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Complete pathological response to transcatheter arterial infusion despite a rapidly progressing recurrent hepatocellular carcinoma with portal vein tumor thrombus: A case report

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ABSTRACT

INTRODUCTION: We report a patient with a rapidly progressing recurrence of hepatocellular carcinoma (HCC) with a portal vein tumor thrombus after radiofrequency ablation of the original lesion, then treated with transcatheter arterial infusion. Radical hepatic resection demonstrated a complete pathological response.

PRESENTATION OF CASE: A 60-year old male with alcoholic cirrhosis and gastric varices was diagnosed with HCC measuring 12 mm in segment 8. He underwent laparoscopic radiofrequency ablation, but recurred three months later. The lesion progressed rapidly and the right portal vein was occluded. He then underwent transcatheter arterial infusion with miriplatin and iodized oil, which was effective in reducing the size of the main lesion and portal vein tumor thrombus. Right anterior sectionectomy was then performed. Pathologically, there were no viable HCC cells in either the main lesion or the portal vein thrombus. He is alive two years and nine months after surgery without recurrence.

DISCUSSION: A rapidly progressing HCC recurrence with portal vein tumor thrombus is usually associated with a poor prognosis. No effective treatments have been reported in this situation except hepatic resection. In this patient the tumor was effectively reduced after three courses of transarterial miriplatin and subsequent radical hepatic resection. This is the first report to achieve a complete pathological response for such an aggressive recurrence after initial radiofrequency ablation.

CONCLUSION: This strategy may result in long-term survival of patients with rapidly progressing recurrent HCC with portal vein thrombus, and further study is warranted.

1. Introduction

Radiofrequency ablation (RFA) for small hepatocellular carcinomas (HCC) is minimally invasive, has good efficacy and is often used as first line therapy [1]. Rapidly progressive recurrence of HCC after RFA has also been reported [2]. If recurrence is accompanied by portal vein tumor thrombus, it generally progresses so rapidly as to be untreatable. We report a patient with a rapidly progressive recurrent HCC with portal vein thrombus after RFA, treated with transcatheter arterial infusion. Radical hepatic resection was then performed which demonstrated a complete pathological response to the therapy.

2. Presentation of case

A 60-year old man with alcoholic liver cirrhosis and gastric varices was found to have an elevated serum alpha-fetoprotein (AFP) to 13 ng/ml and protein induced by vitamin K antagonist-II (PIVKA-II) level of 391 mAU/ml. He underwent contrast enhanced computed tomography (CT) scan which showed a 12 mm tumor which enhanced in the arterial phase and washed out in the equilibrium phase in segment 8, consistent with HCC (Fig 1). Core needle biopsy of the lesion showed moderately differentiated hepatocellular carcinoma that was treated using laparoscopic RFA.

The tumor recurred three months later while we were planning further therapy and progressed rapidly. The right portal vein was totally occluded 144 days after RFA (Fig 2). We initially planned a

Abbreviations: HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; CT, computed tomography; TAI, transcatheter arterial infusion; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K antagonist-II.

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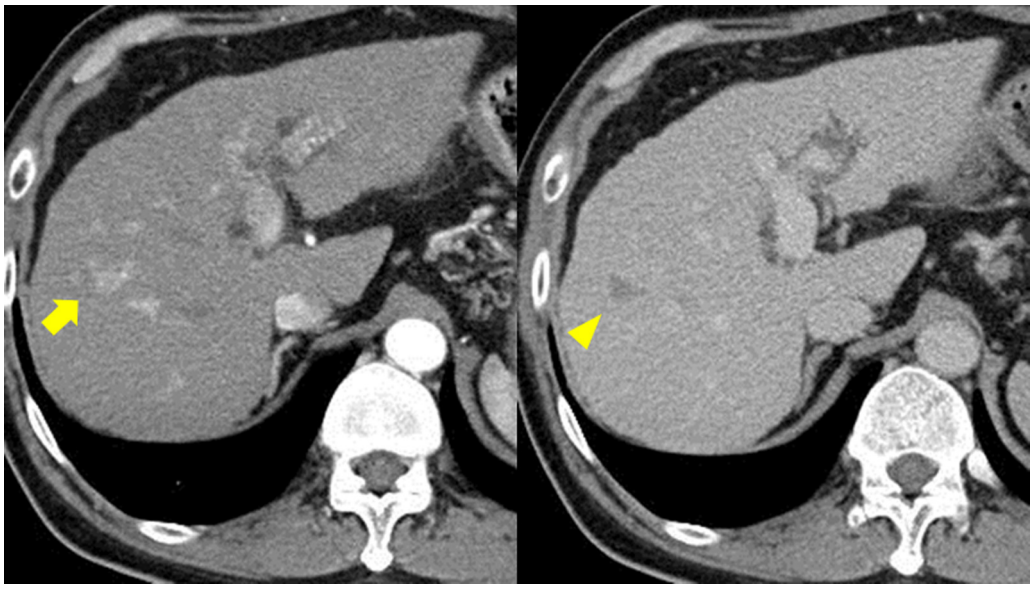

Fig. 1. Contrast enhanced CT scan shows an enhancing 12 mm tumor in the arterial phase (arrow) and wash-out in the equilibrium phase (arrowhead), consistent with an HCC in segment 8.

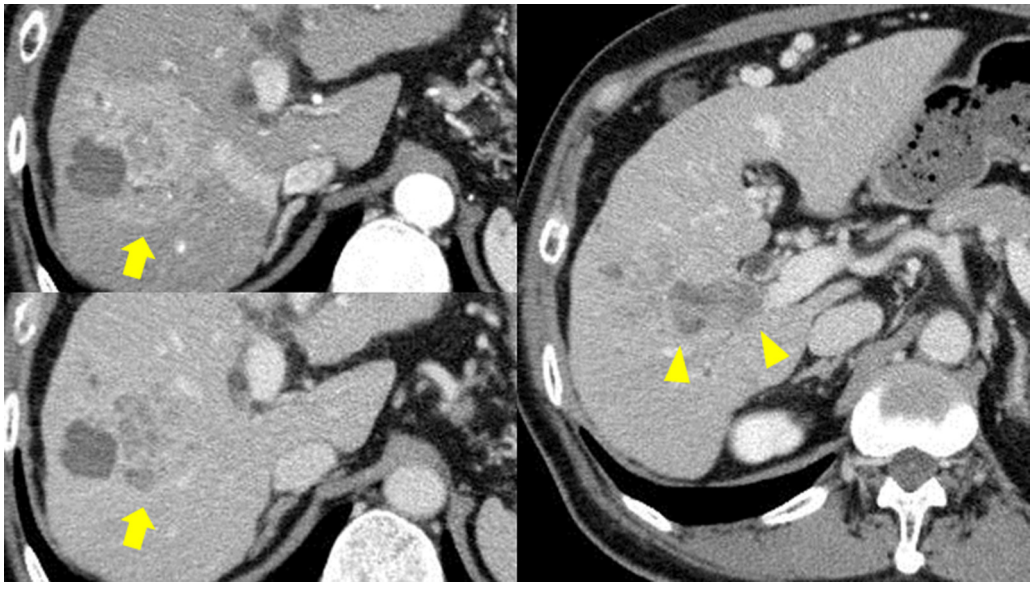

Fig. 2. Enhanced CT scan in the arterial phase shows an enhancing recurrent tumor (upper; arrow) and a relatively hypervascular area due to portal vein thrombus. In the equilibrium phase, the main tumor was washed-out (lower; arrow) and a right portal vein was totally occluded by a tumor thrombus (arrowhead).

radical right hepatectomy, but postponed the procedure while the patient was treated using transcatheter arterial infusion (TAI). The first TAI treatment was given 146 days after RFA, using miriplatin 120 mg and iodized oil 11 ml through an anterior sectional branch of the right hepatic artery (A5/A8) and confirmed accumulation of iodized oil in the main lesion and portal vein thrombus (Fig 3). Peak AFP and PIVKA-II were 139 ng/ml and 8201 mAU/ml respectively at 172 days after RFA, and they then decreased. A second TAI treatment was performed with miriplatin 140 mg and iodized oil 8 ml through the same artery at 180 days after RFA. At 251 days after RFA, a third treatment was given. Angiography demonstrated a large arterial-portal shunt in the tumor with drainage to the para-umbilical veins. Based on this, we then administered miriplatin 140 mg through the right hepatic artery without iodized oil. At 265 days after RFA, a contrast enhanced CT scan showed a marked decrease in size of the main lesion and recanalization of the posterior sectional branch of right portal vein (Fig 4).

At that time, the patient's liver function was classified as Child-Pugh A (score = 5), and the indocyanine green 15 min retention test was 12.1%. A right anterior sectionectomy was then performed at 280 days after RFA. Macroscopic findings showed coagulation necrosis at the tumor site. Microscopically, there were no viable tumor cells at the tumor site. Collapse of the liver parenchyma and organization of the thrombus in the portal vein were found with no malignant cells (Fig 5). The patient is alive two years and nine months after surgery without evidence of recurrence.

3. Discussion

In this patient, a rapidly progressing recurrent HCC with portal vein thrombus after RFA markedly reduced in size after TAI treatment with miriplatin and iodized oil. Subsequently, radical resection was safely performed. This is the first report to demonstrate a complete pathological response of a main tumor lesion and

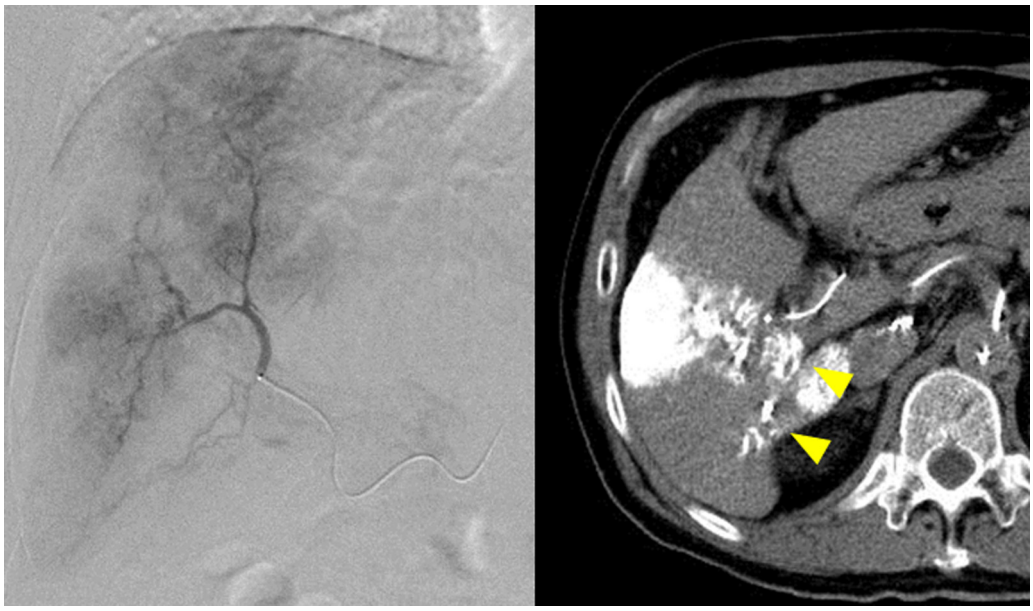

Fig. 3. The first TAI treatment was done through an injection in the anterior sectional branch of the right hepatic artery (A5/A8). At the same time, we confirmed accumulation of iodized oil in the main lesion and portal vein tumor thrombus with plain CT imaging (arrowhead).

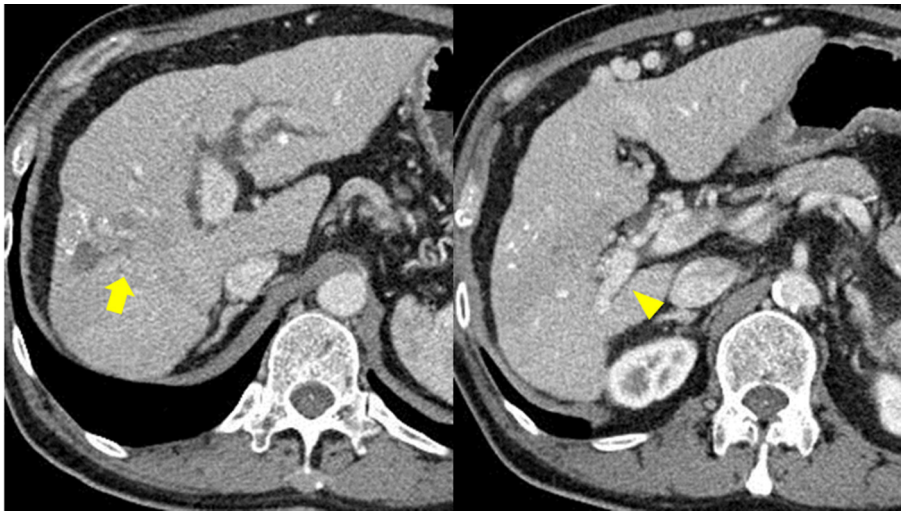

Fig. 4. Enhanced CT scan in the portal phase shows a markedly decrease in size of the main lesion (arrow) and portal vein tumor thrombus. The posterior sectional branch of right portal vein was recanalized (arrowhead).

portal vein thrombus that underwent aggressive growth of recurrent disease following RFA.

RFA for early small HCC lesions is minimally invasive with generally good results and is often used as a first line local therapy [1]. However, rapidly progressive recurrence of HCC lesions after RFA has been reported [2]. The mechanism for the rapid growth has been hypothesized to be dedifferentiation that increases the malignant potential of residual tumor cells [2–4]. The RFA needle creates a path along its track between the tumor site and portal veins, which may increase intra-tumor pressure by thermal coagulation, resulting in dissemination of tumor into the portal veins [2,4,5]. Yamada, et al. reported that local recurrence of HCC after RFA has a high frequency of portal venous invasion [6]. The incidence of rapidly progressive recurrence of HCC after RFA has been reported to be 0.1–4.5% [7–9]. If portal tumor thrombus is accompanied by recurrence, progression of recurrent lesions may accelerate.

Previous reports describe seven patients with rapidly progressing HCC with portal vein thrombus following RFA (Table 1) [10–14]. The time to recurrence following RFA was short (one to six months). Five patients had first-order branch of the portal vein tumor thrombi and underwent TAI and systemic chemotherapy after recurrence. They all died shortly after treatment [11,12,14]. Two patients developed second-order portal vein branch tumor thrombi and underwent radical resection [10,13]. In this situation, the prognosis is poor, but combination therapy including hepatic resection may improve the prognosis. However, resection of HCC with tumor thrombi in the main portal vein is often accompanied by increased risk and associated with a 6–12% postoperative mortality [15,16]. In this patient, treatment reduced the size of the right portal vein thrombus into only the anterior sectional branch, and radical right anterior sectionectomy could be performed. This was an effective strategy to down-stage the tumor and enable a radical resection.

TAI does not employ embolic materials so it is a safe procedure for patients with advanced portal vein thrombi. We observed a marked antitumor effect with a complete pathological response

Table 1
Previous reports of rapidly progressing hepatocellular carcinoma with portal vein tumor thrombus after radiofrequency ablation

Series (Ref.)	Author (year)	Age/gender	Etiology	Site	Size (mm)	Time to recurrence after RFA	Portal invasion after recurrence	Therapy after recurrence	Outcome
1 [10]	Katagiri 2003	34/M	HBV	S7	22	5 M	Second-order branch	Right posterior sectionectomy	13 M alive
2 [11]	Takada 2003	68/F	HCV	S7	27	4 M	First-order branch	TAI	4 M death
3 [11]		64/M	HBV	S6 and S8	16 and 18	6 M	First-order branch	None	2 M death
4 [12]	Portolani 2003	66/F	HCV	S4	20	3 M	First-order branch	Systemic chemotherapy	2 M death
5 [13]	Izai 2005	71/M	HCV	S5 and S6	20 and 20	1 M	Second-order branch	Right hepatectomy	16 M alive
6 [14]	Fushiya 2011	78/M	Alcohol	S5/8	30	4 M	First-order branch	None	5 M death
7 [14]		67/M	HCV	S6	30	4 M	First-order branch	Systemic chemotherapy (5-FU p.o.)	5 M death
8	Present case	60/M	Alcohol	S8	12	3 M	First-order branch	TAI (Miriplatin) →Right anterior sectionectomy	40 M alive

RFA, radiofrequency ablation; TAI, transcatheter arterial infusion.

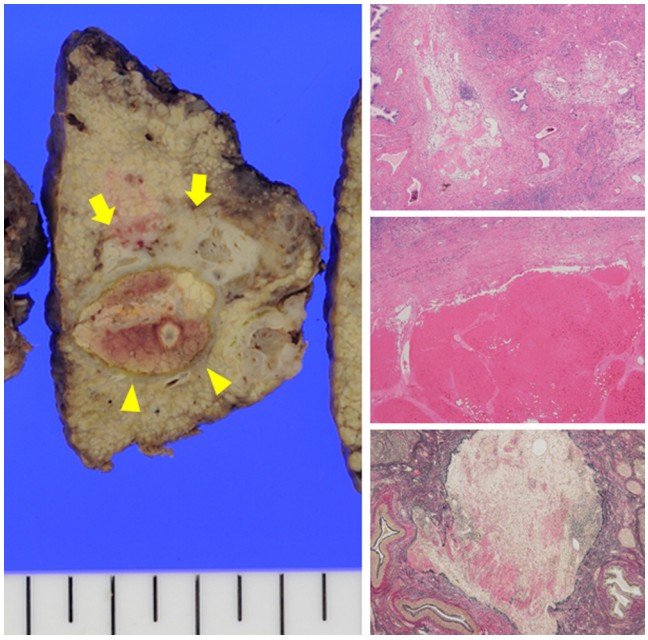

Fig. 5. Macroscopic findings showed a yellowish tumor in the liver (arrow) and an 18 mm-sized whitish area adjacent to it (arrowhead). Microscopic findings showed collapse of the liver parenchyma (upper; a part of arrow, H.E. stain × 4), coagulation necrosis of the tumor (middle; a part of arrowhead, H.E. stain × 4) and organized thrombus in the portal vein (lower; Elastica van Gieson stain × 4). All areas had no viable tumor cells.

following intra-arterial therapy. There are a number of possible effects which may have contributed to this outcome including: (1) The tumor had an abundant arterial blood supply due to the reduction in portal flow caused by the tumor thrombus. (2) The tumor was very sensitive to miriplatin. (3) Repeated TAI was possible because the drug was well tolerated without obvious liver damage. The drug was injected into the anterior sectional branch of the right hepatic artery aiming at a relatively broad area. Therefore, iodized oil accumulated not only in the main tumor mass, but also went to the portal vein thrombus leading to an improved antitumor effect. It is likely that there was no major accumulation of iodized oil in the portal vein thrombus, and control of the main lesion may have contributed to the reduction in size of the tumor thrombus. Transcatheter arterial chemoembolization [17,18] or IFN-α/5-FU combination therapy [19,20] have been reported to be effective in the treatment of advanced portal vein thrombi due to HCC. Yet these therapies may not be effective in patients with recurrence after RFA, which has unique factors such as phenotypic transformation or portal dissemination of the tumor. Further studies are required to determine which strategy is most suitable for the portal vein tumor thrombi developing as a result of rapidly progressing recurrence after RFA.

Development of an arterial-portal shunt after TAI is a difficult complication. Portal vein tumor thrombi may cause an arterial-portal shunt due to arterial feeding, which decreases the effectiveness of TAI therapy and limits imaging of the main tumor, making it difficult to continue TAI. A large arterial-portal shunt can result in portal hypertension, making surgical resection more complicated. Surgery should be considered before the development of an arterial-portal shunt that may cause deterioration in the patient's condition.

4. Conclusions

We successfully performed TAI and subsequent radical hepatic resection in a patient with a rapidly progressing recurrent HCC with portal vein tumor thrombus, which developed after RFA. A remarkable antitumor effect with a complete pathological response was obtained, suggesting that TAI may play an important role in the treatment of this condition. Further studies are required to develop this strategy further for patients with HCC.

Conflict of interest

None.

Sources of funding

None.

Ethical approval

None.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Authors contribution

Masanobu Taguchi: data collection and writing the manuscript.Yasunaru Sakuma: data collection.Hideki Sasanuma: data collection.Naohiro Sata: study design and revision of the manuscript.Alan Kawarai Lefor: critical revision of the manuscript.Takahiro Sasaki: study design and revision of the manuscript.Akira Tanaka: confirming the pathological diagnosis.Yoshikazu Yasuda: study design and revision of the manuscript.

References

[1] R. Lencioni, D. Cioni, L. Crocetti, C. Franchini, C.D. Pina, J. Lera, et al., Early-stage hepatocellular carcinoma in patients with cirrhosis: long-term results of percutaneous image-guided radiofrequency ablation, Radiology 234 (2005) 961–967.
[2] T. Seki, T. Tamai, K. Ikeda, M. Imamura, A. Nishimura, N. Yamashiki, et al., Rapid progression of hepatocellular carcinoma after transcatheter arterial chemoembolization and percutaneous radiofrequency ablation in the primary tumour region, Eur. J. Gastroenterol. Hepatol. 13 (2001) 291–294.
[3] M. Koda, Y. Maeda, Y. Matsunaga, K. Mimura, Y. Murawaki, Y. Horie, Hepatocellular carcinoma with sarcomatous change arising after radiofrequency ablation for well-differentiated hepatocellular carcinoma, Hepatol. Res. 27 (2003) 163–167.
[4] H. Tajima, T. Ohta, K. Okamoto, S. Nakanuma, H. Hayashi, H. Nakagawara, et al., Radiofrequency ablation induces dedifferentiation of hepatocellular carcinoma, Oncol. Lett. 1 (2010) 91–94.
[5] N. Nicoli, A. Casaril, M. Abu Hilal, G. Mangiante, L. Marchiori, M. Ciola, et al., A case of rapid intrahepatic dissemination of hepatocellular carcinoma after radiofrequency thermal ablation, Am. J. Surg. 188 (2004) 165–167.
[6] S. Yamada, T. Utsunomiya, Y. Morine, S. Imura, T. Ikemoto, Y. Arakawa, et al., Expressions of hypoxia-inducible factor-1 and epithelial cell adhesion molecule are linked with aggressive local recurrence of hepatocellular carcinoma after radiofrequency ablation therapy, Ann. Surg. Oncol. 21 (2014) S436–442.
[7] H. Kasugai, Y. Osaki, H. Oka, M. Kudo, T. Seki, Osaka Liver Cancer Study Group. Severe complications of radiofrequency ablation therapy for hepatocellular carcinoma: an analysis of 3891 ablations in 2614 patients, Oncology 72 (2007) 72–75.
[8] K. Shiozawa, M. Watanabe, M. Takahashi, N. Wakui, K. Iida, Y. Sumino, Analysis of patients with rapid aggressive tumor progression of hepatocellular carcinoma after percutaneous radiofrequency ablation, Hepatogastroenterology 56 (2009) 1689–1695.
[9] A. Ruzzenente, G.D. Manzoni, M. Molfetta, S. Pachera, B. Genco, M. Donataccio, et al., Rapid progression of hepatocellular carcinoma after radiofrequency ablation, World J. Gastroenterol. 10 (2004) 1137–1140.
[10] S. Katagiri, K. Takasaki, M. Yamamoto, T. Otsubo, H. Katsuragawa, K. Yoshitoshi, et al., Hepatocellular carcinoma with portal vein tumor thrombosis due to local recurrence after percutaneous radiorfrequency ablation therapy: a case report, Liver Cancer 9 (2003) 74–79 (in Japanese).
[11] Y. Takada, M. Kurata, N. Ohkohchi, Rapid and aggressive recurrence accompanied by portal tumor thrombus after radiofrequency ablation for hepatocellular carcinoma, Int. J. Clin. Oncol. 8 (2003) 332–335.
[12] N. Portolani, G.A. Tiberio, M. Ronconi, A. Coniglio, S. Ghidoni, G. Gaverini, et al., Aggressive recurrence after radiofrequency ablation of liver neoplasms, Hepatogastroenterology 50 (2003) 2179–2184.
[13] J. Izai, H. Kanemoto, K. Matsunaga, T. Ebata, A. Maeda, K. Uesaka, et al., Rapid progression of portal vein tumor thrombus after percutaneous radiofrequency ablation for hepatocellular carcinoma, Jpn. J. Gastroenterol. Surg. 38 (2005) 1318–1323 (in Japanese).
[14] N. Fushiya, Y. Masui, H. Onoda, S. Murakami, H. Nakajima, H. Tajiri, Case report 2 cases of hepatocellular carcinoma recurrence rapid progress in a unusual style after radiofrequency ablation therapy combined with transcatheter arterial infusion chemotherapy, Kanzo 52 (2011) 732–744 (in Japanese).
[15] T.M. Pawlik, R.T. Poon, E.K. Abdalla, I. Ikai, D.M. Nagorney, J. Belghiti, et al., Hepatectomy for hepatocellular carcinoma with major portal or hepatic vein invasion: results of a multicenter study, Surgery 137 (2005) 403–410.
[16] Y.P. Le Treut, J. Hardwigsen, P. Ananian, J. Saïsse, E. Grégoire, H. Richa, et al., Resection of hepatocellular carcinoma with tumor thrombus in the major vasculature: a European case-control series, J. Gastrointest. Surg. 10 (2006) 855–862.
[17] C.S. Georgiades, K. Hong, M. D'Angelo, J.F. Geschwind, Safety and efficacy of transarterial chemoembolization in patients with unresectable hepatocellular carcinoma and portal vein thrombosis, J. Vasc. Interv. Radiol. 16 (2005) 1653–1659.
[18] K.M. Kim, J.H. Kim, I.S. Park, G.Y. Ko, H.K. Yoon, K.B. Sung, et al., Reappraisal of repeated transarterial chemoembolization in the treatment of hepatocellular carcinoma with portal vein invasion, J. Gastroenterol. Hepatol. 24 (2009) 806–814.
[19] H. Ota, H. Nagano, M. Sakon, H. Eguchi, M. Kondo, T. Yamamoto, et al., Treatment of hepatocellular carcinoma with major portal vein thrombosis by combined therapy with subcutaneous interferon-alpha and intra-arterial 5-fluorouracil: role of type 1 interferon receptor expression, Br. J. Cancer 93 (2005) 557–564.
[20] S. Obi, H. Yoshida, R. Toune, T. Unuma, M. Kanda, S. Sato, et al., Combination therapy of intraarterial 5-fluorouracil and systemic interferon-alpha for advanced hepatocellular carcinoma with portal venous invasion, Cancer 106 (2006) 1990–1997.