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REVIEW ARTICLE

Current locoregional therapies and treatment strategies in hepatocellular carcinoma

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ABSTRACT

Locoregional therapies (LRTs) play an important role in the treatment of hepatocellular carcinoma (HCC), with the aim of increasing overall survival while preserving liver function. Various forms of LRT are available, and choosing the best one depends on technical aspects, liver morphology, tumour biology, and the patient's symptoms. The purpose of the present review article is to provide an overview of the current evidence relating to the use of percutaneous ablation, transarterial chemoembolization, and transarterial radioembolization for the curative or palliative treatment of HCC. Special situations are also reviewed, including the combined use of systemic therapy and LRT, indications and techniques for bridging to transplant and downstaging, and the use of LRT to treat patients with HCC and macrovascular invasion.

Key Words Hepatocellular carcinoma, interventional radiology, transarterial radioembolization, chemoembolization, radiofrequency ablation

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INTRODUCTION

Liver cancer is the 2nd leading cause of cancer-related mortality worldwide and therefore a significant health issue[1]. Hepatocellular carcinoma (HCC) accounts for 90% of primary tumours of the liver, with underlying chronic liver disease and cirrhosis secondary to hepatitis B, hepatitis C, alcohol excess, and non-alcoholic steatohepatitis being well-established major risk factors[2,3]. The coexistence of HCC and liver cirrhosis significantly affects mortality, thereby posing a unique clinical challenge: the best treatment strategy has to be based not only on oncologic criteria, but also on liver function. Selecting the most suitable option requires a multidisciplinary approach and taking into account technical aspects, liver morphology, tumour biology, and the patient's symptoms[4].

Locoregional therapies (LRTs) play an important role at all stages of HCC, aiming to increase overall survival (OS) while preserving liver function. The purpose of the present review is to provide an overview of the current evidence relating to the use of LRT strategies for the treatment of HCC.

DISCUSSION

Overview of the Current Recommendations

The Barcelona Clinic Liver Cancer (BCLC) staging system has been the most widely adopted comprehensive assessment tool for guiding therapy in patients with HCC in the Western world. In the decision-making process, the system incorporates extent of tumoural involvement, background liver function, and performance status, highlighting the importance of appropriate patient selection to achieve better disease control, with the primary objective of improving OS before embarking on a specific treatment strategy. The BCLC system has strong supportive data and external validation in various clinical settings in Western countries, and it is endorsed by international societies such as the Canadian Association for the Study of the Liver, the American Association for the Study of Liver Diseases, and the European Association for the Study of the Liver[5–7].

For patients with preserved liver function and a Child–Pugh score (CPS) of A, and who are asymptomatic or have only mild cancer-related symptoms (0 or 1) per the Eastern

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Cooperative Oncology Group (ECOG), several treatment options are available and are directed by disease extent. In patients with a single lesion of 2 cm or smaller (BCLC 0, very early-stage disease), resection or percutaneous thermal ablation are recommended and are considered curative. A wider range of options is available for patients with a single tumour of 2–5 cm or 2–3 lesions each 3 cm or smaller (BCLC A, early-stage disease): resection, liver transplantation, thermal ablation, transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and stereotactic body radiation therapy. The choice is dictated by anatomic considerations and technical parameters. The main approach to patients with unresectable disease restricted to the liver and without vascular invasion, who have preserved liver function and who are clinically asymptomatic (BCLC B, intermediate-stage disease), is TACE. The role of TARE is also being explored in that group, especially as a potential tool for downstaging to transplantation[6].

Within the BCLC system, patients with advanced disease and vascular invasion, and with preserved liver function and an ECOG performance status of 2 or less (BCLC C, advanced-stage disease), would be restricted to systemic therapy only. However, TARE is noninferior to sorafenib and has lower systemic toxicity[8,9]. In patients with end-stage liver disease as indicated by limited liver reserve (CPS C) or those clinically limited by an ECOG performance status of 3 or 4 (BCLC D, terminal stage), best supportive care remains the recommended treatment option[5–7].

Percutaneous Therapy

Ablation

Surgical resection or liver transplantation are the preferred curative treatments in patients classified BCLC 0 or A. However, up to 80% of patients presenting with HCC are not suitable surgical candidates because of poor hepatic reserve, comorbidities, or the multicentricity of lesions[10]. Percutaneous ablation has been shown to be a safe and effective treatment for HCC lesions 3 cm or smaller[11], and that approach has become one of the mainstay treatment options in patients with very early-stage or early-stage disease. Ablative techniques of various types are available, including chemical ablation by percutaneous ethanol injection and thermal techniques such as radiofrequency ablation (RFA) or microwave ablation (MWA). The major advantages of percutaneous ablation are a shorter hospital stay and complication rates lower than are reported with surgery[12].

Percutaneous ethanol injection has been used for decades, and its role is established in treating lesions 2 cm or smaller or in cases in which thermal injury to adjacent structures such as first-order biliary ducts or gas-filled viscera raises concerns. The technique is safe and well tolerated, carries a low cost, and has a high technical success rate. Its complication rate is less than 4%, which is much more favourable than postsurgical complication rates, which have been reported to be as high as 47% in experienced centres[13]. Its main disadvantage is that multiple sessions might be required until complete radiographic ablation is achieved. Over the years, percutaneous ethanol injection has been largely replaced by thermal ablation, with several randomized controlled studies showing that RFA is superior with respect to disease recurrence and OS[14,15].

Radiofrequency ablation has been shown to have a treatment rate and OS comparable to those for liver resection. A technical consideration for RFA is the heat-sink effect, which occurs when the lesion is adjacent to vascular structures, potentially producing a perfusional cool-down and compromising the ablation zone size. Major complication rates range between 2% and 5.7%, with the reported mortality being less than 1%[16]. Complications from RFA include hemorrhage, bile duct injury, liver abscess formation, portal vein thrombosis, and potentially, damage to perihepatic structures such as the diaphragm and bowel[16]. Randomized controlled trials (RCTs) comparing RFA with liver resection have produced conflicting results. A recent meta-analysis suggested that the cause might be heterogeneity of the study populations, small sample sizes, and variation in local surgical approach or expertise[17]. Further RCTs are needed to assess whether RFA is superior to resection or vice versa.

More recently, MWA has been introduced and can be used as an alternative to RFA. Theoretically, compared with RFA, MWA produces larger ablation zones and is less susceptible to the heat-sink effect. In instances in which lesions larger than 3 cm are targeted or the lesion is adjacent to vascular structures larger than 3 mm in diameter, MWA might provide better treatment efficacy[18]. In the available literature, no significant differences in local recurrence, disease progression, or complication rates between MWA and RFA have been demonstrated[10].

Other technologies, such as cryoablation, have been used in the liver, but warrant further investigation. Cryotherapy is associated with the potentially life-threatening complication of cryoshock syndrome, which has deterred operators. It includes disseminated intravascular coagulation, renal failure, and acute respiratory distress syndrome[19].

Transarterial Therapies

TACE

Transarterial chemoembolization promotes tumoural ischemic necrosis by simultaneously delivering a cytotoxic chemotherapeutic agent (most commonly doxorubicin)[20] and blocking the tumour's arterial supply. Key RCTs published in 2002 showed that, compared with best supportive care, TACE significantly increased survival in patients with HCC[21,22]. Llovet *et al.*[21] demonstrated a 10-month increase in OS for patients undergoing TACE (28.6 months vs. 17.9 months, $p = 0.009$), and Lo *et al.*[22] found significantly higher interval survival rates (1-year: 57% vs. 32%; 2-year: 31% vs. 11%; 3-year: 26% vs. 3%; $p = 0.002$). In modern series with better patient selection and superselective embolization technique, a median survival of 40–50 months can be achieved in patients with CPS A disease who are asymptomatic (ECOG 0) with respect to their cancer[23–25]. Those studies support the endorsement, by several international hepatology societies, of TACE as a first-line palliative therapy in patients with intermediate-stage HCC (BCLC B)[5–7].

Two techniques for performing TACE have been described and are well established. Conventional TACE (cTACE) involves the injection of an ethiodized oil emulsion

(Lipiodol: Guerbet, Princeton, NJ, U.S.A.) with the chemotherapeutic agent. The resulting semifluid cytotoxic embolic is retained within the tumour sinusoids and also blocks the peritumoural portal vein branches[26,27]. The feeding arteries are then embolized with particles, amplifying the ischemic effect to the tumour. In the early 2000s, drug-eluting beads (DEBs) were developed with the purpose of promoting the slow release of a chemotherapeutic to the tumour over the course of weeks, while also acting as a definitive embolic agent, thus theoretically increasing the duration and intensity of ischemia, but with fewer systemic side effects[28].

There is no evidence that one TACE technique is superior to another in terms of survival, objective tumour response, or 30-day adverse events (AEs)[29]. Use of DEB-TACE might be associated with a lower incidence of post-embolization syndrome[30] and fewer doxorubicin-related side effects such as alopecia and deterioration in left ventricular ejection fraction[31]. Use of cTACE appears to cause less biliary injury, intrahepatic biloma formation, and liver infarct[32,33], with patients who are non-cirrhotic being at higher risk of developing those complications when undergoing DEB-TACE[33]. The DEB-TACE technique might provide easier technical standardization and facilitate use during clinical trials, although efforts have been made to standardize the use of cTACE[34]. Ultimately, choosing between cTACE and DEB-TACE is based on operator and institutional preferences.

It is still debatable whether TACE should be performed at fixed intervals or "on demand" based on partial response or local recurrence after previous embolization[35]. Clinical scores have been trialled in an attempt to identify the best candidate to receive first TACE (STATE[36], HAP[37]) and to help decide when TACE should be repeated (ART[38], ABCR[39]). However, such predictive scores have produced conflicting results in the literature, and none are currently indicated for decision-making in clinical practice[40]. However, what has been better established is that, when TACE becomes futile, it should not be repeated. Specifically, if significant tumoural necrosis is not achieved after 2 TACE sessions (or if tumour progression in the same area persists despite TACE treatment), or if major disease progression has occurred (including extensive bilobar liver involvement, extrahepatic metastasis, or vascular invasion), TACE should not be repeated because of the lack of clinical benefit and the risk of liver function deterioration[41].

Absolute contraindications for TACE include severely impaired main portal vein flow (resulting from occlusive thrombus, tumoural invasion, or hepatofugal blood flow) because of dependence on the arterial inflow to adequately supply the liver[42]; extensive tumour burden involving almost the entirety of both lobes of the liver, given the lack of a clear survival benefit for this subgroup of patients[41]; decompensated liver function, including CPS 9 or greater, jaundice, clinical hepatic encephalopathy, refractory ascites, or hepatorenal syndrome, because of the high risk of liver failure developing after embolization[43]; and renal insufficiency (creatinine ≥2 mg/dL or creatinine clearance ≤30 mL/min)[44]. Clinical situations that require special attention because of the increased risk of complications after TACE (which could be considered relative contraindications) include untreated esophageal varices at high risk of bleeding[44] or biliary obstruction with total bilirubin 3 mg/dL or greater[45]. Additionally, patients with a biliary–enteric anastomosis or biliary stent crossing the ampulla have a 25% risk per procedure of developing liver abscesses[34]. Starting prophylactic antibiotic therapy with moxifloxacin 400 mg 3 days before TACE and continuing it for 17 days after the procedure might prevent the development of that adverse event[46].

Possible complications of the procedure include post-embolization syndrome (abdominal pain, nausea, and fever) requiring extended hospital stay or readmission in up to 10% of patients[45], liver failure in 3%–5%[45], liver infarction in less than 1%[45], contrast-induced nephropathy or acute renal failure in 3%–10%[45], and a TACE-related 30-day mortality of less than 1%[47].

TARE

Transarterial radioembolization using ^{90}Y as the therapeutic radioisotope (aka TARE-Y90, selective internal radiotherapy, or radioembolization) is a hepatic arterial therapy that exploits the exclusive recruitment by HCC of hepatic arterial angiogenesis to deliver a carrier-based payload of radioactivity directly into the tumour. Sustained beta particle emission results in tumour necrosis as a result of free oxygen radical generation and subsequent irreparable DNA damage, similar in principle to brachytherapy. Currently, glass ^{90}Y microspheres (TheraSphere: Boston Scientific, Nantucket, MA, U.S.A.) and resin ^{90}Y microspheres (SIR-Spheres: Sirtex Medical, Boston, MA, U.S.A.) are approved by Health Canada for clinical use. Outlining the technical differences between the two products falls outside of the scope of this article; those differences have been reported elsewhere[48].

Because of the small size of the radioactive microspheres (30–70 μm), they are able to penetrate into the tumour vasculature with minimal embolic and hypoxic effects, representing a mechanism of action different from that of TACE. In patients with unresectable HCC, time to progression from treatment has been significantly longer with TARE than with TACE (26 months vs. 6.8 months, $p = 0.007$), but with similar median survival duration censored to liver transplantation (18.6 months for TARE vs. 17.7 months for TACE, $p = 0.99$)[49]. Overall, TARE is better tolerated than TACE, with less pain[50] and toxicity after treatment, which, in a prospective comparative study, translated into improved quality of life after TARE[51].

If ablative doses are delivered, TARE can also be used with curative intent. For instance, radiation segmentectomy can be applied in selected lesions for which resection or ablation would be classically indicated but is not possible because of patient comorbidity or anatomic localization[52,53]. Also, for disease localized in one lobe, radiation lobectomy can be used, with the additional benefit of hypertrophy of the contralateral liver (Figure 1)[53–58].

Three major phase III RCTs comparing resin-based TARE with sorafenib in locally advanced HCC have failed to demonstrate statistical superiority with respect to OS and PFS[8]. However, the TARE group experienced better tumour response, improved quality of life, and decreased toxicity[9]. Also, despite the perceived failure of the foregoing trials, a subsequent *post hoc* analysis demonstrated that median

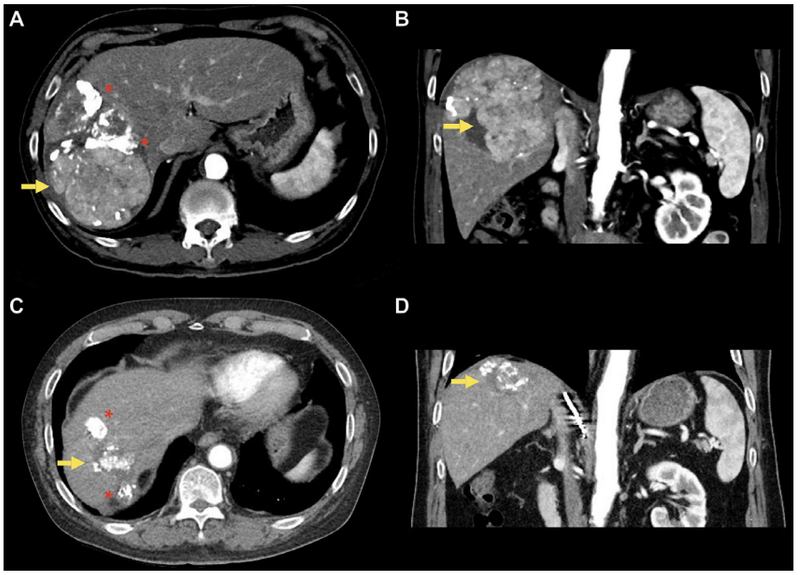

FIGURE 1 (A,B) A large hepatocellular carcinoma centred in the right lobe of the liver (arrow), with ethiodized oil staining after conventional transarterial chemoembolization (asterisk), was treated with transarterial radioembolization using lobectomy radiation dosimetry. (C,D) After 16 months of treatment, a significant reduction in the size of the tumour is evident (arrow), with capsular retraction and atrophy of the superior segments of the right lobe of the liver.

survival was longer for participants who received a radiation dose to the tumour greater than 100 Gy than for those who received 100 Gy or less (14.1 months vs. 6.1 months, $p < 0.001$)[59]. This model of radioactivity administration was further validated using glass microspheres at a higher radioactive dose range[60], thereby substantiating the clinical applicability of the TARE class of therapy and further investigation into radiation dose optimization through more advanced mathematical modelling.

Special Situations

Combined Systemic Therapy and LRT

A growing interest in the incorporation of systemic therapy both in synergy with, and in sequence to, LRT strategies has developed in the recent literature. In a phase III randomized double-blind placebo-controlled trial (STORM), the use of sorafenib has been investigated as adjunct therapy in patients with a complete radiologic response after HCC resection or ablation[61]. The sorafenib and placebo groups showed no difference in median recurrence-free survival (33.3 months vs. 33.7 months, $p = 0.26$), with more grade 3 or 4 drug-related AEs noted in patients who received sorafenib (52% vs. 10%). The authors therefore concluded that sorafenib is not an effective intervention in the adjuvant setting for HCC after resection or ablation.

In a phase II randomized double-blind placebo-controlled study (SPACE), combining sorafenib with TACE in patients with intermediate-stage HCC did not provide a meaningful clinical benefit[62]. Compared with patients receiving TACE alone, those receiving the combined therapy had a similar median time to progression (169 days vs. 166 days, $p = 0.072$). However, in a recently published randomized open-label multicentre trial (TACTICS), in which participants received sorafenib for a longer time than did participants in the SPACE trial, prolonged PFS was achieved in the combined-therapy group (25.2 months vs. 13.5 months, $p = 0.006$)[63].

The combination of sorafenib and resin TARE has also been investigated. A phase II randomized open-label multicentre trial (SORAMIC) comparing the combined therapy with TARE alone found no difference in OS in the intention-to-treat population (12.1 months vs. 11.4 months; $p = 0.953$), but with more grade 3 or 4 AEs in the TARE–sorafenib arm (64.8% vs. 53.3%, $p = 0.036$)[64]. However, a subgroup analysis identified improved survival with the combined therapy in patients 65 years of age and younger (hazard ratio: 0.65; 95% confidence interval: 0.43 to 1.00; $p = 0.046$), in patients who were non-cirrhotic (hazard ratio: 0.46; 95% confidence interval: 0.25 to 0.86; $p = 0.013$), and in patients with HCC not related to alcoholic liver disease (hazard ratio: 0.63; 95% confidence interval: 0.45 to 0.89; $p = 0.009$).

The earlier introduction of systemic therapy into the HCC paradigm might warrant consideration because of the increasing efficacy of newer drugs with respect to OS, time to progression, response rate, and decreased toxicities, as demonstrated with lenvatinib in the REFLECT trial[65]. In a proof-of-concept study comparing lenvatinib with TACE in patients with intermediate-stage HCC scored CPS A and above the up-to-seven criteria, a subanalysis identified patients who were referred for TACE after having to interrupt lenvatinib[66]. A high objective response rate (ORR—complete response or partial response) was noted in 62.5% of those patients, believed to be secondary to the prior use of lenvatinib, resulting in a smaller tumour burden to be treated with TACE. The significant radiographic response with combined

therapy might allow for interval deintensification of LRT and consequently the preservation of liver function.

Systemic therapy might also be used to decrease the pulmonary shunt fraction in patients initially not deemed candidates for TARE[67–69], to permit disease downstaging, to offer curative options to patients who were once palliative[65,70], and to act as a challenge to tumoural physiology and morphology in rapidly progressing disease. Lack of response to systemic therapy would indicate poor tumour biology and the futility of pursuing further LRT, with the exposure of the patient to an unnecessary risk of liver function deterioration.

Case reports have described abscopal effects resulting from the presumed activation of an off-target immunologic response through the combined use of TARE and immunologic agents[71]. The potential synergistic effects of cancer-antigen presentation during LRT and activation of the immune response through immunologic agents have been established[72–74], with phase I and II trials currently being underway. However, the earlier use of immunooncology agents in patients who might become eligible for transplantation is highly controversial, given the theoretically increased risk arising from the immunologic activation of therapy that could have implications for post-transplant rejection.

Bridging and Downstaging

The purpose of liver transplantation in HCC is to increase survival and improve quality of life. Because the waiting time for liver transplantation is frequently longer than 6 months, using LRT to prevent disease progression and transplant list drop-out in patients who are within the Milan criteria is a useful bridging strategy[75]. Patients receiving LRT have a lower risk of dropping out because of tumour progression (2.6% vs. 8.2%, $p = 0.01$) and longer OS after liver transplantation (74.6 months vs. 63.6 months, $p = 0.03$)[76].

In patients who are outside the Milan criteria, LRT might be able to decrease the tumour burden, making more patients eligible for liver transplantation. Downstaging can be successfully achieved in 65.3%–83.4% of patients if strict selection criteria are followed[77,78]. Specifically, the ideal candidate should be scored CPS A, have an alpha-fetoprotein level of 1000 ng/mL or less, and have a maximal tumour diameter sum of 8 cm or less (single lesion ≤8 cm; 2–3 lesions each ≤5 cm and ≤8 cm in sum; 4–5 lesions each ≤3 cm and ≤8 cm in sum)[77,78]. Approximately 50% of patients will require 3 or more sessions of LRT to be adequately downstaged[78], and after successful tumour size reduction and significant tumour necrosis has been achieved, a minimum of 3 months of follow-up should be completed to ensure disease stability before enlistment for transplantation[77–79]. The 5-year survival of patients who are successfully downstaged and undergo liver transplantation is estimated at 77.8%–79.7%, similar to the rate for patients who were always within the Milan criteria and who subsequently underwent transplantation[77,78]—likely because LRT selects for patients with more favourable tumour biology, which is supported by the findings of more differentiated HCC histology and less microvascular invasion on the explants of patients who were successfully downstaged compared with patients who were always within the Milan criteria and did not receive prior LRT[77].

No specific LRT technique has proved to be superior for bridging or downstaging with respect to recurrence-free survival, drop-out from transplantation, and OS[80]. Nonetheless, a comparative study showed that TARE was able to downstage more patients than TACE (58% vs. 31%, $p = 0.023$), with an associated longer time to progression (33.3 months vs. 18.2 months, $p = 0.098$) and longer OS censored to transplantation or resection (35.7 months vs. 18.7 months, $p = 0.18$)[81]. Those findings might be even more pronounced if ablative radiation segmentectomy or lobectomy is performed; however, comparative prospective trials are pending.

Macrovascular Invasion

Locoregional therapies are not formally recommended by clinical guidelines, and systemic therapy is considered the mainstay treatment for patients with advanced HCC, relatively preserved liver function, and an adequate performance status[5–7,82]. In the last several years, there have been significant advances in the options for systemic therapy, including newer molecular targeted agents and immunotherapy[65,83–86]. However, survival remains limited, and there are consequences with therapy that might affect quality of life because of toxicity or rising costs. A continuous effort has therefore been underway to find other treatment options and combinations that will increase survival in patients with advanced disease.

Patients with liver-confined disease, preserved liver function, and subsegmental or segmental portal vein tumour thrombosis (PVTT) might safely benefit from superselective TACE, which, compared with conservative therapy, has been associated with significantly better survival (10.2 months vs. 5.1 months, $p < 0.001$)[87] and, compared with sorafenib, similar survival (14 months vs. 9.7 months, $p = 0.449$)[88]. Nevertheless, those advantages have not been clearly demonstrated for patients with main portal vein invasion, and transarterial embolization in that subset of patients might put them at risk of liver failure.

Because TARE relies on radiation to promote coagulative necrosis of the tumour, theoretically without promoting arterial embolic effect, TARE should be better tolerated than TACE in the setting of PVTT[50]. An OS of 16.2 months has been reported for patients scored CPS A with segmental or subsegmental PVTT; the OS significantly decreases to 5.6–7.7 months for patients scored CPS B or if there is tumour invasion of the main portal vein[89]. The dosimetric technique used for TARE also affects OS. Compared with conventional dosimetry, radiation segmentectomy or lobectomy in patients with preserved liver function and PVTT can achieve significantly longer survival (19.1 months vs. 4.9 months, $p = 0.005$) without significantly increasing liver toxicity[90].

SUMMARY

Although the BCLC staging system guides the most appropriate LRT based on tumour biology, target organ biology, and tumour morphologic characteristics, the real-world decision-making process can be complex. The development of new LRT techniques such as ablative TARE and the encouraging results of sequencing or harmonizing systemic therapy with LRT open new fronts of therapy that have evolved

beyond BCLC recommendations. The multidisciplinary board review therefore becomes of upmost importance in deciding the best treatment strategy for patients with HCC.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: HJL has received fees as an advisory board member for Eisai, Taiho, Merck, Bristol Myers Squibb, Roche, and Ipsen. AM has received speaker fees from Boston Scientific, Terumo Medical, Teleflex, and Medtronic, and fees as an advisory board member for Boston Scientific. DML has received speaker fees from Eisai Pharmaceuticals, Ethicon Endocare/Neuwave; fees as an advisory board member for Merit Medical Systems; and research funding from Boston Scientific for a trial in which he was co-investigator. The remaining authors have no conflicts to disclose.

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