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ORIGINAL ARTICLE

Radiofrequency ablation assisted resection for hepatocellular carcinoma: morbidity, mortality and long term survival

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Summary

Purpose: *Hepatic resection is the mainstay of the curative treatment of primary hepatic tumors, with constantly improving short and long term results. Radiofrequency ablation (RFA)-assisted liver resection is a relatively new method of transection of the liver parenchyma with favorable intra- and perioperative results. The aim of this study was to investigate the oncological efficacy (long term overall survival/OS and disease free survival/DFS) and to confirm the favorable short term morbidity and mortality.*

Methods: *Between May 2004 and January 2007, 28 patients underwent 32 resections with removal of 50 hepatocellular carcinoma (HCC) lesions. The technique of parenchymal transection has been described previously as RFA-assisted liver resection.*

Results: *Thirty-day morbidity and mortality were 42.8 and 0%, respectively. Blood transfusion was necessary for 28.5% of the patients. The median hospital stay was 16.5 days (range 5-34). The 1- and 3-year OS were 92.9 and 65.7%, respectively. The 1- and 3-year DFS were 62.3 and 54.6% respectively. No patient developed metastatic disease or local recurrence at the margin site. Twelve patients (42.9%) developed in–the–liver recurrence away from the resection area.*

Conclusion: *RFA-assisted liver resection is a safe and oncologically efficacious method for the surgical treatment of HCC with results comparable to other surgical techniques.*

Key words: *hepatocellular carcinoma, liver resection, radiofrequency ablation, survival*

Introduction

HCC is the most common primary liver cancer, accounting for approximately 75% of the cases in the United States [1]. It is the third leading cause of cancer-related death worldwide, and the leading cause of death amongst cirrhotic patients [2,3]. Surgical options for managing patients with HCC include tumor resection or liver transplantation.

Liver transplantation is currently the best treatment for HCC and it is considered the only curative treatment option. Five-year survival rates are better than liver resection when patients are carefully selected according to Milan criteria (62-77% vs 26–50%, respectively) [4-7]. However, the shortage of available organs still limits the use of transplantation in the treatment of HCC [8].

Liver resection for HCC is a widely accepted safe treatment method, with very low associated morbidity and mortality rates as a result of advances in both surgical techniques and anaesthetics and critical care [9-12]. Guidelines regarding the treatment of HCC from the European Association for Study of Liver (EASL) [10] and the American Association for Study of Liver Diseases (AASLD) [11] clearly define the role of resection, and when transplantation is indicated.

The two major side effects of liver resection are intra-operative bleeding and biliary leakage,

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particularly with traditional surgical approaches [13]. Blood loss and blood transfusion are known to increase morbidity and mortality in both the postoperative period and in the longer term [14,15]. The prevention of bleeding is particularly difficult in non-anatomical resection, but also in segmental resections and sectionectomies commonly employed in cirrhotic patients to preserve postoperative liver function. A number of techniques has previously been employed to reduce intraoperative blood loss, including hypotensive anaesthesia and vascular occlusion. The occlusion techniques involve clamping of inflow and outflow vessels, which is effective in controlling bleeding. However, they are strongly associated with postoperative hepatic dysfunction, particularly in those with preexisting liver disease [16,17].

Multiple modern techniques and devices aimed at reducing intraoperative bleeding have been used to change the method of liver resection in many centres, providing better results for resection-related morbidity and mortality [18-24]. Among these is the well established RFA-assisted liver resection, first popularized by the Habib's group at Hammersmith Hospital, London, UK [21,23].

The purpose of this study was to present our results of RFA-assisted liver resection for HCC, a well established method of resecting the liver parenchyma, and to assess the oncological efficacy (long term OS and DFS) as well as to confirm the favorable short term morbidity and mortality.

Methods

Study population and eligibility criteria

The data of patients who underwent RFA-assisted hepatectomy with curative intent for HCC in the First Department of Surgery, University of Athens Medical School, "Laiko" Teaching Hospital, Athens, Greece, between May 2004 and January 2007 were collected and analysed.

Grades A or early B on the Child Pugh classification system, preoperative investigations indicating potentially curative resection, satisfactory residual volume of healthy or cirrhotic liver tissue, and absence of extra-hepatic metastatic disease were the eligibility criteria for surgical treatment of liver tumors. Resectability was determined preoperatively by means of US, CT, MRI and PET scan, depending on indications. Intraoperative US was used to ensure resectability and clear surgical margins. Patients with severe comorbidities that precluded major surgery, Child Pugh score C or extrahepatic disease were excluded from surgical treatment.

Liver resections were defined according to Couinaud's anatomic classification of the liver [25]. Resections of more than 3 segments were classified as major hepatectomies. Wedge resections were classified as non-anatomical resections according to Makuuchi's classification of liver resection [26].

Surgical technique

The technique of parenchymal transection in "Laiko" Teaching Hospital has been described previously as RFA-assisted liver resection [27]. Briefly, the RFA needle electrode is inserted in the liver parenchyma, first close to the surface and then deeper. Hemostatic RFA of the liver tissue is accomplished usually in less than a minute, and sharp division follows while the electrode progresses in a nearby area. Sharp division and ablation are carried on in a continuous fashion. For optimal exposure of the cut surfaces of the liver, the open book technique is used. In this way, intrahepatic vessels are clearly visible and safely coagulated before division. When minor hemorrhage occurs, the cut surfaces are approached and pressed together in order to enhance the ablation effect. In addition, the pressure of the liver parenchyma decreases the blood supply to the ablated zone, thereby eliminating the heat-sink phenomenon. Persisting minor haemorrhages or bile leak are controlled using sutures or clips.

Follow up and data collection

Patients were routinely followed up with clinical examination, tumor markers estimation and CT every 6 months. When symptoms occurred, patients were recalled to the follow up clinic earlier than scheduled. The follow up lasted up to March 2009.

Demographics, tumor characteristics, type of liver resection and date and site of recurrence were recorded from the patients' notes. Recurrences were classified as extrahepatic or intrahepatic; intrahepatic recurrence could be either at the surgical margin or at a site not adjacent to the resection area. Recurrences were determined based on clinical, radiological and histopathological evidence. OS was calculated from the day of operation to the day of death or the last follow up and DFS to the date when any type of recurrence was detected. Operative mortality was defined as death occurring within 30 days after surgery or before discharge from the hospital. Morbidity included all postoperative complications.

Statistics

OS and DFS were calculated with the Kaplan-Meier method. Significant predictors of OS and DFS were subjected to multivariate analysis with the Cox proportional hazards method. Life tables were generated according to the Kaplan-Meier survival analysis. Differences in OS or DFS were compared by means of log rank test. A probability of ≤ 0.05 was considered significant. Data were analysed by means of the statistical package SPSS for Windows, version 11.

Results

Twenty-eight patients underwent 32 resections, with removal of 50 lesions overall. Patient and disease characteristics are shown in Table 1.

There were 12 major and 20 minor resections. Patients with minor resections underwent monosegmentectomy (N=6, 37.5%), bisegmentectomy (N=7, 43.75%) and wedge or limited resection (N=3, 18.75%). One patient in the major resection group also had two wedge resections. Two patients in the major resection group also underwent monosegmentectomy. Resection margins were negative in 29 (90.6%) resections, and positive in 3 (9.4%) resections.

Twenty out of 28 patients (71.5%) did not require blood transfusion for their operation. Eight (28.5%) were transfused with a total of 32 units of packed red blood cells, and all received at least 2 units (median 3.7 units per transfused patient). These 8 patients were cirrhotic.

Procedure characteristics and histology are summarized in Table 2.

Postoperatively 2 patients remained in the ICU for 1 and 4 days, respectively. The median hospital stay was 16.5 days (range 5-34). Thirty-day mortality was 0%. Two cirrhotic patients with postoperative bleeding, one from the cut surface of the liver and the other one from the entry point of the drainage tube, were managed successfully by surgery. One case with bile leakage, 2 cases of biloma formation, 5 large pleural effusions, one case of postoperative liver failure and one case of late postoperative liver/pulmonary failure were all successfully managed.

Median follow up was 27.9 months (range 4.5-46.4). Eight patients (28.6%) died during the follow up period and mean OS was 37 ± 4.0

Table 1. Patient and disease characteristics

Characteristics	*N*	*%*
Patients	28	100
Lesions	50	100
Resections	32	100
Age, years, median (range)	63.8 (38-78)	
>70	10	35.7
<70	8	64.3
Gender		
Male	24	85.7
Female	4	14.3
Median maximum tumor diameter (range, cm)	5.57 (1.7-17)	
>5	12	42.9
<5	16	57.1
Cirrhotic liver	24	85.7
Child-Pugh grade A or early B (score 7,8)	24	85.7
Post viral hepatitis	22	78.6
Primary biliary cirrhosis	2	7.1
Hepatitis	22	78.6
B	6	21.4
C	16	37.2
Hepatocellular carcinoma	28	100

Table 2. Procedure characteristics and histology

Characteristics	*N*	*%*
Types of resections		
Major resections	12	42.9
Right hemihepatectomies	6	21.4
Left hemihepatectomies	3	10.7
Right hemihepatectomy +2 wedge resections	1	3.6
Right hemihepatectomy +monosegmentectomy	1	3.6
Left hemihepatectomy +monosegmentectomy	1	3.6
Minor resections	16	57.1
Segmentectomies	13	46.4
Wedge resections	3	10.7
No. of segments resected		
Total	66	
≥4	37	
<4	29	
Lesions resected	50	
Mean number of lesions per patient	1.78	
Time of RFA application, minutes, median (range)	58.5 (20-145)	
Pringle	0	
Patients transfused	8	28.5
PRBCs transfused (units), median (range)	1.35 (0-10)	
Grade		
Well	10	35.7
Moderate	8	28.6
Poor	10	35.7
Margins		
R0	29	90.6 (resections)
R1	3	9.4 (resections)

PRBCs: packed red blood cells, RFA: radiofrequency ablation months (95% confidence interval 29.1-44.8). One- and 3-year OS after RFA-assisted liver resection was 92.9% and 65.7% respectively (Table 3).

No patient developed metastatic disease or local recurrence at the margin site. Twelve patients (42.9%) developed in-the-liver recurrence away from the resection area. Mean DFS was 28.5 ± 5.4 months (95% confidence interval 17.9-39.2). The cumulative DFS was 54.6%. One- and 3-year DFS was 63.3% and 54.6%, respectively (Table 3).

Table 3. Follow up and survival

Variables	*N*	%
Complications	12	12 (42.8)
30-day mortality	0	0
Length of stay in ICU, days, median (range)	2.4 (1-4)	
Length of hospital stay, days, median (range)	16.5 (5-34)	
Follow up, months		
Median	27.9	46.4
Range	4.5-46.4	27.9
Patients alive at the end of follow-up	20	71.4
Mean survival time, months	37±40 95% CI: 29.1-44.8	
OS		65.7
1-year	26	92.9
3-year	18	65.7
Recurrence	12	42.9
Site of recurrence		
In the liver	12	100
Surgical margin	0	0
Systemic	0	0
Recurrent tumors	30	42.9 (patients)
Pattern of recurrence		
Solitary	0	0
2 nodules	6	21.4
3 or more	6	21.4
Mean DFS (months)	28.5±5.4 95% CI: 17.9-39.2	
DFS		
1-year	17	62.3
3-year	15	54.6

ICU: intensive care unit, DFS: disease free survival, OS: overall survival

Discussion

HCC is a major cause of morbidity and mortality worldwide, and hepatic transplantation and resection offer the only potentially curative surgical treatments. There have been several recent reviews regarding the value of transplantation, which has a number of advantages over resection [28-40]. HCC frequently occurs in patients with underlying liver disease, which can be cured simultaneously with the transplant. Indeed in these patients hepatic reserve is often so poor that resection is not possible. Furthermore, HCC is frequently multifocal and not amenable to resection. However, transplantation remains limited due to lack of donor organs.

Resection is a widely accepted, safe treatment for HCC. It is however associated with a number of complications, particularly in patients with pre-existing cirrhosis [41]. Blood loss and blood transfusion contribute to poor short - and long-term outcomes, and the reduction of intraoperative blood loss is a key target for hepatobiliary surgeons. Vascular occlusion techniques that involve clamping the inflow and outflow vessels are effective in controlling bleeding, but are associated with increased morbidity, mortality and postoperative liver dysfunction. They are particularly deleterious in patients with poor hepatic reserve [42,43]. Despite these techniques, the reported volume of blood loss during traditional surgical liver resection is 450-1500ml, dependent primarily on the size of the resection and normality of the existing liver parenchyma [44-48]. As a result, 7-56% of liver resections are reported to require intraoperative blood transfusion [49,50].

Numerous newer techniques that allow for liver parenchyma transection with reduced blood loss have been reported. These include RFA energy, the argon beam coagulator, cavitron ultrasonic surgical aspirator (CUSA), harmonic scalpel and water-jet scalpel [51], and they have contributed to a marked reduction in morbidity and mortality following resection [12,41,52-54].

RFA has been widely used for the *in situ* ablation of unresectable liver and other solid organ tumors [55-58], but it has now been incorporated into routine liver resection, being used to create a line of coagulative necrosis that can subsequently be divided with a scalpel with relatively little blood loss [17,59,60]. This allows both major and minor liver resection, including non-anatomical resection, to be performed without the use of vascular occlusion techniques, and blood transfusion is required only rarely.

Our study confirmed the favorable short-term outcomes associated with RFA-assisted liver resection for HCC; 30-day mortality was 0, and only 2 patients required short periods of ICU admission. The majority of the patients were operated on without the need for blood transfusion, despite 12 major resections. Vascular occlusion techniques were not required in any case.

We also found longer-term OS and DFS following RFA-assisted resection for HCC. The natural history of this disease shows that without treatment there are no survivors at 3 years after initial diagnosis [61]. Older studies in which vascular occlusion techniques and blood transfusion were used in the majority of cases report 3-year OS rates of 30–63% and 3-year DFS of 24-54% [62]. Higher OS and DFS rates have been reported when newer techniques for parenchymal resection are used (mean 3-year OS and DFS 74.4 and 54.4%, respectively) [63], although this is dependent on a number of preoperative factors including preoperative Child-Pugh grade and tumor stage and grade. The OS and DFS we observed in this case series are similar to those previously reported using newer hepatic resection techniques in similar patient groups [63-65].

Our study adds to the growing body of evidence that RFA is a safe and appropriate technique to use for the resection of liver tumors, and is associated with good short- and long-term outcomes.

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