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TOPIC HIGHLIGHT

WJH 6th Anniversary Special Issues (2): Hepatocellular carcinoma

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

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 *et al*[4]	1999	244	11/105 (10%)	NA	69%
Nakajima *et al*[7]	2001	94	12/57 (21%)	Not reached	52%
Sugimachi *et al*[8]	2001	474	78/300 (26%)	NA	47.50%
Minagawa *et al*[9]	2003	334	56/183 (31%)	17%	56%
Chen *et al*[5]	2004	627	34/286 (12%)	NA	56.80%
Taura *et al*[10]	2006	610	55/465 (12%)	NA	NA
Itamoto *et al*[11]	2007	483	70/279 (25%)	10%	50%
Shimada *et al*[12]	2007	319	13/211 (6%)	NA	25%
Tralhão *et al*[6]	2007	190	16/97 (19%)	NA	31%
Liang *et al*[13]	2008	NA	73/853 (9%)	10.50%	27.60%
Choi *et al*[14]	2008	353	9/97 (9%)	NA	78%
Wu *et al*[15]	2009	1177	149/641(23%)	31.80%	56.40%
Kishi *et al*[16]	2011	221	8/134 (6%)	NA	37.50%
Huang *et al*[17]	2012	NA	82/NA	8.20%	22.40%
Tsujita *et al*[18]	2012	NA	112/NA	NA	67.30%
Yamashita *et al*[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.

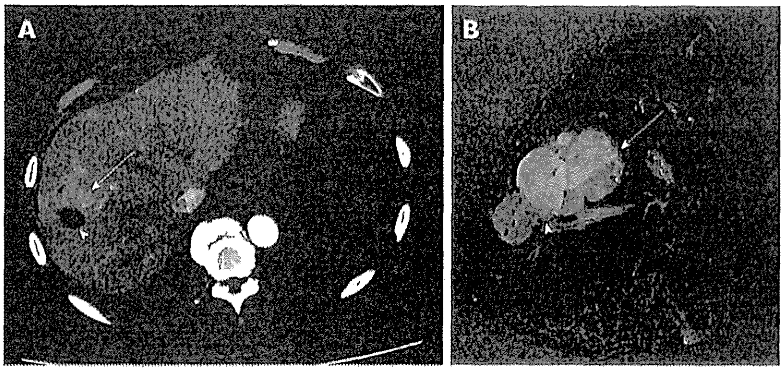

Figure 1 **Recurrent hepatocellular carcinoma adjacent to a radiofrequency ablation scar.** A: Computed tomography showing the tumor with unclear borders with arterial enhancement (arrow) adjacent to the scar (arrowhead); B: Cut surface of the resected specimen showing the recurrent tumor (arrow) and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

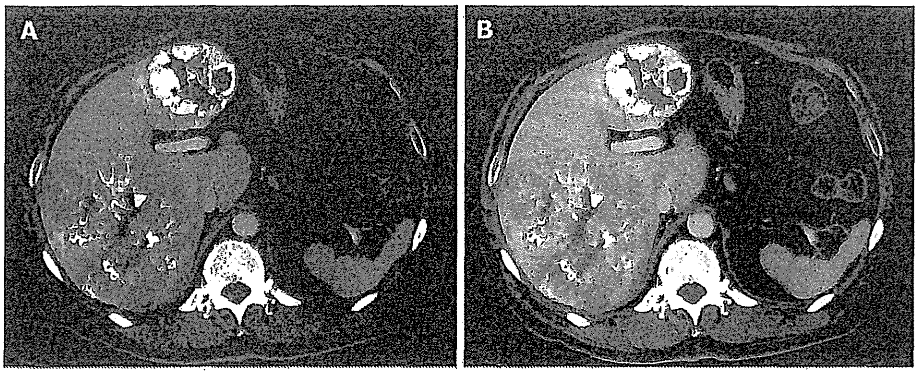

Figure 2 Multinodular hepatocellular carcinomas. Transarterial chemoembolization achieved complete response in one tumor in segment Ⅳ with accumulation of lipiodol showing no arterial enhancement in contrast to the other tumor in segments Ⅵ and Ⅶ that was enhanced in the arterial phase (A) and washed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

Multicentre analysis of long-term outcome after surgical resection for gastric cancer liver metastases

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Background: The efficacy of surgical resection for gastric cancer liver metastases (GCLMs) is currently debated. Hitherto, no large-scale clinical studies have been conducted.

Methods: This retrospective multicentre study analysed a database of consecutive patients with either synchronous or metachronous metastases who underwent surgical R0 resection for GCLM between 1990 and 2010. Clinical data were collected from five cancer centres in Japan. Survival curves were assessed, and clinical parameters were evaluated to identify predictors of prognosis.

Results: A total of 256 patients were enrolled. The mean(s.d.) number of hepatic tumours resected was 2·0(2·4). The surgical mortality rate was 1·6 per cent. Median follow-up was 65 (range 1–261) months. Recurrences were detected in 192 patients (75·0 per cent). The median interval from hepatic resection to recurrence was 7 (range 1–72) months, and the dominant site of recurrence was the liver (72·4 per cent). Actuarial 1-, 3- and 5-year overall and recurrence-free survival rates were 77·3, 41·9 and 31·1 per cent, and 43·6, 32·4 and 30·1 per cent, respectively. Median overall and recurrence-free survival times were 31·1 and 9·4 months respectively. Multivariable analysis identified serosal invasion of the primary gastric cancer (hazard ratio (HR) 1·50; $P = 0·012$), three or more liver metastases (HR 2·33; $P < 0·001$) and liver tumour diameter at least 5 cm (HR 1·62; $P = 0·005$) as independent predictors of poor survival.

Conclusion: Clinically resectable GCLM is rare, but strict and careful patient selection can lead to long-term survival following R0 surgical resection.

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Introduction

Gastric cancer is the most common form of cancer and the second leading cause of cancer death in Japan[1]. Gastric cancer is of major importance, not only in East Asian countries but also globally; it has the sixth highest incidence and is the fourth leading cause of cancer deaths worldwide[2]. Early detection by screening, R0 surgery with D2 lymph node dissection, and appropriate perioperative chemotherapy have improved its prognosis[1], but distant metastases are associated with reduced survival. The liver is a common site of distant metastasis from gastric cancer[3]. Surgical resection is now widely accepted as a potentially curative treatment for colorectal liver metastases, with reported 5-year survival rates of 40–56 per cent[4,5], and its indication has been expanded by progress in surgical procedures and perioperative chemotherapy. Gastric cancer liver metastases (GCLMs) show more aggressive oncological behaviour and heterogeneous characteristics[6]. Other metastatic extrahepatic lesions, such as peritoneal seeding or extensive lymph node metastases, are frequently present, leading to a dismal prognosis and debatable benefits of surgical resection. GCLM is generally considered a systemic disease with an unfavourable prognosis, and chemotherapy is regarded as the first-choice treatment[7,8].

On the other hand, some Japanese surgeons have performed hepatectomy for resectable GCLMs in selected patients. Several publications[9–17] have reported 5-year survival rates of 0–42 per cent after curative resection for GCLMs, but these enrolled only small numbers of patients (fewer than 70), mostly from a single institution. Based on multivariable analysis, many favourable prognostic factors have been suggested, including negative margin (R0) resection, small number of liver metastases, unilobular lesions, small tumour size, absence of serosal exposure of the primary tumour, and synchronous resection. However, the small scale and retrospective design of these studies has limited the value of the results, emphasizing the need for large-scale studies or randomized clinical trials.

However, the rarity of GCLMs makes large randomized studies difficult. To overcome this problem, a retrospective multicentre study was conducted based on a common database from five major cancer centres in Japan. The aims of the study were to evaluate the long-term oncological outcomes of hepatic resection for GCLMs, and to identify prognostic factors for resectable GCLMs using a relatively large patient database.

Methods

This retrospective, multicentre study analysed data from consecutive patients who underwent surgery for GCLMs between January 1990 and December 2010 at five cancer centres in Japan. Surgeons from each hospital provided specified preoperative, operative and postoperative data, using a common database that incorporated precise coding instructions. The data collected were analysed at a data centre in the National Cancer Centre Hospital East, with support from a statistician. The following data concerning hepatic resection were included in the database: age at hepatic resection; sex; timing of hepatic disease (metachronous or synchronous); cause of death; levels of serum carcinoembryonic antigen, α-fetoprotein, carbohydrate antigen 19-9 and albumin; indocyanine green clearance rate; perioperative transfusion; type of hepatic resection; mortality; morbidity; intraoperative blood loss; regimen and route of preoperative chemotherapy; history of local treatment; maximum diameter and number of liver metastases; size of surgical margin; histological type; histological effects of preoperative chemotherapy; regimen and route of adjuvant chemotherapy; and type and treatment for recurrence. Morbidity was divided into major and minor categories, and only major complications (Clavien–Dindo classification grade III or higher[18]) were recorded. The following items relating to surgery for the primary gastric lesion were also included in the database: type of surgery; level of lymph node dissection; tumour and node categories; histological type; pathological degree of lymphatic and venous infiltration of the gastric lesion (each graded from 0 to 3 according to the Japanese classification of gastric carcinoma[19]); and administration of adjuvant chemotherapy after gastrectomy, along with its regimen in metachronous resections. Institutional review board approval was granted at each contributing institution.

Patients were eligible for this study if they underwent partial hepatectomy (surgical R0 resection) for histologically proven synchronous or metachronous GCLMs. Chemotherapy was allowed before and/or after hepatectomy or gastrectomy. Patients found at hepatectomy to have active cancer at other sites were excluded. The surgical indications for hepatectomy for GCLMs between January 1990 and December 2010 were similar at each institution: three or fewer liver metastases at preoperative diagnosis; complete resection of the primary gastric tumour possible (synchronous disease) or already carried out (metachronous disease); and no other unresectable site. Indications were expanded during the study interval to include more liver metastases at the surgeon's discretion.

The International Union Against Cancer seventh TNM classification of gastric cancer[20] was used to describe tumour progression and histological grade. The number of regional lymph nodes was categorized according to the Japanese classification of gastric carcinoma[19]. The types of hepatectomy were classified according to the Brisbane 2000 nomenclature[21].

Statistical analysis

Cumulative overall and recurrence-free survival rates were estimated by the Kaplan–Meier method. Significant differences were determined using the log rank test and $P < 0{\cdot}050$ was considered significant. Parameters influencing survival were identified by univariable analysis and factors with $P < 0{\cdot}050$ were selected for further examination by multivariable analysis. Multivariable regression analysis was carried out using a Cox proportional hazards model to identify independent predictors of survival, and $P < 0{\cdot}050$ was considered statistically significant. All statistical analyses were performed using SPSS® for Windows® version 18.0 (IBM, Armonk, New York, USA).

Results

Data for 257 patients were sent to the data centre for analysis. To concentrate on the oncological outcomes, one patient with metachronous hepatic resection following gastrectomy with incomplete lymph node dissection was excluded. This patient had multiple liver metastases at the initial diagnosis, and underwent hepatic arterial infusion (HAI) and palliative total gastrectomy. The number of hepatic lesions was reduced by HAI, and right hepatectomy was therefore performed after 20 months. The remaining 256 patients were evaluated for long-term outcomes in the present study (*Table 1*).

In patients with metachronous metastases, the median interval between gastrectomy and hepatic resection was

Table 1 Demographic and clinical characteristics

	No. of patients ($n = 256$)
Age (years)*	64 (32–89)
Sex ratio (M : F)	207 : 49
Timing of hepatic metastasis	
Synchronous	106
Metachronous	150
Type of gastrectomy	
Total gastrectomy	99 (38·7)
Distal gastrectomy	140 (54·7)
Proximal gastrectomy	12 (4·7)
Other	5 (2·0)
Type of hepatectomy	
Major	73 (28·5)
Minor	183 (71·5)
No. of hepatic tumours resected†	2·0(2·4)
Maximum size of hepatic tumours (cm)*	3 (0·2–30)
Adjuvant chemotherapy after hepatectomy	
Yes	84 (32·8)
No	172 (67·2)
Follow-up (months)*	65 (1–261)

Values in parentheses are percentages unless indicated otherwise; *values are median (range) and †mean(s.d.).

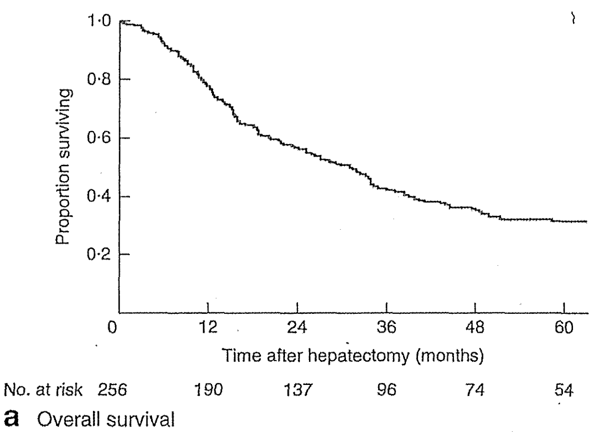
15 (range 4–135) months. The number of hepatic lesions was one in 168 patients (65·6 per cent), two in 44 (17·2 per cent), three in 18 (7·0 per cent) and four or more in 26 patients (10·2 per cent). The surgical mortality rate was 1·6 per cent (4 of 256) and the major morbidity rate (Clavien–Dindo classification grade III or more) was 10·9 per cent (28 of 256). Pathological R0 resection was proven in 89·8 per cent of patients (230 of 256). Chemotherapy was administered before hepatectomy in 17·6 per cent (45 of 256).

Recurrence

Median follow-up was 65 (range 1–261) months. Recurrences were detected in 192 patients (75·0 per cent) during follow-up, and 164 patients died as a result of recurrence. Only seven patients died from other disease. The median interval from hepatectomy to recurrence was 7 (range 1–72) months. The dominant site of recurrence was the liver, in 139 patients (72·4 per cent), followed by lymph nodes in 32 (16·7 per cent), lung in 25 (13·0 per cent) and peritoneum in 15 patients (7·8 per cent). Among the 192 patients with recurrences, 151 (78·6 per cent) underwent treatment for recurrent lesions, including systemic chemotherapy in 104, surgical resection in 26 (20 liver, 3 lung, 2 lymph node, 1 brain), HAI, radiofrequency ablation (RFA) or transcatheter arterial embolization (TACE) in 15, radiation in three, and other treatments in three. Repeat hepatectomy was performed in only 14·4 per cent (20 of 139) of the patients with liver recurrences .

Long-term outcomes and prognostic factors

The actuarial 1-, 3- and 5-year overall and recurrence-free survival rates were 77·3, 41·9 and 31·1 per cent, and 43·6, 32·4 and 30·1 per cent, respectively (*Fig. 1*). Median overall and recurrence-free survival times were 31·1 and 9·4 months respectively. The disease-specific survival curve was almost the same as the overall survival curve. The associations between various factors and unfavourable patient survival were assessed. Univariable analysis revealed several factors associated with poor overall survival (*Table 2*). Similar results were obtained for recurrence-free survival (*Table 2*). There was no significant difference in survival between 106 patients with synchronous GCLMs and 150 patients with metachronous liver metastases. Multivariable analysis identified serosal invasion of the primary gastric cancer, at least three liver metastases and liver tumour



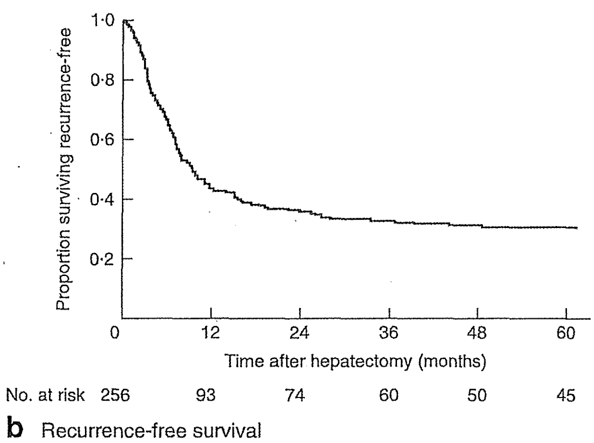


Fig. 1 Kaplan–Meier analysis of **a** overall and **b** recurrence-free survival in 256 patients treated by surgical resection for gastric cancer liver metastases

Table 2 Univariable analysis of overall and recurrence-free survival according to clinicopathological factors

		Overall survival		Recurrence-free survival	
	No. of patients*	Hazard ratio†	P‡	Hazard ratio†	P‡
Age ≥ 65 years	128 (50·0)	0·08 (0·58, 1·05)	0·096	0·75 (0·55, 1·01)	0·055
Male sex	207 (80·9)	1·04 (0·71, 1·52)	0·840	0·96 (0·69, 1·48)	0·959
Metachronous metastasis	150 (58·6)	0·79 (0·59, 1·07)	0·125	0·75 (0·56, 1·02)	0·065
Serosal invasion of primary tumour	73 (28·5)	1·49 (1·08, 2·05)	0·014	1·42 (1·03, 1·95)	0·031
Lymph node involvement	204 (79·7)	1·20 (0·80, 1·81)	0·380	1·22 (0·81, 1·83)	0·354
Histological type (well, moderately differentiated)	173 (67·6)	1·08 (0·78, 1·50)	0·643	1·09 (0·79, 1·52)	0·602
Lymphatic invasion grade 2/3	105 (41·0)	1·91 (1·41, 2·60)	< 0·001	1·79 (1·31, 2·45)	< 0·001
Venous invasion grade 2/3	129 (50·4)	1·27 (0·93, 1·72)	0·132	1·28 (0·94, 1·73)	0·119
Size of largest hepatic tumour ≥ 5·0 cm	59 (23·0)	1·65 (1·18, 2·32)	0·004	1·57 (1·12, 2·20)	0·010
No. of liver metastases ≥ 3	44 (17·2)	2·26 (1·57, 3·26)	< 0·001	2·31 (1·61, 3·33)	< 0·001
Major hepatectomy	73 (28·5)	1·05 (0·75, 1·46)	0·782	1·02 (0·73, 1·43)	0·893
CEA ≥ 5·0 ng/ml	129 (50·4)	1·60 (1·18, 2·17)	0·002	1·59 (1·17, 2·15)	0·003
CA19-9 ≥ 37·0 units/ml	68 (26·6)	1·62 (1·16, 2·25)	0·004	1·56 (1·12, 2·17)	0·008
Systemic chemotherapy after gastrectomy	73 (28·5)	0·77 (0·52, 1·04)	0·082	0·76 (0·54, 1·07)	0·112
Systemic chemotherapy after hepatectomy	84 (32·8)	0·85 (0·61, 1·18)	0·324	0·78 (0·56, 1·08)	0·134

Values in parentheses are *percentages and †95 per cent c.i. CEA, carcinoembryonic antigen; CA, carbohydrate antigen. ‡Log rank test.

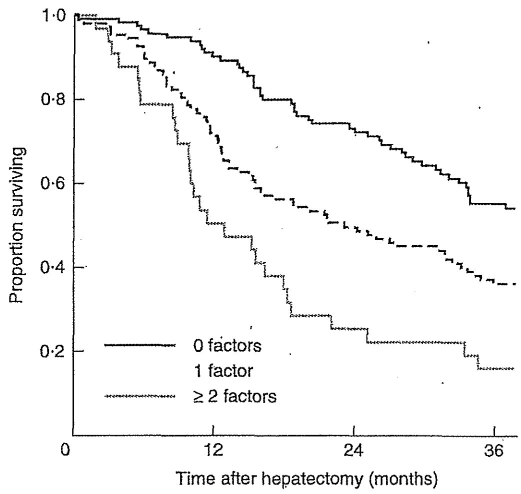
Table 3 Multivariable Cox proportional hazards analysis of overall survival

	Hazard ratio	P
Serosal invasion of primary tumour	1·50 (1·10, 2·05)	0·012
No. of liver metastases ≥ 3	2·33 (1·62, 3·36)	< 0·001
Size of largest hepatic tumour ≥ 5·0 cm	1·62 (1·15, 2·28)	0·005

Values in parentheses are 95 per cent c.i.

diameter 5 cm or more as independent predictors of poor prognosis in terms of overall survival (*Table 3*).

Patients were subsequently assigned to one of three groups based on the presence of none, one, or more than one of these factors. Survival curves revealed significant differences in overall survival between the groups with no factors and one factor (hazard ratio (HR) 1·82, 95 per cent c.i. 1·31 to 2·53; $P < 0·001$), and between the groups with one factor and more than one factor (HR 1·67, 95 per cent c.i. 1·08 to 2·58; $P = 0·020$) (*Fig. 2*). Actuarial 3- and 5-year overall survival rates for patients with no factors were 54·3 and 43·3 per cent respectively, and corresponding rates for those with one factor were 36·0 and 23·6 per cent. In 15 patients with all three factors, there was no survival beyond 36 months.



No. at risk				
0 factors	115	97	75	53
1 factor	108	77	53	37
≥ 2 factors	33	16	8	5

Fig. 2 Kaplan–Meier analysis of overall survival after surgical resection for gastric cancer liver metastases according to the number of predictive factors for poor prognosis

Discussion

Liver resection for GCLMs is not performed frequently at present. In a recent large study from Korea[22], only about 10 per cent of over 10 000 patients with gastric cancer had liver metastases, and only 4 per cent of these patients underwent hepatectomy. The rarity of liver resection for GCLMs makes randomized studies difficult. Consequently, there is currently no consensus on the efficacy of surgical resection for GCLMs. Although the present study had several limitations inherent to its retrospective nature and patient selection bias, its relatively large-scale analysis based on a well prepared database provides valuable information on the indications for surgical resection of GCLMs. The 5-year overall and recurrence-free survival rates of about 30 per cent are promising, but they were obtained in a well selected population. These data suggest that a small subpopulation of patients with GCLMs may benefit from liver resection. There have been concerns regarding the high mortality and morbidity rates associated with liver surgery, especially metachronous resection, where severe adhesions in upper abdominal organs may be present owing to previous surgery. However, the mortality and morbidity rates in the present study were acceptable, suggesting that such operations can be undertaken safely by experienced surgeons.

Nevertheless, it should be emphasized that the median recurrence-free survival time was 9·4 months and half of the recurrences developed within 1 year despite careful patient selection with R0 resection. Still, there were a considerable number of recurrence-free long-term survivors after hepatectomy. This may reflect different tumour subpopulations with varied biological behaviour. This results here strongly suggest the efficacy of surgery in a sub-subpopulation of GCLMs, although only a randomized study can prove this scientifically.

Clinically, it is crucial to identify suitable candidates for liver resection at diagnosis. The number of hepatic tumours and tumour diameter were identified as prognostic factors in previous reports based on small series[9–17]. The present study revealed three independent prognostic factors associated with a poor survival rate, namely serosal invasion of the primary tumour, three or more hepatic tumours, and hepatic tumour size 5 cm or greater. There were significant differences in survival rates between patients with none and one of the three factors, suggesting that non-surgical treatment should be considered when any of these factors is recognized at diagnosis. Patients with fewer factors had more favourable survival rates at 3 or 5 years after hepatectomy. The decision whether or not to perform surgery should be made based on comprehensive clinical information, but hepatectomy should be avoided in patients with all three factors, given that there was no long-term survival among such patients in the present study.

As expected, the most frequent pattern of recurrence was intrahepatic, implying a high incidence of occult micrometastases at the time of hepatectomy. Repeat hepatectomy was performed in only 14·4 per cent of patients. Compared with liver metastases from colorectal cancer, there is less opportunity for repeat hepatectomy for GCLMs because the recurrence pattern is more complex; however, repeat hepatectomy can be considered if the hepatic recurrence is solitary[23].

It is difficult to assess the effectiveness of perioperative chemotherapy based on the results of the present study, given that the strategies varied among institutions and time intervals. Unlike in colorectal cancer, it may not be possible to conduct a randomized trial investigating the effects of perioperative chemotherapy for resectable GCLMs because of the scarcity of candidates. However, taken the potentially aggressive character of this disease and its high recurrence rate, it seems rational to administer perioperative chemotherapy using modern regimens. Preoperative chemotherapy was administered less frequently than postoperative chemotherapy in the present study, although such treatment could theoretically be useful for identifying non-responders to chemotherapy or progressive disease, thus avoiding futile surgery.

As regards other treatment modalities, the Japan Clinical Oncology Group[24] reported a 5-year survival rate of only 1·7 per cent in patients with GCLMs confined to the liver treated by systemic chemotherapy alone. This low survival rate may be explained by the fact that the study population included not only resectable disease, but all patients with GCLMs. TACE and HAI[25] may have the advantage of good local control with delivery of high drug concentrations to the lesion; however, evidence for better survival in gastric cancer is lacking. Few studies[26,27], with small sample sizes, have reported on the application of RFA to GCLMs; in these studies, RFA was recommended for solitary lesions smaller 3 cm in diameter, with some additional limitations regarding tumour location. It is currently not possible to conclude that RFA is more effective than surgery for GCLMs.

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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Optimal Indications for Additional Resection of the Invasive Cancer-Positive Proximal Bile Duct Margin in Cases of Advanced Perihilar Cholangiocarcinoma

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ABSTRACT

Background. The survival benefits of additional resection of the positive proximal ductal margin in cases of perihilar cholangiocarcinoma remain to be elucidated. The purpose of this retrospective study was to clarify the optimal indications for additional resection of the invasive cancer-positive proximal ductal margin (PM)

Methods. All patients who underwent hepatectomy for perihilar cholangiocarcinoma between 2000 and 2011 were analyzed. Surgical variables, the status of the PM, prognostic factors, and survival were evaluated.

Results. A total of 224 patients were enrolled. Additional resection was performed in 52 of 75 positive PMs of invasive cancer, resulting in 43 negative PMs. The survival of patients with a negative PM treated with additional resection ($n = 43$) was significantly worse than that of the patients with a negative PM treated without additional resection ($n = 149$; $P = 0.031$) and did not significantly differ from that of the patients with a positive PM ($n = 32$; $P = 0.215$). A multivariate analysis demonstrated that the carbohydrate antigen 19-9 (CA19-9) level (<64 or ≥64), combined vascular resection, pN, pM, the histological grade, perineural invasion, liver invasion, and R status were independent prognostic factors. Only in the subgroups of CA19-9 < 64 and pM0, the survival of the patients with a negative PM treated with additional resection was significantly better than that of the patients with a positive PM ($P = 0.019$ and $P = 0.021$, respectively).

Conclusions. Additional resection of the invasive cancer-positive PMs may be warranted only in limited patients with a lower level of CA19-9 and no distant metastatic disease.

It is well known that patients treated with noncurative resection of perihilar cholangiocarcinoma have a poor outcome.[1–11] Because obtaining accurate preoperative image assessments of tumor longitudinal or ductal spread is difficult despite modern refinements in imaging modalities, additional resection of the cancer-positive ductal margin based on the intraoperative frozen section diagnosis is sometimes required for R0 resection.[12] However, it remains controversial whether additional resection of the bile duct has a favorable impact on the patient outcomes.[13–15]

In patients with perihilar cholangiocarcinoma, it has been reported that there are other potent prognostic factors in addition to R0 resection, such as lymph node involvement, tumor histology, and the presence of microscopic perineural invasion.[1,2,4–8] This suggests that the survival of patients with advanced or aggressive disease is more dependent on tumor biology or staging than on obtaining a clear surgical margin. Therefore, we hypothesized that the survival benefits of R0 resection following additional resection of the cancer-positive proximal ductal margin would be affected by the status of prognostic factors indicative of the biological tumor behavior or tumor burden. If such prognostic factors could be identified preoperatively or intraoperatively, they would be useful in clinical practice for selecting patients in whom additional resection is more likely to result in improved survival.

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Although the carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels are known to be serologic markers of biliary tract cancer and can be measured preoperatively, few studies have discussed the prognostic value of these markers in patients with perihilar cholangiocarcinoma undergoing resection.

The purpose of this study was to verify prognostic factors, including the levels of CEA and CA19-9, in patients with perihilar cholangiocarcinoma and to clarify the optimal indications for additional resection of the positive proximal ductal margin taking into consideration the status of the prognostic factors.

METHODS

Patients

Data for all patients undergoing resection of perihilar cholangiocarcinoma, including hilar bile duct carcinoma and intrahepatic cholangiocarcinoma involving the hepatic hilum, between January 2000 and December 2011 at the Hepatobiliary and Pancreatic Surgery Division, National Cancer Center Hospital, Japan, were retrospectively reviewed. No patients received neoadjuvant or adjuvant chemotherapy and radiotherapy during this period. Data collection and analysis were performed according to the institutional guidelines conforming to the ethical standards of the Helsinki Declaration.

Preoperative Evaluation and Surgery

Our standard management and surgical procedures for treating perihilar cholangiocarcinoma have been described previously.[2,16,17] The location, extent, and staging of the tumor were evaluated using multidetector-row computed tomography (MDCT), ultrasonography, cholangiography, and magnetic resonance imaging. Patients with extensive invasion of the hepatoduodenal ligament, bulky nodal involvement, and the presence of liver or peritoneal metastasis were excluded as candidates for definitive surgery. Lymph node metastasis of the posterior to upper portion of the pancreatic head and para-aortic lymph nodes, which is classified as metastatic disease in the Union for International Cancer Control (UICC) TNM classification, was not regarded to be a contraindication for surgery, and resection was indicated with careful consideration in each individual case.[18] Preoperative biliary drainage, percutaneous transhepatic biliary drainage, and/or endoscopic retrograde biliary drainage were performed to decompress the biliary tree in the future remnant liver or treat segmental cholangitis. The volume of the entire liver and lobe to be resected was calculated using serial MDCT images. Preoperative portal vein embolization was indicated to decrease the risk of postoperative hepatic failure in patients whose resectional liver parenchymal volume exceeded 60 % of the total liver volume, as described in a previous report.[19] The preoperative serum CA19-9 level in most cases was evaluated immediately prior to surgical treatment after obtaining adequate biliary decompression (the total bilirubin level among 209 of 224 cases was ≤ 3.0 mg/dl), because the preoperative CA19-9 level can be affected by cholestasis or cholangitis.[20–23]

Pathological Evaluation and Additional Resection of the Ductal Margin

In principle, every cut end of the bile duct was submitted for an intraoperative frozen-section examination. The ductal margin status was classified as negative, positive with carcinoma in situ (CIS), or positive with a subepithelial invasive component.[24] One expert pathologist (HO) diagnosed all ductal margins. When the proximal ductal margin (PM) was positive with any type, additional resection was performed in an attempt to secure a clear margin whenever technically possible. When the distal ductal margin (DM) was positive, additional resection, including combined pancreaticoduodenectomy when needed, was performed only when microscopic spread of cancer cells into the intrapancreatic bile duct was the single obstacle to curative resection.

The ductal margin status was histologically assessed based on a review of the frozen section and its refixed permanent section with reference to the extent of the tumor in the formalin-fixed resected specimens, finally classified as described above. In the current study, only patients with a subepithelial invasive component at the ductal margin, not those with CIS, were regarded as having a positive ductal margin, because an CIS without invasive carcinoma at the ductal margin is not related to poorer survival than a negative margin.[25–28] The TNM categories and stage of disease were classified according to the UICC TNM classification.[18]

Statistics

The variables are presented as absolute numbers and percentages or median values and ranges. The statistical analysis was performed using the Chi-square test or Fisher's exact test, when appropriate. Survival was calculated according to the Kaplan-Meier method. A univariate analysis of survival estimates was performed using the log-rank test. Factors found to be significant in the univariate analysis were subjected to a multivariate analysis using the Cox proportional-hazards model (backward elimination method), with variables associated with $P < 0.20$ entered into the final model. In addition, a Cox proportional-hazards model was used to evaluate the interactions between the prognostic factors and the effects of additional resection of the invasive cancer-positive proximal ductal margin on overall survival. $P < 0.05$ was accepted as being statistically significant. The statistical analyses were performed using the Statistical Package for the Social Sciences (version 20.0, SPSS Inc., Chicago, IL).

RESULT

Of 238 consecutive patients with perihilar cholangiocarcinoma who underwent resection, 229 underwent major hepatectomy plus extrahepatic bile duct resection and regional lymphadenectomy. Five patients were excluded from the analysis due to death from postoperative complications, leaving 224 patients enrolled in this study. Almost all patients ($n = 217$) received intraoperative frozen-section examinations of the PM, of which only two frozen section (<1 %) diagnoses were misleading: one lesion regarded as invasive carcinoma on the frozen section was diagnosed as being negative for cancer on permanent histopathology, and one lesion regarded as having an CIS was diagnosed as invasive carcinoma. In both cases, the final PM was negative after additional resection. On the other hand, 208 patients received intraoperative frozen section examination of the DM. In two of the patients with negative margin on frozen section, margin status was changed to positive on permanent pathological diagnosis, with CIS in one patient and with invasive cancer in the other patient. In this study, the status of the initial and final proximal bile duct margin was classified according to the permanent histopathology.

The patient characteristics and clinicopathologic features are summarized in Table 1. Ninety (40 %) patients had Bismuth type IV disease. Forty-five (20 %) patients had distant metastasis (pM1), and in 14 of these patients (31 %), the presence of pM1 disease was detected on an excisional biopsy intraoperatively. In the other 31 patients, pM1 disease was diagnosed on the final pathological examination of the resected specimens. The DM was positive in 21 patients, who did not undergo additional pancreatoduodenectomy due to the failure in getting a negative PM ($n = 14$), the unfit general condition of patients for this additional invasive procedure ($n = 4$), and pM1 disease detected during operation ($n = 2$), and false-negative diagnosis on frozen section ($n = 1$).

A total of 149 patients had a negative PM without additional resection (group A). Of the 75 patients with an initial positive PM, 52 underwent additional resection of the PM, resulting in negative PM in 43 cases (group B) and a final positive PM in the remaining 9 cases. Additional resection was not performed in 19 patients due to technical reasons, in 3 patients due to the patients having high-risk comorbidities, and in 1 patient due to liver metastasis detected intraoperatively. Overall, 32 (14 %) of the 224 patients had a final positive PM, without or with additional resection (group C).

In left hepatectomy, an initial PM was positive in 40 patients. Of those, additional resection resulted in negative margin in 26 (65 %), whereas additional resection was technically not possible in 8 (20 %). In contrast, in right hepatectomy, an initial PM was positive in 27 patients, of whom additional resection resulted in negative margin only in 12 (44 %) and additional resection was technically not possible in 8 (30 %). These results suggested that additional resection of PM tended to be more technically difficult in right hepatectomy than in left hepatectomy, implying that the initial resection of proximal bile duct on the planned line may be performed more accurately in right hepatectomy than in left hepatectomy.

The rate of a positive final surgical margin was 14 % in the PM, 9 % in the DM, and 15 % in the radial margin (circumferential or dissection margin). Accordingly, 159 of the 224 patients (71 %) had histologically negative resection margins (R0), whereas 65 patients (29 %) had margins with tumor involvement (R1).

Survival and Prognostic Factors

The overall survival rate for all patients was 86.1 % at 1 year, 50.8 % at 3 years, and 41.7 % at 5 years. The median survival was 37.9 (2.20–143.7) months, and the median follow-up time was 26.5 (2.20–143.7) months.

The proportion of patients with CIS in PM was 14 % (21/149) in group A and 14 % (6/43) in group B. In group A, the overall survival of patients with CIS (median: 60.6 months) was not significantly different from that of patients without CIS (56.6 months; $P = 0.639$; Fig. 1b). Thus, it seemed to be reasonable that we omitted CIS from positive ductal margins in the present study.

According to a univariate analysis, 17 of the 20 possible clinicopathological prognostic factors were significant (Table 2). The preoperative CA19-9 level was a significant prognostic factor in both the subgroup of patients undergoing preoperative biliary drainage ($P = 0.010$) and the subgroup of patients not undergoing preoperative biliary drainage ($P = 0.008$). A multivariate analysis incorporating the 17 significant factors demonstrated that the preoperative CA19-9 level, combined vascular resection, pN, pM, histological grade, microscopic perineural invasion, microscopic liver invasion, and R were independent prognostic factors (Table 1).

TABLE 1 Clinicopathologic characteristics of groups A, B, and C

Variable, *n* (%)	Total (*n* = 224)	Group A (*n* = 149)	Group B (*n* = 43)	Group C (*n* = 32)	*P* value
Age (yr)[a]	66 (31–82)	65 (31–82)	67 (48–79)	65 (43–82)	0.738
Sex, male	156 (70)	100 (67)	28 (65)	28 (88)	0.058
Preoperative CA19-9 (U/ml)[a]	64 (0–256800)	83 (0–256800)	49 (0–147400)	92 (0–17700)	0.123
Preoperative CEA (ng/ml)[a]	2.5 (1–560)	2.4 (1–560)	2.9 (1–111)	2.1 (1–16)	0.230
Preoperative biliary drainage	134 (60)	85 (57)	23 (54)	26 (81)	0.026*
Preoperative portal vein embolization	110 (49)	80 (57)	15 (35)	15 (47)	0.091
Bismuth type					0.065
I	3 (1)	3 (2)	0 (0)	0 (0)	
II	19 (9)	10 (7)	7 (16)	2 (6)	
III	112 (51)	83 (56)	19 (44)	10 (31)	
IV	90 (40)	53 (36)	17 (40)	20 (63)	
Type of hepatectomy					0.303
Left hepatectomy	97 (43)	57 (38)	26 (61)	14 (44)	
Left trisectionectomy	25 (11)	18 (12)	5 (12)	2 (6)	
Central bisectionectomy	2 (1)	2 (1)	0 (0)	0 (0)	
Right hepatectomy	95 (42)	68 (46)	12 (28)	15 (47)	
Right trisectionectomy	5 (2)	4 (2)	0 (0)	1 (3)	
Combined portal vein resection[b]	46 (21)	25 (17)	13 (30)	8 (25)	0.125
Combined hepatic artery resection[b]	21 (9)	13 (9)	4 (9)	4 (13)	0.802
Combined pancreaticoduodenectomy	13 (6)	7 (5)	6 (14)	0 (0)	0.023*
pT[c]					0.124
1	10 (5)	8 (5)	2 (5)	0 (0)	
2a/2b	70 (31)	48 (32)	13 (30)	9 (28)	
3	54 (24)	40 (27)	11 (26)	3 (9)	
4	90 (40)	53 (36)	17 (40)	20 (63)	
pN1[c]	104 (46)	63 (42)	19 (44)	22 (69)	0.023*
pM1[c]	45 (20)	29 (19)	9 (21)	7 (22)	0.942
Distant lymph node metastasis[d]	29 (13)	17 (11)	6 (14)	6 (19)	
Liver metastasis[d]	22 (10)	15 (10)	4 (9)	3 (9)	
Localized peritoneal dissemination[d]	2 (1)	2 (1)	0 (0)	0 (0)	
pStage[a]					0.336
I	10 (5)	8 (5)	2 (5)	0 (0)	
II	39 (17)	28 (19)	8 (19)	3 (9)	
IIIA/ IIIB	62 (28)	43 (29)	13 (30)	6 (19)	
IVA	68 (30)	41 (28)	11 (26)	16 (50)	
IVB	45 (20)	29 (19)	9 (21)	7 (22)	
Histological grade					0.167
G1 (well)	53 (24)	42 (28)	8 (19)	3 (9)	
G2 (moderately)	153 (68)	96 (64)	32 (74)	25 (78)	
G3 (poorly)	18 (8)	11 (7.4)	3 (7)	4 (13)	
Microscopic lymphatic invasion	97 (43)	54 (36)	22 (51)	21 (66)	0.005*
Microscopic venous invasion	116 (52)	67 (45)	24 (56)	25 (78)	0.003*
Microscopic perineural invasion	141 (63)	85 (57)	27 (63)	29 (91)	0.002*
Microscopic liver invasion	94 (42)	66 (44)	13 (30)	15 (47)	0.214
Positive proximal ductal margin	32 (14)	0 (0)	0 (0)	32 (100)	–
Positive distal ductal margin	21 (9)	9 (6)	1 (2)	11 (34)	<0.001*
Positive radial margin	34 (15)	18 (12)	7 (16)	9 (28)	0.070

TABLE 1 continued

Variable, n (%)	Total ($n = 224$)	Group A ($n = 149$)	Group B ($n = 43$)	Group C ($n = 32$)	P value
R1	65 (29)	12 (17)	8 (19)	32 (100)	<0.001*

Group A, negative proximal ductal margin (PM) without additional resection; group B, negative PM with additional resection; group C, final positive PM

* Significantly difference

[a] Median (range)

[b] Ten patients who underwent combined portal vein and hepatic artery resection overlap in each category

[c] According to the UICC TNM classification 7th edition

[d] Seven patients had both distant lymph node metastasis and liver metastasis; one patient had both distant metastasis and localized peritoneal dissemination

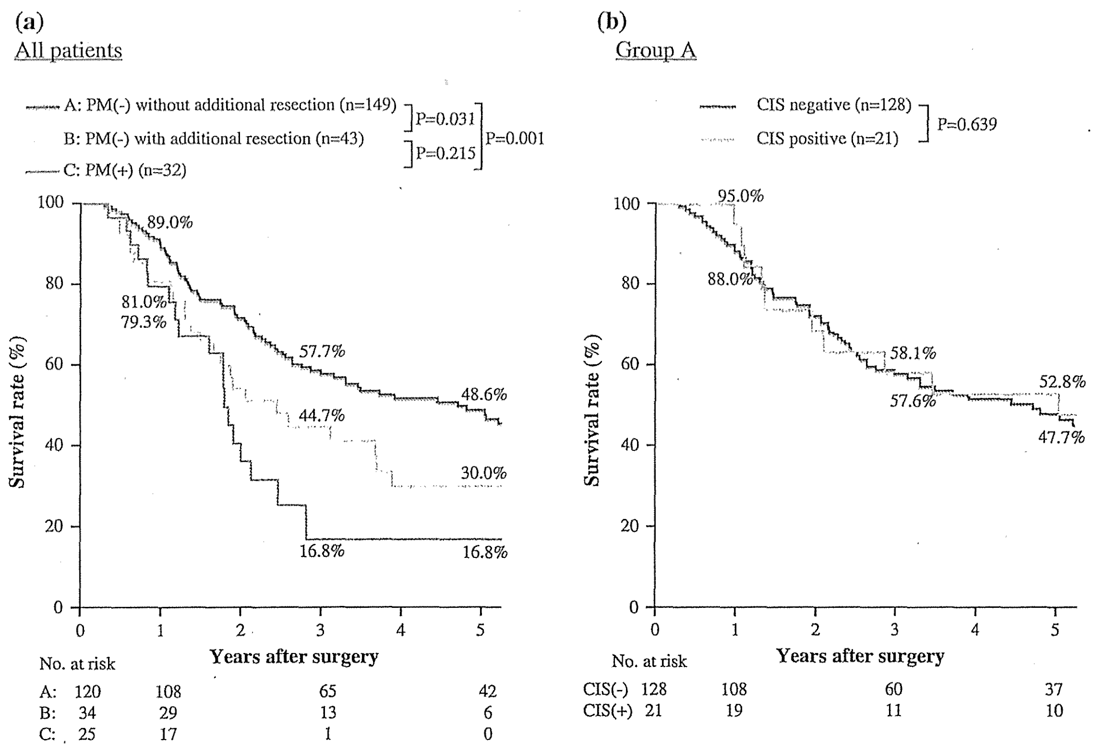

FIG. 1 **a** Overall survival for the entire study population according to the final proximal ductal margin (PM) status: group A, negative PM without additional resection; group B, negative PM with additional resection; group C, final positive PM. The survival of group B was significantly worse than that of group A ($P = 0.031$) and did not differ significantly from that of group C ($P = 0.215$). **b** Overall survival for group A according to the presence of carcinoma in situ (CIS) in the PM

COMPARISON OF GROUP A, B, AND C

The distribution of clinicopathologic characteristics among the three groups are shown in Table 1. Group C was significantly correlated with preoperative biliary drainage ($P = 0.026$), pN1 ($P = 0.023$), microscopic lymphatic invasion ($P = 0.005$), microscopic venous invasion ($P = 0.003$), and microscopic perineural invasion ($P = 0.002$) than group A or group B. The proportion of patients with positive DM was 6 % (9/149) in group A, 2 % (1/43) in group B, and 34 % (11/32) in group C ($P < 0.001$). The proportion of patients with positive radial margin was 12 % (18/149) in group A, 16 % (7/43) in group B, and 28 % (9/32) in group C ($P = 0.070$).

Interactions Between Additional Resection of the PM and Survival

The overall survival was analyzed according to the status of the final PM, namely group A (negative PM without additional resection) versus group B (negative PM with additional resection) versus group C (positive PM;