WHAT WOULD YOU DO?

Portal Vein Tumor Thrombus in the Presence of Locally Advanced Hepatocellular Carcinoma

MODERATOR: SARAH B. WHITE, MD, MS, FSIR

PANEL: RICARDO GARCIA-MONACO, MD, PhD, FSIR; BORIS GUIU, MD, PhD; AND YASUAKI ARAI, MD, FSIR, FCIRSE

CASE PRESENTATION

A 68-year-old man presents with alcohol cirrhosis (Child-Pugh score, A5; ECOG [Eastern Cooperative Oncology Group] performance status, 0–1). His total bilirubin level is 0.7 mg/dL, and his alpha-fetoprotein level is 43.5 ng/mL. CT scans show an 8.3- X 12.1-cm hepatocellular carcinoma (HCC) with invasion into the right portal vein (Figure 1). The patient is classified as Barcelona Clinic Liver Cancer (BCLC) stage C.

How would you manage this patient?

Dr. Garcia-Monaco: The patient has locally advanced disease for which surgical resection is not an option, mainly because of tumor burden and venous invasion. Other possible treatments are transarterial chemoembolization (TACE), yttrium-90 (Y-90) radioembolization, or systemic therapy. I would definitely proceed with Y-90 radioembolization as the treatment of choice in this patient because of its proven advantages

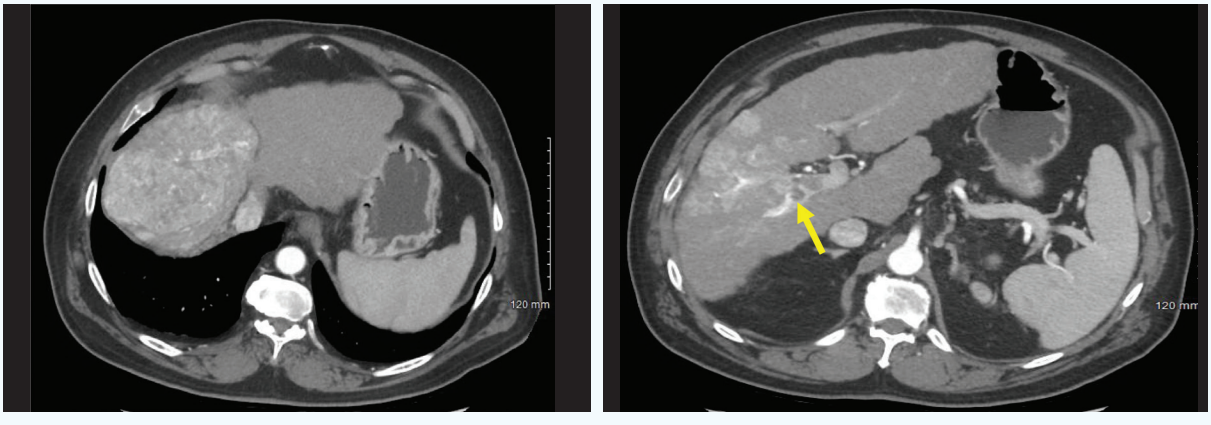

Figure 1. Initial presentation. Contrast-enhanced axial CT scans in the arterial phase at the level of the liver demonstrate a large HCC with portal vein invasion (yellow arrow). Arterioportal shunting is expected given the high attenuation of the contrast in the portal vein.

over TACE in large HCC tumors, the ability to be performed as an outpatient procedure (maybe with just one treatment session), and demonstration of better quality of life (QOL) at follow-up compared to TACE. Although systemic treatment with sorafenib is endorsed by BCLC classification recommendations, I would not recommend it in this case because of its toxicity and the absence of visible extrahepatic metastasis, despite venous invasion. In addition, the recent SARAH randomized controlled trial showed that Y-90 radioembolization provides better QOL as compared with sorafenib.[1]

Prof. Guiu: According to the BCLC treatment algorithm, BCLC C patients should be treated with sorafenib. The other treatment option, although not endorsed by BCLC recommendations, is selective internal radiation therapy (SIRT). Because SIRT is not reimbursed by the health insurance system in France, we would first perform a Tc-99m macroaggregated albumin (MAA) scan to check that complete tumor targeting can be achieved and the optimal Y-90 dose can be delivered to the tumor while preserving nontumoral parenchyma (the left lobe in this case). If both conditions cannot be satisfied, this patient would be treated with sorafenib and tumor response would be reassessed.

Dr. Arai: With regard to portal vein tumor thrombus (PVTT), it is BCLC stage C; however, because there is no extrahepatic lesion, it can be classified as locally advanced HCC. Considering the possibility of this huge HCC causing various symptoms, there is an opportunity to consider effective locoregional interventional radiology (IR) treatment. On the other hand, based on the evidence, sorafenib or lenvatinib is the first choice for this patient, and the response rate of lenvatinib is reported to be > 40%.[2-4] There is no robust evidence that any IR treatment is effective in combination with these molecular targeted agents, and although Y-90 radioembolization may be reasonable, it has not been approved in Japan.

Some data exist on the use of hepatic arterial infusion chemotherapy (HAIC) combined with molecular targeted agents for locally advanced HCC. The SILIUS trial was a randomized controlled trial of sorafenib plus HAIC of cisplatin and fluorouracil, using an implanted port catheter system compared with sorafenib alone. In the subgroup analysis for patients with major PVTT, the combination treatment showed marginally significant prolongation of survival ($P = .05$).[5] In a randomized phase 2 trial of sorafenib plus HAIC of cisplatin compared with sorafenib alone for patients with locally advanced HCC, the combination group also showed significantly prolonged survival.[6] There are some positive reports of conventional TACE (cTACE) for patients with PVTT,[7] and sometimes we can find a reduction in size of PVTT after superselective cTACE in our daily practice; however, the evidence is inadequate.

Therefore, systemic treatment with sorafenib or lenvatinib cannot be denied. If the challenge was allowed, we will try superselective cTACE first; if this is not effective, we will do HAIC combined with a molecular targeted agent.

CASE CONTINUED

Due to portal vein thrombosis (PVT), the decision was made to proceed with Y-90 radioembolization. The patient underwent a Tc-99m MAA shunt study (Figures 2 and 3).

How do you approach patients with large arterioportal shunts (APSs) and large hepatopulmonary shunts (HPSs)?

Prof. Guiu: Very interesting questions, given the absence of clear guidelines. In the context of HCC with tumor thrombosis, APSs can occur through several routes: transvasal (vasa vasorum from a hepatic arterial branch into the lumen of the portal vein), transtumoral, transsinusoidal, or transplexal (ie, through the peribiliary plexus).[8] APSs usually involve small vessels in the absence of previous tumor biopsy and could be responsible for a large APS with direct communication between arterial and portal branches. Consequently, embolization of the APS is often described in the literature, although the type and amount of embolic agent widely vary (eg, calibrated microspheres, drug-eluting beads [DEBs], cTACE, or even glue). In case of a high-flow APS, without information from a previous liver biopsy, I would first inject some droplets of Lipiodol (Guerbet LLC) to explore how fast they circulate (or do not) through the shunt. If direct

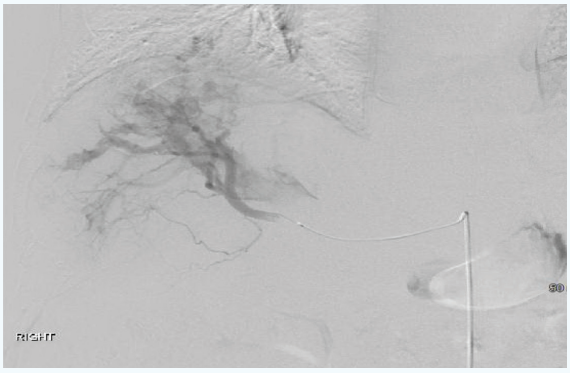

Figure 2. MAA shunt study. Image from a digital subtraction angiogram (DSA) in the arterial phase demonstrating arterioportal shunting and PVTT.

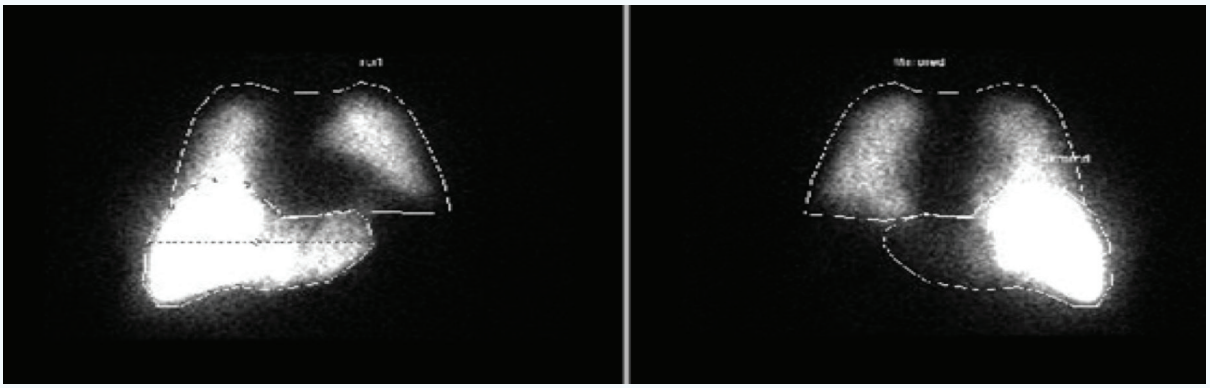

Figure 3. MAA shunt study. Images after infusion of MAA into the right hepatic artery demonstrate a LSF of 19.4%, indicating the existence of a large HPS.

communication between the hepatic artery and the portal vein can be excluded, I would inject 300–500-µm bland beads to occlude the APS.

HPSs also present a very challenging situation, especially in the context of SIRT. SIRT for tumors with high-flow HPSs can result in high radiation exposure to the lungs, placing the patient at high risk of radiation pneumonitis. Additionally, high lung shunt fraction (LSF) has been associated with lower efficacy of SIRT and poor survival.[9,10] HPSs can occur within tumors because of an immature vascular tree and lack of organized capillaries. Again, no clear guidelines exist for the management of large HPSs. To rule out the possibility of direct communication between the artery and hepatic vein (eg, due to an earlier biopsy), Lipiodol droplets can be injected to evaluate the hemodynamics of the HPS. Several techniques have been proposed in the literature, including hepatic vein balloon occlusion, bland embolization, and chemoembolization.[11] Even sorafenib therapy can reduce LSF.[12] I prefer using bland embolization with 300–500-µm microspheres in this context. In case of direct communication between the artery and vein (APS or HPS), coil embolization of the shunt with front- and back-door occlusion is preferred.

Dr. Arai: In this case, the LSF found with the MAA shunt study has no impact on the indication for TACE and HAIC. We should only reexamine the indication for transarterial treatment when a significant major arteriovenous shunt is observed on DSA. When the shunt is simple and accessible, our group will close the shunt with coils or relatively large-sized gelatin particles, then perform TACE. When the shunt is not accessible from the arterial side because of too many fine shunts, we will access the intrahepatic portal vein percutaneously and perform a temporary portal vein occlusion with a balloon catheter and TACE. If this procedure is not suitable for the patient, we will perform HAIC with cisplatin alone or cisplatin and fluorouracil using the port catheter system that was placed. In the case of a severe shunt increasing portal vein pressure, we will access the intrahepatic portal vein percutaneously, perform complete embolization of the portal vein branch receiving arterial flow with coils and glue (Lipiodol and N-butyl cyanoacrylate mixture) under flow control with a balloon catheter, and then perform TACE or HAIC.

Dr. Garcia-Monaco: For large APSs, the best option is to occlude the shunts with coils or glue embolization, but this is not always feasible in clinical practice, as in this case. If the shunt cannot be occluded, transarterial embolization of the tumor component of the shunt is my next step if Y-90 embolization will be performed in the future. Other options include starting with sorafenib for 2 to 3 months and then rechecking on angiography because sorafenib has been shown to decrease the shunting, or after thorough evaluation of the MAA study, determining the safety of performing Y-90 radioembolization despite the APSs.

For large HPSs, based on the manufacturer's recommendation for resin spheres, the Y-90 to be infused should be decreased, but this is only an option if the reduced Y-90 activity would still be tumoricidal. A more reasonable option is to consider the clinical recommendations that the lung absorbed dose should not exceed 30 Gy for any single radioembolization or 50 Gy cumulatively. Thus, a better approach is to estimate the absorbed dose to the lungs in a given patient and proceed if it is in safe limits, despite the shunt. If the estimated absorbed dose is determined to be safe in a patient with normal lung function, radioembolization could be performed.

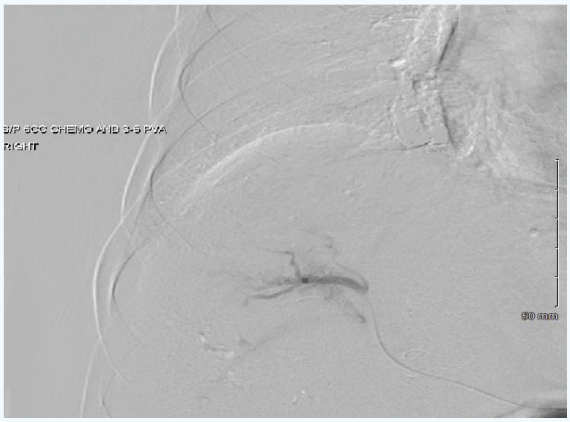

Figure 4. Posttreatment DSA image after completion of cTACE followed by particulate embolization. Note that there is no further visualization of the previously seen large APS.

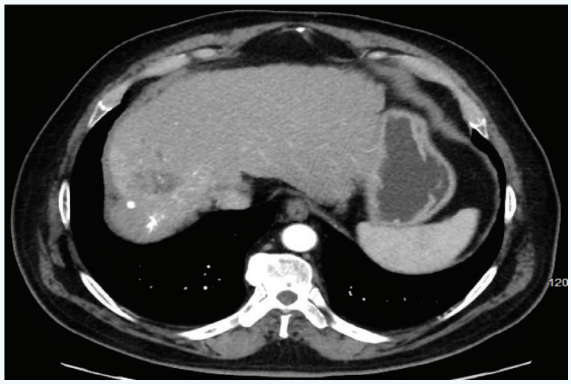

Figure 5. Follow-up axial CT images acquired 6 weeks after the cTACE in the arterial phase demonstrate residual disease at the dome of the liver.

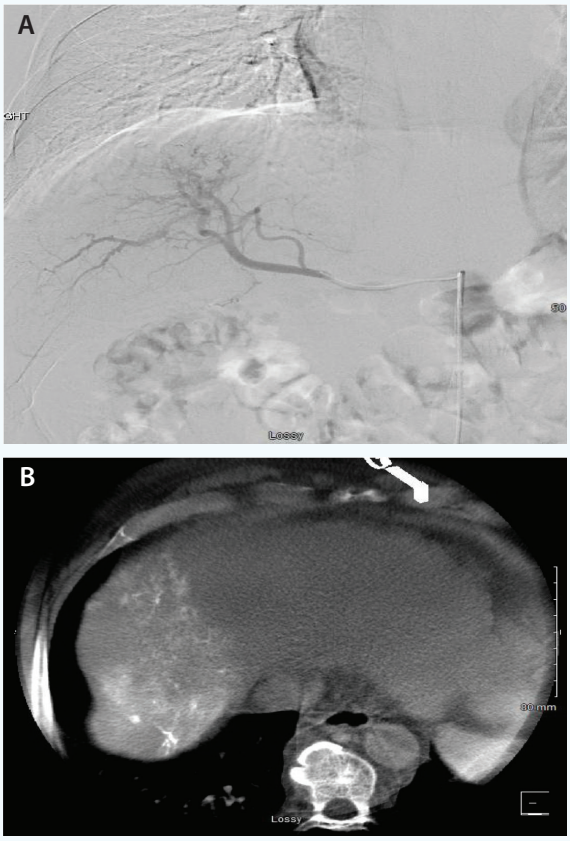

Figure 6. New MAA shunt study. DSA imaging (A) in the arterial phase demonstrating no APS. Cone-beam CT imaging (B) confirms enhancement of residual viable tumor after cTACE 6 weeks earlier.

Although large APSs or HPSs could be managed and would not preclude Y-90 radioembolization in most cases, the operator should balance the risk factors of shunting with the potential benefits of the treatment and sometimes consider other treatment options.

CASE CONTINUED

Treatment with cTACE is initiated (Figure 4) and follow-up CT is performed, which was acquired 6 weeks after the cTACE, and shows residual viable tumor, no further PVT, and no appreciable APS (Figure 5).

What would you do next?

Dr. Arai: If there is a residual viable tumor, we will perform an additional superselective cTACE to achieve a complete response.

Dr. Garcia-Monaco: I would check tumor response with CT or MRI at least 3 months after Y-90 radioembolization. It is sometimes difficult to differentiate residual viable tumor from liver actinic inflammatory changes, which may simulate viable tumor on occasion. If in doubt, assessment of the alpha-fetoprotein level may help. If these tests do not confirm residual tumor viability, I would wait and follow up every 3 months to repeat imaging and retest alpha-fetoprotein levels. Complete tumor response is often noted at follow-up without further treatment.

If residual tumor is still visible after 6 to 9 months, a new Y-90 radioembolization session may be considered, provided that the estimated lung absorbed dose would still be safe. Because the HCC is much smaller than in the patient's initial presentation, another option is to perform cTACE or DEB-TACE to be more cost-effective.

In my opinion, any type of standard intra-arterial locoregional therapy could be indicated in this residual

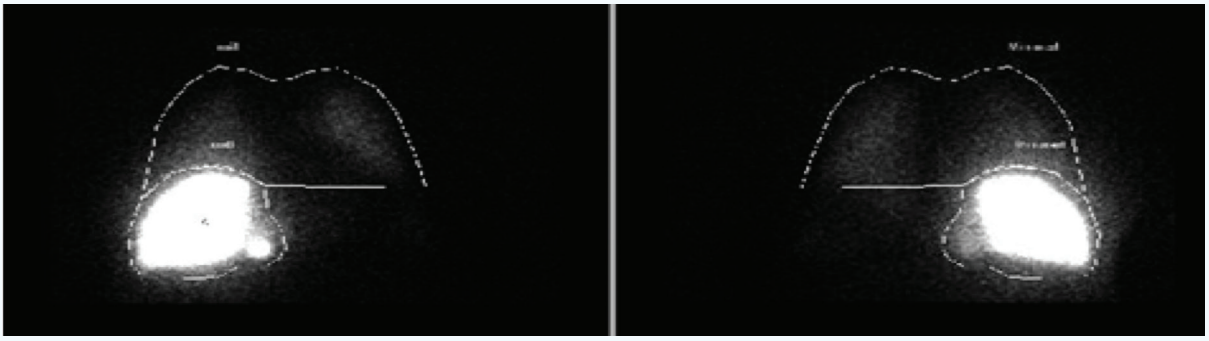

Figure 7. Follow-up Tc-99m MAA shunt study. Images after infusion of MAA into the right hepatic artery demonstrate a LSF of 7.4%, indicating significant improvement in the HPS.

HCC; the choice of which technique to use would depend on individual preferences or local policy.

Prof. Guiu: This patient was treated with TACE and has partially responded based on the follow-up CT. However, overall survival of patients with PVTT treated with TACE, either conventional or with DEBs, does not exceed 5 months.[13] On the contrary, SIRT can provide longer-term survival in such patients.[14,15] Therefore, I would perform a Tc-99m MAA scan to calculate LSF and check for complete tumor targeting with the goal of optimizing Y-90 dose delivery to the tumor (> 205 Gy to the tumor using Y-90 glass microspheres) while sparing the left lobe of the liver.

CASE CONTINUED

A follow-up Tc-99m MAA shunt study is performed. Imaging demonstrates complete resolution of the APS (Figure 6) and a significant decrease in the HPS (Figure 7). The patient then undergoes SIRT with TheraSphere glass microspheres (BTG International) at a dose of 120 mGy to the right hepatic lobe. Follow-up imaging at 3 months demonstrates no residual viable disease. At 2-year follow-up, there continues to be no residual viable tumor, and the patient is listed for transplant. The United Network for Organ Sharing did not grant exception points for HCC, so his model for end-stage liver disease (MELD) score was low, meaning that he likely would not receive a liver transplant.

Therefore, 2 years after the initial diagnosis, the patient is cancer free and he is removed from the transplant list due to a low MELD score and no recurrent cancer (Figure 8).

Do you think this patient should remain on the transplant list? What follow-up would you recommend for this patient?

Prof. Guiu: In France, this patient would not be removed from the list but rather would be noted as having a "temporary contraindication" to transplant given the absence of recurrent cancer and low MELD score. In case of tumor recurrence or cirrhosis decompensation, the temporary contraindication

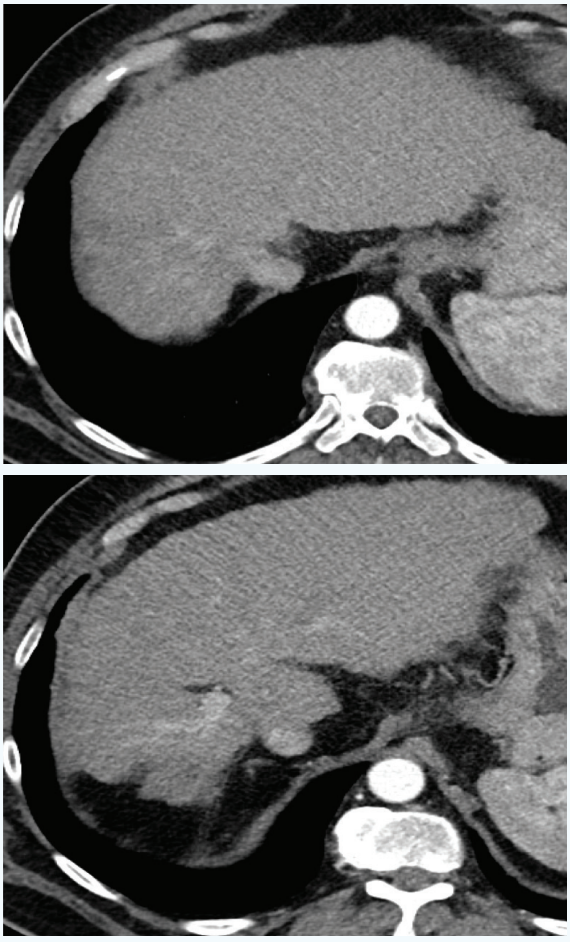

Figure 8. Two-year follow-up imaging indicating no residual viable disease.

can be removed, and the patient takes advantage of the 2-year time frame that he was on temporary contraindication and is moved up on the waiting list for transplant. However, this patient would be 70 years old at that time, and a liver transplant would be difficult unless his general condition were excellent and he had few comorbidities.

Dr. Garcia-Monaco: Now that the patient is 70 years old and cancer free, if his Child-Pugh score is A or worse but he has good liver function, he does not need a liver transplant. I would follow up with clinical evaluation, laboratory testing, and cross-sectional liver imaging every 6 months to rule out HCC recurrence in this oncogenic liver.

Dr. Arai: Based on the patient's clinical course of 2 years, we judge that this lesion has high possibility of cure and would remove him from the transplant list. We would perform follow-up examination of blood chemistry, tumor markers, and contrast-enhanced CT or MRI at 3-month intervals.

SUMMARY

The patient is now 3 years out from the initial cTACE procedure and continues to be cancer free. He continues to undergo screening imaging to assess for new disease. ■

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Sarah B. White, MD, MS, FSIR
Associate Professor of Radiology and Surgical Oncology
Vice Chairman, Radiology Research
Department of Radiology
Division of Vascular & Interventional Radiology
Medical College of Wisconsin
Milwaukee, Wisconsin
sbwhite@mcw.edu
Disclosures: Consultant to Guerbet LLC, Cook Medical, and BTG; research support from Siemens and Guerbet LLC.

Ricardo Garcia-Monaco, MD, PhD, FSIR
Professor and Chairman of Radiology
Head, Section of Vascular and Interventional Radiology
Hospital Italiano de Buenos Aires
Buenos Aires, Argentina
rgmonaco@gmail.com
Disclosures: Consultant to BTG and Boston Scientific Corporation; speaker for Guerbet LLC and Sirtex Medical Inc.

Boris Guiu, MD, PhD
St-Eloi University Hospital
Montpellier, France
b-guiu@chu-montpellier.fr
Disclosures: Speaker for Guerbet LLC, Terumo, Boston Scientific Corporation, and Canon; consultant to Guerbet LLC, Terumo, Boston Scientific Corporation, and BTG.

Yasuaki Arai, MD, FSIR, FCIRSE
Executive Adviser to President
National Cancer Center
Department of Diagnostic Radiology
Interventional Radiology Center
National Cancer Center Hospital
Tokyo, Japan
arai-y3111@mvh.biglobe.ne.jp
Disclosures: Royalties from Sumitomo Bakelite; speaker for Canon Medical, Merit Medical, Terumo International, Sumitomo Bakelite, Boston Scientific Corporation (Japan), Guerbet LLC (Japan), and Guerbet LLC (Asia Pacific).