Pre-operative transarterial chemoembolization for resectable hepatocellular carcinoma adversely affects post-operative patient outcome

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SUMMARY

Background
Long-term outcomes after hepatic resection for hepatocellular carcinoma are not satisfactory because of high recurrence rates.

Aim
To assess whether a single session of pre-operative transarterial chemoembolization affects post-operative outcome.

Methods
We analysed outcomes retrospectively in 334 consecutive patients who underwent hepatic resection for hepatocellular carcinoma, initially judged resectable. Ninety-seven of these patients had each undergone a single session of pre-operative transarterial chemoembolization (transarterial chemoembolization + hepatic resection group), whereas 237 had not (hepatic resection group).

Results
Most clinicopathological characteristics were similar in the two groups. The overall survival rate was significantly higher in the hepatic resection than in the transarterial chemoembolization + hepatic resection group ($P = 0.011$), whereas their disease-free survival rates were comparable ($P = 0.67$). The overall and disease-free survival rates of the transarterial chemoembolization + hepatic resection group with incomplete tumour necrosis were significantly lower than those of the hepatic resection group ($P < 0.001$ and $P = 0.006$, respectively). Multivariate analysis showed that pre-operative transarterial chemoembolization, serum alpha-fetoprotein elevation ($>1000$ ng/mL), tumour size ($>5$ cm) and vascular invasion were independent risk factors for poor overall survival after hepatic resection.

Conclusions
A single session of pre-operative transarterial chemoembolization for initially resectable hepatocellular carcinoma worsens overall survival rate. It may also increase the risk of tumour recurrence in patients who achieve incomplete tumour necrosis.
INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, with hepatic resection (HR) being the treatment of choice. Long-term prognosis after HR for HCC, however, is unsatisfactory, because of the high incidence of post-operative recurrence.1, 2 In most patients, tumours recur in the liver remnant because of intrahepatic metastasis from the primary tumour or multicentric occurrence.3, 4

Transarterial chemoembolization (TACE) has been found to provide significant survival benefit in patients with unresectable HCC.5–7 Thus, TACE has been recommended as first-line therapy for nonsurgical patients with large/multifocal HCC.8 TACE may also downstage unresectable HCC, permitting tumour resection and improving patient prognosis.9–11 Neoadjuvant TACE has been utilized in patients with initially resectable HCC to reduce post-operative recurrence rate and to improve patient survival.12–15 In some centres, a single session of TACE is routinely performed before HR to ensure that additional small satellite HCC nodules are detected on a CT scan performed 2–3 weeks later.16, 17

Several retrospective studies have suggested that pre-operative TACE is safe and can improve overall patient survival14 or disease-free survival.12, 13, 15 In contrast, a randomized-controlled trial showed that pre-operative TACE had no impact on disease-free and overall survival.18 Furthermore, two additional studies found that neoadjuvant TACE worsened the overall survival rate compared with patients who underwent HR alone.19, 20 Most of these studies, however, included patients who underwent HR before the early 1990s, prior to recent progress in imaging modalities and surgical procedures, or patients who had undergone multiple sessions of pre-operative TACE, with prolonged delay in performing surgery.

We wished to assess whether a single session of pre-operative TACE could reduce post-operative tumour recurrence and thus improve overall survival. We therefore, compared long-term outcomes in 97 patients who underwent HR following pre-operative TACE for HCC initially judged to be resectable with outcomes in 237 patients who underwent HR without pre-operative TACE. We also analysed long-term patient outcomes in subgroups stratified by the extent of TACE-induced tumour necrosis.

PATIENTS AND METHODS

Patients

Between January 1995 and December 2000, a total of 422 patients underwent curative HR for HCC in our institution. Of these, 88 patients were excluded because they underwent surgery for palliation or for recurrent HCC after previous treatment(s), because they had undergone multiple sessions of TACE before surgical resection, or because the interval between TACE and HR exceeded more than 16 weeks. Of the remaining 334 patients, 97 had each undergone a single session of pre-operative TACE (TACE + HR group), whereas 237 had not (HR group). None of these patients had received any kind of treatment for their HCC except for TACE prior to HR.

At the time of the initial diagnosis, all tumours were judged to be resectable according to a triphasic spiral dynamic CT scan (GE Lightspeed Qx/I, General Electric Medical Systems, Milwaukee, WI, USA; Siemens Somatom plus S, Forchheim, Germany or Siemens Somatom 16, Munich, Germany) by bolus tracking (time–density curve; precontrast, arterial and venous phase) with a routine slice thickness of 5 mm. Pathological findings of the resected liver specimens showed background cirrhosis in 259 (78%) of 334 patients; all of these patients with cirrhosis had an hepatic function of Child–Pugh class A.

This study was retrospective, and the decision to apply TACE before surgical resection was not controlled intentionally by the authors. Doctors in our institution preferred to perform this procedure, while surgeons did not.

TACE method

Conventional mesenteric arteriography was performed first, and the coeliac artery was catheterized. After assessing the hepatic vascular anatomy, TACE was performed through segmental or subsegmental hepatic arteries, especially for small solitary tumours, whenever possible. When we failed to catheterize tumour feeders or multiple segmental hepatic arteries supplying a large tumour, TACE was performed through the right or left hepatic arteries. In most of cases, a mixture of 10 mL of lipiodol (Lipiodol, Laboratoire Andrè Guerbet, Aulnay-sous-Bois, France) and 1 mg/kg cisplatin (Cisplan, Dong-A Pharm. Co. Ltd, Seoul, Korea) was injected after complete...
emulsification. After then, embolization was performed using gelatine sponge cubes (Gelfoam, Upjohn, Kalamazoo, MI, USA). The median interval between TACE and surgery was 4 weeks (range: 1–16).

Post-operative follow-up

No patient received post-operative adjuvant treatment. The routine post-operative follow-up protocol was identical in all patients and did not discriminate between the two groups; it included biochemical liver function tests, serum alpha fetoprotein (AFP) concentrations and triphasic dynamic CT scan performed every 2–3 months during the first year after surgery, and every 6 months thereafter. In patients with AFP-secreting HCC, recurrences were evaluated according to changes in AFP concentration relative to baseline level. Dynamic CT scan was performed whenever a recurrence was suspected, because of an elevation in the once-decreased AFP levels.

No study patient was taking an anti-viral agent prior to surgery, and only four of the HR group patients had begun taking Lamivudine for hepatitis B virus-associated active hepatitis within 3 years following HR.

Statistical analysis

Unless specified, overall survival was measured from the date of HR to the time of death. Data were censored if a patient remained alive until 31 December 2003. Sixty-one of 334 patients (18%) were lost to follow-up and they were censored at the date of the last observation. There was no significant difference in the rate of follow-up loss between the HR and the TACE + HR group (19% vs. 17%, P > 0.05). Disease-free survival was evaluated from the date of surgery to the time the relapse was detected. Data on disease-free survival were censored if the patient was alive and disease-free at the time of last follow-up.

Data analyses were performed using statistics package SPSS v13 for Windows (SPSS, Chicago, IL, USA). Continuous variables are presented as mean ± s.d. The χ² test was used to compare categorical variables. The disease-free and overall survival curves were estimated according to the Kaplan–Meier method and compared statistically by a log-rank test. Univariate and multivariate analyses were carried out by Cox proportional hazards survival analysis model. A P-value of <0.05 was considered statistically significant.

RESULTS

Clinical and pathological factors

The baseline clinical and pathological factors of the HR and TACE + HR groups are shown in Table 1. The two groups were similar with respect to most of these characteristics, including age, gender, hepatitis B surface antigen status, serum AFP levels, extent of surgical procedures, presence of cirrhosis, tumour number, tumour size, vascular invasion, involvement of resection margin and presence of satellite nodule. In contrast, the presence of capsule invasion was significantly more frequent in the TACE + HR group (P = 0.01).

Overall and disease-free survival rates

The follow-up periods ranged from 7.8 days to 7.5 years with an average (s.d.) of 3.1 (2.0) years. One hundred and thirty (39%) of the 334 patients died during follow-up. The overall survival rate of the HR group was significantly higher than that of the TACE + HR group, irrespective of whether survival time was calculated from the date of tumour detection (P = 0.016, data not shown) or that of surgery (P = 0.011; Figure 1a). The 1- and 5-year survival rates were 89% and 62%, respectively, in the HR group and 75% and 44%, respectively, in the TACE + HR group when calculated from the time of surgery.

Recurrence of HCC was identified in 182 patients (55%) during follow-up. The disease-free survival rates of the two groups did not differ significantly (P = 0.67; Figure 1b). The 1- and 3-year disease-free survival rates were 70% and 49%, respectively, in the HR group and 60% and 46%, respectively, in the TACE + HR group. The median disease-free survival times were 34 months in the HR group and 20 months in the TACE + HR group.

Survival rates relative to the degree of tumour necrosis

To evaluate the per cent necrotic area of the resected tumours in the TACE + HR group, we defined tumour necrosis as complete when the area of necrosis was 95% or more of the total tumour volume by pathological examination. The overall and disease-free survival rates
of the TACE + HR group with complete tumour necrosis were comparable to those of the HR group (P = 0.947 and P = 0.136, respectively, Figure 2). In contrast, the overall and disease-free survival rates of the TACE + HR group with incomplete tumour necrosis were significantly lower than those of the HR group (P < 0.001 and P = 0.006, respectively) or than those of the TACE + HR group with complete tumour necrosis (P = 0.003 and P = 0.001, respectively, Figure 2).

### Table 1. Comparison of baseline clinical and pathological factors between the groups

| Characteristics                  | HR group, n (%) | TACE + HR group, n (%) | P-value |
|----------------------------------|-----------------|------------------------|---------|
| Number of patients               | 237 (100)       | 97 (100)               |         |
| Age (years)                      |                 |                        |         |
| Mean ± s.d.                      | 51.7 ± 10.2     | 48.8 ± 9.2             | 0.113   |
| Sex                              |                 |                        |         |
| Male                             | 194 (82)        | 80 (83)                | 0.894   |
| Female                           | 43 (18)         | 17 (18)                |         |
| Serum HBsAg Positive             | 172 (73)        | 77 (79)                | 0.195   |
| Serum HBsAg Negative             | 65 (27)         | 20 (21)                |         |
| Serum AFP (ng/mL)*               |                 |                        |         |
| £1000                            | 160 (68)        | 63 (65)                | 0.654   |
| >1000                            | 70 (30)         | 31 (32)                |         |
| Surgical procedure               |                 |                        |         |
| £Segmentectomy                   | 91 (38)         | 43 (44)                | 0.315   |
| >Segmentectomy                   | 146 (62)        | 54 (56)                |         |
| Background liver                 |                 |                        |         |
| Noncirrhotic                     | 53 (22)         | 20 (21)                | 0.699   |
| Cirrhotic                        | 182 (77)        | 77 (79)                |         |
| Tumour number                    |                 |                        |         |
| Uninodular                       | 209 (88)        | 84 (87)                | 0.688   |
| Multinodular                     | 28 (12)         | 13 (13)                |         |
| Diameter of tumour (cm)          |                 |                        |         |
| £5                               | 136 (57)        | 48 (50)                | 0.188   |
| >5                               | 101 (43)        | 49 (51)                |         |
| Vascular invasion                |                 |                        |         |
| Yes                              | 45 (19)         | 16 (17)                | 0.541   |
| No                               | 185 (78)        | 80 (83)                |         |
| Capsular invasion                |                 |                        |         |
| Yes                              | 35 (15)         | 26 (27)                | 0.010   |
| No                               | 202 (85)        | 71 (73)                |         |
| Resection margin                 |                 |                        |         |
| Involved                         | 18 (8)          | 8 (8)                  | 0.840   |
| Not involved                     | 219 (92)        | 89 (92)                |         |
| Satellite nodule                 |                 |                        |         |
| Yes                              | 28 (12)         | 17 (18)                | 0.170   |
| No                               | 208 (88)        | 80 (83)                |         |

* Alpha-fetoprotein.
HR, hepatic resection; TACE, transarterial chemoembolization.

Univariate and multivariate analyses of overall and disease-free survival

Clinicopathological factors including patient age, gender, pre-operative serum AFP elevation (>1000 ng/mL), tumour number, tumour size, background cirrhosis, extent of resection, microscopic vascular invasion, capsular containment, surgical resection margin involvement, satellite nodules and pre-operative TACE were examined in relation to overall and disease-free survival rates after HR. Univariate analysis revealed that
pre-operative TACE, serum AFP elevation (>1000 ng/mL), tumour number (multinodular), tumour size (>5 cm), vascular invasion, capsular containment and surgical resection margin involvement influenced overall survival rate after HR (Table 2). Multivariate analysis of these seven significant factors revealed that pre-operative TACE, serum AFP elevation, larger tumour size and vascular invasion independently affected overall survival rate after HR (Table 2).

Univariate analysis of disease-free survival rate showed that incomplete tumour necrosis by pre-operative TACE, pre-operative serum AFP elevation (>1000 ng/mL), tumour number (multinodular), tumour size (>5 cm), vascular invasion, surgical resection margin involvement, background cirrhosis and satellite nodules adversely influenced disease-free survival rate after HR (Table 3). Pre-operative TACE itself was not a significant variable for disease-free survival. Eight significant variables were included in the multivariate analysis, and incomplete tumour necrosis by pre-operative TACE, tumour number (multinodular), vascular invasion, surgical resection margin involvement and background cirrhosis were found to independently affect disease-free survival after HR (Table 3).

DISCUSSION
The results presented here suggest that pre-operative TACE for initially resectable HCC did not reduce the risk of tumour recurrence, and may even have worsened the overall survival rates. These results are in contrast to our initial hypothesis that pre-operative...
TACE would reduce post-operative tumour recurrence and thus improve patient survival, or at least that it would be safe. The decreases in overall and disease-free survival rates were particularly noticeable in patients in whom tumour necrosis was incomplete. These findings are in agreement with those of an earlier prospective trial, which showed that patients with large HCC (>10 cm) who underwent pre-operative TACE had a lower overall survival rate than patients on whom surgery was performed without delay, although the two groups had similar disease-free survival rates.\(^1\) In addition, another recent retrospective study demonstrated lower long-term overall survival rates in patients who received pre-operative TACE than those who did not.\(^2\)

The mechanism by which pre-operative TACE causes a lower overall survival rate and the discrepancy between overall and disease-free survival rates are not clear. Because of the retrospective nature of this study, we could not adequately analyse causes of death. It is possible that the principal cause of death in the TACE + HR group may have been hepatic failure related to a decrease in hepatic functional reserve caused by pre-operative TACE or to increased difficulty in surgical procedures.\(^1\)\(^6\), \(^2\)\(^1\)\(^2\) However, there are no direct data supporting this assumption. Alternatively, the recurrence of HCC in the HR group may have been less extensive than the TACE + HR group, thus reducing the influence to the overall survival. The later estimation was relevant when the survival rates of the HR group were compared with those of the TACE + HR group with incomplete necrosis.\(^2\)\(^1\)\(^2\)

Our results, together with previous findings, support the hypothesis that partial necrosis induced by pre-operative TACE increases the risk of tumour recurrence after surgical resection, which may be because of tumour cell dislodgement into the bloodstream.\(^2\)\(^3\), \(^2\)\(^4\) In cases of partial necrosis, the remaining viable tumour cells are less firmly attached, and thus are more likely to be dislodged into the bloodstream before surgery and to metastasize during HR.

In contrast to our results, several previous retrospective studies have suggested that neoadjuvant TACE is safe and feasible, improving the overall outcome of the patients.\(^1\)\(^2\)–\(^1\)\(^5\) However, most of these studies were

### Table 2. Factors significantly associated with overall survival

| Relative hazard | 95% CI       | P-value |
|-----------------|--------------|---------|
| TACE, transarterial chemoembolization; AFP, alpha-fetoprotein. |

#### Univariate analysis

- Pre-operative TACE
- Serum AFP (>1000 ng/mL)
- Tumour number (multinodular)
- Tumour size (>5 cm)
- Vascular invasion
- Capsule invasion
- Resection margin involvement

#### Multivariate analysis

- Pre-operative TACE
- Serum AFP (>1000 ng/mL)
- Tumour number (two or more)
- Vascular invasion
- Resection margin involvement
- Background cirrhosis
- Satellite nodule

### Table 3. Factors significantly associated with disease-free survival

| Relative hazard | 95% CI       | P-value |
|-----------------|--------------|---------|
| TACE, transarterial chemoembolization; AFP, alpha-fetoprotein. |

#### Univariate analysis

- Incomplete tumour necrosis by pre-operative TACE
- Serum AFP (>1000 ng/mL)
- Tumour number (multinodular)
- Tumour size (>5 cm)
- Vascular invasion
- Resection margin involvement
- Background cirrhosis
- Satellite nodule

#### Multivariate analysis

- Incomplete tumour necrosis by pre-operative TACE
- Tumour number (two or more)
- Vascular invasion
- Resection margin involvement
- Background cirrhosis

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based on data before the early 1990s, when recent progresses in surgical management for HCC were not available. Advances in surgical procedures within the past decade, including the minimization of the spread of tumour cells, have led to a significant improvement in the overall and disease-free survival rates after HR. We estimate that these advances in surgical management for HCC have minimized the role of pre-operative TACE. In addition, although some survival gains may be expected through complete necrosis of HCC by pre-operative TACE, complete necrosis is achieved in fewer than 50% of the cases, and there is no reliable way to predict it.

Pre-operative TACE may enhance the ability to detect additional small HCC nodules on a CT scan performed 2–3 weeks later, which would not be detected by earlier CT scans. These patients might have been excluded from surgery and were not analysed in this retrospective study. This selection bias may have increased the disease-free survival rate in the TACE + HR group; however, it was not higher than that of the HR group. The prognostic disadvantage of pre-operative TACE may therefore exceed its diagnostic advantage in patients with initially resectable HCC. It is likely that our results may have been, at least in part, as a result of recent progress in imaging modalities, including multiphasic CT scans that have made it possible to detect small HCCs without prior lipiodolization, thus improving the curative resection rate. All of the HCC nodules were diagnosed by triphasic CT scan with a routine slice thickness of 5 mm.

This study had several limitations, including its retrospective design, the variable dose of lipiodol injections, and the variability in time between TACE and surgery. To reduce the heterogeneity of patients in each treatment group, we restricted patient enrolment only if their tumours were judged to be resectable at the time of initial diagnosis and only if they had good hepatic function. Only patients, who had undergone HR within 4 months after a single session of TACE, were analysed to assure that TACE had been performed for a neoadjuvant purpose before HR. Most of the variables in the baseline clinical and histopathological findings were comparable between the two groups except for capsule invasion. Moreover, on multivariate analysis, pre-operative TACE itself and incomplete tumour necrosis by TACE were identified as independent risk factors for increased mortality and increased recurrence of HCC, respectively. Capsule invasion was not a significant prognostic factor for the overall or disease-free survival rate on multivariate analyses.

In summary, our findings indicate that pre-operative TACE may adversely affect post-operative patient survival. It may also increase the risk of tumour recurrence, if TACE-induced tumour necrosis is not complete. Even in patients with complete tumour necrosis, the overall and disease-free survival rates were no better than in patients without pre-operative TACE. In conclusion, pre-operative TACE should not be recommended as routine procedure for patients with resectable HCC.

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