Hybrid Ablation using Percutaneous and Endoscopic Approach for Multinodular Hepatocellular Carcinomas

Running Head: Hybrid Ablation for HCC

Toshiro Masuda, Toru Beppu, Takao Mizumoto, Takatoshi Ishiko, Akira Chikamoto, Hiromitsu Hayashi, Hirohisa Okabe, Ryu Otao, Hasita Horlad, Hiroshi Takamori, and Hideo Baba

Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, 1-1-1 Honjo, Kumamoto, 860-8556, Japan

Correspondence Author: Hideo Baba MD, PhD, FACS
Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, 1-1-1, Honjo Kumamoto-shi, Kumamoto 860-8556, Japan
Tel.: +81-96-373-5212; fax: +81-96-371-4378
E-mail address: hdobaba@kumamoto-u.ac.jp

Original Paper, liver section

No fainancial support

Key words: hybrid ablation, hepatocellular carcinoma, radio-frequency ablation, microwave coagulation therapy

ABBREVIATIONS: hepatocellular carcinoma (HCC), radio-frequency ablation (RFA), microwave coagulation therapy (MCT)

ABSTRACT

Background/Aims: To investigate the efficacy and the safety of a hybrid ablation combining a percutaneous and endoscopic approach for multinodular hepatocellular carcinomas.

Methodology: Hybrid ablation consists of a percutaneous approach for deep-sited tumors and an endoscopic approach for superficial ones. Between January 1991 and December 2007, fourty-eight patients with 139 nodules were treated with the hybrid ablation. The perioperative clinical data and prognosis of the hybrid approach group were compared with 15 patients with superficial and deep-sited multinodular HCCs treated by the pure endoscopic ablation.

Results: With regard to the deep-site of the liver tumors, the complete disappearance of tumor enhancement was observed in 76 of 77 tumors (98.7%) in the hybrid ablation group, and 15 of 18 tumors (83.3%) in the pure endoscopic ablation group ($p = 0.02$). The mean operation time (236.5 minutes), the mean amount of intraoperative bleeding (20.3g), the median days of postoperative hospital stay (14 days), major complication rates (10.4%), and the 5-year overall survival (42%) in the hybrid ablation group were similar to the pure endoscopic group.

Conclusions: Hybrid ablation is a clinically useful treatment for multinodular hepatocellular carcinomas located in both superficial and deep-site of the liver

INTRODUCTION

Local ablation therapies, such as radio-frequency ablation (RFA), microwave coagulation therapy (MCT), ethanol injection therapy, and cryoablation are beneficial treatments for small hepatocellular carcinoma (HCC), especially in patients with liver cirrhosis (1-3). A percutaneous approach is comparatively easy and safe to perform, and has now been commonly adopted worldwide (4). However, in patients with tumors located on the surface of the liver, an endoscopic approach via a thoracoscopic or laparoscopic approach must be selected, in order to prevent thermal injury of the surrounding organs, peritoneal hemorrhage, and needle-track or peritoneal seeding of tumor cells (5-8).

In our department, endoscopic ablation was introduced in 1994. In the early period, in treating patients with multinodular HCCs located in both superficial and deeper sites of the liver, a pure endoscopic approach was applied. However, it was relatively difficult to perform an accurate puncture of the deep-sited tumors, resulting in an insufficient therapeutic result. Therefore, we developed a hybrid ablation technique consisted of a percutaneous ablation for deep-sited tumors and an endoscopic ablation for superficial tumors.

The purpose of this study was to investigate the efficacy and the safety of hybrid ablation for multinodular HCCs.

METHODOLOGY

Patients

Between January 1991 and December 2007, 665 patients with HCC underwent RFA or MCT in the Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University. Two hundred eighteen patients were treated with the endoscopic approach and among them, 63 patients had multinodular HCCs located in both superficial and deep-site of the liver. Forty-eight patients were treated with the hybrid ablation and 15 were treated with pure endoscopic ablation. The diagnosis of HCC was mainly confirmed by the diagnostic imaging: ultrasound sonography (US), computed tomography (CT), Magnetic resonance imaging (MRI), CT during arteriography (CTA) and arterio-portography (CTAP), and tumor markers: alpha-fetoprotein (AFP), AFP – L3, protein induced by vitamin K absence.(9) Preoperative fine-needle aspiration cytology was not essentially performed to prevent peritoneal tumor dissemination.(10, 11)

Indications for local ablation therapy with the hybrid approach

Local ablation therapy was mainly selected for the HCC patients with poor liver function, instead of an indication of hepatic resection. The patients with a history of bilioenteric anastomosis or sphincterotomy were excluded from the indications for ablation therapy, because of a high risk for liver abscess formation.(12)

In our department, the percutaneous ablation is performed for the tumors, within 3 nodules, measuring within 3 cm in diameter, with no vascular invasion, and which are not located in a superficial site of the liver. The endoscopic ablation was mainly indicated for superficial tumors, within 3

nodules, within 4 cm in diameter, and without any venous invasion. Superficial tumors were defined as those located within 5 mm-depth from the surface of the liver. Endoscopic ablation can prevent the bleeding from surface of the tumor, the thermal injury of the surrounding organs, and the eruption of tumor cells.(6, 13) In treating patients with multinodular HCCs in mixture of superficial and deeper-site tumors safely and easily, the hybrid ablation was applied. The superficial tumor was ablated with endoscopic approach, while the deep-site tumor was treated with percutaneous approach.

Procedure of hybrid ablation

The procedure was performed under general anesthesia in all of the patients. MCT was performed with monopolar-type electrodes and RFA was achieved with internally cooled electrodes (Cool-tip^{TM}), and a complete tumor ablation with a margin of 5 mm around the tumor was aimed.(2) In the early stage of the introduction of hybrid ablation, a percutaneous approach was initially performed followed by an endoscopic approach. If the endoscopic approach was performed first, then the percutanous US would be possibly unclear because of the pneumoperitoneum. Recently, hybrid ablation was performed with endoscopic ablaion first, followed by the second percutaneous ablation with artificial ascites.(14, 15) At the end of all the procedures, complete coagulation and hemostasis were confirmed endoscopically. Laparoscopic or thoracoscopic US was performed using a 7.5-MHz flexible, linear, side-viewing probe. For superficial tumors, the ablation of the surrounding liver parenchyma was initially performed under direct view or endoscopic US, and finally, the tumor was directly punctured to achieve complete ablation.(16) HCC, smaller than 2cm, can be treated without the

insertion of the needle into the tumor itself.(16)

Assessment of Treatment Efficacy and Follow-Up

At a week after the local ablation therapy, tri-phasic contrast enhanced-CT scan with 5 mm-widths was performed to evaluate the quality of the treatment. An ablated area all around the tumor with no enhancement in the arterial phase was defined as complete tumor necrosis. If the tumor was judged not to be completely ablated, additional sessions of ablation therapy or transarterial chemoembolization were applied. Follow-up consisted of monthly blood tests with monitoring of tumor markers and tri-phasic contrast enhanced-CT scans every 3-4 months. If recurrence of HCC was suspected, additional treatments were attempted according to the pattern of recurrence and the remnant liver function.

Comparison of clinical characteristics of HCC patients treated with the pure endoscopic and the hybrid ablation

In order to arrange the background of tumor numbers, the patients treated with the pure endoscopic ablation were selected as a control, although this group does not include deep-site HCCs. Preoperative clinical parameters such as age, gender, hepatitis B virus surface antigen (HBs–Ag), hepatitis C virus antibody (HCV–Ab), tumor size, tumor number, and the liver damage grade(17) were examined. The surgical parameters included the operation time, amount of intra-operative bleeding, postoperative hospital days, complication rates, and overall survival. All parameters were compared between the pure endoscopic ablation group and the hybrid group.

Statistical analysis

The clinical continuous parameters were expressed as the mean ± standard error. Comparisons between the groups were performed using Student's *t*-test for continuous data and the χ^2 test (or the Fisher's exact test where appropriate) for categorical data. The median postoperative hospital stay was compared using the Mann-Whitney's U test. Overall survival was calculated using the Kaplan-Meier method, and the log-rank test was used to assess differences in survival estimates among the groups. Differences with a p-value less than 0.05 were considered to be significant.

RESULTS

In the hybrid ablation group, there were 139 nodules in 48 patients. Seventy-seven deep-sited nodules were ablated with percutaneous approach and 62 superficial nodules were treated endoscopically. Endoscopic maneuvers were performed with 12 thoracoscopic and 36 laparoscopic approaches. Age, gender, HBs-Ag, HCV-Ab, and liver damage grade, and the mean size of the main tumor were similar in the group of hybrid and pure endoscopic ablation **(Table 1)**. The mean tumor number were 2.9 in the hybrid ablation group and 2.8 in the pure endoscopic ablation group (p=0.84). With regard to the deep-site of the liver tumors, the complete disappearance of tumor enhancement was observed in 76 of 77 (98.7%) in the hybrid ablation group, and 15 of 18 (83.3%) in the pure endoscopic ablation group (p = 0.02). With the superficial site of the liver tumors, the complete disappearance of tumor enhancement was observed in 61 of 62 (98.4%) in the hybrid ablation group, and 35 of 36 (97.2%) in the pure endoscopic ablation group (**Table 2**; p = 1.0).

The mean operation time was 236.5 minutes in the hybrid ablation group and 222.9 minutes in the pure endoscopic group (p = 0.50). The mean amount of intra-operative blood loss was quite low, 20.3g in the hybrid ablation group and 12.9g in the pure endoscopic ablation group (p = 0.60). The median postoperative hospital stay were 14 and 12 days in the two groups (p = 0.16).

No significant differences were observed in the complication rates, 10.4% and 6.7% in the two groups (p = 1.0). One case (2.1%) of lethal complication (pyothorax) was encountered in the hybrid ablation group. A pyothorax (2.1%), a cholecystitis (2.1%), a surgical site infection (2.1%), and

two pleural effusions (4.2%) were obsereved in the hybrid ablation group. No peritoneal tumor disseminations or port-site recurrences has been observed.

The cumulative 5-year overall survival rates were quite similar, 42% and 40% in the hybrid ablation group and the pure endoscopic ablation group, respectively (**Figure 2**, $p = 0.60$; The mean follow-up period was 2.9 years).

DISCUSSION

For HCCs detectable with percutaneous US, percutaneous ablation therapy is less invasive and is considered to be the first-line therapy (18, 19). However, in some patients, a complete ablation is difficult due to the localization of the tumor (18). Especially, in treating HCCs located on the surface of the liver, there are some ablation-specific complications such as thermal injury of the gallbladder, intestine and stomach, bleeding from the tumor, and intra-abdominal seeding of tumor cells (5, 6, 10, 12, 20, 21). Ablation therapy using thoracoscopy or laparoscopy is quite useful to treat tumors that cannot be detected with percutaneous US (22), located close to the visceral organs (22, 23), or located in superficial site of the liver (6). In treating tumors that cannot be detected by percutaneous US, the endoscopic approach allows easier and correct insertion of the needle electrode using endoscopic US in various suitable directions (22). In treating tumors located close to surrounding organs, the endoscopic maneuver can make a direct observation of the tumor and their surrounding structure. The gallbladder, digestive organs, diaphragm, heart, and lung can be protected from burns or misguided punctures. If necessary, additional procedures such as an endoscopic hepatectomy, cholecystectomy, or dissection of blood vessels supplying the tumor can be concurrently performed (8).

For the treatment of superficial liver tumors, the risk of intra-abdominal seeding of tumor cells must be considered (6, 10, 13, 21). Subcapsular HCCs must be ablated by indirect puncture through the nontumorous liver followed by needle track ablation (6). Besides, if a spout of tumor cells or bleeding occurs, sufficient management such as suction of tumor cells, peritoneal lavage with saline, or hemostasis can be promptly

achieved via the endoscopic approach (8). Inversely, in treating tumors located in deep-site of the liver, it is slightly difficult to achieve an accurate puncture via the pure endoscopic approach. In fact, in treating tumors located in deep-site of the liver with the pure endoscopic ablation, a skillful freehand-puncture technique using a linear type probe and a guide needle is needed (16, 24). With regard to the deep-site of the liver tumors, In order to treat multiple tumors located in deep-site of the liver, we developed a hybrid ablation using percutaneous and endoscopic approaches in a session. In the hybrid ablation group, complete disappearance of tumor enhancement was achieved in 98.7% of tumors located in deep-site of the liver and 98.4% of tumors located in the superficial site of the liver. Especially in deep-site of the liver tumors, it was easier to treat with the percutaneous approach, resulting in the high rate of complete disappearance of tumor enhancement compared to the pure endoscopic group (83.3%).

In the hybrid ablation group, although both the percutaneous and endoscopic approach was needed, the mean amount of operation time, intra-operative bleeding, the median postoperative hospital stay, and the rate of complications were equivalent to the pure endoscopic group. Previous studies reported that the incidence of major complications after local ablation therapy was low (2.0 to 3.0%), and there were few treatment-related deaths (7, 12, 20, 25, 26). In the current study, major complication was encountered by a case (2.1%) in the hybrid ablation group, regardless of containing many superficial HCCs (6, 12, 20). In addition, no thermal injury of the intestines, subcapsular hematoma, and tumor recurrences at the port site or peritoneal dissemination was observed. The cumulative 5-year overall survival rate in the hybrid ablation group was 42%. The reported 5-year overall survival of

HCC patients treated with local ablation therapy were 20 – 55% (27-32). Yan *et al.* reported that the number of tumors affects HCC patients' prognosis and the 5-year survival of patients with multinodular HCCs was 34.2% (32). The current data was quite acceptable with a relatively long mean follow-up period (2.9 years), even though all the patients had multinodular HCCs which is reported to be a significant poor prognostic factor (32-34).

In conclusion, the hybrid ablation technique concurrently using both the percutaneous and endoscopic approach is considered to be a quite useful treatment for patients with a mixture of superficial and deep-sited HCCs with regard to its short and long term therapeutic effect and safety.

REFERENCES

1 **Lau WY, Leung TW, Yu SC, Ho SK:** Percutaneous local ablative therapy for hepatocellular carcinoma: a review and look into the future. Annals of surgery 2003;237:171-9.

2 **Masuda T, Beppu T, Ishiko T, Horino K, Komori H, Hayashi H, et al.:** Thermal Ablation Using Microwave Coagulation Therapy (MCT) and Radiofrequency Ablation (RFA) for Hepatocellular Carcinoma. Thermal medicine 2007;23:123-31.

3 **Guan YS, Liu Y:** Interventional treatments for hepatocellular carcinoma. Hepatobiliary Pancreat Dis Int 2006;5:495-500.

4 **Livraghi T:** Tumor dissemination after radiofrequency ablation of hepatocellular carcinoma. Hepatology (Baltimore, Md 2001;34:608-9; author reply 10-1.

5 **Tanaka S, Shimada M, Shirabe K, Taketomi A, Maehara S, Tsujita E, et al.:** Surgical radiofrequency ablation for treatment of hepatocellular carcinoma: an endoscopic or open approach. Hepato-gastroenterology 2009;56:1169-73.

6 **Poon RT, Ng KK, Lam CM, Ai V, Yuen J, Fan ST:** Radiofrequency ablation for subcapsular hepatocellular carcinoma. Annals of surgical oncology 2004;11:281-9.

7 **Jansen MC, van Hillegersberg R, Chamuleau RA, van Delden OM, Gouma DJ, van Gulik TM:** Outcome of regional and local ablative therapies for hepatocellular carcinoma: a collective review. Eur J Surg Oncol 2005;31:331-47.

8 **Beppu T, Ishiko T, Masuda T, Hayashi H, Komori H, Okabe H, et al.:** Endoscopic local ablation therapy (ELAT) for hepatocellulcar carcinoma. Thermal medicine 2007;2:63-70.

9 **Bruix J, Sherman M:** Management of hepatocellular carcinoma. Hepatology (Baltimore, Md 2005;42:1208-36.

10 **Stigliano R, Marelli L, Yu D, Davies N, Patch D, Burroughs AK:** Seeding following percutaneous diagnostic and therapeutic approaches for hepatocellular carcinoma. What is the risk and the outcome? Seeding risk for percutaneous approach of HCC. Cancer Treat Rev 2007.

11 **Livraghi T, Lazzaroni S, Meloni F, Solbiati L:** Risk of tumour seeding after percutaneous radiofrequency ablation for hepatocellular carcinoma. The British journal of surgery 2005;92:856-8.

12 **Mulier S, Mulier P, Ni Y, Miao Y, Dupas B, Marchal G, et al.:** Complications of radiofrequency coagulation of liver tumours. The British journal of surgery 2002;89:1206-22.

13 **Llovet JM, Vilana R, Bru C, Bianchi L, Salmeron JM, Boix L, et al.:** Increased risk of tumor seeding after percutaneous radiofrequency ablation for

single hepatocellular carcinoma. Hepatology (Baltimore, Md 2001;33:1124-9.

14 **Minami Y, Kudo M, Kawasaki T, Chung H, Ogawa C, Inoue T, et al.:** Percutaneous ultrasound-guided radiofrequency ablation with artificial pleural effusion for hepatocellular carcinoma in the hepatic dome. Journal of gastroenterology 2003;38:1066-70.

15 **Kondo Y, Yoshida H, Shiina S, Tateishi R, Teratani T, Omata M:** Artificial ascites technique for percutaneous radiofrequency ablation of liver cancer adjacent to the gastrointestinal tract. The British journal of surgery 2006;93:1277-82.

16 **Beppu T, Horino K, Komori H, Masuda T, Hayashi H, Okabe H, et al.:** Advances in endoscopic surgery for hepatocellular carcinoma. Journal of Microwave Surgery 2008;26:67-72.

17 **Ikai I, Arii S, Kojiro M, Ichida T, Makuuchi M, Matsuyama Y, et al.:** Reevaluation of prognostic factors for survival after liver resection in patients with hepatocellular carcinoma in a Japanese nationwide survey. Cancer 2004;101:796-802.

18 **Santambrogio R, Podda M, Zuin M, Bertolini E, Bruno S, Cornalba GP, et al.:** Safety and efficacy of laparoscopic radiofrequency ablation of hepatocellular carcinoma in patients with liver cirrhosis. Surgical endoscopy 2003;17:1826-32.

19 **Yokoyama T, Egami K, Miyamoto M, Watanabe H, Hasegawa H, Iida S, et al.:** Percutaneous and laparoscopic approaches of radiofrequency ablation treatment for liver cancer. Journal of hepato-biliary-pancreatic surgery 2003;10:425-7.

20 **Livraghi T, Solbiati L, Meloni MF, Gazelle GS, Halpern EF, Goldberg SN:** Treatment of focal liver tumors with percutaneous radio-frequency ablation: complications encountered in a multicenter study. Radiology 2003;226:441-51.

21 **Imamura J, Tateishi R, Shiina S, Goto E, Sato T, Ohki T, et al.:** Neoplastic seeding after radiofrequency ablation for hepatocellular carcinoma. The American journal of gastroenterology 2008;103:3057-62.

22 **Teramoto K, Kawamura T, Takamatsu S, Nakamura N, Kudo A, Noguchi N, et al.:** Laparoscopic and thoracoscopic approaches for the treatment of hepatocellular carcinoma. American journal of surgery 2005;189:474-8.

23 **Abe T, Shinzawa H, Wakabayashi H, Aoki M, Sugahara K, Iwaba A, et al.:** Value of laparoscopic microwave coagulation therapy for hepatocellular carcinoma in relation to tumor size and location. Endoscopy 2000;32:598-603.

24 **Hozumi M, Ido K, Hiki S, Isoda N, Nagamine N, Ono K, et al.:** Easy and accurate targeting of deep-seated hepatic tumors under laparoscopy with a forward-viewing convex-array transducer. Surgical endoscopy 2003;17:1256-60.

25 **Livraghi T, Meloni F, Di Stasi M, Rolle E, Solbiati L, Tinelli C, et al.:** Sustained complete response and complications rates after radiofrequency

ablation of very early hepatocellular carcinoma in cirrhosis: Is resection still the treatment of choice? Hepatology (Baltimore, Md 2008;47:82-9.

26 **Gillams AR:** Image guided tumour ablation. Cancer Imaging 2005;5:103-9.

27 **Xu HX, Lu MD, Xie XY, Yin XY, Kuang M, Chen JW, et al.:** Prognostic factors for long-term outcome after percutaneous thermal ablation for hepatocellular carcinoma: a survival analysis of 137 consecutive patients. Clinical radiology 2005;60:1018-25.

28 **Machi J, Bueno RS, Wong LL:** Long-term follow-up outcome of patients undergoing radiofrequency ablation for unresectable hepatocellular carcinoma. World journal of surgery 2005;29:1364-73.

29 **Lencioni R, Cioni D, Crocetti L, Franchini C, Pina CD, Lera J, et al.:** Early-stage hepatocellular carcinoma in patients with cirrhosis: long-term results of percutaneous image-guided radiofrequency ablation. Radiology 2005;234:961-7.

30 **Tateishi R, Shiina S, Teratani T, Obi S, Sato S, Koike Y, et al.:** Percutaneous radiofrequency ablation for hepatocellular carcinoma. An analysis of 1000 cases. Cancer 2005;103:1201-9.

31 **Raut CP, Izzo F, Marra P, Ellis LM, Vauthey JN, Cremona F, et al.:** Significant long-term survival after radiofrequency ablation of unresectable hepatocellular carcinoma in patients with cirrhosis. Annals of surgical oncology 2005;12:616-28.

32 **Yan K, Chen MH, Yang W, Wang YB, Gao W, Hao CY, et al.:** Radiofrequency ablation of hepatocellular carcinoma: Long-term outcome and prognostic factors. European journal of radiology 2008;67:336-47.

33 **Yamanaka Y, Shiraki K, Miyashita K, Inoue T, Kawakita T, Yamaguchi Y, et al.:** Risk factors for the recurrence of hepatocellular carcinoma after radiofrequency ablation of hepatocellular carcinoma in patients with hepatitis C. World J Gastroenterol 2005;11:2174-8.

34 **Izumi N, Asahina Y, Noguchi O, Uchihara M, Kanazawa N, Itakura J, et al.:** Risk factors for distant recurrence of hepatocellular carcinoma in the liver after complete coagulation by microwave or radiofrequency ablation. Cancer 2001;91:949-56.

FIGURE LEGENDS

Figure 1 A multinodular HCC successfully treated with the hybrid ablation. The percutaneous and endoscopic approach was both used in a session of ablation therapy. A HCC located in a deep-site in the liver (arrow) was ablated via the percutaneous approach (a, c) and a tumor located in superficial site of the liver (arrow head) was treated via the endoscopic approach (b, d).

Figure 2 Overall survivals in the hybrid and the pure endoscopic ablation group. Cumulative 5-year overall survival rates were similar, namely 42% and 40% in the two groups.