Original article

Single-stage resection and microwave ablation for bilobar colorectal liver metastases

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Background: **Patients undergoing liver resection combined with microwave ablation (MWA) for bilobar colorectal metastasis may have similar overall survival to patients who undergo two-stage hepatectomy, but with less morbidity.**

Methods: **This was a multi-institutional evaluation of patients who underwent MWA between 2003 and 2012. Morbidity (90-day) and mortality were compared between patients who had MWA alone and those who underwent combined resection and MWA (CRA). Mortality and overall survival after CRA were compared with published data on two-stage resections.**

Results: **Some 201 patients with bilobar colorectal liver metastasis treated with MWA from four high-volume institutions were evaluated (100 MWA alone, 101 CRA). Patients who had MWA alone were older, but the groups were otherwise well matched demographically. The tumour burden was higher in the CRA group (mean number of lesions 3·9 *versus* 2·2; $P = 0·003$). Overall (31·7 *versus* 15·0 per cent; $P = 0·006$) and high-grade (13·9 *versus* 5·0 per cent; $P = 0·030$) complication rates were higher in the CRA group. Median overall survival was slightly shorter in the CRA group (38·4 *versus* 42·2 months; $P = 0·132$) but disease-free survival was similar (10·1 *versus* 9·3 months; $P = 0·525$). The morbidity and mortality of CRA compared favourably with rates in the existing literature on two-stage resection, and survival data were similar.**

Conclusion: **Single-stage hepatectomy and MWA resulted in survival similar to that following two-stage hepatectomy, with less overall morbidity.**

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Introduction

Over their natural course, half of all colorectal cancers metastasize to the liver. Recent advances in chemotherapy have led to the introduction of newer and more effective chemotherapeutic agents that have improved median survival in the palliative setting from 8 months to up to 20 months[1,2]. Despite current advances, liver resection remains the mainstay of treatment for patients with hepatic metastases, with an encouraging 5-year survival rate of up to 50 per cent when combined with contemporary chemotherapy[3–5].

Over the past decade, improvements in preoperative liver function assessment and multidisciplinary treatments have extended the indications for hepatic resection to include larger tumours, multiple foci of disease and bilobar disease. These treatments include liver augmentation strategies such as portal vein embolization[6,7] and associating liver partition with portal vein ligation for staged hepatectomy[8], or tumour burden-reducing strategies such as systemic or hepatic arterial chemotherapy[9] and ablative therapies[10]. Despite these improvements, there remains a subset of patients with multiple bilobar liver metastases in whom complete resection of the hepatic metastases is not feasible. To overcome this, a strategy of two-stage resection (TSR) has recently been advocated as a way of treating these diseases[11–13]. This approach allows hypertrophy of the remaining liver after a planned first-stage resection, thereby enabling a second operation with curative intent[14–16]. There have been encouraging reports of this

strategy, with good results for patients completing the intended second stage of the TSR[17–19].

Ablative techniques have been developed to enable local control of tumours while limiting damage to surrounding healthy parenchyma[20–22]. Microwave ablation (MWA) has recently been gaining favour in the treatment of both primary and metastatic unresectable hepatic lesions[22,23]. This method uses electromagnetic waves to induce tumour necrosis[24]. The potential benefits of MWA include consistently higher intratumoral temperatures, larger ablation volumes, faster ablation times, ability to use multiple probes, improved convection profile and optimal heating of cystic masses[24–26].

With a multimodal approach including MWA, hepatic resection and chemotherapy, improved survival may be achieved in patients whose tumours were initially deemed unresectable[27]. This approach of a single-stage combined resection and ablation (CRA) comprises ablation of selected lesions along with resection of others[28,29]. The present study evaluated the efficacy of this strategy in the treatment of bilobar colorectal liver metastases. The hypothesis was that CRA would be superior to TSR with regard to complications and overall outcomes.

Methods

This study was a review of a prospectively collected hepatobiliary database at four institutions – University of Louisville, Medical College of Wisconsin, Ohio State University and Carolinas Medical Center – over a 9-year interval. Institutional review board approval was obtained before initiation of the study. Consecutive patients with bilobar hepatic disease who underwent MWA from 2003 to 2012 were identified and included in the analysis. These patients were compared with consecutive patients who underwent liver resection in combination with MWA for metastatic colorectal liver cancers. Tumours were regarded as resectable if the anticipated hepatic parenchymal transection plane yielded a tumour-free margin, and in combination with ablation preserved an adequate hepatic remnant. MWA was used to eradicate lesions that were not amenable to surgical resection. Patients with extrahepatic metastases were excluded. Patients with prohibitive medical co-morbidities did not undergo tumour resection.

The decision to undertake ablation was based predominantly on three factors: whether the size of the lesion to be ablated was less than 3·5–4·0 cm; whether it was located such that a thermal ablative treatment could performed safely without damaging vital inflow or outflow structures; and whether ablation would spare sufficient normal hepatic parenchyma in patients undergoing CRA.

The present results were compared with published outcomes of TSR[17–19], using a methodology similar to that described previously[30].

All adverse events were recorded in accordance with the latest Clavien–Dindo classification of surgical complications[31]. Adverse events were recorded during the hospital stay and for 90 days after each treatment. Major complications were defined as a grade III complications or higher. Operative mortality was defined as death within 90 days of operation. Follow-up was carried out every 3 months for the first year and then every 6 months up to 5 years. It included triphasic CT of the abdomen with liver protocol and measurement of carcinoembryonic antigen level, with CT of the chest at every other follow-up visit.

Statistical analysis

Group characteristics were compared by means of Fisher's exact and Kruskal–Wallis tests. Survival was plotted using the method of Kaplan–Meier and compared using the log rank test. $P < 0{\cdot}050$ was considered statistically significant.

Data on TSR from three comparative studies[17–19] are presented in tabular form for descriptive purposes. Data from these three reports were also pooled and compared with the present experience in a *post hoc* fashion. Only the ordinal and categorical variables were analysed, using Fisher's exact or χ^2 test.

Results

Two hundred and one consecutive patients from a combined four-institution prospective database were evaluated (*Table 1*) . Of these, 100 underwent MWA alone and 101 had CRA. The median age was 62·7 (i.q.r. 55·6–70·5) years in MWA group and 59·7 (50·2–63·3) years in the CRA group. The median difference was 3 (mean 4·9, 95 per cent c.i. 3·9 to 10·4) years ($P = 0{\cdot}001$).

The use of induction treatment was similar in both groups. In the MWA group, 75 patients (75·0 per cent) received induction chemotherapy compared with 81 (80·2 per cent) in the CRA group ($P = 0{\cdot}448$). A similar number of patients received preoperative arterial therapy (0 *versus* 3 respectively; $P = 0{\cdot}153$) and radiotherapy (1 *versus* 3; $P = 0{\cdot}332$). Major resections (defined as more than 3 segments)[32] were performed in 46 patients (45·5 per cent) in the CRA group. Median hospital stay was significantly shorter in the MWA group: 4 (i.q.r. 2–6) days compared with 6 (5–8) days in the CRA group ($P < 0{\cdot}001$) (*Table 2*). There was one perioperative death in the CRA group from the sequelae of an anastomotic leak.

Table 1 Comparison of demographic and baseline data between microwave ablation alone and combined resection and ablation groups

	Microwave ablation alone ($n = 100$)	Combined resection and ablation ($n = 101$)	P‡
Age (years)*	62·7 (55·6–70·5)	59·7 (50·2–63·3)	0·001§
Sex ratio (M : F)	38 : 62	38 : 63	0·914
Ethnicity			0·128
White	90	86	
Black	8	12	
Hispanic	0	2	
Other	2	1	
Synchronous disease	61 (61·0)	64 (63·4)	0·432
CEA (ng/ml)†	76 (0·5–4577)	90·5 (0·5–4585)	0·312§
Total no. of lesions*	2·2 (2–3)	3·9 (2–4)	0·003§
Largest lesion (cm)*	2·8 (2·4–3·8)	2·1 (1·9–3·1)	0·613§
Mean clinical risk score	3	4	0·313§
Neoadjuvant chemotherapy	75 (75·0)	81 (80·2)	0·448
Intra-arterial therapy	0 (0)	3 (3·0)	0·153
Radiotherapy	1 (1·0)	3 (3·0)	0·332

Values in parentheses are percentages unless indicated otherwise; values are *median (i.q.r.) and †median (range). CEA, carcinoembryonic antigen. ‡Fisher's exact test, except §Kruskal–Wallis test.

Table 2 Comparison of outcomes between microwave ablation alone and combined resection and ablation groups

	Microwave ablation alone ($n = 100$)	Combined resection and ablation ($n = 101$)	P‡
Major resection	–	46 (45·5)	–
Positive resection margins			–
R0	–	87 (86·1)	
R1	–	13 (12·9)	
R2	–	1 (1·0)	
Complications	15 (15·0)	32 (31·7)	0·006
High-grade complications	5 (5·0)	14 (13·9)	0·030
Duration of hospital stay (days)*	4 (2–6)	6 (5–8)	< 0·001§
Overall survival after diagnosis (months)†	52·4 (45·5, 59·2)	49·7 (44·7, 54·6)	0·031¶
Recurrence-free survival (months)*	9·3 (7·5–11·1)	10·1 (7·9–12·2)	0·525¶

Values in parentheses are percentages unless indicated otherwise; values are *median (i.q.r.) and †median (95 per cent c.i.). ‡Fisher's exact test, except §Kruskal–Wallis test and ¶log rank test.

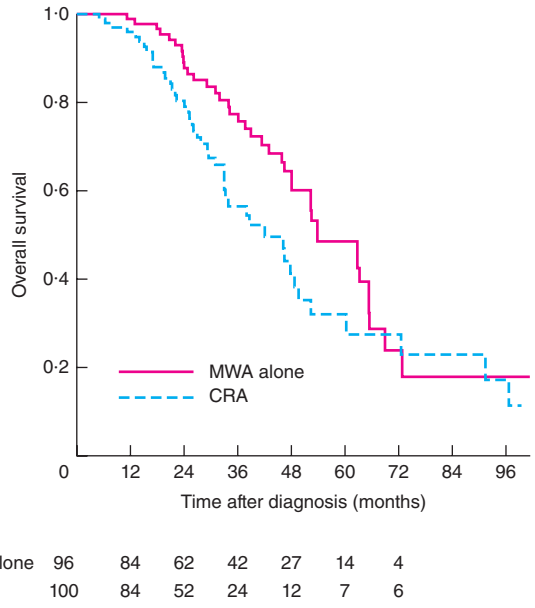

Fig. 1 Overall survival after microwave ablation (MWA) alone *versus* combined resection and ablation (CRA)

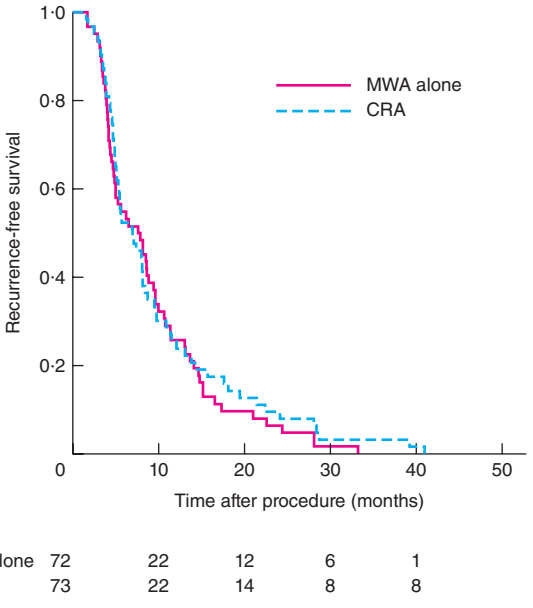

Fig. 2 Recurrence-free survival after microwave ablation (MWA) alone *versus* combined resection and ablation (CRA)

A total of 47 patients (23·4 per cent) experienced 69 complications. The complication rate for CRA was 31·7 per cent (32 of 101), significantly higher than that for MWA alone (15·0 per cent, 15 of 100) ($P = 0·006$) (*Table 2*). For the cohort overall, the median complication grade was II for patients who had a complication. There was no incidence of liver failure. Common complications included prolonged ileus (8), wound infection (7), intra-abdominal abscess (5, of which 2 required reoperation), arrhythmias (5), anastomotic leak (3, all requiring intervention), urinary tract infections (3) and bile leaks (4).

Table 3 Comparison of published series of two-stage resection with combined resection and ablation data from the present study

	Two-stage resection					
	Tsai *et al.*[19] (*n* = 35)	Wicherts *et al.*[18] (*n* = 41)	Brouquet *et al.*[17] (*n* = 65)	Pooled data (*n* = 141)	Combined resection and ablation (*n* = 101)	*P*#
Age (years)*	56·7(9·6)†	58·4	52 (35·3–69·4)	55·0	59·7 (36·7–82·4)	–
Male sex	26 (74)	22 (54)	47 (72)	95 (67·4)	63 (62·4)	–
CEA (ng/ml)*	24·4	319·4	397 (1–17 000)	–	90·5 (0·5–4585)	–
Synchronous disease	27 (77)	33 (80)	52 (80)	112 (79·4)	64 (63·4)	0·001
Neoadjuvant chemotherapy	24 (69)	39 (95)	48 (74)	111 (78·7)	81 (80·2)	0·874
Overall complications				89 (63·1)	32 (31·7)	< 0·001
1st stage	9 (26)	8 (20)	16 (25)	33 (23·4)		
2nd stage	9 (26)	24 (59)	23 (35)	56 (39·7)		0·105
High-grade complications		n.r.		23 of 100 (23·0)‡	14 (13·9)	0·033
1st stage	3 (9)		2 (3)			
2nd stage	6 (17)		12 (18)			
Bile leak	n.r.		n.r.		4 (4·0)	
1st stage		0 (0)				
2nd stage		5 (12)				
Postoperative haemorrhage	n.r.		n.r.		1 (1·0)	
1st stage		1 (2)				
2nd stage		0 (0)				
Sepsis	n.r.	n.r.	n.r.		1 (1·0)	
Relaparotomy for complication			n.r.	6 of 76 (8)‡	5 (5·0)	0·323
1st stage	2 (6)	1 (2)				
2nd stage	1 (3)	2 (5)				
Liver-related mortality§	n.r.			6 of 106 (5·7)‡	0 (0)	0·007
1st stage		0 (0)	0 (0)			
2nd stage		3 (7)	3 (5)			
Overall 90-day mortality	n.r.			6 of 106 (5·7)‡	1 (1·0)	0·021
1st stage		0 (0)	0 (0)			
2nd stage		3 (7)	3 (5)			
Median overall survival after procedure (months)	16	42	n.r.		38·4	
Median overall survival after diagnosis (months)	n.r.	57§	n.r.		49·7	
5-year survival after diagnosis (%)	n.r.	31	51¶		40·4	
1-year disease-free survival (%)	39·4	n.r.	39·4		38·3	

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.), except †mean(s.d.). ‡Only two studies were included in this comparison as one study did not report this specific complication. §Only for patients completing both stages of two-stage resection. ¶Intention-to-treat analysis. CEA, carcinoembryonic antigen; n.r., not reported. #Pooled two-stage resection *versus* combined resection and ablation (Fisher's exact test).

Four patients were readmitted within 90 days (2·0 per cent). Seven patients (2 MWA, 5 CRA; total rate 3·5 per cent) underwent a reoperation; this was not statistically different between the two groups ($P = 0·144$). The primary reasons for reoperation were anastomotic leak, bile leak and, in one patient, a retained drain. High-grade complications or major complications, defined as Clavien–Dindo III or higher, were experienced by 19 patients in total (9·5 per cent); the rate was higher in the CRA group (13·9 *versus* 5·0 per cent; $P = 0·030$). A larger number of lesions was predictive of more complications (mean number of lesions 4·0 *versus* 2·7 in patients with and without complications respectively; $P = 0·005$). Neoadjuvant chemotherapy was protective with regard to complications: 11 (7·1 per cent) of 156 patients who received neoadjuvant chemotherapy experienced complications compared with eight (18 per cent) of 45 who did not have chemotherapy ($P = 0·042$).

Fourteen (13·9 per cent) of the patients who underwent CRA had positive margins; 13 (12·9 per cent) had an R1 resection (microscopically positive margin), whereas only one had an R2 resection (grossly positive margin).

Median overall survival for the whole cohort was 51·9 months from diagnosis, and 40·9 months after ablation. Median overall survival from the time of diagnosis was longer in the MWA group: 52·4 (95 per cent c.i. 45·5 to 59·2) months *versus* 49·7 (44·7 to 54·6) months in the CRA group ($P = 0·031$) (*Fig. 1*, *Table 2*). Median overall survival after the procedure was shorter in the CRA group (38·4 *versus* 42·2 months; $P = 0·132$) but disease-free survival was similar (10·1 *versus* 9·3 months respectively; $P = 0·525$) (*Fig. 2*, *Table 2*).

The incidence of incomplete ablation was 2·0 per cent (2 patients) in the CRA group and 2·0 per cent (2 patients) in the MWA group. The rate of non-ablation but liver-only

recurrence was 5·0 per cent (5 patients) for CRA and 5·0 per cent (5 patients) for MWA alone; rates of extrahepatic recurrence alone were 41·6 per cent (42 patients) and 50·0 per cent (50 patients) respectively, and rates of both liver and extrahepatic recurrence were 51·5 per cent (52 patients) and 42·0 per cent (42 patients). Survival data were also compared in patients who received induction chemotherapy and those who did not. Patients who received induction chemotherapy before CRA had a signficantly longer median overall survival after diagnosis than those who did not: 54·3 (95 per cent c.i. 46·8 to 59·8) compared with 42·4 (31·1 to 52·9) months respectively ($P = 0·021$).

The present CRA results were compared with data for TSR reported recently by Tsai *et al.*[19], Wicherts and colleagues[18] and Brouquet and co-workers[17] (*Table 3*). Overall, there was a total of 141 patients in the TSR cohort, of whom 123 eventually completed the second-stage hepatectomy for bilobar lesions. The present CRA group was similar to the TSR cohorts with respect to the proportion of patients who had undergone induction chemotherapy (78·7 *versus* 80·2 per cent; $P = 0·874$). Tumour burden was lower than that in one of the other studies[19], where it was recorded in a similar fashion with respect to the median number of lesions and size of ablated tumours.

To gauge the total number of complications, the combined morbidity rate of both procedures in the TSR group was compared with the complication rate for CRA; based on this comparison, the complication rate for the TSR group was significantly higher: 63·1 per cent (89 of 141) *versus* 31·7 per cent (32 of 101) ($P < 0·001$) (*Table 3*). The rate of high-grade complications was also significantly higher after TSE: 23·0 per cent (23 of 100) *versus* 13·9 per cent (14 of 101) ($P = 0·033$). Complications such as bile leak, bleeding, sepsis and relaparotomy were statistically similar in the studies that recorded them specifically. At the second stage of TSR, the total rate of complications (39·7 per cent, 56 of 141) and high-grade complications (18·0 per cent, 18 of 100) were statistically similar to those after CRA ($P = 0·105$ and $P = 0·173$ respectively) (*Table 3*).

The 90-day liver-related mortality rate was significantly lower after CSR than TSR: 0 per cent *versus* 5·7 per cent (6 of 106) respectively ($P = 0·007$). The overall 90-day mortality rate was also significantly better for CRA (1·0 *versus* 5·7 per cent; $P = 0·021$).

Median survival from the time of ablation was 38·4 months for CRA in the present study, similar to that of Wicherts *et al.*[18] at 42 months, but longer than the 16 months reported by Tsai and colleagues[19]. Comparing the 5-year survival rates after diagnosis, Brouquet and colleagues reported a more favourable rate of 51 per cent compared with 40·4 per cent in the present series.

Discussion

The use of a single-stage strategy of resection combined with ablation was previously reported mostly in single-centre studies with small numbers[33–36]. Most of these studies used radiofrequency ablation as the primary method of ablation *versus* a microwave technique, which is more efficacious with larger lesions and around areas of heat-sink concern[37]. The present large series adds to the data on combined resection with MWA, and provides longer follow-up than described previously[38], leading to more robust survival and recurrence analyses. In the study subgroup analysis, the disease burden with respect to number of lesions and clinical risk score was significantly higher in the CRA group than in the ablation-only group, underlining the need for such a strategy to treat bulkier disease. This group also underwent more neoadjuvant chemotherapy, confirming the pretreatment bias for potentially more radical procedures.

The median hospital stay and morbidity rate for CRA described here compare favourably with those of other strategies for bilobar disease. With regard to efficacy, an acceptable R0 rate (microscopically negative margin) was achieved, again comparing favourably with rates in the existing literature. The median overall survival and recurrence-free survival for a single-stage combined approach are respectable.

With regard to short-term outcomes, CRA was a significantly safer procedure than TSR with respect to morbidity and mortality. Just the morbidity of the second stage of TSR was higher (albeit without statistical significance) than that of the CRA strategy employed here. The safety of CRA is underlined by that fact that there were no liver-related deaths in this study. Rates of complications such as bile leak, haemorrhage and relaparotomy were also higher with the TSR strategy. A major liver resection was undertaken in about half the patients in the present CRA study group, in addition to ablations in the residual liver. This is a strong testament to the use of this approach as a surrogate for a parenchymal preservation strategy (ablation) in combination with resection in selected patients. Median survival times were respectable in these patients with large-volume disease.

The 5-year survival rate after diagnosis for CRA in the present series was lower than that for TSR in the study of Brouquet and colleagues[17], although all patients in the latter study received induction therapy compared with only 80 per cent here. This highlights the importance of

systemic chemotherapy in this situation and heavy pretreatment with a selection of more favourable tumour biology. With the availability of better second- and third-line chemotherapeutics, this strategy is more promising.

This study is limited by its retrospective multi-institutional nature, with a potential for selection bias. It was not possible to ascertain the total number of patients with initially resectable (and/or ablatable) lesions who progressed on neoadjuvant chemotherapy, so an intention-to-treat analysis was not possible. The tumour burden was lower than that reported in recent studies. Strictly speaking, making a comparison with a previously published study is challenging, although it has been done before[30], as it often overlooks the clinically relevant variables. To compensate, only ordinal and categorical variables were analysed. Despite these limitations, the use of single-stage hepatectomy and MWA for contralateral disease was found to be safe and effective in appropriate patients, with short- and long-term outcomes similar to those of two-stage hepatectomy but less overall morbidity.

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