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Role of hepatectomy for recurrent or initially unresectable hepatocellular carcinoma

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Abstract

As a result of donor shortage and high postoperative morbidity and mortality after liver transplantation, hepatectomy is the most widely applicable and reliable option for curative treatment of hepatocellular carcinoma (HCC). Because intrahepatic tumor recurrence is frequent after loco-regional therapy, repeated treatments are advocated provided background liver function is maintained. Among treatments including local ablation and transarterial chemoembolization, hepatectomy provides the best long-term outcomes, but studies comparing hepatectomy with other nonsurgical treatments require careful review for selection bias. In patients with initially unresectable HCC, transarterial chemo- or radio-embolization, and/or systemic chemotherapy can down-stage the tumor and conversion to resectable HCC is achieved in approximately 20% of patients. However, complete response is rare, and salvage hepatectomy is essential to help prolong patients' survival. To counter the short recurrence-free survival, excellent overall survival is obtained by combining and repeating different treatments. It is important to recognize hepatectomy as a complement, rather than a contraindication, to other nonsurgical treatments in a mul-

tidisciplinary approach for patients with HCC, including recurrent or unresectable tumors.

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Key words: Hepatocellular carcinoma; Hepatectomy; Repeat hepatectomy; Conversion therapy; Multidisciplinary treatment

Core tip: Previous studies comparing hepatectomy with other nonsurgical treatments for hepatocellular carcinoma (HCC) evaluated which provided superior survival benefit. However, considering the high recurrence rate after curative loco-regional treatment, and limited indications for hepatectomy because of background liver damage, it is important to recognize hepatectomy as a complement to other nonsurgical treatment, rather than a contraindication. A multidisciplinary approach combining and repeating different treatments prolongs patients' survival with HCC, including those with recurrent or initially unresectable tumors.

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INTRODUCTION

Liver transplantation is the most promising strategy for radical treatment for hepatocellular carcinoma (HCC) because it eradicates both the tumors and the background damaged liver; hepatectomy is second. However, high perioperative morbidity and mortality, and a shortage of donors limit application of liver transplantation. Poon *et al*^[1,2] reported that although the risk of postoperative

Table 1 Repeat resection rate, 5-year recurrence-free survival rate, and overall survival rate after repeat hepatectomy in previous studies

Ref.	Year	Number of primary hepatectomy	Number of second hepatectomy/HCC recurrence after primary hepatectomy	5-yr recurrence free survival after repeat hepatectomy	5-yr overall survival after repeat hepatectomy
Poon <i>et al</i> ^[4]	1999	244	11/105 (10%)	NA	69%
Nakajima <i>et al</i> ^[7]	2001	94	12/57 (21%)	Not reached	52%
Sugimachi <i>et al</i> ^[8]	2001	474	78/300 (26%)	NA	47.50%
Minagawa <i>et al</i> ^[9]	2003	334	56/183 (31%)	17%	56%
Chen <i>et al</i> ^[5]	2004	627	34/286 (12%)	NA	56.80%
Taura <i>et al</i> ^[10]	2006	610	55/465 (12%)	NA	NA
Itamoto <i>et al</i> ^[11]	2007	483	70/279 (25%)	10%	50%
Shimada <i>et al</i> ^[12]	2007	319	13/211 (6%)	NA	25%
Tralhão <i>et al</i> ^[6]	2007	190	16/97 (19%)	NA	31%
Liang <i>et al</i> ^[13]	2008	NA	73/853 (9%)	10.50%	27.60%
Choi <i>et al</i> ^[14]	2008	353	9/97 (9%)	NA	78%
Wu <i>et al</i> ^[15]	2009	1177	149/641 (23%)	31.80%	56.40%
Kishi <i>et al</i> ^[6]	2011	221	8/134 (6%)	NA	37.50%
Huang <i>et al</i> ^[17]	2012	NA	82/NA	8.20%	22.40%
Tsujita <i>et al</i> ^[18]	2012	NA	112/NA	NA	67.30%
Yamashita <i>et al</i> ^[19]	2013	791	163/308 (53%)	29%	60%

HCC: Hepatocellular carcinoma; NA: Not assessed.

tumor recurrence was low after transplantation, the long-term prognosis after transplantation was comparable to patients who underwent hepatectomy among patients with Child-Pugh class A background liver disease. Therefore, hepatectomy remains a reliable and widely applicable surgical treatment; however, the main limitation is that it is not indicated in patients with impaired liver function resulting from cirrhosis irrespective of the etiology of the liver disease. Multimodal therapy combining nonsurgical treatments including local ablation and transarterial chemoembolization (TACE) with hepatectomy and/or liver transplantation have been advocated for recurrent HCC, multinodular HCC, or initially unresectable HCC. This review was aimed to evaluate the role of hepatectomy among the various treatments for recurrent or advanced HCC.

Hepatectomy for recurrent HCC following local treatment

Because HCC usually develops in the injured liver, tumors frequently recur even after curative local treatment. The incidence of intrahepatic recurrence within 2 years after primary hepatic resection is 70%^[3]. However, because recurrences occur most commonly in the remnant liver, comprising 85%-90% of initial recurrence sites^[3], repeat hepatectomy or other local treatment is indicated. In general, treatments are selected based on the same criteria as the primary HCC. Several studies compared the results of repeat hepatectomy with nonsurgical treatment and showed that repeat hepatectomy was associated with a better prognosis^[4-6]. However, these studies were retrospective analyses and may have included the selection bias that the repeat hepatectomy group usually included patients with better background liver function and less multinodular tumors. Repeat hepatic resection is indicated for only a limited proportion of patients (6%-53%) and the 5-year overall survival after second

hepatectomy is reported as 22%-78%^[4-19]. The repeat resection rate, 5-year recurrence-free survival rate, and overall survival rate after second hepatectomy in these studies are summarized in Table 1. The difference in the survival rate would probably have been influenced by the difference in the background liver damage, types of recurrence, and tumoral factors such as size, number, and vascular invasions, but precise assessment was difficult due to the insufficient data. A small number of studies reported the outcomes after a third or fourth hepatectomy^[15,19]. In the two series evaluating the outcomes of 1117 and 791 patients who underwent primary hepatectomy for HCC, a second, third, and fourth hepatectomy was performed in 23% (149/641) and 53% (163/308), 37% (35/96), and 65% (36/55), and 27% (8/30) and 69% (9/13) of the patients with recurrence, respectively. Five-year overall survival after a second and third hepatectomy was 56% and 59% in Wu *et al*'s^[15] series and 60% and 43% in Yamashita *et al*'s^[19] series, respectively. Factors related to both primary and recurrent tumors such as tumor size, number, and vascular invasion and also the degree of background liver damage as assessed by Child-Pugh class, indocyanine green retention rate, or platelet counts were reported as prognostic predictors. Recurrence-free interval and/or type of recurrence, multicentric occurrence or intrahepatic metastases^[17,20], were also commonly reported to be prognostic predictors in several studies. Intrahepatic metastases usually occur *via* the portal vein, and are therefore associated with portal vein invasion. Distinction of them is important because intrahepatic recurrence is associated with malignant behavior compared to multicentric occurrence. Differentiation is possible by histopathological examination as defined by the Liver Cancer Study Group of Japan (Table 2)^[21] but there is no established method to differentiate intrahepatic metastases *vs* multicentric occurrence preoperatively, an issue requiring further research.

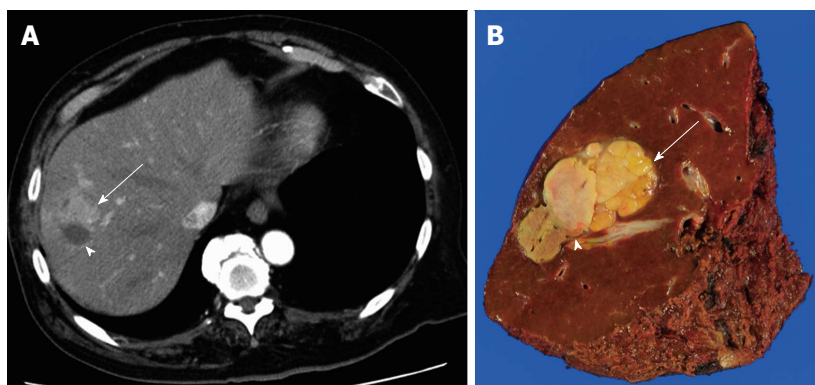


Figure 1 Recurrent hepatocellular carcinoma adjacent to a radiofrequency ablation scar. A: Computed tomography showing the tumor with unclear borders with arterial enhancement (arrow) adjacent to the scar (arrowhead); B: Cut surface of the resected specimen showing the recurrent tumor (arrow) and radiofrequency ablation scar (arrowhead).

Table 2 Three types of definition of intrahepatic metastases by the Liver Cancer Study Group of Japan^[21]

	Definition
1	Tumors clearly growing from portal vein tumor thrombi
2	Tumors surrounding a large main tumor with multiple satellite nodules
3	A small solitary tumor that is near the main tumor and histologically similar to or less differentiated than the main tumor

It is important that hepatectomy and other local treatments be considered complementary and not exclusive. The dissociation between low recurrence-free survival and rather high overall survival shown in Table 1 reflects the slow progression of the disease and the importance of repeating treatment, usually TACE. Repeating locoregional treatment such as ethanol injection (PEI), radiofrequency ablation (RFA), or TACE, for intrahepatic recurrence prolongs patient survival^[10,22-25], and provides a comparable prognosis after RFA compared with repeat hepatectomy^[7,12,13,24]. Taura *et al*^[10] compared the long-term outcomes of 610 patients with HCC who underwent hepatectomy before 1990 and after 1991. There was no change in the disease-free survival (early *vs* late period, 28% *vs* 26%, respectively, at 5 years), but survival after tumor recurrence increased significantly in the later period (12% *vs* 22% at 5 years) and overall survival also improved (39% *vs* 58% at 5 years). The authors concluded that increased application of RFA to solitary intrahepatic recurrence, which was the most common type of recurrence, contributed to the improved prognosis^[10]. Kishi *et al*^[16] reported that the number rather than the type of treatment for tumor recurrence was associated with prolonged survival.

As was referred in the beginning of the introduction, liver transplantation is the most promising, and salvage liver transplantation for recurrent HCC, which have been reported with 5-year survival rate of 54%-61% could be a choice of treatment because these figures were comparable with that after primary liver transplantation for HCC that was 59%-72%^[26-29]. However, shortage of do-

nor organ, expensive medical costs, and contraindication for elderly patients preclude popularization of this strategy. Indication for salvage transplantation have not been established, but various factors including recurrence free survival, microvascular involvement, satellite nodules, as well as tumor number and size at the time of primary hepatectomy and/or transplantation should be considered. Further, intention-to-treat analyses comparing patients who underwent hepatectomy with liver cirrhosis of potentially eligible for transplantation and patients listed for primary liver transplantation showed comparable overall (5-year survival; hepatectomy *vs* listed for transplantation; 66% *vs* 58%; *P* = NS) and disease-free (41% *vs* 54%; *P* = NS) survival mainly due to the influence of waiting period^[30]. Another intention-to treat analysis also showed the limited value of salvage transplantation with only 28% of transplantability rate and comparable prognosis with the patients with liver resection^[31].

Salvage hepatectomy for refractory HCC after other local treatment

Here, the term “refractory HCC” is defined as HCC recognized as remnant, unresponsive, or locally recurred tumor at the site treated with locoregional treatment such as ablation or TACE. The indications for hepatectomy are dictated by the degree of background liver damage, while the indications for RFA are limited less by the degree of liver damage and more by tumor size and location, especially with respect to major vascular structures. We occasionally experience difficult complete resection after local recurrence or remnant HCC after RFA because of unclear tumor borders (Figure 1). Several studies have shown that locally recurrent HCCs after RFA were more invasive because of lower tumor differentiation grade, capsule invasion, and vascular invasion, resulting in the need for extensive liver resection with increased operation time and blood loss^[32-36]. In such cases, repeat RFA is rarely indicated and salvage hepatectomy should be the first-choice treatment. The mechanism of aggressive tumor behavior is not clear. Increased intratumoral pressure by RFA may favor intravascular tumor spread^[37,38]. Diffi-

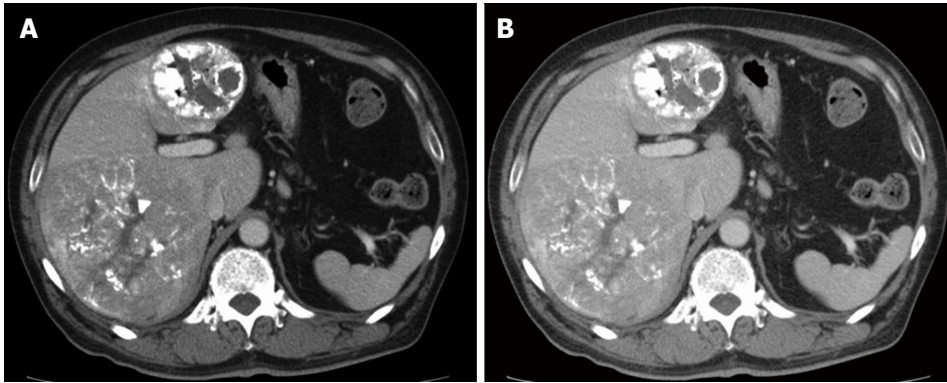


Figure 2 Multinodular hepatocellular carcinomas. Transarterial chemoembolization achieved complete response in one tumor in segment IV with accumulation of lipiodol showing no arterial enhancement in contrast to the other tumor in segments VI and VII that was enhanced in the arterial phase (A) and washed out in the portal phase (B).

culty in early diagnosis of recurrence because of blended necrotic and active areas without a clear delineation may also be a factor^[34]. Although recurrence after salvage hepatectomy for these recurrent tumors is frequent, with 5-year recurrence-free survival of 0%-33%, 5-year overall survival is reported as 43%-67%^[34-36]. Whether surgical resection or RFA should be selected for HCC that are amenable to both treatments is a controversial issue^[39,40], and which is better is still in debate. In a randomized controlled trial by Huang *et al.*^[41] comparing surgical resection and RFA in patients with HCC meeting the Milan criteria^[42], 115 patients were enrolled in each group and both recurrence-free and overall survival was better in the resection group (resection *vs* RFA: 5-year recurrence-free survival, 51.3% *vs* 28.7%, $P = 0.017$; 5-year overall survival, 75.7% *vs* 54.8%, $P = 0.001$)^[41]. Hasegawa *et al.*^[43] reported the results of a Japanese nationwide survey comparing the results of surgical resection, RFA, and PEI in patients with no more than three HCC tumors and with none over 3 cm. A total of 12968 patients with 5361, 5548, and 2059 patients undergoing surgical resection, RFA, and PEI, respectively, were analyzed, and the 5-year recurrence was 63.8%, 71.7%, and 76.9%, respectively (surgical resection *vs* RFA, $P = 0.0001$; RFA *vs* PEI, $P = 0.0001$) and the 5-year overall survival was 71.1%, 61.1%, and 56.3%, respectively (surgical resection *vs* RFA, $P = 0.0001$; RFA *vs* PEI, $P = 0.005$). Although these were the outcomes for the treatment of primary HCC and there have been no established evidence suggesting which of the hepatectomy or ablation is better first choice for recurrent HCC, these results suggest that surgical resection should be selected as a first-line treatment for HCC that is amenable to either surgical resection or ablation, and curative resection should be attempted for local recurrence after ablation for as long as possible.

In the treatment of multinodular HCC, surgical resection can be complementary with other nonsurgical therapies to obtain good long-term prognosis even though TACE is usually indicated for multinodular HCC, rather than surgical resection. The guidelines for HCC treatment from the American Association for the Study of Liver

Diseases and the European Association for the Study of the Liver^[44,45], based on the Barcelona Clinic Liver Cancer criteria^[46] recommend hepatic resection only for patients with solitary tumor without portal hypertension. In the Japanese guidelines, surgical resection is indicated for patients with up to three tumors. For four or more tumors, TACE or transarterial infusion is indicated as the first-choice treatment^[47]. We occasionally experience multinodular HCCs treated with repeated TACE showing complete necrosis of a large proportion of the tumors with a small number of remnant viable tumors (Figure 2). It is still unclear whether salvage hepatic resection of the remaining viable tumors is beneficial. A small number of studies have shown benefits with a multimodal approach by combining hepatic resection with simultaneous ablation^[48] or reduction surgery followed by ablation and adjuvant TACE or arterial infusion therapy^[49]. However, these were retrospective studies with a small number of patients and the details of the exact number of tumors were not provided. Furthermore, differentiation between intrahepatic metastasis and multicentric occurrence is important, as discussed earlier, and criteria as to the number of nodules indicated for hepatectomy remains unclear.

Hepatectomy for down-staged HCC for initially unresectable tumors

In contrast to colorectal liver metastases, in which systemic chemotherapy and/or hepatic artery infusion chemotherapy can convert the unresectable tumor to resectable in > 40% of patients^[50-52], HCC conversion therapy has not been established.

Yao *et al.*^[53] proposed the University of California, San Francisco down-staging protocol inclusion criteria for liver transplantation as: (1) one lesion > 5 cm and up to 8 cm; (2) two to three lesions with at least one lesion > 3 cm and not exceeding 5 cm, with a total tumor diameter up to 8 cm; or (3) four to five lesions with none > 3 cm, with a total tumor diameter up to 8 cm. The authors reported that down-staging was successful in 43/61 patients (71%) and 35 patients underwent liver transplantation with a 4-year survival after transplantation

of 92%^[53]. Lei *et al*^[54] applied the criteria to hepatectomy and reported the outcomes of 66 of 102 patients (59%) with successful down-staging by TACE and/or RFA. Of the 66 patients, 31 and 35 patients underwent liver transplantation and hepatectomy, respectively, and both recurrence-free (68% and 60% at 5 years, respectively) and overall survival (77% and 69% at 5 years, respectively) were comparable^[54]. TACE and/or hepatic artery infusion therapy is usually used as the down-staging treatment. The conversion rate from unresectable to resectable HCC by these modalities was reported as 13%-18%, with a 5-year survival of 49%-56%^[55,56].

In contrast to colorectal liver metastases, in which pathologic response is correlated with the prognosis after curative hepatectomy^[57], such correlation was not necessarily confirmed in patients with HCC. Of note, Ravaioli *et al*^[58] reported that incomplete necrosis by TACE was an independent predictor of poor recurrence-free survival after liver transplantation. Furthermore, several studies showed that preoperative TACE was associated with an increased risk of extrahepatic metastases^[59-61]. This might be explained by Adachi *et al*^[62] hypothesis that viable HCC cells are less firmly attached and likely to spill into the bloodstream during intraoperative manipulation after incomplete response to TACE. Because complete necrosis is rarely obtained, especially for large tumors, the routine application of preoperative TACE for resectable HCC is not recommended. However, based on results showing that a proportion of patients can undergo curative resection following down-staging by TACE and obtain long-term survival, aggressive loco-regional treatment to attempt curative resection should be adopted in patients with initially unresectable HCCs.

The development of other treatment strategies for unresectable HCC such as radioembolization by yttrium-90^[63] or systemic treatment combining cisplatin/interferon α -2b/doxorubicin/fluorouracil (PIAF)^[64] may increase the rate of conversion. Lau *et al*^[65] reported that 49 of 285 patients (17%) underwent salvage surgery following down-staging by intra-arterial yttrium-90 microspheres or PIAF for initially unresectable HCC and obtained a 5-year survival rate of 57%. Notably, 8 of the 49 patients had extrahepatic metastases initially and these patients also obtained long-term survival with a 5-year survival rate > 40% and neither the extension of the disease nor the degree of tumor pathologic response was associated with the prognosis. Although relatively high response rates are obtained with PIAF, frequent adverse events such as neutropenia and thrombocytopenia preclude wide application, especially in patients with cirrhosis^[64,66]. In a recent study by Kaseb *et al*^[67], an independent predictor of an objective response to PIAF was the use of five or more cycles. The authors suggested that patient selection is important because only responding patients will have an improved prognosis with curative hepatectomy.

To discuss the issue of conversion, it should be noted that the definition of “unresectable” cannot be unani-

mous and differ according to extension of the tumor, background liver function, and surgeons' judgments. It is also important to recognize that “technically” and “oncologically optimally” resectable are not necessarily the same. It is, however, certain that conversion rate for HCC is still unsatisfactory and the all reports referred above are retrospective studies with small number of patients. Further development of effective treatment for downstaging is expected.

CONCLUSION

Although hepatectomy is indicated for only a small proportion of patients with recurrent or down-staged HCC after primary treatment, an excellent prognosis is obtained if curative resection is achieved, especially for tumors with a multicentric occurrence pattern, rather than intrahepatic metastases. Preoperative differentiation of the two patterns is a future research issue. Even in initially unresectable HCCs, hepatectomy plays a key role in a multidisciplinary approach.

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