

Regional Hyperthermia in the Treatment of Primary Hepatic Carcinoma

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Background and Objectives: The purpose of this research was to investigate the clinical significance of regional hyperthermia in the treatment of primary hepatic carcinoma (PHC).

Methods: The regional hyperthermia (60°C) was used whenever there was suspicion of residual cancer tissues on the edge of the hepatic resection. The hyperthermia was maintained for about 5–20 min depending on the size and the amounts of residual nodulus. If there was obvious necrosis on the hyperthermia-treated site, the solidified tissues were removed. Otherwise, the solidified tissues were kept in situ.

Results: There were 68 cases of PHC patients in this study. The patients were divided into 4 groups: A, lobectomy, 14 cases; B, lobectomy plus regional hyperthermia, 12 cases; C, regional hepatectomy, 16 cases; D, regional hepatectomy plus regional hyperthermia, 26 cases. All patients were followed after their operations. The mean survival time of the 4 groups was as follows: Group A, 346.5 days (186–921 days); Group B, 432.6 days (254–1189 days); Group C, 525.4 days (192–1016 days); and Group D, 1142 (from 318 days to seven years and two months) days. There were significant differences between Groups A and B ($P < 0.01$) and between Groups C and D ($P < 0.01$). It seems that regional hyperthermia on the hepatic resection edge can prolong patients' survival time.

Conclusions: Regional hyperthermia on the hepatic resection edge is helpful for prolonging patients' survival time in the treatment of primary hepatic carcinoma.

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KEY WORDS: primary hepatic carcinoma; hepatectomy; hyperthermia

INTRODUCTION

Primary hepatic carcinoma (PHC) is one of the most common malignant tumors in China. There are 10–30 male cases of PHC per 100,000 population each year. The mortality of PHC is the highest among all cancers. Furthermore, PHC patients are much younger than patients with other solid tumors. Most patients have middle or advanced PHC when the diagnosis is made. Therefore, better prognosis in the treatment of PHC is urgently needed.

Although surgical resection is the choice of treatment for PHC, there are many cases in which the tumor cannot be removed when their diagnosis is made because of advanced illness. In other cases, the cancer recurred very soon after hepatectomy. So, in recent decades, scientists

and physicians have been trying to develop new regimens to treat PHC to achieve better prognosis. Hyperthermia is one of these regimens. Since 1985 [1], we have used regional hyperthermia to treat advanced PHC or have used it as a complementary method to surgical resection. The primary results of regional hyperthermia are promising.

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MATERIALS AND METHODS

There were 68 total cases of PHC entered into this research study, beginning from 1985. Fifty-four cases were male and 14 were females. The patients' age range was 24–70 years (mean, 48.2). Of the 68 cases, 44 (64.7%) were α -fetoprotein positive, and 88.6% had accompanying liver cirrhosis caused by hepatitis B. All cases were diagnosed by pathological techniques.

According to the differences of treatment methods, the patients were divided into the following groups: Group A consisted of 14 cases that had lobectomy. Nine lobectomies were right and 5 were left hemihepatectomies. The resection line was 3–5 cm from the tumor edge. There was no obvious residual tumor on the hepatic resection edge. Group B comprised 12 cases that had lobectomy plus regional hyperthermia. Nine cases had right and 3 had left hemihepatectomies. The resection line was 3–5 cm from the tumor edge. There were suspected cancerous residues on the resection edge. Group C was 16 cases of regional hepatectomy. Hepatic cancer was resected around the edge of tumor. The dissection line was <3 cm from the tumor edge. Group D consisted of 26 cases of regional hepatectomy plus regional hyperthermia.

Techniques of Regional Hyperthermia

The hyperthermic instrument was designed by ourselves [1]. The output power of the high-frequency therapy apparatus is 35 MHz, 400 W. Its radiator can produce hyperthermia (60–100°C) in the area with which it comes in contact. The temperature rises 5°C/min. When the temperature reaches 60°C and maintains for 20 min, the regional hyperthermia can result in the devitalization of tumor cells and the solidification of the treated tissues, the necrotic liver tissues can be as deep as 3–5 cm [1,2]. The regional hyperthermic treatment was used whenever there was suspicion of residual cancerous tissues on the edge of resection. If the size of residues was about or over 2 cm in diameter, or there were several small foci in a regional area, the hyperthermia usually lasted 20 min. When the resection line was close to major intrahepatic portal branches, or the diameter of the residual noduli was ≤ 0.5 cm, the hyperthermia was maintained for 5 min or a little longer. If there was obvious necrosis on the hyperthermia-treated site, the solidified tissues were removed. Otherwise, the solidified tissues were kept in situ.

Statistics

Survival time was calculated as the number of days from the first operation to death. A univariate analysis was used to compare the differences in survival time between groups of patients, that were calculated with Excel 97 software (Microsoft, Redmond, WA). $P < 0.05$

was regarded as statistically significant and $P < 0.01$ as very significant.

RESULTS

Both the surgery alone groups and the surgery plus regional hyperthermia groups recovered smoothly after their operations. No subphrenic abscess or secondary hemorrhage was found. Primary hepatic carcinoma in each removed hepatic piece was confirmed by professional pathologists. But, no biopsy was done on the resection edge that remained behind either when the surgery was going on or after operation. There were several cases in each group that cancer cells could be seen on the edge of resection under microscopy. Group A had 3 cases, Group B was 4 cases, Group C consisted of 4 cases, and Group D comprised 6 cases. There was no statistical difference between Groups A and C and Groups B and D ($P > 0.05$). There were total 20 cases (29.4%) that needed to debride necrotic tissues in the hyperthermia-treated site because there was obvious necrosis at the end of the hyperthermia session. They were usually the patients who there were obvious cancer residues on the resection edge, or the diameter of residues was ≥ 2 cm, and the time of hyperthermia was often ≥ 20 min. Similar adjuvant chemotherapy was maintained in every patient after their operations.

All of the PHC patients were followed routinely after their operations. The patients who were lost to follow-up were considered to have died of the illness. The longest survival time was 7 years 2 months; the shortest was 6 months. The mean survival times in the 4 groups after surgical treatment was as follows: Group A (lobectomy), 346.5 days (range, 186–921); Group B (lobectomy plus regional hyperthermia), 432.6 days (range, 254–1189); Group C (regional lobectomy), 525.4 days (range, 192–1016); Group D (regional lobectomy plus regional hyperthermia), 3 years 47 days (range, from 318 days to seven years and two months). There were significant differences between groups A and B ($P = 0.009865$) and Groups C and D ($P = 0.008575$). It seemed that regional hyperthermia applied to the hepatic resection edge after hepatectomy could prolong patients' survival time. There were no obvious side effects or discomfort after regional hyperthermia. The patients recovered smoothly after operations.

CASE REPORT

A 48-year-old man complained of right upper quadrant discomfort and dull ache, accompanied by weakness. A slightly enlarged liver was felt on physical examination. No jaundice, ascites, or liver tenderness was found. Laboratory examination showed that the patient was positive for α -fetoprotein and hepatitis B surface antigen. Ultrasonography showed that there was a solid hepatic mass (4 × 3 cm) in the left lobe. No obvious satellite

nodules around the mass were found. The patient underwent left regional hepatectomy on May 6, 1986. There were suspicious residual nodules of tumor on the edge of resection. The resection edge was treated with regional hyperthermia. The regional temperature reached 60°C and kept 10 min. After operation, the patient received chemotherapy (5-fluorouracil, mitomycin) routinely at 3, 9, 15, and 21 months after operation and once a year after the beginning of the third year. He took traditional Chinese medicines on intervals. At 6.5 years after operation, the patient died of heart attack.

DISCUSSION

PHC is one of the most common cancers in China. The prognosis of PHC is still bad despite the progress of medical science and techniques in recent decades. Because most patients have advanced PHC when they are first diagnosed, surgical resection remains the treatment of choice these patients [3].

Early discovery, early diagnosis, and early surgery have been the key methods in improving the remote effects in the treatment of PHC [3]. To kill cancer cells and preserve the normal hepatic cells as much as possible, comprehensive treatment is needed. Hepatic artery ligation or embolization, embolization chemotherapy, alcoholic injection into the tumor, immunotherapy, and radiation plus hepatectomy are accepted regimens for the treatment of PHC [3,4]. It is clear that the nature of PHC is to invade and disseminate inside the liver or along intrahepatic portal branches, so it is not uncommon that there are satellite nodules surrounding the cancerous mass. This might be one of the reasons why the hepatectomy is far from a promising procedure in the treatment of PHC. Some authors [5] reported recently that, after hepatic resection for PHC, the recurrence and metastasis rates in 1, 3, and 5 years were 19.8%, 48.2%, and 74.6%, respectively. Recurrence and metastasis rates are high despite the size of the tumor [5]. According to our material, the patients with lobectomy had the shortest postoperative life expectancy, and the patients with regional hepatectomy plus regional hyperthermia had the

longest life expectancy. Furthermore, both Groups B and D (with regional hyperthermia) survived longer than Groups A and C (without regional hyperthermia). It seems that regional hyperthermia has a positive effect on prolonging patients' lives after hepatectomy.

The possible mechanism for this result might be that there were occult cancer cells or nodules on the resection edge of the liver after lobectomy or regional hepatectomy. The significance of regional hyperthermia is that it destroys the occult cancer cells with heat.

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COMMENTARY

The authors present interesting data on the possible value of regional hyperthermia in improving patient survival by applying heat to the resection surface of the remaining hepatic parenchyma after liver resection for primary hepatic carcinoma. The presumed mechanism is the destruction of microscopic residual, satellite foci of tumor near the resection surface of the remaining liver, which, if left intact, account for some of the recurrences observed with surgical treatment alone. The data presented are certainly encouraging, but given the complexity of the subject and the various prognostic parameters, it will take a prospectively randomized study to answer definitively this issue.

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