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TUMOUR REVIEW

Treatment outcomes for hepatocellular carcinoma using chemoembolization in combination with other therapies

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Summary
Background: Although transarterial chemoembolization (TACE) improves survival in patients with hepatocellular carcinoma (HCC), it is not known if TACE combined with other treatments is beneficial. Aim: To evaluate the evidence for improved outcomes in HCC with a multimodal treatment approach involving TACE.
Method: PubMed search for all cohort and randomized trials (n = 84) evaluating TACE combined with other therapies; meta-analysis performed where appropriate.
Results: A meta-analysis involving 4 RCTs showed a significant decrease in mortality favouring combination treatment (TACE plus percutaneous ablation) compared to monotherapy in patients with either small (<3 cm) or large HCC nodules (>3 cm) (OR, 0.534; 95% CI, 0.288–0.990; p = 0.046). TACE combined with local radiotherapy improved survival in patients

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with tumour thrombosis of the portal vein in 7 non-randomized studies. Two RCTs and 13 non-randomized studies showed that TACE prior to hepatic resection does not improve survival nor tumour recurrence. Conversely, 2 RCTs and 5 comparative studies showed that transarterial injection of chemotherapeutic drugs mixed with lipiodol (TOCE) following hepatectomy confers survival benefit and less tumour recurrence. TACE before liver transplantation is safe and reduces drop-out rate from the waiting list, but there is no current evidence of improvement in subsequent survival or recurrence rate.

Conclusions: A combined approach involving TACE and percutaneous ablation improves survival. Adjuvant TOCE improves outcome after hepatectomy. TACE is useful to control tumours burden while on the waiting list for OLT. Multimodal treatment seems to be the best way to optimize TACE outcomes in HCC.

Introduction

Liver cancer is the fifth most common cancer in the world and its incidence is increasing worldwide. In 80% of cases hepatocellular carcinoma (HCC) is a complication of cirrhosis and is the main cause of death among these patients in Europe.[1]

Consensus about a common treatment strategy for patients with HCC has not been reached worldwide, even if several proposals have been published. The most recent one is the Barcelona-Clinic Liver Cancer (BCLC) staging classification and treatment schedule.[1] Since radical therapies, including resection, liver transplantation and percutaneous ablation (percutaneous ethanol injection (PEI) and radiofrequency (RF)), are applicable in only 30—40% of patients with HCC[1] according to this algorithm, the majority need different approaches.

Several alternative therapeutic strategies have been proposed but only chemoembolization has been shown to improve survival.[2] Although this procedure is becoming more common in clinical practice, there is no consensus about the optimal schedule or technique of embolization.[3]

In particular, the role of transarterial chemoembolization (TACE) either compared to other therapies or combined with other therapies has not been subject to guidelines or been part of therapeutic algorithms. Therefore, the aim of this review is to evaluate the evidence for improved outcomes with TACE added to other therapies for HCC.

Search strategy and selection criteria

Studies were identified by searching Medline using the following key words: ''hepatocellular carcinoma'' or ''HCC'' or ''hepatic tumour'' or ''liver tumour'' or ''hepatic cancer'' or ''liver cancer'' and ''TACE'' or ''TAE'' or ''chemoembolization'' or ''embolization'' and ''clinical trials'' in English and non-English language. We also manually searched general reviews on HCC and references from published clinical trials.

Articles were excluded if they dealt with liver metastases, recurrence of HCC after hepatectomy, if they did not relate to a therapeutic intervention (e.g. comparison of diagnostic methods), or if they did not report sufficient data (see list below).

Following these exclusions we evaluated 84 articles published between 1989 and December 2005; among these, 11 dealt with chemoembolization alone compared to other treatments and the remaining 73 with chemoembolization combined with other therapies.

In each study, we extracted the following information using a structured proforma:

- Country of origin, duration of study and number of patients.
- Patient characteristics, aetiology and severity of the underlying liver disease and tumour extent.
- Transarterial method used: use of anticancer drugs and lipiodol, their dosage and delivery, embolization method, schedule, mean number of courses and selectivity of embolization, hospital stay and periprocedural care (e.g. utilization of antibiotics as prophylaxis).
- Outcomes: survival, tumour response (WHO Criteria) and complications.

Meta-analysis was performed when there were sufficient randomized studies to evaluate.

Management of patients with HCC

Chemoembolization as sole therapy versus other therapies

There were 11 studies involving 5131 patients comparing TACE to other treatments: radiofrequency ablation ($n = 1$), percutaneous acetic acid injection (PAI) ($n = 1$), percutaneous ethanol injection ($n = 1$) ^{131}iodine-lipiodol radiotherapy ($n = 2$), liver resection ($n = 5$) and transplantation ($n = 1$).

The median number of patients in each study was 117 (range: 39—3225). Two were RCTs[4,5] and three were multicenter;[6—8] the mean duration of each study was 4 ± 1.5 years. Six were conducted in Asia (3 Japanese, 1 Chinese and 2 Taiwanese), 4 in Europe (1 French, 1 Italian, 1 English and 1 German) and 1 from the USA. Results from these trials support the algorithm in the BCLC treatment schedule, in which chemoembolization is indicated in patients with Child A or B cirrhosis and with more than 3 HCC nodules (Table 1).

A large retrospective multicenter study of 3225 Japanese patients[8] compared groups with equivalent baseline prognosis who had been subjected to liver resection ($n = 1656$), TAE ($n = 1067$), PEI ($n = 302$), radiotherapy ($n = 14$) or chemotherapy ($n = 186$). In patients with Stage I disease (clinical

Table 1 Chemoembolization compared to other therapies

Article	RCT	Arms	No. of patients	Tumour extent	Survival rate (%)				Statistics
					1 year	2 year	3 year	5 year	
Ryu (1997)	No	HP	1656	na			62.2	41.3	HP versus PEI: ns
		PEI	302	na			69.3	46.1	TAE worse than HP/PEI ($p < 0.01$)
		TAE	1067	na			25.6	9.4	TAE better than chemo/RT
		Chemotherapy	186	na			6.8	4.5	
		RT	14	na			7.1	0	
Rose (1998)	No	HP	22	na	69	52	43		OLT and HP better (if possible!!!)
		TACE	40	na	35	20	11		
		Chemotherapy	16	na	30	15			
		OLT	8	na	87	87	58		
		Control	31	na	6.4				
Hasse (1996)	Yes	TACE	20	pT3 or pT4	50.1	35.4			ns
		HP	19	pT3 or pT4	31.6	14.2			
Ohnishi (1987)	No	HP	34	<50 mm	75.5	62.1	46.2		Child A: better HP
		Chemotherapy	25	<50 mm	31.6	18.3	12.2		Child B: better TACE
		TACE	20	<50 mm	68.8	60.7	45.5		Child C: ns
		Control	17	<50 mm	43.9	12.8	0		
Kanematsu (1993)	No	HP	67	37 mm	89.6	79.1	74.6	54.6	Better HP ($p < 0.05$)
		TACE	20	41 mm	90	60	50	17.5	
Dalla Palma (1997)	No	PEI (uni)	215 all	$n = 1$ <50 mm	92	72	72		PEI better
		TACE (uni)		$n = 1$ <50 mm	84	72	52		
		PEI (multi)		$n = 2–3$	74	52	28		
		TACE (multi)		$n = 2–3$	81	70	50		TACE better if $n = 3$
		TACE ($n > 3$)		$n > 3$	86	45	30		TACE better
		Control/tamoxifene ($n > 3$)		$n > 3$	50	30	20		(Only first 2 yrs)
Huo (2004)	No	TACE	195	<60 mm	90		58	27	ns
		PAI	115	<60 mm	91		54	20	TACE better in large (3–6 cm) HCC
Raoul (1997)	Yes	^{131}I-Lp	65	na	38.5	21.8	13.6		ns
		TACE	64	na	42.2	22.1	2.8		^{131}I-Lp less side effects
Bhattacharya (1995)	No	TOCE	69	na	25	6			ns
		^{131}I-Lp	26	na	25	0			
Hsieh (2004)	No	TACE	40	Child B/C	90	57			Lps RF better ($p = 0.003$)
		Laparoscopic RF	20	Child B/C	96	70			
		Control	40	Child B/C	63	20			
Huang (2004)	No	HP	599	Uni 75%; 57 mm	79	66	57	44	HP best ($p = 0.0001$)
		TAE/TACE	157	Uni 66%; 47 mm	71	52	38	26	
		Control	62	Uni 73%; 55 mm	56	32	21	4	

stage according to the Liver Cancer Study Group in Japan[9]), who had ⩽3 tumours all ⩽30 mm in size, survival after resection and PEI did not differ, while survival after TAE was significantly worse. In patients with Stage I disease with tumours >30 mm, whatever the number of tumours, survival was better following resection than TAE. In patients with Stage II disease with ⩽3 tumours all ⩽30 mm in size PEI had the best survival compared to either surgery or TAE. In patients with Stage II disease with ⩽3 tumours, some >30 mm in size, who underwent resection had a better survival than those who underwent TAE; while in patients with Stage II disease with >3 tumours there was no significant difference in patient survival between resection and TAE. There was no data reported about survival in patients with Stage III disease.

Therefore, this study suggests chemoembolization should be used for multinodular (>3 nodules) HCC, only if Stage II disease. In Stage I disease, even if HCC is multinodular (>3 nodules), resection achieved a better survival than TAE, in contrast to BCLC treatment schedule recommendations.

Therapies, not considered in the BCLC treatment schedule, that seem to be a promising alternative to chemoembolization in selected patients are ^{131}iodine radiotherapy and laparoscopic radiofrequency ablation. In particular, a RCT[5] showed that transarterial ^{131}I-labeled lipiodol ($n = 65$) was as effective as TACE ($n = 64$) with a similar survival rate at 1 (38.5% versus 42.2%), 2 (21.8% versus 22.1%) and 3 years (13.6% versus 2.8%) but was better tolerated by patients with fewer side effects: both liver failure and gastrointestinal bleeding after treatment were less frequent as compared to TACE. Similar results were obtained with ^{131} iodine radiotherapy compared to trans-oil chemoembolization (TOCE) in a non-randomized study.[10] Another non-randomized study[11] showed that laparoscopic radiofrequency ablation ($n = 20$) resulted in better survival and fewer complications than TACE ($n = 40$) in patients with decompensated liver cirrhosis (Child B or C).

Chemoembolization as an adjuvant or neo-adjuvant therapy

There were 73 studies dealing with chemoembolization combined with other treatments for HCC: 15 (1688 patients) evaluated TACE combined with percutaneous ethanol injection (PEI) (3 RCTs), 1 (108 patients) evaluated TACE combined with PAI, 7 (299 patients) evaluated TACE combined with radiofrequency (RF) ablation (1 RCT), 7 (586 patients) evaluated TACE combined with local radiotherapy (RT), 15 (1336 patients) evaluated TACE prior to hepatic resection (2 RCTs), 7 (986 patients) evaluated TOCE after hepatectomy (2 RCTs) and 10 (1807 patients) evaluated TACE prior to liver transplantation.

TACE + PEI

Percutaneous ethanol injection (PEI) can be a curative therapy for small HCC (<30 mm); the purpose of using TACE prior to PEI is either to reduce the size of larger tumours in order to subsequently apply percutaneous treatment or to combine the necrotizing effects of both procedures in order to achieve a more complete tumour necrosis (Table 2).

A RCT by Koda et al.[12] demonstrated a significant decrease in recurrence rate in small HCC using TACE followed by PEI ($n = 26$) versus PEI alone ($n = 26$) but there was no significant improvement in survival. A comparative study[13] in patients with small HCC showed there was a similar decrease in recurrence rate using TACE plus PEI ($n = 32$) compared to TACE alone ($n = 37$), but again no advantage in survival.

Because of the enhanced ethanol diffusion secondary to necrotic changes produced by TACE, PEI combined with TACE could theoretically also achieve good results in larger HCC (>30 mm) as first suggested by Tanaka et al.[14] In two RCTs,[15,16] TACE prior to PEI ($n = 53$) achieved a significant improvement in disease-free survival in patients with large HCC (3—8 cm) compared to TACE alone ($n = 52$), but again the survival rate was similar. The most recent of these RCTs[16] resulted in a survival benefit of the combination treatment versus monotherapy TACE in a subgroup of patients with HCC Okuda Stage I. Six comparative studies showed a significant increase in survival with TACE performed before PEI ($n = 366$) compared to TACE alone ($n = 682$) in large HCC nodules (>20—30 mm).

Another comparative study,[17] evaluated large and small HCC together ($n = 87$) and showed increased survival with TACE performed 10 days before PEI ($n = 39$) compared to either treatment alone (TACE: $n = 33$; PEI: $n = 15$). Considering all the RCTs and the comparative studies and also 4 cohort studies ($n = 203$) using the combination therapy TACE + PEI, the mean survival rates at 1, 2, 3 and 5 year in large HCC (largest diameter >20—30 mm) were 83 ± 17%, 66 ± 20%, 55 ± 24% and 37 ± 9%, respectively.

A RCT[18] comparing transarterial embolization (TAE) performed before percutaneous tumour ablation (PEI or RF) ($n = 22$) versus percutaneous ablation alone ($n = 20$), in uninodular HCC less than 50 mm diameter, showed no significant difference in either survival or HCC recurrence rate. However, when the authors considered only the group of patients in which PEI was combined to TAE ($n = 12$) versus PEI alone ($n = 14$), even if the HCC was small in size, there was a significant increase ($p = 0.043$) in disease-free survival in the TAE + PEI group. The combined treatment seems to result in more benefit when chemoembolization is performed before PEI, than before RF ablation. Further trials assessing this issue should be performed.

TACE + PAI

A comparative study[19] showed significantly better survival with TACE used before acetic acid injection (PAI) ($n = 53$) compared to PAI alone ($n = 55$) in uninoduar HCC <5 cm. The survival rate at 1 and 3 year for the combination therapy was 100% and 69%, respectvely, compared to 96% and 32%, respectvely, for PAI alone; the objective response was 90% for the combination therapy versus 82% for PAI alone.

TACE + RF ablation

TACE can be used combined with radiofrequency (RF). Radiofrequency ablation is most often used to treat small lesions measuring 3—4 cm in diameter. As tumour size increases, the therapeutic response decreases due to the limited size of the coagulation necrosis induced by the activation of the RF system. Blood flow promotes heat loss

Table 2 TACE combined with PEI

Article	RCT	Arms	No. of patients	Single (%)	Size (mm)	No. of TACE	Survival rate (%)				Statistics	Recurrence rate (%)				Statistics
							1 year	2 year	3 year	5 year		1 year	2 year	3 year	5 year	
Koda (2001)	Yes	TACE + PEI	26	61.5	<30		100	94.4	80.8	40.4	ns	8.7		19.3		$p = 0.057$
		PEI	26	57.7			91.3	81.6	65.9	37.7		26.9		80.1		
Kamada (2002)	No	TACE + PEI	32	56	<30	1	90		65	50	ns	42		69	84	$p < 0.01$
		TACE	37	57		2.9	86		44	22		65		92		
Bartolozzi (1995)	Yes	TACE + PEI	26	69	48	1	100	86.7	72.2		ns	15.4	35.6	48.4		$p < 0.05$
		TACE	27	52	51	Multiple	92.6	69.7	43.4			51.9	64.1	70.1		
Becker (2005)	Yes	TACE + PEI	27	48	>50: 63%		61.5	38.7			ns					
		TACE	25	36	>50: 68%		62.9	18			$p = 0.04$ (Okuda I)					
Tanaka (1992)	No	TACE + PEI	15	100	>30		100	85	85		$p < 0.01$					
		TACE	15	100	>30		68	37	0							
Yamamoto (1997)	No	TACE + PEI	50		>20		95	72.5	50		p					
		TACE	50		>20		92.5	57.5	20							
Allgaier (1998)	No	PEI	15	93	>50: 27%		70	0								
			33	21	>50: 61%	2.6	44	0								
			39	38	>50: 64%	2.9	78	56			$p = 0.001$					
			45	44	>50: 62%		15	0								
Yasuda (1999)	No	TAE + PEI	58				54.6									
		TAE + PEI + RF	44				81.1									
Lubienski (2004)	No	TACE + PEI	22		Large		55	39	22		$p = 0.002$					
		TACE	28		Large		21	4	4							
Chen (2004)	No	TOCE + PEI	179		96 (20—150)		80.5		58.6	29.6	$p < 0.01$					
		TOCE	496		96 (20—150)		68.5		27.8	7.2						
Greten (2005)	No	TACE + PEI	52				92		16							
		TACE	49				54		29							
		PEI	69				49		21							
Hasuike (1992)	No	TACE + PEI	10	80												
Kato (1994)	No	TACE + PEI	24		>30		87	65.2								
Bartolozzi (1997)	No	TACE + PEI	86		53		92	83	69	47						
Tanaka (1998)	No	TACE + PEI	83	66	>30		100		68	35						

so that reducing or eliminating blood flow during RF procedures increases the volume of ablation. Therefore, it seems to be reasonable to perform RF ablation after blocking the hepatic artery blood flow supplying the tumour; since this can be achieved by either using a balloon catheter or injecting embolizing agents,[20] performing TACE before RF could be beneficial.

Four cohort studies[21–24] involving 142 patients have shown that performing TACE prior to RF ablation is a feasible, safe, and useful treatment method that can achieve good therapeutic results in compensated cirrhotics (Child A or B) with small HCC nodules (20–50 mm). In this select group of patients the mean overall survival rate at 1 and 2 year was 97 ± 6% and 81 ± 20%, respectively, and the mean objective response (WHO criteria) was 93 ± 10%. One study[24] reported 2 major complications in 46 patients undergoing TACE + RF (6.5%): one hepatic failure and one death of unknown origin, the day after the procedure, both in Child C patients.

A prospective study by Koda et al.[25] did not report any significant difference in complication rate after RF ablation comparing TACE before RF ($n = 28$) versus RF alone ($n = 25$); the complication rate was 20.7% and 20.0%, respectively (especially ascites).

Meta-analysis: combination therapy (TACE + percutaneous ablation) versus monotherapy

We performed a meta-analysis with 4 RCTs[12,15,16,18] (199 patients) comparing combination therapy (TACE plus PEI in 3 RCTs[12,15,16] and TACE plus percutaneous ablation (PEI or RF) in 1 RCT[18]) versus monotherapy (TACE alone in 2 RCTs,[15,16] PEI alone in 1 RCT[12] and PEI or RF alone in another RCT[18]), with respect to survival using the number of patients reported as dead at the end of follow-up (see Fig. 1).

One RCT[12] involved only patients with small HCC (size of main nodule <30 mm), two RCTs[15,16] involved patients with main nodule size of HCC between 30 and 80 mm and another RCT[18] involved only uninodular HCC with largest diameter between 20 and 50 mm.

Our meta-analysis showed a significant decrease in mortality favouring combination treatment (TACE plus percutaneous ablation) compared to monotherapy (TACE alone or percutaneous ablation alone) (OR, 0.534; 95% CI, 0.288–0.990; $p = 0.046$). Due to the limited number of trials and patients there are wide confidence intervals, but all trials show the combined approach to be better than monotherapy alone.

Theoretically, TACE can decrease tumour resistance to perfusion with ethanol and can disrupt any intratumoral septa as a result of induced tumour necrosis,[26] hence, facilitating ethanol diffusion into the lesion. In addition, embolization may reduce ethanol wash out of the tumour enhancing its toxic effect. Furthermore, the embolization of the blood vessels feeding the tumour by TACE has been shown to reduce heat loss and, therefore, increase the volume of ablation during RF.[20] Further RCTs assessing the effect of combined therapy with TACE are required.

TACE + radiotherapy

Patients with HCC and tumour thrombosis of the main trunk of the portal vein have been considered poor candidates for TACE because of the risk of necrosis of the non-cancerous portion of the liver and risk of worsening hepatic function. The combination of local radiotherapy, which has been reported to have some effect, not only on the main tumour but also on the tumourous thrombosis of the portal vein, together with selective TACE is a reasonable approach in these cases.

We found 7 studies,[27–30] all from Asia, involving 586 patients which used local radiotherapy combined with TACE. Two retrospective comparative studies ($n = 276$) showed a significant increase in survival of TACE + RT compared with TACE alone. Considering all the 7 studies (2 comparative studies and 5 cohort studies), which included only patients with Child A or B cirrhosis with large HCC nodules (median tumour size = 85 mm) and presence of PVT in a median of 66% of the patients, the mean survival rate at 1, 2 and 3 years was: 62 ± 25%, 30 ± 17% and 21 ± 7%, respectively. Median survival time was 15 months and the mean objective response (WHO criteria) was 69 ± 17%.

There were 2 treatment-related deaths (within 30 days) due to acute liver failure and gastro-intestinal bleeding. These are reasonable outcomes keeping in mind that these are difficult and complicated patients. RCTs assessing the efficacy and safety of this combined treatment in patients with PVT are needed.

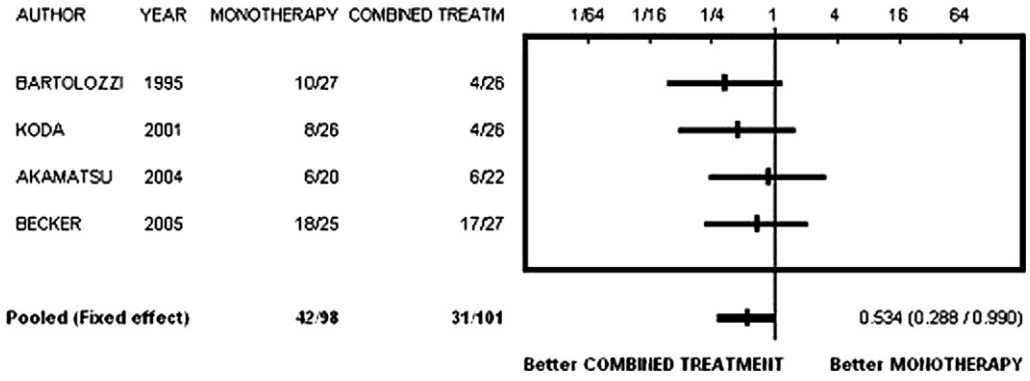

Figure 1 Meta-analysis of 4 RCTs (199 patients) comparing combination therapy (TACE plus percutaneous ablation) versus monotherapy (either TACE or percutaneous ablation) using the number of patients reported as dead at the end of follow-up.

Table 3 Neoadjuvant chemoembolizaton + hepatectomy versus hepatectomy alone

Articles	RCTs	Arms	No. of patients	Single (%)	Size (mm)	Survival rate (%)				Statistics	Disease-free survival
						1 year	2 year	3 year	5 year		
Wu (1995)	Yes	TACE + HP	24	73	143	74	42	38	32	Worse (large HCC)	ns
		HP	28	78	145	96	80	60	60		
Yamasaki (1996)	Yes	TACE + HP	50		31	90	86	80	63	ns	ns
		HP	47		33	87	81	77	62		
Lu (1999)	No	TOCE + HP (size: 2—8 cm)	24		43	87		42	35	ns	ns
		HP (size: 2—8 cm)	57		46	91		61	37		
		TOCE + HP (size: >8 cm)	20		107	90		53	42	Better ($p = 0.01$)	Better ($p = 0.06$)
		HP (size: >8 cm)	19		106	72		33	11		
Paye (1998)	No	TACE + HP	24	62	78	88	70	67		ns	ns
		HP	24	75	73	70	68	62			
Gerunda (2000)	No	TACE + HP	20		37	85			43	ns	Better ($p < 0.02$)
		HP	20		41	71			38		
Di Carlo (1998)	No	TACE + HP	55		<50	87		70	39	Better ($p < 0.02$)	Better ($p < 0.05$)
		HP	45		<50	79		38	19		
Harada (1996)	No	TACE + HP	98	61		90.8	84	78		ns	ns
		HP	33	63		97	88	67			
Uchida (1996)	No	TOCE + HP	60	82	37	88.3	75	61	24	Worse ($p < 0.05$)	ns
		HP	68	74	44	82	72	72	63		
Majno (1997)	No	TACE + HP	49	80	50	63.3	42.9	32.7		ns	Better
		HP	27	70	40	63	37	22.2			
Adachi (1993)	No	TACE + HP	46	100	26						ns
		HP	26	100	21						
Nagasue (1989)	No	TACE + HP	31	71		74	61	32		ns	ns
		HP	107	63		77	57	45			
Imaoka (1989)	No	TACE + HP	51		<100						ns
		HP	52		<100						
Lygidakis (1996)	No	TACE + HP + immunotp	49			85	54	42	42	Better	
		HP	42			57	15	15	15		
Zhang (2000)	No	TOCE + HP	120							Time: 90.1 months	
Cheng (2000)	No	Lipiodol + OH + HP	20		90	95					

TACE before hepatic resection

Two RCTs and 11 comparative and 2 cohort studies have evaluated the effect of TACE performed before hepatic resection (Table 3). One RCT[31] comparing the combination of TACE with hepatectomy ($n = 50$) versus hepatectomy alone ($n = 47$) for HCC $\leqslant$5 cm did not show any significant difference either in mortality or recurrence rate after surgery. The other RCT[32] in patients with large HCC (diameter $\geqslant$10 cm) demonstrated that TACE prior to hepatectomy ($n = 24$) resulted in worse survival than hepatectomy alone ($n = 28$) as it increased operative difficulties and delayed the surgery (no significant difference in disease-free survival). The authors concluded that neoajuvant TACE should be avoided in this group.

Moreover, a comparative study[33] demonstrated a reduced survival in patients who received TOCE before undergoing hepatectomy ($n = 60$) compared to patients receiving hepatectomy alone ($n = 68$) with no significant difference in disease-free survival. Conversely, a retrospective study[34] in 120 patients showed an increase in survival in patients with HCC 8 cm or more in diameter when TACE was combined with hepatectomy compared to surgery alone. However, no significant difference was shown in smaller HCC (2–8 cm diameter). In addition, a prospective study[35] in 110 patients showed a significantly better survival with TACE prior to hepatectomy in HCC $\leqslant$5 cm.

Further studies[36–42] comprising 608 patients showed no significant difference in both overall survival rate and disease-free survival rate. Only a non-randomized study[43] comparing resection alone versus resection plus pre-operative TACE and targeted post-operative locoregional immunochemotherapy showed a significant improvement in survival with the combined treatment. The mean survival rate at 1, 2, 3 and 5 year achieved with neoadjuvant TACE and hepatic resection was 82 ± 11%, 63 ± 21%, 47 ± 19% and 39 ± 17%, respectively.

Our review of 13 studies (2 RCTs and 11 non-randomized comparative trials) evaluating pre-operative TACE, adding 4 studies to the studies considered by Mathurin et al.,[44] confirms the same result: there is no evidence of a significant improvement in survival when chemoembolization is used before hepatic resection and neither does it reduce recurrence rates.

Adjuvant TACE following hepatic resection

Hepatic resection can be a curative treatment for HCC even if tumour recurrence complicates 70% of cases at 5 years (combining true recurrence and de novo tumours). The purpose of post-operative chemoembolization is to eliminate any shed tumour cells potentially released by surgical manipulation of the liver and also to destroy small intrahepatic metastases that may not have been detected during surgery. Since the damage to liver parenchyma caused by hepatic resection is not fully repaired in the post-operative period, especially in cirrhotic livers, chemoembolization using gelatin sponge has not been utilized as it could contribute to hepatic insufficiency. Transarterial-oil chemoembolization (TOCE) or Lipiodolization (hepatic arterial injection of chemotherapeutic drugs mixed with lipiodol) has therefore been used in these cases, which is known not to result in massive necrosis.

Table 4 Adjuvant TOCE + hepatectomy versus hepatectomy alone

Article	RCT	Arms	No. of patients	Single (%)	Size (mm)	Survival				Time (month)	Statistics	Disease-free survival
						1 year	2 year	3 year	5 year			
Li (1995)	Yes	HP + TOCE	47	na	na	97.9	85.5	69.5		14.8	Better ($p < 0.001$)	Better ($p < 0.01$)
		HP	47	na	na	72.3	52.7	35.1		8.6		
Izumi (1994)	Yes	HP + TOCE	23	25	na	87		56.6	50.3	49	ns	Better ($p < 0.05$)
		HP	27	59	na	81		53.4	28.8	41		
Takenaka (1995)	No	HP + TOCE	17	82	38	100	100	100			Better	Better ($p = 0.001$)
		HP	19	74	19	94.7	94.7	89.5				
Asahara (1999)	No	HP + TOCE	68	na	<10			79.1	54.5		Trend ($p = 0.086$)	Better (0.006)
		HP	67	na	<11			69.2	38.1			
Tanaka (1999)	No	HP + TOCE	24	75	na	100	79.2	79.2			Better ($p < 0.05$)	Better ($p < 0.01$)
		HP	41	80	na	89.7	74.2	62.8				
Cheng (2004)	No	HP + TOCE + thy	18	83	na					10	Thy better ($p = 0.002$)	ns
		HP + TOCE	23	91	na					7	TOCE ns	
		HP	16	100	na					8		
Ren (2005)	No	HP + TOCE	185	>50 or multi: 42%		97.4		70.4	50.1		ns	ns
		HP	364	>50 or multi: 48%		93.5		75.8	62.4		Better in high risk HCC	

There are two RCTs and five non-randomized studies comparing hepatectomy alone with hepatectomy and adjuvant TOCE (Table 4). One RCT[45] resulted in increased survival and disease-free survival using TOCE after hepatectomy ($n = 47$) compared to hepatectomy alone ($n = 47$). The other RCT[46] had a reduced recurrence rate (the 1-, 2-, 3- and 4-year disease-free survival rates were 64.5%, 54.9%, 32% and 25.6%, respectively, for adjuvant TOCE and 43%, 22%, 11.7% and 5.9%, respectively, for hepatectomy alone; $p < 0.05$) but no benefit was seen concerning overall survival.

Four comparative studies[47–50] again showed a significant improvement, or a strong trend in one study[47] ($p = 0.086$), with adjuvant TOCE ($n = 150$) versus liver resection alone ($n = 143$) for both disease-free survival and overall survival. Another recent retrospective comparative study[51] (549 patients) reported a statistically significant difference ($p = 0.02$) in survival with TOCE prior to resection but only in patients with risk factors for residual tumour (52.3% of total patients) which were tumours with a diameter more than 5 cm, multiple nodules and vascular invasion.

In our series of 7 studies (986 patients), the mean disease-free survival rate at 1 and 3 years in patients receiving post-operative adjuvant TOCE was 84 ± 14%, 62 ± 25%, respectively, compared to 40 ± 19%, 26 ± 18%, respectively, in patients receiving only hepatectomy. Moreover, the mean survival rate of patients having TOCE after hepatic resection at 1, 2, 3 and 5 years was 96 ± 5%, 88 ± 11%, 76 ± 14% and 52 ± 2%, respectively, compared to 86 ± 9%, 74 ± 21%, 64 ± 19% and 43 ± 17%, respectively, in patients having only hepatic resection; the median survival time in adjuvant TOCE group was 29.5 months (range: 10–49 months) with a gain of 5 months with respect to the median survival rate of the group undergoing only hepatectomy.

The meta-analysis of Mathurin et al.,[44] involving 4 RCTs (the 2 RCTs[45,46] above and 2 other RCTs performing post-operative transarterial ^{131}I-lipiodol and transarterial chemotherapy – without lipiodol) and 3 non-randomized trials,[47,49,50] showed a significant improvement in both survival and in the cumulative probability of tumour-free survival.

Our review, adding another two recent studies,[48,51] shows similar benefit of adjuvant TOCE in prolonging survival after hepatectomy. In addition, there may be a particular advantage in using adjuvant TOCE in patients with high risk HCC (>5 cm, multiple and vascular invasion), where there is increased risk of post-operative recurrence.

Two other meta-analyses performed by Mathurin et al.,[44] the first including one RCT (67 patients) and one non-randomized trial (31 patients) evaluating post-operative systemic therapy (oral 5-FU) and the second considering 3 RCTs evaluating a post-operative combination of systemic and transarterial chemotherapy cycles of IV epirubicin + oral 5-FU and 1 session of TA epirubicin ($n = 56$); cycles of IV epirubicin and 3 sessions of TA cisplatin ($n = 66$); 1 session of TA epirubicin and oral 5-FU ($n = 88$), showed that none of these approaches significantly improved survival after hepatic resection in patients with HCC, so that the transarterial route appears to be important.

At present, given these data, only post-operative TOCE and not systemic chemotherapy should be performed in clinical practice. In addition, a prospective randomised

Table 5 TACE + OLT

Article	Arms	No. of patients	Single (%)	Size (mm)	Waiting time	No. of TACE	Survival rate(%)				p	Disease-free survival (%)				p	Complications	p
							1 year	2 year	3 year	5 year		1 year	2 year	3 year	5 year			
Majno (1997)	TACE + OLT	54	2 no	47		2	87		65	55	ns	78		63	57	ns	43 (HA:0; biliary:9)	ns
	OLT	57	2 no	38			77		69	62		74		66	59		31 (HA:5; biliary:10)	
Oldhafer (1998)	TOCE + OLT	21				2.4	61		48		ns						3 deaths(pneumonia)	
	OLT	21					61		54								0	
Saborido (2004)	TACE + OLT	18	67	<30:67%		1	83		61	61	ns				54	ns	No HA complication	ns
	OLT	28	68	<30:32%			77		59	38					39		No HA complication	
Decaens (2005)	TACE + OLT	100	6	36	126	1				59.4	ns				67.5	ns		
	OLT	100	52	39	129					59.3					64.1			
Richard (2000)	TACE + OLT	47		54		1.5											HA complication: 8; HAT:13	ns
	OLT	1154															HA complication: 5; HAT:6	
Harnois (1999)	TACE + OLT	24	Majority	36	167							91	84					
Graziadei (2003)	TACE + OLT	49	46	<50	178	2.5	97.8	97.8		94								
	TACE + OLT	10		>50	254	5.1	82	55		41								
Maddala (2004)	TACE + OLT	46	76	<30:54%	211					74							1 HA thrombosis	
Herber (2005)	TACE + OLT	35		42	366	5.3						93.3		82.5	82.5			
Roayaie (2002)	TOCE + OLT + chem	43	56	All >50	142	1.5	90	72	58	44					48		2 deaths (ALF)	

trial[52] and a retrospective study[53] have also demonstrated a benefit in disease-free and overall survival using intra-arterial ^{131}iodine-lipiodol after curative resection compared to resection alone. New RCTs should be performed to better assess the outcome of post-operative intra-arterial treatment (TOCE, TACE and ^{131}iodine-lipiodol).

TACE before liver transplantation

Orthotopic liver transplantation (OLT) has been shown to be the best treatment for early-stage HCC. Patients with one nodule smaller than 5 cm or up to three nodules smaller than 3 cm (Milan Criteria) achieve a 70% survival at 5 years after OLT with a recurrence rate lower than 15%.[54] Because of the shortage of donors and a steadily increasing waiting time for transplantation, tumour progression while waiting on the list, and the consequent increasing drop-out rate (up to 20—50% if the waiting time exceeds 12 months[1]) have become an important problem.

We considered 5 comparative studies involving 1600 patients and five cohort studies involving 197 patients assessing the role of TACE prior to OLT (Table 5). Four studies,[40,55—57] involving patients with one single HCC nodule smaller than 5 cm or three nodules smaller than 3 cm (Milan Criteria), did not show any significant difference in either disease-free survival or overall survival between TACE before OLT ($n = 193$) versus OLT alone ($n = 206$). In particular, Majno et al.[40] showed that preoperative TACE (an average of 2 sessions) induced significant downstaging (50% reduction of the maximum diameter of the tumour) of tumours >3 cm in 52%, and complete tumour necrosis in 26% as assessed at explant. The presence of these 2 factors was associated with a better disease-free survival, similar to that of patients with smaller tumours ($\leqslant$3 cm). Therefore, these authors suggested that TACE before liver transplantation should be used in patients with large HCC (>3 cm) and response to treatment should be regarded as a strong argument to proceed to liver transplantation. Moreover, Majno et al.[40] did not find any difference in either post-OLT morbidity (arterial and biliary complications) or mortality in patients receiving TACE.

Perez et al.[57] confirmed that there were no differences in post-operative complications with or without TACE, with no cases of hepatic artery thrombosis in either group. Conversely, Oldhafer et al.[56] reported a higher risk of developing immediate post-operative infective complications (3 cases of fatal pneumonia versus none) in patients receiving TACE before transplantation (2.4 mean number of session); 2 of the 3 cases of fatal pneumonia occurred in patients undergoing OLT within 30 days from the last TACE. The authors tried to explain the development of these severe pneumonias by underlying the fact that TACE may temporarily decrease the patient immune function. They suggested that an interval of more than 4 weeks should pass between the last TACE session and liver transplantation. Richard et al.[58] also showed no statistical difference in hepatic arterial thrombosis or other hepatic artery complications after OLT comparing patients treated with TACE pre-transplantation ($n = 47$) (1.5 mean number of session) or transplantation alone ($n = 1154$): 8% of patients in TACE group developed hepatic arterial thrombosis after OLT versus 5% in non-TACE group; 13% of patients developed other hepatic arterial complications (pseudoaneurysm, stenosis or anastomotic disruption) after OLT in TACE group versus 6% in non-TACE group.

Four cohort studies[59—62] (154 patients) showed good results in terms of reduced recurrence and increased survival in patients with HCC fulfilling Milan Criteria and receiving pre-OLT TACE. In particular, in the study by Graziadei et al.,[59] 49 patients (2.5 mean number of sessions) achieved a survival rate of 94% at 5 years with a recurrence rate of only 2%; no patient required removal from the waiting list despite a mean waiting time of about 200 days.

Considering all 206 patients with HCC, fulfilling Milan Criteria, undergoing TACE prior to OLT in the above studies (median number of TACE sessions: 2 (1—5) median waiting time: 178 days (126—366)), the mean disease-free survival rate at 1, 3 and 5 year was: 66 ± 8%, 48 ± 14%, 52 ± 13%, respectively, and mean overall survival rate at 1, 3 and 5 year was: 58 ± 14%, 44 ± 9%, 57 ± 16%, respectively. Hence, chemoembolization can be used as a ''holding therapy'' in order to prevent tumour growth during the waiting time. Moreover, there is no evidence that performing TACE prior to OLT may increase post-operative vascular complications.

Roayaie et al.[63] performed pre-OLT TACE (1.5 mean number of sessions) and post-operative systemic chemotherapy in 43 patients with HCC nodules more than 5 cm diameter (outside Milan Criteria) achieving a disease-free survival and overall survival at 5 years of 48% and 44%,

Table 6 Histological assessment of response on explant

Article	RCT	Arms	No. of patients	Single (%)	Size (mm)	No. of TACE	Necrosis on explant (%)		
							Complete	>50	Average
Yamasaki (1996)	Yes	TACE + HP	50		31		8	80	75
Harada (1996)	No	TACE + HP	105	64	<50:69%		28		
Paye (1998)	No	TACE + HP	24	62	78	1.6	4	37	
Lu (1999)	No	TOCE + HP (size: 2—8 cm)	24		43		0	21	
		TOCE + HP (size: >8 cm)	20		107		10	60	
Gerunda (2000)	No	TACE + HP	20		37				81
Majno (1997)	No	TACE + OLT	54	2 no	47	2	28		
Oldhafer (1998)	No	TOCE + OLT	21			2.4	28	67	
Decaens (2005)	No	TACE + OLT	100	6	36	1	16	50	
Maddala (2004)	No	TACE + OLT	46	76	<30:54%		15	100	
Wong (2004)	No	TACE + OLT	6						64

respectively; patients with tumours measuring 5–7 cm had significantly longer recurrence-free survival compared with those with larger (>7 cm) tumours. Graziadei et al.[59] performed TACE (5.1 mean number of sessions) in 15 patients with advanced HCC (outside Milan Criteria) waiting for transplantation achieving a 5-year survival rate of 31% in an intention-to-treat analysis and a 4-year survival rate of 41% considering only the 10 patients transplanted.

TACE used to downstage advanced HCC prior to liver transplantation, in order to expand current selection criteria, may seem a reasonable approach. However, it is likely that it will result in a higher recurrence rate after OLT and a reduced survival rate compared to patients with early-stage tumour. This strategy does not seem promising and lacks biological plausibility. In fact, Grasso et al., in a retrospective study[64] of 96 patients transplanted for HCC, have shown that only the diameter of the largest nodule pre-transplant predicted recurrence after LT, such that the probability of no recurrence was associated with nodules $\leqslant$3.5 cm on pre-operative imaging.

Histological assessment of response to TACE on explanted or resected specimens

The amount of tumour necrosis determined by TACE was assessed histologically on the explanted livers in 5 studies performing pre-OLT TACE (227 patients) and on resected specimens after hepatectomy in another 5 studies performing neoadjuvant TACE (243 patients) (Table 6).

Complete tumour necrosis was achieved in a median of 15% of treated nodules (range: 0–28%); tumour necrosis more than 50% was achieved in a median of 60% of nodules (21–100%). There was no correlation between the amount of tumour necrosis induced by TACE and the size of nodule treated. No study reported the presence of a correlation between the amount of tumour necrosis and the recurrence rate.

Conclusion

Chemoembolization has been used in patients with HCC not suitable for curative therapy according to the BCLC treatment schedule. In this subset of selected patients it improves survival compared to supportive treatment or systemic chemotherapy.[2] Currently, none of the therapeutic algorithms used for HCC consider the role of TACE combined with other therapies. The aim of our review was to evaluate the evidence for improved outcomes in HCC with a multimodal treatment approach involving TACE.

Four RCTs[12,15,16,18] individually showed that combined treatment with TACE and percutaneous ablation (PEI or RF) in patients with either small (<3 cm) or large HCC nodules (>3 cm) improved tumour-free survival compared to monotherapy, but not overall survival. Our meta-analysis involving these 4 RCTs showed a significant decrease in mortality favouring combination treatment (TACE plus percutaneous ablation) compared to monotherapy (either TACE alone or percutaneous ablation alone) (OR, 0.534; 95% CI, 0.288–0.990; $p = 0.046$).

Moreover, six non-randomized comparative studies showed that TACE combined with PEI increased survival rate in patients with large (>3 cm) HCC; in four cohort studies, TACE has been shown to be useful and safe when performed prior to RF ablation as it reduces blood flow and, therefore, heat loss during the RF procedure. Therefore, we suggest that a treatment regimen based on a combined intravascular and percutaneous (especially PEI) approach is the next route to be pursued in order to improve the survival of patients with HCC not suitable for surgery. RCTs should be performed to evaluate the real efficacy of this promising multimodal treatment in this scenario.

A combined treatment involving TACE and local radiotherapy has documented improved survival in patients with tumour thrombosis of the portal vein in five cohort studies and two comparative non-randomized studies (all from Asia). These studies justify randomized studies to confirm these observations.

A combined intra-arterial and surgical approach is effective only when transarterial therapy is used after hepatic resection and not before resection. Our review, considering the same 2 RCTs[31,32] and 6 more studies (4 studies evaluating neo-adjuvant TACE and 2 studies evaluating adjuvant TOCE) than in a previous review,[44] showed that chemoembolization prior to hepatic resection does not improve survival nor tumour recurrence. Conversely, our review of 7 studies showed that TOCE, which involves only hepatic intra-arterial infusion and not embolization, following hepatic resection confers survival benefit – median survival rate at 3 year in adjuvant TOCE group compared to hepatectomy alone group was 75% versus 66% – and less recurrence – median disease-free survival rate at 3 year was 65% versus 20%.

Several cohort studies have shown that chemoembolization is a safe procedure when used before liver transplantation with the aim to delay or inhibit tumour progression during the waiting time. It does not increase the risk of post-OLT hepatic arterial thrombosis. However, five comparative non-randomized studies have failed to demonstrate an improvement in either survival or recurrence rates after transplantation using adjuvant TACE compared to OLT alone. Hence, TACE can be safely performed prior to liver transplantation in order to reduce the drop-out rate from the waiting list. However, RCTs formally assessing the efficacy of this procedure in improving patient survival post-OLT are not available and should be performed. In addition, there is no current evidence suggesting that the downstaging of tumours, with respect to the Milan Criteria, reduces the risk of tumour recurrence to that expected by selecting patients within Milan Criteria, so that randomized studies of downstaging are needed although difficult to perform and/or results of downstaging compared to matched patients and HCC transplanted within Milan Criteria.

References

1. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003;**362**:1907–17.
2. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. *Hepatology* 2003;**37**:429–42.
3. Marelli L, Stigliano R, Triantos C, Senzolo M, Cholongitas E, Davies N, et al. Transarterial therapy for hepatocellular carcinoma (HCC) in cirrhosis: is embolization as effective as chemoembolization? Systematic review of cohort and randomized studies. *Cardiovasc Inter Rad* 2006, in press.

4. Hasse F, Mehring UM, Castaneda F, Jager H, Mathias KD, Lohlein D. Comparison of liver resection with sequential transarterial chemoembolization in stage pT3 or pT4 hepatocellular carcinoma. *Langenbecks Arch Chir Suppl Kongressbd* 1996;**113**: 208–10.
5. Raoul JL, Guyader D, Bretagne JF, Heautot JF, Duvauferrier R, Bourguet P, et al. Prospective randomized trial of chemoembolization versus intra-arterial injection of 131I-labeled-iodized oil in the treatment of hepatocellular carcinoma. *Hepatology* 1997;**26**:1156–61.
6. Dalla PL, Pozzi MR, Sponza M, Bartolozzi C, Lencioni R, Florio F, et al. Diagnostic imaging and interventional therapy in hepatocarcinoma. Multicenter study of 290 cases. *Radiol Med (Torino)* 1997;**94**:30–6.
7. Huang YH, Chen CH, Chang TT, Chen SC, Wang SY, Lee PC, et al. The role of transcatheter arterial embolization in patients with resectable hepatocellular carcinoma: a nationwide, multicenter study. *Liver Int* 2004;**24**:419–24.
8. Ryu M, Shimamura Y, Kinoshita T, Konishi M, Kawano N, Iwasaki M, et al. Therapeutic results of resection, transcatheter arterial embolization and percutaneous transhepatic ethanol injection in 3225 patients with hepatocellular carcinoma: a retrospective multicenter study. *Jpn J Clin Oncol* 1997;**27**:251–7.
9. Primary liver cancer in Japan. Clinicopathologic features and results of surgical treatment. Liver Cancer Study Group of Japan. *Ann Surg* 1990;**211**:277–87.
10. Bhattacharya S, Novell JR, Dusheiko GM, Hilson AJ, Dick R, Hobbs KE. Epirubicin-lipiodol chemotherapy versus 131iodine-lipiodol radiotherapy in the treatment of unresectable hepatocellular carcinoma. *Cancer* 1995;**76**:2202–10.
11. Hsieh CB, Chang HM, Chen TW, Chen CJ, Chan DC, Yu JC, et al. Comparison of transcatheter arterial chemoembolization, laparoscopic radiofrequency ablation, and conservative treatment for decompensated cirrhotic patients with hepatocellular carcinoma. *World J Gastroenterol* 2004;**10**:505–8.
12. Koda M, Murawaki Y, Mitsuda A, Oyama K, Okamoto K, Idobe Y, et al. Combination therapy with transcatheter arterial chemoembolization and percutaneous ethanol injection compared with percutaneous ethanol injection alone for patients with small hepatocellular carcinoma: a randomized control study. *Cancer* 2001;**92**:1516–24.
13. Kamada K, Kitamoto M, Aikata H, Kawakami Y, Kono H, Imamura M, et al. Combination of transcatheter arterial chemoembolization using cisplatin-lipiodol suspension and percutaneous ethanol injection for treatment of advanced small hepatocellular carcinoma. *Am J Surg* 2002;**184**:284–90.
14. Tanaka K, Okazaki H, Nakamura S, Endo O, Inoue S, Takamura Y, et al. Hepatocellular carcinoma: treatment with a combination therapy of transcatheter arterial embolization and percutaneous ethanol injection. *Radiology* 1991;**179**:713–7.
15. Bartolozzi C, Lencioni R, Caramella D, Vignali C, Cioni R, Mazzeo S, et al. Treatment of large HCC: transcatheter arterial chemoembolization combined with percutaneous ethanol injection versus repeated transcatheter arterial chemoembolization. *Radiology* 1995;**197**:812–8.
16. Becker G, Soezgen T, Olschewski M, Laubenberger J, Blum HE, Allgaier HP. Combined TACE and PEI for palliative treatment of unresectable hepatocellular carcinoma. *World J Gastroenterol* 2005;**11**:6104–9.
17. Allgaier HP, Deibert P, Olschewski M, Spamer C, Blum U, Gerok W, et al. Survival benefit of patients with inoperable hepatocellular carcinoma treated by a combination of transarterial chemoembolization and percutaneous ethanol injection – a single-center analysis including 132 patients. *Int J Cancer* 1998;**79**:601–5.
18. Akamatsu M, Yoshida H, Obi S, Sato S, Koike Y, Fujishima T, et al. Evaluation of transcatheter arterial embolization prior to percutaneous tumor ablation in patients with hepatocellular carcinoma: a randomized controlled trial. *Liver Int* 2004;**24**:625–9.
19. Huo TI, Huang YH, Wu JC, Chiang JH, Lee PC, Chang FY, et al. Sequential transarterial chemoembolization and percutaneous acetic acid injection therapy versus repeated percutaneous acetic acid injection for unresectable hepatocellular carcinoma: a prospective study. *Ann Oncol* 2003;**14**:1648–53.
20. Rossi S, Garbagnati F, Lencioni R, Allgaier HP, Marchiano A, Fornari F, et al. Percutaneous radio-frequency thermal ablation of nonresectable hepatocellular carcinoma after occlusion of tumor blood supply. *Radiology* 2000;**217**:119–26.
21. Buscarini L, Buscarini E, Di Stasi M, Quaretti P, Zangrandi A. Percutaneous radiofrequency thermal ablation combined with transcatheter arterial embolization in the treatment of large hepatocellular carcinoma. *Ultraschall Med* 1999;**20**:47–53.
22. Seki T, Tamai T, Nakagawa T, Imamura M, Nishimura A, Yamashiki N, et al. Combination therapy with transcatheter arterial chemoembolization and percutaneous microwave coagulation therapy for hepatocellular carcinoma. *Cancer* 2000;**89**:1245–51.
23. Yamakado K, Nakatsuka A, Akeboshi M, Shiraki K, Nakano T, Takeda K. Combination therapy with radiofrequency ablation and transcatheter chemoembolization for the treatment of hepatocellular carcinoma: short-term recurrences and survival. *Oncol Rep* 2004;**11**:105–9.
24. Veltri A, Moretto P, Doriguzzi A, Pagano E, Carrara G, Gandini G. Radiofrequency thermal ablation (RFA) after transarterial chemoembolization (TACE) as a combined therapy for unresectable non-early hepatocellular carcinoma (HCC). *Eur Radiol* 2006;**16**:661–9.
25. Koda M, Ueki M, Maeda Y, Mimura KI, Okamoto K, Matsunaga Y, et al. The influence on liver parenchymal function and complications of radiofrequency ablation or the combination with transcatheter arterial embolization for hepatocellular carcinoma. *Hepatol Res* 2004;**29**:18–23.
26. Higuchi T, Kikuchi M, Okazaki M. Hepatocellular carcinoma after transcatheter hepatic arterial embolization. A histopathologic study of 84 resected cases. *Cancer* 1994;**73**:2259–67.
27. Ishikura S, Ogino T, Furuse J, Satake M, Baba S, Kawashima M, et al. Radiotherapy after transcatheter arterial chemoembolization for patients with hepatocellular carcinoma and portal vein tumor thrombus. *Am J Clin Oncol* 2002;**25**:189–93.
28. Li B, Yu J, Wang L, Li C, Zhou T, Zhai L, et al. Study of local three-dimensional conformal radiotherapy combined with transcatheter arterial chemoembolization for patients with stage III hepatocellular carcinoma. *Am J Clin Oncol* 2003;**26**:e92–9.
29. Tazawa J, Maeda M. Radiation therapy combined with transcatheter arterial chemoembolization for hepatocellular carcinoma. *Nippon Rinsho* 2001;**59**(Suppl. 6):743–7.
30. Yamada K, Izaki K, Sugimoto K, Mayahara H, Morita Y, Yoden E, et al. Prospective trial of combined transcatheter arterial chemoembolization and three-dimensional conformal radiotherapy for portal vein tumor thrombus in patients with unresectable hepatocellular carcinoma. *Int J Radiat Oncol Biol Phys* 2003;**57**:113–9.
31. Yamasaki S, Hasegawa H, Kinoshita H, Furukawa M, Imaoka S, Takasaki K, et al. A prospective randomized trial of the preventive effect of pre-operative transcatheter arterial embolization against recurrence of hepatocellular carcinoma. *Jpn J Cancer Res* 1996;**87**:206–11.
32. Wu CC, Ho YZ, Ho WL, Wu TC, Liu TJ, P'eng FK. Preoperative transcatheter arterial chemoembolization for resectable large hepatocellular carcinoma: a reappraisal. *Br J Surg* 1995;**82**:122–6.
33. Uchida M, Kohno H, Kubota H, Hayashi T, Yamanoi A, Kimoto T, et al. Role of preoperative transcatheter arterial oily

chemoembolization for resectable hepatocellular carcinoma. *World J Surg* 1996;**20**:326–31.
34. Lu CD, Peng SY, Jiang XC, Chiba Y, Tanigawa N. Preoperative transcatheter arterial chemoembolization and prognosis of patients with hepatocellular carcinomas: retrospective analysis of 120 cases. *World J Surg* 1999;**23**:293–300.
35. Di CV, Ferrari G, Castoldi R, De Nardi P, Bergamo C, Taccagni G, et al. Pre-operative chemoembolization of hepatocellular carcinoma in cirrhotic patients. *Hepatogastroenterology* 1998;**45**:1950–4.
36. Adachi E, Matsumata T, Nishizaki T, Hashimoto H, Tsuneyoshi K, Sugimachi K. Effects of preoperative transcatheter hepatic arterial chemoembolization for hepatocellular carcinoma. The relationship between postoperative course and tumor necrosis. *Cancer* 1993;**72**:3593–8.
37. Gerunda GE, Neri D, Merenda R, Barbazza F, Zangrandi F, Meduri F, et al. Role of transarterial chemoembolization before liver resection for hepatocarcinoma. *Liver Transplant* 2000;**6**:619–26.
38. Harada T, Matsuo K, Inoue T, Tamesue S, Inoue T, Nakamura H. Is preoperative hepatic arterial chemoembolization safe and effective for hepatocellular carcinoma? *Ann Surg* 1996;**224**: 4–9.
39. Imaoka S, Sasaki Y, Shibata T, Fujita M, Kasugai H, Kojima J, et al. A pre-operative chemoembolization therapy using lipiodol, cisplatin and gelatin sponge for hepatocellular carcinoma. *Cancer Chemother Pharmacol* 1989;**23**(Suppl.):S126–8.
40. Majno PE, Adam R, Bismuth H, Castaing D, Ariche A, Krissat J, et al. Influence of preoperative transarterial lipiodol chemoembolization on resection and transplantation for hepatocellular carcinoma in patients with cirrhosis. *Ann Surg* 1997;**226**:688–701.
41. Nagasue N, Galizia G, Kohno H, Chang YC, Hayashi T, Yamanoi A, et al. Adverse effects of preoperative hepatic artery chemoembolization for resectable hepatocellular carcinoma: a retrospective comparison of 138 liver resections. *Surgery* 1989;**106**:81–6.
42. Paye F, Jagot P, Vilgrain V, Farges O, Borie D, Belghiti J. Preoperative chemoembolization of hepatocellular carcinoma: a comparative study. *Arch Surg* 1998;**133**:767–72.
43. Lygidakis NJ, Tsiliakos S. Multidisciplinary management of hepatocellular carcinoma. *Hepatogastroenterology* 1996;**43**: 1611–9.
44. Mathurin P, Raynard B, Dharancy S, Kirzin S, Fallik D, Pruvot FR, et al. Meta-analysis: evaluation of adjuvant therapy after curative liver resection for hepatocellular carcinoma. *Aliment Pharmacol Ther* 2003;**17**:1247–61.
45. Li JQ, Zhang YQ, Zhang WZ, Yuan YF, Li GH. Randomized study of chemoembolization as an adjuvant therapy for primary liver carcinoma after hepatectomy. *J Cancer Res Clin Oncol* 1995;**121**:364–6.
46. Izumi R, Shimizu K, Iyobe T, Ii T, Yagi M, Matsui O, et al. Postoperative adjuvant hepatic arterial infusion of lipiodol containing anticancer drugs in patients with hepatocellular carcinoma. *Hepatology* 1994;**20**:295–301.
47. Asahara T, Itamoto T, Katayama K, Ono E, Dohi K, Nakanishi T, et al. Adjuvant hepatic arterial infusion chemotherapy after radical hepatectomy for hepatocellular carcinoma – results of long-term follow-up. *Hepatogastroenterology* 1999;**46**: 1042–8.
48. Cheng SQ, Wu MC, Chen H, Shen F, Yang JH, Cong WM, et al. Transcatheter hepatic arterial chemoembolization and thymosin alpha1 in postoperative treatment of hepatocellular carcinoma. *Zhonghua Zhong Liu Za Zhi* 2004;**26**:305–7.
49. Takenaka K, Yoshida K, Nishizaki T, Korenaga D, Hiroshige K, Ikeda T, et al. Postoperative prophylactic lipiodolization reduces the intrahepatic recurrence of hepatocellular carcinoma. *Am J Surg* 1995;**169**:400–4.
50. Tanaka K, Shimada H, Togo S, Takahashi T, Endo I, Sekido H, et al. Use of transcatheter arterial infusion of anticancer agents with lipiodol to prevent recurrence of hepatocellular carcinoma after hepatic resection. *Hepatogastroenterology* 1999;**46**:1083–8.
51. Ren ZG, Lin ZY, Xia JL, Ye SL, Ma ZC, Ye QH, et al. Postoperative adjuvant arterial chemoembolization improves survival of hepatocellular carcinoma patients with risk factors for residual tumor: a retrospective control study. *World J Gastroenterol* 2004;**10**:2791–4.
52. Lau WY, Leung TW, Ho SK, Chan M, Machin D, Lau J, et al. Adjuvant intra-arterial iodine-131-labelled lipiodol for resectable hepatocellular carcinoma: a prospective randomised trial. *Lancet* 1999;**353**:797–801.
53. Boucher E, Corbinais S, Rolland Y, Bourguet P, Guyader D, Boudjema K, et al. Adjuvant intra-arterial injection of iodine-131-labeled lipiodol after resection of hepatocellular carcinoma. *Hepatology* 2003;**38**:1237–41.
54. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996;**334**:693–9.
55. Decaens T, Roudot-Thoraval F, Bresson-Hadni S, Meyer C, Gugenheim J, Durand F, et al. Impact of pretransplantation transarterial chemoembolization on survival and recurrence after liver transplantation for hepatocellular carcinoma. *Liver Transplant* 2005;**11**:767–75.
56. Oldhafer KJ, Chavan A, Fruhauf NR, Flemming P, Schlitt HJ, Kubicka S, et al. Arterial chemoembolization before liver transplantation in patients with hepatocellular carcinoma: marked tumor necrosis, but no survival benefit? *J Hepatol* 1998;**29**:953–9.
57. Perez SB, Meneu JC, Moreno E, Garcia I, Moreno A, Fundora Y. Is transarterial chemoembolization necessary before liver transplantation for hepatocellular carcinoma? *Am J Surg* 2005;**190**:383–7.
58. Richard III HM, Silberzweig JE, Mitty HA, Lou WY, Ahn J, Cooper JM. Hepatic arterial complications in liver transplant recipients treated with pretransplantation chemoembolization for hepatocellular carcinoma. *Radiology* 2000;**214**:775–9.
59. Graziadei IW, Sandmueller H, Waldenberger P, Koenigsrainer K, Nachbaur K, Jaschke W, et al. Chemoembolization followed by liver transplantation for hepatocellular carcinoma impedes tumor progression while on the waiting list and leads to excellent outcome. *Liver Transplant* 2003;**9**: 557–63.
60. Harnois DM, Steers J, Andrews JC, Rubin JC, Pitot HC, Burgart L, et al. Preoperative hepatic artery chemoembolization followed by orthotopic liver transplantation for hepatocellular carcinoma. *Liver Transplant Surg* 1999;**5**:192–9.
61. Herber S, Schneider J, Brecher B, Hohler T, Thelen M, Otto G, et al. TACE: therapy of the HCC before liver transplantation – experiences. *Rofo* 2005;**177**:681–90.
62. Maddala YK, Stadheim L, Andrews JC, Burgart LJ, Rosen WK, Kremers WK, et al. Drop-out rates of patients with hepatocellular cancer listed for liver transplantation: outcome with chemoembolization. *Liver Transplant* 2004;**10**: 449–55.
63. Roayaie S, Frischer JS, Emre SH, Fishbein TM, Sheiner PA, Sung M, et al. Long-term results with multimodal adjuvant therapy and liver transplantation for the treatment of hepatocellular carcinomas larger than 5 centimeters. *Ann Surg* 2002;**235**: 533–9.
64. Grasso A, Stigliano R, Morisco F, Martines H, Quaglia A, Dhillon AP, et al. Liver transplantation and recurrent hepatocellular carcinoma: predictive value of nodule size in a retrospective and explant study. *Transplantation* 2006; **81**(11):1532–41.