
REVIEW ARTICLE

A Non-invasive Weapon: Image-guided Radiotherapy for Hepatocellular Carcinoma

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ABSTRACT

The high prevalence of chronic hepatitis B virus infection in Hong Kong makes hepatocellular carcinoma one of the area's most important solid tumours. Late presentation and underlying cirrhosis mean that many hepatocellular carcinomas are inoperable at first presentation. For many years, radiotherapy was a poor option for inoperable hepatocellular carcinoma because of low hepatic tolerance of radiation and technical limitations in the delivery of radiotherapy. A variety of technological advances in the areas of diagnostic imaging, radiotherapy planning, motion management, and image guidance during radiotherapy delivery have overcome most of the barriers to effective application of radiotherapy in hepatocellular carcinoma. In the Department of Clinical Oncology at Pamela Youde Nethersole Eastern Hospital, image-guided radiotherapy has achieved excellent results in 59 patients with liver-confined hepatocellular carcinoma, and the treatment is well tolerated. The one-year local control rate and one-year overall survival rate were 91% and 71%, respectively. Our experience and other published data indicate that image-guided radiotherapy can be considered the treatment of choice for patients with hepatocellular carcinoma who prefer non-surgical intervention.

Key Words: Carcinoma, hepatocellular; Radiotherapy, image-guided; Treatment outcome

中文摘要

一種非侵入性武器：影像引導放射治療肝癌

羅麗柔、吳偉棠、賈亦尊、楊美雲

在香港，慢性乙型肝炎病毒感染的高患病率使肝癌成為本地最重要的實體腫瘤之一。遲診及伴有不同程度的肝硬化令很多肝癌病例在診症時已無法用手術治療。多年來，由於肝臟細胞對輻射的抵受力度低，以及傳送放射治療的技術困難，放射治療對於無法用手術切除的肝細胞癌來說並不是一個好的選擇。隨著科技的進步，診斷成像、放射治療計劃、移動管理、放療期間的圖像引導各種技術已經跨過障礙，令放射治療可以應用在肝癌上。東區尤德夫人那打素醫院的臨床腫瘤科利用影像引導放射治療，替59名癌細胞局限在肝臟的病人進行治療，並取得極佳的效果，病人耐受性亦相當好：一年局部控制率為91%，一年存活率為71%。我們的經驗和其他公佈的數據均顯示，圖像引導放射治療可以是那些選擇非手術介入治療的肝癌患者的首選療法。

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common solid cancer globally, with more than 600,000 new cases diagnosed each year.¹ HCC is highly prevalent in Hong Kong because of the high rates of hepatitis B virus infection in the population, and the incidence is rising.² There is also a rising incidence of HCC in western populations, e.g. in the United States, driven by growing rates of chronic hepatitis C virus infection.³

In the past, surgery has been the mainstay of treatment for early stage HCC⁴; however, the majority of HCC cases are inoperable because of late disease presentation and underlying cirrhosis. Alternatives to surgery for liver-confined HCC include ablation therapy such as radiofrequency ablation (RFA), transarterial chemoembolisation (TACE), radioembolisation, and external beam radiotherapy (RT).

CLINICAL EXPERIENCE WITH IMAGE-GUIDED RADIOTHERAPY FOR HEPATOCELLULAR CARCINOMA

Historically, RT has had a low position in the hierarchy of treatment options for HCC because of the liver's low radiation tolerance and the consequent difficulty in delivering an adequate radiation dose to the tumour.⁵⁻⁷ This problem is further complicated by the need for a wide treatment margin on the radiation field to account for breathing movements. However, RT for HCC is now feasible as a result of improved understanding of the partial liver tolerance to radiation as well as a variety of technological advances in diagnostic imaging, RT planning, motion management, and image guidance during RT delivery.

Law et al⁸ recently published their experience using high-dose image-guided RT (IGRT) to treat 33 patients with liver-confined HCC between May 2006 and December 2009 at Pamela Youde Nethersole Eastern Hospital (PYNEH); the updated series now extends to December 2011 and comprises 59 patients (Law AL et al, unpublished data, 2012). These patients had liver-confined primary HCC and a reasonable Eastern Cooperative Oncology Group performance status (0-2), but were ineligible for, or refused, surgery or RFA. Patients with clinical ascites or distant metastases were excluded from the series. The clinical target volume (CTV) for RT included the gross tumour volume (determined radiologically) plus an 8-mm margin, while

the planning target volume (PTV) extended a further 5 mm in the lateral direction and 8 mm in the crano-caudal direction beyond the CTV.

In the treatment room, daily high-quality kV images were obtained prior to each treatment session to align patients precisely and reduce inter-fractionation error. Lipiodol was used to define the tumour site, or the diaphragm was the surrogate for treatment adjustment if lipiodol was not used. A real-time position management system was used to monitor patient respiration during treatment in order to adjust for intra-fraction motion. A block with infrared reflective markers was placed on the patient's abdomen while they were supine. The movement of the block by the patient's respiration was recorded with an infrared camera to create a 'breathing trace'. A computer workstation processed the signals to generate appropriate triggers for computed tomography (CT) image acquisition, simulator fluoroscopy, and radiation delivery. The effect of tumour movement was reduced by performing CT image acquisition and treatment delivery only when the maximum linear motion of the tumour site was 5 mm; in some patients this involved free breathing and respiratory gating for treatment, while others were treated during voluntary breath holding.

Patients received high-dose conformal RT at a prescribed dose to the PTV of 55 Gy over 10 fractions. In terms of dose constraints, the mean dose to the normal liver was <22 Gy and the maximal permitted dose to the spinal cord was 34 Gy. In addition, no more than 33% of the kidney volume should receive >18 Gy.

In the first year following treatment, the follow-up schedule comprised a clinic visit one month after RT, and clinic follow-up with serial CT scans at 3, 6, 9, and 12 months post-RT. In the second year, patients were followed up every four months and had an annual CT scan, and subsequent follow-up was six monthly. The Response Evaluation Criteria In Solid Tumors was used to gauge clinical response with abdominal magnetic resonance imaging (MRI) employed if needed.

Clinical Results with Image-guided Radiotherapy

The baseline characteristics of the 59 patients in the series are shown in Table 1. In 52 patients, lipiodol was used to define the lesion position for image guidance, and diaphragmatic position was used in the remainder. Respiratory control was achieved with free breathing

plus respiratory gating in 26 patients, 22 patients performed breath holding, and 11 were free breathing without gating during treatment as they had minimal diaphragmatic movement. The 55 Gy target dosage was achieved in 78% of patients.

The median follow-up period was 16.4 months; 30% of patients achieved a complete response, a further 22% demonstrated a partial response, 42% had stable disease, and 7% developed progressive disease. Table 2 presents additional data of outcomes.

The treatment was well tolerated; no grade 4 toxicities were observed, and grade 3 toxicities occurred in nine patients (2 leukopaenia, 1 elevated liver enzymes, and 6 elevated bilirubin). None of the patients experienced radiation-induced liver disease.

Comparison with Other Published Studies

The one-year overall survival (OS) rate of 71% with IGRT in this series compares favourably with studies using other treatment modalities, including that of Hong et al⁹ who reported a one-year OS of 100% following RFA in a younger population than that of the current

Table 1. Baseline characteristics of patients with hepatocellular carcinoma treated with image-guided radiotherapy at Pamela Youde Nethersole Eastern Hospital (n = 59).

Characteristic	Data*
Median (range) age (years)	69 (47-89)
Male:female	39 : 20
HBV carrier : HCV carrier : other	38 : 10 : 11
Child-Pugh stage A : B	47 : 12
Prior TACE	44 (75%)
No. of lesions	
Single	36 (61%)
Multiple (range, 2-6)	23 (39%)
Median gross tumour volume (mL)	23.6
Median (range) extent (cm)	2.8 (1-9.3)

Abbreviations: HBV = hepatitis B virus; HCV = hepatitis C virus; TACE = transarterial chemoembolisation.

* Data are shown as No., No. (%), or otherwise indicated.

Table 2. Clinical outcomes in patients with hepatocellular carcinoma treated with image-guided radiotherapy at Pamela Youde Nethersole Eastern Hospital (n = 59).

Clinical outcome	% of patients*
Local control	83%
Outside-field intrahepatic failure	59%
Distant metastases	15%
Median survival (months)	17
1-Year overall survival rate (%)	71
1-Year local control rate (%)	91

* Unless otherwise indicated.

study, and Lo et al¹⁰ who reported a one-year OS of 57% after TACE. In a recent review of studies of RT for HCC, one-year local control (LC) rates after fractionated RT for HCC ranged from 61 to 78%, with one-year OS rates from 35 to 72%.¹¹ After stereotactic body RT, one-year LC and one-year OS rates ranged from 65 to 100% and 48 to 93%, respectively.¹¹ The one-year LC rate in the present study was 91%. Thus, the clinical experience with IGRT at PYNEH in Hong Kong is similar to the worldwide experience.

CASE ILLUSTRATIONS

Patient 1

A 75-year-old woman was unsuitable for TACE because of hepatic artery dissection. Six months after RT, her CT scan showed no enhancement at the tumour site, although some fatty change was evident along the RT portal. The patient was progression-free for five years post-RT; subsequently, recurrence developed at the original tumour site, but the patient chose conservative management.

Patient 2

An 89-year-old woman presented with a 5.6-cm HCC and a normal baseline alpha fetoprotein (AFP) level. She was unable to tolerate TACE because of abdominal pain and vomiting. RT was administered and the tumour was no longer radiographically visible six months post-treatment (Figure 1). An MRI performed 12 months post-RT confirmed that there was no viable tumour, and the patient remains well and active three years after RT treatment.

Patient 3

An 83-year-old woman with HCC not amenable to RFA due to poor ultrasound visibility did not want TACE because of her advanced age. One month after RT treatment, her AFP level dropped to 35 from 18,270. Although the patient progressed well for six months, she subsequently developed lung metastases.

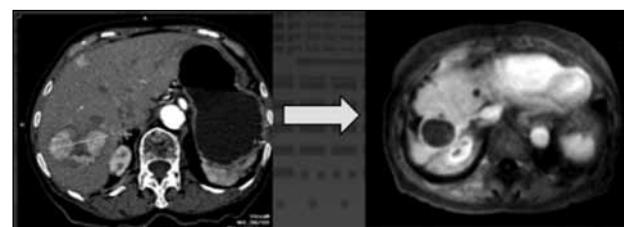


Figure 1. Radiographic resolution of a large hepatocellular carcinoma is apparent on magnetic resonance imaging 12 months after radiotherapy.

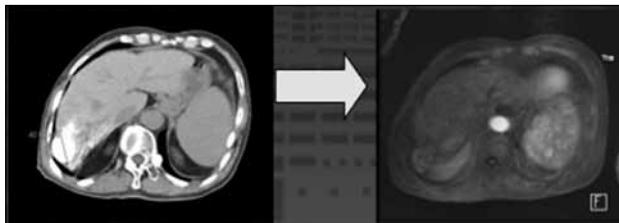


Figure 2. Eighteen months after radiotherapy, the 4-cm hepatocellular carcinoma adjacent to the hepatic capsule and duodenum was shown to be non-viable on magnetic resonance imaging.

Patient 4

A 76-year-old man presented with a 4-cm HCC adjacent to the hepatic capsule and duodenum. The tumour position precluded the use of RFA or TACE because of the risk of capsular rupture and limited the RT dose to the tolerance of the duodenum. Clinical remission was achieved 18 months after RT (Figure 2); the patient remains well after 3.5 years of follow-up with no evidence of disease relapse.

Patient 5

A 59-year-old man presented with dual hepatic lesions after failed RFA. After RT, MRI showed no viable tumour but some post-RT portal changes. The patient is well after four years of follow-up.

CONCLUSION

Use of IGRT for liver-confined primary HCC at PYNEH has achieved excellent LC results and the treatment is well tolerated. IGRT can also be used safely as an adjunct to TACE. Thus, IGRT can be considered the treatment of choice for HCC patients who prefer non-surgical intervention.

In the future, RT could have a more important role in the treatment algorithm for HCC as it has potential as a bridge to liver transplant, may benefit patients with

portal invasion when used alone or with sorafenib, and palliative low-dose RT could be offered in symptomatic late-stage disease to relieve hepatic progression.¹² As outside-treatment field intra-hepatic progression is the most common cause of failure after RT, further research is needed to determine whether RT plus TACE or RT plus systemic therapy could improve outcomes.

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