Randomized clinical trial

Randomized clinical trial of chemoembolization plus radiofrequency ablation *versus* partial hepatectomy for hepatocellular carcinoma within the Milan criteria

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Background: **This study aimed to compare sequential treatment by transcatheter arterial chemoembolization (TACE) and percutaneous radiofrequency ablation (RFA) with partial hepatectomy for hepatocellular carcinoma (HCC) within the Milan criteria.**

Methods: **In a randomized clinical trial, patients with HCC within the Milan criteria were included and randomized 1 : 1 to the partial hepatectomy group or the TACE + RFA group. The primary outcome was overall survival and the secondary outcome was recurrence-free survival.**

Results: **Two hundred patients were enrolled. The 1-, 3- and 5-year overall survival rates were 97·0, 83·7 and 61·9 per cent for the partial hepatectomy group, and 96·0, 67·2 and 45·7 per cent for the TACE + RFA group ($P = 0·007$). The 1-, 3- and 5-year recurrence-free survival rates were 94·0, 68·2 and 48·4 per cent, and 83·0, 44·9 and 35·5 per cent respectively ($P = 0·026$). On Cox proportional hazard regression analysis, HBV-DNA (hazard ratio (HR) 1·76; $P = 0·006$), platelet count (HR 1·00; $P = 0·017$) and tumour size (HR 1·90; $P < 0·001$) were independent prognostic factors for recurrence-free survival, and HBV-DNA (HR 1·61; $P = 0·036$) was a risk factor for overall survival. The incidence of complications in the partial hepatectomy group was higher than in the TACE + RFA group (23·0 *versus* 11·0 per cent respectively; $P = 0·024$).**

Conclusion: **For patients with HCC within the Milan criteria, partial hepatectomy was associated with better overall and recurrence-free survival than sequential treatment with TACE and RFA. Registration number: ACTRN12611000770965 (http://www.anzctr.org.au/).**

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Introduction

Hepatocellular carcinoma (HCC) remains a major clinical challenge in many parts of the world. For patients with HCC within the Milan criteria, the best treatment is liver transplantation, especially for those with decompensated liver cirrhosis[1]. Unfortunately, the demand far exceeds the availability of liver grafts. Alternative ways to treat these patients are needed urgently. Both liver resection and radiofrequency ablation (RFA) are likely to be good alternative treatment options[2–8]. Liver resection is considered the first-line treatment for small liver cancers, with a survival rate of 60–70 per cent at 5 years, and RFA has been proposed as an alternative to liver resection when treating small HCC of less than 3 cm in diameter, as it achieves similar overall survival (OS) in these patients[6,9,10]. With increasing tumour size, local recurrence is more common and RFA is less appropriate as a treatment with curative intent. It has been reported[11–14] that transcatheter arterial chemoembolization (TACE) can help RFA to increase the ablation area and achieve a better survival outcome. The present trial was undertaken to compare the sequential treatment of TACE and RFA *versus* partial hepatectomy in the treatment of HCC within the Milan criteria.

Methods

From June 2006 to April 2009, all patients with HCCs within the Milan criteria in the Third Department of Hepatic Surgery at Eastern Hepatobiliary Surgery Hospital were considered for enrolment in the study. The diagnosis of HCC followed the criteria of the American Association

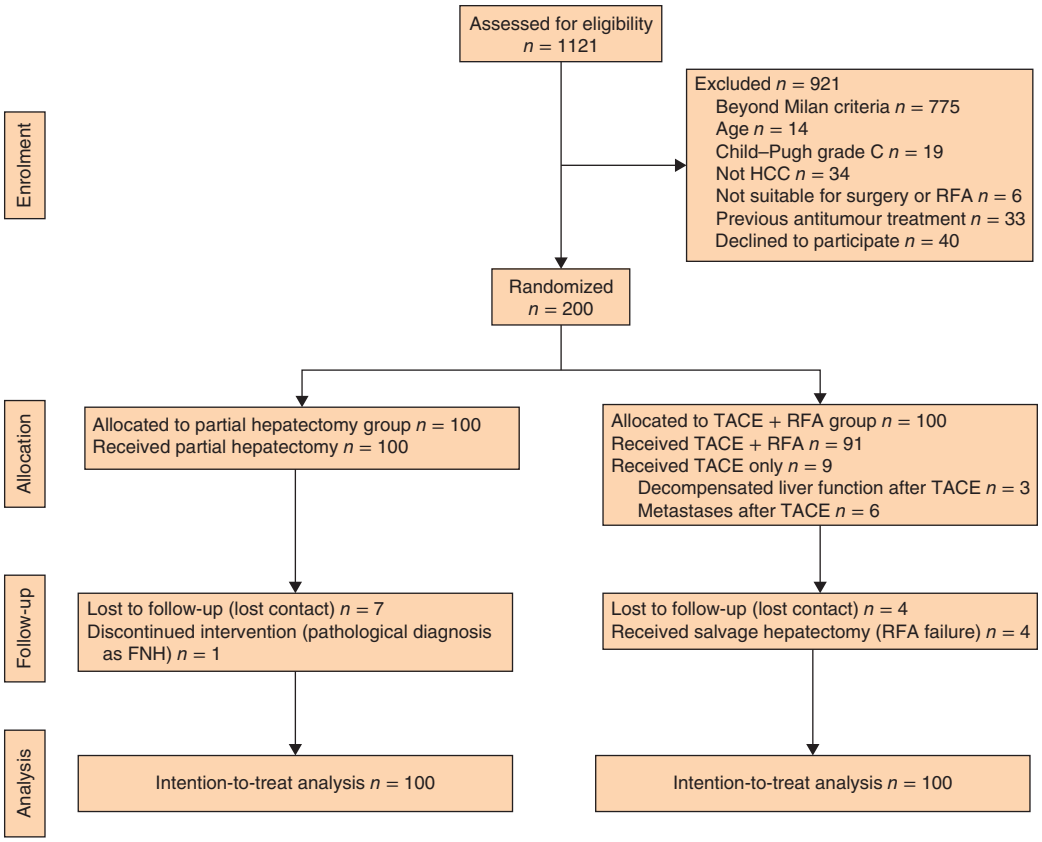

Fig. 1 CONSORT diagram for the trial. HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization; FNH, focal nodular hyperplasia

for the Study of the Liver Diseases[15]. Inclusion criteria were: no previous treatment for cancer; age between 18 and 80 years; a solitary HCC nodule of 5 cm or less, or up to three nodules of 3 cm or less in size; treatable by either partial hepatectomy or TACE plus RFA; Child–Pugh grade A or B. Exclusion criteria were: radiological appearance of macroscopic vascular invasion or extrahepatic metastases; contraindications to hepatectomy, TACE or RFA.

Study design

As different treatment methods were used in this trial, double-blinding was impractical. Patients were randomized in a 1:1 ratio to the two groups, using random numbers. The random allocation sequence was generated from a computer by a research assistant who was not involved in the study. After the surgeons had informed patients about the study and the treatment plan, and obtained written informed consent, they then informed the research assistant who assigned participants to the interventions according to the random allocation. The time between randomization and treatment was less than 1 week. The trial was approved by the Ethics Committee of Eastern Hepatobiliary Hospital before it started, and registered retrospectively at the Australian New Zealand Clinical Trials Registry (ACTRN12611000770965).

Partial hepatectomy

Partial hepatectomy was carried out under general anaesthesia through a right subcostal incision. Non-anatomical liver resection was performed to resect the tumour with a margin of at least 1 cm. For patients with a tumour adjacent to major vessels, and when a margin of 1 cm could not be achieved, the tumour was resected with as much margin as possible to avoid residual tumour. For patients with multiple tumours, either a single liver resection was carried out when the lesions were adjacent to one another, or multiple resections were performed. Pringle's manoeuvre was used routinely with a clamp–unclamp cycle of 15 min–5 min. Hepatic parenchymal transection was performed using the clamp crushing method.

Sequential treatment of TACE and RFA

Patients in the TACE + RFA group first received TACE and then RFA within 4 weeks. TACE was done using a Seldinger technique with femoral arterial puncture under local anaesthesia. The hepatic artery supplying the tumour was cannulated selectively. Lipiodol® Ultra-Fluide (Guerbet Laboratories, Aulnay-Sous-Bois, France) 5–10 ml, doxorubicin 40 mg and fluorouracil 1000 mg were injected. When treating patients with multiple tumours, after arteriography the tumour-feeding artery to each tumour was cannulated and an emulsion of drugs, as described above, was injected. All of this was done in a single session.

RFA was performed percutaneously using high-frequency induced thermotherapy equipment with 15-G needle electrodes (Berchtold Medizin-Elektronik, Tuttlingen, Germany). If the tumour diameter was less than 3 cm, a single electrode was used. For larger tumours, multiple ablations were applied. Under real-time ultrasound guidance (EUS-405; Hitachi Medical Systems, Tokyo, Japan), an electrode was inserted into the tumour with the tip reaching the distal margin. The pump was then activated for saline injection at a rate of 2 ml/min during ablation. The radiofrequency unit was used with an output power of 60 W for 6–20 min, depending on the size of the tumour.

Outcomes and follow-up

The primary endpoint of the trial was OS and the secondary endpoint was recurrence-free survival (RFS). Both were calculated from date of treatment to date of tumour recurrence or death. Local tumour recurrence in the TACE + RFA group was defined as one of the following within 4 weeks of treatment: iodized oil deposited in the treated nodule on the margin or out of the ablative area on contrast-enhanced CT; an enhanced area within the ablative area or less than 1 cm from its border on imaging with contrast-enhanced CT or MRI; growth of the ablative area. Residual tumour after RFA was considered as local tumour recurrence. In the partial hepatectomy group, local tumour recurrence was defined as tumour recurrence in the surgical area or less than 1 cm from its border.

All patients were assessed by three-phase CT or MRI, liver function tests and serum α-fetoprotein (AFP) level 4 weeks after treatment, with follow-up every 3 months thereafter. At each follow-up visit, ultrasonography of the liver, liver function tests and AFP determination were performed routinely. Chest X-ray and three-phase CT/MRI were done every 6 months. Patients with tumour recurrence were treated actively with liver resection, RFA, TACE or transplantation, as indicated. Postoperative complications were ranked according to the modified Dindo–Clavien classification[16].

Table 1 Preoperative clinical data

	Partial hepatectomy ($n = 100$)	TACE + RFA ($n = 100$)
Age (years)*	49 (30–76)	52 (31–80)
Sex ratio (M : F)	94 : 6	86 : 14
Total bilirubin (μmol/l)*	15·6 (6·8–38·8)	15·7 (1·7–46·8)
ALT (units/l)*	39·7 (13·0–523·5)	35·2 (6·8–158·6)
AST (units/l)*	35·7 (16·0–760·4)	34·3 (14·9–150·1)
Prothrombin time (s)*	11·8 (9·6–24·2)	11·8 (10·0–19·6)
Serum albumin (g/l)*	44·6 (31·5–79·0)	43·5 (25·6–79·0)
Platelet count ($\times 10^9$/l)*	132 (18–269)	136 (19–351)
HBsAg-positive	90	87
HBeAg-positive	30	39
HBV-DNA (units/l)		
<1000	57	47
≥1000	43	53
Child–Pugh grade		
A	98	96
B	2	4
AFP (μg/l)†		
≤20	50	32
>20	50	68
Tumour diameter (cm)*	3·0 (0·6–5·0)	2·8 (0·6–5·0)
Tumour no.		
Single	91	86
Multiple	9	14
MELD score*	5 (–4 to 16)	5 (–2 to 15)

*Values are median (range). TACE, transcatheter arterial chemoembolization; RFA, percutaneous radiofrequency ablation; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; AFP, α-fetoprotein; MELD, Model for End-stage Liver Disease. †$P = 0·010$ (χ^2 test).

Sample size

Sample size was calculated assuming an α risk of 0·05, a β risk of 0·2 with a power of 80 per cent, and a survival rate difference of 19 per cent between the two groups in year 4 (TACE + RFA *versus* hepatectomy: 49 *versus* 68 per cent). The data were obtained from previous retrospective studies in the authors' institution carried out with small sample sizes and with the inherent risk of selection bias. The number of patients in each group was estimated to be 75. Assuming a drop-out rate of 20 per cent, at least 94 patients were required in each group.

Statistical analysis

OS and RFS were calculated from the date the patients received treatment. All patients were followed up until death or until 12 November 2013. When a patient was lost to follow-up, RFS and OS were calculated to the

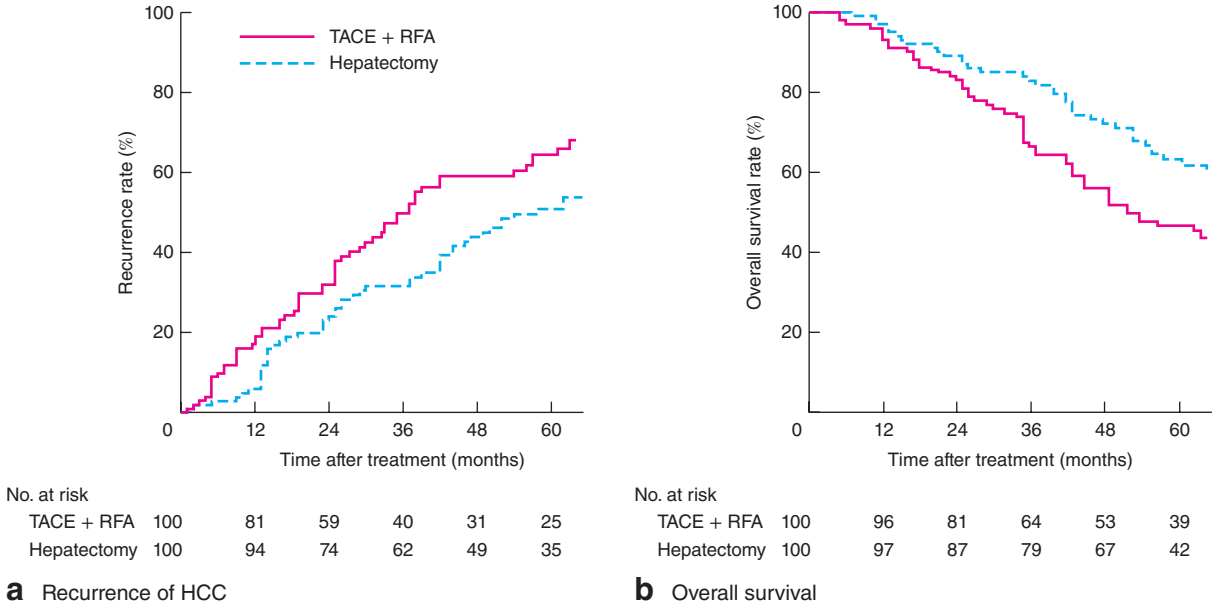

Fig. 2 **a** Recurrence rate and **b** overall survival in patients with hepatocellular carcinoma (HCC) following treatment with transcatheter arterial chemoembolization (TACE) plus radiofrequency ablation (RFA) or hepatectomy. **a** $P = 0{\cdot}026$, **b** $P = 0{\cdot}007$ (log rank test)

date of last follow-up. In patients with multiple tumours, only tumours with the largest diameter were included in the analysis. Once an ablated lesion showed local tumour recurrence, all other tumours of that patient were censored at the same time.

All data were analysed using SPSS® version 18.0 statistical software (IBM, Armonk, New York, USA) or the R program with the cmprsk package (R Foundation for Statistical Computing, Vienna, Austria). Data are presented as median (range) for quantitative variables and as absolute frequencies for qualitative variables. Comparison of continuous data between the two groups was done using Student's *t* test for normally distributed data and the Mann–Whitney *U* test for data with a non-normal distribution. Categorical data were compared with the χ^2 test or Fisher's exact test as appropriate. An intention-to-treat analysis was followed when performing survival analysis. OS and RFS rates were calculated using the life-table method; comparisons between the two groups and survival curves were constructed with both the Kaplan–Meier method, using the log rank test, and the competing adjusted model, using Gray's test. Univariable and multivariable Cox proportional hazards regression analysis was used to estimate prognostic factors influencing OS and RFS; all variables with $P < 0{\cdot}100$ on univariable comparison were subjected to multivariable analysis. All tests were two-sided, and the difference was considered significant when $P < 0{\cdot}050$.

Results

From June 2006 to April 2009, 1121 patients with hepatocellular carcinoma were treated in the Third Department of Hepatic Surgery at Eastern Hepatobiliary Surgical Hospital, of whom 775 had disease beyond the Milan criteria. Of the 346 patients with liver cancer within the Milan criteria, 200 were enrolled in the study (*Fig. 1*). Among these 200 patients, 173 were positive for hepatitis B surface antigen (HBsAg), six were positive for anti-hepatitis C virus (anti-HCV), four were positive for both HBsAg and anti-HCV, and 17 were negative for both HBsAg and anti-HCV. Of the 177 patients with positive HBsAg, 91 had detectable hepatitis B virus (HBV) DNA and received antiviral treatment with nucleoside analogues. Of the ten patients with positive anti-HCV, four had detectable HCV-RNA and received interferon.

Follow-up ranged from 5 to 85 (median 56) months. In the hepatectomy group, all 100 patients had a successful partial hepatectomy. Median tumour diameter was 3·0 cm, and median distance between tumour and resection margin was 1·7 cm. After treatment, one patient had a pathological diagnosis of focal nodular hyperplasia, seven were lost to follow-up, and one underwent salvage liver transplantation for postoperative liver failure. In the TACE + RFA group, RFA was performed after TACE within a median of 8 (range 1–23) days. Median tumour diameter was 2·8 cm and median diameter of the ablated area was 4·2 cm; the median distance between tumour and ablation margin

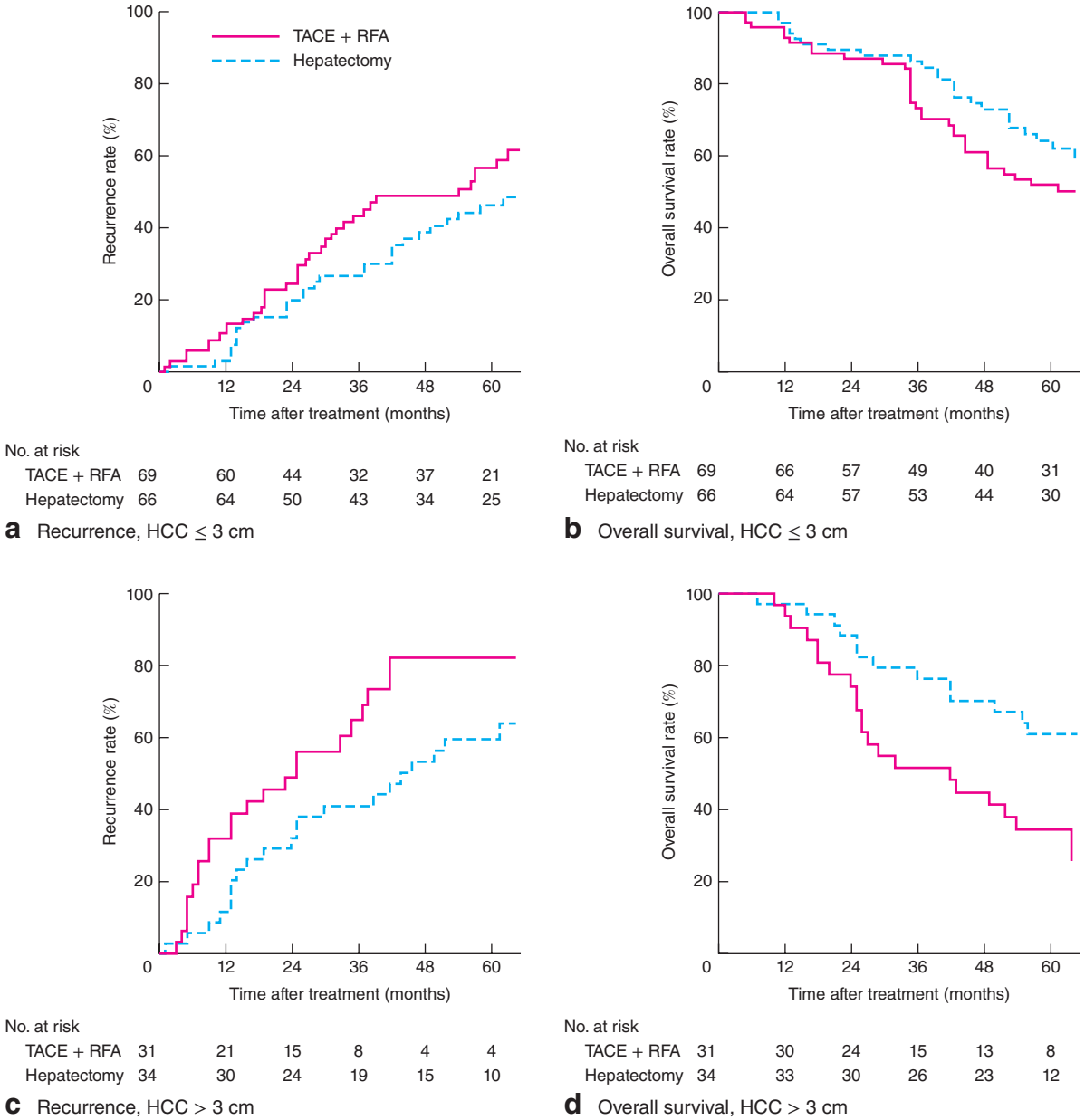

Fig. 3 a,c Recurrence rate and **b,d** overall survival in patients with hepatocellular carcinoma (HCC) following treatment with transcatheter arterial chemoembolization (TACE) plus radiofrequency ablation (RFA) or hepatectomy, according to HCC size: **a,b** 3 cm or less; **c,d** more than 3 cm. **a** $P = 0{\cdot}135$, **b** $P = 0{\cdot}112$, **c** $P = 0{\cdot}032$, **d** $P = 0{\cdot}012$ (log rank test)

was 0·7 cm. During follow-up, four patients were lost to follow-up, four underwent salvage hepatectomy for RFA failure and nine received TACE alone (liver dysfunction, 1; low platelet count, 2; metastases after TACE, 6). The resection margin in the partial hepatectomy group was wider than the ablated margin in the TACE + RFA group (median 1·7 *versus* 0·7 cm respectively; $P < 0{\cdot}001$). Local tumour progression occurred in one patient in the partial hepatectomy group and 18 in the TACE + RFA group ($P < 0{\cdot}001$).

Preoperative clinical data for the patients are shown in *Table 1*. The only significant difference between the groups was in AFP level. On an intention-to-treat analysis, the 1-, 3- and 5-year OS rates were 97·0, 83·7 and 61·9 per cent

Table 2 Univariable and multivariable Cox proportional hazards regression analyses of factors associated with recurrence and survival

		Multivariable analysis	
	Univariable *P*	Hazard ratio	*P*
Recurrence-free survival			
HBsAg (positive *versus* negative)	0·021	1·69 (0·76, 3·74)	0·197
HBV-DNA (< 1000 *versus* ≥ 1000 units/l)	0·006	1·76 (1·18, 2·62)	0·006
Platelet count	0·008	1·00 (0·99, 1·00)	0·017
Total bilirubin	0·022	1·01 (0·98, 1·04)	0·625
Albumin	0·082	1·00 (0·97, 1·03)	0·959
Child–Pugh grade (A *versus* B)	0·017	1·62 (0·58, 4·51)	0·353
Tumour diameter	0·009	1·90 (1·55, 2·34)	< 0·001
Group (TACE + RFA *versus* hepatectomy)	0·028	0·69 (0·47, 1·03)	0·070
Overall survival			
HBsAg (positive *versus* negative)	0·088	1·42 (0·63, 3·21)	0·402
HBeAg (positive *versus* negative)	0·076	1·20 (0·77, 1·87)	0·430
HBV-DNA (< 1000 *versus* ≥ 1000 units/l)	0·003	1·61 (1·03, 2·51)	0·036
Platelet count	0·006	1·00 (0·99, 1·00)	0·149
Albumin	0·040	0·99 (0·96,1·02)	0·653
Child–Pugh grade (A *versus* B)	0·019	2·07 (0·78, 5·55)	0·147
MELD score	0·024	1·02 (0·96, 1·09)	0·474
Group (TACE + RFA *versus* hepatectomy)	0·008	0·68 (0·44, 1·05)	0·084

Values in parentheses are 95 per cent c.i. HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; TACE, transcatheter arterial chemoembolization; RFA, percutaneous radiofrequency ablation; HBeAg, hepatitis B e antigen; MELD, Model for End-stage Liver Disease.

in the partial hepatectomy group, and 96·0, 67·2 and 45·7 per cent in the TACE + RFA group. The 1-, 3- and 5-year RFS rates were 94·0, 68·2 and 48·4 per cent, and 83·0, 44·9 and 35·5 per cent respectively. Using Kaplan–Meier analysis, there was a significant difference between the two groups in both RFS ($P = 0·026$) and OS ($P = 0·007$) (*Fig. 2*). When using the Gray's test for competing risk analysis, there was a difference in OS ($P = 0·003$) but not in RFS ($P = 0·119$). On further subgroup analysis, there were no differences in either RFS ($P = 0·135$) or OS ($P = 0·112$) between the 69 patients with HCC of 3 cm or less who received TACE + RFA and the 66 who underwent partial hepatectomy (*Fig. 3*). For patients with HCC larger than 3 cm, there was a difference in both RFS ($P = 0·032$) and OS ($P = 0·012$) between the 31 patients in the TACE + RFA group and the 34 in the partial hepatectomy group.

On multivariable Cox proportional hazards regression analysis, HBV-DNA, platelet count and tumour size were independent prognostic factors for RFS, whereas HBV-DNA was the only independent prognostic factor for OS (*Table 2*).

There was no 30- or 90-day mortality after treatment in either group. The incidence of complications in the partial hepatectomy group was 23·0 per cent *versus* 11·0 per cent in the TACE + RFA group ($P = 0·024$). Complications in the partial hepatectomy group included pleural effusion (Dindo–Clavien grade III, 8 patients), biliary fistula (grade IIIa, 5), abdominal ascites (grade II, 4), liver dysfunction (grade II, 2), pneumonia (grade II, 2), wound infection (grade I, 1) and abdominal infection (grade II, 1), whereas in the TACE + RFA group complications included pleural effusion (grade IIIa, 3; grade II, 1), liver dysfunction (grade II, 3), abdominal ascites (grade II, 1; grade I, 2) and abdominal bleeding (grade II, 1).

Discussion

Liver transplantation is probably the best treatment for small HCC, but alternatives are commonly used because of organ shortage. It is still controversial as to whether partial hepatectomy or RFA is the better alternative treatment for small HCC. Several studies and trials[4,7,17,18] have favoured liver resection because of its lower local recurrence rate, and better RFS or OS. However, other studies[5,6,8] have shown local ablative therapy to produce OS or RFS rates comparable to or even better than those of liver resection.

TACE is a regional therapy that treats HCC by obstructing tumour vessels and providing regional chemotherapy. Theoretically, it can reduce heat loss during RFA, increase the ablative area and also treat satellite tumour foci that were not detected by CT or MRI before treatment. Some studies[12,14] have shown that the sequential treatment of TACE and RFA increases the therapeutic effect, especially in large HCC. Thus, sequential treatment of TACE and RFA may achieve better or similar therapeutic effects compared with partial hepatectomy. Three retrospective studies[19–21] have compared these two treatments, but no randomized clinical trials have yet been reported.

The results of the present trial showed that sequential treatment with TACE and RFA was associated with worse RFS and OS than partial hepatectomy. This differs to some extent from previously published work[19–21]. Kagawa and colleagues[19] showed that sequential treatment with TACE and RFA resulted in similar OS but worse RFS, compared with surgical resection. Yamakado and co-workers[20] and Kim *et al.*[21] found no obvious difference in either OS or RFS. Patients in the Kagawa and Yamakado studies[19,21] mostly had HCV-related HCC, whereas the majority of patients in the present study had HBV-related HCC. A further limitation of these studies was that they were not randomized.

Although the therapeutic effect of RFA can be enhanced after TACE owing to hepatic blood inflow occlusion with reduced heat loss, most heat loss by convection occurs when the ablative spot is adjacent to large hepatic vessels, and these cannot be embolized by TACE. In the present study, TACE and RFA resulted in worse survival outcomes than partial hepatectomy. The potential harmful effects of TACE have been shown in a previous study from the authors' unit[22]. In that study, TACE before liver resection produced worse results than liver resection alone because some resectable HCCs progressed to unresectability when patients developed deranged liver function following TACE. In addition, some authors[23,24] have pointed out that TACE is not necessary when RFA can completely ablate the tumour, and it may even increase the occurrence of adverse events. The smaller the tumour, the less it is necessary to combine TACE with RFA; HCC of less than 3 cm is generally accepted as an indication for treatment with RFA alone[25]. Subgroup analysis showed that OS and RFS were comparable between TACE + RFA and hepatectomy when tumour size was 3 cm or less, but worse in the TACE + RFA group when the tumour was greater than 3 cm in diameter.

In this study the resection margin in the partial hepatectomy group was larger than the ablated margin in the TACE + RFA group. When tumours are located adjacent to major hepatic vessels, it is difficult to obtain an ideal margin by either liver resection or RFA. However, RFA has a higher risk of incomplete ablation because of the possible 'heat sink' effect. It has been reported[26] for HCC of 3 cm or more that 29 per cent had vascular invasion and 12 per cent had satellites. Thus, a sufficiently wide surgical or ablative margin is necessary to achieve cure. Both the surgical and the ablative margin were independent prognostic factors for OS in patients with HCC[27,28]. Furthermore, even when tumours were shown radiologically to be ablated completely, viable tumour cells could still be found in the ablated area, and residual tumour rates were shown to be as high as 37 per cent in HCC of 3 cm or above[29]. Incomplete ablation enhances invasiveness and metastasis of HCC, resulting in a worse prognosis[30,31]. This may explain why patients in the partial hepatectomy group had better long-term survival than those in the TACE + RFA group in the present study.

There are a few limitations to this study. First, patients in the TACE + RFA group had a higher AFP level than those in the partial hepatectomy group. Although AFP was shown not to be a prognostic factor in this study, it has been reported in other studies[32,33] to be a risk factor for prognosis. Second, this trial was conducted in a single centre and included patients who mostly had HBV-related HCC. A large-scale, multicentre, randomized clinical trial is needed to confirm the findings of the present study. Third, most patients in the TACE + RFA group had no histological diagnosis. However, the misdiagnosis rate should be very low (1·0 per cent in the partial hepatectomy group in the present study). Data on liver cirrhosis in the TACE + RFA group could not be provided for the same reason. Fourth, the trial was registered retrospectively at the Australian New Zealand Clinical Trials Registry.

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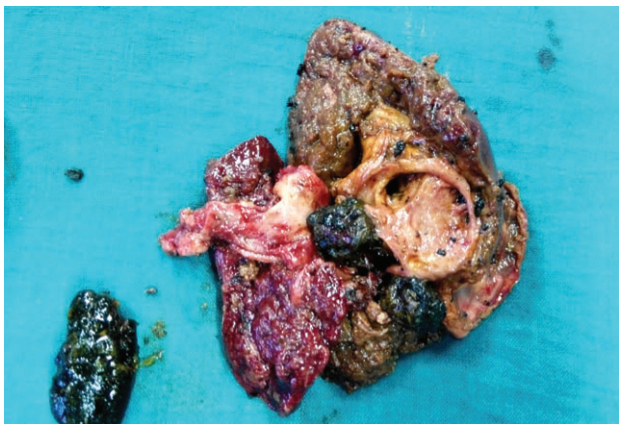
Snapshot quiz

Snapshot quiz 16/3

Question: This lesion was removed from the liver. What is it?



The answer to the above question is found on p. 373 of this issue of *BJS*.

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