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LIVER CANCER

Preventive effect of regional radiotherapy with phosphorus-32 glass microspheres in hepatocellular carcinoma recurrence after hepatectomy

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Abstract

AIM: To evaluate the preventive effects of phosphorus-32 glass microspheres (P^{32}-GMS) in the recurrence of massive hepatocellular carcinomas (HCCs) after tumor resection.

METHODS: Twenty-nine patients with massive HCCs received local P^{32}-GMS implantation after liver tumors were removed, while the other 38 patients with massive HCCs were not treated with P^{32}-GMS after hepatectomies. The radioactivity of the blood, urine and liver were examined. The complications, HCC recurrence and overall survival rates in the patients were analyzed.

RESULTS: P^{32}-GMS implanted in the liver did not cause systemic absorption of P^{32}. There were no significant differences of postoperative complications between the patients with and without P^{32}-GMS treatment. The short-term (six months and 1 year) and long-term (2, 3 and over 3 years) recurrence rates in patients who received P^{32}-GMS radiotherapy were significantly decreased, and the overall survival rates in this group were significantly improved.

CONCLUSION: P^{32}-GMS implantation in the liver can significantly decrease the postoperative recurrence and improve the overall survival in HCCs patients after hepatectomy. This therapy may provide an innovative method in prevention of HCC recurrence after operation.

Key words: Hepatocellular carcinoma; Recurrence; Phosphorus-32 glass microspheres; Hepatectomy

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in southeastern China. The mortality of this disease has ranked as the second highest in cancer nationwide and responsible for an estimated one million deaths annually since the 1990s, and its morbidity is increasing among males[1,2]. Currently, the prognosis of HCC mainly depends on the results of surgical treatment of the tumors. The surgical treatments include the tumor resection and liver transplantation, which offer the only chance for radical treatment of HCC patients[3].

Clinically, with the characteristics of rapid infiltrating growth, early local and/or distant metastasis and high postoperative recurrence, the massive HCCs are usually diagnosed when they are at advanced stages with poor prognosis. The recurrence rate of intrahepatic carcinomas varies from 36.8% to 82%, which caused death in about 50% of the patients[4-7]. Prevention of cancer recurrence and metastasis after curative surgical resection has become a key issue for improvement of the surgical outcome and long-term survival of the patients.

In the past decades, many adjuvant interventional therapies have been continuously extended as a result of the technical development of locoregional approaches for HCCs. The combined multimodal therapies have played important roles in preventing postoperative recurrence of HCCs. Recently, nuclide labeled with undegradable micro-carriers has become a new radioactive therapy for malignant liver cancers.

Phosphorus-32 (P^{32}) is a radioisotope which emits

relatively high energy beta particles as it decays. Recent experimental studies and clinical trials showed that intrahepatic arterial application of P^{32} labeled with undegradable glass microsphere could cause death of tumor cells in the animal model and reduce the size of the tumor[8-10]. However, this therapy was only reported for unresectable liver cancers. Since the postoperative recurrence of HCC is closely related with the peritumor micrometastasis and portal vein tumor invasion[11,12], development of the local radiotherapy may provide a method to prevent the recurrence of HCCs after radical hepatectomy. In this study, the outcome and complications of implantation of phosphorus-32 glass microspheres (P^{32}-GMS) in a series of patients with massive HCCs were analyzed after hepatectomy. We present for the first time the preventive effect of the local radiation therapy with P^{32}-GMS in HCC recurrence after radical hepatectomy.

MATERIALS AND METHODS

P^{32}-GMS preparation

P^{32}-GMS was generated by activation of standardized glass microspheres through a nuclear-chemical reaction, in which the nonradioactive P^{31} (P^{31}-GMS, cold sphere) was transformed into the radioactive P^{32} glass microsphere (provided by Nuclear Power Research Institute of China). The diameter of glass sphere is between 46 μm and 76 μm, with radioactivity of 550-3700 MBq/g per unit and P^{32} elution rate of less than 0.1% within 30 d. The radioactive nuclide purity was more than 99% with the physical half-life 14.28 d, and the average β ray energy was 0.695 MeV (maximum energy 1.711 MeV) per disintegration, and soft tissue penetration distance was 3.2 mm in average (maximum 8.0 mm). The P^{32}-GMS suspension was prepared by mixing P^{32}-GMS with 1 mL super-liquid iodized oil or 50% glucose solution to a concentration of 100 g/L on oscillator.

Implantation of P^{32}-GMS

The P^{32}-GMS suspension was soaked into a piece of the absorbable gelatin sponge. After hepatectomy, the gelatin sponge was buried within the liver resection surface during closure. The dose of P^{32}-GMS implantation depends on the size of the tumor and calculated by the formula: $Dt = 34.6 \times T \times C \times \sum\Delta i\ (1\text{-}E^{-0.693t/T})$. The mean dose of radiation for the patients was 5.27 ± 0.27 Gy. The total tissue absorbed dose after radioactive P^{32} disgregation was 135.18 Gy in average.

Patients

From June 1999 to September 2003, 67 patients were diagnosed as having HCCs and underwent hepatectomy. Among them, 29 patients received P^{32}-GMS radiotherapy after hepatectomy (group A), and the other 38 patients without radiotherapy after operation served as controls (group B). The patients' age, sex, preoperative intervals, tumor size, hepatitis B virus (HbsAg) infection rate, positive alpha-fetoprotein (α-FP), microvenous tumor invasion in both groups were evaluated.

After surgery, the liver radioactivity distributions were measured by a photo-emission computed tomography (ECT) on postoperative d 1, 7 and 14. The radioactivity of blood and urine were also measured daily with γ-ray counter in the first postoperative week and on postoperative d 14. The postoperative complications including death, subdiaphragm infection, bile leakage, leucopenia, jaundice, and pleura effusion and/or ascites were analyzed in each group. The survival of the patients (six months, 1 year, 2 years, 3 years and over 3 years) and cancer recurrence rates were compared between the two groups.

Table 1 General information of patients in groups A and B

	Group A (n = 29)	Group B (n = 38)	P value
Age (yr)	53.83 ± 2.20	55.26 ± 6.67	$P > 0.05$
Sex (male/female)	24/5	32/6	$P > 0.05$
Tumor size (cm)	7.58 ± 2.50	7.76 ± 3.13	$P > 0.05$
Preoperative interval (d)	23.34 ± 2.45	21.79 ± 4.19	$P > 0.05$
HbsAg positive rate (%)	75.9	81.58	$P > 0.05$
α-FP positive rate (%)	65.5	72.97	$P > 0.05$

Statistical analyses

The data were expressed as the mean ± SEM and mean ± SD. Differences between groups were compared using Kaplan-Meier method, un-paired Student's t test, and Chi-square. A P value less than 0.05 was defined as significant. All data were analyzed using SPSS11.5 statistics software (SPSS Inc., Chicago, IL).

RESULTS

Patients

The general information of the HCC patients is shown in Table 1. The average tumor size was 7.58 ± 2.50 cm in group A and 7.76 ± 3.13 cm in group B. There was no significant difference between the two groups. The positive rates of alpha-fetoprotein (α-FP) were 65.5% and 72.97% in groups A and B, respectively ($P > 0.05$). The postoperative pathologic examination revealed that the microvenous tumor invasion rate was 10.3% in group A and 13.16% in group B, respectively ($P > 0.05$). The comparisons of other parameters also showed no significant differences between the two groups.

Radioactivity

In patients of group A, the β rays of P^{32} in liver was detected by ECT (Figure 1), and the postoperative disgregation of radioactivity is shown in Figure 2. The radioactivity of P^{32} decreased on postoperative d 7 and d 14 when compared with postoperative d 1. The half life of P^{32} was about 14 d. The disgregation of the P^{32} radioactivity in liver matched the dynamic eradication of the radioisotope P^{32}.

The radioactivity in blood and urine was also measured in group A. The results showed that there was no significant radioactivity enhancement in blood and urine after P^{32}-GMS was implanted (Figure 3), which indicated that P^{32} was not systemically absorbed in the patients.

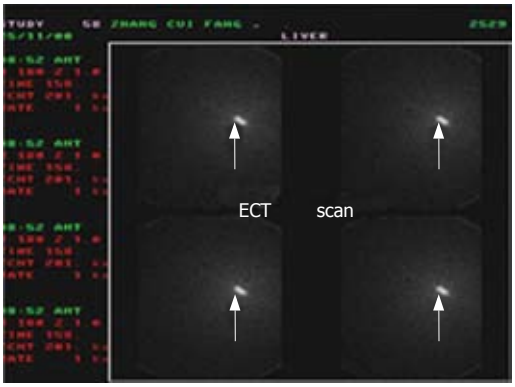

Figure 1 Liver ECT scan. Arrow: The site where P^{32}-GMS was implanted.

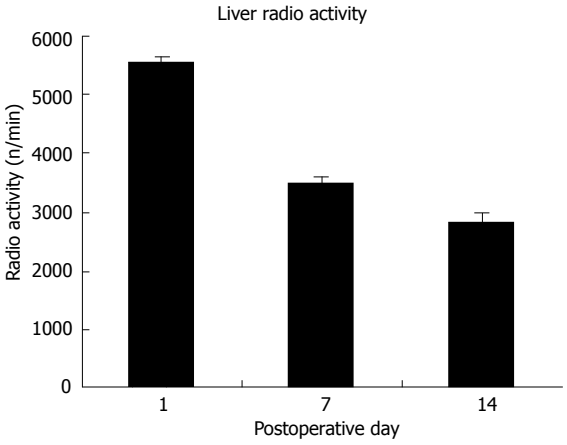

Figure 2 P^{32} Radioactivity in liver of the patients with P^{32}-GMS (n/min). The radio activity of P^{32}-GMS decreased on POD 7 and POD 14 as compared with POD 1. (POD = postoperative day).

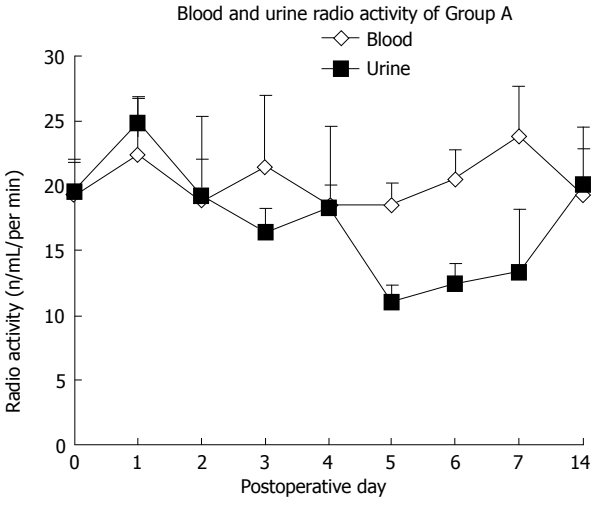

Figure 3 Radioactivity in blood and urine of the patients with P^{32}-GMS (n/mL/min). The radio activity in blood and urine were low. It was familiar with the sample without P^{32}-GMS implanted (d 0).

Complications

There was no perioperative patient death within 30 d after surgery in both groups. After hepatectomy, liver failure occurred in 3 patients (10.3%) of group A and 3 patients (7.89%) of group, respectively. The morbidity of other postoperative complications was also compared between the two groups (Table 2). There were no significant differences between the two groups.

Table 2 Postoperative complications in patients with and without P^{32}-GMS radiotherapy, *n* (%)

Complications	Group A (*n* = 29)	Group B (*n* = 38)	*P* value
Liver failure	3 (10.3)	3 (7.89)	$P > 0.05$
Perioperative death	0	0	$P > 0.05$
Subdiaphragm infection	1 (3.45)	2 (5.26)	$P > 0.05$
Bile leakage	0	0	$P > 0.05$
Leukopenia	0	0	$P > 0.05$
Jaundice	1 (3.45)	2 (5.26)	$P > 0.05$
Liver wound rupture	0	0	$P > 0.05$
Pleural effusion and/or ascites	5 (17.24)	5 (13.15)	$P > 0.05$

Table 3 HCC recurrence rates in patients with and without P^{32}-GMS, *n* (%)

Postoperative intervals	Group A (*n* = 29)	Group B (*n* = 38)	*P* value
6 mo	4 (13.8)	15 (39.5)	$P = 0.021^a$
1 yr	7 (24.1)	20 (52.6)	$P = 0.018^a$
2 yr	13 (44.8)	29 (76.3)	$P = 0.008^b$
3 yr	18 (62.1)	33 (86.8)	$P = 0.018^a$
Over 3 yr	18 (62.1)	33 (86.8)	$P = 0.018^a$

$^aP < 0.05$; $^bP < 0.01$.

Table 4 Survival rates in patients with and without P^{32}-GMS, *n* (%)

Postoperative intervals	Group A (*n* = 29)	Group B (*n* = 38)	*P* value
6 mo	28 (96.6)	35 (92.1)	$P = 0.454$
1 yr	27 (79.3)	27 (71.1)	$P = 0.024^a$
2 yr	22 (75.9)	17 (44.7)	$P = 0.010^b$
3 yr	19 (65.5)	8 (21.1)	$P = 0.000^b$
Over 3 yr	14 (48.3)	8 (21.1)	$P = 0.018^a$

$^aP < 0.05$; $^bP < 0.01$.

Recurrence rate and survival rate

The recurrent risk was estimated in both groups. The follow-up investigations showed that the short-term (6 mo and 1 year) and long-term recurrence rates at 2, 3 and over 3 years in group A were significantly reduced when compared with those who did not receive preventative radiotherapy (Table 3).

Although there was no significant difference in the six-month survival rates between two groups, the overall survival rates at 1 year, 2 years, 3 years and over 3 years in group A were significantly higher than those patients without radiotherapy (Table 4). Figure 4 shows a case of a 56-year-old woman who was diagnosed having progressive liver cancer. The patient received preventive P^{32}-GMS implantation at a dose of 6.83 Gy radioactivity after hepatectomy. There were no signs of liver radiation damage and cancer recurrence in the CT scans during the 4-year follow-up.

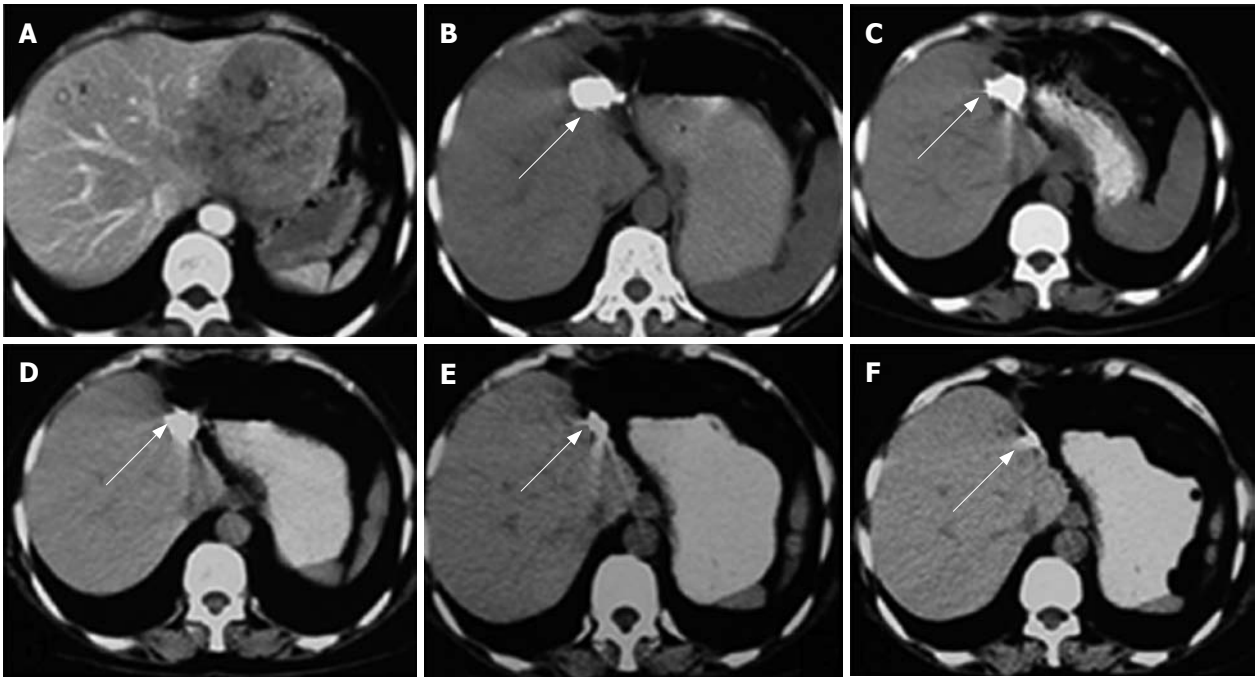

Figure 4 CT scan of the HCC patient who underwent hepatectomy and P^{32}-GMS treatments in 4 years following-up. **A**: Liver CT scan showing a progressive liver tumor prior to hepatectomy; **B**: Liver CT scan after hepatectomy; **C**: Liver CT scan at first postoperative year; **D**: Liver CT at second postoperative year; **E**: Liver CT at third postoperative year; **F**: Liver CT at fourth postoperative year. Arrows: implanted P^{32}-GMS.

DISCUSSION

The radical hepatectomy is now considered a major choice for the patients with resectable HCC. Recent development of surgical techniques and perioperative management have remarkably reduced the death that is caused by surgery[13,14]. In the past two decades, the advanced techniques of the curative tumor resection has also significantly improved the long-term survival of the patients. A recent report has shown that about a 50% survival rate has been achieved for the patients treated with surgery in a five-year follow-up[15]. However, the high postoperative recurrence rate is still a major problem for the long-term survival of the patients with HCCs after hepatectomy.

It has been reported that the 5-year recurrence rate of HCCs after curative resection ranges from 38% to 61.5%[16,17]. The recurrent peak is found at six months or 1 year after operation and most of the early postoperative recurrence is intrahepatic metastasis[18], which is attributed to the characteristics of vascular invasion propensity of HCCs. The appearance of tiny tumors through venous invasion in the liver is the main sign for potential HCC recurrence after surgery[19-29]. The intrahepatic metastasis of the tumor cells through the portal venous system is believed to be an important mechanism for HCC recurrence[24,30,31].

Since the tumors usually are located close to the major vessels or the severe liver cirrhosis coexists, extensive excision of liver frequently results in hepatic failure. The microvenous tumor embolus or existence of the residual tumor in the margin of remnant liver due to inadequate resection may cause the early postoperative recurrence of HCCs. Therefore, combination of adjuvant interventional therapies may play an important role in preventing postoperative recurrence of HCCs.

Several adjuvant interventional therapies for preventing postoperative recurrence of HCCs were investigated around the world. Some adjuvant approaches were effective in reducing the postoperative recurrence of HCC and improving survival of the patients. The postoperative transcatheter arterial chemoembolization (TACE) was shown to postpone the peak of recurrence rate in patients from 6 to 12 mo. However, the recurrence rate in the group with TACE treatment was even higher than that of the control group without TACE at a 18-mo follow-up[32]. One study showed that postoperative application of interferon alpha might postpone the recurrence of the HBV-related HCC after curative resection and improve the overall survival of patients[33]. In another study, postoperative intra-arterial injection of iodine131 labeled lipiodol (131I-Lip) was found to decrease the HCC recurrence rate in patients after hepatectomy, improving the 1-, 2-, and 3-year survival rates when compared with the survival rates in the control group receiving no 131I-Lip treatment[34]. The adjuvant chemotherapy was not effective in preventing the postoperative recurrence[35].

The mechanisms of the anticancer effect of P^{32}-GMS have been discussed. The experimental studies showed that the β-ray energy could directly destroy or injure the DNA of tumor cells while inducing death of the cells. Simultaneously, the β-ray irradiation could induce generation of several types of free radicals and superoxides, which could damage the tumor cells[36]. The β-ray was also found to induce the apoptosis of tumor cells[37,38]. In an experimental study in the nude mice model, intra-mass injection of P^{32}-GMS into the implanted human liver cancer was found to cause the death of many

tumor cells[9]. In some studies, intra-tumor injection of P^{32} chromic phosphate resulted in remarkable regression of the tumors[39,40]. The current study was to examine if local implantation of P^{32}-GMS in the liver after hepatectomy could decrease the risk of postoperative tumor recurrence.

In our study, the short-term (six months and 1 year) and the long-term (2, 3 and over 3 years) recurrence rates were significantly decreased in patients who received P^{32}-GMS radiotherapy. Decrease of tumor recurrence results in significant increase of survival of the patients. These findings demonstrated that the implantation of P^{32}-GMS in the liver after hepatectomy can provide a preventive effect in postoperative recurrence of HCC and improve the overall survival of the patients. This preventive effect of P^{32}-GMS is probably through damaging the tumor cells from the microvenous tumor embolus in the margin of remnant liver. However, the implantation of P^{32}-GMS under liver incision edge may not prevent the tumor recurrence from the distant intrahepatic metastasis prior to hepatectomy or the multi-centric HCCs.

Our study has also shown that there were no significant differences in postoperative complications between the patients receiving P^{32}-GMS radiotherapy and the patients without radiotherapy after surgery. No side effects of P^{32}-GMS implantation were observed and no radiation was detected in both blood and urine samples in the patients with P^{32}-GMS treatment. These results further confirmed the safety of local implantation of P^{32}-GMS in the liver.

In conclusion, P^{32}-GMS implantation in the liver after the resection of HCC can significantly decrease the postoperative recurrence of HCC, and improve the overall survival in the patients. This radiotherapy will not cause any side effects and complications, and may provide an innovative method for the prevention of HCC recurrence after hepatectomy.

COMMENTS

Background

Hepatocellular carcinoma (HCC) is one of the most common malignancies related to a high mortality globally. In recent years, the surgical treatments, including the tumor resection and liver transplantation, offer the only chance for radical treatment of HCC patients. Clinically, the massive HCCs are usually diagnosed at advanced stages, and the prevention of cancer recurrence and metastasis after curative hepatectomy has become a key issue for the improvement of the overall survival of the patients.

Research frontiers

In recent years, nuclide labeled with nontoxic and undegradable micro-carriers such as phosphorus-32 glass microsphere (P^{32}-GMS) has gained much attention as a new radioactive therapy for malignant liver tumors.

Innovations and breakthroughs

Some experimental studies and clinical trials have shown cytocidal effect of local intrahepatic irradiation of P^{32}-GMS in unresectable liver cancers. However, the study of evaluating the preventive effect of the local radiation therapy with P^{32}-GMS in HCC recurrence after radical hepatectomy has not been reported.

Applications

Through evaluating the pharmacology, toxicology and clinical effect, P^{32}-GMS was considered as a helpful therapeutic weapon combined with surgical and other nonsurgical treatment of liver cancer.

Terminology

P^{32}-GMS, which is transformed from nonradioactive P^{31}-GMS by activating the standardized glass microspheres through nuclear-chemical reaction, is the nuclide labeled nontoxic and undegradable micro-carriers. Recently, P^{32}-GMS and yttrium-90 glass microsphere have been successfully developed as a new radioactive medicine for treating malignant liver neoplasms.

Peer review

This report is the first study to evaluate the preventive effect of the local radiation therapy with P^{32}-GMS on HCC recurrence after radical hepatectomy. Although more studies are needed to confirm the safety and effect of the new medicine, it will be beneficial to the prognosis and treatment of HCC patients in the near future.

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