

Liver resection with thrombectomy for patients with hepatocellular carcinoma and tumour thrombus in the inferior vena cava or right atrium

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Background: Hepatocellular carcinoma (HCC) with tumour thrombus (TT) in the inferior vena cava (IVC) or right atrium (RA) is a rare advanced disease state with a poor prognosis. The aim of this study was to examine survival after surgical resection.

Methods: Patients with HCC and TT of either the IVC or RA, who underwent liver resection between February 1997 and July 2017, were included. Their short- and long-term outcomes and surgical details were analysed retrospectively.

Results: Thirty-seven patients were included; 16 patients had TT in the IVC below the diaphragm, eight had TT in the IVC above the diaphragm, and 13 had TT entering the RA. Twelve patients had advanced portal vein TT (portal vein invasion (Vp) greater than Vp3 and Vp4), ten had bilobar disease, and 12 had extrahepatic disease. There were no in-hospital deaths, although two patients died within 90 days. Median survival did not differ between patients who had resection with curative intent (18.7 months) and those with residual tumour in the lung only (20.7 months), but survival was poor for patients with residual tumour in the liver (8.3 months).

Conclusion: Liver resection with thrombectomy for advanced HCC with TT in the IVC or RA is safe and feasible, leading to moderate survival.

Funding information

No funding.

Paper accepted 10 December 2019

Published online 3 February 2020 in Wiley Online Library (www.bjsopen.com). DOI: 10.1002/bjs5.50258

Introduction

Hepatocellular carcinoma (HCC) with macrovascular invasion is classified as an advanced malignancy, according to the Barcelona Clinic Liver Cancer staging system; palliative chemotherapy including sorafenib or regorafenib is recommended for treatment^{1–4}. HCC with tumour thrombus (TT) in the inferior vena cava (IVC) or right atrium (RA) is a further advanced disease state that occurs in 2.0–3.8 per cent of patients^{5,6}. The prognosis of these patients is extremely poor, with a median overall survival (OS) of 2–5 months for those who remain untreated^{7,8}. This status may present as an oncological emergency that is occasionally complicated by pulmonary infarction, secondary Budd–Chiari syndrome, heart failure

or ball-valve thrombus syndrome, and these patients are at risk of sudden death from pulmonary embolism or occlusion of the tricuspid valve^{9–11}.

The only potentially curative option for HCC with TT in the IVC or RA is liver resection with thrombectomy. Although previous studies^{8,12–15} have reported median OS of 16.7–30.8 months in patients undergoing curative resection, the survival benefits remain unclear. In addition, limited data are available to determine whether differences in the leading edge of the TT affect the perioperative course or long-term outcome, despite improvement in the safety of liver resection¹⁶, or to clarify the indications for resection in patients with remote metastases. Moreover, little is known about the optimal surgical procedures for these patients, such as cardiopulmonary bypass (CPB),

venovenous bypass and IVC reconstruction with artificial vascular graft^{17,18}.

The aim of this study was to investigate short- and long-term outcomes of patients with HCC and TT in either the IVC or RA who had liver resection with thrombectomy.

Methods

All patients with HCC and TT in the IVC or RA who underwent liver resection at Yamaguchi University Hospital, Osaka University Hospital and Osaka International Cancer Institute between February 1997 and July 2017 were included in the study. Prospectively collected clinical and pathological data were analysed retrospectively.

The study was approved by the institutional review board of each institution (protocol number: Yamaguchi University, H30-029; Osaka University, 18195; Osaka International Cancer Institute, 18107), and was conducted in accordance with the ethical standards of the 2013 Declaration of Helsinki. Informed consent was waived because this was a retrospective cohort study.

Diagnostic criteria

HCC was diagnosed using contrast-enhanced CT, primarily with early enhancement in the arterial phase, followed by washout in the portal or late phase, as well as MRI, hepatic artery angiography and ultrasonography. The presence of TT in the portal vein (PVT) and in the IVC or RA was diagnosed using the above preoperative imaging modalities, confirmed by final pathological findings, and categorized according to the Japanese staging system¹⁹. Macroscopic residual tumour was also diagnosed using perioperative imaging modalities and categorized according to the Japanese staging system¹⁹. ECG-gated multislice spiral CT and transoesophageal echocardiography were used in the latter phase of this study to examine the location of the leading edge of the TT and adjacent structures, including the diaphragm and tricuspid valve in some patients. Furthermore, TT in the IVC or RA was classified into three types according to the leading edge of the TT¹⁴: type I, inferior hepatic (TT in the IVC below the diaphragm); type II, superior hepatic (TT in the IVC above the diaphragm, but still outside the RA); and type III, intracardiac (TT entering the RA). This classification scheme has been illustrated in a review article by Sakamoto and Nagano¹⁰.

Indication for resection

The indication for resection and/or preoperative therapy for each patient was discussed at a multidisciplinary cancer

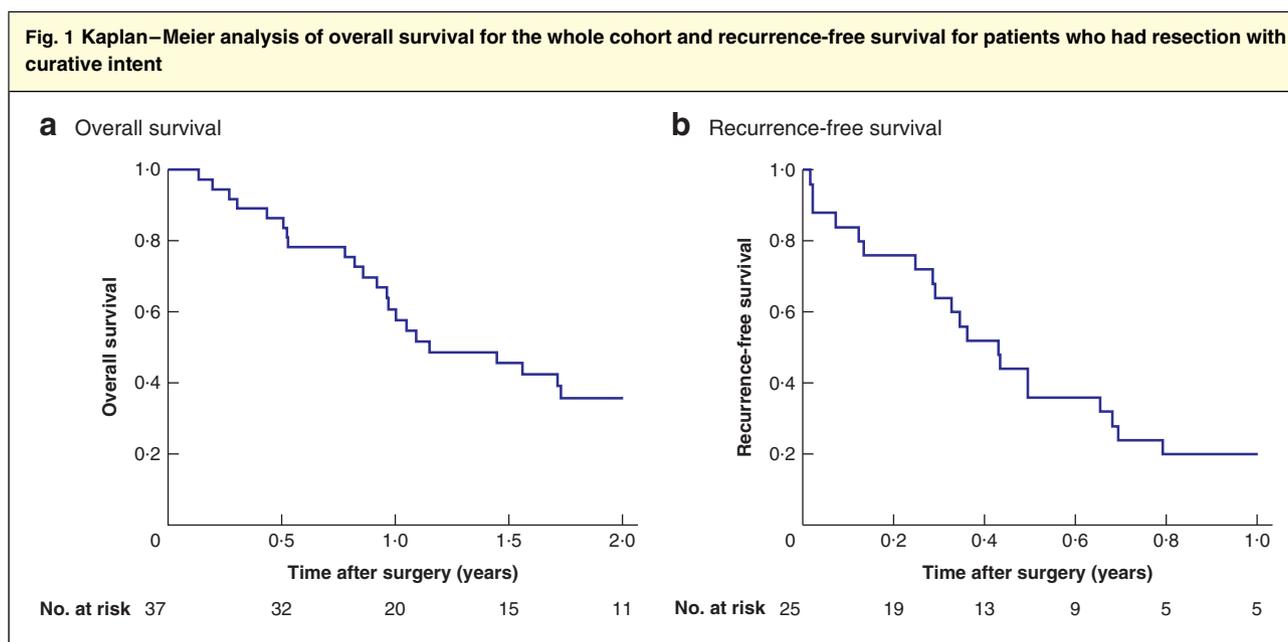
board at each institution, comprising hepatopancreatobiliary surgeons, hepatologists and medical oncologists, taking into account the patient's condition and the state of tumour, including location of the TT. Although resection with curative intent was the basis of the surgical indication, symptomatic patients with tumours, including those with secondary Budd–Chiari syndrome and heart failure, and patients considered an oncological emergency (for instance those with a moving tumour plug and a high risk of pulmonary artery tumour embolism or of tricuspid valve occlusion) also had active resection, even if this was expected to be excision with macroscopic residual tumour (R(+)) under the condition that distant metastasis was controlled. Impairment of liver function was assessed by blood biochemistry tests, including the indocyanine green retention rate at 15 min. Liver resection was conducted with or without the intermittent Pringle's manoeuvre with intraoperative ultrasound guidance. Intraoperative transoesophageal echocardiography was also used to monitor movement of the leading edge of the TT, as well as the dissemination of TT fragments by manipulation, especially in patients with type III TT.

The indication of CPB for type III TT was determined as follows. After laparotomy, a median sternotomy was performed to prepare for thrombectomy. When the TT reached the tricuspid valve, CPB was used. The superior vena cava and infrahepatic IVC were clamped after liver resection, and blood flow was bypassed to the ascending aorta via CPB. The RA was incised under CPB, and the TT was removed under direct vision. When the TT could

Table 1 Baseline patient characteristics

	No. of patients* (n = 37)
Age (years)†	66 (61–75)
Sex ratio (M : F)	30 : 7
Hepatitis B virus infection	16
Hepatitis C virus infection	14
Serum albumin (g/dl)†	3.6 (3.3–4.0)
Serum total bilirubin (mg/dl)†	0.70 (0.50–0.90)
Prothrombin time (%)†	74.5 (66.0–85.6)
Platelet count (10 ⁴ /μl)†	16.0 (11.5–23.2)
ICGR15 (%)†	17.5 (13.8–25.5)
Child–Pugh grade	
A	27
B	10
Serum AFP (ng/ml)†	316 (29–8968)
Serum DCP (munits/ml)†	3023 (359–20 500)

*Unless indicated otherwise, †values are median (i.q.r.). ICGR15, indocyanine green retention rate at 15 min; AFP, α-fetoprotein; DCP, des-γ-carboxythrombin.



a Overall survival for the 37 study patients. **b** Recurrence-free survival for the 25 patients who had resection with curative intent.

be pulled downward by mobilizing the liver caudally, an attempt was made to clamp the RA just proximal to the right atrial TT (RATT), while avoiding damage to the coronary sinus or tricuspid valve. If the haemodynamics were stable with no appearance of arrhythmia under multiple clamping trial of the RA, it was judged that CPB was not necessary. In this scenario, the RA could be incised and the TT removed using RA clamping without CPB. Postoperative complications were recorded and scored according to the Clavien–Dindo classification²⁰. Postoperative mortality was defined as any death during postoperative hospital stay.

Follow-up after liver resection

All patients were followed up in the outpatient clinic every 3 months after surgery; their condition was assessed by means of liver function tests, estimation of tumour markers, enhanced CT or MRI. Bone scintigraphy or PET was performed when extrahepatic recurrence was suspected. Recurrence was confirmed based on the findings of more than two imaging modalities. For patients with recurrence, therapy including resection, transarterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC), sorafenib, or systemic chemotherapy with fluorouracil (5-FU) plus cisplatin or oral fluoropyrimidine, was administered based on tumour spread and liver function.

Statistical analysis

All statistical analyses were performed with EZR software version 1.37 (Saitama Medical Centre, Jichi Medical University, Saitama, Japan)²¹, which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are presented as median (i.q.r.) values and analysed with the Mann–Whitney *U* test. Categorical variables were analysed using the χ^2 test or Fisher's exact test, as appropriate.

The Kaplan–Meier method was used to calculate recurrence-free survival (RFS) and OS, with differences evaluated by the log rank test. Independent prognostic factors for OS and RFS were analysed using Cox proportional hazard regression modelling in a stepwise manner. The following 15 variables were examined as potential risk factors for poor survival: age above 70 years, serum platelet count below 100 000/ μ l, Child–Pugh grade B, gastro-oesophageal varices, presence of liver cirrhosis, poorly differentiated or undifferentiated cancer cells, serum α -fetoprotein level above 10 000 ng/ml, presence of PVTT (portal vein invasion (Vp) 2–4), tumour size greater than 10 cm, three or more tumours, presence and site of macroscopic residual tumour, presence of remote metastasis, preoperative treatment, distribution of tumour (unilobar or bilobar), and classification of IVC/RA TT. Cut-off values for continuous variables were determined

Table 2 Baseline patient and tumour characteristics according to classification of tumour thrombus in inferior vena cava or right atrium

	Type I (n = 16)	Type II (n = 8)	Type III (n = 13)	P†
Age (years)*	66.0 (60.5–75.0)	68.0 (63.0–73.0)	67.0 (63.0–72.0)	0.868‡
Sex ratio (M : F)	13 : 3	6 : 2	11 : 2	0.861
HBV infection	10	1	5	0.060
HCV infection	6	3	5	0.998
Gastro-oesophageal varices	4	1	1	0.431
Albumin (g/dl)*	3.6 (3.1–4.0)	3.6 (3.4–3.9)	3.6 (3.5–4.0)	0.711‡
Total bilirubin (mg/dl)*	0.7 (0.5–0.8)	0.75 (0.65–0.83)	0.8 (0.7–1.0)	0.433‡
Prothrombin time (%)*	82.9 (72.0–89.0)	71.3 (62.5–83.0)	74.0 (65.0–77.0)	0.147‡
Platelet count (10 ⁴ /μl)*	19.3 (12.0–22.2)	12.4 (11.1–19.6)	16.5 (12.6–23.8)	0.715‡
ICGR15 (%)*	15.0 (11.5–23.5)	17.8 (15.8–21.8)	24.3 (14.0–26.0)	0.533‡
Child–Pugh grade				0.247
A	13	4	10	
B	3	4	3	
AFP (ng/ml)*	499 (188–9435)	29 (12–4052)	337 (55–8697)	0.370‡
DCP (munits/ml)*	2141 (374–20 593)	1669 (24–653 168)	5000 (40–361 200)	0.992‡
Tumour size (cm)*	7.6 (5.4–12.5)	7.2 (6.3–13.1)	8.0 (4.5–10.5)	0.994‡
No. of tumours				0.126
1–2	5	4	9	
≥ 3	11	4	4	
Distribution				0.417
Unilobar	12	7	8	
Bilobar	4	1	5	
Nature of tumour				0.228
Primary	7	6	9	
Recurrent	9	2	4	
Extent of PVTT				0.942
Vp0–2	11	5	9	
Vp3–4	5	3	4	
Extrahepatic disease				0.714
Lung	4	3	1	
Adrenal gland	2	0	1	
Lymph node	1	0	0	
Tumour differentiation				0.174
Moderate	4	0	0	
Poor	10	7	12	
Undifferentiated	2	1	1	
Fibrosis grade				0.632
0–2	6	3	7	
3–4	10	5	6	
Preoperative treatment	4	3	3	
TACE	3	1	2	
HAIC	1	1	1	
Embolization	0	1	0	

*Values are median (i.q.r.). HBV, hepatitis B virus; HCV, hepatitis C virus; ICGR15, indocyanine green retention rate at 15 min; AFP, α-fetoprotein; DCP, des-γ-carboxythrombin; PVTT, portal vein tumour thrombus; Vp, invasion of the portal vein; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy. † χ^2 or Fisher's exact test, except ‡Mann–Whitney *U* test.

according to previous reports^{12,13}. Of these 15 factors, those with $P < 0.250$ in univariable analysis were entered into the Cox model using stepwise elimination. $P < 0.050$ was considered statistically significant.

Results

A total of 37 patients were included in this study (Osaka University, 28; Yamaguchi University, 8; Osaka International Cancer Institute, 1). The median duration of

Table 3 Operative procedures and surgical outcomes according to classification of tumour thrombus in inferior vena cava or right atrium

	Type I (n = 16)	Type II (n = 8)	Type III (n = 13)	P [¶]
Major hepatectomy†	9	6	10	0.437
Procedure for IVC reconstruction				0.281
Simple suture	16	7	11	
With patch	0	1	2	
With vascular graft	0	0	0	
THVE	5	5	11	0.015
Venovenous bypass	0	0	1	0.387
CPB	0	1	3	0.136
Duration of surgery (min)*	496 (379–551)	498 (427–627)	560 (526–676)	0.140#
Estimated blood loss (ml)*	1895 (835–2513)	3555 (2553–5470)	4940 (3400–6120)	0.010#
RBC transfusion required	10	7	12	0.119
FFP transfusion required	7	6	11	0.057
Extent of resection				0.670
R(–)	10	5	10	
R(+)	6	3	3	
Site of residual tumour				
Intrahepatic only	0	0	1	
Lung only	3	2	1	
Intrahepatic and lung	1	1	1 (+ adrenal gland)	
Other organ	2 (LN 1, TT in SpV 1)	0	0	
Postoperative hospital stay (days)*	28 (22–44)	33 (22–39)	29 (23–41)	0.904#
Complication				0.096
Yes	6	5	10	
No	10	3	3	
Details of complications§				
Pulmonary artery embolism	1 (II)	2 (II and III)	3 (II 2, III 1)	
Ascites and pleural effusion	4 (I 1, II 3)	1 (III)	2 (I, II)	
Surgical-site infection	2 (II, III)	0	1 (I)	
Arrhythmia	0	1 (II)	2 (II)	
Portal vein thrombus	1 (II)	0	0	
Bowel obstruction	0	1 (III)	0	
Bile leak	0	0	2 (III)	
In-hospital mortality	0	0	0	1.000
90-day mortality	1	0	1	0.736

*Values are median (i.q.r.). †More than three Couinaud segments. §Clavien–Dindo classification grades are shown in parentheses. IVC, inferior vena cava; THVE, total hepatic vascular exclusion; CPB, cardiopulmonary bypass; R(–), resection with no macroscopic residual tumour; R(+), resection with macroscopic residual tumour; RBC, red blood cell; FFP, fresh frozen plasma; LN, lymph node; TT, tumour thrombus; SpV, splenic vein. ¶ χ^2 or Fisher's exact test, except #Mann–Whitney *U* test.

follow-up was 13.0 (i.q.r. 9.5–27.5) months. Baseline characteristics of the patients are shown in *Table 1*. The median OS for all 37 patients was 13.8 months (*Fig. 1a*) and the median RFS for the 25 patients who had surgery with curative intent was 5.2 months (*Fig. 1b*).

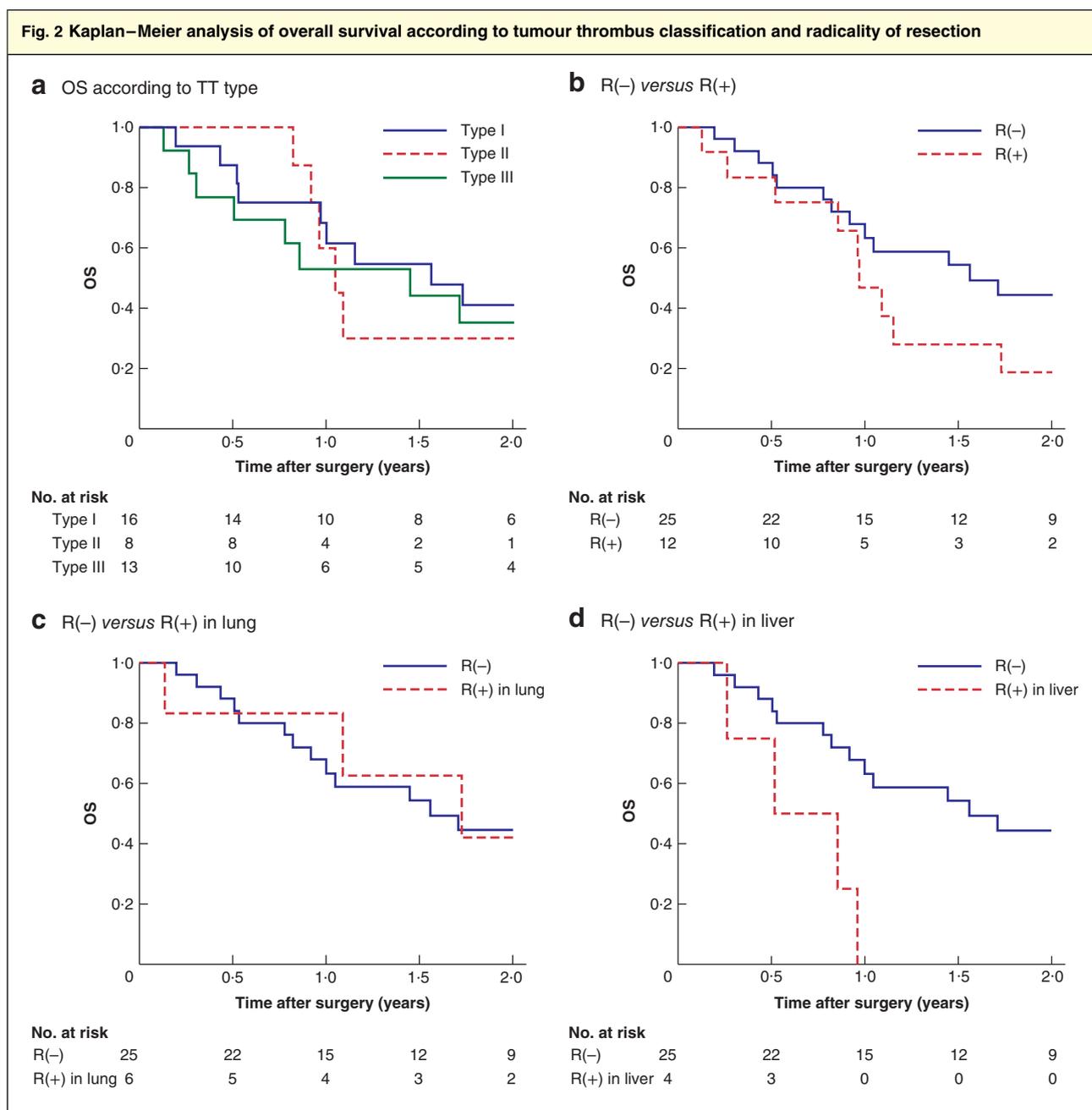
Characteristics of patients according to thrombus type

Patients' demographic backgrounds and tumour characteristics were similar in the three TT groups (type I,

16 patients; type II, 8; type III, 13) (*Table 2*). Preoperative treatment, including TACE, HAIC with radiotherapy and transarterial embolization, was performed in four patients with type I, in three with type II, and in three with type III TT.

Operative procedure and surgical outcome

Operative procedures and short-term outcomes for patients in the three TT groups are shown in *Table 3*. Although the incidence of major hepatic resection was



Overall survival (OS) according to a classification of tumour thrombus (TT) type, b R(-) versus R(+) resection, c R(-) versus R(+) resection in lung only, and d R(-) and R(+) resection in the liver. a $P = 0.767$, b $P = 0.172$, c $P = 0.907$, d $P = 0.009$ (log rank test).

similar, the need for total hepatic vascular exclusion was greater for patients with type II (5 of 8 patients) and type III (11 of 13) TT than in those with type I (5 of 16) ($P = 0.015$). IVC reconstruction with simple suture closure was possible in most patients. An active venovenous bypass (VVB) was done in one patient with a type

III thrombus, and CPB was required for one patient with type II and three patients with type III TT. The rate of resection with curative intent with no macroscopic residual tumour (R(-)) was similar in the three groups. Duration of surgery and estimated blood loss increased from type I to type II to type III TT. Although the frequency of

complications increased in a similar manner, median postoperative length of hospital stay was similar and the in-hospital mortality rate was zero in all groups. Two patients died within 90 days of surgery: a 66-year-old man with type I thrombus died on postoperative day 71 from recurrence in the liver after resection with curative intent, and a 75-year-old woman with type III thrombus died on day 48 from residual tumour in the lung. Both patients were discharged, but they died from aggressive cancer progression. Pulmonary artery embolism and arrhythmia, which were considered characteristic complications for this procedure compared with the standard operation, occurred, all in patients who had not required VVB or CPB.

Postoperative therapy for resection with residual tumour

Twelve patients had residual tumours: lung only, six patients; lymph node, one patient; peritoneum and TT in the splenic vein, one; remnant liver only, one; remnant liver and lung, two; remnant liver, lung and adrenal gland, one patient (Table 3).

Systemic chemotherapy with 5-FU plus cisplatin or oral fluoropyrimidine was administered to four patients with residual tumour in the lung only, one patient with lymph node metastasis, and one patient with peritoneal dissemination. One patient with residual tumour in the lung had radiotherapy, followed by complete remission. HAIC was administered to three patients with residual tumour in the remnant liver.

Long-term patient outcomes

OS was not significantly different between the three TT groups ($P = 0.767$). For type I, median OS was 18.7 months, and 1-, 3- and 5-year OS rates were 61, 34 and 17 per cent. The respective values were 12.6 months, and 60, 30 and 30 per cent for type II, and 17.4 months, and 53, 26 and 13 per cent for type III TT (Fig. 2a). RFS was similar in the three groups (Fig. S1, supporting information).

Outcomes were similar for the ten patients who had preoperative treatment and the 27 who did not (median OS 30.9 versus 13.8 months respectively; $P = 0.306$) (Fig. S2, supporting information), and for the 23 patients with PVTT (Vp2–4) and the 14 without PVTT (Vp0–1) (median OS 12.6 versus 26.8 months respectively; $P = 0.191$) (Fig. S3, supporting information).

OS was also similar in patients who had surgery with curative intent (R(-)) and those with residual tumours (R(+)) ($P = 0.172$) (Fig. 2b), and in patients

Table 4 Type of recurrence and treatment

	Type I (n = 9)	Type II (n = 5)	Type III (n = 8)
Site of first recurrence			
Intrahepatic only	5	3	4
Lung only	1	0	1
Intrahepatic and lung	1	1	1
Other organ	2	1	2
Treatment for first recurrence			
Resection	0	0	1 (brain)
TACE	3	1	2
HAIC	0	0	1
Systemic chemotherapy	2	0	2
Sorafenib	2	0	0
Radiotherapy	1	0	0
Best supportive care	1	4	2

TACE, transcatheter arterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy.

with Child–Pugh grade A and those with grade B disease ($P = 0.060$) (Fig. S4, supporting information). OS and RFS were similar in patients treated during the early period (before sorafenib was prescribed in Japan, 1986–2008) and the later period (after sorafenib introduction, 2009–2017) (Fig. S5a,b, supporting information). Although OS was no different between the 25 patients who had resection with curative intent and the six with macroscopic residual tumour in the lung only (median OS: 18.7 versus 20.7 months respectively; $P = 0.907$) (Fig. 2c), the four patients with macroscopic residual tumour in the liver (in liver alone, 1 patient; liver and lung, 2; liver and adrenal gland, 1) had poorer OS than those with no residual tumour (median OS 8.3 versus 18.7 months respectively; $P = 0.009$) (Fig. 2d).

Type of recurrence and treatment

The first recurrence occurred most frequently only in the remnant liver for all types of TT (type I, 5 patients; type II, 3 patients; type III, 4 patients), followed in frequency by multiple metastases in other organs, such as the adrenal gland, brain and bone, and then by multiple metastases in the remnant liver and lung (Table 4). TACE was used most frequently to treat recurrence.

Prognostic factors for overall survival and recurrence

Age above 70 years and residual tumour in the liver were identified as prognostic factors for OS in the Cox regression analysis (Table 5). In addition, age above 70 years,

Table 5 Multivariable analysis of prognostic factors for overall and recurrence-free survival

	Hazard ratio	P
Overall survival		
Age > 70 years	0.37 (0.16, 0.88)	0.024
Residual tumour in liver	5.22 (1.56, 17.43)	0.007
Recurrence-free survival		
Age > 70 years	0.12 (0.03, 0.41)	0.001
Platelet count < 100 000/ μ l	0.10 (0.01, 0.90)	0.040
Distribution of tumour (unilobar)	0.18 (0.05, 0.69)	0.013

Values in parentheses are 95 per cent confidence intervals.

platelet count below 100 000/ μ l and unilobar tumour distribution were identified as prognostic factors for longer RFS (Table 5).

Discussion

This multi-institutional retrospective study found that liver resection with thrombectomy for TT of the IVC or RA leads to moderate survival in patients undergoing macroscopic complete resection or with residual tumour only in lung, with acceptable postoperative safety. The multivariable analysis revealed that residual tumour in the remnant liver was an independent prognostic factor for OS.

Little is known about TT of the IVC or RA owing to its rarity, and the therapeutic options and their indications, including resection, remain controversial²². The novel finding of this large case series, describing details of operative procedures, as well as short- and long-term patient outcomes, was that the OS of patients with residual tumours in the lung alone after resection was similar to that of patients who had resection with curative intent.

Some authors have reported the median OS for best supportive care of patients with this stage of HCC to be 2–5 months^{7,8}, and 4.5–10.1 months for those receiving treatment other than resection^{8,12}. Recently, Kokudo and colleagues¹², in an analysis of data from the Liver Cancer Study Group of Japan database, reported excellent patient outcomes for patients with HCC and IVC TT who received systemic chemotherapy or HAIC, with a median OS of 15.4 months. In contrast, for surgical resection, promising median OS results in these patients have been reported as 16.7–30.8 months^{8,12,13,15}. These reports imply that resection should be incorporated in the multidisciplinary treatment of this advanced disease. Further investigation is needed to elucidate the indications for resection in patients with IVC/RA TT, by

comparing outcomes with those of patients who had chemotherapy.

Although the long-term outcomes were not different among the various TT types, as proposed by Li *et al.*¹⁴, this classification was useful to select the operative procedure, especially for patients requiring CPB, as well as to predict the short-term surgical outcome. In addition, hepatic resection with thrombectomy for IVC/RA TT was performed safely in the present cohort. As HCC is less likely to invade the vascular wall, combined resection of the IVC wall, or reconstruction with artificial vascular graft, was not needed in most of the patients. In addition, the TT could be pulled downward into the IVC, even in type III disease, by mobilizing the liver caudally¹⁰. However, thrombectomy under CPB should be performed immediately when the TT has reached the tricuspid valve, owing to the potential for occlusion¹⁰. The present authors' criteria for determining a CPB indication could be useful to perform this procedure safely.

The characteristic complications of this surgery, such as pulmonary embolism and arrhythmia, require special attention as they can be life-threatening. Although a recent report²³ observed cardiac events in only 0.9 per cent of patients after hepatectomy, these events, including pulmonary embolism and arrhythmia, occurred in seven of the 37 patients in the study. Furthermore, cardiac events occurred, all in patients who had not required VVB or CPB, contrary to expectations; however, considering the procedures used, it is not hard to imagine that the risk of cardiac events is extremely high, whether or not extracorporeal circulation was used. Although the in-hospital mortality rate was zero in the present study, surgeons should be aware of these complications and treat them as soon as possible.

The authors acknowledge several limitations to this study. First, it was retrospective with a limited number of patients, and thus could include selection bias. This study also lacked an appropriate control group of patients with HCC with TT who were not considered for resection. One reason for the similar long-term outcomes among the different TT classifications could be selection bias caused by fewer non-curative resections performed in the type III group. Second, the study period for this analysis was long. Preoperative and postoperative treatment strategies and treatment options after recurrence, including use of sorafenib³, have changed during the study interval; however, this limitation could not be avoided for this analysis of a small cohort of patients with TT in the IVC or RA, and outcomes of patients between the early and late study period (before and after sorafenib

use in Japan) were similar. Further investigation, including a meta-analysis from retrospective analyses, could elucidate the surgical benefits and the indications for this disease.

One-third of the patients in this study had PVTT, which is a well known prognostic factor for HCC²⁴. The frequent coexistence of PVTT and IVC/RA TT may be due to the epithelial–mesenchymal transition induced in these advanced tumours^{13,25}; therefore, it is important to remove PVTT completely during thrombectomy. Although PVTT was not identified as a prognostic factor in the present study, this could be due to the small sample size. In addition, almost all patients experienced recurrence after resection with curative intent. Although the liver was the first site of recurrence in half of the patients, the remaining patients had recurrence in extrahepatic sites, which usually occurs in only 6.7–15.5 per cent of those who have resection with curative intent^{26,27}.

The present findings strongly suggest that development of a novel treatment strategy to control macroscopic or occult residual tumour is needed urgently to improve patient outcomes, especially for patients with residual tumour in the liver or those experiencing aggressive cancer progression after resection. No RCTs have demonstrated the efficacy of adjuvant or neoadjuvant therapy to improve outcomes after resection for HCC, with or without TT^{2,22,28}, and the outcomes were similar in patients with and those without preoperative treatment in the present study. However, preoperative²⁹ and postoperative³⁰ chemotherapy, including HAIC, could potentially be used to identify patients with aggressive tumour progression and to prevent recurrence after resection. In addition, favourable local control has been reported recently for radioembolization³¹ and external-beam radiotherapy³² for HCC with macrovascular invasion, and could be a preoperative treatment option. For patients with extrahepatic residual tumour, S-1³³ and molecularly targeted drugs such as sorafenib^{3,34}, lenvatinib³⁵, regorafenib¹, ramucirumab^{36,37} and cabozantinib³⁸ have shown promise. Novel strategies including these drugs could improve the outcomes of patients with this advanced stage disease, confer more significance on surgery, and consequently expand the indication for surgery.

Acknowledgements

The authors thank Editage (www.editage.jp) for English-language editing.

Disclosure: The authors declare no conflict of interest.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.