Radiological response predicts survival following transarterial chemoembolisation in patients with unresectable hepatocellular carcinoma

D. Y. Kim*,†,‡, H. J. Ryu*,†, J. Y. Choi§, J. Y. Park*†,‡, D. Y. Lee*, B. K. Kim*†,‡, S. U. Kim*†,‡, S. H. Ahn*†,‡, C. Y. Chon*†& K.-H. Han*†,‡

*Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea.
†Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea.
‡Liver Cirrhosis Clinical Research Center, Seoul, Korea.
§Department of Radiology, Yonsei University College of Medicine, Seoul, Korea.
¶Department of Interventional Radiology, Yonsei University College of Medicine, Seoul, Korea.

Correspondence to:
Dr K.-H. Han, Department of Internal Medicine, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, 120-752 Seoul, Korea.
E-mail: gihankhys@yuhs.ac

Publication data
Submitted 15 January 2012
First decision 24 February 2012
Resubmitted 12 March 2012
Accepted 15 March 2012
EV Pub Online 8 April 2012

SUMMARY

Background
It remains unclear whether initial compact lipiodol uptake after transarterial chemoembolisation (TACE) is associated with improved survival in patients with hepatocellular carcinoma (HCC).

Aim
To reveal the clinical relevance of compact lipiodolisation after TACE.

Methods
We studied 490 patients with unresectable HCC who had first been treated with TACE. Compact lipiodolisation was defined as the absence of an arterial enhancing lesion, reflecting complete lipiodol uptake, as assessed by dynamic computed tomography (CT) 1 month after treatment. The rate of initial compact lipiodolisation was analysed according to multiplicity and size of tumour, and survival of patients who achieved compact lipiodolisation was compared to that of patients who did not.

Results
Of the 490 patients, 409 (83.5%) were in Child–Pugh class A and 81 (16.5%) in class B. The rate of initial compact lipiodolisation in single HCCs was higher than that in multinodular HCCs (33.7% vs. 14.6%, P < 0.001). Among single HCCs, the rate of compact lipiodolisation in tumours ≤5, 5–10 and >10 cm was 46.6%, 13.6%, and 0% respectively. The 1-, 3- and 5-year survival rates of patients with compact uptake were 92.7%, 70.7% and 52.4% compared to 60.8%, 28.0% and 16.9% in patients with noncompact lipiodolisation. Multivariate analysis revealed that Child–Pugh class, alpha-fetoprotein level, tumour node metastasis stage, portal vein thrombosis and initial compact lipiodolisation were independent predictors of survival.

Conclusions
Initial compact lipiodol uptake after transarterial chemoembolisation is associated with improved survival in patients with unresectable hepatocellular carcinoma. Accordingly, initial complete lipiodolisation should be considered a relevant therapeutic target.

Aliment Pharmacol Ther 2012; 35: 1343–1350

© 2012 Blackwell Publishing Ltd
doi:10.1111/j.1365-2036.2012.05089.x
INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common malignant tumour with a rising global incidence, and is responsible for a half million deaths annually worldwide.\(^1\) Despite the recent development of many treatment modalities, HCC continues to have a poor prognosis. Potential curative treatment modalities such as resection, ablation and liver transplantation have been considered to be the most effective treatments for HCC. However, fewer than 20% of HCC patients have been treated surgically, mainly because of associated complicating cirrhosis and advanced stage of cancer at diagnosis.\(^2\), \(^3\)

Since transcatheter arterial embolisation was introduced to treat HCC by Doyon et al.\(^4\) in 1974, it has evolved into using gelatin sponge particles, anticancer agents, lipiodol and super selective catheterisation.\(^5\)–\(^7\) A meta-analysis showed that transarterial chemoembolisation (TACE) improved survival in patients with unresectable HCC, thus ending a controversy for survival benefits of TACE.\(^8\) Currently, TACE is being widely used and has become the standard treatment modality for patients with unresectable, specifically those with intermediate-stage HCC.\(^9\)–\(^11\)

Despite the positive survival benefit of TACE, it has some limitations as a palliative treatment modality. It can lead to incomplete necrosis of hypovascular or large tumours and therefore might need repeated treatments, which can result in a tapered tumour-feeding artery and deterioration of liver function.\(^12\)–\(^13\)

Therefore, previous studies have evaluated the predictive factors that influence survival for patients with HCC after TACE to maximise the effects of TACE. Among these predictive factors, which also include alpha-fetoprotein (AFP) level, tumour size, Child–Pugh grade and portal vein thrombosis, complete tumour necrosis has been suggested as a useful predictor of survival for HCC treated with TACE.\(^14\)–\(^20\) At a practical level, it is difficult to assess the degree of tumour necrosis by computed tomography (CT) scan after TACE because of the radiopaque lipiodol. Instead, the post-TACE response is evaluated by the degree of lipiodol uptake, and this method is actually compatible with assessment by modified Response Evaluation Criteria in Solid Tumor (RECIST)\(^21\) as a lesion that has taken up lipiodol is no more enhanced in arterial phase in dynamic CT.

A recent study has shown that complete response at 1 month following percutaneous ablation correlates with improved survival.\(^22\) However, there are few clinical studies addressing the clinical relevance of compact lipiodolisation; in other words, whether a complete response by modified RECIST is associated with improved survival in unresectable HCC.\(^11\)

In the present study, we investigated whether compact lipiodol uptake after TACE could predict survival in patients with unresectable HCC and identified independent predictors of survival in these patients.

PATIENTS AND METHODS

Patients

From December 2002 to November 2007, a total of 1437 new HCC patients were admitted to the liver unit of Severance Hospital, Yonsei University College of Medicine, Seoul, Korea. Of these, 816 patients were treated by TACE as an initial treatment modality, and 621 patients who initially received treatments other than TACE were excluded. We also excluded the 326 patients who were Child C, tumour node metastasis (TNM) stage 1,\(^23\) IV-B or who received surgical resection or transplantation after TACE. Thus, the remaining 490 patients were included and analysed in this study. This study was approved by the institutional review board of our hospital.

Definitions and follow-up

The diagnosis of HCC was mainly based on reliable imaging modalities of dynamic CT, magnetic resonance imaging and angiography according to the European Association for the Study of the Liver guidelines,\(^24\) and/or pathological findings obtained by gun biopsy. The tumour size was defined as the longest diameter of the HCC or, in case of multiple nodules, as the sum of the maximum diameter of all tumours. Lipiodol uptake after TACE was retrospectively assessed by an experienced radiologist (JY Choi) who was blind to clinical information. Initial response was defined as compact lipiodolisation with absence of an enhanced and delayed washout lesion as assessed by a contrast-enhanced CT scan 1 month after TACE. Likewise, an initial nonresponse was defined as noncompact lipiodol uptake that represents any enhancing lesion in the arterial phase (and washout in delayed phase) remaining after TACE. Disease recurrence was defined as the re-appearance of HCC after achievement of initial response. One month after initial TACE, all patients underwent dynamic CT, and their responses to TACE were evaluated by comparing CT scans taken before and after TACE, together with surveys of patterns of lipiodol uptake and residual tumour viability. If the lipiodol uptake was compact in...
each nodule in the follow-up CT scan, the patients were followed up every 3 months by clinical examination and serum biochemistry, including AFP levels and CT. Upon detection of recurrence, patients were considered for repeated TACE or other treatment.

Transarterial chemoembolisation
The TACE procedure was as follows: after obtaining angiographic access, approximately 10 mL of iodised oil (lipiodol; Guerbet, Aulnay-sous-Bois, France) mixed with adriamycin was injected via a catheter, the tip of which was advanced into the proper hepatic artery. This was followed by selective embolisation of the feeding artery with gelatin sponge particles (Gelfoam; Upjohn, Kalama-zoo, MI). The dose of lipiodol was adjusted according to the size of the tumour. Gelfoam pieces with non-ionic contrast medium were injected via a catheter until the hepatic arterial branches were occluded. We used a 5-Fr 75-cm Rösch hepatic catheter and a MicroFerret-18-infusion catheter (Cook, Bloomington, IN, USA).

Statistical analysis
The rate of initial compact lipiodolisation was analysed according to tumour multiplicity and size, and survival of patients with compact uptake was compared to that of patients with noncompact lipiodolisation. Comparisons were performed using Student’s *t*-test for continuous variables and the chi-square or Fisher’s exact test for categorical variables. Overall survival was defined as the time from TACE to death or final follow-up visit, and recurrence-free survival was defined as the time from TACE to recurrence. Cumulative analysis of overall and recurrence-free survival was performed using the Kaplan–Meier method, and statistical comparisons were based on the log rank test. The Cox regression model was used to evaluate independent prognostic factors. All analyses were performed using the Statistical Program for Social Sciences (SPSS 13.0 for Windows; SPSS, Chicago, IL, USA), and *P* < 0.05 indicated statistical significance.

RESULTS

Patient characteristics
The patient characteristics are summarised in Table 1. The median follow-up period was 20.8 [interquartile range (IQR) 8.9–39.5] months. The median age was 60 years (range, 27–84), and the ratio of males to females was 382:108 (78.0%/22.0%). The most common aetiology of HCC was hepatitis B virus infection; 393 (80.2%) and 82 (16.7%) patients were positive for hepatitis B surface antigen and anti-hepatitis C virus respectively. Serum AFP levels were ≥ 400 ng/mL in 179 (29.6%) patients. Child–Pugh class for liver function was class A in 409 patients (83.5%) and class B in 81 patients (16.5%).

Tumour characteristics
The stage distribution of patients was TNM stage II in 204 (41.6%), stage III in 201 (41%) and stage IV-A in 85 (17.4%). Two hundred and two (41.2%) patients had single HCCs and 288 (58.8%) had multiple HCCs. Among the single HCCs, the number of patients with tumour size 2–3, 3–5, 5–10 and >10 cm was 63 (31.2%), 70 (34.6%), 44 (21.8%) and 25 (12.4%) respectively (Table 2).

Compact lipiodolisation
The rate of initial compact lipiodolisation in single HCCs was higher than that of multiple HCCs [68/202 (33.7%) vs. 42/288 (14.6%) respectively; *P* < 0.001]. Among single HCCs, the rate of complete lipiodol uptake in tumours of size 2–3, 3–5, 5–10 and >10 cm was 29/63 (46.0%), 33/70 (47.1%), 6/44 (13.6%) and 0/25 (0%) respectively. Among multiple HCCs, the rate of complete lipiodol uptake in tumours <3, 3–5, 5–10 and >10 cm was 24/98 (24.5%), 14/66 (21.2%), 4/63 (6.3%) and 0/61 (0%) respectively (Table 3).

Overall survival
The median follow-up was 20.8 months, with a median survival of 23.4 months. The 1-, 3- and 5-year survival

| Table 1 | Clinical characteristics of patients |
|-----------------|-----------------|
| Variables       | Patients        |
| Median age, years | 60 (27–84)      |
| Gender (M/F)    | 382/108 (78.0%/22.0%) |
| Aetiology       |                |
| HBV             | 393 (80.2%)     |
| HCV             | 82 (16.7%)      |
| Non B-non C     | 15 (3.1%)       |
| Ascites         | 82 (13.6%)      |
| Bilirubin, mg/dL| 0.8 (0.2–13.4)  |
| Albumin, g/dL   | 3.8 (2.9–4.9)   |
| ALT, IU/L       | 41 (12–406)     |
| AFP, >400 ng/mL | 179 (29.6%)     |
| Child–Pugh class, A/B | 409/81 (83.5%/16.5%) |
| Median follow-up, months | 20.8 (IQR 8.9–39.5) |

HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-feto-protein; TNM, tumour node metastasis; IQR, interquartile range.
rates of patients with initial compact lipiodolisation were 92.7%, 70.7% and 52.4%, respectively, compared with 60.8%, 28% and 16.9% in patients who failed to achieve compact lipiodol uptake ($P < 0.001$) (Figure 1a). In both Child–Pugh class A and B, the survival of initial responders was significantly higher than that of nonresponders ($P < 0.001$) (Figure 1b). The initial responders also showed higher survival than nonresponders for patients with TNM stage II and III ($P < 0.001$). However, for TNM stage IV-A, there was no difference in survival between patients with and without compact lipiodolisation ($P = 0.105$) (data not shown).

### Predictors of survival
In multivariate analyses of survival, independent predictors of survival were found to be Child–Pugh class [odds ratio (OR), 0.674; 95% confidence interval (CI), 0.475–0.955; $P = 0.027$], tumour size, TNM stage, portal vein thrombosis (OR, 0.585; 95% CI, 0.411–0.834; $P = 0.003$) and compact lipiodol uptake (OR, 0.390; 95% CI, 0.269–0.566; $P < 0.001$) (Table 4).

### Recurrence-free survival
We also investigated recurrence-free survival for patients who achieved complete lipiodol uptake after TACE. The recurrence-free survival was defined as the time until the appearance of a new viable portion after complete response. Patients with tumour size $>5$ cm showed poor recurrence-free survival: the median recurrence-free survival time was 19.5 months for HCC smaller than 5 cm, compared with 2.9 months for HCC larger than 5 cm ($P < 0.001$) (Figure 2a). Patients with multiple tumours also showed poor recurrence-free survival: 20 months for single HCC vs. 7.7 months for multiple HCCs ($P = 0.002$) (Figure 2b). A separate, detailed analysis for multiple HCCs showed that survival after TACE was directly related to the number of tumours (Figure 2c).

Multivariate analysis using the Cox model showed that the number of tumours and tumour size $>5$ cm were independent predictors of recurrence-free survival (Table 5).

### DISCUSSION
Transarterial chemoembolisation is considered the gold standard of therapy for patients with intermediate-stage HCC and has been shown to result in a survival benefit compared with the best supportive care. Although there is no agreement on a standard technique, protocol or drug regimen, most of the institutions performing TACE typically use doxorubicin, cisplatin or mitomycin C mixed with lipiodol (iodinised poppy seed oil), which functions as a vehicle for these drugs and is fixed preferentially in the HCC nodule, thus prolonging exposure of the neoplastic cells to chemotherapy.\(^{25}\) Currently, modified RECIST is the standard criteria for the assessment of treatment response and progression of HCC with consideration of loss of vascularity and tumour necrosis rather than tumour size reduction. Although lipiodol has been widely adopted in TACE protocols, its efficacy has not been demonstrated. Furthermore, lipiodol can mask assessment of residual vascularity on CT imaging following TACE. The clinical relevance of compact lipiodol deposition in all HCC nodules assessed 1 month after

---

**Table 2 | Tumour characteristics**

| Variables        | Patients |
|------------------|----------|
| TNM stage        |          |
| II               | 204 (41.6) |
| III              | 201 (41.0) |
| IV-A             | 85 (17.4)  |
| Tumour size (single nodule) |          |
| 2–3 cm           | 63 (31.2)  |
| 3–5 cm           | 70 (34.6%) |
| 5–10 cm          | 44 (21.8)  |
| >10 cm           | 25 (12.4)  |
| *Tumour size (multiple nodules) |          |
| <3 cm            | 98 (34.0)  |
| 3–5 cm           | 66 (22.9)  |
| 5–10 cm          | 63 (21.9)  |
| >10 cm           | 61 (21.2)  |

Values within parenthesis are expressed in percentage. TNM, tumour node metastasis.

* Sum of maximum diameter.

**Table 3 | Rate of initial compact lipiodolisation relating tumour multiplicity and size**

| Variables          | Values         | P-value |
|--------------------|----------------|---------|
| Multiplicity       |                |         |
| Single             | 68/202 (33.7)  | $<0.001$|
| Multiple           | 42/288 (14.6)  |         |
| Size in single HCC |                |         |
| 2–3 cm             | 29/63 (46.0)   | $<0.001$|
| 3–5 cm             | 33/70 (47.1)   |         |
| 5–10 cm            | 6/44 (13.6)    |         |
| >10 cm             | 0/25 (0)       |         |
| Size in multiple HCC |              |         |
| <3 cm              | 24/98 (24.5)   | 0.004   |
| 3–5 cm             | 14/66 (21.2)   |         |
| 5–10 cm            | 4/63 (6.3)     |         |
| >10 cm             | 0/61 (0)       |         |

HCC, hepatocellular carcinoma.

Values within parenthesis are expressed in percentage.
TACE is not well known, even though this compact lipiodolisation is an important therapeutic target for almost all interventional radiologists or physicians.

The present study shows that initial complete lipiodol uptake by TACE directly predicts better patient survival compared with patients with incomplete uptake. This correlation between survival and response to TACE was also observed regardless of subgroup stratified according to liver function (Child class) or tumour stage (TNM).

Single HCC had a higher probability of compact lipiodolisation than multiple HCC (33.7% vs. 14.6%, \( P < 0.001 \)) despite the intention of superselective TACE in multinodular HCC. It is of note that, among single HCCs, tumour size determined the rate of compact deposition of lipiodol. As in single HCC, initial response to TACE was dependent on the sum of tumour size in

![Figure 1](https://example.com/figure1.png)

**Figure 1** | Overall survival according to initial response. (a) Patients with compact lipiodol uptake had a better survival than those who failed to achieve compact uptake (\( P < 0.001 \)). (b) The survival of patients with initial compact lipiodolisation was significantly higher than that of patients without compact lipiodol uptake in both Child class A and B (\( P < 0.001 \)). (c) Regardless of tumour node metastasis stage II or III, complete lipiodol uptake resulted in a better survival (\( P < 0.001 \)).
multiple HCC, with 6.3% compact lipiodolisation in HCC lesion sized 5–10 cm and none for those >10 cm.

The two observations that complete lipiodolisation after TACE depends on the tumour size and that compact lipiodol deposition within HCC is associated with patient survival confirm that homogeneous lipiodolisation should be reflected in the therapeutic goals of TACE. The pattern of iodised oil labelling has also been found to be a prognostic indicator in a previous study, in which the 1- and 3-year survival rates of patients with complete nodular uptake were 76% and 20% respectively.26 Our data show that patients with compact lipiodol uptake had excellent survival with 1-, 3- and 5-year survival rates of 92.7%, 70.7% and 52.4%, respectively, despite the fact that they did not receive subsequent resection. This result suggests that initial complete lipiodol uptake could lead to a survival outcome comparable to resection, even though TACE is considered a palliative method.27, 28 However, it is important to keep in mind the limitations of TACE in intermediate or advanced HCC because HCC lesions larger than 5 cm rarely achieved such compact lipiodolisation after TACE in either single or multiple HCCs. Combined modality using external radiation therapy or radiofrequency ablation (RFA) might be an option in HCC that are too large to be controlled by TACE alone. Previously, Shim et al. reported that 2-year survival rates in HCC patients treated with TACE plus external radiation were 63%, compared to 42% in TACE alone, if the tumour size of HCC was 5–7 cm.29 In another study, Rossi et al. reported that combined TACE and RFA offered a positive outcome in 90% of 62 cirrhotic patients with HCC with a median diameter of 47 mm (range 35–85 mm).30

In the analysis of recurrence-free survival among HCC patients who achieved initial compact lipiodol uptake after TACE, patients with tumours larger than 5 cm showed significantly shorter recurrence-free survival than those with tumours < 5 cm (2.9 months vs. 19.5 months, P < 0.001). Furthermore, the recurrence-free survival was significantly shorter for multiple HCCs compared with single HCCs (7.7 months vs. 20 months, P < 0.001), and was proportionally reduced as the number of HCC nodules increased (Figure 2). Recent studies have reported

---

Table 4 | Multivariate analysis for prognostic factors of survival

| Variables                      | Odds ratio (95% CI)       | P-value |
|-------------------------------|---------------------------|---------|
| Liver function                |                           |         |
| Child–Pugh class (A/B)        | 0.674 (0.475–0.955)       | 0.027   |
| BUN (mg/dL)                   | 0.996 (0.973–1.020)       | 0.750   |
| Prothrombin activity (%)      | 0.992 (0.982–1.003)       | 0.148   |
| Tumour size (vs. 2–3 cm)      |                           |         |
| 3–5 cm                        | 0.603 (0.407–0.893)       | 0.012   |
| 5–10 cm                       | 0.553 (0.378–0.809)       | 0.002   |
| >10 cm                        | 0.674 (0.475–0.956)       | 0.027   |
| TNM stage (vs. II)            |                           |         |
| III                           | 0.519 (0.303–0.889)       | 0.017   |
| IV-A                          | 0.633 (0.431–0.929)       | 0.019   |
| PVT                           | 0.585 (0.411–0.834)       | 0.003   |
| Initial response              | 0.390 (0.269–0.566)       | <0.001  |

BUN, blood urea nitrogen; TNM, tumour node metastasis; PVT, portal vein thrombosis.

---

Figure 2 | Recurrence-free survival after compact lipiodolisation. (a) Patients with tumour size >5 cm showed poor recurrence-free survival (P < 0.001). (b) The recurrence-free survival of patients with multiple hepatocellular carcinomas (HCCs) was worse than that of patients with single HCCs (P = 0.002). (c) The probability of recurrence increased proportionally as the number of tumours increased.
that TACE using drug-eluting beads (DEB) could provide better outcomes than conventional TACE especially in patients with more advanced disease. However, there has been no study comparing between conventional TACE using lipiodol and DEB-TACE in terms of recurrence-free survival. Radioembolisation, another liver-directed therapy, might be an alternative in multiple nodular HCC. In a European multi-institutional study, survival after radioembolisation with yttrium-90 seemed to be promising for the subset of patients with intermediate-stage HCC and more than five nodules.

To determine the best treatment strategy to overcome recurrence, the most common problem with TACE, it will be necessary to conduct a randomised trial comparing conventional TACE vs. DEB-TACE or yttrium-90 radioembolisation. Apparently, the efficacy of combination of TACE and anti-angiogenic therapy such as sorafenib also warrants further studies for patients with multinodular and large HCC.

In conclusion, we found that initial compact lipiodol deposition in HCC nodules by TACE is a predictor of survival irrespective of liver function or tumour stage. Compact lipiodolisation clearly depended on the tumour diameter with tumours larger than 5 cm having a lower probability of complete response. Together with multiplicity, tumour size >5 cm was also a determining factor in recurrence after initial compact lipiodolisation. Alternative locoregional or combined modalities could be adopted to control HCC which is not anticipated to be treated effectively by conventional TACE using lipiodol.

**ACKNOWLEDGEMENTS**

Declaration of personal interests: None. Declaration of funding interests: This study was funded in part by the GlaxoSmithKline Research Fund of the Korean Association for the Study of the Liver, and in part by the Korean Healthcare Technology R&D Project, Ministry of Health and Welfare, Republic of Korea, A102065. Writing support was provided by Kyle J Muir of Fred Hutchinson Cancer Research Center (no funding).

**REFERENCES**

1. El-Serag HB. Hepatocellular carcinoma: an epidemiologic view. J Clin Gastroenterol 2002; 35(Suppl. 2): S72–8.
2. Jarnagin WR, Gonen M, Fong Y, et al. Improvement in peripoperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. Ann Surg 2002; 236: 397–406.
3. Imamura H, Seyama Y, Kokudo N, et al. One thousand fifty-six hepatocemities without mortality in 8 years. Arch Surg 2003; 138: 1198–206.
4. Doyon D, Mouzon A, Jourde AM, Regensberg C, Frileux C. Hepatic, arterial embolization in patients with malignant liver tumours. Ann Radiol (Paris) 1974; 17: 593–603.
5. Matui O, Miyayama S, Sanada J, et al. Interventional oncology: new options for interstitial treatments and intravascular approaches: superselective TACE using iodized oil for HCC: rationale, technique and outcome. J Hepatobiliary Pancreat Sci 2010; 17: 407–9.
6. Konno T, Maeda H, Iwai K, et al. Effect of arterial administration of high-molecular-weight anticancer agent SMANCS with lipid lymphographic agent on hepatoma: a preliminary report. Eur J Cancer Clin Oncol 1983; 19: 1053–65.
7. Ohishi H, Uchida H, Yoshimura H, et al. Hepatocellular carcinoma detected by iodized oil. Use of anticancer agents. Radiology 1985; 154: 25–9.
8. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology 2003; 37: 429–42.
9. Bronowicki JP, Vetter D, Dumas F, et al. Transcatheter oily chemoembolization for hepatocellular carcinoma. A 4-year study of 127 French patients. Cancer 1994; 74: 16–24.
10. Takayasu K, Ariti S, Ikai I, et al. Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. Gastroenterology 2006; 131: 461–9.
11. Stefanini GF, Amorati P, Biselli M, et al. Efficacy of transarterial targeted treatments on survival of patients with hepatocellular carcinoma. An Italian experience. Cancer 1995; 75: 2427–34.
12. Morimoto M, Numata K, Kondou M, Nozaki A, Morita S, Tanaka K. Midterm outcomes in patients with intermediate-sized hepatocellular carcinoma: a randomized controlled trial for determining the efficacy of radiofrequency ablation combined with transcatheter arterial chemoembolization. Cancer 2010; 116: 5452–60.
13. Lencioni R, Chen XP, Dagher L, Venook AP. Treatment of intermediate/advanced hepatocellular carcinoma in...
the clinic: how can outcomes be improved? Oncologist 2010; 15(Suppl. 4): 42–52.

14. Llad L, Virgili J, Figueras J, et al. A prognostic index of the survival of patients with unresectable hepatocellular carcinoma after transcatheter arterial chemoembolization. Cancer 2000; 88: 50–7.

15. O’Suilleabhain CB, Poon RTP, Yong JL, Ooi GC, Tso WK, Fan ST. Factors predictive of 5-year survival after transarterial chemoembolization for inoperable hepatocellular carcinoma. Br J Surg 2003; 90: 325–31.

16. Liem MS, Poon RT, Lo C, Tso W, Fan S. Outcome of transarterial chemoembolization in patients with inoperable hepatocellular carcinoma eligible for radiofrequency ablation. World J Gastroenterol 2005; 11: 4465–71.

17. Lee HS, Kim KM, Yoon JH, et al. Therapeutic efficacy of transcatheter arterial chemoembolization as compared with hepatic resection in hepatocellular carcinoma patients with compensated liver function in a hepatitis B virus-endemic area: a prospective cohort study. J Clin Oncol 2002; 20: 4459–65.

18. Shim JH, Kim KM, Lee YJ, et al. Complete necrosis after transarterial chemoembolization could predict prolonged survival in patients with recurrent intrahepatic hepatocellular carcinoma after curative resection. Ann Surg Oncol 2010; 17: 869–77.

19. Riaz A, Miller FH, Kulik LM, et al. Imaging response in the primary index lesion and clinical outcomes following transarterial locoregional therapy for hepatocellular carcinoma. JAMA 2010; 303: 1062–9.

20. Cabibbo G, Genco C, Di Marco V, et al. Predicting survival in patients with hepatocellular carcinoma treated by transarterial chemoembolization. Aliment Pharmacol Ther 2011; 34: 196–204.

21. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Institute of Canada. J Natl Cancer Inst 2000; 92: 205–16.

22. Sala M, Llovet JM, Vilana R, et al. Initial response to percutaneous ablation predicts survival in patients with hepatocellular carcinoma. Hepatology 2004; 40: 1352–60.

23. Ueno S, Tanabe G, Nuruki K, et al. Prognostic performance of the new classification of primary liver cancer of Japan (4th edition) for patients with hepatocellular carcinoma: a validation analysis. Hepatology 2002; 24: 395–403.

24. Bruix J, Sherman M, Llovet JM, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 2001; 35: 421–30.

25. Maleux G, van Malenstein H, Vandeveeye V, et al. Transcatheter chemoembolization of unresectable hepatocellular carcinoma: current knowledge and future directions. Dig Dis 2009; 27: 157–63.

26. Laura L, Joan V, Joan F, et al. A prognostic index of the survival of patients with unresectable hepatocellular carcinoma after transcatheter arterial chemoembolization. Cancer 2000; 88: 50–7.

27. Koniaris LG, Levi DM, Pedroso FE, et al. Is surgical resection superior to transplantation in hepatocellular carcinoma? Ann Surg 2011; 254: 527–37.

28. Arii S, Yamaoka Y, Futagawa S, et al. Results of surgical and nonsurgical treatment for small-sized hepatocellular carcinomas: a retrospective and nationwide survey in Japan. Hepatology 2000; 32: 1224–9.