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MINIREVIEWS

Palliative external-beam radiotherapy for bone metastases from hepatocellular carcinoma

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Abstract

The incidence of bone metastases (BMs) from hepatocellular carcinoma (HCC) is relatively low compared to those of other cancers, but it has increased recently, especially in Asian countries. Typically, BMs from HCC appear radiologically as osteolytic, destructive, and expansive components with large, bulky soft-tissue masses. These soft-tissue masses are unique to bone metastases from HCC and often replace the normal bone matrix and exhibit expansive growth. They often compress the peripheral nerves, spinal cord, or cranial nerves, causing not only bone pain but also neuropathic pain and neurological symptoms. In patients with spinal BMs, the consequent metastatic spinal cord compression (MSCC) causes paralysis. Skull base metastases (SBMs) with cranial nerve involvement can cause neurological symptoms. Therefore, patients with bony lesions often suffer from pain or neurological symptoms that have a severe, adverse effect on the quality of life. External-beam radiotherapy (EBRT) can effectively relieve bone pain and neurological symptoms caused by BMs. However, EBRT is not yet widely used for the palliative management of BMs from HCC because of the limited number of relevant studies. Furthermore, the optimal dosing schedule remains unclear, despite clinical evidence to support single-fraction radiation schedules for primary cancers. In this review, we outline data describing palliative EBRT for BMs from HCC in the context of (1) bone pain; (2) MSCC; and (3) SBMs.

Key words: Hepatocellular carcinoma; Metastasis; Radiotherapy; Palliative therapy; Spinal cord compression; Skull base metastasis

Core tip: Due to a lack of clinical data, external-beam radiotherapy (EBRT) for bone metastases (BMs) from hepatocellular carcinoma (HCC) is still not widely used as a palliative therapy component, and the optimal dosing schedule remains unclear. BMs from HCC typically occur as expansive, bulky soft-tissue masses; they exhibit expansive growth that compresses the peripheral nerves, spinal cord, or cranial nerves, causing both bone and neuropathic pain, and neurological symptoms. In this review, we outline the data describing palliative EBRT for BMs from HCC to treat bone pain, spinal compression, and skull base metastases.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer in men worldwide[1]. The rate of bone metastases (BMs) in extrahepatic metastasis is reported to be approximately 20%[2]. The incidence of BMs in HCC patients has historically been low compared with those of other cancers, but has recently increased[3]. Previously,

Table 1 Incidence of bone metastases in clinical studies *n* (%)

Ref.	Study period	Patients	Extrahepatic Ms	Incidence of BMs	Rate of BMs in extrahepatic Ms
Kuhlman *et al*[13]	1979-1985	300		22 (7.3)	
Liaw *et al*[14]	1983-1887	395		20 (5)	
Katyal *et al*[15]	1992-1997	403	148 (36.7)	41(10.2)	28
Fukutomi *et al*[3]	1978-1987	269		12 (4.5)	
	1988-1997	404		52 (12.9)	
Natsuizaka *et al*[5]	1995-2001	482	65 (13.5)	25 (5.2)	38.50
Uchino *et al*[2]	1990-2006	2386	342 (14.3)	87 (3.6)	25.40
Senthilnathan *et al*[16]	2000-2008	209	51 (18)	5 (2)	10

BMs: Bone metastases; Ms: Metastases.

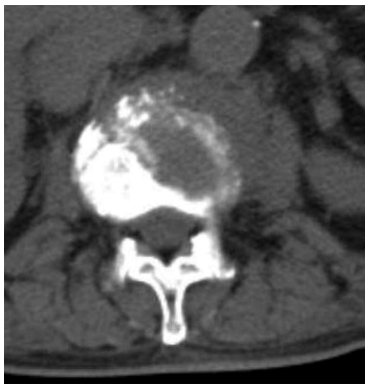

Figure 1 Typical computerized tomography image of a lumbar spinal bone metastasis from hepatocellular carcinoma. The bone metastasis shows osteolytic, destructive, and expansive components with soft-tissue masses.

clinicians did not focus on BMs in advanced HCC because of their low incidence, and the prognosis of these patients was generally poor[4]. Recently, the prognosis and management of HCC have improved as a result of novel imaging techniques and multidisciplinary treatment approaches. BMs are now diagnosed more frequently in HCC patients with extrahepatic metastases[5]. BMs themselves rarely affect patient survival; however, they are the most common source of moderate and severe cancer pain[6,7] and can cause neurological symptoms[7]. In patients with spinal BMs, the consequent metastatic spinal cord compression (MSCC) causes paralysis. Skull base metastases (SBMs) with cranial nerve involvement can cause neurological symptoms. External-beam radiotherapy (EBRT) can effectively relieve bone pain[7,8] and the neurological symptoms caused by BMs[7,9]. However, EBRT has not been widely used in the palliative management of BMs from HCC because only a few reports have been published that focus on its use to relieve pain and neurological symptoms. In this review, we will outline the data pertaining to the use of EBRT for BMs from HCC.

INCIDENCE OF BMs

HCC is accompanied by BMs in 6%-20% of patients in autopsy studies[10-12]. The incidence of BMs in HCC patients has been reported to be relatively low; 2%-12.9% in clinical studies, and 7.3%-38.5% in patients with extrahepatic metastases (Table 1)[2,3,5,13-16]. However, BM incidences of 10.2% and 12.9% were reported by Katyal *et al*[15] and Fukutomi *et al*[3], respectively, which are higher than previously reported rates. According to Katyal *et al*[15], this difference may have been the result of current treatment regimens that utilize combined chemotherapy and chemoembolization to prolong survival. Fukutomi *et al*[3] compared the incidence of BMs in two chronological periods (1987-1997 and 1998-1997). BMs were found in 4.5% of patients in the first decade and 12.9% of patients in the second decade. The increased incidence of bone metastasis was attributed to the prolonged survival of HCC patients due to improved diagnosis and treatment. Bone scintigraphy and computed tomography (CT) have been used widely as imaging modalities for BMs, and magnetic resonance imaging (MRI) has often been performed in recent studies. MRI is useful in cases in which the bone scan is negative and the BMs have properties of soft tissue masses[17]. In three recent studies, the incidence of BMs was reported to be 2%-5.4%[2,5,16]. However, the rate of BMs in patients with extrahepatic metastases is relatively high (25.4%-38.5%)[2,5], except in one report from the United States[16]. In a recent study, Natsuizaka *et al*[5] found that extrahepatic metastases were relatively common, and more than 65% of the study patients had early-stage tumors that would not be expected to metastasize.

RADIOLOGICAL FEATURES

Most BMs from HCC are located in the vertebrae, followed by the pelvis, ribs, sternum, limb bones, and cranium[18], which is a similar distribution to the BMs of other tumor types[19]. The distribution of BMs in HCC is similar to that observed in previous studies[3,4,8]. The lower-thoracic and lumbar vertebrae are common sites for vertebral BMs[18]. The reported incidence of skull metastases varies widely; 3.5%-30%[4,7,8,14].

Radiographically, typical BMs from HCC appear as expansible, destructive findings with large soft-tissue masses[13]. Most BMs are osteolytic and thus detectable using CT[14,19] (Figure 1). However, HCC patients rarely exhibit either purely osteolytic or osteoblastic lesions[13,19]. Soft-tissue masses are unique to BMs of HCC and have been observed in 39%-85.4% of patients[8,18-20]. These

Table 2 Studies of external radiotherapy to treat painful bone metastases from hepatocellular carcinoma

Ref.	Patients (*n*)	Sites (*n*)	Fraction dose	Pain relief (CR)	Dose-response relationship	Comments
Roca *et al*[27]	26	37	MFs 30-50 Gy	79% (44%)	NR	11 lesions (with CTx)
Kaizu *et al*[28]	57	99	MFs 20-65 Gy	83.8% (33%)	Better pain relief TDF ⩾ 77	16 lesions (with TAE) Tumor volume (NS)
Matsuura *et al*[29]	38	44	MFs 26-60 Gy	91% (32%)	NR	Tumor regression (> 40 Gy)
Seong *et al*[7]	51	77	MFs 12.5-50 Gy	73%	Better pain relief BED > 43 Gy	With neurological symptoms (25%)
He *et al*[8]	205	205	MFs 32-66 Gy	99.5% (29.80%)	NR	Higher retreatment rate (with soft-tissue masses)
Hayashi *et al*[30]	28	48	MFs 20-52 Gy SF 8 Gy	83% (17%) MFs: 87% (17%) SF: 75% (17%)	NR	Longer pain relief (> 36 Gy) No spinal compression No neuropathic pain

MFs: Multiple fractions; SF: Single fraction; CR: Complete relief; NR: No dose response; TDF: Time, dose, and fractionation factor; BED: Biologically effective dose; NS: No significant difference; CTx: Chemotherapy; TAE: Transcatheter arterial embolization.

soft-tissue masses can replace the normal bone matrix and exhibit expansive growth, frequently within the vertebral body. Paravertebral masses have been shown to grow inward to encapsulate and destroy the bone matrix[18]. These masses often compress peripheral nerves, the spinal cord[21], or cranial nerves[22], causing not only bone pain but also neuropathic pain[6] and neurological symptoms.

RADIOTHERAPY FOR BONE PAIN

EBRT is prescribed most frequently to relive pain from BMs and the efficacy of EBRT for treating BMs has been well established[23]. Generally, pain relief is obtained in 60%-90% of treated patients, but the sites of primary tumors from these reports were mainly in the lung, breast, and prostate[23-26]. There have only been a few studies of EBRT for HCC BMs, but they show that 73%-99.5% of patients obtained overall pain improvement and 17%-44% of patients achieved complete pain relief (Table 2)[7,8,27-30]. Except for a report from China[8], these studies were retrospective analyses with a small sample size; however, the reported results for overall pain relief are similar to those obtained for BMs of other primary tumors. HCC is often complicated by liver failure, and narcotic drugs may induce hepatic coma. Therefore, EBRT may play an important role in relieving the pain from BMs, thus minimizing the use of narcotic drugs for pain relief.

Soft-tissue masses with BMs often cause neuropathic pain, spinal compression, and pathological fractures, and these issues were evaluated simultaneously with bone pain relief in some previous reports. The pain assessments differed among the studies; two recent studies[8,30] evaluated pain relief using the International Bone Metastases Consensus Working Party Guidelines[31,32] with some modifications. Even after considering the differences among studies, it has been shown that EBRT is equally effective for the relief of pain caused by BMs from HCC, as well as metastases from other primary tumors.

Various EBRT dosage and fractionation schedules have been used to treat pain, ranging from an 8 Gy single fraction (SF) to multiple fractions (MFs). An SF of 8 Gy delivered in one day is more convenient for the patient and more cost effective compared with schedules employing MFs. However, MFs that deliver a higher total dose than an SF may have increased biological effects on the tumor. In a randomized controlled trial conducted by the Radiation Therapy Oncology Group (RTOG 9701)[33] in which an SF (8 Gy) was compared with MFs (30 Gy in 10 fractions over 2 wk), it was demonstrated that both schedules provided equivalent pain relief. Furthermore, the RTOG trial found a significantly lower rate of acute toxicity with an SF compared to MFs, although there was no significant difference in late toxicity (*e.g.*, pathologic fractures). Similar findings concerning the pain relief after treatment based on an SF or MFs have also been reported[26,34]. Similarly, according to other recent studies including a meta-analysis, both SF and MF-based treatments have provided equivalent pain relief, although SF treatment often requires re-treatment[23-25,35]. In terms of pain relief, most previous studies failed to show a dose-response relationship for BMs from other primary cancers. For BMs from HCC, Roca *et al*[27], Matsuura *et al*[29], and He *et al*[8] also found no apparent dose-response relationship for pain relief. In contrast, Kaizu *et al*[28] and Seong *et al*[7] did find a dose-response relationship, although in the former study, 15 of the 57 patients analyzed[28] underwent transcatheter arterial embolization of BMs in addition to EBRT, and 25% of the patients in the study by Seong *et al*[7] had neurological symptoms with bone pain. He *et al*[8] also found no dose-response relationship for pain relief, but higher complete pain relief rates were obtained using higher radiation doses. Furthermore, they observed that the re-treatment rate was higher among patients with expansible soft-tissue masses and noted an increased presence of residual cancer cells in these patients relative to those lacking soft-tissue extension. Matsuura *et al*[29] reported a lack of observed tumor regression at doses < 40 Gy and that 3 patients treated

with doses ≥ 40 Gy (40 Gy, 46 Gy, and 60 Gy) survived for > 6 years without recurrence. Pain caused by BMs can originate directly from the bone, or as a result of nerve root compression, or muscle spasms in the lesion area (*i.e.*, neuropathic pain)[7]. In a randomized trial of radiotherapy for neuropathic pain caused by BM, Roos *et al*[36] (Trans-Tasman Radiation Oncology Group) compared the efficacy of SF (8 Gy) to MFs (20 Gy/5 fraction) treatment and concluded that an SF was not as effective as MFs; the outcomes with SF treatment were generally poor, although the difference was not statistically significant. In that study, the most frequent primary tumor sites were the lung and prostate. For patients with BMs from HCC that cause neuropathic pain through nerve root compression, a higher radiation dose may be needed to shrink the soft-tissue mass and provide pain relief.

Nearly all previous studies[7,8,27-29] involving BMs of HCC used MF schedules and evaluated both bone pain and neuropathic pain. We conducted a retrospective evaluation of the palliative efficacy of EBRT, excluding cases with spinal cord compression or neuropathic pain[30] and assessed different dosing schedules for BMs from HCC with soft-tissue masses. Our analysis included a relatively small number of patients (28 patients, 42 sites), and the overall response rates were 75% and 87% for SF and MF treatment, respectively; this difference was not significant. Patients undergoing high-dose MFs (≥ 36 Gy in total) achieved on average a significantly longer duration of pain relief than those undergoing SF or moderate-dose MF therapy (≤ 30 Gy in total). The median durations of overall pain relief for MFs were 3.8 and 1.8 mo after SF treatment. These results were similar to those reported for other series involving different primary cancers[24,25,34]. In our study, we found that EBRT effectively palliated painful BMs from HCC, that an 8 Gy SF and MFs resulted in equivalent pain relief, and that high-dose MF schedules may result in longer lasting pain relief.

Soft-tissue masses are unique to BMs from HCC and often cause both bone and neuropathic pain. In HCC patients with neuropathic pain, higher RT doses using an MF schedule are usually necessary because of the presence of soft-tissue masses. It is critical to discriminate between these different pain types, and large-scaled cohort studies are necessary to determine an optimal radiotherapy plan in terms of doses and fractions for each.

RADIOTHERAPY FOR SPINAL BMs

Spinal BMs often cause not only pain but also MSCC, which primarily develops in one of three ways[37]: (1) the continued growth and expansion of vertebral BMs into the epidural space; (2) neural foraminal extension *via* a paraspinal mass; and (3) the destruction of vertebral cortical bone, leading to vertebral body collapse and the displacement of bony fragments into the epidural space. SCC secondary to BMs from HCC can develop in any of these ways because typical these metastases have an expansible and destructive nature and give rise to soft-tissue masses[13].

MSCC is estimated to occur in approximately 5%-10% of all cancer patients[37]. The most common primary sites are the breast and lung[37,38]; however, the rate of MSCC resulting from BMs from HCC is unclear. MSCC that diminishes motor function and causes paraplegia is considered an oncological emergency requiring urgent treatment[38]. Conventionally, MSCC has been managed with corticosteroids and high-dose EBRT. EBRT is an effective treatment for MSCC and has been included in standard care. Rades *et al*[38] retrospectively analyzed the use of 5 radiotherapy schedules (8 Gy, 20 Gy/5 fractions, 30 Gy/10 fractions, 37.5 Gy/15 fractions, and 40 Gy/20 fractions) for MSCC treatment and found that motor function improved by 26%-31%, post-treatment ambulation was achieved in 63%-74% of cases, and that all 5 schedules provided similar functional outcomes. Rades *et al*[38] therefore recommended a schedule of 8 Gy for patients with a poor survival prognosis and 30 Gy/10 fractions for other patients. Maranzano *et al*[39] reported that 76% of patients achieved full recovery, or at least were still able to walk, after EBRT with doses > 30 Gy over a 2 wk period in combination with steroids, and that the most important response predictors were an early diagnosis and favorable histology. For MSCC specifically caused by HCC, Maranzano *et al*[39] reported a median duration of improvement of only 1 mo, which was shorter than the duration observed for other cancers, including breast cancer, for which it was 12 mo. Nakamura *et al*[9] reported a retrospective series of 24 ambulatory patients with MSCC derived from HCC. Five patients (21%) underwent salvage therapy and 4 (21%) had become non-ambulatory by the last follow-up. The ambulatory rates at 3 and 6 mo were 85% and 63%, respectively. Nakamura *et al*[9] concluded that EBRT with a biologically effective dose range of 39-50.7 Gy (total radiation dose range, 30-39 Gy) was not sufficient to prevent MSCC-related paralysis and that dose escalation *via* a precise radiation technique should be evaluated. In MSCC caused by BMs from HCC, it will probably be important to shrink and control the soft-tissue masses. Therefore, higher radiation doses are needed to prevent MSCC-related paralysis. For patients with a good survival prognosis, high-precision radiation therapy [intensity-modulated radiotherapy (IMRT) or stereotactic irradiation (STI)] should be considered for the delivery of higher radiation doses, whilst sparing the spinal cord and reducing the risk of radiation myelitis. In addition to EBRT, surgery is being re-evaluated for the palliative management for MSCC. The results of a randomized trial reported by Patchell *et al*[40], showed that direct decompressive surgery with postoperative EBRT was more effective at restoring ambulation than EBRT alone.

Vargas *et al*[41], Somerset *et al*[42] and Doval *et al*[21] showed in case reports that patients with MSCC derived from HCC who were treated with laminectomy or resection of the epidural lesion had a good clinical course. Vargas *et al*[41] concluded from their case report that surgi-

cal therapies such as direct decompression of the tumor with postoperative EBRT or vertebral body resection with stabilization should be considered in patients for whom surgery could be expected to succeed.

RADIOTHERAPY FOR SBMs

SBMs occur in 4% of cancer patients[43] and often cause pain or cranial nerve palsies. Because of their rarity, SBMs have received limited attention in the published medical literature. Their clinical manifestation depends on the metastatic cranial nerve invasion site. In a review by Laigle-Donadey *et al*[43], the most common primary cancers from which SBMs originated were prostate (38%) and breast cancer (20%). The incidence of SBM from HCC has been reported to be 0.4%-1.6%[44-47] and until 2009, only 25 such cases had been reported[38]. However, the incidence of SBM from HCC increased significantly during the period between 1990 and 2001[39]. SBM without other osseous metastases is an unusual finding and cranial nerve deficits are found in 96% of cases in which the SBM was derived from HCC[38]. Radiotherapy is usually the standard treatment for SBM and has been used to treat 70% of patients[43]. EBRT provides excellent pain relief and often leads to the regression of cranial nerve dysfunction, which lasts until death in most cases. There is consensus that the rate of neurological improvement is closely related to the length of time to EBRT following the onset of symptoms[43]. Vikram *et al*[48] reported that 87% of patients for whom EBRT was initiated < 1 mo after the onset of symptoms in contrast to 25% for whom EBRT was initiated ⩾ 3 mo after the onset of symptoms. However, the appropriate doses and fractions to use in EBRT for SBMs have still not been agreed upon. Discrepancies with respect to the dose-response relationship can be explained by the different radiosensitivity of each primary tumor. In cases involving SBMs from HCC, higher radiation doses are needed to improve the neurological symptoms by resolving the compression and invasion of cranial nerves caused by soft-tissue masses. Nozaki *et al*[47] reported a case in which multiple SBMs from HCC were successfully treated with EBRT. They found that slightly higher radiation doses (50 Gy/20 or 25 fractions) were delivered and improvements in neurological symptoms and tumor regression were achieved. However, EBRT places certain organs at risk, including the brain stem, optic nerve, and optic chiasm. Stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT) are more recent therapeutic options for SBMs. They are high-precision radiation therapies in which delivery is accurate to within one to two millimeters and are performed in a non-surgical procedure that delivers precisely targeted radiation at much higher doses than traditional radiotherapy in a single dose (SRS) or fractionated regimen (SRT). This treatment is only possible because of the development of highly advanced radiation technologies such as the gamma knife, and high-precision linear accelerators that permit maximum dose delivery within the target while minimizing the dose to organs at risk. In a report of HCC cases treated by gamma knife radiosurgery, the clinical symptoms improved in 61% of the patients after treatment and tumor control was achieved in 67% of cases[49]. Gamma knife radiosurgery is particularly useful for small tumors (diameter < 30 mm)[36]. Stereotactic radiotherapy *via* Novalis, a high-precision linear accelerator, can administer high doses to tumors while sparing normal structures and organs at risk, thus being a useful EBRT technique for SBM treatment[50]. In a study utilizing Novalis, all 11 cases (including 1 HCC case) achieved and maintained local control until the end of the follow-up period or death. SBM remains a challenge with respect to EBRT planning and delivery.

SURVIVAL ASSOCIATED WITH BMs

The 1-year survival rate after EBRT initiation or the diagnosis of BMs has been reported to be 13.8%-32.4%, with a 5-7.4 mo median survival time[7,8,13,29,30]. Unfavorable significant prognostic factors of patients with BMs have been reported as lower performance status, multifocal BMs, tumor stage ⅣA, metastasis to other organs, higher tumor marker levels, uncontrolled intrahepatic tumors, and ascites at the initial presentation[4,7,8,29].

The prognosis of patients with MSCC is worse than for patients with only BMs. According to Nakamura *et al*[9], the median observed survival duration for all patients was 5.1 mo and the overall 6-mo survival rate was 38%.

SBMs are generally late events and occur at a stage when many patients have already developed disseminated disease, particularly other BMs[43]; 71% of these patients were reported to have died within a short period of between 11 d and 9 mo after the onset of neurological symptoms[40].

CONCLUSION

Soft-tissue masses are unique to BMs from HCC and often cause both bone and neuropathic pain, and neurological symptoms. EBRT is effective for the relief of painful symptoms resulting from BMs, MSCC, and SBMs from HCC. However, the optimal dose and fraction schedules for bone pain palliation remain unclear. Large-scaled cohort studies are necessary to determine the optimal radiotherapy doses and fractions to treat both bone pain and neuropathic pain. MSCC and SBMs remain a challenge for EBRT. High-precision radiation therapy (IMRT or STI) should be considered for the delivery of higher radiation doses with sparing of normal tissues.

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