be regarded as reference data for the usefulness of Asian transcatheter arterial chemoembolization for HCC, and the results of Asian transcatheter arterial chemoembolization in this study might be used as a reference arm for the development of new therapies for unresectable HCC in the future. Several reasons for the superior survival of our study compared with Llovet's study (12) may be pointed out. The first is the treatment interval between repeated sessions. In our study, treatment was repeated on demand, whereas in Llovet's study treatment was repeated regularly with a scheduled interval (see earlier). The second reason is the transcatheter arterial chemoembolization techniques. Experience with transcatheter arterial chemoembolization is much greater in Japan and Korea than it is in Western countries, and various microcatheter systems and CT angiography systems were used in our study. The third reason is the selection bias of the enrolled patients. No significant differences in patient characteristics were observed between our study and Llovet's study; however, the patients of our study might have had better backgrounds in hepatic function or tumor condition. It has been speculated that host genetic factors and environmental factors may affect the tumor behavior, which may account for the differences between our study and the Llovet et al (12) study.

This study has several limitations. It is a single-arm, non–randomized controlled study, and it is impossible to clarify the difference of results compared with other studies, although no statistically significant differences were observed in patient characteristics. Also, in this cooperative study of two countries, there might be some differences in the details of transcatheter arterial chemoembolization techniques and medical care to the patients. However, these limitations do not have a major influence on the interpretation of our results because this study was carried out as a prospective clinical study.

Drug-eluting beads have been introduced more recently as a new embolic material for transcatheter arterial chemoembolization (23,24). Combination therapy using transcatheter arterial chemoembolization and molecularly targeted agents, such as sorafenib, has also been reported (25,26). The survival benefit of transcatheter arterial chemoembolization for unresectable HCC has been confirmed by the results of several randomized controlled trials (6,11,12) and meta-analyses (14,15), and transcatheter arterial chemoembolization has been recognized as an effective palliative treatment option for advanced HCC. However, the optimal transcatheter arterial chemoembolization procedures, including combination with anticancer agents and embolic material; optimal timing of the transcatheter arterial chemoembolization procedures; proper patient selection for transcatheter arterial chemoembolization; and survival benefit of the combination of molecularly targeted agents with transcatheter arterial chemoembolization have not yet been fully clarified. To improve the survival of patients with advanced HCC treated with transcatheter arterial chemoembolization, these problems should be resolved by prospective trials.

In conclusion, Asian transcatheter arterial chemoembolization, which has been widely used for many years in Asian countries, showed a favorable efficacy for unresectable HCC in patients without curative treatment options, with reasonable survival data and tolerable adverse events. Our data suggest Asian transcatheter arterial chemoembolization can be regarded as one of the standard treatments in this field, and these study results could be useful as reference data for future trials of transcatheter arterial chemoembolization.

ACKNOWLEDGMENT

This study was supported in part by Grants-in-Aid for Cancer Research from the Ministry of Health, Labour, and Welfare of Japan and the National Cancer Center Research and Development Fund.

We thank the members of the Clinical Research Data Center, Clinical Trial Office, for their support with the data management (Ms. Michiyo Tada and Mr. Yushi Nagai) and the members of the study committee for safety and efficacy monitoring (Dr. Nobushige Hayashi, Dr. Yasuhiro Matsumura, and Dr. Kei Muro).

REFERENCES

1. Matsuda T, Marugame T, Kamo KI, Katanoda K, Ajiki W, Sobue T. The Japan Cancer Surveillance Research Group. Cancer incidence and incidence rates in Japan in 2005: based on data from 12 population-based cancer registries in the Monitoring of Cancer Incidence in Japan (MCIJ) Project. Jpn J Clinl Oncol 2011; 41:139–147.
2. Ikai I, Arii S, Okazaki M, et al. Report of the 17th Nationwide Follow-up Survey of Primary Liver Cancer in Japan. The Liver Cancer Study Group of Japan. Hepatol Res 2007; 37:676–691.
3. Kudo M, Izumi N, Kokudo N, et al. Management of hepatocellular carcinoma in Japan: consensus-based clinical practice guidelines proposed by the Japan Society of Hepatology (JSH) 2010 Updated Version. Dig Dis 2011; 29:339–364.
4. Bruix J, Sherman M. Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. Hepatology 2005; 42:1208–1236.
5. Shin SW. The current practice of transarterial chemoembolization for the treatment of hepatocellular carcinoma. Korean J Radiol 2009; 10: 425–434.
6. Lin DY, Liaw YF, Lee TY, Lai CM. Hepatic arterial embolization in patients with unresectable hepatocellular carcinoma—a randomized controlled trial. Gastroenterology 1988; 94:453–456.
7. Pelletier G, Roche A, Ink O, et al. A randomized trial of hepatic arterial chemoembolization in patients with unresectable hepatocellular carcinoma. J Hepatol 1990; 11:181–184.
8. Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire. A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. N Engl J Med 1995; 332: 1294–1296.
9. Pelletier G, Ducreux M, Gay F, et al. Treatment of unresectable hepatocellular carcinoma with lipiodol chemoembolization: a multicenter randomized trial. J Hepatol 1998; 29:129–134.
10. Bruix J, Llovet JM, Castells A, et al. Transarterial embolization versus symptomatic treatment in patients with advanced hepatocellular carcinoma: results of a randomized controlled trial in a single institution. Hepatology 1998; 27:1578–1583.
11. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002; 35:1164–1171.
12. Llovet JM, Real MI, Montana X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002; 359:1734–1739.

13. Doffoël M, Bonnetain F, Bouché O, et al. Multicentre randomised phase III trial comparing tamoxifen alone or with transarterial lipiodol chemoembolisation for unresectable hepatocellular carcinoma in cirrhotic patients (Fédération Francophone de Cancérologie Digestive 9402). Eur J Cancer 2008; 44:528–538.
14. Cammà C, Schepis F, Orlando A, et al. Transarterial chemoembolization for unresectable hepatocellular carcinoma: meta-analysis of randomized controlled trials. Radiology 2002; 224:47–54.
15. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology 2003; 37:429–442.
16. Kawai S, Tani M, Okamura J, et al. Prospective and randomized trial of lipiodol-transcatheter arterial chemoembolization for treatment of hepatocellular carcinoma: a comparison of epirubicin and doxorubicin (second cooperative study). The Cooperative Study Group for Liver Cancer Treatment of Japan. Semin Oncol 1997; 24(2 suppl 6):S6–38–S6-45.
17. Yamada R, Sato M, Kawabata M, Nakatsuka H, Nakamura K, Takashima S. Hepatic artery embolization in 120 patients with unresectable hepatoma. Radiology 1983; 148:397–401.
18. Nakamura H, Hashimoto T, Oi H, Sawada S. Transcatheter oily chemoembolization of hepatocellular carcinoma. Radiology 1989; 170:783–786.
19. Uchida H, Ohishi H, Matsuo N, et al. Transcatheter hepatic segmental arterial embolization using lipiodol mixed with an anticancer drug and Gelfoam particles for hepatocellular carcinoma. Cardiovasc Intervent Radiol 1990; 13:140–145.
20. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis 2010; 30:52–60.
21. Miyayama S, Matsui O, Yamashiro M, et al. Ultraselective transcatheter arterial chemoembolization with a 2-F tip microcatheter for small hepatocellular carcinomas: relationship between local tumor recurrence and visualization of the portal vein with iodized oil. J Vasc Interv Radiol 2007; 18:365–376.
22. Ji SK, Cho YK, Ahn YS, et al. Multivariate analysis of the predictors of survival for patients with hepatocellular carcinoma undergoing transarterial chemoembolization: focusing on superselective chemoembolization. Korean J Radiol 2008; 9:534–540.
23. Lencioni R, Malagari K, Vogl T, et al. A randomized phase II trial of a drug eluting bead in the treatment of hepatocellular carcinoma by transcatheter arterial chemoembolization [abstract 4598]. J Clin Oncol. 26 2008(suppl):.
24. van Malenstein H, Maleux G, Vandecaveye V, et al. A randomized phase II study of drug-eluting beads versus transarterial chemoembolization for unresectable hepatocellular carcinoma. Onkologie 2011; 34:368–376.
25. Kudo M, Imanaka K, Chida N, et al. Phase III study of sorafenib after transarterial chemoembolisation in Japanese and Korean patients with unresectable hepatocellular carcinoma. Eur J Cancer 2011; 47:2117–2127.
26. Lencioni R, Llovet JM, Han G, et al. Sorafenib or placebo in combination with transarterial chemoembolization with doxorubicin-eluting beads for intermediate-stage hepatocellular carcinoma: phase II, randomized, double-blind SPACE trial [abstract LBA154]. J Clin Oncol 2012; 30(suppl 4).

World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v19.i6.951

World J Gastroenterol 2013 February 14; 19(6): 951-954
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

CASE REPORT

Successful balloon-occluded retrograde transvenous obliteration for bleeding duodenal varices using cyanoacrylate

Rintaro Hashimoto, Keitaro Sofue, Yoshito Takeuchi, Kentaro Shibamoto, Yasuaki Arai

Rintaro Hashimoto, Keitaro Sofue, Yoshito Takeuchi, Kentaro Shibamoto, Yasuaki Arai, Department of Diagnostic Radiology, National Cancer Center Central Hospital, Tokyo 104-0045, Japan

Author contributions: Hashimoto R wrote the manuscript and performed additional data analysis; Sofue K wrote the manuscript and revised it critically for important intellectual content; Takeuchi Y and Shibamoto K performed procedures; and Arai Y helped by final approval of the version to be published.

Correspondence to: Keitaro Sofue, MD, Department of Diagnostic Radiology, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. keitarosofue@yahoo.co.jp
Telephone: +81-3-35422511 Fax: +81-3-35475989
Received: August 19, 2012 Revised: September 11, 2012
Accepted: October 30, 2012
Published online: February 14, 2013

Abstract

A 76-year-old woman with hepatitis C cirrhosis presented with tarry stools and hematemesis. An endoscopy demonstrated bleeding duodenal varices in the second portion of the duodenum. Contrast-enhanced computed tomography revealed markedly tortuous varices around the wall in the duodenum. Several afferent veins appeared to have developed, and the right ovarian vein draining into the inferior vena cava was detected as an efferent vein. Balloon-occluded retrograde transvenous obliteration (BRTO) of the varices using cyanoacrylate was successfully performed in combination with the temporary occlusion of the portal vein. Although no previous publications have used cyanoacrylate as an embolic agent for BRTO to control bleeding duodenal varices, this strategy can be considered as an alternative procedure to conventional BRTO using ethanolamine oleate when numerous afferent vessels that cannot be embolized are present.

Key words: Bleeding duodenal varices; Balloon-occluded retrograde transvenous obliteration; Cyanoacrylate; Combination therapy; Temporary portal vein occlusion

Hashimoto R, Sofue K, Takeuchi Y, Shibamoto K, Arai Y. Successful balloon-occluded retrograde transvenous obliteration for bleeding duodenal varices using cyanoacrylate. *World J Gastroenterol* 2013; 19(6): 951-954 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i6/951.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i6.951

INTRODUCTION

Bleeding duodenal varices is a rare complication in patients with portal hypertension, occurring in only 0.4% of these patients, and is often life-threatening because of the difficulty in diagnosis and treatment[1]. Treatment options include a surgical procedure, endoscopic treatment[2], and endovascular treatment, including transjugular intrahepatic portosystemic shunts (TIPS)[3,4] and balloon-occluded retrograde transvenous obliteration (BRTO)[5-10]. Although several studies have reported successful results using BRTO alone[5-8], some difficult cases with large varices or numerous collaterals requiring a combined approach have been reported[7,9], and no previous publications have used cyanoacrylate as an embolic agent for BRTO to control bleeding duodenal varices. We herein report a case with bleeding duodenal varices that were successfully embolized using cyanoacrylate and BRTO in combination with temporary occlusion of the portal vein.

CASE REPORT

A 76-year-old woman with liver cirrhosis secondary to hepatitis C presented with tarry stools and hematemesis. An urgent endoscopy demonstrated bleeding varices in the second portion of the duodenum (Figure 1A). She had no esophageal or gastric varices. Although banding

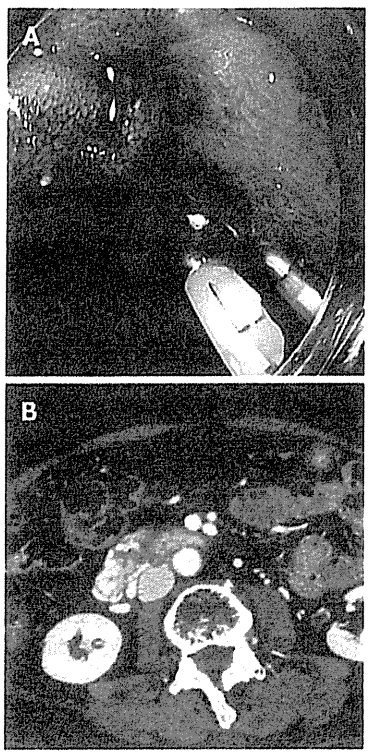


Figure 1 Endoscopy and computed tomography of the duodenum. A: Endoscopy demonstrates bleeding varices in the second portion of the duodenum; B: Contrast-enhanced computed tomography reveals markedly tortuous varices around the wall in the second and third portion of the duodenum.

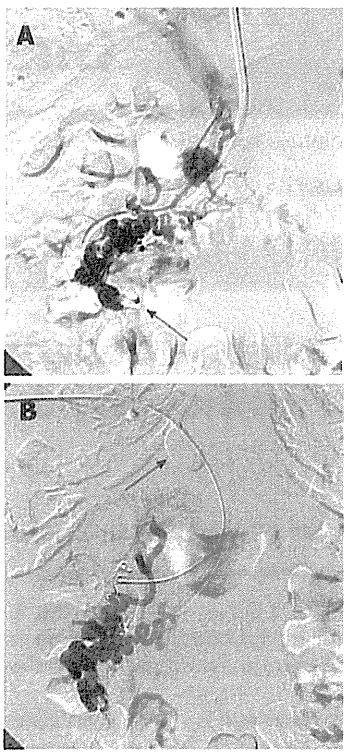


Figure 2 Balloon-occluded retrograde venography. A: Balloon-occluded retrograde venography (BRTV) shows the dilated efferent vein and the duodenal varices, but the contrast material quickly disappears through several afferent veins. Note that the balloon was inflated in the right ovarian vein (arrow); B: BRTV with occlusion of the main portal trunk (arrow) after embolization of one of the afferent veins reveals the complete opacification of the duodenal varices.

and clipping for the varices was attempted, the bleeding continued and frequent blood transfusions were required. Laboratory findings were as follows: red blood cell, 232 $\times 10^4/\mu L$; hemoglobin, 6.8 g/dL; hematocrit, 20.4%; platelets, 96 000/mL; total bilirubin, 1.36 mg/dL; serum albumin, 3.3 g/dL; and prothrombin time, 15.7 s (reference, 11.3 s). Neither ascites nor encephalopathy was observed. Child-Pugh's classification was graded as B. Contrast-enhanced computed tomography (CT) revealed markedly tortuous varices around the wall in the second and third portion of the duodenum (Figure 1B). Several afferent veins of the varices appeared to have developed, and the right ovarian vein draining into the inferior vena cava was detected as an efferent vein. We planned BRTO to embolize the duodenal varices after obtaining informed consent from the patient.

An 8-French guiding sheath introducer was inserted into the inferior vena cava *via* the right internal jugular vein. A 5.2-French, 9-mm cobra-shaped balloon catheter was inserted into the efferent vein through the right ovarian vein, and the balloon was inflated to occlude the efferent vein. Balloon-occluded retrograde venography (BRTV) showed that the dilated efferent vein and the duodenal varices were filled with contrast material, but the contrast material quickly disappeared through several afferent veins (Figure 2A). Because BRTO alone may have failed to achieve adequate sclerosant accumulation because of the leakage into the portal vein, antegrade transhepatic embolization of the afferent veins was attempted.

A 5-French sheath introducer was inserted through the left lateral portal branch, and one of the afferent veins was embolized using two microcoils (MicroNester coil; Cook, Inc, Bloomington, Indiana, United States). However, several remaining afferent veins could not be embolized, and the contrast material also disappeared through the afferent veins. We then placed a balloon catheter into the main portal trunk to control the hepatopetal flow of the afferent veins. BRTV with occlusion of the main portal trunk revealed the disappearance of the hepatopetal portal flow and complete opacification of the duodenal varices (Figure 2B). A microcatheter was coaxially advanced to the duodenal varices through the retrograde route, and a total of 4 mL of 20% cyanoacrylate with ethiodized oil was injected into the duodenal varices (Figure 3).

The following day, a contrast-enhanced CT examination confirmed the complete accumulation of the ethiodized oil replacement in the duodenal varices (Figure 4) and the patency of either portal vein or systemic circulation. Liver function was preserved after the procedure. Four days after the procedure, an endoscopy showed that hemostasis of the bleeding duodenal varices had been achieved. No evidence of bleeding of the duodenal varices was found on follow-up CT and endoscopy examinations performed four months after the procedure.

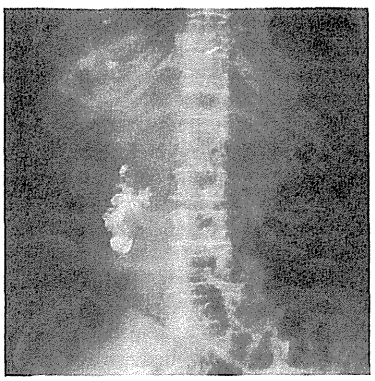


Figure 3 Radiograph after embolization of the duodenal varices demonstrates complete and adequate accumulation of the ethiodized oil in the varices.

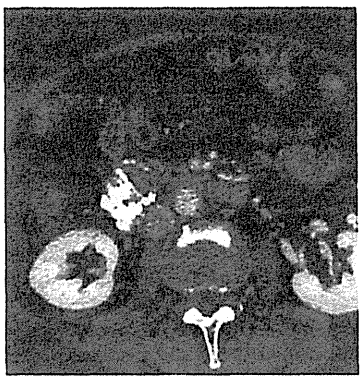


Figure 4 Contrast-enhanced computed tomography after embolization of the duodenal varices shows the complete accumulation of ethiodized oil in the varices.

DISCUSSION

BRTO is an established endovascular treatment for gastric varices[11] but has only been described for the treatment of bleeding duodenal varices in a few reports with limited numbers of clinical patients[5-10]. The advantages of BRTO over TIPS for duodenal varices are that it can completely embolize targeted varices and that it does not reduce portal flow, avoiding further exacerbation of hepatic function and encephalopathy without a significant mortality rate[4,8]. However unlike gastric varices, successful treatment with BRTO alone for duodenal varices is not always feasible and often require combined therapies with an endoscopic or anterograde transhepatic approach, as significant communications or complex hemodynamics between the efferent and afferent veins often complicate treatment and necessitate combined therapy[7,9].

In the present case, some of the afferent veins may have enabled collateral hepatopetal flow during balloon occlusion of the afferent vein, and pressure among the duodenal varices varied, resulting in insufficient filling with the contrast material. At first, coil embolization was attempted *via* a transhepatic portal venous approach, as reported by previous investigators[5,7-9], but not all the afferent veins could be embolized because of the difficulty in catheterizing the tortuous vessels. Second, we performed temporary balloon occlusion of the portal vein. This method was effective because a change in the hemodynamics of the duodenal varices occurred. Temporary occlusion of the main portal trunk may increase the pressure of hepatopetal flow, and the direction of flow in the afferent veins changes from hepatopetal to hepatofugal. This mechanism is similar to that of temporary balloon occlusion of the splenic artery during BRTO for gastric varices to control the portal pressure gradient[12].

In our case, we used cyanoacrylate, not ethanolamine oleate, as a sclerosant. Every investigator has used ethanolamine oleate as the most suitable sclerosant during BRTO for duodenal varices[5-10]. However, ethanolamine oleate was not suitable in our case, because it requires several hours to achieve full effort and may increase the risk of portal venous thrombosis under temporary portal venous balloon occlusion. On the other hand, cyanoacrylate rapidly solidifies with fast polymerization upon exposure to an ionic solution[13], and we believe that this was the best way of minimizing the duration of portal venous occlusion. The potential shortcomings of cyanoacrylate are adhesion to the balloon catheter system or inadvertent embolization upon balloon removal. This should be kept in mind as a note of caution whenever attempting to use cyanoacrylate. To prevent this complication, it would be advantageous to ensure that a microcatheter is advanced to the targeted duodenal varices and only duodenal varices are embolized, with minimal volume of cyanoacrylate.

Endoscopic injection sclerotherapy using cyanoacrylate has been performed as an effective measure[2], but it has the drawback of perforation, tissue injury, and unclear visualization because of massive hemorrhage. Moreover, endoscopic injection of cyanoacrylate also carries a risk of embolism of either portal vein or systemic circulation[14]. Endovascular injection of cyanoacrylate can prevent untargeted embolization such as portal vein or pulmonary artery, confirming the hemodynamics of the duodenal varices using contrast material.

Bleeding duodenal varices is a rare condition that is difficult to diagnose and is potentially life-threatening. BRTO using cyanoacrylate was successfully performed for control of bleeding duodenal varices in the present case. This is an alternative procedure to conventional BRTO using ethanolamine oleate when insufficient filling of the varices with sclerosant occurs and several afferent vessels cannot be adequately embolized.

REFERENCES

1 **Hashizume M**, Tanoue K, Ohta M, Ueno K, Sugimachi K, Kashiwagi M, Sueishi K. Vascular anatomy of duodenal varices: angiographic and histopathological assessments. *Am J Gastroenterol* 1993; **88**: 1942-1945 [PMID: 8237946]

2 **Kang HY**, Lee WK, Kim YH, Kwon BW, Kang MS, Kim SB, Song IH. Ruptured duodenal varices arising from the main portal vein successfully treated with endoscopic injection sclerotherapy: a case report. *Korean J Hepatol* 2011; **17**: 152-156 [PMID: 21757987 DOI: 10.3350/kjhep.2011.17.2.152]

3 **Lopera JE**, Arthurs B, Scheuerman C, Sandoz C, Petersosn S, Castaneda-Zuniga W. Bleeding duodenal: varices treatment by TIPS and transcatheter embolization. *Cardiovasc Intervent Radiol* 2008; **31**: 431-434 [PMID: 17593432]

4 **Kim MJ**, Jang BK, Chung WJ, Hwang JS, Kim YH. Duodenal variceal bleeding after balloon-occluded retrograde transverse obliteration: treatment with transjugular intrahepatic portosystemic shunt. *World J Gastroenterol* 2012; **18**: 2877-2880 [PMID: 22719200 DOI: 10.3748/wjg.v18.i22.2877]

5 **Haruta I**, Isobe Y, Ueno E, Toda J, Mitsunaga A, Noguchi S, Kimura T, Shimizu K, Yamauchi K, Hayashi N. Balloon-occluded retrograde transvenous obliteration (BRTO), a promising nonsurgical therapy for ectopic varices: a case report of successful treatment of duodenal varices by BRTO. *Am J Gastroenterol* 1996; **91**: 2594-2597 [PMID: 8946993]

6 **Ohta M**, Yasumori K, Saku M, Saitsu H, Muranaka T, Yoshida K. Successful treatment of bleeding duodenal varices by balloon-occluded retrograde transvenous obliteration: a transjugular venous approach. *Surgery* 1999; **126**: 581-583 [PMID: 10486613 DOI: 10.1016/S0039-6060(99)70102-9]

7 **Ota K**, Okazaki M, Higashihara H, Kokawa H, Shirai Z, Anan A, Kitamura Y, Shijo H. Combination of transileocolic vein obliteration and balloon-occluded retrograde transvenous obliteration is effective for ruptured duodenal varices. *J Gastroenterol* 1999; **34**: 694-699 [PMID: 10588186 DOI: 10.1007/s005350050321]

8 **Sonomura T**, Horihata K, Yamahara K, Dozaiku T, Toyonaga T, Hiroka T, Sato M. Ruptured duodenal varices successfully treated with balloon-occluded retrograde transvenous obliteration: usefulness of microcatheters. *AJR Am J Roentgenol* 2003; **181**: 725-727 [PMID: 12933468]

9 **Zamora CA**, Sugimoto K, Tsurusaki M, Izaki K, Fukuda T, Matsumoto S, Kuwata Y, Kawasaki R, Taniguchi T, Hirota S, Sugimura K. Endovascular obliteration of bleeding duodenal varices in patients with liver cirrhosis. *Eur Radiol* 2006; **16**: 73-79 [PMID: 15856238 DOI: 10.1007/s00330-005-2781-2]

10 **Tanaka O**, Ohno K, Ohno T, Tomioka H, Shimizu S, Yamagami T, Nishimura T. Should balloon-occluded retrograde transvenous obliteration be the first-line interventional radiologic treatment for bleeding duodenal varices? A case report and review of the literature. *Acta Radiol* 2008; **49**: 32-36 [PMID: 17963080 DOI: 10.1080/02841850701633049]

11 **Fukuda T**, Hirota S, Sugimoto K, Matsumoto S, Zamora CA, Sugimura K. "Downgrading" of gastric varices with multiple collateral veins in balloon-occluded retrograde transvenous obliteration. *J Vasc Interv Radiol* 2005; **16**: 1379-1383 [PMID: 16221910 DOI: 10.1016/S1051-0443(07)61912-5]

12 **Kiyosue H**, Tanoue S, Kondo Y, Maruno M, Takaji R, Matsuoto S, Ueda S, Mori H. Balloon-occluded retrograde transvenous obliteration of complex gastric varices assisted by temporary balloon occlusion of the splenic artery. *J Vasc Interv Radiol* 2011; **22**: 1045-1048 [PMID: 21708324 DOI: 10.1016/j.jvir.2010.12.028]

13 **Pollak JS**, White RI. The use of cyanoacrylate adhesives in peripheral embolization. *J Vasc Interv Radiol* 2001; **12**: 907-913 [PMID: 11487670 DOI: 10.1016/S1051-0443(07)61568-1]

14 **Miyakoda K**, Takedatsu H, Emori K, Inoue H, Toyonaga A, Mitsuyama K, Tsuruta O, Sata M. N-butyl-2-cyanoacrylate (histoacryl) glue in the right atrium after endoscopic injection for a ruptured duodenal varix: complication of histoacryl injection. *Dig Endosc* 2012; **24**: 192 [PMID: 22507099 DOI: 10.1111/j.1443-1661.2011.01185.x]

P- Reviewer Rerknimitr R **S- Editor** Jiang L
L- Editor O'Neill M **E- Editor** Li JY

Upsala Journal of Medical Sciences. 2013; 118: 16–22

informa
healthcare

ORIGINAL ARTICLE

Tumor response evaluation criteria for HCC (hepatocellular carcinoma) treated using TACE (transcatheter arterial chemoembolization): RECIST (response evaluation criteria in solid tumors) version 1.1 and mRECIST (modified RECIST): JIVROSG-0602

YOZO SATO[1], HIROKAZU WATANABE[2], MIYUKI SONE[2], HIROAKI ONAYA[2], NORIAKI SAKAMOTO[2], KEIGO OSUGA[3], MASAHIDE TAKAHASHI[2], YASUAKI ARAI[2] AND JAPAN INTERVENTIONAL RADIOLOGY IN ONCOLOGY STUDY GROUP (JIVROSG)

[1]*Department of Diagnostic and Interventional Radiology, Aichi Cancer Center Hospital, Nagoya, Japan,* [2]*Department of Diagnostic Radiology, National Cancer Center Hospital, Tokyo, Japan, and* [3]*Department of Diagnostic Radiology, Osaka University Graduate School of Medicine, Osaka, Japan*

Abstract

Background. Two standard sets of criteria are used to evaluate the tumor response of hepatocellular carcinoma (HCC): RECIST (Response Evaluation Criteria in Solid Tumors) and modified RECIST (mRECIST). The purpose was to compare two tumor response evaluation criteria, RECIST version 1.1 and mRECIST, for HCC treated using transcatheter arterial chemoembolization (TACE).

Methods. The radiological findings of patients who underwent TACE for HCCs in a multicenter clinical trial were examined. Sixty-five lesions in 21 patients treated with TACE without mixing iodized-oil were evaluated. The tumor size was evaluated by measuring the entire lesion, including the necrotic part, using RECIST version 1.1, whereas only the contrast-enhanced part observed during the arterial phase was measured using mRECIST. Five radiologists independently measured each lesion twice. To evaluate the inter-criteria reproducibility, the complete response (CR) rate, the response rate, the kappa statistics, and the proportion of agreement (PA) for response categories were calculated. The same analyses were conducted for inter- and intra-observer reproducibility.

Results. In the inter-criteria reproducibility study, the CR rate and the response rate obtained using mRECIST (56.9% and 79.7%) were higher than those obtained using RECIST version 1.1 (9.2% and 43.1%). In the inter- and intra-observer reproducibility study, mRECIST exhibited an 'almost perfect agreement', while RECIST version 1.1 exhibited a 'substantial agreement'.

Conclusions. Considerable differences in the CR rate and the response rate were observed. From the viewpoint of the high inter- and intra-observer reproducibility, mRECIST may be more suitable for tumor response criteria in clinical trials of TACE for HCC.

Key words: *Hepatocellular carcinoma, modified RECIST, RECIST version 1.1, reproducibility, tumor response*

Introduction

Two standard sets of criteria are used to evaluate the tumor response of hepatocellular carcinoma (HCC) treated using loco-regional therapy, such as transcatheter arterial embolization (TACE): RECIST (Response Evaluation Criteria in Solid Tumors) criteria (1) and modified RECIST (mRECIST) criteria (2).

RECIST criteria were published by the National Cancer Institute in 2000 with the objective of unifying

Correspondence: Hirokazu Watanabe, Department of Diagnostic Radiology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. Fax: +81-3-3542-3815. E-mail: hirwatan@ncc.go.jp

(Received 8 June 2012; accepted 6 September 2012)

ISSN 0300-9734 print/ISSN 2000-1967 online
DOI: 10.3109/03009734.2012.729104

the criteria used for response assessments. These criteria evaluate the unidimensional measurement of the longest diameter of the tumor lesions and have been used in most oncology trials. However, a number of questions and issues have arisen, leading to the development of revised RECIST (version 1.1) criteria (3). In the RECIST version 1.1 criteria, the major changes included the number of lesions to be assessed, the assessment of pathological lymph nodes, confirmation of a response, disease progression, and the necrotic tumor size (i.e. in cases where a lesion which was solid at baseline has become necrotic in the center, the longest diameter of the entire lesion should be followed).

In 2000, a panel of experts on HCC from the European Association for the Study of the Liver (EASL) agreed that estimating the reduction in viable tumor volume (as recognized using enhanced spiral computed tomography (CT)) should be considered the optimal method for assessing the local response to treatment in patients with HCC (4). Since then, most authors reporting the results of loco-regional therapy for HCC have evaluated tumor response according to this recommendation (5,6).

The aforementioned expert panel continued the concept of viable tumor endorsed by EASL and adapted the unidimensional measurement as a substitute for the bidimensional one in the determination of tumor response for target lesions in HCC (7). These amendments confirmed the American Association for the Study of Liver Disease (AASLD)–Journal of the National Cancer Institute (JNCI) guidelines and were defined as 'modified RECIST (mRECIST)' criteria (2). Therefore, mRECIST criteria were developed for loco-regional therapies to HCC. On the other hand, RECIST version 1.1 criteria were developed for systemic therapies; however, RECIST version 1.1 criteria are used in many oncology trials including loco-regional therapies for the treatment of HCC.

A study investigating the inter-criteria reproducibility between the older versions of criteria (RECIST version 1.0 and EASL) has been reported (8). Furthermore, a comparative study of tumor response by the updated criteria (RECIST version 1.1 and mRECIST) has been published (9). However, to the best of our knowledge, the inter- and intra-observer reproducibility between RECIST version 1.1 and mRECIST has not been investigated or reported.

Using these standardized criteria for evaluating tumor response in clinical trials, reproducible results should be obtained by all investigators. For a surrogate marker such as tumor response for therapy, both 'precision' (observer consistency study) and 'accuracy' (validation study comparing to gold standard) are evaluated. From the viewpoint of 'precision', we compared RECIST version 1.1 and mRECIST criteria by evaluating the inter- and intra-observer reproducibility.

The purpose of the present study was to clarify the differences in tumor response as evaluated using two updated sets of criteria (RECIST version 1.1 and mRECIST) by assessing the inter-criteria reproducibility. Moreover, another purpose of the present study was to investigate which set of criteria was superior for use as tumor response evaluation criteria in clinical trials of TACE for HCC by assessing the inter- and intra-observer reproducibility.

Materials and methods

We analyzed the radiological findings of patients who underwent pan-hepatic TACE for multiple HCCs in a multicenter clinical trial. In this trial, the eligibility criteria included patients with untreated, bilobar multiple HCCs, compensated Child–Pugh A or B cirrhosis, and the absence of vascular invasion or extrahepatic spread. TACE was performed using cisplatin (IA call, Nihon-Kayaku; 35–65 mg/m^2) and gelatin particles without mixing iodized-oil. The present study was conducted in accordance with the Helsinki Declaration, and the protocols were approved by the institutional review board. Informed written consent for the treatment protocols, including the secondary use of treatment-associated documents, was obtained from each patient. Twenty-one patients were entered from 19 July 2005 to 15 May 2007.

Image analysis

All patients underwent a dynamic study performed using a multi-slice CT scanner with non-ionic contrast medium. CT scans were obtained within two weeks before TACE and one month after TACE. Tumor assessments were made using a 5-mm interval, and axial images were obtained during the unenhanced phase, the arterial phase, and the portal venous or equilibrium phase.

Tumor response evaluation

Response was defined according to RECIST version 1.1 criteria measuring the entire lesion, including the necrotic part. On the other hand, mRECIST were used to evaluate the lesion taking tumor necrosis, recognized by the non-enhanced areas, into account. Both guidelines adopted the unidimensional measurement (Figure 1).

According to RECIST version 1.1 criteria, a complete response (CR) was defined as the disappearance

of all target lesions; a partial response (PR) was defined as at least a 30% decrease in the sum of the longest diameter of the target lesions; progressive disease (PD) was defined as at least a 20% increase in the sum of the longest diameter of the target lesions; and stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor a sufficient increase to qualify for PD.

According to mRECIST criteria, CR was defined as the absence of enhanced tumor areas during the arterial phase, reflecting complete tissue necrosis; PR was defined as at least a 30% decrease, PD was defined as at least a 20% increase in the sum of the longest diameter in the enhanced tumor areas; and SD was defined using the same definition as that used in RECIST version 1.1 criteria.

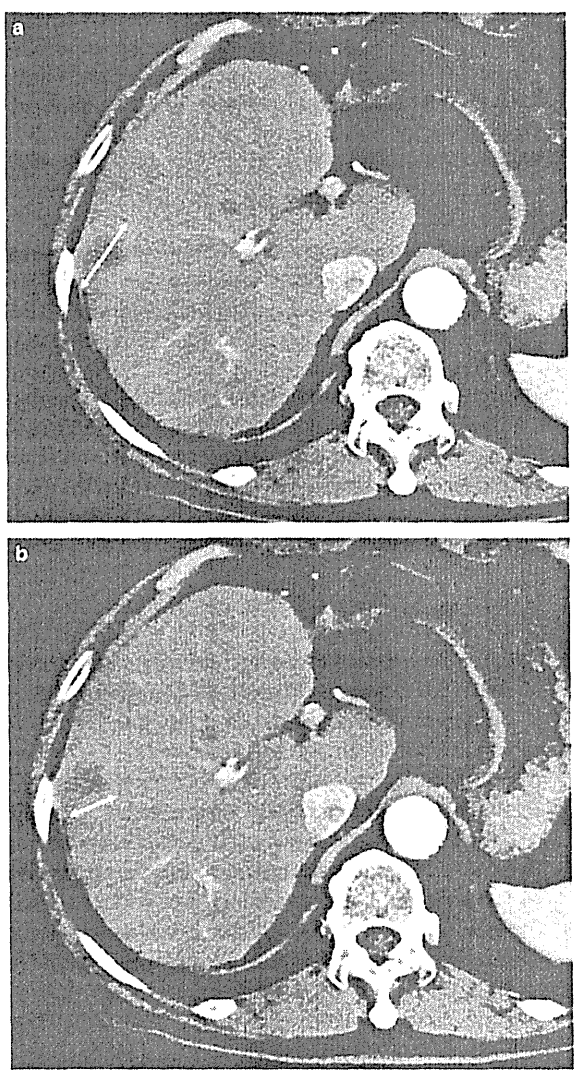


Figure 1. A: RECIST ver. 1.1: Response was defined according to a unidimensional measurement of the entire lesion, including the necrotic part. B: mRECIST: Response was defined according to a unidimensional measurement of the viable part, excluding the necrotic part.

Evaluation methods

Five observers measured 65 lesions in 21 patients independently. A total of 325 measurements were made for the first measurement. The second measurement was performed independently by the same five observers. The sum of the longest diameters for all the target lesions was calculated for baseline and post-treatment. The baseline sum was used as the reference from which the objective tumor response could be calculated. The percentage changes were calculated as the post-treatment value divided by the pre-treatment value. The percentage changes were then classified using RECIST version 1.1 and mRECIST tumor response classification systems. Tumor response was categorized as CR, PR, SD, or PD based on both sets of criteria. Furthermore, the CR rate and the response rate were also calculated.

All the images were collected from each institution and supplied to the Japan Interventional Radiology in Oncology Study Group (JIVROSG) Data Center using the WEB system.

Analysis of inter-criteria reproducibility

To examine the inter-criteria reproducibility between RECIST version 1.1 and mRECIST criteria, we estimated the kappa statistics and the proportion of agreement for the CR, PR, SD, and PD categories among the five observers. The data for the first measurements were analyzed to evaluate the inter-criteria reproducibility.

Analysis of inter-observer reproducibility

To examine the inter-observer reproducibility among the five observers, we estimated the kappa statistics and the proportion of agreement. Each pair yielded 10 pairs for comparison. The data for the first measurements were analyzed to evaluate the inter-observer reproducibility.

Analysis of intra-observer reproducibility

The data for the first and second measurements were compared to assess the intra-observer reproducibility for the same observer. The intra-observer reproducibility for the same observer yielded five pairs for comparison.

Statistics

Kappa statistics were performed to determine the concordance/agreement of the tumor response criteria. The potential kappa values ranged from −1.0 (complete disagreement) through 0 (chance agreement) to 1.0 (complete agreement). Interpretations of the strength of the agreement determined using the kappa values were given by adopting the criteria (9). The kappa values of the two agreements were compared for statistical significance using a paired *t* test. Comparisons between groups were done using the Fisher exact test. A conventional *P* value of 0.05 was considered statistically significant. All analyses were conducted using SPSS (version 17.0).

Results

Patient population

Sixty-five untreated lesions in 21 patients treated using pan-hepatic TACE were evaluated. The patients' characteristics were as follows (Table I), median age (range): 68 years (27–74 years); sex (male/female): 19/2; hepatitis C virus/hepatitis B virus/others: 12/3/6; Child–Pugh A/B: 20/1; total number of nodules (range): 65 nodules (1–5 nodules); mean tumor size (range): 20 mm (10–132 mm).

Inter-criteria reproducibility

The inter-criteria reproducibility using RECIST version 1.1 and mRECIST criteria is summarized in Tables II and III. Five observers measured 65 lesions independently, for a total of 325 measurements. According to RECIST version 1.1 criteria, the CR rate and the response rate were 9.2% and 43.1%, respectively; according to mRECIST criteria, the CR rate and the response rate were 56.9% and 79.7% (Table II).

Among the 185 CR lesions that were identified using mRECIST criteria, RECIST version 1.1 criteria classified the same responses as PR for 89 lesions, SD for 64 lesions, and PD for 2 lesions (Table III). The kappa value was 0.149 (95% CI 0.098–0.201), and the proportion of agreement was 35.5% (Table III).

Table I. Patients and characteristics.

No. of patients	21
Age, median (range)	68 (27–74)
Sex (male/female)	19/2
HCV/HBV/others	12/3/6
Child–Pugh A/B	20/1
No. of nodules, all (range)	65 (1–5)
Mean tumor size (range), mm	20 (10–132)

HCV = hepatitis C virus; HBV = hepatitis B virus.

Inter-observer reproducibility

The inter-observer reproducibility among the five observers was analyzed using the data for the first measurements, with each pair yielding 10 pairs for comparison. These 10 pairs for comparisons, or 650 measurements, are collectively shown in Table IV. For the inter-observer reproducibility for RECIST version 1.1, the kappa value was 0.628 (95% CI 0.571–0.684), and the proportion of agreement was 78.8%. For the inter-observer reproducibility for mRECIST, the kappa value was 0.829 (95% CI 0.792–0.866), and the proportion of agreement was 90.0%.

Intra-observer reproducibility

The intra-observer reproducibility was analyzed from the data for the first and second measurements, with each pair yielding five pairs for comparison. These five pairs for comparisons, or 325 measurements, are collectively shown in Table V. For the intra-observer reproducibility for RECIST version 1.1, the kappa value was 0.643 (95% CI 0.565–0.722), and the proportion of agreement was 79.4%. For the intra-observer reproducibility for mRECIST, the kappa value was 0.900 (95% CI 0.858–0.942), and the proportion of agreement was 94.2%.

Discussion

The inter-criteria reproducibility study between RECIST version 1.0 and EASL guidelines, and a comparative study of tumor response by RECIST and mRECIST have been reported (8,9). However, no information is available concerning the inter-observer reproducibility in those reports. In addition to performing an inter-criteria reproducibility study, we also estimated the inter- and intra-observer reproducibility to investigate which set of criteria (RECIST version 1.1 or mRECIST) is superior for performing tumor response evaluations in clinical trials of TACE for HCC.

Inter-criteria reproducibility

An evaluation of the tumor response according to RECIST version 1.0 and EASL guidelines after loco-regional therapies in patients with HCC has been reported. RECIST missed all the CRs obtained by

Table II. Inter-criteria reproducibility between RECIST version 1.1 and mRECIST criteria. Number of lesions (%).

Response category	Complete response	Partial response	Stable disease	Progressive disease	Overall response[a]
Response criteria					
RECIST	30 (9.2)	110 (33.8)	180 (55.4)	5 (1.5)	140 (43.1)
	$P < 0.001$				$P < 0.001$
mRECIST	185 (56.9)	74 (22.8)	65 (20)	1 (3)	259 (79.7)

[a]Complete response + partial response.
RECIST = Response Evaluation Criteria in Solid Tumors; mRECIST = modified RECIST.

Table III. Inter-criteria reproducibility between RECIST version 1.1 and mRECIST criteria: distribution chart.

		RECIST				
		Complete response	Partial response	Stable disease	Progressive disease	Total
mRECIST	Complete response	30	89	64	2	185
	Partial response	0	21	53	0	74
	Stable disease	0	0	63	2	65
	Progressive disease	0	0	0	1	1
Total		30	110	180	5	325

Proportion of agreement = 35.5%. Kappa = 0.149.

tumor necrosis and underestimated the extent of the partial tumor response because of tissue necrosis (8).

In our inter-criteria reproducibility study comparing RECIST version 1.1 and mRECIST criteria, similar results were obtained. The CR rate and the response rate obtained using mRECIST criteria were higher than those obtained using RECIST version 1.1 criteria (56.9% versus 9.2%, $P < 0.001$; 79.7% versus 43.1%, $P < 0.001$).

According to mRECIST criteria, if a tumor that was solid at baseline became entirely necrotic, all the tumors were evaluated as CR. On the other hand, using RECIST version 1.1 criteria, the necrotic tumor was evaluated as a non-CR based on the measurement of the entire lesion, leading to a different conclusion, such as PR, SD, or PD (Figure 2). Among 185 CR lesions that were identified using mRECIST criteria, 155 lesions (83.8%) were evaluated as non-CR using RECIST version 1.1 criteria. In particular, two lesions evaluated as CR using mRECIST criteria were categorized as PD using RECIST version 1.1 criteria; thus, two sets of criteria produced opposite conclusions (Table III). As the tumor size was very small and a 20% increase was thought to be within the range of measurement error, these two lesions were identified as PD using RECIST version 1.1 criteria. In some cases, this event might be caused by an increase in the necrotic tumor size secondary to chemoembolization. Therefore, the inter-criteria reproducibility between RECIST version 1.1 and mRECIST criteria for loco-regional therapy achieving complete tumor necrosis may have a low concordance.

The differences in the CR rate and the response rate between RECIST version 1.1 and mRECIST criteria indicate that the researchers should ascertain the presence or absence of 'm' (mRECIST? or RECIST?).

Table IV. Inter-observer reproducibility.

	Kappa	Proportion of agreement (%)
Inter-observer reproducibility		
RECIST	0.628 (95% CI 0.571–0.684)	78.8
mRECIST	0.829 (95% CI 0.792–0.866)	90.0

Inter- and intra-observer reproducibility

Standardized tumor response evaluation systems are considered to be reliable in clinical trials when they are reproducible among different observers. The importance of inter-observer reproducibility for any

Table V. Intra-observer reproducibility.

	Kappa	Proportion of agreement (%)
Intra-observer reproducibility		
RECIST	0.643 (95% CI 0.565–0.722)	79.4
mRECIST	0.900 (95% CI 0.858–0.942)	94.2

classification scheme has been discussed previously for other grading systems (10-14). Clinical investigators must take into account inter-observer reproducibility in tumor response evaluations, which can greatly affect the results of clinical trials.

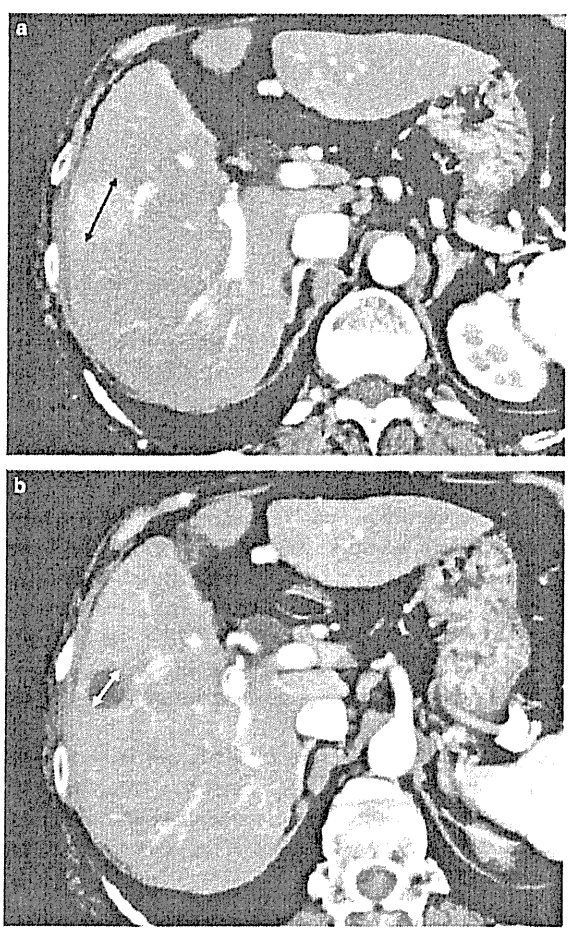


Figure 2. A: CT before TACE: Both criteria (RECIST version 1.1 and mRECIST) measured the longest diameter of the tumor. B: CT after TACE: The tumor had become entirely necrotic. The tumor response was evaluated as CR using mRECIST criteria (i.e. no measurement) and as non-CR using RECIST version 1.1 criteria (i.e. the measurement of the longest diameter of the entire tumor).

In our inter- and intra-observer reproducibility study, the kappa value and the proportion of agreement using mRECIST criteria ('almost perfect agreement') were higher than those for RECIST version 1.1 criteria ('substantial agreement'). In consideration of the high inter- and intra-observer reproducibility, mRECIST can be more recommended for use as tumor response criteria in clinical trials of TACE for HCC.

The present study had several limitations. The number of patients was relatively small, and the analyses were performed not on a per-patient basis, but on a per-lesion basis. To investigate which set of criteria was superior as tumor response criteria in clinical trials of TACE for HCC, the observer consistency study (inter- and intra-observer reproducibility between the two updated sets of criteria) were investigated in this study. A validation study comparing the updated criteria to the gold standard (i.e. overall survival) should be encouraged in future studies.

In conclusion, considering the differences in the CR rate and the response rate between RECIST version 1.1 and mRECIST criteria, close attention must be paid to the criteria used for a precise interpretation of the tumor response outcome. Furthermore, mRECIST criteria may be more suitable for tumor response criteria in clinical trials of TACE for HCC, compared with RECIST version 1.1 criteria, from the viewpoint of the high inter- and intra-observer reproducibility.

Acknowledgements

This study was undertaken as JIVROSG-0602. A part of this study was shown as a poster presentation at the meeting of the Cardiovascular and Interventional Radiological Society of Europe, Lisbon 2009.

Declaration of interest: This work was supported by the Grant-in-Aid for Cancer Research from the Japanese Ministry of Health, Labour and Welfare (20-15). The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

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

2. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010;30:52–60.
3. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228–47.
4. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol. 2001;35:421–30.
5. Varela M, Real MI, Burrel M, Forner A, Sala M, Brunet M, et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. J Hepatol. 2007;46:474–81.
6. Sala M, Llovet JM, Vilana R, Bianchi L, Solé M, Ayuso C, et al. Initial response to percutaneous ablation predicts survival in patients with hepatocellular carcinoma. Hepatology. 2004;40:1352–60.
7. Llovet JM, Bisceglie AD, Bruix J, Kramer BS, Lencioni R, Zhu AX, et al. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst. 2008;100: 698–711.
8. Forner A, Ayuso C, Varela M, Rimola J, Hessheimer AJ, de Lope CR, et al. Evaluation of tumor response after locoregional therapies in hepatocellular carcinoma. Are response evaluation criteria in solid tumors reliable? Cancer. 2009;115:616–23.
9. Edeline J, Boucher E, Rolland Y, Vauléon E, Pracht M, Perrin C, et al. Comparison of tumor response by response evaluation criteria in solid tumors (RECIST) and modified RECIST in patients treated with sorafenib for hepatocellular carcinoma. Cancer. 2012;118:147–56.
10. Landis JR, Koch GG. The measurement of observer agreement for caterogical data. Biometrics. 1977;33:159–74.
11. Watanabe H, Kunitoh H, Yamamoto S, Kawasaki S, Inoue A, Hotta K, et al. Effect of the introduction of minimum lesion size on interobserver reproducibility using RECIST guidelines in non-small cell lung cancer patients. Cancer Sci. 2006;97: 214–18.
12. Al-Aynati M, Chen V, Salama S, Shuhaibar H, Treleaven D, Vincic L. Interobserver and intraobserver variability using the Fuhrman grading system for renal cell carcinoma. Arch Pathol Lab Med. 2003;127:593–6.
13. Hagen PJ, Hartmann IJ, Hoekstra OS, Stokkel MP, Postmus PE, Prins MH. Comparison of observer variability and accuracy of different criteria for lung scan interpretation. J Nucl Med. 2003;44:739–44.
14. Travis WD, Gal AA, Colby TV, Klimstra DS, Falk R, Koss MN. Reproducibility of neuroendocrine lung tumor classification. Hum Pathol. 1998;29:272–9.

Cardiovasc Intervent Radiol (2013) 36:272–275
DOI 10.1007/s00270-012-0421-1

CASE REPORT

Life-threatening Cerebral Edema Caused by Acute Occlusion of a Superior Vena Cava Stent

Keitaro Sofue · Yoshito Takeuchi · Yasuaki Arai · Kazuro Sugimura

Received: 21 February 2012 / Accepted: 22 April 2012 / Published online: 17 May 2012

Abstract A71-year-old man with advanced lung cancer developed a life-threatening cerebral edema caused by the acute occlusion of a superior vena cava (SVC) stent and was successfully treated by an additional stent placement. Although stent occlusion is a common early complication, no life-threatening situations have been reported until now. Our experience highlights the fact that acute stent occlusion can potentially lead to the complete venous shutdown of the SVC, resulting in life-threatening cerebral edema, after SVC stent placement. Immediate diagnosis and countermeasures are required.

Keywords Cancer · Emergency medicine · Endovascular treatment · Interventional oncology · Recanalization · Superior vena cava stent insertion · Vena cava · Venous intervention

Introduction

Malignant obstruction of the superior vena cava (SVC) can be caused by various types of cancer, and patients with SVC syndrome (SVCS) have a dismal prognosis in terms of survival and quality of life [1]. Percutaneous metallic stent placement for malignant SVC obstruction has been established as a palliative procedure for the relief of symptoms, with limited complications [2–4]. Several investigators have reported early complications, including bleeding during anticoagulation or fibrinolytic therapy, pericardial tamponade, acute pulmonary edema, pulmonary embolism, and stent thrombosis [2–5]. However, to our knowledge, no reports have described an acute occlusion of a SVC stent causing a life-threatening situation. This brief report is the first description of an acute stent occlusion of an SVC stent causing life-threatening cerebral edema; the case was successfully managed by the placement of an additional stent.

K. Sofue (✉) · Y. Takeuchi · Y. Arai
Department of Diagnostic Radiology, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
e-mail: keitarosofue@yahoo.co.jp

Y. Takeuchi
e-mail: yotake62@qg8.so-net.ne.jp

Y. Arai
e-mail: arai-y3111@mvh.biglobe.ne.jp

K. Sofue K. Sugimura
Department of Radiology, Graduate School of Medicine, Kobe University, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe-shi, Hyogo-ken 650-0017, Japan
e-mail: sugimura@med.kobe-u.ac.jp

Case Report

A 71-year-old man presented with symptoms of SVCS including facial and neck edema and worsening dyspnea. He had been diagnosed as having lung squamous cell carcinoma involving the right upper lobe bronchus with mediastinal lymph node metastases, and he had been initially treated with chemotherapy and radiotherapy. However, the SVCS symptoms steadily worsened over a 3 week period. Computed tomography (CT) revealed tight stenosis of the SVC and bilateral brachiocephalic veins (BCV) (Fig. 1A, B). Endovascular stent placement was scheduled as a palliative treatment to relieve the SVCS symptoms.

After establishing a transfemoral venous access with a 7F introducer sheath (Medikit, Tokyo, Japan), retrograde cavography through a 6.5 F multipurpose catheter (Selecon Catheter; Terumo, Tokyo, Japan) confirmed a 4-cm-long severe stenosis of the SVC (Fig. 1C). The catheter and a

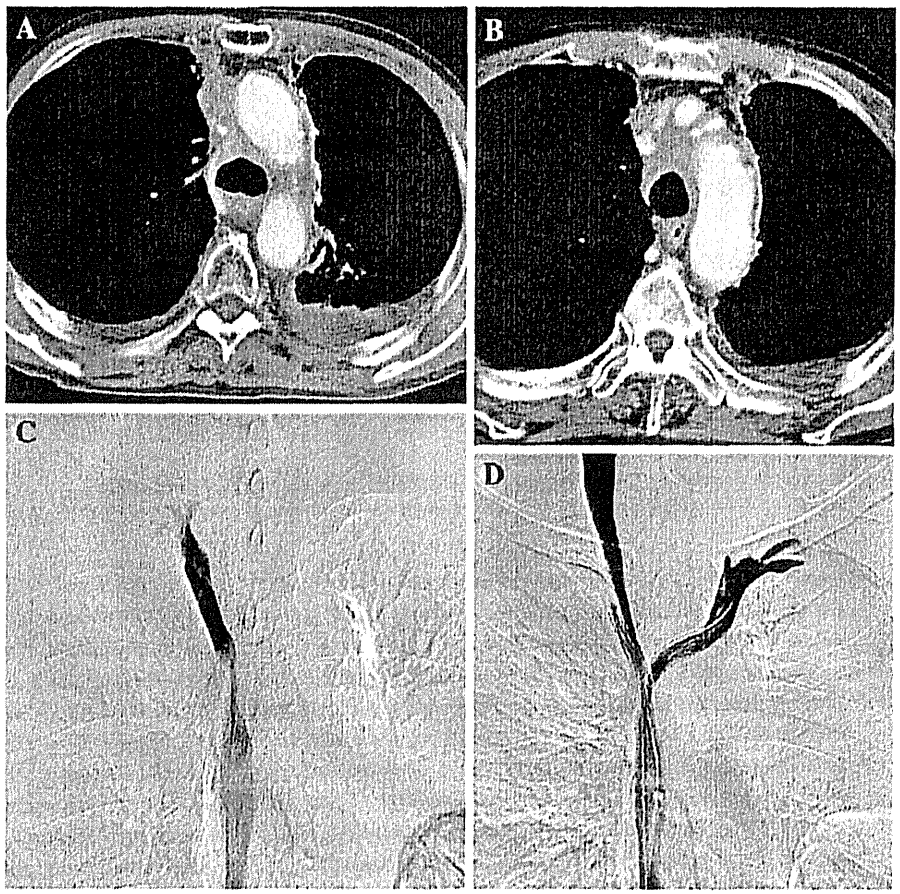


Fig. 1 **A** Contrast-enhanced CT scan reveals tight stenosis of the SVC caused by a right upper mediastinal tumor, without associated thrombosis. **B** Left brachiocephalic vein is also compressed by the tumor. **C** Venography with the catheter projecting in the right brachiocephalic vein reveals the 4-cm-long stenosis of the SVC and right brachiocephalic vein. **D** Postprocedural venography after placement of 2 stents reveals good flow through the graft

0.035 inch angled hydrophilic guide wire (Radifocus Guide Wire M; Terumo, Tokyo, Japan) were traversed across the stricture and advanced into the SVC. The guide wire was exchanged to a 0.035 inch guide wire (Amplatz extrastiff guide wire; William Cook, Bjaeverskov, Denmark) and the introducer sheath was exchanged to a 12 F introducer sheath (Cook-Z Stent Vena Caval and Venous Design Radiopaque Band Introducer Set; William Cook, Bjaeverskov, Denmark). After injection of 3,000 U of heparin and predilatation of the lesion with a 15 mm balloon catheter (Maxi LD; Cordis/Johnson &Johnson, Oostende, The Netherlands), a 16-mm-diameter, 60-mm-long self-expandable metallic stent (Spiral Z stent; Medicos Hirata, Osaka, Japan) [6] was then deployed from the SVC into the right BCV, and a 14 mm diameter, 40 mm long stent was placed in the left BCV and partially into the SVC through the interstices of the first stent. Postdilatation with a 15 mm balloon catheter was performed to fully expand the placed stents. Postprocedural venography confirmed an excellent flow of the SVC and its tributaries (Fig. 1D). Anticoagulation therapy (15,000 IU/day of heparin) continued for 3 days after the procedure. The SVCS symptoms were relieved within the next day.

On the fifth day after the SVC stent placement, the patient experienced acute respiratory distress with cyanosis, distention of the bilateral neck veins, swelling of the face, and confusion. Within half an hour, he developed hypotension and a disturbance of consciousness, and cardiopulmonary resuscitation using endotracheal intubation was undertaken. An urgent CT examination of the head revealed cerebral edema, and a CT examination of the chest demonstrated the complete occlusion of the placed stents (Fig. 2A). We decided to recanalize the occluded stents because we suspected that acute stent occlusion had caused the cerebral edema.

Transfemoral cavography through a 6.5 F multipurpose catheter confirmed the complete occlusion of the placed stents by a thrombus, and a 0.035 inch hydrophilic guide wire (Radifocus; Terumo) easily traversed the occluded stent (Fig. 2B). Thrombolysis was undertaken with 240,000 IU of urokinase, and the thrombus was crushed with a balloon catheter. A 14-mm-diameter, 60-mm-long spiral Z stent was then placed across the SVC into the right BCV to facilitate the full expansion with a 15 mm balloon catheter. Postprocedural venography revealed excellent flow through the replaced stent (Fig. 2C). Anticoagulation

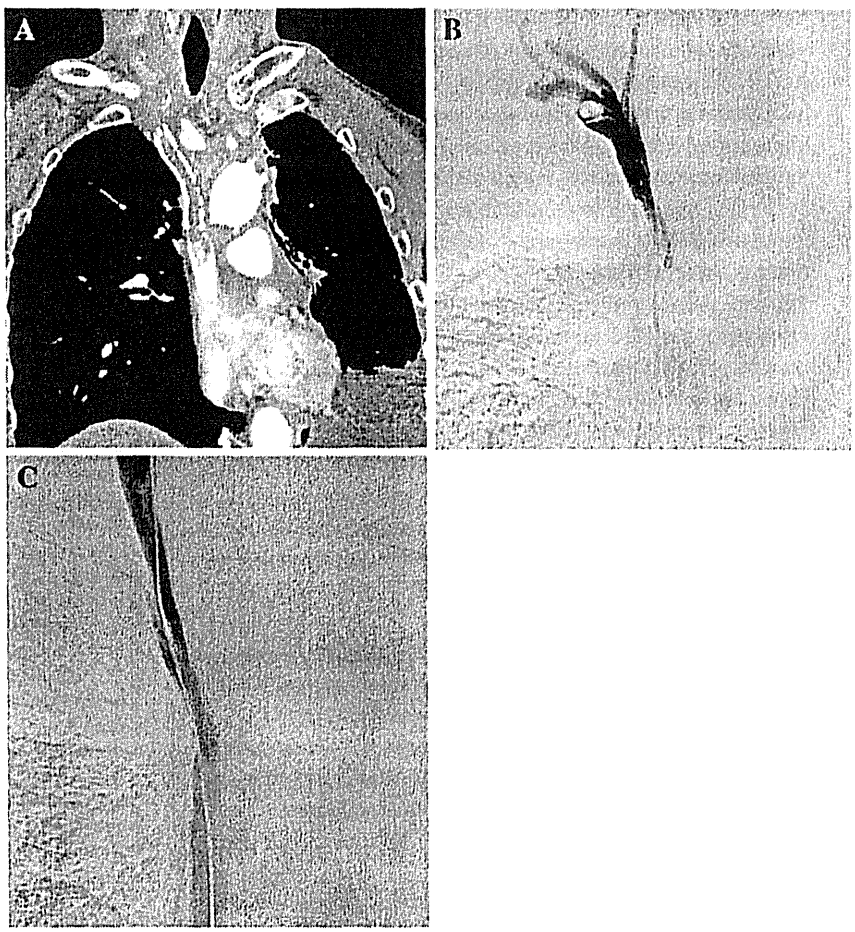


Fig. 2 **A** Coronal reconstructed image of contrast-enhanced CT of the chest demonstrates complete occlusion of the SVC stents by thrombosis. **B** Venography with the catheter projecting in the right brachiocephalic vein reveals the complete occlusion of the SVC stents. **C** A final venography performed after the second intervention reveals excellent flow through the graft in the additional replaced stent

therapy with 15,000 IU/day of heparin was continued for 7 days, with subsequent conversion to warfarin sodium.

On the day after the second intervention, cardiorespiratory insufficiency and the disturbance in consciousness were gradually relieved, and the patient was extubated 2 days later. He was discharged 20 days after the procedure and finally died of his primary disease 3 months later, with no recurrence of SVCS.

Discussion

Complications after SVC stent placement can be classified as early and late. Early complications can occur within the first postoperative week [2, 5] and can occasionally lead to a life-threatening situation [2–6]. Although stent occlusion is a common early complication [2, 7, 8], the acute occlusion of an SVC stent leading to a potentially life-threatening situation has not been previously reported.

Our patient presented with worsening clinical symptoms that developed into a life-threatening situation because of a thrombosed SVC stent. These severe symptoms may have arisen as a result of a complete venous shutdown that occurred before the collateral veins had a chance to develop and a complete obstruction below the entry of the azygos vein. Previous investigators have argued that symptom severity depends on the speed at which the obstruction develops [1, 7, 9] and the complete obstruction of the SVC and azygos vein [10], and their findings support the clinical situation we describe. Additionally, venous hypertension in the upper torso caused by the acute occlusion of the SVC probably raised the intracranial pressure, as previously reported by Rabinstein and Wijdicks [11], resulting in the brain edema observed in our case. In this situation, SVC obstruction is considered a medical emergency, and immediate diagnosis and countermeasures, such as recanalization and additional stent placement, are indispensable to avoid possibly irreversible cerebral injury from severe intracranial hypertension with secondary global anoxia [1, 10, 11].

In our case, bilateral BCV recanalization and stent placements may cause acute stent thrombosis. This finding agrees with the report of Dinkel et al. [8] in that the left BCV may become occluded when the left stent end meets

the right stent at a blunt angle at the confluence of the SVC. Our findings also agree with those reported by Dartevelle et al. [12]in that the unilateral BCV revascularization was sufficient and provided a higher flow through the graft than when both the BCV were revascularized. Several investigators have also emphasized that unilateral stent placement for SVC obstruction was sufficient and effective, and was associated with a lower rate of recurrent obstruction than bilateral stent placement [5, 6, 8, 10]. Additionally, the proximal end of the stent in the left BCV protruded partially into the SVC stent and did not expand sufficiently in our case. This partial stent-in-stent placement may also have interfered with the flow through the SVC, thereby inducing thrombosis. Another explanation is that the use of the spiral Z stent may result in acute thrombosis. The spiral Z stent has a larger open-mesh steel stent that has nearly the same relative openness of the cell/interstice size to Gianturco Z stent [6]. The insufficient compression of tumor due to the open-mesh structure of the stent may result in acute thrombosis [3, 6, 10].

Moreover, SVC obstruction often contains thrombus, and a paraneoplastic hypercoagulation state combined with the presence of a foreign body may increase the risk of acute thrombosis after SVC stent placement. Also in our case, extensive thrombus may develop after initial treatment. In this situation, long-term anticoagulation may prevent stent occlusion, as some investigators recommended [3, 5–8, 10].

Acute occlusion of the SVC stent sometimes occurs; however, it is extremely rare for this complication to cause a life-threatening situation. This brief report highlights the fact that the acute occlusion of an SVC stent and complete venous shutdown of the SVC may induce life-threatening cerebral edema. We conclude that immediate diagnosis and countermeasures are indispensable for the relief of this situation because clinical improvement depends on the presence of irreversible cerebral injury.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Wilson LD, Detterbeck FC, Yahalom J (2007) Clinical practice. Superior vena cava syndrome with malignant causes. N Engl J Med 356:1862–1869
2. Charnsangavej C, Carrasco CH, Wallace S et al (1986) Stenosis of the vena cava: preliminary assessment of treatment with expandable metal stents. Radiology 161:295–298
3. Nguyen NP, Borok TL, Welsh J et al (2009) Safety and effectiveness of vascular endoprosthesis for malignant superior vena cava syndrome. Thorax 64:174–178
4. Fagedet D, Thony F, Timsit J-F et al (2011) Endovascular treatment of malignant superior vena cava syndrome: results and predictive factors of clinical efficacy. Cardiovasc Intervent Radiol. doi:10.1007/s00270-011-0310-z
5. Uberoi R (2006) Quality assurance guidelines for superior vena cava stenting in malignant disease. Cardiovasc Intervent Radiol 29:319–322
6. Nagata T, Makutani S, Uchida H et al (2007) Follow-up results of 71 patients undergoing metallic stent placement for the treatment of a malignant obstruction of the superior vena cava. Cardiovasc Intervent Radiol 30:959–967
7. Marcy PY, Magne N, Bentolila F et al (2001) Superior vena cava obstruction: Is stenting necessary? Support Care Cancer 9:103–107
8. Dinkel HP, Mettke B, Schmid F et al (2003) Endovascular treatment of malignant superior vena cava syndrome: is bilateral wall stent placement superior to unilateral placement? J Endovasc Ther 10:788–797
9. Schraufnagel DE, Hill R, Leech JA, Pare JAP (1981) Superior vena cava obstruction: Is it a medical emergency? Am J Med 70:1169–1174
10. Ganeshan A, Hon LQ, Warakaulle DR et al (2009) Superior vena caval stenting for SVC obstruction: current status. Eur J Radiol 71:343–349
11. Rabinstein AA, Wijdicks EF (2009) Fatal brain swelling due to superior vena cava syndrome. Neurocritical Care 10:91–92
12. Dartevelle PG, Chapelier AR, Pastorino U et al (1991) Long-term follow-up after prosthetic replacement of the superior vena cava combined with resection of mediastinal-pulmonary malignant tumors. J Thorac Cardiovasc Surg 102:259–265

BRIEF REPORT

Malignant Inferior Vena Cava Syndrome and Congestive Hepatic Failure Treated by Venous Stent Placement

Yozo Sato, MD, Yoshitaka Inaba, MD, Hidekazu Yamaura, MD, Haruyuki Takaki, MD, and Yasuaki Arai, MD

ABSTRACT

A 65-year-old woman with liver metastases from colon cancer and tumor thrombus extending from the right hepatic vein (HV) to the right atrium (RA) presented with marked lower-extremity edema and massive ascites. Computed tomography showed tumor thrombus completely occluding the inferior vena cava (IVC) and HV ostia. Recanalization of the IVC and HVs was performed. Metallic stents were placed in tandem from the superior vena cava to the IVC through the RA, and additional metallic stents were placed in the left HV. The patient's symptoms were relieved, and there was no recurrence of these symptoms for 19.5 months until death.

ABBREVIATIONS

HV = hepatic vein, IVC = inferior vena cava, LHV = left hepatic vein, RA = right atrium, RHV = right hepatic vein, SVC = superior vena cava

Malignant obstruction of the inferior vena cava (IVC) can lead to IVC syndrome, ascites, and marked lower-extremity and truncal edema (1). If the level of obstruction is cephalad of the hepatic veins (HVs), liver function deteriorates, and there is marked ascites (2). These symptoms may improve with the development of collateral circulation, but the improvement is partial in most cases (3). Venous stent placement has been reported to be an effective palliative procedure for IVC obstruction (1–7). This report describes venous stent placement in a case of IVC syndrome and congestive hepatic failure caused by tumor thrombus completely occluding the IVC.

From the Department of Diagnostic and Interventional Radiology (Y.S., Y.I., H.Y.), Aichi Cancer Center Hospital, Nagoya; Department of Radiology (H.T.), Mie University School of Medicine, Tsu; and Department of Diagnostic Radiology (Y.A.), National Cancer Center Hospital, Tokyo, Japan. Received January 8, 2012; final revision received June 24, 2012; accepted June 29, 2012. Address correspondence to Y.S., Department of Diagnostic and Interventional Radiology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan; E-mail: ysato@aichi-cc.jp

None of the authors have identified a conflict of interest.

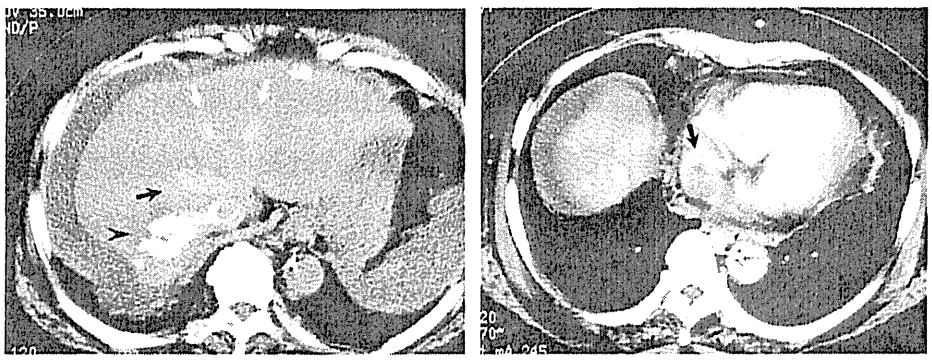
J Vasc Interv Radiol 2012; 23:1377–1380

http://dx.doi.org/10.1016/j.jvir.2012.06.035

CASE REPORT

Our institutional review board requires no approval for publication of retrospective case reports such as this.

A 65-year-old woman was referred to our hospital for initial treatment of sigmoid colon cancer with multiple liver metastases. Computed tomography (CT) revealed tumor thrombus extending from the right HV (RHV) to the IVC. She had received hepatic arterial infusion chemotherapy for multiple liver metastases and then underwent sigmoidectomy. CT imaging 3 months after surgery showed that the liver metastases and tumor thrombus were smaller. However, 5 months after surgery, the patient presented with a sudden onset of marked lower-extremity edema and massive ascites. CT imaging showed acute thrombus formation in the left HV (LHV) and middle HV caused by tumor thrombus regrowth completely occluding the IVC and HV ostia, as well as tumor thrombus extending to the right atrium (RA; Fig 1). The laboratory findings showed borderline hepatic failure (Table). Bearing in mind her bleeding tendency in the setting of hepatic failure, immediate thrombolytic and anticoagulant therapy was undertaken with low-dose urokinase (240,000 IU/d) and heparin (10,000 IU/d) for 4 days, but this did not result in improvement in liver function, and the patient's Eastern Cooperative Oncology Group performance status worsened from grade 2 to grade 3. After written informed consent was



a. b.

Figure 1. **(a)** Unenhanced CT image reveals high density because of acute thrombus formation in LHV (white arrows) and middle HV (black arrow). Calcification of liver metastases in the RHV are indicated by the arrowhead. **(b)** Enhanced CT image shows tumor thrombus extending from the RHV to the RA (arrow).

Table. Laboratory Data

Parameter	Preprocedure			Postprocedure	
	27 d	4d	1 d	6 d	18 d
AST (U/L)	19	245	815	32	23
ALT (U/L)	12	139	347	39	17
ALP (U/L)	338	415	506	287	378
T-bil (mg/dL)	1.3	5.4	6.2	3.4	1.9
INR	1.22	2.20	2.33	1.53	1.29

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, INR = International Normalized Ratio, T-bil = total bilirubin.

obtained, recanalization of the IVC and HVs via an endovascular approach was attempted.

Venography performed via the right common femoral vein access revealed complete obstruction of the hepatic segment of the IVC (Fig 2a). Metallic stent placement from the superior vena cava (SVC) to the IVC through the RA was planned to prevent stent migration into the RA. However, the stent delivery sheath (14-F Z-stent, vena caval and venous design with radiopaque band introducer set; William Cook Europe, Bjaeverskov, Denmark) could not be passed as a result of tight IVC occlusion. A 0.035-inch Radifocus M guide wire (Terumo, Tokyo, Japan) was inserted from the right femoral vein and snared from a transjugular venous access route. Therefore, the 14-F stent delivery system was introduced via the femoral vein with a transjugular pull-through approach. Four metallic stents (two 80 mm long and 20 mm in diameter and two 80 mm long and 18 mm in diameter; Spiral Z-stent; Cook, Bloomington, Indiana) were placed from the SVC to the IVC in tandem, overlapping each other.

Then, metallic stent placement in the HVs was attempted. Venography of the LHV by a retrograde injection via the recanalized IVC through the Z-stent interstices revealed thrombus formation caused by tumor occluding the HV ostia. A guide wire inserted from a transjugular approach could not penetrate the stent struts, and an ultrasound (US)–guided approach was unsuccessful as a result of poor image quality. Under fluoroscopic guidance, puncture of the LHV with a thrombus, which had retained contrast media, was performed percutaneously (Fig 2b, 2c). After guide wire insertion via transhepatic approach to the RA, balloon angioplasty of the vena cava stents was performed (balloon 80 mm long and 20 mm in diameter). Eventually, three metallic stents (tandem stents 80 mm long and 10 mm in diameter and 60 mm long and 10 mm in diameter [LUMINEXX; C. R. Bard, Covington, Georgia] and another stent 80 mm long and 10 mm in diameter [S.M.A.R.T.; Cordis, Bridgewater, New Jersey]) were placed in the LHV side by side with the IVC stents (Fig 2d). Venography via the femoral vein and the LHV showed good blood flow (Fig 2e, 2f). Postoperative thrombolytic and anticoagulant therapy including low-dose urokinase (240,000 IU/d) and heparin (10,000 IU/d) was administered intravenously for 4 days, and then aspirin therapy was continued. The patient's symptoms were almost relieved by 4 days after treatment, and liver function had improved at 18 days after stent placement (Table). The patient subsequently underwent radiation therapy for the tumor thrombus in the IVC and RA. US examination 3 and 18 days after the procedure demonstrated LHV and IVC stent patency.

After radiation therapy, the patient again underwent hepatic arterial infusion chemotherapy and systemic chemotherapy. Follow-up enhanced CT demonstrated vena cava stent patency (Fig 3). There was no recurrence of IVC syndrome and congestive hepatic failure until the patient's death as a result of underlying disease 19.5 months after the procedure.

DISCUSSION

Malignant caval obstruction is traditionally treated with radiation therapy and, in selected patients, chemotherapy or surgery (4,8). However, symptomatic relief is often delayed, and the initial edema induced by radiation therapy

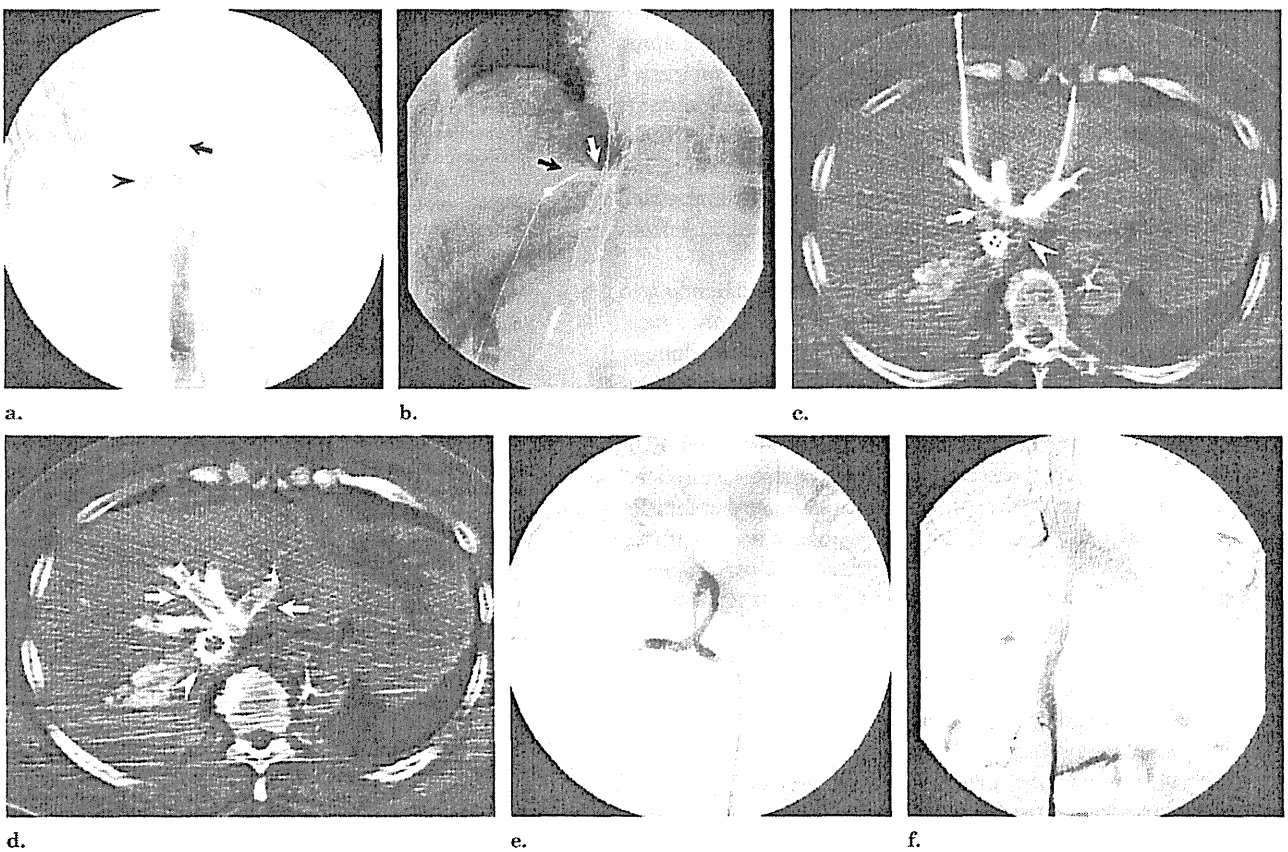


Figure 2. **(a)** Venography shows complete obstruction of the hepatic segment of the IVC (arrow). Catheter and coils for hepatic arterial infusion chemotherapy (arrowhead) are shown. **(b)** Puncture of the LHV under fluoroscopic guidance was performed successfully in the presence of retained contrast medium (black arrow) with a thrombus (white arrow). **(c)** HV ostia are occluded by tumor thrombus (arrowhead), and there is thrombus in the LHV (arrow). **(d)** Metallic stents are placed in the LHV (arrows) side by side with the IVC stents (arrowhead). **(e, f)** Venography via femoral vein and LHV shows good blood flow.

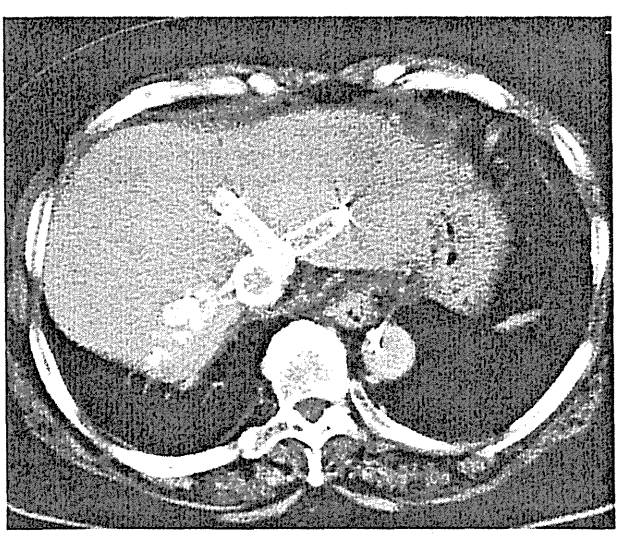


Figure 3. Enhanced CT image 4 months after the procedure demonstrates vena cava stent patency.

exacerbates the presenting symptoms before a beneficial effect is obtained. Surgical management is associated with significant morbidity, and many of these patients are poor operative candidates because of their limited life expectancy (1).

In some reports, malignant caval obstruction has been treated with stent placement, and symptomatic relief is obtained in 78%–100% of patients (3–6,9–12). This procedure has been used widely because of the rapid and sustained relief of symptoms (1).

However, in cases with intraluminal tumor invasion, the clinical symptomatic improvement rate is lower than in cases with extrinsic compression (12). This is because tumor ingrowth causes recurrent occlusion of the stent-implanted portion, and a lack of vascular endothelial cells encourages thrombophilia at the site of the intraluminal tumor invasion. Several approaches for the prevention of in-stent restenosis from tumor ingrowth have been attempted, including the use of smaller gaps between stent struts and covered stents (13).

According to previous reports, there have been complications when stents were placed in the venous system, including fever, pain, acute thrombosis, stent migration, bleeding caused by anticoagulant therapy, and septic shock (3–6,9–11). Charnsangavej et al (14) reported intracardiac stent migration as a complication of venous stent place-