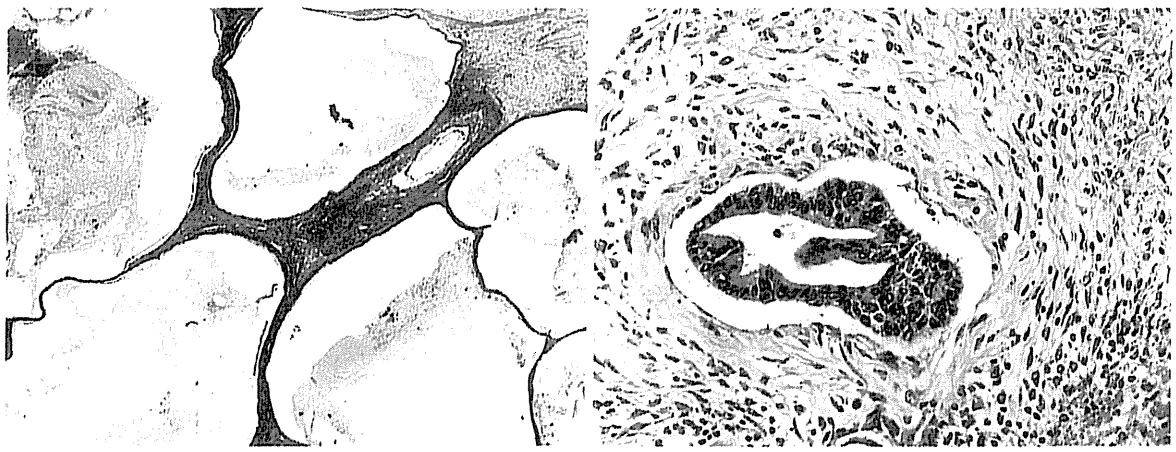

写真6 摘出標本の病理学的所見（HE染色 左：弱拡大，右：強拡大）

表1 患者背景

	N（range）	%
平均年齢	35.0（17～83）	
平均腫瘍径（cm）	18.1（10～40）	
術式		
付属器切除術	23	50.0
卵巣嚢腫摘出術	18	39.1
付属器切除術＋卵巣嚢腫摘出術	3	6.5
付属器切除術＋部分大網切除術（＋骨盤リンパ節生検）	2*	4.3
術後病理診断		
悪性度		
良性	37	80.4
境界悪性	8	17.3
悪性	1	2.1
組織型		
漿液性	3	6.5
粘液性	20	43.4
成熟奇形腫	11	23.9
子宮内膜症性嚢胞	11	23.9
明細胞腺癌	1	2.1

*リンパ節生検を施行した例と施行しなかった例が1例ずつ

表2 手術成績

	mean（range）
皮切の長さ（cm）	6.7（4～14）
手術時間（min）	110.3（35～210）
出血量（ml）	189.4（30～1,050）
腫瘍内容量（ml）	2,662.3（650～21,000）

じた．10例（21.7%）みられた腫瘍摘出時の被膜破綻は，子宮内膜症等を伴い腫瘍に強固な癒着があったため剝離時に生じたものが多かった．今後の課題として本手法の適応・工夫についてさらなる検討が必要と思われた．

巨大卵巣腫瘍の定義は明確になされていないが，文献的報告では最大の卵巣腫瘍は1905年にSpohn[4]が報告した164kgであり，本邦では20～60kgの症例[5)~7)]報告が散見される．これらの巨大卵巣腫瘍に対する麻酔管理の問題点として特に呼吸不全・循環不全が挙げられる．すなわち腫瘍の圧迫による換気不全は術前の仰臥位を困難にし，腫瘍の摘出による急激な圧迫の解除は透過性亢進型肺水腫をきたしうる．中井ら[5]の報告では，39kgの卵巣腫瘍症例において手術直前に半座位で局麻下にて嚢腫を穿刺し内容物37Lを2.5時間かけて吸引したのち，開腹手術を合併症なく施行した．口分ら[6]の報告では，23kgの卵巣腫瘍に対して仰臥位で全身麻酔を導入後に21Lの内容物を20分かけて吸

引したのち開腹手術を施行するも，術中に肺水腫が発症したとしている．また腫瘍の圧迫解除は腹圧低下により急激な血圧低下を起こす．半澤ら[7]の報告では，53 kgの卵巣腫瘍に対して手術入室前に35Lの内容物を35時間かけて吸引しその後開腹手術にて10Lの内容物を5分で吸引し腫瘍を摘出したところ，術中・術後に血圧低下が起こったとしている．前述の症例報告の通り対策としては腫瘍内容物の吸引に時間をかけることである．しかし，合併症が発症しやすい腫瘍の大きさ，吸引時間の基準は明らかではなく，個々の症例における術前の呼吸循環状態・PSに合わせて検討していく必要がある．

結　論

当院では臍上を越える10cm以上の卵巣腫瘍に対してNo Leak法と称した小切開手術を行っており，最大21kgの卵巣腫瘍に対しても安全に施行し得た．しかし問題点として癒着などにより手術創を延長せざるを得ない症例，術中に内容物が漏出する症例もみられ，症例の適応と手技の工夫について検討を要すると考えられる．また胸郭を圧迫するような巨大卵巣腫瘍症例では呼吸・循環不全等の周術期合併症をどう回避するかあらかじめ考慮しなければならない．

“千葉産科婦人科学会平成23年度冬期学術講演会で発表した”

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Long-term survival in patients with clear cell adenocarcinoma of ovary treated with irinotecan hydrochloride plus cisplatin therapy as first-line chemotherapy

Shiro Kunito, Satoshi Takakura, Chie Nagata, Motoaki Saito, Nozomu Yanaihara, Kyosuke Yamada, Aikou Okamoto, Hiroshi Sasaki, Kazunori Ochiai and Tadao Tanaka

Department of Obstetrics and Gynecology, The Jikei University School of Medicine, Tokyo, Japan

Abstract

Aim: Several previous reports showed that irinotecan hydrochloride plus cisplatin (CPT-P) was a candidate first-line chemotherapy regimen for clear cell adenocarcinoma of the ovary (CCC). However, long-term survival in CCC patients treated with CPT-P as first-line chemotherapy remains to be determined. The aim of the present study was to evaluate the long-term results of CPT-P as first-line chemotherapy for CCC.

Material and Methods: We performed a retrospective review of 31 patients with CCC who were treated with CPT-P between 1996 and 2004.

Results: The median follow-up period was 91 months. The estimated 8-year overall survival (OS) rate in all patients was 64.5%, while the rate in 18 stage I, 21 stage I/II, and 10 stage III/IV patients was 88.9%, 85.7%, and 20.0%, respectively. The estimated 8-year OS rate in patients with pT1/pT2 disease was 87.0%, while the 3-year OS rate in patients with pT3 disease was 0%. Univariate analysis using the log–rank test revealed that Eastern Cooperative Oncology Group performance-status 1, pT3 stage, and presence of residual disease (stage II-IV) were significantly correlated with shortened patient survival. Multiple regression analysis revealed that pT3 predicted worse OS in patients with CCC than pT1 ($P < 0.001$) or pT2 disease ($P < 0.005$).

Conclusion: The long-term results suggest CPT-P as a candidate in first-line chemotherapy for CCC in not only stage I, but also in optimally debulked stage II-IV patients with pT1/pT2 disease.

Key words: adenocarcinoma, chemotherapy, clear cell, ovary.

Introduction

Clear cell adenocarcinoma of the ovary (CCC) is the second most common type of ovarian epithelial cancer in Japan, representing 23.4% of ovarian carcinomas.[1] It is characterized by its association with endometriosis and frequent mutations of ARID1A and PIK3CA.[2] Conventional platinum-based chemotherapy regimens yielded a poorer prognosis in patients with CCC than in patients with serous cystadenocarcinoma of the ovary.[3–5] Paclitaxel plus carboplatin (TC) is generally considered to be the 'gold standard' regimen for treatment of epithelial ovarian carcinomas according to the results of several randomized phase III trials.[6–8] This regimen has been used widely for all histological subtypes of epithelial ovarian carcinoma, including CCC. However, only 2–5% of the patients enrolled in these randomized trials had CCC.[6–8]

It was reported that combination chemotherapy with irinotecan hydrochloride plus cisplatin (CPT-P) was

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Reprint request to: Dr Satoshi Takakura, Department of Obstetrics and Gynecology, The Jikei University School of Medicine, 3-25-8 Nishi-shinbashi, Minato-ku, Tokyo 105-8461, Japan. Email: stakakur@jikei.ac.jp

effective for primary advanced and recurrent or resistant CCC.[9–12] We also reported short-term results of CPT-P therapy in 20 patients with CCC.[13] One retrospective study reported that progression-free survival (PFS) in patients with optimally resected stage II-IV CCC treated with CPT-P was significantly better than that with paclitaxel plus platinum.[12] It was reported that the CPT-P regimen was tolerable as first-line chemotherapy and manageable with respect to hematologic and non-hematologic toxicities.[13,14]

The Japanese Gynecologic Oncology Group (JGOG) conducted a randomized phase II study comparing CPT-P with TC as first-line chemotherapy in patients with CCC (JGOG3014). The results showed a strong tendency toward increased PFS in patients with residual disease of less than 2 cm in the CPT-P group, although the difference was not statistically significant ($P = 0.056$). Moreover, the relative risk of disease progression in the TC group was significantly higher than that in the CPT-P group (2.945; 95% confidence interval [CI], 1.052 to 8.246).[15] Although the toxicity profile of each arm differed, toxicity was well tolerated in both arms.[15] These reports suggest CPT-P as a candidate first-line chemotherapy regimen for CCC. At present, the JGOG and the Gynecologic Cancer Intergroup (GCIG) are performing an international cooperative randomized phase III trial of TC versus CPT-P as first-line chemotherapy for CCC (GCOG/JGOG3017 ovarian trial, accrual closed).

However, long-term survival in CCC patients treated with CPT-P as first-line chemotherapy remains to be determined. The median follow-up period in JGOG3104, in an earlier report by Takano M *et al.* and in our previous report was only 31.6, 28.0, and 41.5 months, respectively.[12,13,15] The aim of the study was to evaluate the long-term results of CPT-P as first-line chemotherapy for CCC. We retrospectively reviewed outcomes in 31 CCC patients treated with CPT-P as first-line chemotherapy at The Jikei University Hospital following initial surgery. The median follow-up period in this study was 91 months.

Patients and Methods

Between 1996 and 2004, 31 patients with CCC were treated with CPT-P by the Gynecology Service of The Jikei University Hospital following initial surgery. Of these, 29 patients underwent initial surgery at The Jikei University Hospital and two were referrals from other hospitals. A diagnosis of pure-type CCC was made in all these patients. Pure-type CCC was diagnosed as follows: (i) The tumor growth pattern is tubulocystic, papillary, solid, or a combination of two or all of these; (ii) The tumor cells contain cytoplasm which is optically clear with hematoxylin staining, or project in a hobnail or peglike pattern into neoplastic lumens, or display a combination of the clear and hobnail patterns; and (iii) Less than 10% of another epithelial carcinoma pattern is present. Clinical staging was assessed according to the International Federation of Gynecology and Obstetrics (FIGO, 1988).

Patients received irinotecan hydrochloride (60 mg/m^2) intravenously over 90 min on days 1, 8, and 15 and cisplatin (60 mg/m^2) intravenously over 1–2 h on completion of irinotecan hydrochloride infusion on day 1 every 4 weeks for a total of five to six courses. Only patients with stage Ia disease received three courses. Patients received pre- and post-chemotherapy hydration to avoid cisplatin-induced nephrotoxicity. In all patients, anti-emetic prophylaxis consisted of serotonin type 3 receptor antagonists and corticoids. Dose levels and the timing of the schedule were modified to avoid severe side-effects.

In patients with measurable disease, tumor response was evaluated according to the World Health Organization criteria (1979) and assessed by commuted tomography or magnetic resonance imaging. A complete response (CR) was defined as the disappearance of all clinical and radiologic evidence of tumor for at least 4 weeks; a partial response (PR) was defined as a decrease of 50% or more in the sum of the products of the longest perpendicular diameters of all measurable lesions for at least 4 weeks; progressive disease (PD) was defined as an increase of more than 25% in the sum of the products of the perpendicular diameters of all measurable lesions or the appearance of new lesions. All other circumstances were considered to indicate no change (NC). Second-look laparotomy (SLL) was performed in 15 patients who showed no clinical evidence of disease after completion of chemotherapy.

Survival information was available on all patients. Ten patients were followed until death. Overall survival (OS) was assessed from the date of initial surgery to the time of death or last contact. Progression-free survival was defined as the time from initial surgery until progression, death, or last contact. Patient survival was calculated by using the Kaplan–Meier method and the significance of differences between groups was assessed by the log–rank test. The multiple Cox regression model was used to explore the impact of specific prognostic factors on OS.

Table 1 Patient characteristics

Characteristic	No. patients	
Age (years)		
30–39	2	
40–49	11	
50–59	12	
60–70	6	
ECOG performance status		
0	24	
1	7	
CA125 (U/mL)		
–35	6	
36–99	10	
100–999	11	
1000–	3	
Unknown	1	
FIGO stage		(Sub-stage)
I	18	(Ia-4, Ic-14)
II	3	(IIa-1, IIc-2)
III	6	(IIIb-1, IIIc-5)
IV	4	
pT stage		
T1	19	
T2	4	
T3	8	
Residual disease		(Stage II-IV)
None	22	(4)
≤2 cm	2	(2)
>2 cm	7	(7)

ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics.

Results

Patient characteristics

Patient characteristics are listed in Table 1, including age, Eastern Cooperative Oncology Group (ECOG) performance status (PS), serum CA125 level, FIGO stage, pT stage, and residual disease diameter. Median age was 51 years (range: 36–70 years). A PS of 0 and 1 was observed in 24 and 7 patients, respectively. Median serum CA125 level was 77 U/mL (range: 8–1989 U/mL). Eighteen patients were in stage I, 3 in stage II, 6 in stage III, and 4 in stage IV. Twenty-nine of 31 patients were staged in our institute. Thirteen of 18 patients in stage I and all patients in stage II underwent appropriate staging surgery, including retroperitoneal systemic lymphadenectomy from the paraaortic nodes to the pelvic nodes (LNX). One patient (No. 2) underwent bilateral salpingo-oophorectomy (BSO) and omentectomy (OMTX) due to the presence of venous thromboembolism (VTE) and pulmonary thromboembolism (PE), while 2 (Nos 11 and 17) underwent fertility-sparing surgery consisting of at least unilateral salpingo-oophorectomy (USO) and OMTX. Among 10 patients in stage III-IV, 5 underwent maximal cytoreductive surgery, 1 underwent total abdominal hysterectomy (TAH), BSO and OMTX, 1 underwent TAH and BSO, and 3 underwent BSO and OMTX. Two patients were staged in other hospitals and they refused re-staging laparotomy in our hospital. Among them, 1 patient (No. 1) received TAH and BSO and 1 (No. 6) received USO. Nineteen patients had pT1 disease, 4 had pT2, and 8 had pT3. All 6 patients in stage III had pT3M0 disease. One patient in stage IV had pT1N0M1 disease, 1 had pT2NxM0 disease, 1 had pT3N0M1 disease and 1 had pT3NxM0 disease (Table 2). Twenty-two patients had no residual disease after initial surgery, 2 had residual disease of less than or equal to 2 cm, and 7 had residual disease of greater than 2 cm.

Treatment administration

The proportion of patients in stage Ia who received the planned three cycles of CPT-P therapy was 75.0% (3/4; 95% CI, 19.4–99.4%). One patient only received two cycles, because grade 4 diarrhea developed during the second course and she subsequently received TC therapy. The proportion of patients in stage Ic-IV who received the planned five to six cycles of CPT-P therapy was 92.6% (25/27; 95% CI, 75.7–99.0%). One patient received only four cycles of CPT-P therapy, because grade 3 pancytopenia occurred during the fourth course. One patient only received three cycles of CPT-P therapy due to disease progression.

Clinical response to chemotherapy

Clinical response was assessed in the 4 patients with clinically measurable disease. Clinical response results are listed in Table 2. A CR was observed in 2 patients (Nos 24 and 25) with measurable disease and the response duration was 7 months and 15 months, respectively. One patient (No. 30) showed NC, and the time-to-progression was 5 months. Therefore, there were 2 CRs, 1 NC and 1 PD among the 4 assessable patients, and the overall response rate was 50% (95% CI, 6.7% to 93.2%).

Second-look laparotomy

Second-look laparotomy was performed in 15 patients who showed no clinical evidence of disease after completion of chemotherapy, and the results are presented in Table 2. Among 10 patients with no residual tumor after initial surgery who underwent SLL, the findings were negative in 9. The remaining patient

Table 2 Efficacy and survival

Patient no.	FIGO stage	pTNM classification	Residual tumor	Clinical response	SLL findings	Site of first recurrence	Time to first recurrence (months)	Prognosis (months)
1	Ia	pT1aNxM0	None		Not done	Vagina, Pelvic lymph node	22	NED, 153
2	Ia	pT1aNxM0	None		Positive			NED, 139
3	Ia	pT1aN0M0	None		Not done			NED, 102
4	Ia	pT1aN0M0	None		Not done			NED, 98
5	Ic	pT1cN0M0	None		Negative			NED, 188
6	Ic	pT1cNxM0	None		Negative			NED, 76
7	Ic	pT1cN0M0	None		Negative			NED, 157
8	Ic	pT1cN0M0	None		Negative			NED, 165
9	Ic	pT1cN0M0	None		Not done			NED, 86
10	Ic	pT1cN0M0	None		Not done	Diaphragm, Pulmonary effusion	18	DOD, 28
11	Ic	pT1cNxM0	None		Not done			NED, 118
12	Ic	pT1cN0M0	None		Not done			NED, 109
13	Ic	pT1cN0M0	None		Not done			NED, 99
14	Ic	pT1cN0M0	None		Negative			NED, 91
15	Ic	pT1cN0M0	None		Negative			NED, 96
16	Ic	pT1cN0M0	None		Not done			NED, 86
17	Ic	pT1cN0M0	None		Not done	Liver, Pelvic cavity	46	DOD, 56
18	Ic	pT1cN0M0	None		Negative			NED, 82
19	IIa	pT2aN0M0	None		Negative			NED, 121
20	IIc	pT2cN0M0	None		Negative	Abdominal cavity	55	DOD, 115
21	IIc	pT2cN0M0	None		Not done	Liver, Diaphragm	27	DOD, 38
22	IIIb	pT3bN0M0	≤2 cm		Positive	Liver	19	DOD, 31
23	IIIc	pT3cN1M0	>2 cm		Negative	Liver, Diaphragm	20	DOD, 27
24	IIIc	pT3cNxM0	>2 cm	CR	Positive	Abdominal cavity	10	DOD, 14
25	IIIc	pT3cNxM0	>2 cm	CR	Negative	Liver	18	DOD, 31
26	IIIc	pT3cNxM0	>2 cm		Not done	Abdominal cavity	8	DOD, 11
27	IIIc	pT3cNxM0	>2 cm	PD	Not done			DOD, 13
28	IV	pT3cNxM1	>2 cm		Not done	Liver, Para-aortic lymph node	9	DOD, 13
29	IV	pT1cN0M1	None		Not done			NED, 127
30	IV	pT3cN0M1	>2 cm	NC	Not done			DOD, 8
31	IV	pT2cNxM1	≤2 cm		Negative			NED, 120

CR, complete response; DOD, dead of disease; FIGO, International Federation of Gynecology and Obstetrics; NC, no change; NED, no evidence of disease; PD, progressive disease; SLL, second-look laparotomy.

(No. 2), who initially underwent BSO and OMTX due to the presence of VTE and PE, subsequently received TAH and LNX at SLL. Metastasis to the lymph nodes was detected by subsequent pathological examination. She received five cycles of CPT-P therapy following SLL and was still alive with no evidence of disease at 130 months from SLL. Among 5 patients with residual tumor after initial surgery who underwent SLL, the results were negative in 3 (Nos 23, 25, and 31) and positive in 2 (Nos 22 and 24). Of the 2 patients in whom the results were positive, macroscopic disease of less than 3 mm was observed in patient No. 22. Although she subsequently received six cycles of TC therapy following SLL, the disease recurred at 11 months after SLL, and death occurred at 23 months after SLL. Again, while patient no. 24 showed no macroscopic disease, the results were positive on washing cytology. Although she subsequently received three cycles of CPT-P therapy, disease recurred at 3 months after SLL, and death occurred at 7 months after SLL. Among the 12 patients in whom the results were negative at SLL, 3 died of disease at 106 months (No. 20), 19 months (No. 23), and 24 months (No. 25) after SLL; the other 9 patients were alive with no evidence of disease at 68–180 months after SLL (median: 112 months).

Clinical course and prognostic factors

The median follow-up period was 91 months (range: 8–188 months). Time-to-first recurrence, site of first recurrence and prognosis in each patient are shown in Table 2. Clinically persistent disease was observed in 2 patients (Nos 27 and 30) receiving CTP-P therapy.

Time-to-progression in these 2 patients was 3 and 7 months after initial surgery, respectively, with death due to disease occurring at 13 and 8 months after initial surgery, respectively. Among the other 29 patients, recurrence of disease was observed in 11, and the median interval to first recurrence was 19 months (range: 8–55 months). While recurrence of disease was observed within 2 years in 8 of these 11 patients, it was later than 3 years in 2 (No. 17: 46 months, No. 20: 55 months). In 6 of these 11 patients, first relapse occurred in the liver. No difference was observed in first recurrent site between early and advanced stage cases. Eight of these 11 patients received second-line chemotherapy. Among them, 7 were treated with paclitaxel plus platinum and one was treated with only oral etoposide due to cerebral infarction. In the remaining 3 patients, 2 received best supportive care due to poor general condition and 1 refused chemotherapy after secondary debulking surgery. Nevertheless, 10 of these 11 patients died of disease within 3–60 months (median: 10 months) from the date of first recurrence, with 9 of the 10 patients dying within 13 months. In 1 patient (No. 20), in whom recurrence was observed at 55 months after initial surgery, death occurred at 60 months from the date of first recurrence, and she was the only patient who died at over 5 years from initial surgery. Only 1 patient (No. 1), in whom recurrence was observed at 22 months after initial surgery, was alive with no evidence of disease at 131 months after second reduction surgery.

The estimated 1-, 3-, 5- and 8-year PFS rate for stage I-IV patients was 83.9% (95% CI, 70.9–96.8%), 64.5% (95% CI, 47.7–81.4%), 58.1% (95% CI, 40.7–75.4%), and 58.1% (95% CI, 40.7–75.4%), respectively. The PFS curves for patients in stages I, Ic, I-II and III-IV are shown in Figure 1. The estimated 3-, 5- and 8-year OS rate for 31 stage I-IV patients was 71.0% (95% CI, 55.0–86.9%), 64.5% (95% CI, 47.7–81.4%) and 64.5% (95% CI, 47.7–81.4%), respectively. The estimated 3-, 5- and 8-year OS rates and OS curves for patients in stages I, Ic, I-II and III-IV are shown in Table 3 and Figure 2, respectively. A significant difference was observed in OS curves between patients in stage I-II and those in stages III/IV ($P < 0.001$ by the log–rank test), and relative risk of death for stages III/IV patients as compared with that for stages I/II patients was 7.723 (95% CI, 2.868–20.800) (Table 3, Fig. 2).

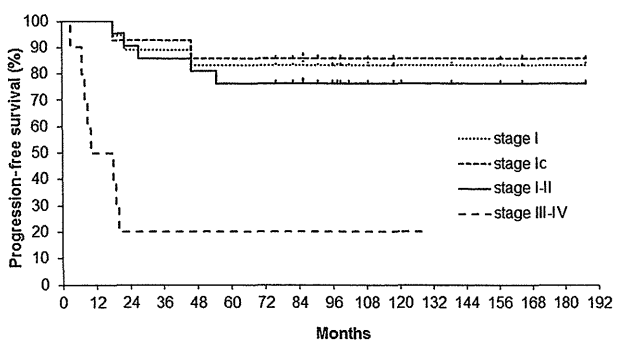

Figure 1 Progression-free survival curves by International Federation of Gynecology and Obstetrics stage.

The estimated 3-, 5- and 8-year OS rates in patients aged over or under 50 years, in those with ECOG PS 0 or PS1, in those with <100 U/mL or ≥100 U/mL serum CA125 levels, in those with pT1/pT2 or pT3 disease, in those with pM0 or pM1 disease, and in stage II-IV patients with or without residual disease are summarized in Table 3. The significance of the OS distribution in each group as assessed by the log–lank test is also summarized in Table 3. A significant difference was observed in OS curves between patients with ECOG PS 0 and those with ECOG PS 1 ($P = 0.005$ by the log–rank test), and relative risk of death in patients with ECOG PS 1 as compared with that in patients with ECOG PS 0 was 4.357 (95% CI,1.547–12.272). The estimated 3-, 5- and 8-year OS rates in patients with pT1-2 disease were 95.7% (95% CI, 87.3–100%), 87.0% (95% CI, 73.25–100%), and 87.0% (95% CI, 73.25–100%), respectively, while the estimated 3-year OS rate in patients with pT3 disease was 0%. A significant difference was observed in OS curves between patients with pT1/pT2 and those with pT3 disease ($P < 0.001$ by the log–rank test), and relative risk of death in patients with pT3 as compared with that in patients with pT1/pT2 disease was 14.956 (95% CI, 6.343–35.266) (Fig. 3). A significant difference in OS curves was detected between patients in stage II-IV with or without residual disease, and relative risk of death in patients with as compared with that in patients without residual disease was 4.009 (95% CI, 1.078–14.910). No significant difference was observed in OS by age ($P = 0.856$), serum CA125 level ($P = 0.104$), or pM stage ($P = 0.456$).

Multivariate analysis using the Cox regression model was performed to further assess the factors targeted, and the results are shown in Table 4. The analysis indicated that pT3 predicted worse OS in patients with CCC than pT1 ($P < 0.001$) or pT2 disease ($P < 0.005$). No patients in stages I/II showed residual disease. In contrast, among 10 patients in stages III/IV, 9 had residual disease, while only 1 patient (No. 29) with pT1N0M1 (malignant pulmonary effusion) had no residual

Table 3 Estimated overall survival rates and relative risk of death

Variable (No. patients)	Overall survival rate (%) 3-year	5-year	8-year	Risk ratio	95% CI	*P*-value (log–rank test)
Age (years)						0.855
<50 ($n = 13$)	84.7	69.2	69.2	1		
≥50 ($n = 18$)	61.1	61.1	61.1	1.111	0.357; 3.464	
ECOG performance status						0.005
0 ($n = 24$)	83.3	75.0	75.0	1		
1 ($n = 7$)	28.6	28.6	28.6	4.357	1.547; 12.272	
CA125 (U/mL)						0.104
<100 ($n = 16$)	93.8	81.3	81.3	1		
≥100 ($n = 14$)	50.0	50.0	50.0	2.619	0.820; 8.365	
FIGO stage						<0.001
I–II ($n = 21$)	95.2	85.7	85.7	1		
I ($n = 18$)	94.4	88.9	88.9			
Ic ($n = 14$)	92.9	85.7	85.7			
III–IV ($n = 10$)	20.0	20.0	20.0	10.384	3.133; 34.419	
pT stage						<0.001
pT1/pT2 ($n = 23$)	95.7	87.0	87.0	1		
pT3 ($n = 8$)	0	0	0	14.956	6.343; 35.266	
pM stage						0.456
pM0 ($n = 27$)	74.1	66.7	66.7	1		
pM1 ($n = 4$)	50.0	50.0	50.0	1.768	0.402; 7.631	
Residual tumor (stage II-IV)						0.038
Absence ($n = 4$)	100.0	75.0	75.0	1		
Presence ($n = 9$)	11.1	11.1	11.1	4.009	1.078; 14.910	

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics.

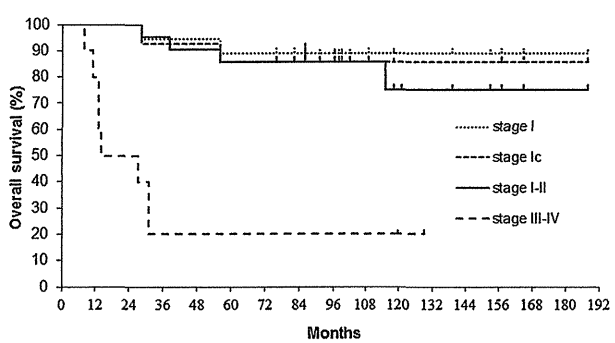

Figure 2 Overall survival curves by International Federation of Gynecology and Obstetrics stage.

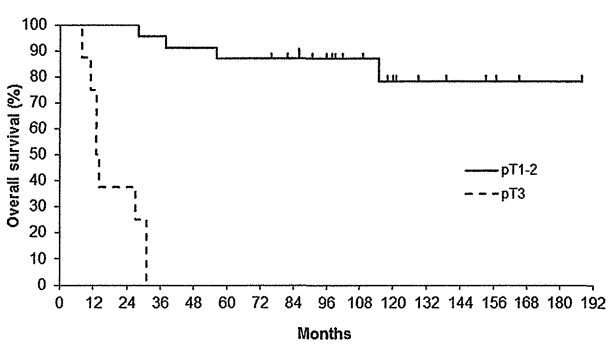

Figure 3 Overall survival curves by pT stage.

Table 4 Multiple regression overall survival analysis

Variable		Risk ratio	95% CI	*P*-value
Age		1.076	0.981; 1.181	0.119
ECOG performance status 0 versus 1		2.595	0.344; 19.562	0.355
CA125 (U/mL)		1.001	0.999; 1.003	0.290
pT stage	pT1 versus pT3	358.423	19.335; 6666.667	<0.001
	pT2 versus pT3	60.864	3.582; 1030.928	0.005
pM stage	pM0 versus pM1	2.846	0.366; 22.109	0.317

CI, confidence interval; ECOG: Eastern Cooperative Oncology Group.

tumor. These results show that the presence or absence of residual disease is strongly correlated with pT stage. Therefore, this parameter was not included in this model.

Discussion

Previous retrospective and prospective reports have suggested CPT-P as a candidate first-line chemotherapy regimen for CCC.[9–15] However, long-term survival in CCC patients treated with CPT-P therapy as first-line chemotherapy remains to be determined. The aim of this study was to evaluate the long-term results of CPT-P as first-line chemotherapy for CCC. We retrospectively reviewed outcomes in 31 CCC patients treated with CPT-P as first-line chemotherapy at The Jikei University Hospital following initial surgery.

Sugiyama *et al.* reported a retrospective review of 101 patients with CCC, 97 (95%) of whom received conventional platinum-based chemotherapy after initial surgery, and the estimated 3- and 5-year OS rate in 38 stage Ic patients was 76.8% and 60.1%, respectively.[3] Rubin *et al.* reported that the estimated 5-year PFS rate in 22 stage I patients with CCC treated with conventional platinum-based chemotherapy after initial surgery was approximately 60%.[5] In a retrospective review of 178 patients with CCC, Mizuno *et al.* reported that of 178 patients, 52 were treated with conventional platinum-based chemotherapy, 39 with bleomycin, vinblastine and cisplatin, 34 with carboplatin and cisplatin, 20 with TC, and 10 with other regimens. In the same study, the estimated 5- and 8-year OS rate in 101 stage I patients was 85.8% and 82.3%, respectively, while that in 69 stage Ic patients was 81.3% and 76.5%, respectively, and the OS rate in stage Ic patients decreased until 103 months.[16] In the present study, the estimated 5- and 8-year OS rate in 18 stage I patients was 88.9% and 88.9%, respectively, while that in 14 stage Ic patients was 85.7% and 85.7% respectively (Table 3, Fig. 2). No recurrence of disease or death was observed in any of the patients in stage I at over 5 years after initial surgery. Although we cannot make an exact comparison between OS or PFS rates in this study and those of previous reports, it seems that the long-term prognosis in stage I patients with CCC treated with CPT-P is better than that in stage I patients treated with conventional platinum-based chemotherapy. Takano *et al.* retrospectively reviewed 172 CCC patients consisting of 46 treated with CPT-P and 126 with paclitaxel plus platinum (median follow-up period, 28.0 months). It was reported that there was no significant difference in PFS in patients in stage I between the two treatment groups ($P = 0.95$).[12] The long-term results of the present study taken together with those of previous reports, however, now suggest CPT-P as a candidate in first-line chemotherapy for stage I patients with CCC.

Multiple regression analysis in this study revealed that not only pT1 ($P < 0.001$), but also pT2 stage ($P < 0.005$) predicted a better OS in patients with CCC than pT3 (Table 4). In fact, the estimated 8-year OS rate in 23 patients with pT1/pT2 disease was 87.0%, while the estimated 3-year OS rate in patients with pT3 disease was 0% (Table 3, Fig. 2). Additionally, the estimated 5- and 8-year OS rate in 19 patients with pT1c/pT2 disease was 84.2% and 84.2%, respectively. Although we cannot make an exact comparison between the OS rates observed in this study and those in the previous report by Sugiyama *et al.*, it seems that the long-term prognosis in CCC patients with pT1c/pT2 disease treated with CPT-P is better than that in CCC patients in stage Ic treated with conventional platinum-based chemotherapy.[3] In this study, 4 of 5 stage II-IV patients with pT1/pT2 disease had no residual tumor after initial surgery, and the remaining patient had residual disease of less than or equal to 2 cm. Takano *et al.* retrospectively reviewed 47 CCC patients consisting of 15 optimally debulked (<1 cm) stage II-IV patients treated with CPT-P and 32 optimally debulked (<1 cm) stage II-IV patients treated with paclitaxel plus platinum and noted that PFS in the CPT-P group was significantly better than that in the paclitaxel plus platinum group in the group with stage II-IV optimal cytoreduction ($P = 0.03$).[12] In JGOG3014, comparing CPT-P with TC as first-line chemotherapy in patients with CCC, PFS in patients without or with residual disease of less than 2 cm tended to be longer in the CPT-P group, although the difference was not statistically significant.[15] Takano *et al.* also reported that only residual tumor was an independent prognostic factor for PFS and that absence of residual disease predicted better PFS than presence of residual disease in stage Ic (ascites/malignant washing)-IV patients with CCC.[17] The present results taken together with those of previous reports suggest that CPT-P therapy contributes to improvement of long-term prognosis in CCC patients in not only stage I, but also optimally debulked (especially, completely debulked) stage II-IV with pT1/pT2 disease patients, as compared with conventional platinum-based chemotherapy and TC therapy.

Sugiyama *et al.* reported that only 3 of 27 patients (11.1%) with CCC responded to conventional

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platinum-based chemotherapy. Progressive disease was noted in 22 patients (81.5%) and NC was only found in 2.[3] It was previously reported that CPT-P therapy was effective for primary advanced and recurrent or resistant CCC. Objective responses were obtained in 2 of 3 and 2 of 8 patients with primary advanced CCC,[10,15] as well as in 1 of 3 and 2 of 5 patients with recurrent or resistant CCC.[9,11] In the present study, 2 of 4 patients with primary advanced CCC and measurable residual disease after initial surgery responded to CPT-P therapy. Seven of 8 patients in stages III/IV showed no clinical evidence of disease after completion of their chemotherapy programs. Five of these 7 patients underwent SLL (all of them had had macroscopic residual disease at initial surgery). Among these, the results were negative in 3 and positive in 2. In 1 patient in whom the results were positive on SLL, evidence was only available on peritoneal washing cytology, with no macroscopic traces of disease. On the other hand, it was previously reported that TC therapy was effective for primary advanced and recurrent CCC. Objective responses were obtained in 8 of 15 patients and 2 of 5 patients with primary advanced CCC,[15,18] as well as in 3 of 13 patients with recurrent CCC.[18] The present results taken together with those of previous reports suggest that CTP-P, as well as TC therapy, may be more effective for CCC than conventional platinum-based chemotherapy.

In the present study, the estimated 3- and 5-year OS rate in stage III/IV patients treated with CPT-P therapy was 20.0% and 20.0%, respectively. Sugiyama *et al.* reported that the estimated 3- and 5-year OS rate in 31 stage III and IV CCC patients treated with conventional platinum-based chemotherapy was 23.5% and 23.5%, and 11.4% and 11.4%, respectively.[3] Goff *et al.* reported that the 3- and 5-year survival rate in 24 stage III CCC patients treated with conventional platinum-based chemotherapy was less than 25% and 0%, respectively.[4] It seems that the prognosis in stage III/IV patients with CCC treated with CPT-P therapy is not better than that in patients treated with conventional platinum-based chemotherapy. In the present study, among 10 stage III/IV patients, 7 had T3 disease with residual disease greater than 2 cm, 1 had T3 disease with residual disease less than or equal to 2 cm, 1 had T2 disease with residual disease less than or equal to 2 cm, and 1 had T1 disease with no residual disease. The estimated 3-year OS rate in patients with pT3 disease was 0% in this study. Takano *et al.* reported that the presence of residual disease predicted a worse PFS than the absence of residual disease in CCC patients.[17] They also reported that no significant difference was observed in the PFS curve between CCC patients treated with CPT-P and those treated with paclitaxel plus platinum in stage II-IV with residual disease greater than 1 cm, and that the estimated 2-year PFS rate was approximately 20% in both groups.[12] The present results taken together with those of previous reports suggest that neither CPT-P nor TC therapy offers an improved prognosis in CCC patients with both T3 and residual disease after initial surgery compared with conventional platinum-based chemotherapy, although the survival benefit of CTP-P therapy for CCC patients with completely debulked T3 disease remains to be determined. Recently, various targeted therapeutics have been explored in the management of ovarian cancer. At present, the Gynecologic Oncology Group (GOG) is performing a phase II evaluation of temsirolimus (CCI-779) in combination with TC followed by temsirolimus (CCI-779) consolidation as first-line therapy in the treatment of stage III-IV CCC (GOG268, NCT01196429). It is also evaluating sunitinib malate (SU11248) in the treatment of persistent or recurrent CCC in a phase II study (GOG254, NCT00979992). The Scottish Gynecological Cancer Trials Group is planning to open a randomized phase II study of BIBF1120 versus chemotherapy in recurrent CCC of the ovary or endometrium, the results of which should be of some interest.

Taken together with those of earlier reports, our current long-term results suggest that CPT-P is a potential candidate as first-line chemotherapy for CCC in not only stage I, but also optimally debulked (especially, completely debulked) stage II-IV patients with pT1/pT2 disease. The data from this study, however, are limited, and we do not expect them to lead to any immediate alteration in first-line chemotherapy for CCC. The JGOG and GCIG are currently conducting an international cooperative randomized phase III trial of TC versus CPT-P as first-line chemotherapy for CCC (GCOG/JGOG3017 ovarian trial, accrual closed), and the results are eagerly awaited.

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Disclosure

The authors declare that there is no conflict of interest.

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CLINICAL STUDY

Prospective Study of Transcatheter Arterial Chemoembolization for Unresectable Hepatocellular Carcinoma: An Asian Cooperative Study between Japan and Korea

Masafumi Ikeda, MD, Yasuaki Arai, MD, Sang Joon Park, MD, Yoshito Takeuchi, MD, Hiroshi Anai, MD, Jae Kyu Kim, MD, Yoshitaka Inaba, MD, Takeshi Aramaki, MD, Se Hwan Kwon, MD, Seiichiro Yamamoto, PhD, Takuji Okusaka, MD, Japan Interventional Radiology in Oncology Study Group (JIVROSG), and Korea Interventional Radiology in Oncology Study Group (KIVROSG)

ABSTRACT

Purpose: To evaluate the safety and efficacy of transcatheter arterial chemoembolization used for the treatment of unresectable hepatocellular carcinoma (HCC) with an Asian cooperative prospective study between Japan and Korea.

Materials and Methods: Patients with unresectable HCC unsuitable for curative treatment or with no prior therapy for HCC were enrolled. The patients underwent transcatheter arterial chemoembolization with emulsion of Lipiodol and anthracycline agent, followed by embolization with gelatin sponge particles, which was repeated on an as-needed basis. The primary endpoint was 2-year survival rate, and the secondary endpoints were adverse events and response rate.

Results: The 2-year survival rate of 99 patients was 75.0% (95% confidence interval, 65.2%–82.8%). The median time-to-progression was 7.8 months, and the median overall survival period was 3.1 years. Of 99 patients, 42 (42%) achieved a complete response, and 31 (31%) had a partial response. The response rate was 73% using modified Response Evaluation Criteria in Solid Tumors. The grade 3–4 toxicities included increased alanine aminotransferase level in 36%, increased aspartate aminotransferase level in 35%, thrombocytopenia in 12%, and abdominal pain in 4% of patients. All other toxicities were generally transient.

Conclusions: Asian transcatheter arterial chemoembolization demonstrated sufficient safety and reasonable efficacy as a standard treatment for unresectable HCC. These results could be useful as reference data for future trials of transcatheter arterial chemoembolization.

ABBREVIATIONS

AFP = alpha fetoprotein, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CI = confidence interval, FAS = full analysis set, HCC = hepatocellular carcinoma, PIVKA II = protein induced by vitamin K absence or antagonist-II, RECIST = Response Evaluation Criteria in Solid Tumors

Primary liver cancer accounted for > 38,000 and 15,000 deaths per year in Japan and Korea, respectively; it is the fourth most common cause of death after lung, stomach, and colorectal cancers in Japan, and it is the third most

From the Division of Hepatobiliary and Pancreatic Oncology (M.I.), National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, 277-8577, Japan; and Department of Diagnostic Radiology (Y.A., Y.T.) and Hepatobiliary and Pancreatic Oncology Division (T.O.), National Cancer Center Hospital, Tokyo, Japan; and Department of Radiology (S.J.P.), Sun General Hospital, Daejeon, Korea; and Department of Radiology (H.A.), Nara Medical University, Kashihara, Japan; and Department of Radiology (J.K.K.), Chonnam University Hospital, Korea; Department of Diagnostic and Interventional Radiology (Y.I.), Aichi Cancer Center Hospital, Nagoya, Japan; and Division of Diagnostic Radiology (T.A.), Shizuoka Cancer Center, Shizuoka, Japan; and Department of Radiology (S.H.K.), Kyung Hee University Medical Center, Korea; and Cancer Information Services and Surveillance Division (S.Y.), Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan.
Received May 29, 2012; final revision received December 28, 2012; accepted January 7, 2013. Address correspondence to M.I.; E-mail: masikeda@east.ncc.go.jp

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common cause of death after lung and stomach cancers in Korea (1). Of all primary liver cancers, approximately 95% in Japan and 85% in Korea are hepatocellular carcinomas (HCCs), which are mostly attributable to chronic hepatitis or liver cirrhosis caused by persistent infection with hepatitis C or B viruses. Hepatitis B infection is more prevalent in Korea, whereas hepatitis C infection is more common in Japan (2). Despite these differences in etiology, the treatment strategy for HCC is the same in Japan and Korea. Curative therapies, such as hepatic resection or liver transplantation, are applicable in only a small proportion of patients because of excessive tumor invasion or poor hepatic function or both. Although local ablative therapy, such as radiofrequency ablation, has an effectiveness equivalent to that of hepatic resection for HCCs $\leq$ 3 cm in size and with three or fewer nodules, it is unsuitable for tumors $>$ 3 cm or for multiple tumors. For this stage of HCC, transcatheter arterial chemoembolization is the main therapeutic option (3–5). Transcatheter arterial chemoembolization has been shown to prolong survival significantly in several randomized controlled trials compared with chemotherapy alone (6) or conservative treatment (7–13). Meta-analyses (14,15) have also demonstrated a clear survival benefit of transcatheter arterial chemoembolization for unresectable HCC (**Table 1**).

Transcatheter arterial chemoembolization with Lipiodol (Guerbet; Roissy CdG, France) and anthracycline agents followed by embolization with gelatin sponge particles has been widely used as a practical standard treatment in Asian countries for $>$ 30 years (16). Transcatheter arterial chemoembolization was used in Asian countries long before the confirmation of its survival benefit in randomized controlled trials (6–13) because these techniques were originally developed in Japan (17–19) and spread among Asian countries. However, no prospective clinical study has been fully conducted to provide convincing data that can support this treatment. Additionally, there are many technique differences between Asian transcatheter arterial chemoembolization and transcatheter arterial chemoembolization performed in Western countries. The so-called conventional transcatheter arterial chemoembolization reported in Western studies differs from Asian transcatheter arterial chemoembolization in the details of the treatment. A prospective clinical study was conducted to evaluate Asian transcatheter arterial chemoembolization for unresectable HCC. The aim of this study was to evaluate the safety and efficacy of Asian transcatheter arterial chemoembolization with a single-arm, Japan-Korea cooperative prospective study.

MATERIALS AND METHODS

Patient Eligibility

Eligible patients for study entry had unresectable HCC that was unsuitable for curative treatments. Patient inclusion criteria were as follows: histologically or clinically diagnosed HCC excluding mixed type; no previous treatment for HCC; not a candidate for hepatic resection, liver transplantation, or local ablative therapy; hypervascular lesion showing enhancement in the early phase on computed tomography (CT) or magnetic resonance (MR) imaging with bolus contrast injection; no tumor thrombosis in the first branch or main portal vein; Eastern Cooperative Oncology Group performance status of 0–2; Child-Pugh classification of A or B; adequate hematologic, hepatic, renal, and cardiac function (leukocytes $\geq$ 3,000/mm^3, platelets $\geq$ 50,000/mm^3, serum bilirubin $\leq$ 3.0 mg/dL); age $\geq$ 20 years old; and written informed consent.

The exclusion criteria were as follows: extrahepatic metastasis; hepatic vein invasion or biliary invasion; ruptured tumor; prior biliary enteric bypass or endoscopic transampullary stent placement or percutaneous biliary drainage; clinically significant refractory ascites or pleural effusion; severe arterioportal or arteriovenous shunts in the liver; allergy to contrast medium precluding angiography; severe and active comorbidity such as heart disease or renal disease; hepatic encephalopathy or severe mental disorder; active gastrointestinal bleeding; active concomitant malignancy; pregnancy, lactation, or childbearing potential in women; and men who are sexually active and not willing or able to use medically acceptable forms of contraception. The inclusion and exclusion criteria were almost same as those in the clinical trial conducted by Llovet et al (12).

The pretreatment evaluation required a complete history and physical examination and baseline assessments of organ function. In addition, contrast-enhanced CT or MR imaging of the abdomen and x-ray or CT of the chest were performed before treatment for staging to assess the local extension of the tumor and to exclude the presence of distant metastasis.

Transcatheter Arterial Chemoembolization Procedure

Patients with unresectable HCC underwent transcatheter arterial chemoembolization using an emulsion of epirubicin or doxorubicin and Lipiodol followed by gelatin sponge injection. The dose of anticancer agents and Lipiodol used in transcatheter arterial chemoembolization was determined according to tumor size; only the maximum doses were defined in this study: 100 mg/body for epirubicin, 70 mg/body for doxorubicin, and 20 mL for Lipiodol. Epirubicin or doxorubicin dissolved in aqueous nonionic contrast medium was mixed with Lipiodol to form an emulsion using the pumping technique. The resulting emulsion had to be injected immediately. Transcatheter arterial chemoembolization was performed as follows: (i) tumor enhancement and the feeding artery were confirmed using abdominal angiography; (ii) a catheter was inserted into the feeding artery of the HCC, and the emulsion containing epirubicin or doxorubicin with Lipiodol was injected; (iii) embolization of the feeding artery was achieved using small pieces of gelatin sponge until the disappearance of tumor stain; (iv) the therapeutic effect

Table 1. Randomized Controlled Trials of Transcatheter Arterial Embolization with Conservative Therapy

Author, Year	Treatment	No. Patients	Response Rate (%)	1-y Survival (%)	2-y Survival (%)	*P* Value	Treatment Duration	Embolic Material	Anticancer Agent	Lipiodol
Lin et al, 1988 (6)	Transcatheter arterial embolization	21	62	42	25		Monthly	Gelatin sponge	None	Absent
	Transcatheter arterial embolization + 5-FU	21	48	20	20		Monthly		5-FU	Absent
	5-FU	21	9.5	13	13	< .005	Monthly		5-FU	
Pelletier et al, 1990 (7)	Transcatheter arterial chemoembolization	21	33	24	NA		2nd, 6th, 12th mo	Gelatin sponge	Doxorubicin	Absent
	Best supportive care	21	0	33	NA	NS				
GRETCH, 1995 (8)	Transcatheter arterial chemoembolization	50	16	62	38		Every 2 mo	Gelatin sponge	Cisplatin	Present
	Best supportive care	46	5	43	26	.13				
Pelletier et al, 1998 (9)	Transcatheter arterial chemoembolization + TMX	37	24	51	24		Every 3–4 mo	Gelatin sponge	Cisplatin	Present
	TMX	36	5.5	55	26	.77				
Bruix et al, 1998 (10)	Transcatheter arterial embolization	40	55	70	49		On demand	Gelatin sponge + coil	None	Absent
	Best supportive care	40	0	72	50	.72				
Lo et al, 2002 (11)	Transcatheter arterial chemoembolization	40	27	57	31		Every 2–3 mo	Gelatin sponge	Cisplatin	Present
	Best supportive care	39	2.6	31	11	.002				
Llovet et al, 2002 (12)	Transcatheter arterial chemoembolization	40	35	82	63		Every 2–6 mo	Gelatin sponge	Doxorubicin	Present
	Transcatheter arterial embolization	37	43	75	50		Every 2–6 mo	Gelatin sponge		
	Best supportive care	35	0	63	27	.009				
Doffoël et al, 2008 (13)	Transcatheter arterial chemoembolization	62	NA	51	25		Every 2–6 mo	Gelatin sponge	Epirubicin	Present
	TMX	61	NA	46	22	.68				

5-FU = 5-fluorouracil; NA = not available; TMX = tamoxifen.

was confirmed using contrast-enhanced CT or MR imaging (bolus injection) after 6 weeks ± 2.

The treatment was repeated if tumor progression was observed. The treatment could also be repeated even without tumor progression for disease control on an as-needed basis. If no residual tumor was found, transcatheter arterial chemoembolization was not performed periodically, and a follow-up contrast-enhanced CT or MR imaging examination was repeated every 3 months ± 2. When tumor recurrences were observed on a follow-up CT or MR imaging examination, the transcatheter arterial chemoembolization procedure was repeated. The protocol treatment was discontinued if any of the following criteria for the discontinuation of the protocol therapy occurred: obvious tumor progression at the site of treatment at an evaluation performed 6 weeks ± 2 after transcatheter arterial chemoembolization, tumor thrombosis in the first branch or main portal vein, intended use of another appropriate therapy for persistent or recurrent tumors, grade 4 nonhematologic toxicities other than aspartate aminotransferase (AST) or alanine aminotransferase (ALT), an accumulated dose of epirubicin > 750 mg/m^2 body surface area or an accumulated dose of doxorubicin > 500 mg/m^2 body surface area, or technical difficulties associated with the performance of transcatheter arterial chemoembolization. If the protocol therapy was discontinued, another anticancer treatment was allowed without restriction. Also, if transcatheter arterial chemoembolization was effective in reducing the tumor and the patient was eligible for other curative therapies, hepatic resection or local ablative therapy was allowed.

Response and Toxicity Assessment

Contrast-enhanced CT or MR imaging was performed at 6 weeks ± 2 after transcatheter arterial chemoembolization and every 3 months ± 2 thereafter. The tumor response was evaluated according to the modified Response Evaluation Criteria in Solid Tumors (RECIST) (19). Serum alpha fetoprotein (AFP) and protein induced by vitamin K absence or antagonist-II (PIVKA II) levels were measured at 6 weeks ± 2 after the first transcatheter arterial chemoembolization procedure. The AFP or PIVKA II response was assessed for patients who had a level before treatment of 100 ng/mL or ≥ 100 mAU/mL; a positive response was defined as a reduction by > 50% compared with the level before treatment. Regarding the adverse events that were observed, the incidence per grade based on the worst grade of the adverse events in an individual case was calculated. The severity of all adverse events was evaluated according to the National Cancer Institute Common Terminology Criteria for adverse events, version 3.0. Overall survival was measured from the date of initial treatment to the date of death or the date of the last follow-up examination. Time-to-progression was defined as the time from the date of the initial treatment to the first documentation of progression. The period until the discontinuation of transcatheter arterial chemoembolization was defined as the time from the date of the initial treatment to the discontinuation of the protocol therapy. The overall survival time and time-to-progression were calculated using the Kaplan-Meier method.

Statistical Considerations

The aim of this clinical study was to evaluate the safety and efficacy of Asian transcatheter arterial chemoembolization and to confirm the reproducibility of the therapeutic effect compared with that observed in a randomized controlled trial conducted by Llovet et al (12). The primary endpoint of this trial was the 2-year survival rate, and the secondary endpoints were overall survival, the response rate, and the frequency of adverse events. The number of enrolled patients was determined using the confidence interval (CI) method based on the assumption that the 2-year survival rate in the transcatheter arterial chemoembolization group studied by Llovet et al (12) was 63%. Because the enrollment of 100 patients in this study would ensure a 10% two-sided CI, we planned to enroll 100 patients. This clinical study was a multicenter cooperative study conducted in Japan and Korea, and the annual registration of 100 patients was feasible. The total study period was set as 3 years, estimating that case accrual would occur during the first year and that the remaining 2 years would serve as the follow-up period to determine the 2-year survival rate. This population was defined as the full analysis set (FAS), including any patients who received at least one course of the study treatment and excluding any patients who withdrew their informed consent to participate in this study. This open-label, multiinstitutional, single-arm prospective study was approved by the review board of each institution and was conducted in accordance with the Declaration of Helsinki. This trial was registered in UMIN Clinical Trials Registry (http://www.umin.ac.jp/ctr/index-j.htm), identification number (UMIN000000975). Patient registration and data collection were managed by the clinical research data center of the clinical trial office at the National Cancer Center in Japan. The quality of data was ensured through careful review by the data center staff and the coordinating investigator of this study. All the data were frozen on January 31, 2011, and all the analyses were performed by a statistician (S.Y.).

RESULTS

Patient Characteristics

Between January 2008 and January 2009, 102 patients were enrolled in this trial at 19 institutions in Japan and 8 institutions in Korea (**Table 2**). Three patients were excluded from the analysis because they withdrew their informed consent, and all their data were extracted from the study. The characteristics of the remaining 99 FAS patients are listed in **Table 3**.

Table 2. Enrolled Institutions and Numbers of Patients

Institution	No. Enrolled Patients
National Cancer Center Hospital East	12
National Cancer Center Hospital	12
Nara Medical University	10
Chonnam University Hospital	7
Aichi Cancer Center Hospital	6
Shizuoka Cancer Center	6
Kyung Hee University Medical Center	6
Ishikawa Prefectural Central Hospital	4
Kobe University	4
The Catholic University of Korea Uijeongbu St Mary's Hospital	4
The Cancer Institute Hospital of JFCR	3
Shinshu University	3
Fukuoka University	3
Keijinkai Teine Hospital	2
Niigata Cancer Center	2
Okinawa Prefectural Nanbu Medical Center & Children's Medical Center	2
Catholic University St Paul's Hospital	2
Cheju National University Hospital	2
Korea University Anam Hospital	2
Samsung Medical Center	2
Seoul National University Hospital	2
Tochigi Cancer Center	1
Ryugasaki Saiseikai Hospital	1
The Jikei University School of Medicine	1
Aichi Medical University	1
Shitennoji Hospital	1
Hyogo College of Medicine	1

Table 3. Patient Characteristics (n = 99)

Characteristics	No. Patients (%)
Korea	24 (24%)
Japan	75 (76%)
Age (y)	
Median	70
Range	45–84
Sex	
Male	67 (68%)
Female	32 (32%)
ECOG performance status	
0	86 (87%)
1	12 (12%)
2	1 (1%)
Hepatitis B surface antigen positive	19 (19%)
Hepatitis C virus antibody positive	52 (53%)
Child-Pugh classification	
A	80 (81%)
B	19 (19%)
Ascites present	5 (5%)
Maximum tumor size (mm)	
Median	39
Range	11–110
No. tumors	
Single	34 (34%)
Multiple	65 (66%)
Tumor distribution	
Unilobar	64 (65%)
Bilobar	35 (35%)
AFP (ng/dL)	
Median	35.4
Range	1.8–102,700
Protein induced by vitamin K absence or antagonist-II (mAU/mL)	
Median	154
Range	0.02–66,400

AFP = alpha fetoprotein; ECOG = Eastern Cooperative Oncology Group.

Transcatheter Arterial Chemoembolization Procedure

A median of two transcatheter arterial chemoembolization procedures (range, one to nine procedures) were performed during the follow-up period. Transcatheter arterial chemoembolization using epirubicin was performed in 76 patients (77%), and transcatheter arterial chemoembolization using doxorubicin was performed in 25 patients (25%). Mainly epirubicin was used in Japan, whereas mainly doxorubicin was used in Korea. However, doxorubicin was administered together with mitomycin and cisplatin in two patients, which was judged as a serious deviation from the study's protocol. The median doses of epirubicin, doxorubicin, and Lipiodol were 45 mg/body (range, 10–70 mg/body), 40 mg/body (range, 10–60 mg/body), and 5 mL (range, 1.5–20 mL). The artery used for the administration of the anticancer agent in the initial transcatheter arterial chemoembolization was the subsegmental branch in 51 patients (37%), the segmental branch in 42 patients (30%), the left or right hepatic artery in 35 patients (25%), and other arteries such as the inferior phrenic artery in 10 patients (7%). There were 62 patients (63%) who discontinued the protocol treatment. The median period until transcatheter arterial chemoembolization discontinuation was 17.8 months. After the discontinuation of this protocol treatment, 59 patients (60%) received subsequent therapy including hepatic arterial infusion chemotherapy (14 patients), transcatheter arterial chemoembolization with other anticancer agents (13 patients), local ablation (13 patients), systemic chemotherapy (10 patients), radiotherapy (6 patients), and hepatic resection (3 patients).

Adverse Events

The adverse events associated with the first transcatheter arterial chemoembolization procedure observed in the 99 FAS patients are listed in Table 4. Grade 3 or higher anemia, neutropenia, and thrombocytopenia occurred in 1 (1%), 1 (1%) and 12 (12%) patients. In patients undergoing

Table 4. Adverse Events of First Transcatheter Arterial Chemoembolization (n = 99)

	No. Patients (%)			
	Grade 1*	Grade 2*	Grade 3*	Grade 4*
Hematologic toxicity				
Leukocytes	30 (30)	12 (12)	0 (0)	0 (0)
Neutrophils	11 (11)	14 (14)	1 (1)	0 (0)
Hemoglobin	53 (54)	14 (14)	1 (1)	0 (0)
Platelets	45 (45)	25 (25)	11 (11)	1 (1)
Nonhematologic toxicity				
Malaise	42 (42)	10 (10)	0 (0)	0 (0)
Anorexia	37 (37)	4 (4)	0 (0)	0 (0)
Nausea	22 (22)	4 (4)	0 (0)	0 (0)
Vomiting	10 (10)	1 (1)	0 (0)	0 (0)
Fever	55 (56)	9 (9)	0 (0)	0 (0)
Abdominal pain	24 (24)	12 (12)	4 (4)	0 (0)
Alopecia	1 (1)	0 (0)	–	–
Gastrointestinal hemorrhage	0 (0)	0 (0)	1 (1)	0 (0)
Liver abscess	0 (0)	0 (0)	1 (1)	0 (0)
Bilirubin	28 (28)	36 (36)	2 (2)	0 (0)
AST	28 (28)	32 (32)	30 (30)	5 (5)
ALT	26 (26)	31 (31)	31 (31)	5 (5)
Alkaline phosphatase	57 (58)	4 (4)	1 (1)	0 (0)
Hypoalbuminemia	49 (49)	35 (35)	0 (0)	–
Creatinine	12 (12)	3 (3)	0 (0)	0 (0)

ALT = alanine aminotransferase; AST = aspartate aminotransferase.
* Grading according to Common Terminology Criteria for Adverse Events, version 3.0.

transcatheter arterial chemoembolization for unresectable HCC, the most common nonhematologic toxicities were hepatic dysfunction, as indicated by increased AST, ALT, and bilirubin levels. Grade 3 or higher AST, ALT, abdominal pain, and bilirubin nonhematologic toxicities were observed in 35 (35%), 36 (36%), 4 (4%), and 2 (2%) patients; these toxicities were transient so the patients recovered within 1 month. No treatment-related deaths occurred in this series. During this protocol treatment, serious adverse events were observed in two patients (2%). One patient developed a grade 5 spontaneous perforation of the small intestine because of paralytic ileus occurring 32 days after transcatheter arterial chemoembolization. This patient had a past history of multiple surgeries of the ileus, and the incident was judged as being unrelated to the transcatheter arterial chemoembolization treatment by an independent data monitoring committee. The other patient developed a grade 3 gastrointestinal hemorrhage on day 2 after the transcatheter arterial chemoembolization procedure. This hemorrhage was caused by Mallory-Weiss syndrome as a result of frequent vomiting after transcatheter arterial chemoembolization; the patient recovered without any specific treatment. No cumulative toxicities, including cardiac toxicity, were reported in this study.

Tumor Response

All 99 treated patients were included in the response evaluation, and the tumor response at 6 weeks ± 2 after the first transcatheter arterial chemoembolization procedure was evaluated using modified RECIST. A complete response was shown in 42 patients (42%), and 31 patients (31%) had a partial response, producing an overall response rate of 73% (95% CI, 64%–82%). Stable disease was present in 18 patients (18%), and 7 patients (7%) had progressive disease. Serum AFP and PIVKA II levels were reduced by > 50% in 76% and 90% of the patients who had a level before treatment of ≥ 100 ng/mL and ≥ 100 mAU/mL, respectively.

Overall Survival and Time-to-Progression

Of the 99 patients, 86 had developed disease progression at the time of the analysis. The median time-to-progression was 7.8 months. The pattern of disease progression was locoregional recurrence in 66 patients (67%), a new lesion in the liver in 53 patients (54%), vascular invasion in 8 patients (8%), and distant metastases in 8 patients (8%). At the time of the analysis, 33 patients had died, and the median survival time, 1-year survival rate, and 2-year survival rate for all 99 patients were 3.1 years, 89.9% (95% CI, 81.7%–94.3%), and 75.0% (95% CI, 65.2%–82.8%) (**Fig 1**). In addition, the median survival time, 1-year survival rate, and 2-year survival rate of 97 patients, calculated after excluding the two patients treated with doxorubicin together with mitomycin and cisplatin, were also almost the same (data not shown). The 2-year survival rates were 77.4% in Japan and 67.0% in Korea ($P = .57$) (**Fig 2**).

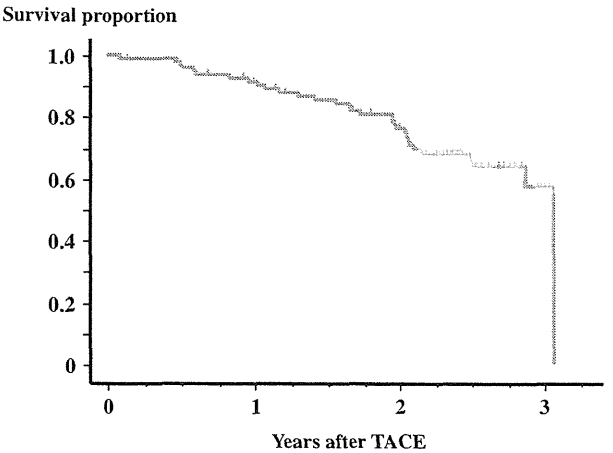

Figure 1. Overall survival and progression-free survival curves for 99 patients who underwent transcatheter arterial chemoembolization (TACE) for unresectable HCC. The tick marks indicate censored cases. (Available in color online at *www.jvir.org.*)

DISCUSSION

The survival benefit of transcatheter arterial chemoembolization for unresectable HCC has been confirmed by several randomized controlled trials (6,11,12) and meta-analyses (14,15). However, there is no consensus on the standard method of transcatheter arterial chemoembolization regarding the use of anticancer agents, embolic material, technical details, and the treatment schedule. The term "conventional transcatheter arterial chemoembolization" or "classic transcatheter arterial chemoembolization" has been widely used in the literature more recently. Common understanding is that conventional transcatheter arterial chemoembolization refers to Lipiodol chemoembolization, no matter what drug or embolic agent is used. However, there is no definition or consensus in terms of technical aspects of conventional transcatheter arterial chemoembolization. Conventional transcatheter arterial chemoembolization lacks consistency and includes a wide variety of anticancer drugs and dosages and techniques, which precludes the comparison of the previous studies of transcatheter arterial chemoembolization. For example, transcatheter arterial chemoembolization procedures with Lipiodol using a single drug or combination of two or three drugs and procedures with or without particulate embolic agents including gelatin sponge, polyvinyl alcohol, and spherical beads all have been referred to as "conventional transcatheter arterial chemoembolization." The schedule of conventional transcatheter arterial chemoembolization treatments has also been inconsistent among previous studies; transcatheter arterial chemoembolization was performed regularly in some studies and on an as-needed basis in others. Conventional transcatheter arterial chemoembolization cannot be justified as being the standard transcatheter arterial chemoembolization when conducting a randomized trial evaluating new treatments such as drug-eluting beads.

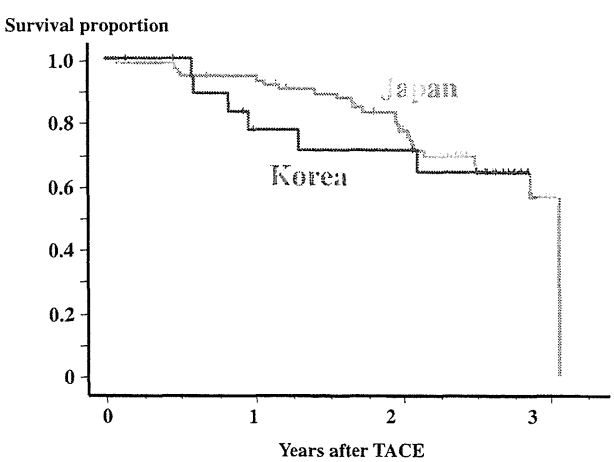

Figure 2. Comparison of overall survival curves between Japan (red line) and Korea (blue line). The tick marks indicate censored cases. TACE = transcatheter arterial chemoembolization. (Available in color online at *www.jvir.org.*)

Asian transcatheter arterial chemoembolization is characterized by using anthracycline agents with Lipiodol and gelatin sponge in an on-demand basis. It may be categorized as conventional transcatheter arterial chemoembolization; however, the technique is different from other conventional transcatheter arterial chemoembolization procedures. Elucidation of Asian transcatheter arterial chemoembolization by a prospective clinical study is warranted to develop better and new treatments for HCC. Because a randomized controlled trial comparing transcatheter arterial chemoembolization with a conservative therapy as a control is not feasible in countries such as Korea and Japan, where Asian transcatheter arterial chemoembolization has been performed as a practical standard therapy for a long time, we decided to conduct a single-arm prospective study to clarify the treatment efficacy and safety of Asian transcatheter arterial chemoembolization.

For comparison with the results of Llovet et al (12), which was the most notable study and had the most favorable antitumor effect among eight randomized controlled trials (**Table 1**) (6–13), the eligibility criteria except age and cardiac ejection fraction (**Table 5**) and study endpoints were set to be same. However, regarding transcatheter arterial chemoembolization procedures, we maintained the Asian transcatheter arterial chemoembolization in this study. With regard to the comparison of the patient characteristics between our study and the Llovet et al (12) study (**Table 5**), the median age before transcatheter arterial chemoembolization was slightly younger and the proportions of men and patients infected with hepatitis C virus were slightly higher in Llovet's study than in the present study. The hepatic reserves, as indicated by the Child-Pugh classification and the presence of ascites, were favorable in our study. The tumor-related factors were similar between our study and their study. The numbers of transcatheter arterial chemoembolization treatment sessions were also similar. Statistically, no significant differences in the patient characteristics were observed between our study and their study.

Table 5. Differences between Current Study and Llovet's Study

		Current Study (n = 99)		Llovet's Study (n = 40)		*P* Value
Eligibility criteria						
Age		Not limited		≤ 75 y		
Cardiac ejection fraction		Not limited		< 50%		
Treatment						
Anticancer agent		Doxorubicin or epirubicin		Doxorubicin		
Maximum dose of anticancer agents		Doxorubicin, 70 mg/body; epirubicin, 100 mg/body		75 mg/m^2		
Maximum dose of Lipiodol		20 mL		10 mL		
Periods of transcatheter arterial chemoembolization		On demand		Periodically		
Patient characteristics*						
Age (y)	Mean [95% CI]	69	[65–75]	63	[61–66]	
Sex	Male	67	(68)	32	(80)	
	Female	32	(32)	8	(20)	.21
ECOG performance status	0	86	(87)	35	(88)	
	1	12	(12)	4	(10)	
	2	1	(1)	1	(3)	.77
Hepatitis B surface antigen	Positive	19	(19)	4	(10)	.28
Hepatitis C virus antibody	Positive	52	(53)	33	(82)	.002
Child-Pugh classification	A	80	(81)	31	(78)	
	B	19	(19)	9	(23)	.83
Ascites	Present	5	(5)	6	(15)	.10
Maximum tumor size (mm)	Mean [95% CI]	42	[30–48]	49	[40–58]	
No. tumors	Single	34	(34)	13	(32)	
	Multiple	65	(66)	26	(65)	.99
Tumor distribution	Bilobar	35	(35)	19	(47)	.55
Antitumor effects						
Response evaluation		Modified RECIST		WHO criteria		
Response rate		73.7%		35%		< .0001
Overall survival						
1 y		89.9%		82		
2 y		75.0%		63		
Median (y)		3.1		2.1		

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; RECIST = Response Evaluation Criteria in Solid Tumors; WHO = World Health Organization.
* Unless otherwise indicated, values are number (%).

Patients with advanced HCC treated with transcatheter arterial chemoembolization tend to experience severe myelosuppression and hepatotoxicity because most of them have liver cirrhosis, which is usually associated with compromised hepatic function, leukocytopenia, and thrombocytopenia. However, in this study, the hematologic toxicities were very mild because small amounts of epirubicin (median, 45 mg/body) and doxorubicin (median, 40 mg/body) were used as combined anticancer agents. Hepatotoxicity, as indicated by increases in AST and ALT levels, was frequently observed (grade 3–4 increased AST, 35%; grade 3–4 increased ALT, 36%), but these toxicities were transient. There were no treatment-related deaths, and transcatheter arterial chemoembolization was generally tolerated in patients with advanced HCC.

In 2006, when this study was initially planned, we planned to evaluate the tumor response according to our original modified RECIST version 1.0. The concept of our modified RECIST, which evaluate tumor response based on the change in the viable part of the HCC, had been adapted into the study protocol. Unexpectedly, this concept was similar to that of modified RECIST advocated by Lencioni and Llovet in 2010 (20), which are now often used to evaluate tumor response in patients with advanced HCC. Therefore, we evaluated the response rate according to modified RECIST. The response rate in this study was very high (73%), possibly because approximately two-thirds of the transcatheter arterial chemoembolization procedures were performed subsegmentally (37%) or segmentally (30%). In Japan and Korea, transcatheter arterial chemoembolization might be performed more selectively and carefully (21,22).

The median survival time, 1-year survival rate, and 2-year survival rate for all 99 FAS patients were 3.1 years, 89.9%, and 75.0%, and no significant differences were observed between the Japanese and Korean patients. A favorable overall survival was obtained in our study, and the result was superior to the result reported by Llovet et al (12) (2-y survival, 63%). In addition, the 2-year survival rate for all subgroups in this study except for the Child-Pugh B subgroup and the subgroup with ascites seemed to be superior to Llovet's study (**Table 6**). Our results could

Table 6. Subgroup Analysis of Patients Treated with Transcatheter Arterial Chemoembolization

		n	2-y Survival (%)	*P* Value
Host-related variables				
Age (y)	≥ 70	49	72.7	
	< 70	50	76.9	.86
Sex	Male	67	77.6	
	Female	32	69.0	.36
Hepatitis B surface antigen	Positive	19	66.2	
	Negative	80	77.1	.87
Hepatitis C virus antibody	Positive	52	75.5	
	Negative	47	74.5	.14
Ascites	Present	5	40.0	
	Absent	94	77.1	.03
Performance status	0	86	77.8	
	1–2	13	52.7	.18
Child-Pugh classification	B	19	39.1	
	A	80	83.7	< .0001
Country	Korea	24	67.0	
	Japan	75	77.4	.57
Tumor-related variables				
No. tumors	Single	34	87.3	
	Multiple	65	68.7	.007
Maximum tumor size (cm)	> 3.0	64	66.1	
	≤ 3.0	35	90.6	.02
Tumor stage (UICC 6th edition)	III	57	66.7	
	I or II	42	89.6	.0008
AFP (ng/mL)	< 100	62	82.6	
	≥ 100	35	63.7	.14
PIVKA II (mAU/mL)	≥ 100	49	64.6	
	< 100	37	84.5	.12
Treatment-related variables				
Epirubicin		73	76.7	
Doxorubicin		23	65.4	.50

AFP = alpha fetoprotein; PIVKA II = protein induced by vitamin K absence or antagonist-II; UICC = Union Internationale Contre le Cancer (International Union Against Cancer).