Title

Endoscopic versus open radiofrequency ablation for treatment of small hepatocellular carcinoma

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Abstract

Background Surgical radiofrequency ablation (RFA) for hepatocellular carcinoma (HCC) is associated with superior oncological outcome in comparison with percutaneous RFA. This study aimed to retrospectively evaluate the relative perioperative safety and postoperative outcome of the laparoscopic or thoracoscopic approach versus the open approach to RFA for small HCC.

Methods A retrospective analysis was performed in 55 consecutive patients who underwent open (n=32) or laparoscopic/thoracoscopic (LTS) RFA (n=23) for primary unresectable HCC between January 2005 and December 2010. Baseline characteristics, survival/recurrence rates and complications after treatment were compared between the two groups.

Results There was a trend showing that LTS RFA was performed for tumors located in the anterior segment (e.g., segments III, V, VIII). The LTS RFA group had a significantly lower intraoperative blood loss, shorter operation time and shorter postoperative hospital stay, compared with the open RFA group. No major postoperative complications occurred in patients who underwent LTS RFA. No significant differences in overall survival, recurrence-free survival and local recurrence rates were observed

between the two groups.

Conclusions In consideration of operative invasiveness and postoperative recovery, LTS RFA is superior to the open approach in patients with small HCC. Moreover, the surgical outcome did not differ between the two approaches. LTS RFA can be considered to be a useful procedure for ablation therapy.

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignant disease worldwide and the third greatest cause of cancer-related death [1]. Hepatic resection has been shown to be most efficacious for certain subtypes of HCC [2-4]; however, resection of the cirrhotic and/or steatotic liver always carries a high risk of intraoperative hemorrhage and postoperative hepatic failure. Thus, small HCCs that are not amenable to hepatic resection are often treated using ablation therapies such as percutaneous ethanol injection, radiofrequency ablation (RFA), and microwave coagulation therapy [5-8].

The RFA techniques include percutaneous RFA (p-RFA) and surgical RFA (s-RFA; i.e., laparoscopic, thoracoscopic and open approaches). When employing p-RFA, there is the possibility of severe complications occurring at risky locations, such as with HCC nodules adjacent to a large vessel or an extrahepatic organ [9, 10]. Moreover, it has been reported that a subcapsular location is a risk factor for local recurrence after p-RFA [11, 12]. Since 2000, we have been employing s-RFA as an alternative to p-RFA for such patients, and reported a lower complication rate and a better survival compared with p-RFA [13].

Although several studies have shown the benefits of endoscopic RFA using laparoscopy or thoracoscopy [14-16], in laparoscopic/thoracoscopic (LTS) procedures it is not easy to puncture the target with an RFA needle under laparoscopic ultrasound guidance. The ablation area may become inadequate because the puncture angle is less flexible compared with the open approach. This study aimed to retrospectively evaluate the relative perioperative safety and postoperative outcome between LTS and open approach RFA for small HCC.

Patients and methods

Patients

From January 2005 to December 2010, we performed s-RFA for primary unresectable HCC with impaired liver function, and/or with difficult location by percutaneous approach in 55 patients (40 men, 15 women; median age 66 y, range 49 – 83 y). The median tumor size was 2.2 (range 1.0 - 3.0) cm. LTS RFA was performed in 23 patients and open RFA in 32 patients. The laparoscopic approach was used in 15 patients and the thoracoscopic approach in 8 patients. Among the 32 patients in the open group, 21 operations were performed under laparotomy and 11 under thoracotomy. LTS RFA was performed in patients with superficial tumors or extrahepatic protrusive tumors. When

there was a history of laparotomy of the upper abdomen and extensive intraabdominal adhesions were expected, open RFA was chosen.

RFA electrode and generator

A radiofrequency generator (RF 3000; Boston Scientific, Natick, MA, USA) with maximum power output of 200 W was used for these procedures. Energy was delivered through a 17-gauge expandable electrode needle (LeVeen Needle Electrode; Boston Scientific). This needle houses 10 retractable curved electrodes that, when deployed, assume the configuration of an umbrella. After one ablation, the procedure produces a ball-shaped ablated area 2.5-3.0 cm in diameter. The ablation algorithm is based on tissue impedance, and ablation is considered successful if the device impedes out.

Laparoscopic/thoracoscopic RFA

After induction of general anesthesia, 2 to 3 trocars are placed into the abdomen. Under laparoscopic ultrasound guidance, the RFA needle is deployed into the tumor bed and the tumor, and a 1-cm margin of normal liver are ablated. To obtain a safety margin around the nodule, ablation was performed 1 to 6 times per lesion. When the tumor was in segment VIII or VII, close to the diaphragm, the electrode was inserted through the

right diaphragm under thoracoscopy.

Open RFA

Open RFA can be indicated for patients who are considered suitable for open surgery with numerous, or deeply located tumors that cannot be accurately accessed by LTS approach. When tumors were located near the subhepatic inferior vena cava or gastrointestinal tract, open RFA was also selected. The route of open RFA was assessed by intraoperative ultrasound on the liver surface. The distance between the tumor and other vulnerable organs or vessels could be enlarged when the operator rotated the liver.

Assessment of technical effectiveness and follow-up

The technical effectiveness of ablation is commonly assessed by findings on contrast-enhanced computed tomography (CT) at 1 week after the operation. After discharge, all patients were followed up by serological examination [alpha-fetoprotein (AFP) and des-γ-carboxy prothrombin levels] and radiological examinations (ultrasound and CT) every 3 months. Clinical courses of the patients were monitored for at least 5 years after operation or until the time of death. The median follow-up period was 26.6 months (range 2.8-77.0 months).

Statistical Analysis

Values for continuous variables are presented as means ± SE. Differences between the two groups were analyzed using the unpaired *t* test for continuous variables and the χ^2 test for categorical variables. Survival curves and recurrence-free survival curves were calculated by the Kaplan-Meier method and compared by the log-rank test. A *p* value of less than 0.05 was considered significant.

Results

The clinical and radiographic variables of patients who underwent open and LTS RFA are shown in Table 1. Significant differences were found between the two groups in three parameters: age, ICGR 15, and tumor size. Open RFA was performed for 51 tumors in 32 patients, and LTS RFA for 33 tumors in 23 patients. Table 2 shows tumor locations for RFA between two groups. A trend indicated that LTS RFA was performed for tumors located in the anterior segment (e.g., segments III, V, VIII). Operative characteristics and clinical outcomes after surgery are shown in Table 3. In comparison with the LTS RFA group, the open RFA group had significantly longer operation time (p=0.02) and higher intraoperative blood loss (p=0.02) and postoperative hospital stay

(p=0.04), despite the comparatively preserved liver function. No major complications were reported in any patient with the two groups.

Cumulative overall survival rates after open RFA were 95% at 3 and 5 years, while those after LTS RFA were 77% at 3 and 5 years, respectively (Fig. 1). There was no significant difference in survival rates between the two groups (p=0.52). With regard to the cause of death, one patient (50% of deaths) in the LTS RFA group died from causes other than hepatic diseases (i.e., tumor progression, hepatic failure, variceal rupture or other complications of cirrhosis). Recurrence-free survival rates after open RFA were 55% at 1 year and 9% at 3 years, while those after LTS RFA were 64% at 1 year 31% at 3 years, respectively (Fig. 2), with no significant difference between the two groups (p=0.48). Local recurrence was observed in 3 cases after open RFA and in one case after LTS RFA (Fig. 3). There was no significant difference in local recurrence rates between the two groups (p=0.39).

Discussion

RFA has been utilized as a less invasive and curative treatment for small HCC that are not amenable to hepatic resection [17, 18]. Although RFA can be performed safely using percutaneous or surgical techniques, several reports, including ours, have shown lower

rates of postoperative complications and local recurrences in s-RFA at risky locations, such as with HCC nodules adjacent to a large vessel or extrahepatic organ [9-13].

S-RFA has been performed through the open approach by thoracotomy or laparotomy and through the endoscopic approach by laparoscopy or thoracoscopy. Several studies showed no significant differences in postoperative complications and disease-free survival between open and laparoscopic/thoracoscopic (LTS) RFA and that LTS RFA is suitable for the treatment of unresectable HCCs with operative safety and effectiveness [19-21]. We have selected the approach for s-RFA so that safety and curability of operation should not decrease. Consequently, the median size of tumors was small and tumors were located mainly in the anterior segment (e.g., segment III, V, VIII) in LTS RFA compared with open RFA in this study. Operation time and intraoperative blood loss with LTS RFA were significantly less compared with open RFA. No major complications were observed with LTS RFA and the postoperative hospital stay was significantly shorter than with open RFA. It is considered that LTS RFA is a minimally invasive treatment.

There was no significant difference in overall survival, recurrence-free survival and local recurrence rates between the two groups. It was reported that a large tumor was a significant independent risk factor for local recurrence after RFA [17, 18]. In this study,

the primary size of tumors in patients with no local recurrence was 2.3 ± 0.1 cm, and patients who had local recurrence had tumors 2.9 ± 0.1 cm. Thus, the tumors in patients with local recurrence were significantly larger than in patients without local recurrence. Tumor location was reported as another risk factor for local recurrence [10]. Teratani et al. defined so-called high-risk locations as those near large vessels such as a primary or secondary branch of the portal vein, the base of hepatic veins, or the inferior vena cava, or a lesion near extrahepatic organs [9]. In this study, tumors in many cases in the open RFA group were located in high-risk locations, and patients with local recurrence had tumors near large vessels (data not shown). It was suggested that RFA for nodules adjacent to large vessels might often result in incomplete necrosis because of a heat sink effect [17, 22]. To address such problems, combination therapy using chemoembolization before RFA suppresses hepatic blood flow and increases the volume of the ablative zone [23, 24]. The beneficial effects of combination therapy with ethanol injection have been reported [25, 26]. Although we have performed Pringle's maneuver during the ablation to reduce the heat sink effect in the high-risk locations, local recurrences were not controlled completely. Development of a new device is considered to be necessary.

In conclusion, we have shown that laparoscopic/thoracoscopic RFA for patients with

small HCC provides overall and recurrence-free survival rates similar to those achieved by open RFA. Although a limitation of approach under the laparoscope or thoracoscope exists, laparoscopic/thoracoscopic RFA is a minimally invasive treatment and is considered to be one of the useful procedures for RFA.

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Figure legends

Fig. 1 Overall survival rate after treatment. No significant difference in the survival rate was observed between the two groups.

Fig. 2 Recurrence-free survival rate after treatment. No significant difference in the recurrence-free survival rate was observed between the two groups.

Fig. 3 Local recurrence rates after treatment. No significant difference in local recurrence rates was observed between the two groups.