

Defining the role of palliative radiotherapy in bone metastasis from primary liver cancer: an analysis of survival and treatment efficacy

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ABSTRACT

Aims and background. Primary liver cancer is the fourth leading cause of cancer-related death worldwide and is still associated with a poor prognosis. Hepatocellular carcinoma and cholangiocarcinoma are known to cause bone metastasis resulting in pain, neurologic impairment and risk of fracture. Palliative radiotherapy is the treatment of choice in symptomatic bone lesions and is usually performed as percutaneous fractionated radiotherapy.

Methods and study design. From June 1987 to December 2009, 41 patients (median age, 64 years) with bone metastasis received radiotherapy in our department. The analyzed patients were treated for 67 sites of bone lesions. We analyzed the applied fractionation schedules and the preferred sites of metastasis and symptoms, evaluated the therapeutic outcome in terms of symptomatic improvement, and described the prognosis of these patients.

Results. Main indication for palliative radiotherapy was pain in 94% of all cases. Most frequent radiation protocols were 10 x 3 Gy (20 patients) and 20 x 2 Gy (19 patients). Median applied overall dose was 39 Gy (range, 4-48 Gy) and median single dose was 2.5 Gy (range, 1.8-4 Gy). The median duration of the radiotherapeutic treatment was 15 days (range, 2-24 days) and in 12 cases treatment was discontinued. The overall response rate to palliative radiotherapy in bone metastasis was 77%. Median overall survival in both cholangiocarcinoma and hepatocellular carcinoma patients was 4.2 months after initiation of radiotherapy (range, 0.2-38.9).

Conclusions. Considering the poor prognosis of patients with bone metastasis in hepatocellular carcinoma and cholangiocarcinoma, with a poor median survival of 3.7-5.0 months according to our study and existing literature, shorter radiotherapy schedules or even single-fraction irradiation can be considered.

Introduction

Patients suffering from primary liver cancer still have a poor prognosis. Liver cancer is the fourth leading cause of cancer-related death in the world and the second most common cancer in China¹. There is also an increasing incidence in western countries, with growing oncologic relevance. It is known that hepatocellular carcinoma (HCC) can be accompanied by bone metastasis in approximately 3-20%, with the incidence increasing over the past years²⁻⁵. In the last few years, there has been a tendency towards detection of more metastasized stages in HCC, which can be partially explained by an improvement in diagnostics and therapeutic procedures leading to longer survival of patients with advanced cancer disease^{6,7}.

One of the main sites of tumor metastasis in HCC is the skeleton, especially the vertebral bodies⁸. In most situations, patients are diagnosed with only one or two metastases of liver tumors. The preferred treatment of symptomatic bone metastasis is ex-

Key words: bone metastasis, cholangiocarcinoma, hepatocellular carcinoma, palliative radiotherapy, primary liver cancer.

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ternal beam radiotherapy. Indications for palliative radiotherapy usually are pain and/or morphological instability of the bone structure. It has been shown that radiotherapy is an effective and safe treatment in osseous lesions from HCC⁹⁻¹². The standard therapeutic overall doses for treatment of bone metastasis are between 30 and 50 Gy BED. In case of a marked soft tissue extension of bone metastases, higher radiation doses might be required⁸.

There are considerable epidemiologic differences in the incidence of HCC. High incidence regions are, for example, eastern Asia, with age-adjusted rates for liver cancer of approximately 30 per 100,000 in Japan, 50 per 100,000 in Korea and 55 per 100,000 in China, whereas in Europe and the United States, the rate is consistently below 10 per 100,000¹³. Known risk factors for developing primary liver cancer are also different and region specific. Whereas HCC is predominantly induced by hepatitis B and C viruses and aflatoxins in Asia and Africa, the main etiological factor of Caucasian HCC is liver cirrhosis, in most cases induced by alcohol-toxic liver disease¹⁴. It could be shown that the outcome for Asian patients suffering from HCC was worse than that of Non-Asian patients in a US-based population concerning 1-year survival estimates¹⁵. Until now, existing literature data on palliative therapy of advanced and metastatic primary liver carcinoma consist almost completely of Asian patient collectives, thereby reflecting the epidemiology of the disease. To date, no data are available on the outcome of Caucasian patients treated with radiotherapy for metastasized HCC.

With the present study, we describe the outcome of Caucasian patients with bone metastases from primary liver cancer including HCC, Klatskin tumors and cholangiocarcinoma (CCC) who underwent palliative external beam radiotherapy. We reviewed the clinical records and analyzed patient characteristics, treatment schedules, response to therapy and overall survival. Since only data from Asian patient collectives are available, we present a short literature overview and analyze differences in treatment modality and outcome.

Patients and methods

From June 1987 to December 2009, 41 patients (33 male, 8 female) with bone metastases from primary liver tumors such as HCC (30 patients, 48 lesions) and CCC (11 patients, 19 lesions) received radiotherapeutic treatment in our department. The analyzed patients were treated for 67 sites of bone lesions. The median age was 64 years (range, 36-80). Patient characteristics are summarized in Table 1.

Confirmation of bone metastasis was performed radiologically by computed tomography, in some cases also by bone scintigraphy. Serum levels of alpha-fetoprotein or a biopsy for histological study were evaluated when

Table 1 - Patient and treatment characteristics

Characteristic	
No. of patients	41
No. of lesions	67
Age, yr (median, range)	64 (36-80)
M/F (no.)	33/8
CCC (n = 11)	
Age, yr (median, range)	60 (40-73)
No. treated lesions	19
Male	7
Female	12
HCC (n = 30)	
Age, yr (median, range)	64 (51-80)
No. treated lesions	48
Male	42
Female	6

CCC, cholangiocarcinoma; HCC, hepatocellular carcinoma.

available. Patients were followed regularly after radiotherapy including clinical assessment, alpha-fetoprotein and radiological imaging. All patients were discussed in an interdisciplinary setting. Information on follow-up with clinical data on treatment response was available in 44 of 55 cases (80%).

The standard radiotherapy protocols included a fractionation regimen of 10 × 3 Gy (20 lesions, 30%) and 20 × 2 Gy (18 lesions, 27%) (Table 2). In 49% of all treatments (33/67 lesions), a hypofractionated protocol was applied with single fractions between 2.5 and 4 Gy. In 42% of the irradiated metastases (28/67 lesions), a conventional fractionation was applied. In another 6 cases, patients first underwent a normofractionation but then switched to a hypofractionated protocol because of a worse performance status.

Radiotherapy was usually performed 5 days per week. The median treatment time was 15 days. In case of ra-

Table 2 - Response to therapy and survival

Treatment response		
No evaluation because of treatment discontinuation		12/67 (18%)
Evaluated		44/55 (80%)
Not evaluated		11/55 (34%)
Improved		34/44 reported (77%)
Not improved		10/44 reported (23%)
Survival		
CCC + HCC	OS (median, range)	4.2 mo (0.2-38.9)
	6-mo OS	16/41 patients (39%)
	12-mo OS	6/41 patients (15%)
CCC	OS (median, range)	5.0 mo (0.5-9.7)
	6-mo OS	6/11 patients (46%)
	12-mo OS	0/11 patients (0%)
HCC	OS (median, range)	3.7 mo (0.2-38.9)
	6-mo OS	10/30 patients (33%)
	12-mo OS	6/30 patients (20%)

OS, overall survival; CCC, cholangiocarcinoma; HCC, hepatocellular carcinoma.

diotherapy of bone metastases in the vertebrae, the target volume included the non-invaded adjacent corpora vertebrae (cranial and caudal direction).

Overall survival was calculated from the first day of radiotherapy using the Kaplan-Meier method. Statistical testing of significance between survival rates was performed using the logrank method. All calculations were performed with SPSS 18.0 for Windows (SPSS Inc, Chicago, Ill, USA).

At the time of analysis, 40 patients (88%) with 64 lesions (85%) had died. One patient (3 lesions) was still alive at the time of analysis. Information on clinical symptoms was derived from patient medical records or radiological reports. Informed consent was obtained from all patients prior to start of radiotherapeutic treatment.

Results

Palliative indications for radiotherapy were pain (63 lesions, 94%), neurologic complications (9 lesions, 13%) and instable lesion with risk of pathologic fracture (6 lesions, 9%) (Table 3). Isolated or additional symptomatic spinal cord compression was seen in 9 patients (13%). Rare reasons for radiotherapy were a paresis of the nervus abducens in case of metastasis to the clivus and adjuvant radiotherapy after complete excision of a bone lesion. Twelve lesions (12/67, 18%) were excluded from the analysis because the radiotherapy protocol was not completed (severe deterioration of the patient's performance status). The most common site of bone metastases was the vertebra (34 lesions, 51%), followed by the pelvis (11 lesions, 16%), ribs (8 lesions, 12%), scapula (4 lesions, 6%), sternum (4 lesions, 6%), skull (3 lesions, 4%) and long bones (3 lesions, 4%). Eleven patients received palliative radiotherapy at multiple sites (≥2), and in at least 21 lesions, a documented large additional soft tissue mass related to the bone lesion was found (Figure 1).

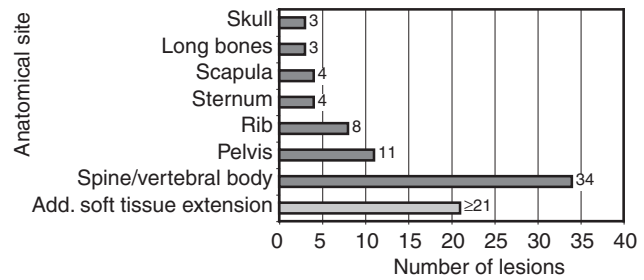


Figure 1 - Localization of lesions. Evaluated bone lesions (n = 67) and anatomical site.

The overall response rate to palliative radiotherapy in case of painful bone metastases was evaluated in 35 of 44 documented cases (80%), showing symptom reduction in 34/44 patients (77%) and no improvement in 10/44 (23%) (Table 2). Among these lesions, there was a response in 11/15 (73%) cases in the group of patients with CCC, and in HCC patients there was an improvement in 23/29 cases (79%).

All patients were treated by percutaneous, fractionated radiotherapy with single fractions of 1.8-4 Gy (median dose, 2.5) and overall doses of 4-48 Gy (median dose, 39) (Table 2). In 12 cases (18%), radiotherapy had to be withdrawn because of a deterioration of the patient's performance status. Our analysis included treatments from three decades: 70% of all lesions were treated with an overall dose of at least 30 Gy; for 9 lesions, a total dose of a minimum 30 Gy was prescribed but could not be administered because of treatment breaks. A total dose of only 8 Gy (single fraction 2 Gy) was successfully applied in only 1 case (early treatment in 1989).

Over the years, different fractionation schemes have been used. The most frequently applied schemes were 10 × 3 Gy (14 cases) and 20 × 2 Gy (16 cases), depending on the clinical situation and the overall performance status of the patients. In 82% of all treatments, overall doses of at least 30 Gy were applied. The median prescribed dose was 30 Gy (range, 20-45) for CCC patients and 36 Gy (range, 4-33) for HCC patients.

Figure 2 shows the percentage of treatment time in relation to the overall survival time for 20 selected treatment procedures. For approximately 30% of all treatments (20/67 lesions), patients were treated for more than 20% of their residual lifetime. In 5 cases, treatment lasted longer than 50% of the patient's residual lifetime.

Median overall survival in both CCC and HCC patients was 4.2 months after the start of radiotherapy, with a range of 0-38.9 months (Table 2). Patients with CCC showed a median overall survival of 5.0 months (range, 0.5-9.7), whereas HCC patients had a median overall survival of 3.7 months (range, 0.2-38.9). The overall survival rates after 6 months and 1 year were 38% and 13%, respectively (Figure 3). No significant difference in survival was found between the two groups (P = 0.774) according to the logrank method.

Table 3 - Details of radiotherapy

Radiotherapy indication	
Pain	63/67 lesions (94%)
Instability	6/67 lesions (9%)
Neurological impairment	9/67 lesions (13%)
Radiotherapy	
Overall dose (median, range)	39 Gy (4-48 Gy)
Single dose (median, range)	2.5 Gy (1.8-4)
Frequent treatment schedules	10 × 3 Gy, 20 lesions 20 × 2 Gy, 19 lesions 13 × 3 Gy, 2 lesions
Hypofractionation (SF 2.5, 3, 4 Gy)	33/67 lesions (49%)
Conventional fractionation (SF 2 Gy)	28/67 lesions (42%)
Normo- & hypofractionation	6/67 lesions (9%)
Re-radiotherapy	0
Treatment days (median, range)	15 (2-24 days)
Early discontinuation	12/67 treatments (18%)

SF, single fraction.

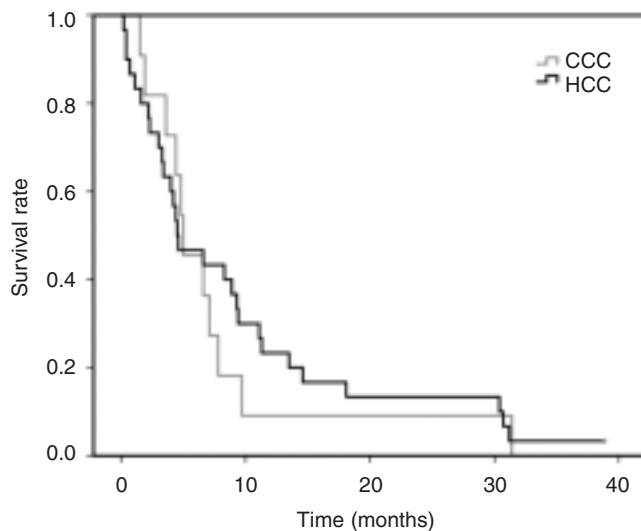


Figure 2 - Analysis of survival. Kaplan-Meier estimate of survival for all treated patients (n = 41).

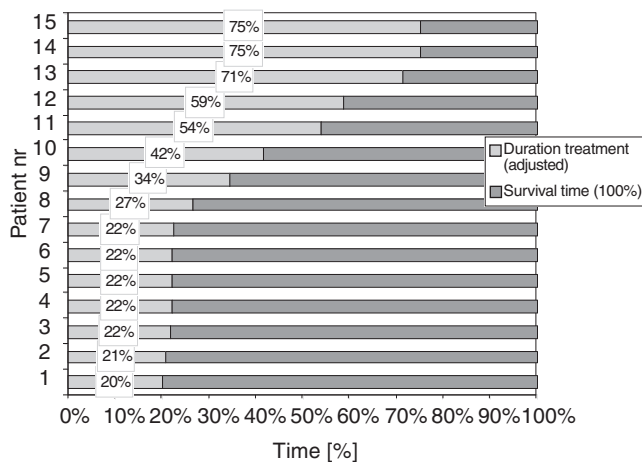


Figure 3 - Duration of radiotherapeutic treatment and remaining lifetime. Presentation of the 15 patients with the longest treatment duration referring to the remaining lifetime. Lifetime of the individual patient was set to 100%, treatment time was adjusted to this value.

Re-irradiation of previously irradiated lesions was not reported in our analysis.

Discussion

Most of the patients included in the study were treated with normofractionated schedules. Fractionation schedules have been discussed in the past, and in the palliative setting, hypofractionated regimens are recommended in international recommendations^{16,17}. Even normofractionated schedules, which are rarely used in palliative radiotherapy, were used in a relatively high percentage of cases (42% of all treatments). This can possibly be explained by the uncommonly large tu-

mor volumes due to a high percentage of soft-tissue extensions in HCC and CCC. Such a finding surely has to be seen as critical, because this patient group has a very poor prognosis (median survival of 3.7-5 months, 6-month overall survival of only 38%). The median number of treatment days was 15, which in fact means three weeks of treatment when radiotherapy is performed five times a week. In 20 selected patients the treatment period retrospectively exceeded 20% of their remaining lifetime, and five patients were under treatment for more than 50% of their remaining lifetime. In the context of the reported treatment breaks (12 lesions) and decreased life expectancy (only one third of patients will survive the first 6 months after treatment), the relatively long time of radiotherapeutic treatment should be questioned.

In the study, all patients received multifractionated schedules for bone metastasis, in most cases 10 × 3 Gy. This is in accord with other published regimens for bone metastases from HCC, where single-fraction schedules are rarely applied^{8,12,18}. Improvement of pain symptoms was reached in 72.7%¹², 83.8%¹⁸ and 99.5%⁸, whereas patients had a median survival of 5.9 months¹², 5 months¹⁸ and 7.4 months⁸. Nevertheless, we are able to demonstrate comparable results in the present study, with pain relief in 77% after treatment and a median overall survival of 5 months.

Prognosis of patients with metastasized primary liver cancer is limited. The incidence of bone metastases from HCC has increased over the past years and is in most cases detected by pain symptoms or neurological signs⁵. Generally, palliative external beam radiotherapy is an effective and safe treatment for bone metastases from liver tumors^{8-10,12,18}. Overall doses of 30-50 Gy given in normofractionated or hypofractionated schedules are sufficient for pain reduction and bone stabilization in most cases^{8,12,18}.

Recently, He *et al.*⁸ detected only a borderline significance between radiation dose and response rate, but the analysis of more than 200 treated patients indicated a higher response rate in the sense of complete or partial remission after application of total doses of ≥38 Gy. The authors also carried out a separate analysis in which bone lesions with an additional soft tissue extension were compared to bone-only metastasis but failed to prove a significant dose-response relationship. Even if there was no difference in required overall radiation dose in both groups, patients with soft-tissue extension had a significantly higher risk for re-treatment. In our study, we also observed a distinct number of bone lesions with considerable soft-tissue extensions (at least 11 patients with at least 21 additional soft-tissue extensions), but we did not perform a stratification of patients according to tumor growth pattern due to the small patient number.

Several randomized clinical trials have proven the efficacy, safety and also non-inferiority of a single-fraction

tion radiation schedule with 1×8 Gy compared to a widely accepted multifractionated schedule with regard to pain relief^{16,17,19,20}. Available guidelines therefore suggest a single-fraction schedule, nevertheless taking into account individual patient prognosis and performance score. Patients with a bad prognosis will potentially benefit from shorter treatment duration because of a limited life expectancy. However, in individual cases even in the palliative setting, survival of patients may be longer. Today we know that the ability of physicians to predict survival in terminally ill cancer patients is unreliable, and the prediction may be incorrect in a high percentage of cases²¹. A consequence of this will be the prescription of inadequate therapeutic regimens in a certain number of cases²².

The herein presented patient characteristics and related outcome are comparable to data from the literature. Reduction of pain or neurologic symptoms can be achieved with overall radiation doses of 30-50 Gy in normo- or hypofractionated schedules. It is known that overall survival is predominantly determined by Karnofsky status, intrahepatic tumor control and the presence of cerebral or visceral metastasis. Considering the poor prognosis of patients with bone metastasis in primary liver cancer, with a median survival of 4.2 months according to our study and existing literature, shorter radiotherapy schedules or even single-fraction irradiation can be considered.

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