Perspective of the Treatment for Small Hepatocellular Carcinoma : Hepatic Resection or Radiofrequency Ablation ?

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Perspective of the Treatment for Small Hepatocellular Carcinoma: Hepatic Resection or Radiofrequency Ablation ?

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Abstract

The long-term outcome of hepatocellular carcinoma (HCC) patients is influenced by parameters related to the tumor and the underlying chronic liver disease (CLD). Surgical treatment includes hepatic resection (HR) and liver transplantation (LT). In HCC with mild or without CLD, resection is the treatment of choice; however, resection of the cirrhotic liver and/or steatotic liver always carries a high risk of intraoperative hemorrhage and postoperative hepatic failure. Thus, in the presence of cirrhosis, LT is considered to be the gold-standard in patients within Milan or UCSF criteria. Unfortunately, the shortage of liver donors restricts the availability of transplantation in a timely manner. Recently, short and long term results after HR for HCC patients with CLD have been improved due to both early detection and low morbidity. This improvement has led to a renewed interest in HR for HCC in the presence of CLD. Ablation techniques such as radiofrequency ablation therapy (RFA) have also been developed as a therapy for small HCC. The following article focuses on the current role of HR and RFA in the treatment of small HCC.

Key words: Hepatocellular carcinoma, Radiofrequency ablation therapy, Hepatic resection, Liver Damage

Introduction

Hepatocellular carcinoma (HCC) is a global health problem, ranking as the fifth most common cancer and the third most frequent cancer death worldwide.[1) Globally there are reports to indicate a rising incidence of HCC.[1,2) The highest rate is seen in the countries of South-East Asia and Africa, but the incidence of HCC has increased steadily, particularly in the Western counties. An etiologic association between hepatitis B viral infection and the development of HCC has been established with a relative risk 200 times greater than in non-infected individuals. Hepatitis C virus (HCV) is also proving an important etiologic factor for HCC with an incidence rate of 7% at 5years and 14% at 10 years. HCV infection is accounting for 80% of the cases in Japan and HCV, alcohol, and nonalcoholic steatohepatitis being responsible for most cases in the United States and Europe. Genetic, congenital, metabolic and environmental factors have also implicated in HCC occurrence. The prognosis depends on tumor stage and degree of liver disorder, which affect the tolerance to invasive treatments.

Although surgery remains the gold standard treatment for HCC in patients with or without cirrhosis, only 30% of patients are candidates for surgical resection. In a few percent of eligible patients, liver transplantation (LT) has also been employed. In addition to hepatic resection (HR) and LT, percutaneous ablation is also considered as a treatment option which offers a high rate of complete response and thus potential for a cure. In selected patients,

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a 5-year survival rate more than 60% can be achieved after surgery.[3-5] However, in patients with advanced HCC, the consequent improvement in long-term survival is still poor because of the high rate of recurrence or the development of intrahepatic metastases that disseminate via the portal vein or spread to other parts of the liver. Nevertheless, the management of HCC, especially in early stage of tumors, has showed major changes over the last few decades. For instance, earlier detection through various screening methods that use ultrasonographic evaluation and serological tumor-marker analyses (e.g. alpha-fetoprotein and des-gamma carboxyprothrombin) in high-risk populations has improved outcomes. More accurate patient assessment by using new-era imaging modalities contributes the selection between surgical and local treatment options.

Hepatic Resection for HCC

The determination of hepatic preserve is significant when HR is considered. The healthy liver has a great capability for regeneration and adjusts to the metabolic requirements of the host after HR due to hypertrophy of the residual liver. Therefore, even in patients with a large tumor, extensive resection is possible. In healthy liver, up to 70% of the parenchyma can be relatively removed with safe. Otherwise, the reduced functional preserve capacity in patients with cirrhosis of the liver limits the choice of surgical therapy.

The surgical procedure is usually selected based on the extent of the tumor and preservation of hepatic function, which was assessed by the classification of liver damage according to ICGR15, hepaplastine test, and a grade of hepatitis activity index (HAI) scores estimated by examination of preoperative fine-needle biopsies, as previously reported.[6-8] Furthermore, volumetric studies can be used to define the residual parenchyma exactly. If liver function allowed, anatomic resection (segmentectomy, sectoriectomy, and lobectomy or more) are employed, especially in Japan.[9,10] In the other cases, non-anatomic resection (partial resection and wedge resection) is performed.

Recent reports from several high-volume centers revealed a less than 5% mortality rate compared to a higher incidence reported 10 years ago.[3-5] Japanese surgeons including us also report very low mortality (< 1%).[11] Blood transfusion requirements have also been restricted from 80% to 20% in major reference centers. This was accomplished by bloodless techniques with intermittent inflow occlusion (i.e. the Pringle maneuver) and better selection of candidates with single lesion and absence of portal hypertension.[12] Numerous technical improvements such as the use of ultrasonographic dissectors and bipolar and argon beamer coagulation could diminish intra-operative blood loss.

For patients with inadequate or borderline remnant parenchyma, hypertrophy of the prospective liver remnant can be induced by preoperative portal vein embolization (PVE). In certain circumstances, an unfavorable location of the tumor and involvement of the confluence of the three hepatic veins and either the caval vein or the retrohepatic caval vein can render resection by conventional techniques impossible. In these rare cases, special techniques such as in situ resection or ex vivo bench surgery can be used.

The 5-year survival rate after resection in patients with solitary lesions of less than 5 cm, no vascular invasion, and a negative surgical margin of at least 1 cm, is reported to be greater than 70%.[13] However, in patients with cirrhosis, despite a decrease in the operative mortality rate and improved results after HR, overall survival after the resection of HCC has increased a little due to absence of effective adjuvant treatment to eliminate postoperative recurrence. Several reports show that postoperative chemoprevention using newer antiviral agents (e.g. interferon-alpha and lamivudine) seem to prolong the disease-free survival by decreasing the occurrence of the secondary growth of new tumor.[14-17]

Radiofrequency Ablation (RFA) for HCC

Percutaneous ethanol injection (PEI) and Radiofrequency ablation (RFA) are the most common ablation techniques worldwide. RFA of liver tumors was pioneered in 1993 by Rossi et al.[18] There is also evidence that percutaneous RFA is superior to EI and should be preferred for the treatment of small HCC among available ablation techniques.

RFA induces deep thermal injury in hepatic tissue while sparing the normal parenchyma. Its basic principle includes generation of high-frequency alternating current (400 MHz) which causes ionic agitation and conversion to heat, with subsequent evaporation of intracellular water which leads to coagulation necrosis.

The area of the injury depends on the size, position and shape of the electrode used. RFA has been performed by percutaneous, laparoscopic or open techniques.[19,20] Percutaneous RFA is usually performed under sedation against severe pain. The disadvantages of this method are considered the inability for vascular inflow occlusion through percutaneous approach, and difficult access to deep tumors located near blood vessels, or neighboring the diaphragm or the bowel. In Japan, even primary tumor is treated percutaneously, however, the main indication is recurrences after open procedures and patients with poor performance status in Europe. The electrode is placed through normal liver tissue close to the tumor margin and guided by ultrasound (US). The tissue is ablated at a temperature > 90 °C for 5-12 minutes or until the impedance increases rapidly although multiple overlapping ablations are necessary to completely destroy a tumor exceeding 3cm in diameter.

Applying RFA through an open procedure may contribute better access and visualization of nodules than laparoscopic or percutaneous delivery, while at the same time adjacent structures can be securely safeguarded.[21,22] Intraoperative ultrasonography provides very good resolution of the tumor and RFA treatment, giving this way the operator the chance to treat the lesion adequately.[21] All these factors seem to increase long-term oncological control provided by surgical RFA compared to percutaneous RFA.[11,21] Limitations related to the physics of the RFA process is larger than that of HR. Tissue charring causes increased impedance that results in decreased energy absorption and a smaller treated tissue volume. Although large amounts of tissue can be ablated in vitro, the charring and “heat sink phenomenon” are difficult to overcome. Radiographic assessment of the ablated lesion should be delayed for 2-4 weeks following treatment due to the inability to distinguish between edematous tissue surrounding the lesion and a residual tumor early after the ablation. The extent of necrosis can be more accurately assessed by helical CT, MRI or a color Doppler scan with bubble contrast.

HR versus RFA for Small HCC

Although numerous studies have shown the benefits of RFA,[23-25] there are some retrospective studies comparing resection versus ablation for small HCC.[11,26,27,28,29,30] (Table 1) They show better disease-free and overall survival rates for patients who undergo HR compared to those treated by RFA. However this benefit was clearer for lesions above 3 cm in diameter. For small HCC including tumors less than 3 cm an equivalent outcome for HR and RFA was demonstrated in three studies[26,28,30] although the findings have to be interpreted with caution due to non-randomization.

In other reports, Yu et al.[31] also reported a beneficial effect of HR compared with RFA in 105 HCC patients. They showed differences in recurrence rates (resection 19%, RFA 39%) and disease-free interval after treatment (resection 392 days, RFA 160 days). Otherwise, Ikeda et al.[32] showed that the cost-effectiveness of RFA for the treatment of small HCC was superior to that of surgery. Hong et al.[27] also reported that RFA was as effective as HR for the treatment of single small HCC in patients with well-preserved liver function, in terms of the incidence of remote recurrence and the patients’ likelihood of achieving overall and/or recurrence-free survival.

As shown in Table 1, the Liver Cancer Study Group of Japan[33] published a large, prospective study, including 7185 patients with small HCC (less than 3 lesions with each and smaller than 3 cm in diameter). All patients had the grade of Liver Damage A or B cirrhosis mostly due to hepatitis C. The cohort were divided into those undergoing HR (n = 2857) versus percutaneous ablation with RFA (n = 3022). The comparison of the groups showed that the time-to-recurrence rate was significantly lower for the resection group. Locoregional ablation by RFA was an independent predictor of poorer outcomes in terms of recurrence compared to HR in the multivariate analysis. Although patients in the resection group had better liver function in regard to Liver Damage with ICG clearance, implying that the groups are not homogenous; however, the size of the study is huge and expresses the heterogenicity of this disease within a regular day basis.

A different series of procedures comes from the Surveillance, Epidemiology and End Results (SEER) database[34]. During the period of 1998 - 2003, patients with HCC within the Milan criteria (< 5 cm or no more than three lesions of < 3 cm in largest diameter) were selected based on absence of extrahepatic disease and vascular invasion. In this series, the actuarial overall survival was compared for LT (n = 428), HR (n = 426), and ablation (n = 328). LT had the best outcome followed by HR and locoregional ablation. HR had also a significant better long-term survival rate compared to ablation. In the

Table 1. Summary of the studies comparing hepatic resection (HR) versus local ablative therapies for HCC.

Author (Ref. no)	Year (Study period)	Study type (Comparison)	Liver function	Tumor number & size	Outcome
Vivarelli M (26)	2004 (1998-2002)	Retrospective (HR (n=79) vs. RFA (n=79)	Child A/B	ND ND	Better disease-free and overall survival for HR
Hong SN (27)	2005 (1999-2001)	Retrospective (HR (n=93) vs. RFA (n=55)	Child A	Solitary < 4cm	Lower tumor recurrence for HR
Huang GT (35)	2005 (1998-2002)	RCT (HR (n=38) vs. PEI (n=38)	Child A/B	<= 2 < = 3cm	Equivalent recurrence and survival
Wakai T (28)	2006 (1990-2002)	Retrospective (HR (n=85) vs. Ablation (n=64)	ND	ND < 4cm	Lower tumor recurrence and better survival for HR
Chen MS (36)	2006 (1999-2004)	RCT (HR (n=90) vs. RFA (n=71)	Child A (ICG < 30%)	Solitary < 5cm	Equivalent disease-free and overall survival
Lupo L (29)	2007 (1999-2006)	Retrospective (HR (n=42) vs. RFA (n=60)	Child A/B	Solitary 3-5cm	Equivalent disease-free and overall survival
Guglielmi A (30)	2008 (1996-2006)	Retrospective (HR(n=91) vs. RFA (n=109)	Child A/B	ND < 6cm	Better disease-free and overall survival for HR
Abu-Hilal M (37)	2008 (1991-2003)	Matched cohort (HR (n=34) vs. RFA (n=34)	Child A/B	Solitary 1-5cm	Better disease-free survival for HR
Schwarz RE (34)	2008 (1998-2003)	SEER database (HR (n=426) vs. Ablation (n=328)	ND	Milan Milan	Better overall survival for HR
Hasegawa K (33)	2008 (2000-2003)	Prospective survey (HR (n=2,857) vs. RFA (n=3,022)	Child A/B	< 3 < 3cm	Lower tumor Recurrence for HR
Ueno S (11)	2009 (2000-2005)	Prospective survey (HR (n=123) vs. RFA (n=110)	Liver damage A/B	Milan Milan	Better disease-free and overall survival for HR

ND, not defined; RCT, randomized controlled trial; SERR, surveillance epidemiology and end results; RFA, radiofrequency ablation; PEI, percutaneous ethanol injection; ICG 15, indocyanine-green retention at 15min; Milan criteria: single lesion < 5cm , or no more than three lesions < 3cm.

multivariate analysis, HR was superior to ablation.

So far, two randomized controlled trials (RCTs) comparing HR and ablation have been published[39,40]. The RCT by Huang et al.[35] used PEI as the ablative method. He included patients with less than 2 lesions smaller than 3 cm each. Similar recurrence and overall survival was reported but had significant drawbacks such as a small sample size and the fact that it was not based on a power calculation. In the other RCT, Chen et al. used RFA, meanwhile, 19 of 90 patients (21%) who were randomized for RFA converted to HR[36]. These facts demonstrate the need for further RCTs comparing HR versus percutaneous ablation for small HCC in patients with preserved liver function and absence of portal hypertension. In conclusion, HR and local ablation such as RFA are effective treatment modalities for small HCC. Although two RCTs found equivalent outcomes for HR and ablation, there is evidence from the large US and Japanese series reviewed herein that HR offers a better outcome than locoregional ablation. Since the majority of data comes from retrospective studies, further RCTs are warranted to define the exact value of HR and RFA for small HCC.

It is our belief [11], that in patients with small HCCs within the Milan criteria, HR should still be employed for those patients with a single tumor and well-preserved liver function. RFA should be chosen for patients with an unresectable single tumor or those with multinodular tumors, regardless of the grade of liver damage. In order to increase long-term oncological control, surgical RFA seems preferable to percutaneous RFA, if the patient's condition allows them to tolerate surgery.

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小肝癌治療の展望：肝切除ならびにラジオ波焼灼療法の対比から

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肝細胞癌患者の長期予後は、腫瘍ならびに非癌部肝組織障害度の双方により規定される。

外科的治療としては肝切除と肝移植が挙げられるが、肝障害がないか軽度の患者は肝切除のよい適応である。しかしながら、肝硬変や脂肪肝を伴う場合には、常に術中出血や術後肝不全の高い危険性を伴う。それ故、肝硬変合併で、かつミラノあるいはUCSF基準内肝癌においては肝移植がゴールドスタンダードであるが、至適時期にそれを行うにはドナー確保の面での制限もあり容易ではない。

最近の肝切除の短期・長期予後は、早期発見と手術合併症軽減策により向上してきている。さらに、ラジオ波焼灼療法のような局所療法も小肝癌治療として進歩してきている。本稿では、小肝癌治療における肝切除とラジオ波焼灼療法の役割に焦点をあて詳述する。