

ORIGINAL ARTICLE

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## Analysis of short and long term therapeutic effects of radiofrequency hyperthermia combined with conformal radiotherapy in hepatocellular carcinoma

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### Summary

**Purpose:** To investigate the immediate and long term therapeutic effects of radiofrequency hyperthermia combined with conformal radiotherapy in patients with hepatocellular carcinoma (HCC).

**Methods:** Data was collected from 80 patients with HCC. All of the patients had confirmed primary HCC according to their clinical symptoms, imaging examinations, biochemical examinations and pathology. Patients were randomly divided into control group and experimental group, with 40 cases each. Patients in the control group were treated with conformal radiotherapy while patients in the experimental group were treated with conformal radiotherapy combined radiofrequency hyperthermia. Finally, the short and long term outcomes were compared between the groups.

**Results:** The levels of bilirubin, ALT and prothrombin time (PT) in both groups reduced after treatment and the reduction was more pronounced in the experimental group. In

both groups of patients albumin was elevated and in the experimental group this elevation was significantly more pronounced ( $p < 0.05$ ). The total efficiency for patients in the experimental group was significantly higher than that in the control group ( $p < 0.05$ ). Follow-up results showed that 6-month and 1-year recurrence and mortality rates were significantly lower in the experimental group compared with the control group ( $p < 0.05$ ).

**Conclusion:** Radiofrequency hyperthermia combined conformal radiotherapy is remarkably effective in treating patients with HCC, which could effectively reduce the damages of radiotherapy to the liver, enhance the patient's tolerability and improve the patients' short and long term survival.

**Key words:** conformal radiotherapy, curative effect, liver cancer, radiofrequency hyperthermia

### Introduction

Primary HCC is a quite aggressive malignancy and is usually insensitive to chemotherapy and radiotherapy. When first diagnosed, the disease is in stages 3 or 4 in most of the cases, precluding patients from surgical treatment [1-3]. In the past, HCC was usually treated with conservative therapies. Nowadays, with the emergence and development of three-dimensional conformal radiotherapy technology, which is quite safe and effective, this modality has been widely applied in

the treatment of inoperable HCC. A relevant study has pointed out that the combination of radiofrequency hyperthermia with conformal radiotherapy can effectively improve the treatment outcome of HCC [4].

In order to further assess the short and long term therapeutic effects of radiofrequency hyperthermia combined conformal radiotherapy for the treatment of HCC we investigated 80 HCC patients to assess the outcomes in the short and long term.

We found that radiofrequency hyperthermia combined conformal radiotherapy is remarkably effective in treating patients with HCC.

## Methods

### Patients

Data from 80 cases of primary HCC treated in our hospital from March 2012 to March 2014 were collected. HCC diagnosis was confirmed from clinical symptoms, imaging examinations, biochemical examinations and pathological studies. Patients who suffered from secondary liver cancers, severe hepatic, renal and blood coagulation dysfunctions, serious heart and brain diseases, and less than 12-month expected survival were excluded. After obtaining approval from our hospital ethics committee and informed consent of patients and their families, all of the patients were randomly divided into two groups: the control group and the experimental group, each with 40 cases. The control group included 22 males and 18 females, aged from 39-72 years (mean 51.6±4.4). Their tumor diameter ranged from 3.1-15.2 cm (mean 6.9±1.2). The experimental group included 24 males and 16 females aged from 40-73 years (mean 52.7±5.3). Their tumor diameter ranged from 3.2-15.1 cm (mean 6.7±2.1). The comparison of the two groups showed no statistically significant differences ( $p>0.05$ ).

### Methods

All of the patients were diagnosed with advanced HCC, which precluded them from surgical treatment. The control group was treated with classic conformal radiotherapy. The patients were maintained at supine position, with hands lifted up to forehead, fixed with a body model, and marked the relative positions clearly of their surface and the treatment table to reduce position deviations. While maintaining the patients in supine fixed position, CT scan was performed. Subsequently, the patients were administered 200 ml of oral contrast agent and after 10 min abdominal contrast-enhanced CT was performed with 5mm slices and data was transmitted via network connections. Next, 3D treatment planning system was used for designing the treatment planning. The contours of the patients' surface and essential organs were sketched. For large tumors sketch was required to extend outward for 1 cm and the size of planning target volume was externally expanded upward and downward for 2 cm, and leftward and rightward for 1.5 cm on the basis of tumor size. For adjacent lesions less than 2 cm the target regions were sketched according to a single lesion, and for adjacent lesions more than 2 cm the target regions were sketched respectively. Then, doses for noncoplanar or coplanar irradiation were determined based on the sketched target regions. Irradiation fields were designed according to a previous report [5]. Generally 3-5

conformal fields and 4-6 coplanar or noncoplanar fields were selected and the irradiation frequency was once a day, 5 days/week [3].

Patients in the experimental group were treated by conformal radiotherapy combined radiofrequency hyperthermia. Thermotherapeutic machine was used to implement radiofrequency hyperthermia for 2 times a week from the first day of conformal radiotherapy. The frequency was adjusted at 40MHz, with polar plate diameter at about 25 cm. Noninvasive heating was conducted for 1 hr each time, 1-2 times per week and the therapeutic power was set at about 600W with the reflective power within 5%. Then, the temperature and power curve of each heating was recorded and the controlled skin surface temperature was about 41°C [6].

### Efficacy determination

To analyze and compare the differences between the two groups of patients on their liver functions (total bilirubin, albumin, ALT, PT) the patients' short term therapeutic effects were evaluated 3 months after treatment, and definitions were made as follows: Complete remission: disappearance of all clinical symptoms and lesions; Partial remission: significantly improved clinical symptoms and lesions' shrinkage more than 50%; Disease stabilization: alleviated clinical symptoms and lesions' shrinkage 25-50%; Aggravation: no significant improvement of clinical symptoms and no significant changes of the lesion(s) or even appearance of new lesion(s).

Effective rate of treatment was the sum of complete remission+partial remission+stabilization) / total number of the enrolled patients x 100%.

The differences between the groups concerning recurrence and mortality rates were compared and analyzed 6 months and 1 year after treatment.

### Statistics

SPSS 19.0 software was used for statistical analyses. Data was presented as mean ±standard deviation. Student's t-test was used for comparisons between groups. Data was presented by number of cases or percentages and  $\chi^2$  test was applied in the comparisons between groups. A p value <0.05 was considered as statistically significant.

## Results

### Comparison on liver function between the two groups

Differences in bilirubin, albumin, ALT and PT levels between the two groups before treatment had no statistical significance ( $p>0.05$ ). The bilirubin, ALT and PT levels reduced after treatment in both groups, and the reduction was more pronounced in the experimental group ( $p<0.05$ ). Albumin of both groups was elevated, and in the

**Table 1.** Comparison on liver function between the two groups of patients before and after treatment. Values are mean±standard deviation

Group	Bilirubin (µmol/L)		Albumin (g/L)		ALT (U/L)		PT(s)	
	Before	After	Before	After	Before	After	Before	After
Experimental	41.3±6.7	21.6±4.2	20.4±3.3	43.9±5.1	346.2±15.7	75.2±11.2	21.7±2.4	15±36.6
Control	39.8±5.5	28.7±3.6	22.6±4.1	36.5±6.2	315.4±21.3	90.4±16.7	19.3±2.8	16.4±3.2
t	0.815	2.346	0.917	2.569	0.417	3.015	0.813	2.347
p	0.342	0.032	0.634	0.028	0.108	0.025	0.932	0.041

ALT: alanine aminotransferase, PT: prothrombin time, Pt(s): prothrombin time (second)

**Table 2.** Comparison of short term therapeutic effects between the two groups of patient

Group	Cases	Complete remission	Partial remission	Stable disease	Progressive disease	Total efficiency* %
		N (%)	N (%)	N (%)	N (%)	
Experimental	40	4 (10)	13 (32.5)	7 (17.5)	16 (40)	60.0
Control	40	2 (5)	11 (27.5)	6 (15)	21 (52.5)	47.5
x <sup>2</sup>		-	-	-	-	3.614
p		-	-	-	-	<0.001

\*Complete remission+Partial remission+Stabilization/Total no.of cases

experimental group it was significantly more elevated (experimental group 43.9±5.1 vs control group 36.5±6.2,  $p < 0.05$ , Table 1).

#### Comparison of short term therapeutic effects between the two groups

The total therapeutic efficacy in the experimental group was significantly higher than that in the control group ( $p < 0.001$ ) (Table 2).

#### Comparison of long term therapeutic effects between the two groups

Follow-up results showed that 6-month and 1-year recurrence and mortality rates of patients in the experimental group were significantly lower than those in the control group ( $p < 0.001$ ) (Table 3).

## Discussion

Primary HCC is the most common liver malignancy. Its incidence ranks fifth and mortality

ranks third among all kinds of tumors. A large number of reports has proven that most liver cancers could be associated with cirrhosis [1-6]. The risk of surgical treatment is relatively high. Although the excision extension is not so large, the patients are vulnerable to severe hepatic failure after operation, which enhances the risk of mortality. During early disease, HCC usually shows no specific symptoms. By the time patients visit the clinic for the first time, most of them have already moderately or advanced stage, and hence have lost the chance of surgical treatment. No more than 20% of the patients are fit for radical operation, which results in a poor overall prognosis and short survival [7]. Previous treatments in moderate/advanced HCC patients were mainly focused on palliation [6]. However, with the continuous development of medical technology, molecular targeted therapy and hyperthermia have been widely applied in the treatment of patients in such stages. Especially, radiotherapy and hyperthermia have attracted great attention among researchers and clinicians.

**Table 3.** Comparison of long term therapeutic effects between the two groups of patients

Group	Cases	6-month recurrence rate	6-month mortality rate	1-year recurrence rate	1-year mortality rate
		N (%)	N (%)	N (%)	N (%)
Experimental	40	4 (10.0)	2 (5.0)	11 (27.5)	5 (12.5)
Control	40	6 (15.0)	4 (10.0)	16 (40.0)	8 (20.0)
x <sup>2</sup>		3.437	4.313	4.602	4.563
p		<0.001	<0.001	<0.001	<0.001

Radiation therapy could be applied to a broader number of patients. Patients in somewhat good general condition, free from serious cirrhosis or liver function damage, free from ascites, jaundice etc. could be treated by radiation therapy. Even with ascites and jaundice certain patients could also be treated by radiation therapy if their ascites and jaundice are a result of tumor's compression on the hepatic hilar region and if their condition permits. Related studies have shown that radiotherapy had obvious advantages in the treatment of patients with middle and advanced HCC [8,9]. Conventional radiation therapy could hardly kill the tumor cells radically, and would result in serious damages to adjacent tissues and organs. Conformal radiotherapy can effectively overcome such shortcomings and achieve better results. Conformal radiotherapy increased the irradiation dose in the tumor tissue and reduced the dose to the adjacent tissues, thus increasing its efficacy and decreasing its side effects.

Hyperthermia is an important auxiliary tool for the treatment of tumors, and its combination with radiotherapy and chemotherapy has a significant therapeutic effect. Results of relevant studies have shown that the biological coordination of radiotherapy and hyperthermia was mainly manifested in the following cases: Firstly, toxic side effects to cells complemented with each other. In general, the sensitivity of cells in S phase of the cell cycle to radiotherapy is lower but to hyperthermia it is relatively high. And while the sensitivity of anoxic cells to radiotherapy is lower, to hyperthermia is relatively stable [10,11]. Secondly, from cell survival curves, it is rather obvious that, under sub-high temperature tumor, blood

flow increases rapidly and oxygen partial pressure also increases, which leads to improvement of the anoxic condition of cells and enhancement of the sensitivity of the radiation greatly. The cell oxygen partial pressure can be maintained above 24% after radiation therapy [12,13]. Thirdly, hyperthermia can block the repair of radiation-damaged cells by effectively reducing the activity of DNA polymerase, preventing thus the repair of DNA single strand breaks [14,15]. In our study, patients in the experimental group were treated by radiofrequency hyperthermia combined with conformal radiotherapy. The results of our study showed that no differences existed in bilirubin, albumin, ALT and PT levels between the two groups of patients before treatment ( $p>0.05$ ) (Table 1). The bilirubin, ALT and PT levels in both groups of patients were reduced after treatment, and this reduction was more pronounced in the experimental group. In both groups albumin was elevated and in the experimental group it was significantly more elevated ( $p=0.028$ , Table 1). Moreover, the short and long term therapeutic results of the experimental group were significantly better compared with the controls, indicating that radiofrequency hyperthermia combined with conformal radiotherapy is remarkably effective in treating patients with HCC (Tables 2 and 3).

## Conclusions

Radiofrequency hyperthermia combined with conformal radiotherapy is remarkably effective in treating patients with HCC, and can successfully reduce the damages of radiotherapy to the liver, is well tolerated and improves the long term survival.

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