ORIGINAL ARTICLE

Stereotactic radiotherapy for hepatocellular carcinoma: report of a local single-centre experience

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Objective To evaluate the efficacy and toxicities of stereotactic radiotherapy for unresectable hepatocellular carcinoma.

Design Retrospective study.

Setting Prince of Wales Hospital, Hong Kong.

Main outcome measures Treatment outcome and toxicities.

Patients During the period of 2000 to 2004, 16 patients with hepatocellular carcinoma treated with stereotactic radiotherapy were reviewed.

Results Of the 16 patients, 11 had assessable responses. For local control, there were two complete and three partial responses, five with stable disease and one with progressive disease, giving a local response rate of 45% and control rate of 91%. The median survival was 23 months. The 1-year and 3-year overall survival rates were 62% and 28%, respectively. The most frequent site of recurrence was intrahepatic but outside the irradiated field. Two patients with Child-Pugh B cirrhosis developed radiation-induced liver disease. No other grade 3/4 toxicities were recorded.

Conclusion Stereotactic radiotherapy gives high local control rates and has the potential to prolong survival in patients with hepatocellular carcinoma. It is safe and tolerable in Child-Pugh A patients.

Introduction

Hepatocellular carcinoma (HCC) is a major health care problem in Hong Kong and other parts of the world, and is associated with a high mortality.[1] Depending on the tumour stage and the background liver function of each patient, different treatment modalities including surgery, loco-ablative, transarterial and/or systemic therapy are frequently employed in its treatment.[2] Conventionally, radiotherapy is not regarded as a favourable treatment modality for HCC, owing to worries about limited hepatic tolerance of radiation and potential complications associated with radiation injury to the non-tumourous liver.[3-5]

Recent advances in three-dimensional conformal radiotherapy have allowed radiation beams to be more focused on and conform to the tumour site in the liver. Such progress not only permits higher radiation dose delivery to the target tumour but also avoids excessive dosing of normal liver tissue and adjacent organs. In recent years, the feasibility of external radiotherapy to treat primary or metastatic liver tumours has been explored globally in a number of centres. In carefully selected patients with liver tumours, most studies have consistently reported encouraging efficacy with a favourable safety profile.[6] However, there have been scanty published local data on the efficacy and toxicity of radiotherapy in patients with HCC.

In the Prince of Wales Hospital, HCC patients are cared for in the Joint Hepatoma Clinic by a multidisciplinary team consisting of oncologists, surgeons, and interventional radiologists. During the period of 2000 to 2004, we had the opportunity of administering stereotactic radiotherapy (SRT) to a series of patients with HCC. In this paper, we aimed to report data on the outcome and safety profile of SRT in the treatment of HCC in our centre.

Methods

Study population

This was a retrospective single-centre study reviewing the use of SRT in the treatment of HCC from May 2000 to November 2004. Eligibility criteria for patients included: (1)

Key words
Carcinoma, hepatocellular; Chemoembolization, therapeutic; Liver neoplasms; Radiotherapy, conformal; Survival analysis

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intrahepatic tumour not amenable to surgery or other loco-ablative therapy; (2) SRT undertaken as the treatment for HCC. Prior treatment apart from radiotherapy was allowed, while patients with extra-hepatic involvement (including regional lymph node involvement and/or distant metastases) were excluded from the study. The diagnosis of HCC was confirmed by histology or characteristic radiological findings in patients with hepatitis B–related cirrhosis and/or elevated alpha-fetoprotein (AFP) levels.

Treatment

The SRT procedures entailed gross tumour volume (GTV) which was delineated on arterial phase images using three-phase diagnostic computed tomography (CT). The planning target volume (PTV) was normally generated from GTV by adding a 2-cm margin in all directions; to avoid excessive estimated dose to the liver, 1-cm margins were accepted. No more than 30% of liver volume was allowed to receive greater than 30 Gy (V30 <30%). Patients were instructed to hold their breath at the end of expiration position during the planning CT and during treatment. The ExacTRA system (BrainLab, Germany) with facilities of stereotaxy was used to improve positioning reproducibility. Six infrared body surface markers were placed at patient's sternum and rib cage. Infrared cameras detected and confirmed the correct positioning of the markers before each treatment. Radiation dose was given at 4.5 Gy for 10 daily fractions normally. For the cases where the PTV encompassed hepatic portal area or gall bladder, the dose was 2.5 Gy for 18 to 20 fractions. For cases where the PTV included the bowel, the dose was 1.8 Gy for 28 to 30 fractions. The biological effective dose for tumour control, taking $\alpha/\beta=10$ was similar in these three-dose fractionations (65.3 Gy, 62.5 Gy, and 63.7 Gy, respectively).

Outcome assessment

All patients were followed up every 4 to 8 weeks after radiotherapy, with laboratory investigations when clinically indicated. We attempted to identify lesions by reassessment CT at around 4 to 6 months after day 1 of SRT, to arrive at an objective evaluation of treatment outcome. Response of the target irradiated lesion (local control) and overall tumour response (local control plus non-target lesions) were evaluated according to RECIST (Response Evaluation Criteria in Solid Tumors) separately.[7] Patients with clinical evidence of progressive disease before reassessment imaging were considered as having progressive disease as the final response outcome. The AFP value before and after radiotherapy was also studied to evaluate the serological response. A drop of AFP value by more than 20% after treatment was defined as an AFP response, as reported previously.[8] Patients with evidence of responding or stable disease were observed clinically and radiologically, while those with evidence of progressive disease were offered salvage therapy whenever possible, which depended on staging, liver function, and each individual's performance status. Survival time was measured from the date of radiotherapy to the date of death or last contact. Survival time was calculated using the Kaplan-Meier method. Any toxicity or adverse reactions noted during 6 months of completion of radiotherapy was reviewed. The severity was graded according to CTCAE (Common Terminology Criteria for Adverse Events) version 3.0 criteria.

肝癌的立體定位放射治療：一所分區醫院的經驗報告

目的 探討立體定位放射治療對不宜手術切除的肝癌的治療成效及毒性。

設計 回顧研究。

安排 香港威爾斯親王醫院。

主要結果測量 治療成效及毒性。

患者 2000至2004年期間，接受立體定位放射治療的16位肝癌患者。

結果 16位患者中，11位可作評估。兩位病灶完全緩解，3位部份有效，5位病灶穩定，1位病灶惡化。病灶的反應率為45%，局部控制率為91%。生存期中位數為23個月。1年及3年的總體生存率分別為62%和28%。最常見的復發方式為放射範圍外肝內復發。兩位Child-Pugh B級肝硬化的病人出現因放療引致的肝炎。除此之外，沒有出現3/4級的毒性。

結論 對於原發性肝癌，立體定位放射治療能提供較高的局部控制率，或有助延長病人存活時間。對於Child-Pugh A級肝硬化的病人，立體定位放射治療是安全的，並有良好的耐受性。

Results

Baseline characteristics

From May 2000 to November 2004, 16 HCC patients were treated with SRT, of whom 15 (94%) were male. The median patient age was 58 (range, 23-69) years. Most (81%) were chronic hepatitis B carriers. The lesion sizes ranged from 1 to 7 cm, with a median of 3 cm. Twelve of them had Okuda stage A disease while the remaining four patients belonged to Okuda stage B. Regarding their background liver function, 12 were Child-Pugh A and 4 in Child-Pugh B. Prior to treatment their AFP values and other characteristics are listed in Table 1.

TABLE 1. Baseline characteristics and treatment outcomes of patients with hepatocellular carcinoma*

Patient No.	Sex/age (years)	Hepatitis status	Okuda stage	Child-Pugh grading	Ascites	Pre-treatment AFP (ng/mL)	Post-treatment AFP (ng/mL)
1	M/66	B	A	A	No	30	20
2	M/69	B	A	B	Yes	22	14
3	M/65	B	B	A	No	1800	259
4	M/23	B	A	A	No	6700	426
5	M/57	B	B	B	Yes	40	17
6	M/51	B	A	A	No	1300	148
7	M/58	B	A	A	Yes	7400	4000
8	M/51	B	A	A	No	492	208
9	M/58	B	B	A	No	235	49
10	M/51	B	B	B	No	438	600
11	M/69	C	A	A	No	3	5
12	M/59	NA	A	A	No	1859	161
13	M/51	B	A	A	No	61	12
14	F/54	NA	A	A	No	16	12
15	M/40	B	A	A	No	2459	11 400
16	M/61	B	A	B	Yes	8629	82

* AFP denotes alpha-fetoprotein, ALT alanine aminotransferase, CR complete response, DM distant metastasis, HP hepatic progression outfield failure, LD longest diameter, NA not available, PD progressive disease, PR partial response, RILD radiation-induced liver disease, RT radiotherapy, SD stable disease, and SRT stereotactic radiotherapy

† Censored (alive)

Outcome

The median follow-up time was 24 (range, 2-54) months. The PTV ranged from 37 to 341 cc and the median was 134 cc. Eleven of the patients had reassessment imaging suitable for evaluation of response. The other five patients did not have suitable radiological assessment for the following reasons: two had multifocal recurrences after radiotherapy which made it unreliable to identify the original irradiated lesion for reassessment; one

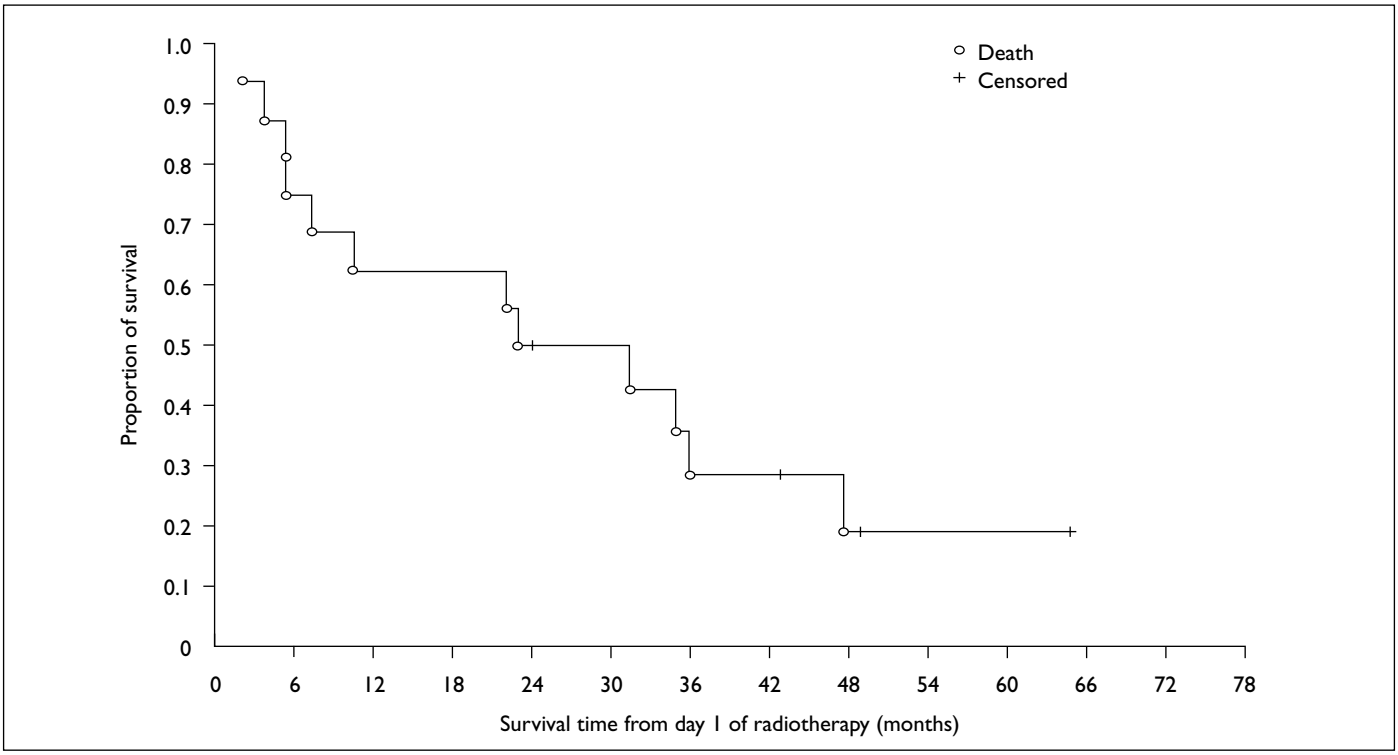

FIG 1. Overall survival of patients

Size of target lesion (LD/cm)	Local response	Site of failure	Overall survival (months)	Remarks
4.2	SD	HP	36	-
2	PD	HP	23	-
3.3	NA	NA	5	Died of non-cancer cause
5	PR	HP/DM	35	Severe abdominal pain during RT
4.5	NA	NA	4	Died of RILD
2	PR	NA	54†	Liver transplant done after SRT
7	SD	PD	11	-
6	SD	DM	5	-
1 and 2.5	SD	HP	48	-
4.5	NA	HP	2	Original lesion could not be ascertained
5	CR	CR	31	-
2	CR	CR	49†	Deranged ALT after RT
6	NA	NA	43†	Defaulted follow-up
2	SD	SD	7	-
2	NA	HP/DM	22	Original lesion could not be ascertained
2	PR	PR	24†	RILD

defaulted follow-up; and two died before their scan. Concerning the local control of the target lesion, two had complete responses, three achieved partial responses, five had the disease remained stable, and in one it was radiologically progressive. Thus, there was a local response rate of 45% and control rate of 91%. As regards the subsequent sites of failure, intrahepatic progression outside the irradiated field was the most frequent pattern, followed by distant metastasis. Among the 14 patients with elevated AFP levels (>20 ng/mL) before treatment, in 12 patients AFP levels responded after completion of radiotherapy. At the time of data analysis, 12 of the 16 patients died while four were still alive. The median overall survival was 23 months, and the 1-year and 3-year overall survival rates were 62% and 28%, respectively (Fig 1).

Toxicity

Two patients developed radiation-induced liver disease (RILD), one of whom recovered and one died. Both patients had background Child-Pugh B liver cirrhosis and ascites prior to radiotherapy. Both patients were found to have elevated alanine aminotransferase (ALT) levels followed by jaundice 4 to 6 weeks after completion of radiotherapy. Another patient with Child-Pugh A cirrhosis had deranged ALT levels up to 8 times of upper normal limit, which normalised spontaneously without evidence of liver failure. One patient complained of right upper quadrant pain during radiotherapy, which was relieved after oral morphine therapy. No other grade 3 or higher toxicities were documented.

Discussion

In this study, we demonstrated that SRT was feasible in a local population of HCC patients. The local control rate was high, with a 3-year survival rate of 28%; in this series there were also two long-term survivors. The results concur with reports from centres in other parts of the world. For example, in 2004, Liu et al[9] studied the use of radiotherapy in patients with HCC refractory to transarterial chemoembolisation (TACE) and reported similar rates of 3-year survival (32%) and disease control (77%). Apart from use as a single treatment, radiotherapy has also been studied for the management of HCC in combination with transarterial therapy.[10-17] In those studies, the radiotherapy doses ranged from 25 to 90 Gy, which involved fractional doses of 1.5 Gy twice a day to 8 Gy per fraction. The reported response rates were 10 to 91%, while the 1-year survival rate was 47 to 93% and 3-year survival was 11 to 27%. The results of these studies are summarised in Table 2.[9,10,12-17]

From the current data, it appears that radiotherapy offers excellent local control for HCC patients. For example, one of our patients with a small 2-cm HCC (Fig 2a) in close proximity to the diaphragm (considered unsuitable for other local treatments) was treated with 7-beam SRT (Fig 3). The patient received a total of 50 Gy over 20 fractions (2.5 Gy/fraction), and included the heart as part of the radiation field. Reassessment contrast CT showed that

TABLE 2. Summary of literature on radiotherapy with or without transarterial chemoembolisation*

Study	No. of patients	Liver function (No.)	Treatment	RT dose in Gy (dose/Fr)	Response	Median survival (months)	Overall survival rate
Ben-Josef et al,[10] Michigan, 2005	35	Child's A (35)	RT + hepatic arterial FudR	40-90 (1.5/Fr, bid)	CR 3% PR 7% SD 31%	15.2	1-Year 57% 3-Year 11%
Liu et al,[9] China, 2004	44	Child's A (32); Child's B (12)	Primary RT (39 failed TACE)	39.6-60.0 (1.8/Fr)	CR 14% PR 48% SD 25%	15.2	1-Year 60% 3-Year 32%
Zeng et al,[12] China, 2004	54	Child's A (44); Child's B (10)	TACE + RT	36-60 (2/Fr)	CR 6% PR 70% SD 24%	20.0	1-Year 72% 3-Year 24%
Seong et al,[13] Korea, 2003	158	Child's A (117); Child's B (41)	TACE + RT	25.2-50.0 (1.8/Fr)	CR 0.6% PR 67% SD 26%	16.0	1-Year 59% 2-Year 30% 5-Year 9%
Li et al,[14] China, 2003	45	No Child's C	TACE x 2 → RT → TACE x 2	50.4 (1.8/Fr)	CR 13% PR 77% SD 8%	23.5	1-Year 68% 3-Year 22%
Wu et al,[15] China, 2004	94	Child's A (43); Child's B (51)	TACE + RT	48-60 (4-8/Fr)	CR 13% PR 78% SD 6%	25.0	1-Year 93% 3-Year 26%
Guo et al,[16] China, 2003	76	Child's A (63); Child's B (13)	TACE + RT	30-50 (1.8-2/Fr)	CR 7% PR 41% SD 40%	19.0	1-Year 64% 5-Year 19%
Park et al,[17] Korea, 2005	59	Child's A (38); Child's B (3)	RT (48 failed TACE); 51% with PVT	30-55 (2-3/Fr)	CR 8% PR 58% SD 25%	10.0	1-Year 47% 2-Year 27%

* bid denotes twice a day, CR complete response, FudR floxuridine, PVT portal vein thrombosis, PR partial response, RT radiotherapy, SD stable disease, and TACE transarterial chemoembolisation

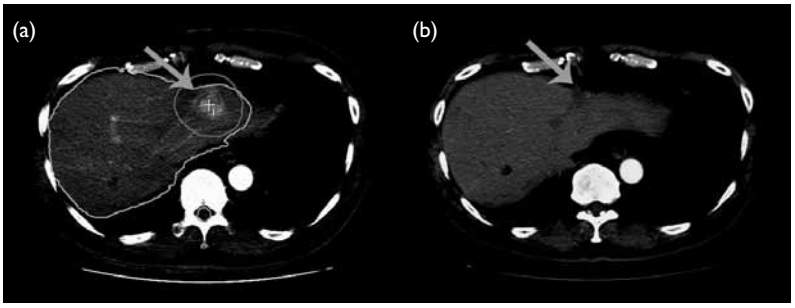

FIG 2. Patient No. 12: (a) Pre-treatment computed tomogram showing a 2-cm contrast enhanced lesion (arrow). (b) 12-Month post-treatment computed tomogram showing no contrast enhancement (arrow), reported as non-viable

the original lesion had become hypodense without contrast enhancement, suggesting non-viable tumour (Fig 2b). Another of our patients had had a 2-cm HCC at baseline, and had liver transplantation at 6 months after radiotherapy. Subsequently, pathology of the liver specimen revealed that the primary lesion had regressed to two small lesions measuring 0.4 and 0.2 cm with surrounding extensive fibrous scarring. The ability of radiotherapy to achieve local control of tumour is encouraging, and is of potential therapeutic significance for patients whose tumours are difficult to be accessed by percutaneous loco-ablative therapy. To address this issue, further prospective studies are required, including a direct comparison of SRT and loco-ablative therapy for HCC patients.

On the other hand, outfield recurrence in the form of intrahepatic recurrences or distant metastasis was the predominant pattern of radiotherapy failure. This could be due to microscopic dissemination before radiotherapy or de-novo HCC within cirrhotic liver. At the time of study, local or systemic adjuvant therapy was not used because of paucity of data supporting as well as lack of effective agents. In view of emerging targeted therapy in HCC,[18,19] combining systemic agents with radiotherapy provides theoretical benefit in reducing outfield failure, and this approach is currently being tested in a number of clinical trials.[20,21]

Higher-dose radiotherapy is associated with improved survival, as demonstrated in a number of studies. Park et al[22] reported a dose-response relationship in local radiotherapy for HCC. In this study, 158 patients were treated from January 1992 to March 2000 with the three-dimensional conformal radiotherapy, combined with TACE as primary treatment, or as salvage after TACE failure. The objective response rate in patients treated with doses of <40 Gy, 40-50 Gy and >50 Gy in 1.8-Gy daily fraction were 29%, 69% and 77%, respectively. In the Samsung Medical Center, South Korea, Park et al[17] found that biological effective doses higher than 50 Gy (α/β=10) were associated with higher response

rates (73% with >50 Gy vs 47% with <50 Gy; P=0.0299). Using multivariate analyses, studies from Seong et al[13] and Ben-Josef et al[10] consistently demonstrated that the radiation dose was an independent factor affecting survival after HCC. In daily practice, further increases of the total radiation dose are usually limited by toxicities to surrounding non-tumourous liver, especially in cirrhotic patients. Recent advances in techniques, such as image-guided radiotherapy, which synchronises delivery of radiation with respiratory movements of individual patients, may minimise the need for broader margins and permit higher doses of radiotherapy targeted to the tumours.

Among the various toxicities associated with radiotherapy in the treatment of liver tumours, RILD is the most well-documented toxicity. The classical RILD described in the literature is very similar to veno-occlusive disease.[3] Patients usually present with anicteric ascites, tender hepatomegaly and elevated liver enzyme levels, which typically manifest 2 weeks to 4 months following radiotherapy. This toxicity occurred in two of our patients and contributed to one mortality. There was no specific treatment for RILD, hence it is crucial to identify risk factors. Dawson et al[23,24] found that the mean liver dose and male gender were significantly associated with RILD. In addition, a Taiwan group[11] reported that hepatitis B positivity and Child-Pugh B cirrhosis were the independent risk factors for development of RILD. In another study on a Chinese population,[25] it was associated with advanced tumour stage, large GTV, portal vein thrombosis, acute hepatic toxicity and Child-Pugh B cirrhosis; only Child-Pugh B cirrhosis turned out to be significant in multivariate analysis. The Korean group[26] found that the total liver volume receiving more than 30 Gy was the only independent risk factor for RILD. Taking all such information into consideration, to minimise the chance of RILD radiotherapy is best avoided in patients with Child-Pugh B cirrhosis or advanced tumour in liver. Other commonly reported toxicities of radiotherapy for HCC include: fatigue, nausea, hepatic discomfort, subcapsular bleeding, and obstructive jaundice. Late toxicities including thrombocytopaenia, colitis, bowel obstruction, fistula formation, and rib pain may also occur a few months after treatment. In our series, all patients could complete the whole course of treatment without interruption, while only one developed hepatic pain and was treated with analgesics.

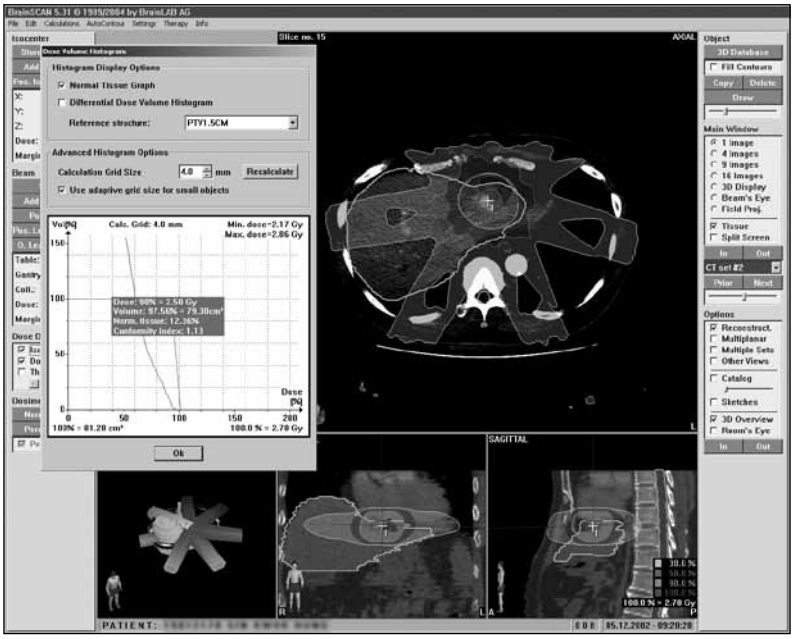

FIG 3. 7-Beam stereotactic radiotherapy

In summary, we demonstrated that SRT is a feasible treatment option for HCC patients. It offers good local control with tolerable toxicity in patients with preserved background liver function. To improve the efficacy of SRT treatment for HCC, future research should focus on identification of optimal dose fractionations and incorporation of novel radiotherapy techniques to improve the therapeutic ratio. In view of frequent recurrences outside the irradiated field, combination of radiotherapy with novel targeted systemic agents need to be rigorously evaluated in future studies.

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