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EDITORIAL

Treatment of hepatocellular carcinoma accompanied by portal vein tumor thrombus

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Abstract

The prognosis of patients with hepatocellular carcinoma (HCC) accompanied by portal vein tumor thrombus (PVTT) is generally poor if left untreated: a median survival time of 2.7-4.0 mo has been reported. Furthermore, while transcatheter arterial chemoembolization (TACE) has been shown to be safe in selected patients, the median survival time with this treatment is still only 3.8-9.5 mo. Systemic single-agent chemotherapy for HCC with PVTT has failed to improve the prognosis, and the response rates have been less than 20%. While regional chemotherapy with low-dose cisplatin and 5-fluorouracil or interferon and 5-fluorouracil via hepatic arterial infusion has increased the response rate, the median survival time has not exceeded 12 (range 4.5-11.8) mo. Combined treatment consisting of radiation for PVTT and TACE for liver tumor has achieved a high response rate, but the median survival rates have still been only 3.8-10.7 mo. With hepatic resection as monotherapy, the 5-year survival rate and median survival time were reportedly 4%-28.5% and 6-14 mo. The most promising results were reported for combined treatments consisting of hepatectomy and TACE, chemotherapy, or internal radiation. The reported 5-year survival rates and median survival times were 42% and 31 mo for TACE followed by hepatectomy; 36.3% and 22.1 mo for hepatectomy followed by hepatic arterial infusion chemotherapy; and 56% for chemotherapy or internal radiation followed by hepatectomy.

Key words: Hepatocellular carcinoma; Portal vein tumor Thrombus; Hepatic resection; Transcatheter arterial chemoembolization; Chemotherapy; Radiation

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INTRODUCTION

Recent progress in imaging techniques has permitted the diagnosis of hepatocellular carcinoma (HCC) at an early stage. However, portal venous invasion is still found in 12.5%-39.7% of patients with HCC[1-5]. According to the 16th National Survey for Primary Liver Cancer in Japan, 808 of 5130 patients (16%) who received hepatic resection had macroscopic portal venous invasion[6]. Portal venous invasion is a crucial factor that can worsen the prognosis of patients with HCC. It often leads to extensive spreading of the tumor throughout the liver, and can increase portal venous blood pressure, resulting in the fatal rupture of esophageal varices, and can decrease portal flow which causes ascites, jaundice, hepatic encephalopathy, and liver failure. Previous studies have reported that the median survival time of patients with portal venous invasion was 2.7-4 mo if left untreated[7,8]. To improve this short-term prognosis, various treatments have been applied, however, no standard treatment exists. In this paper, we review recent approaches to this disease.

TRANSCATHETER ARTERIAL CHEMOEMBOLIZATION

Transcatheter arterial chemoembolization (TACE) is a widely used palliative treatment for HCC that is unsuitable for radical treatments. Some investigators have noted that TACE was contraindicated for patients with portal vein tumor thrombus (PVTT), because it carried a potential risk of ischemic liver damage[9]. In contrast, other authors suggested that TACE might be safely performed in patients with PVTT if they have good hepatic reserve and collateral circulation around the portal trunk[10-13]. Yamada *et al*[9] performed TACE in 9 patients with obstruction of the main portal vein. Five of these patients died of hepatic insufficiency within 1 mo after TACE. In autopsy studies of 3 patients who died of hepatic insufficiency, extensive necrosis of tumor tissue and surrounding liver parenchyma was observed[9]. Based on these results, they concluded that TACE was contraindicated in patients with HCC in which the tumor has invaded the major portal vein. This opinion

Table 1 Transcatheter arterial chemoembolization for HCC with portal vein tumor thrombus

Lead author	Yr	*n*	Location of tumor thrombus	Treatment	Mortality within 1 mo (%)	Response rate (%)	Median survival time (mo)
Yamada R *et al*[9]	1983	9	Vp4	TACE	55.5	-	-
Okazaki M *et al*[10]	1991	48	Vp2	TACE	6.5	-	4.3
		56	Vp3	TACE	8	-	4
		59	Vp4	TACE	5.6	-	3.8
Raoul JL *et al*[14]	1994	27	Vp3, 4	^{131}I-labeled lipiodol	0	40	6
Chung JW *et al*[12]	1995	110	Vp3, 4	TACE	2.7	28	6
Georgiades CS *et al*[13]	2005	32	Vp3, 4	TACE	0	-	9.5

Vp2: 2nd order branches of the portal vein; Vp3: 1st order branches of the portal vein; Vp4: the main trunk of the portal vein.

is now supported by many clinicians even after some authors have shown that TACE is safe for these patients. One hundred sixty three patients with HCC accompanied by PVTT (48 at the 2nd portal branch, 56 at the 1st portal branch, and 59 at the main portal trunk) received TACE, and the median survival time and mortality rate within 1 mo for these patients were 4.3 mo and 6.5%, 4.0 mo and 8.0%, and 3.8 mo and 5.6% respectively[10]. The authors concluded that there was no difference in risk according to the location of portal invasion and the mortality rate was comparable to that of hepatic resection at the time[10] (Table 1). Based on these results, they suggested that the selection criteria for TACE in patients with HCC that invaded the main portal vein were the presence of cavernous transformation and a serum total bilirubin level of less than 2.0 mg/mL[10,11]. To avoid the interruption of hepatic arterial flow and subsequent hepatic insufficiency by TACE, Raoul *et al*[14] introduced internal radiation therapy using ^{131}I-labeled Lipiodol in patients with these conditions. Twenty seven patients with HCC, stage Ⅰ or Ⅱ by the classification of Okuda, accompanied by PVTT in the 1st branches of the portal vein or the portal trunk were randomly assigned to an ^{131}I-labeled Lipiodol group (n = 14) or a Control group (n = 13). The survival rates at 3, 6, and 9 mo were 71%, 48%, and 7% for the ^{131}I-labeled Lipiodol group and 10%, 0%, and 0% for the Control group ($P < 0.01$): the response rate and median survival time of the treated group were 40% and 6 mo[14]. Chung *et al*[12] performed TACE in 110 patients with HCC that invaded the 1st branch of the portal vein or the main portal vein: the response rate was 28% and the median survival time was 6 mo. In their series, hepatic insufficiency developed in 10 patients and 3 of them died within 1 mo after TACE, and the tumor extended to more than 2 sectors in all 10 of these patients. This tumor extent was a significant factor in predicting the efficacy of therapy, and they concluded that TACE was effective and safe if the extent of the tumor was limited and liver function was preserved[12]. Georgiades *et al*[13] reported that TACE was safe and effective for these patients. Thirty two patients with unresectable HCC that completely occluded the main portal vein or the right, left, or both the right and left portal veins underwent TACE. The mortality rate within 1 mo was zero and there was no evidence of TACE-related hepatic infarction or liver failure. The median survival time was 9.5 mo and the Child-Pugh score was the prognostic factor that was most strongly related to survival[13].

Despite the widespread use of TACE for patients with unresectable HCC and the demonstration that TACE is safe for patients with PVTT, the efficacy of TACE in these patients has long been controversial. Randomized controlled trials performed in the 1990s have found that this approach does not confer any survival benefits compared to conservative management[15-19]. Although tumor growth has been shown to be inhibited, survival has not been shown to be prolonged by this treatment[17]. Llovet *et al*[20] published the results of a randomized controlled trial that was stopped early because TACE provided a statistically significant survival benefit in selected patients; survival rates at 1 and 2 years were 82% and 63% for TACE versus 63% and 27% for supportive care, respectively. Lo *et al*[21] also demonstrated a significant survival benefit in patients with unresectable HCC treated with chemoembolization. The 1-, 2-, and 3-year survival rates in TACE-treated patients were 57%, 31%, and 26%, compared with 32%, 11%, and 3%, respectively, in the controlled group[21]. In a meta-analysis of randomized controlled trials, patients treated with chemoembolization showed a significantly decreased 2-year mortality rate with an odds ratio of 0.53 (95% CI, 0.32-0.89; $P = 0.017$)[22].

CHEMOTHERAPY

Many chemotherapeutic agents have been studied for their anti-HCC activity. The pyrimidine anti-metabolic agent 5-fluorouracil (5-FU) was the first reported chemotherapeutic agent tested in the treatment of HCC. However, an overall response rate of about 10% and a median survival of 3 to 5 mo have discouraged further use of 5-FU as a single agent[23,24]. Other agents tested include doxorubicin[23,25], which has a reported single-agent activity of 25% and yields a survival advantage when compared with no treatment[25]. There seems to be a general consensus that no single-agent systemic chemotherapy has an objective response rate of more than 25%. Okada *et al* reported the results of systemic chemotherapy in 71 patients with unresectable HCC (Table 2)[26]. The agents were changed from Tegafur to Doxorubicin, Tegafur plus Uracil, Etoposide, Mitoxantrone, Interferon-gamma, Cisplatin, and 5-FU over time and the response rate ranged from 0% to 20%[26]. Among these patients, 22 had tumor thrombus in the main portal vein. The median

Table 2 Chemotherapy for hepatocellular carcinoma with portal vein tumor thrombus

Lead author	Yr	*n*	Location of tumor thrombus	Route	treatment	Response rate (CR+PR) (%)	Median survival time (mo)
Systemic chemotherapy							
Okada S *et al*[26]	1992	22	Vp4	S	Tegaful, doxorubicin, MTX, CDDP, 5-FU, *etc.*	-	3.9
Low dose CDDP & 5-FU							
Ando E *et al*[28]	1996	9	Vp4	R	CDDP, 5-FU	44	9.2
Itamoto T *et al*[29]	2002	7	Vp3, 4	R	5-FU + CDDP	33	7.5
Yamasaki T *et al*[30]	2002	6	Vp3, 4	R	CDDP, 5-FU/+ leucovorin	0	4.5
Interferon & 5-FU							
Patt YZ *et al*[32]	1993	29[1]	-	S	5-FU + Interferon-α	22	-
Urabe T *et al*[33]	1998	16	Vp3, 4	R	MTX, 5-FU, cisplatin, Interferon-α	46.7	7
Kaneko S *et al*[34]	2002	34	Vp3, 4	R	5-FU, CDDP, MTX, + Interferon-α + Leucovorin	44	11 (CR + PR) 3.5 (SD + PD)
Sakon M *et al*[35]	2002	8	Vp3, 4	R	5-FU + Interferon-α	63	-
Ota H *et al*[36]	2005	55	Vp3, 4	R	5-FU + Interferon-α	43.6	11.8
Obi S *et al*[37]	2005	116	Vp3, 4	R	5-FU + Interferon-α	52	6.9

[1]Including all patients with HCC. S: Systemic chemotherapy; R: Regional chemotherapy *via* hepatic artery; MTX: methotrexate; CDDP: cisplatin.

survival time of these patients was 3.9 mo, while that of the 49 patients without this condition was 7.3 mo ($P < 0.05$)[26]. Since cisplatin and 5-FU have been reported to exhibit a synergistic effect, this combination has been widely used for various malignancies[27]. The results of the administration of low-dose cisplatin and 5-FU by repeated arterial infusion in nine patients with HCC and PVTT in the main portal trunk was reported by Ando *et al*[28]: the response rate was 44.4% and the median survival time was 9.2 mo. Seven patients with HCC and PVTT in the 1st branches of the portal vein or the main portal trunk received the same regimen: the response rate was 33%, and the median survival time was 7.5 mo[29]. Yamasaki *et al*[30] showed that the addition of leucovorin to this protocol significantly increased the survival time in a randomized study in 19 patients. Among them, 6 had PVTT in the major portal veins: their response rate and median survival time were 0% and 4.5 mo, respectively[30].

Recombinant interferon alpha has been found to be superior to doxorubicin for the treatment of inoperable HCC[31]. Combined treatment with 5-FU and alpha-interferon for HCC patients was first reported by Patt *et al* in 1993[32]. The response rate was reportedly 22%[32]. Urabe *et al*[33] treated 16 patients with HCC and PVTT in the main trunk or the major branches of the portal vein by intrahepatic infusion of methotrexate, 5-FU, and cisplatin, and administered alpha-interferon subcutaneously. The response rate and median survival rate were 46.7% and 7 mo, respectively[33]. The results of combined treatment using alpha-interferon, cisplatin, methotrexate, 5-FU, and leucovorin were reported by the same group: the response rate was 44% and the median survival time was 11 mo for 13 patients who had a complete response or partial response, and 3.5 mo for 16 patients who had stable or progressive disease[34]. Combined intra-arterial 5-FU and subcutaneous alpha-interferon therapy for 8 patients with HCC accompanied by PVTT in the major portal vein was reported by Sakon *et al*[35]: one patient died at 5 mo, the remaining 7 patients were alive after 3-15 mo, and the response rate was 63%. In another study by this group in 2005, 55 patients received this treatment, and 8 (14.5%) showed a complete response, 16 (29.1%) showed a partial response, 4 (7.3%) showed no response, and 27 (49.1%) showed progressive disease[36]. The median survival time and 5-year survival rate were 11.8 mo and 16.4%, respectively[36]. Using this combination protocol, Obi *et al*[37] treated 116 patients with unresectable HCC accompanied by PVTT in the main trunk or the 1st branches of the portal vein: the response rate was 52%, and the median survival time was 6.9 mo.

While the response rate for single-agent systemic treatment for unresectable HCC is less than 25%, combined treatment with cisplatin plus 5-FU or alpha-interferon plus 5-FU using hepatic arterial infusion remarkably increased the response rate from 33% to 63%, and the median survival time was prolonged to 11 mo in patients with an active response, although there appears to be no benefit in patients without an active response.

RADIATION

Radiotherapy for HCC has been infrequently used in the treatment of HCC because the liver has a low tolerance to whole-organ irradiation[38,39]. However, some authors have reported that the tolerance dose for the liver depends on the volume of liver irradiated, and a small volume of liver tissue can tolerate a higher dose of radiotherapy[40]. Radiotherapy for patients with HCC and PVTT was first reported by Chen *et al* (Table 3)[41]. Ten patients with PVTT in the 1st branches of the portal vein received irradiation for PVTT and TACE for liver tumor, and the response rate was reportedly 100%[41]. The same protocol was used by Tazawa, Yamada, and Ishikura in 24, 8, and 20 patients[42-44]. Objective responses of PVTT ranged from 37.5% to 50%, and the median survival times were 9.7 mo in responders and 3.8 mo in non-responders[42-44]. With advances in three-dimensional planning tools, three-dimensional conformal radiotherapy (3-D CRT) allows clinicians to escalate radiotherapy doses to the tumor and minimize radiotherapy doses to normal tissue, such as normal liver parenchyma, small bowel, and spinal cord. Combined treatment consisting of 3-D CRT for PVTT

Table 3 Radiation for hepatocellular carcinoma with portal vein tumor thrombus

Lead author	Yr	*n*	Location of tumor thrombus	Treatment	Response rate of PVTT (%)	Median survival time (mo)
Chen SC *et al*[41]	1994	10	Vp2	TACE for liver tumor + Radiation (30-50 Gy) for PVTT	100	-
Tazawa J *et al*[42]	2001	24	Vp3, 4	TACE for liver tumor + Radiation (50 Gy) for PVTT	50	CR PR; 9.7 NC PD; 3.8
Yamada K *et al*[43]	2001	8	Vp3	Radiation (60 Gy) for PVTT followed by TACE for liver tumor	37.5	-
Ishikura S *et al*[44]	2002	20	Vp3	TACE + Radiation	50	5.3
Yamada K *et al*[45]	2003	19	Vp3	3-D CRT for PVTT (60 Gy) followed by TACE for liver tumor	57.9	7
Hata M *et al*[53]	2004	12	Vp3, 4	Proton beam therapy (50-72 Gy)	100	27 (24%: 5-YSR)
Nakagawa K *et al*[46]	2005	52	Vp2, 3, 4	3-D CRT for PVTT (60 Gy)	50	(15.2%; 3-YSR)
Zeng ZC *et al*[47]	2005	44		Radiation (50 Gy, 36-60)	45.5	8
Kim DY *et al*[50]	2005	59	Vp3, 4	3-D CRT	45.8	CR PR; 10.7 NC PD; 5.3
Lin CS *et al*[48]	2006	43	Vp3, 4	Conventional: 22 3-D CRT: 21	Con: 75 3-D CRT: 83	Con: 6.0 3-D CRT: 6.7
Hsu WC *et al*[49]	2006	53	Vp3, 4	3-D CRT and thalidomide	50	-

3-D CRT: Three-dimensional conformal radiation therapy; YSR: Year survival rate.

Table 4 Hepatic resection for hepatocellular carcinoma with portal vein tumor thrombus

Lead author	Yr	Number of patients	Location of tumor thrombus	Treatment	Operative mortality rate (%)	5-Year survival rate (%)	Median survival time (mo)
Kumada K *et al*[54]	1990	13	Vp4	Hx.	-	-	-
Yamaoka Y *et al*[55]	1992	29	Vp3, 4	Hx.	11	(11.6:3YSR)	-
Ikai I *et al*[56]	1998	29	Vp4	Hx.	-	4	-
		29	Vp3	Hx.	-	11	-
Ohkubo T *et al*[57]	2000	47	Vp2, 3, 4	Hx.	0	23.9	14
Wu CC *et al*[58]	2000	15	Vp4	Hx.	0	26.4	-
		97	Vp1, 2, 3	Hx.	3.1	28.5	-
Minagawa M *et al*[59]	2001	18	Vp2, 3, 4	TACE → Hx.	0	42	31
Fukuda S *et al*[60]	2002	19	Vp3, 4, Vv2, 3, B3, 4	Hx. → HAI *etc.*	0	36.3	22.1
Poon RT *et al*[61]	2003	20	Vp3, 4, Vv2	Hx.	5.7	13.3	6
Lau WY *et al*[62]	2004	7	Vp4	PIAF→Hx. or Yttrium 90 ia + doxorubicin iv → Hx.	4.1	56	[a]
Pawlik TM *et al*[63]	2005	102	Vp3, Vv2, 3	Hx.	5.9	10	11
Ikai I *et al*[64]	2006	78	Vp3, Vp4	Hx.	3.8	10.9	8.9
Le Treut YP *et al*[65]	2006	26	Vp3, 4, Vv2, 3	Hx.	11.5	13	9
Zhou J *et al*[66]	2006	381	Vp2, 3, 4	Hx.	-	12	-

[a]Survival curves remain above a survival rate of 50%. PIAF: Doxorubicin, CDDP, 5-FU iv + Interferon-α sc; Hx.: Hepatic resection; HAI: Hepatic arterial infusion chemotherapy; Vv2: The main trunk of hepatic vein; Vv3: The inferior vena cava; B3: 1st order branches of bile duct; B4: The common hepatic duct; YSR: Year survival rate.

and TACE for liver tumor was reported by Yamada *et al*[45]: the response rate and median survival time were 57.9% and 7 mo. Nakagawa *et al*[46] treated 52 patients with HCC and PVTT at the 2nd and 1st branches of the portal vein or the main portal trunk followed by percutaneous ablation therapy, TACE, or both for liver tumor: the response rate was 50%, and the 3- and 5-year survival rates were 15.2% and 5.1%. Five or fewer liver tumors and TACE after radiation independently predicted a favorable prognosis[46]. The response rates of 3-D CRT for PVTT have reportedly ranged from 45.8% to 83%, and the median survival times ranged from 5.3 mo to 7 mo[47-49]. Kim *et al*[50] reported that the median survival time was 10.7 mo in responders and 5.3 mo in non-responders.

Since proton beam irradiation enables excellent dose localization to the target compared to conventional photon irradiation, Matsuzaki *et al* applied it to the treatment of HCC[51,52]. Twelve patients with HCC and PVTT at the 1st branches or the trunk of the portal vein received proton beam irradiation for PVTT and liver tumor: the response rate and median survival time were 100% and 27 mo[53].

HEPATIC RESECTION

In the early days of a surgical approach for patients with HCC accompanied by PVTT, the goal was to prevent the rapid aggravation of portal hypertension and esophagogastric varices, and to improve the short-term prognosis. Reports of surgical therapy for these patients are shown in Table 4. Kumada *et al*[54] first reported surgical techniques in 13 patients who had tumor thrombus in the portal trunk. They described the resection

techniques; balloon catheter methods, an open method, and resection of occluded portal segment followed by portal reconstruction[54]. Yamaoka *et al*[55] performed tumor thrombectomy combined with hepatic resection in 29 patients with HCC and PVTT in the 1st branch or the portal trunk. While their primary purpose was to avoid impeding the rupture of esophageal varices, they reported an unexpectedly high 3-year survival rate of 11.6%[55]. Ikai *et al*[56] reported the outcome of 150 patients with stage Ⅳ-A HCC who underwent hepatic resection. The 5-year survival rate of 29 patients with tumor thrombi in the 1st branch of the portal vein was 11%, which was not significantly different from that of 29 patients with tumor thrombi in the portal trunk (4%)[56]. Ohkubo *et al*[57] reported the results of 47 patients with portal tumor thrombus in the 1st-2nd branches of the portal vein or the portal trunk who underwent hepatic resection. The 3- and 5-year survival rates were 33.2% and 23.9%, respectively, and the indicators of a favorable prognosis were curative hepatic resection, tumor size less than 10 cm, and absence of intrahepatic liver metastases[57]. Wu *et al*[58] reported that among 368 patients with HCC who underwent curative liver resection, 15 received concomitant liver resection and partial resection of the main portal vein because of apparent tumor thrombi extension to the portal bifurcation, and 97 had HCC which invaded intrahepatic portal branches, as confirmed on pathological examination, but did not involve the portal bifurcation. The 5-year survival rates of the former and latter groups were 26.4% and 28.5% ($P = 0.33$)[58]. They pointed out that intramural invasion was found at the site of thrombi adhesion to the portal vein cuff in 11 of 15 patients in the former group[58]. Minagawa *et al*[59] reported a high survival rate in these patients with the combination of TACE followed by hepatic resection. Eighteen patients who had HCC and gross portal tumor thrombus in the 1st-2nd branch or trunk of the portal vein showed a 5-year survival rate of 42% by preoperative TACE and hepatic resection, while none of the patients who received regional chemotherapy, TACE as monotherapy, or ligation of the portal vein survived more than 1.5 years[59]. The sole independent predictor of a favorable prognosis was hepatic resection[59]. Fukuda *et al*[60] reported that 19 patients with HCC and tumor thrombi in the 1st branch or trunk of the portal vein, inferior vena cava, or extrahepatic bile duct underwent hepatic resection with thrombectomy, and received hepatic arterial infusion chemotherapy after resection as adjuvant therapy. The 5-year survival rate of these patients was 36.3%[60]. Poon *et al*[61] reported that the prognosis of patients with HCC classified as stage Ⅳ in the tumor-node-metastasis classification of the International Union Against Cancer was not homogenous according to the 4 categories. In their paper, the 5-year survival rate of patients with HCC involving the 1st branches or trunk of the portal vein or major branches of the hepatic vein was 13.3%[61]. Lau *et al*[62] reported that 49 patients with initially unresectable HCC received nonsurgical treatment, such as systemic chemotherapy or intra-arterial yttrium-90 microspheres followed by salvage surgery. The 5-year survival rate of these 49 patients was 57%[62]. Their series included 7 patients with HCC involving the main portal vein, and the 5-year survival rate of these 7 patients was 56%[62]. Pawlik *et al*[63] analyzed the prognostic factors in 102 patients with HCC involving major portal or hepatic venous branches who were treated by hepatic resection in 5 hepatobiliary centers, and the significant predictors of a poor prognosis were moderate to severe fibrosis (Ishak grade 3 to 6) and high-grade neoplasm (Edmondson-Steiner grade Ⅲ and Ⅳ), and the operative mortality and 5-year survival rate of these 102 patients were 5.9% and 10%. Ikai *et al*[64] also analyzed the prognostic factors in 78 patients with HCC and tumor thrombus in the 1st branch or trunk of the portal vein, and the independent predictors of a favorable prognosis were absence of ascites, prothrombin activity >/= 75%, and maximal tumor diameter < 5 cm. In their series, the mortality rate and 5-year survival rate were 3.8% and 10.9%[64]. In 108 patients who underwent major hepatic resection for HCC, Le Treut *et al*[65] compared 26 who had HCC with PVTT in the portal or hepatic vein to 82 without PVTT: operative mortality and median survival time were 11.5% and 9 mo in the former group and 8.5% and 41 mo in the latter group. Zhou *et al*[66] reported a large series of hepatic resections: 381 patients with HCC and PVTT at the 1st-2nd branches or the trunk of the portal vein were treated by hepatic resection, and the 5-year survival rate of these patients was 12%.

CONCLUSION

In these reports, the median survival times were less than 12 mo without hepatic resection. While we can not exclude the possibility that this is the result of a selection bias, the most promising results were obtained with combined treatments that included hepatic resection. This analysis suggests that this disease does not have a homogenous prognosis, and therefore it is important to select patients who have a good prognosis and to treat these patients with combined treatments.

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