

Effects of three-dimensional conformal radiotherapy and image-guided radiotherapy on patients with liver cancer

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ABSTRACT

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Keywords: Hepatocellular carcinoma, image-guided radiotherapy, three-dimensional conformal radiotherapy, safety, prognosis.

Background: This study focuses on analyzing the effects of three-dimensional conformal radiotherapy (3DCRT) and image-guided radiotherapy (IGRT) on the safety and prognosis of individuals with hepatocellular carcinoma (HCC).

Materials and

Methods: Eighty cases of HCC individuals admitted between January 2023 and December 2023 were studied; the control group received IGRT intervention with 34 cases; the research group received 3DCRT intervention with 46 cases. The safety (incidence of grade 1, 2, and 3 hepatic toxic side effects), prognosis, range of lower extremity computed tomography angiography-planned target volume (CTV-PTV) externally, and efficacy of the treatment were comparatively analyzed. **Results:** The data manifested that the incidence of grade 1 toxicity in the research group exceeded that in the control group, but the incidence of grade 3 toxicity in the research group was lower, and the 1-year and 2-year survival rates in the research group were greater. The median survival time in the research group was longer than that in the control group. The range of CTV-PTV exposure in the left and right, head and foot, anterior and posterior aspects was lower than that in the control group. In addition, the CR+PR rate was significantly higher in the research group. **Conclusion:** These outcomes revealed that IGRT is more suitable for HCC patients than 3DCRT, which not only has a certain degree of safety, but also can help to significantly improve the prognosis.

INTRODUCTION

Hepatocellular carcinoma (HCC) ranks as the seventh most familiar tumor worldwide and is the second leading factor in tumor-related deaths, occurring in Asia, Africa, and in the elderly and male populations^(1, 2). According to epidemiological data, the risk of liver cancer is increasing, and it is expected that the number of cases will surpass 1 million in 2025. HCC is the most frequently occurring form of liver cancer^(3, 4). Obesity, diabetes, heavy drinking, chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, and exposure to aflatoxin might increase the likelihood of developing liver cancer⁽⁵⁾.

For early-stage HCC, the treatment choices are surgical resection, liver transplantation, and percutaneous transluminal puncture⁽⁶⁾. Radiotherapy, on the other hand, is a non-invasive localized therapeutic action by directly and indirectly causing Deoxyribonucleic Acid (DNA) double-strand breaks through ionizing radiation⁽⁷⁾. As a non-surgical alternative therapy, it is often used in advanced HCC patients, and the current scenario of the use of this therapy is gradually becoming more and more common⁽⁸⁾. Image-guided radiotherapy (IGRT) and Three-dimensional conformal radiotherapy (3DCRT) are two important

radiotherapy techniques. The underlying technology of 3DCRT is closely linked to computerized computation, optimization, and virtual reconstruction techniques, whereby the radiation treatment planning software system determines the radiation target volume, field of view shape, and angle, calculates the model dose based on the Computed Tomography (CT) scan, and determines the target dose based on the tolerated dose of the adjacent normal tissues and the underlying liver^(9, 10). Previous studies have shown that 3DCRT can be used for the treatment of extensive vascular infiltration in HCC and may also help patients to preserve hepatic functional reserve as well as prolong survival⁽¹¹⁾. Also, Lim *et al.*⁽¹²⁾ reported that high dose 3DCRT (median radiotherapy dose of 54 Gy per day) for individuals with small HCC (<5 cm) who are not qualified for other local modalities of treatment is a proven therapeutic option, which is beneficial in improving local control as well as prolonging overall survival. By using IGRT, a form of radiation therapy in the form of imaging, the accuracy and precision of the treatment process can be maximized, and the radiation dose can be minimized, thus reducing the negative effects of the treatment process on normal tissues⁽¹³⁾. This therapy can improve the prospect of individuals with tumors such as HCC with the help of

imaging techniques such as portal vein imaging, indoor medical imaging with CT, MR, or ultrasound to cover the tumor at a suitable and sufficient dose of radiation while preserving normal tissues⁽¹⁴⁾.

However, there is a limited number of studies focusing on the safety and prognostic effects of 3DCRT versus IGRT in patients with HCC. For example, Takeda *et al.*⁽¹⁵⁾ found that stereotactic radiotherapy could enhance local control and overall survival in HCC individuals with a maximum tumor size of ≤ 4 cm, providing a certain degree of safety. Garin *et al.*⁽¹⁶⁾ discovered that selective internal radiotherapy with a personalized dose regimen for individuals with unresectable regionally progressed HCC significantly improved the objective remission rate and reduced the risk of serious adverse events compared to a standard dose regimen.

The uniqueness of this research resides in its comprehensive analysis of the safety and prognostic effects of 3DCRT and IGRT in HCC patients. By comparing these two radiotherapy techniques, we aim to provide more reliable and optimized management strategies for HCC patients undergoing radiotherapy.

MATERIALS AND METHODS

Patient information

The enrollment comprised eighty HCC patients admitted between January 2023 and December 2023. The control group (n=34) received IGRT intervention, the research group (n=46) with 3DCRT intervention. The difference in general data was not statistically remarkable($P>0.05$) and was clinically comparable. It received approval from our Ethics Committee, and the subjects signed and furnished informed consent.

Selection criteria

Inclusion criteria: diagnosis confirmed by pathology and meets diagnostic criteria for primary HCC; meets Child-Pugh grading criteria; meets Barcelona staging (BCLC); has not received other treatments, e.g., surgery, liver transplantation, local ablation, or biologic therapies; has complete and accurate clinical and imaging data; and has normal cognitive and communication skills.

Exclusion Criteria: those with hepatic function Child-Pugh grade C; those with abnormal coagulation function and contrast agent allergy; those with extensive systemic metastasis and large amount of ascites; those with combination of cardiac, pulmonary and renal insufficiency; those with combination of other malignant tumors; and those with psychological disorders and poor adherence.

Planning

For the control group (IGRT intervention):

1. Positioning: using the Elekta Autonomous Breathing Coordination program (ABC) to select out the end of inspiration or near the end of inspiration to induce the patient. The patient's maximum respiratory depth was measured, and the threshold was set to 60% of the maximum inspiratory volume. Before positioning, let the patient inhale oxygen for more than 20min;

2. Making a treatment plan: Elekta Precise Plan and Pannicale3 plan are used for designing and confirming the treatment plan;

For the research group (3DCRT intervention): The patient took the supine position, hands uplifted to hold the elbow on the forehead, and the position was fixed by a vacuum body mold.

Radiotherapy

For the control group (IGRT intervention): Online correction and treatment were carried out after using BC and cone beam CT scanning (SIMENS, Germany), and the threshold value at the time of positioning was the respiratory control threshold value. After completing the task of acquiring cone - beam CT images, the pendulum deviation in the three directions of right and left X, head angle Y, and anterior and posterior Z in front of the cone - beam CT was solved based on the neighboring tissue contours, such as iodized oil images, the outer edges of the liver, etc., on the basis of grayscales and manual matching of the cone - beam CT images and the planned CT images. A second cone - beam CT scan was performed after treatment to derive the deviation data for which the images were matched. Details of the location of the lesion under image guidance can be seen in figure 1.

For the research group (3DCRT intervention): Under the calm breathing state, a 5mm thin-layer spiral CT scan was performed consecutively, and the scanning range was from 3 - 5 cm above the top of the diaphragm to 3 - 5 cm below the lower edge of the liver. Then, the localized CT images were transmitted to the planning system, and the diagnostic radiologists and radiotherapists worked together to sketch the gross target volume (GTV). The clinical target volume (CTV) was augmented by 0.5 - 1.0 cm on the basis of GTV, while the planning target volume (PTV) was broadened by 1 - 1.5 cm up and down on the basis of CTV, and 0.5 - 1.0 cm left and right anterior and posterior exteriors. A total of 3 - 5 coplanar fields were set up, and the treatment plan was evaluated and optimized using a dose volume histogram (DVH) to cover PTV with a 90% isodose curve, controlling the exposure of organs at risk (normal liver tissue, duodenum, stomach, pancreas, and spinal cord, etc.) within the normal tolerance range. A 6MV - X - ray linear gas pedal was used to execute the treatment plan, with a split dose of 2.6 - 3.2 Gy/times, 5 times/week, totally 48 - 60 Gy.

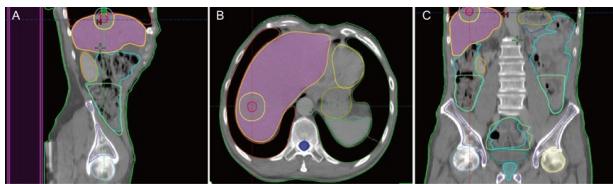


Figure 1. Location of the lesion under image guidance.

A. Sagittal plane: Shows the location of the lesion in the sagittal plane under image guidance. **B.** Cross section: Displays the cross-sectional view of the lesion's location. **C.** Coronal plane: Illustrates the position of the lesion in the coronal plane.

Evaluation indicators

Safety By using the National Cancer Institute's toxicity criteria, hepatic toxicities were rated, having grade 1 as mild, grade 2 as moderate, and grade 3 as severe, and the period from the date of initiating radiotherapy to within the third month was considered for counting.

Prognosis Following hospital discharge, all individuals were followed up every 2 months using electrical visits, follow-up visits, and examination of pathological data. The 1-year and 2-year survival rate, and median survival period were noted in both groups.

CTV-PTV external range Alignment deviations of cone-beam CT images and localized CT images were measured before and after radiotherapy, and the calculation of the CTV-PTV ex-vivo range of radiotherapy for HCC after applying IGRT was strictly based on the Stroom formula $PTV_{ex-vivo} = 2.0 \sum_{(total)} + 0.7 \sum_{(total)}$.

Efficacy The UICC criteria of complete remission (CR), partial remission (PR), no change (NC), and progression disease (PD) were used to evaluate the recent efficacy. CR: clinical symptoms were completely alleviated; PR: clinical symptoms were somewhat relieved; NS: clinical symptoms were not relieved nor worsened; PD: clinical symptoms worsened.

Statistical analysis

Statistical software SPSS 23.0 (SPSS Statistics Inc., Chicago, IL, USA) was utilized to analyze the data. Measurement data were described by mean \pm SEM, and t-test was employed for comparison between groups, and paired t-test was for those between prior to and following treatment. Counting data were statistically described by frequency (percentage) and compared by χ^2 test. Kaplan-Meier was applied to plot survival curves. $P<0.05$ indicates a remarkable distinction.

RESULTS

General data of patients in both groups

The general data of both groups such as gender (24/10 vs. 29/17), age (56.09 ± 7.18 vs. 54.76 ± 7.02),

Child-Pugh classification (27/7 vs. 35/11), BCLC stage (1/22/11 vs. 6/30/10), tumor location (left lobe/right lobe/bilobar: 4/20/10 vs. 4/28/14), and number of tumors (1/ 2/ more than 2: 14/5/15 vs. 20/3/13) were not statistically significant when tested ($P>0.05$) (table 1).

Table 1. General data of patients enrolled in the study.

| Indexes | Control group (n=34) | Research group (n=46) | χ^2/t | P |
|--|----------------------|-----------------------|------------|-------|
| Gender (male/female) | 24/10 | 29/17 | 0.498 | 0.481 |
| Age (year) | 56.09 ± 7.18 | 54.76 ± 7.02 | 0.830 | 0.409 |
| Child-Pugh classification (A/B) | 27/7 | 35/11 | 0.124 | 0.725 |
| BCLC stage (A/B/C) | 1/22/11 | 6/30/10 | 3.120 | 0.210 |
| Tumor location (left lobe/right lobe/bilobar) | 4/20/10 | 4/28/14 | 0.205 | 0.903 |
| Number of tumors (1/ 2/ more than 2) | 14/5/15 | 20/3/13 | 1.646 | 0.439 |

Note: BCLC: Barcelona staging.

Safety of patients

The incidence of Level I hepatic toxic side effects was higher in the research group as opposed to the control group (76.09% vs. 52.94%, $P<0.05$), whereas the incidence of Level II hepatic toxic side effects was comparable to that of the control group (23.91% vs. 38.24%, $P>0.05$), and the incidence of Level III hepatic toxic side effects was lower in relative to the control group (0.00% vs. 8.82%, $P<0.05$) (table 2).

Table 2. Safety of patients.

| Hepatic toxic side effects | Control group (n=34) | Research group (n=46) | χ^2 | P |
|----------------------------|----------------------|-----------------------|----------|-------|
| Level I | 18 (52.94) | 35 (76.09) | 4.684 | 0.030 |
| Level II | 13 (38.24) | 11 (23.91) | 1.910 | 0.167 |
| Level III | 3 (8.82) | 0 (0.00) | 4.217 | 0.040 |

Prognosis of patients in both groups

The 1-year and 2-year survival proportions of the research group exceeded those of the control group, and the median survival span was longer than that of the control group ($P < 0.05$) (figures 2-3, table 3).

Range of CTV-PTV externalization in both groups

The range of CTV-PTV externalization, both right and left, anterior and posterior, and head and foot, was lower in the research group compared with the control group ($P<0.01$) (figure 4).

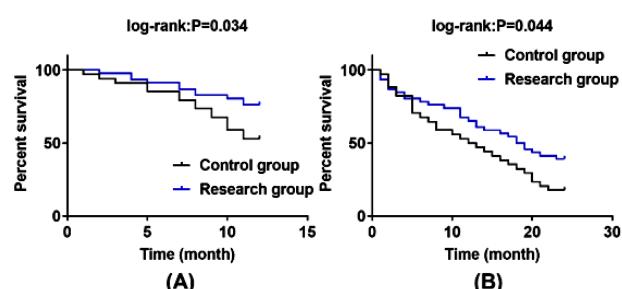


Figure 2. A-B: Comparison of 1-year and 2-year survival rate.

A. 1 - year survival rate: Compares the 1 - year survival rate between groups. **B.** 2 - year survival rate: Shows the comparison of the 2 - year survival rate between groups.

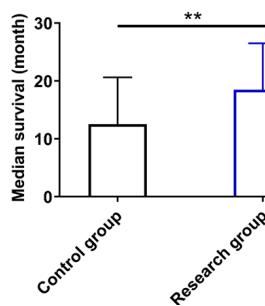


Figure 3. Comparison of median survival. Illustrates the comparison of median survival between groups, with a significant difference indicated by ** $P < 0.01$.

Table 3. Prognosis of patients.

| Prognosis | Control group (n=34) | Research group (n=46) | χ^2/t | P |
|----------------------|----------------------|-----------------------|------------|-------|
| 1-year survival rate | 18 (52.94) | 35 (76.09) | 4.684 | 0.030 |
| 2-year survival rate | 6 (17.65) | 18 (39.13) | 4.297 | 0.038 |
| Median survival | 12.50±8.11 | 18.50±7.99 | 3.299 | 0.002 |

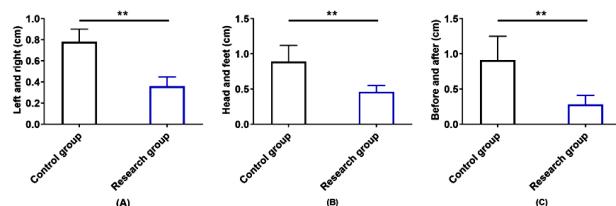


Figure 4. Comparison of range of CTV-PTV externalization in both groups. **A.** Comparison of range of CTV-PTV externalization (left and right) between both groups. **B.** Comparison of range of CTV-PTV externalization (head and foot) between both groups. **C.** Comparison of range of CTV-PTV externalization (before and after) between both groups. Note: ** $P < 0.01$. CTV-PTV: computed tomography angiography-planned target volume.

Efficacy of both groups of patients

The percentage of CR + PR in the research group exceeded that in the control group (82.61% vs. 61.76%), and the variation was remarkable ($P < 0.05$) (table 4).

Table 4. Clinical efficacy of patients in both groups.

| Efficacy | Control group (n=34) | Research group (n=46) | χ^2 | P |
|--|----------------------|-----------------------|----------|-------|
| Complete remission | 4 (11.76) | 8 (17.39) | | |
| Partial remission | 17 (50.00) | 30 (65.22) | | |
| No change | 6 (17.65) | 5 (10.87) | | |
| Progression disease | 7 (20.59) | 3 (6.52) | | |
| Complete remission + Partial remission | 21 (61.76) | 38 (82.61) | 4.388 | 0.036 |

DISCUSSION

The novelty of this study lies in its comprehensive analysis of the safety and prognostic effects of 3DCRT and IGRT in HCC patients. By comparing these two radiotherapy techniques, we aim to provide more reliable and optimized management strategies for HCC patients undergoing radiotherapy.

Previous studies have shown that 3DCRT can be used for the treatment of extensive vascular infiltration in HCC and may help preserve hepatic functional reserve as well as prolong survival (17, 18). In addition, high dose 3DCRT for individuals having

small HCC (<10 cm) who are not qualified for other local treatment approaches is a proven therapeutic option, beneficial in improving local control and overall survival (19). IGRT, on the other hand, has been noted to improve biochemical tumor control in individuals having a high risk of prostate cancer, while reducing the risk of advanced urotoxicity (20).

In our study, the research group had a higher level of grade I hepatic toxicities (76.09% vs. 52.94%) and a lower level of grade III hepatic toxicities (0.00% vs. 8.82%) compared to controls, suggesting that HCC patients undergoing IGRT intervention are significantly safer. This finding corresponds to the results of Becker - Schiebe *et al.* (21), who found that IGRT intervention in 102 patients undergoing radical radiotherapy reduced radiation - related gastrointestinal side effects. Zhang *et al.* (22) also reported that IGRT for individuals having abdominal lymph node metastases from HCC not only had less late hepatotoxicity, but also had significant advantages regarding short - term survival and local control.

Regarding survival data, the research group demonstrated significantly higher 1 - year survival (76.09% vs. 52.94%), 2 - year survival (39.13% vs. 17.65%), and a longer median survival ((18.50±7.99) months vs. (12.50±8.11) months) in opposition to the control group. These outputs are comparable with those found in the study by Kurniawan *et al.* (23), where the 1 - year survival rate of BCLC A and BCLC B HCC individuals was 47.9% - 73.9%. A meta - analysis by Liu *et al.* (24) revealed that the 2 - year survival rate of individuals with unresectable HCC was in the range of 13.2% - 30.3%, which is also comparable to our findings. However, Yoon *et al.* (25) found that IGRT for individuals with locally advanced HCC compared to 3DCRT improved 3 - year survival without increasing the number of serious toxicity events, which is not exactly the same as our findings.

Regarding the CTV - PTV external range data, the CTV - PTV external range of the research group was smaller as opposed to that of the control group in the left - right, anterior - posterior, and head - foot aspects. This resembles the discoveries of Chen *et al.* (26), who noted that IGRT intervention aided in reducing the extent of CTV - PTV externalization during the treatment of patients with anal cancer without the additional need for PTV margins, and also reduced treatment - related toxic side effects.

In the efficacy data, the research group presented a greater CR + PR rate than the control group (82.61% vs. 61.76%). This suggests that IGRT intervention in HCC patients is more efficacious. The advantages of IGRT in terms of efficacy in this study may be attributed to its high accuracy during treatment, mainly in terms of the ability to provide accurate aiming, normal tissue manifestation, radiation dispensation, and adaptive planning of patients' anatomical and biological alterations as time

go by (27).

CONCLUSION

To sum up, IGRT intervention in HCC patients has a certain degree of safety, which can considerably lower the danger of grade III hepatic toxicities, improve the 1- and 2-year survival rates, prolong the median survival, and reduce the scope of CTV-PTV externalization, as well as having a high objective remission rate.

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Conflicts of interests: No conflict of interest.

Ethical consideration: Sanctioned by the Ethic Committee of Shengjing Hospital of China Medical University (2023PS566K).

Author contribution: F.X., conducted the study design and implementation, including the recruitment of patients and the collection of data, took part in the specific operations of the experiment and the recording of data, and also participated in the writing of the article. P.X., was responsible for guiding and supervising the entire study, and checked the writing and revision of the article.

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