions at risk microscopically (usually 5 mm of contiguous tissue) and an internal target volume (ITV) was created if 4DCT was used to account for respiratory motion. Planning target volume (PTV) expansions ranging from 2-5 mm were applied to account for set-up error. Dose fractionation schemes ranged from 20 Gy/1 to 50 Gy/5. Selection was based on lesion size, location and whether there were adjacent critical organs at risk. For example, patients with smaller lesions away from organs at risk were frequently treated with a 2 fraction regimen, whereas patients with PTVs that extended into the joint space, were treated with a maximum of 30 Gy/5, with the joint itself limited to maximum dose of 27.5 Gy Intensity modulated radiation therapy (IMRT, 61/104 lesions) or volumetric modulated arc therapy (VMAT, 45/106 lesions) techniques were used to generate treatment plans using the Pinnacle (Philips Medical Systems, Madison, WI) treatment planning system.

Treatment was delivered with an Elekta Synergy or Axesse linear accelerator (Elekta AB, Stockholm, Sweden), image-guidance using a kilovoltage cone-beam computed tomography (CBCT) and positional correction with a Hexapod robotic couch permitting 6 degrees-of-freedom patient positioning (Elekta AB, Stockholm, Sweden). Treatment was delivered daily, twice weekly or every other day. Typically, a follow-up with computed tomography (CT) or MRI specific to the treated areas was performed every 2–4 months following SBRT for the first two years and approximately every six months thereafter.

Outcomes

Local control (LC) was assessed independently for each bone metastasis based on radiologist and radiation oncologist interpretation. LC was defined as lack of progression at the treated site based on serial imaging. Local recurrence was further categorized as in-field if within the region of the PTV, or marginal if in contact with the PTV margin (marginal recurrence). An accompanying rise in PSA was also recorded for prostate patients to confirm local recurrence. Each local recurrence was independently reviewed by a blinded radiation oncologist for confirmation.

Statistical analysis

Descriptive statistics were used to document the relevant patient, tumour and treatment characteristics. Continuous measures were summarized using mean, median, standard deviation and range, whereas categorical measures were summarized using counts and percentages. Chi square and Fisher's exact test were used to examine bivariate relationships for both local recurrence and fracture with patient characteristics. To account for clustered data structure (more than one record from a patient), Generalized Estimating Equations (GEE) was used to examine bivariate relationships for both local recurrence and fracture with tumour characteristics and dose–volume factors. Overall survival (OS) was calculated from the last day of SBRT to death or last follow up using Kaplan–Meier product-limit method. Time to both local recurrence and fracture were evaluated in months from the end of SBRT to event, or death, or last follow-up. The cumulative incidence of local recurrence and fracture were calculated using the Fine and Grey competing risk method considering death as a competing risk [5]. All analyses were carried out using SAS version 9.3 (SAS Institute, Cary, NC).

Results

A total of 81 patients with 106 non-spine bone metastases were treated, and baseline characteristics are summarized in Table 1. The median patient age was 66.4 years (range, 36–86 years). The median and mean follow up were 9.8 months and 13.0 months, respectively (range, 1.0–45.6 months). Most patients, 75/81 (92.6%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 prior to the start of treatment, and the majority were asymptomatic (59/106; 53.8%). Treated bone metastases were most commonly located in the pelvis (44/106; 41.5%) and almost half were sclerotic (52/106; 49.1%). Oligometastatic disease was the predominant rationale for treating with SBRT (51/81, 63%). Co-registration of a volumetric MRI to the planning CT was performed for 31/106 (29.2%) lesions. The most common dose fractionation schemes were 30 Gy/5 (30.2%) and 35 Gy/5 (42.5%) fractions (Table 2). The mean and median BED were 54.5 Gy and 52.8 Gy, respectively (range, 37.5–100.0 Gy). The mean PTV volume was 110.3 cm^3 (range, 2.2–644.9 cm^3).

Median OS for the entire cohort was 13.5 months (range, 0.2–45.7) and 1 and 2-year OS from completion of SBRT was 71.9% and 62.5%, respectively (Fig. 1). Local recurrence was observed in 8/106 (7.5%) bone metastases, and the cumulative incidence of local recurrence was 4.7%, 8.3% and 13.3% at 6 months, 18 months and 24 months respectively. (Fig. 2) The mean and median time to local recurrence was 11.8 and 5.5 months respectively, (range, 3.9–23.4 months). Five of the eight (62.5%) local failures were marginal.

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