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ORIGINAL ARTICLE

Analyses of clinical efficacy of ultrasound-guided radiofrequency ablation in liver cancer adjacent to the gallbladder and its prognosis

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Summary

Purpose: *To explore the clinical efficacy of ultrasound-guided radiofrequency ablation (RFA) in liver cancer adjacent to the gallbladder and to analyze its prognosis.*

Methods: *80 patients with liver cancer adjacent to the gallbladder, who were admitted to our hospital from January 2015 to April 2018, were enrolled and divided into the Observation group (n=40) and the Control group (n=40). All of the patients underwent cholecystectomy and lymph node dissection combined with postoperative chemotherapy. RFA was performed in the Observation group, while radical cholecystectomy and radical hepatectomy were conducted simultaneously in the Control group. Follow up was by telephone, and tumor-associated factor levels, liver function and cellular and humoral immune function-related indicators at 1 month after intervention, tumor size before and after treatment and cases of normal alpha-fetoprotein (AFP) level and tumor disappearance after treatment were compared between the two groups. The complications rates during treatment (increase in transaminases, elevation of bilirubin, intratumoral hemorrhage, bile duct injury and gastrointestinal perforation), clinical efficacy and 1-year survival in the two groups were statistically analyzed.*

Results: *At 1 month after intervention, the Observation group had substantially lower levels of tumor-associated factors AFP, carbohydrate antigen 19-9 (CA19-9) and carcinoembryonic antigen (CEA) ($p<0.05$), obviously lower levels of liver function indicators aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBIL), indirect bilirubin (IBIL) and direct bilirubin (DBIL) ($p<0.05$), but distinctly higher levels of immunoglobulin G (IgG), IgA and IgM, cluster of differentiation 4^+ ($CD4^+$), $CD8^+$ and $CD4^+/CD8^+$ ($p<0.05$) than the Control group. Before and after treatment, the tumor size in the Observation group was smaller than in the Control group ($p<0.05$). The Observation group exhibited notably more cases of normal APF level and tumor disappearance after treatment ($p<0.05$), markedly lower incidence rates of increase in transaminases, elevation of bilirubin, intratumoral hemorrhage, bile duct injury and gastrointestinal perforation during treatment ($p<0.05$) than the Control group. Additionally, the rate of stable disease (SD) was notably higher and the 1-year survival rate was higher in the Observation group than in the Control group ($p<0.05$).*

Conclusions: *RFA for liver cancer adjacent to the gallbladder can effectively lower the levels of tumor markers, improve liver function and enhance immunity, with a few operative complications and high efficacy, so it has a positive impact in prolonging the survival of patients.*

Key words: *ultrasound guidance, radiofrequency ablation, liver cancer adjacent to gallbladder, clinical efficacy, clinical prognosis*

Introduction

Gallbladder carcinoma is one of the most common malignant tumors in the biliary system, and patients with this disease account for over 40% of the total cases of biliary malignant tumors [1].

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Primary liver cancer is one of the most common gastrointestinal malignancies, over 90% of which are hepatocellular carcinoma [2,3]. In particular, it is prone to being complicated with viral hepatitis, such as viral hepatitis B and C [4], with morbidity rate obviously raised worldwide [5]. The liver and gallbladder are anatomically close, and malignant tumors develop simultaneously in the liver and gallbladder, which tends to exhibit a correlation [6]. In cases of liver metastasis from gallbladder carcinoma, the initial clinical manifestation is dominated by gallbladder carcinoma, and dilatation of the intrahepatic and extrahepatic bile ducts can be caused by the ductus cysticus and hepatic duct metastases of tumor cells, while patients experiencing invasion of liver cancer into the gallbladder tend to be complicated with chronic hepatitis and cirrhosis and even accompanied by portal vein tumor thrombosis. It has been found in auxiliary examinations that the primary liver cancer patients have an increased level of alpha fetoprotein (AFP) at an early stage, while those with primary cholangiocarcinoma patients show no obvious increase in AFP level. Additionally, the patients with liver cancer adjacent to the gallbladder can exhibit early manifestations of both liver cancer and gallbladder carcinoma.

RFA is now an efficacious treatment available for liver cancer with the merits of small trauma, rapid postoperative recovery and minimal invasion [7]. A study indicated that patients with small liver cancer who are treated with RFA have an obviously higher postoperative survival rate and quality of life than those undergoing conventional open and laparoscopic surgical resections [8]. RFA is performed based on the principle of physical energy conversion, in which the electric energy is converted into heat energy to spur the detachment of stiff and necrotic masses at the tumor site, thereby achieving the treatment purpose [9]. The present study explored the application value of RFA in liver cancer adjacent to the gallbladder.

Methods

General information

A total of 80 patients with liver cancer adjacent to the gallbladder, who were admitted to our hospital from January 2015 to April 2018, were enrolled in this study. After enrollment, written informed consent was signed by all the patients or their next of kin, and the study was approved by the Ethics Committee of our hospital. Before enrollment, all the patients were preliminarily diagnosed through magnetic resonance imaging (MRI) or CT examinations, and the diagnosis was confirmed via pathological biopsy.

Inclusion criteria: Patients with diameter of liver tumors not greater than 5 cm, those with less than 3 lesions and the total diameter shorter than 5 cm and those with liver function lower than grade B based on the Child-Pugh classification before treatment.

Exclusion criteria: Patients with a definite history of portal vein thrombosis complicated with extrahepatic distant metastasis, those with coagulation disorders, platelet abnormalities, severe dysfunction of the heart, lung, liver or kidney, or mental illness, those who were allergic to medications, or those who refused to undergo surgery. According to a random number table, all the patients were divided into the following two groups:

Observation group (n=40): There were 26 males and 14 females, aged 19-51 years (mean 43.3±2.9), including 33 cases of complicated cirrhosis, 21 cases of complicated hepatitis B, 6 cases of complicated hepatitis C and 4 cases with no histories of hepatitis and cirrhosis, and with disease duration of 1-6 months (mean 3.2±0.3). Moreover, according to the ultrasonographic findings, the maximum diameter of tumors was 3.1-5.0 cm (mean 4.0±0.4), and there were 1-3 tumors (mean 2.1±0.2), which were 1.0-2.5 cm away from the gallbladder (mean 1.8±0.3).

Control group (n=40): There were 25 males and 15 females, aged 19-51 years (mean 43.3±2.9), including 34 cases of complicated cirrhosis, 20 cases of complicated hepatitis B, 5 cases of complicated hepatitis C and 4 cases with no histories of hepatitis and cirrhosis, and with disease duration of 1-6 months (mean 3.3±0.3). Additionally, the ultrasonographic findings revealed that the maximum diameter of tumors was 3.0-5.0 cm (mean 4.1±0.4), and that there were 1-3 tumors (mean 2.0±0.2), which were 1.0-2.5 cm away from the gallbladder (mean 1.9±0.3). The comparisons of the sex, age, incidence rates of complicated cirrhosis and hepatitis, disease duration, the maximum diameter and number of tumors and their distance from the gallbladder showed no statistically significant differences ($p>0.05$).

Methods

All the patients underwent cholecystectomy and lymph node dissection combined with postoperative chemotherapy that was based on FP regimens (5-fluorouracil+cisplatin). In the Observation group, RFA was performed for liver tumor using the cooled radiofrequency therapy system (Weili, USA) with electrode length of 15.0-20.0 cm, tip length of 2.0-3.0 cm, power of 60-150 W, frequency of 500 kHz, set temperature of 50-90°C, guided by the GE Voluson S6 color Doppler machine at the frequency of 3.5 MHz and its equipped puncture guiding apparatus. The patients first received local anesthesia, and they were kept in supine position intraoperatively. After disinfection, ultrasound-guided puncture was performed at the lesion site, and then ultrasound-guided radiofrequency treatment was conducted with intraoperative ablation range of 0.5-1.0 cm beyond the margins of the visible tumor lesions as much as possible. During puncture, the lesions near the gallbladder were accessed along the place parallel or vertical to the gallbladder, and the electrode insertion direc-

tion was timely adjusted to avoid damaging the pleura, while in cases of a larger volume of tumors and/or more lesions, fan-shaped puncture was carried out for positioning, and the needle electrode was retained over 1.5 cm away from the gallbladder wall during operation to avoid gallbladder perforation. In addition, radical cholecystectomy and radical hepatectomy were conducted simultaneously in the Control group.

Observation indicators

All of the patients were followed up by telephone, and the tumor-associated factor levels, liver function and cellular and humoral immune function-related indicators at 1 month after intervention, tumor size before and after treatment and cases of normal AFP level and tumor disappearance after treatment were compared between the two groups, and the incidence rates of the complications during treatment, such as increase in transaminases, elevation of bilirubin, intratumoral hemorrhage, bile duct injury and gastrointestinal perforation, clinical efficacy and 1-year survival were statistically analyzed in the two groups.

Evaluation criteria

AFP≤25 μg/L, CA19-9 ≤37 kU/L, and CEA ≤20 μg/L (determined via enzyme-linked immunosorbent assay), liver function-related indicators AST and ALT: 0-40 U/L (measured by the Reitman-Frankel method), TBIL: 2-20 μmol/L, IBIL: 0-14 μmol/L and DBIL: 0-7 μmol/L (determined via bilirubin oxidase), cellular immune function-related indicators $CD4^+$, T lymphocyte count (using flow cytometry) and the ratio of $CD4^+/CD8^+$, and humoral immune function related indicators IgG: 23.6-9.6 mg/L, IgA: 3.14-4.66 mg/L and IgM: 3.05-3.85 mg/L (measured through immunoturbidimetry. The clinical efficacy was comprehensively assessed based on the treatment outcomes of solid tumors: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD).

Statistics

SPSS 20.0 (IBM, Armonk, NY, USA) was used for statistical processing, and measurement data were expressed as mean±standard deviation. The means were compared between the two groups using t-test, and the intergroup rate comparison was made using x^2 test. P<0.05 suggested that the difference was statistically significant.

Results

Comparisons of tumor-associated factor levels between the two groups at 1 month after intervention

At 1 month after intervention, the levels of tumor-associated factors, AFP, CA19-9 and CEA, in the Observation group were markedly lower than those in the Control group (p<0.05) (Table 1).

Comparison of liver function after intervention between the two groups

At 1 month after intervention, the Observation group had obviously lower levels of liver function indicators, AST, ALT, TBIL, IBIL and DBIL, than the Control group (p<0.05) (Table 2).

Comparisons of cellular and humoral immune function-related indicators between the two groups at 1 month after intervention

At 1 month after intervention, the levels of the humoral immune function-related indicators, IgG, IgA and IgM, in the Observation group were obviously higher than those in the Control group (p<0.05), and the levels of the cellular immune function-related indicators, $CD4^+$ and $CD8^+$, and the ratio of $CD4^+/CD8^+$ were evidently higher than those in the Control group (p<0.05) (Table 3 and 4).

Table 1. Comparisons of tumor-associated factor levels between the two groups (mean±SD)

	AFP (μg/L)	*CA19-9 (kU/L)*	*CEA (μg/L)*
Observation group	23.3±2.1	36.5±2.6	19.1±2.1
Control group	49.9±3.5	102.3±5.7	67.9±5.3
t	41.217	66.426	54.139
p	0.000	0.000	0.000

Table 2. Comparison of liver function after intervention between the two groups (mean±SD)

	AST (U/L)	*ALT (U/L)*	*TBIL (μmol/L)*	*IBIL (μmol/L)*	*DBIL (μmol/L)*
Observation group	40.5±6.3	33.9±6.4	11.3±1.5	7.1±1.6	4.9±1.3
Control group	60.1±4.7	71.6±9.0	19.5±2.1	17.1±1.3	11.3±1.2
t	15.771	21.590	20.096	30.679	22.879
p	0.000	0.000	0.000	0.000	0.000

For abbreviations see text

Table 3. Comparisons of humoral immune function-related indicators between the two groups at 1 month after intervention (mean±SD)

	IgG	*IgA*	*IgM*
Observation group	14.1±1.3	4.6±0.8	4.6±0.5
Control group	3.3±0.5	1.4±0.3	2.7±0.3
t	49.040	23.687	20.608
p	0.000	0.000	0.000

Table 4. Comparisons of cellular immune function-related indicators between the two groups at 1 month after intervention (mean±SD)

	$CD4^+$ (%)	*$CD8^+$ (%)*	*$CD4^+/CD8^+$*
Observation group	36.3±2.7	31.6±2.9	2.0±0.1
Control group	21.2±1.9	25.3±1.6	1.3±0.1
t	49.040	12.030	31.305
p	0.000	0.000	0.000

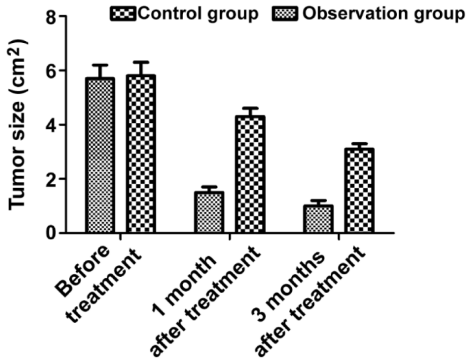

Figure 1. Comparison of tumor size between the two groups before and after treatment. The tumor size in the Observation group is smaller than that in the Control group at any time point (p=0.000).

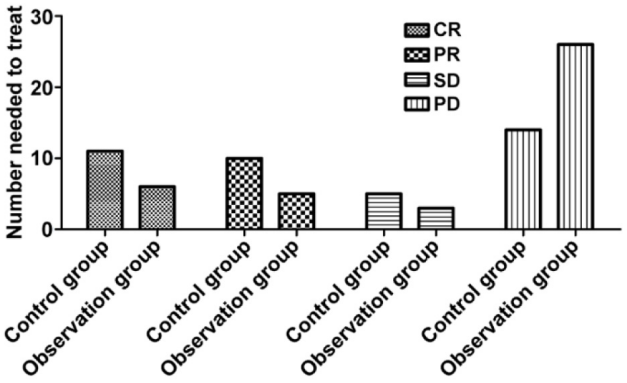

Figure 2. Comparison of clinical efficacy between the two groups. The rate of SD in the Observation group is dramatically higher than that in the Control group (p<0.05).

Comparison of tumor size between the two groups before and after treatment

Before treatment and at 1 and 3 months after treatment, the mean tumor sizes in the Observation group were 4.7±0.5 cm^2, 1.5±0.2 cm^2 and 1.0±0.2 cm^2, respectively, while those in Control group were 4.8±0.5 cm^2, 4.3±0.3 cm^2 and 3.1±0.2 cm^2, respectively, showing that the Observation group had smaller tumor sizes at 1 and 3 months after treatment than the Control group (t=49.115 and 46.957, p=0.000) (Figure 1).

Comparisons of cases of normal AFP level and tumor disappearance between the two groups after treatment

The Observation group had significantly more cases of normal AFP level and tumor disappearance than the Control group (p<0.05) (Table 5).

Comparisons of complications between the two groups

The incidence rates of increase in transaminases, elevation of bilirubin, intratumoral hemorrhage, bile duct injury and gastrointestinal perforation in the Observation group were remarkably lower than those in the Control group (p<0.05) (Table 6).

Comparison of clinical efficacy between the two groups

After 1-year follow-up, there were 11 cases of CR (27.5%), 10 cases of PR (25.0%), 5 cases of SD (12.5%) and 14 cases of PD (35.0%) in the Observation group, while the Control group had 6 cases of CR (15.0%), 5 cases of PR (12.5%), 3 cases of SD (7.5%) and 26 cases of PD (55.0%), and the rate of SD in the Observation was substantially higher than that in the Control group (x^2=7.200, p=0.014) (Figure 2).

Table 5. Comparisons of cases of normal AFP level and tumor disappearance between the two groups after treatment

	Cases of normal AFP level *n*	*Cases of tumor disappearance* *n*
Observation group	25	19
Control group	11	8
x^2	9.899	6.765
p	0.002	0.009

Table 6. Comparisons of complications between the two groups

	Increase in transaminases *n*	*Elevation of bilirubin* *n*	*Intratumoral hemorrhage* *n*	*Bile duct injury* *n*	*Gastrointestinal perforation* *n*
Observation group	1	2	2	1	1
Control group	10	14	15	1	1
x^2	6.746	9.453	10.756	0.000	0.000
p	0.009	0.002	0.001	1.000	1.000

Comparison of 1-year survival between the two groups

The Observation group exhibited a higher 1-year survival rate than the Control group [72.5% (n=29) *vs.* 47.5% (n=19)] (x^2=5.208, p=0.022).

Discussion

Liver cancer adjacent to the gallbladder belongs to primary carcinoma of the liver and its pathogenesis remains to be fully elucidated, which is normally considered to be associated with environmental factors, diet, living habits and heredity [10]. The preferred treatment for liver cancer adjacent to the gallbladder is surgical resection, but it is characterized by large trauma, slow postoperative recovery and many complications, and even cannot be accepted by some patients [11]. As RFA technique develops, it has a significant clinical value for some liver cancer patients who are unable and/or unwilling to undergo surgical resection, and particularly, it can remarkably raise the local control rate and has fewer surgical traumas in the treatment of early isolated small liver cancer. What's more, a study manifested that the comprehensive clinical value of RFA is higher than that of surgical resection [12]. The spatial relation between liver cancer adjacent to the gallbladder and the gallbladder can be identified through ultrasound guidance [13], and since doctors with experience in skillfully puncturing know the tumor size and position during treatment, ultrasound-guided puncture is performed at an accurate site, thus substantially improving the safety of operations [14].

In the present study, the patients with liver cancer adjacent to the gallbladder underwent RFA in the Observation group, while those in the Control group received chemotherapy alone. After 1-month of follow-up, the Observation group showed remarkably lower levels of tumor-associated factors AFP, CA19-9 and CEA than the Control group. Moreover, the comparison of liver function between the two groups showed that the levels of liver function indicators AST, ALT, TBIL, IBIL and DBIL, were remarkably higher in the Observation group than those in the Control group. The above results suggest that, compared with conventional surgical intervention, RFA can lower the levels of the tumor-associated factors to a larger extent and improve the liver function of patients in the treatment of liver cancer adjacent to the gallbladder. Additionally, the cellular and humoral immune function-related indicators were compared between the two groups, and the results revealed that the levels of the cellular and humoral immunity indicators in the Observation group were evidently higher than those in the Control group at 1 month after intervention. Comparison of tumor size before and after treatment showed that the tumor size in the Observation group was smaller than that in the Control group at 1 and 3 months after treatment, suggesting that after operation, the volume of tumors remarkably shrunk in patients with liver cancer adjacent to the gallbladder compared with that in patients receiving chemotherapy alone. Meanwhile, the cases of normal AFP level and tumor disappearance were compared between the two groups after treatment, which revealed that

the Observation group had notably more cases of normal AFP level and tumor disappearance than the Control group, further indicating that RFA can significantly increase the clearance rate of AFP and the complete tumor elimination rate in patients with liver cancer adjacent to the gallbladder. Finally, the comparisons of the clinical efficacy and 1-year survival between the two groups revealed that the Observation group had a notably higher rate of SD and a higher 1-year survival rate than the Control group.

In the Observation group, the radiation treatment parameters were timely adjusted based and multi-point overlapping ablations were appropriately conducted, dramatically deactivating the tumor cells. Since RFA may cause gallbladder perforation and acute cholecystitis [15], puncture paths are selected under ultrasound guidance, effectively raising the success rate and safety of the puncture [16]. Additionally, scalable electrodes and monopolar internally-cooled electrodes are switched intraoperatively, greatly raising the surgical safety, and the infusion of sterile saline into the gallbladder fossa for bluntly expanding the liver and separating it from the gallbladder is also of great value for the improvement in surgical safety [17]. Finally, with the clinical application of ultrasound technique and the proficiency of doctors in ultrasound-guided puncture during treatment, the tumor size and site can be clearly observed [18], and the puncture path, angle and depth are promptly adjusted [19] to better interfere in tumor-nourishing blood vessels, thereby significantly improving the surgical effect [20].

Conclusions

In conclusion, RFA for liver cancer adjacent to the gallbladder can effectively lower the levels of tumor markers, improve liver function and enhance body immunity, with only a few operative complications and high efficacy, so it has a positive implication in prolonging the survival of patients.

Conflict of interests

The authors declare no conflict of interests.

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