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INTERVENTIONAL RADIOLOGY

ORIGINAL ARTICLE

Definitive locoregional therapy (LRT) versus bridging LRT and liver transplantation with wait-and-not-treat approach for very early stage hepatocellular carcinoma

Peiman Habibollahi
Stephen Hunt
Therese Bitterman
Terence P. Gade
Michael C. Soulen
Gregory Nadolski

PURPOSE
Since the change in the United Network for Organ Sharing (UNOS) policy excluding patients with very early stage hepatocellular carcinoma (veHCC, single tumor nodule <2 cm) from receiving Model for End-stage Liver Disease (MELD) exception points, patients eligible to receive liver transplantation (LT) who fall in this category are commonly treated with locoregional therapy (LRT) after progression to UNOS T2 stage (1 nodule of 2–5 cm or up to 3 nodules, none above 3 cm). The aim of the current study is to compare the outcomes of patients treated with bridging LRT and LT with wait-and-not-treat approach with patients treated with definitive LRT.

METHODS
A retrospective study has been performed on patients with veHCC evaluated in multidisciplinary liver tumor clinic of a large academic center between 2004–2011. Patients eligible for LT were assigned to the wait-and-not-treat group while patients who were not eligible were assigned to the definitive LRT group. Tumor size, time to treatment, severity of liver disease, recurrence and survival from time of detection were reviewed and recorded.

RESULTS
A total of 19 patients were identified and treated with definitive LRT while 57 patients were treated with bridging LRT prior to LT after disease progression to T2 stage. Patients in the definitive LRT group were older (70.4±10.2 years vs. 58.7±5.9 years, $P < 0.001$) and had more comorbid conditions compared with the wait-and-not-treat group. Mean survival for definitive LRT group at the end of 5 years was 34.3±6.0 months with a median of 30.3 months (95% CI, 5.7–55.0 months) compared with 48.7±2.6 months for the wait-and-not-treat group, respectively (median not reached). The 3- and 5-year survival rates were 53.3% and 33.3% for the definitive LRT group compared with 78.9% and 68.4% for the patients in the wait-and-not-treat group. Survival rate at the end of 5 years was significantly better for the wait-and-not-treat group ($P = 0.013$).

CONCLUSION
Based on the findings of current retrospective study, treating veHCC (UNOS T1 stage) patients listed for LT with bridging LRT after disease progression to T2 stage appears to be safe and effective with high 5-year survival rates.

Hepatocellular carcinoma (HCC) is associated with poor prognosis with a median survival of 6 to 20 months from the time of diagnosis (1, 2). In the past decades, HCC incidence and mortality have risen in the United States similar to many other parts of the world (3, 4). Currently, the standard treatment for patients with unresectable HCC tumor within Milan criteria is liver transplantation (LT), which allows successful treatment of both HCC and the underlying liver dysfunction with very low cancer recurrence rates (5–7). Previous studies have shown that prognosis after LT is excellent with 5-year survival rates of about 70% (8, 9). However, the limited numbers of available organs and growing number of patients on LT waitlist has led to longer waiting periods, which can result in disease progression, increasing the risk of waitlist drop-out (10).

Model for end-stage liver disease (MELD) score has been used since February 2002 for organ allocation to patients on liver transplant waitlist (11) which accurately predicts patients' short-term survival while on the waitlist (12, 13). Since implementation of this policy by the United Network for Organ Sharing (UNOS), MELD exception points were assigned to HCC pa-

From PIGI Laboratory (P.H., S.H., T.P.G., G.N. ✉ *Gregory.Nadolski@uphs.upenn.edu*) University of Pennsylvania, Philadelphia, PA, USA; Departments of Radiology (P.H., S.H., T.P.G., M.C.S., G.N.) and Hepatology and Gastroenterology (T.B.), Hospital of the University of Pennsylvania, Philadelphia, PA, USA.

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tients to allow additional waitlist priority due to added risk of HCC progression beyond UNOS T2 stage (1 nodule of 2–5 cm or up to 3 nodules, none above 3 cm), which would preclude LT (14). There have been several refinements to the original policy and since March 2005, these exception points are only given to patients with T2 stage disease (11).

The effectiveness of locoregional therapy (LRT) in preventing drop-out from waitlist has been documented (15, 16). Prior to excluding UNOS T1 stage patients (1 tumor nodule <2 cm) from receiving MELD exception points, it was reasonable to immediately offer LRT to patients with UNOS T1 stage HCC to maximize time from diagnosis to tumor progression and reduce the risk of waitlist drop-out. After this major policy change, an alternate approach was taken in which most T1 stage HCC patients who were candidates for LT were closely monitored until disease progression to T2 stage in order to receive the MELD exception points, thereby postponing bridging LRT until this point. At the same time, definitive LRT continued to be offered to patients who were not deemed appropriate LT candidates. Prior studies have compared the outcomes of patients with very early stage HCC using either bridging or definitive radiofrequency ablation (RFA) (17–20). We have performed a retrospective study comparing the outcomes of T1 stage HCC patients receiving bridging LRT (RFA or transcatheter arterial chemoembolization [TACE]) with LT after progression to T2 stage with immediate definitive LRT in HCC patients who were not LT candidates.

Methods

A retrospective study was designed and executed at a tertiary referral university hospital. Institutional Review Board approval was obtained (IRB approval number: 827908), which also waived the need for obtaining informed consent given the retrospective nature of the study. Electronic medical records as well as institutional interventional radiology procedure database (HI-IQ, Conexys) and institutional transplant listing database were used for a comprehensive search to identify all patients diagnosed with and treated for very early stage HCC (veHCC, single HCC nodule <2 cm) between March 2004 and December 2011. This particular start date was chosen due to change in the UNOS policy not to assign MELD exception points to HCC patients with UNOS T1 stage HCC (17). The American Association of Liver Disease (AASLD) guidelines were used to make the HCC diagnosis on the imaging studies and/or liver biopsy (21).

Upon identification of UNOS T1 HCC nodules, all patients were prospectively reviewed and evaluated at the center's multidisciplinary HCC tumor board for treatment planning. Patients who were potentially eligible to be listed for LT, were followed clinically with interval imaging every 3 months until the tumors were beyond UNOS T1 stage in order to receive MELD exception points and subsequently were treated with bridging LRT (TACE or RFA) if expected to remain on waitlist for longer than another 6 months. Patients who were not eligible for receiving LT secondary to advanced age or comorbidities were treated with definitive TACE or RFA. Available records were carefully reviewed for patient, tumor, and treatment characteristics, as well as patient survival and possible cause of death. Biochemical and clinical data at time of listing were used to calculate the MELD and Child-Pugh score (CPS) at the time of listing. As an index of disease severity and liver function, total bilirubin was also recorded. Patients with inadequate follow-up from initial diagnosis and treatment were excluded from the study.

All available imaging was reviewed and tumor characteristics were recorded including the number and size in accordance with mRECIST and AASLD criteria (21, 22). Types of LRT received by the patients were also identified and recorded through retrospective review of the available institutional medical and interventional radiology databases.

All LRT procedures were carried out by the standard methods used at our center after obtaining informed consent for the procedure and preprocedural evaluation. Briefly, TACE was performed by selective infusion of emulsified chemotherapy agent (50 mg of doxorubicin; Adriamycin, Pharmacia-Upjohn) and ethiodized oil (Lipiodol, Guerbet Laboratories) into the tumor followed by selective hepatic artery embolization with either 100–300 micron Embospheres (Merit Medical Systems, Inc.) or equal sized polyvinyl alcohol particles (Contour PVA, Boston Scientific). Boston Scientific standard commercially available RFA probes and system were used for the RFA procedures.

Statistical analysis

Patient survival at 3 and 5 years from the time of HCC diagnosis were used as the primary end-points of the study. SPSS software (V.20, IBM Corp.) was used to perform the statistical analysis. *P* values less than 0.05 were considered statistically significant. Categorical and continuous variables were compared using chi-square and student t-test, respectively. Fisher's exact test was used for the analysis of categorical variable when the expected cell count was less than 5. Kaplan-Meier curve was used for survival analysis. All quantitative values are presented as mean±standard deviation.

Main points

- Observing UNOS T1 stage HCC patients without LRT until disease progression to T2 stage and receiving MELD exception points (wait-and-not-treat strategy) is safe without increasing the risk of delisting.
- Patients with UNOS T1 stage HCC managed with wait-and-not-treat strategy have acceptable long-term survival rates following combination of bridging LRT and liver transplantation when they progress into T2 stage.
- UNOS T1 stage HCC patients treated with curative intent LRT without liver transplantation have significantly lower survival rates compared with the patients treated with wait-and-not-treat approach followed by LRT and LT at T2 stage.

Results

Overall 81 patients were identified as meeting the inclusion criteria during the predefined study period (March 2004 to December 2011). Patients who were not eligible for LT were assigned to the definite LRT group and patients eligible for LT wait listing were assigned to the wait-and-not-treat group. Patients in the wait-and-not-treat group underwent active surveillance until the tumors were beyond T1 stage and received bridging LRT after receiving MELD exception points if they were expected to be on waitlist for more than 6 months. Overall, 19 patients were assigned to definitive LRT and 62 patients to wait-and-not-treat group. Five patients were excluded in the wait-and-not-treat group due to lack of sufficient clinical data and follow up. Patient characteristics are listed in Table 1. Patients in the definitive LRT group were older compared to patients in the wait-and-not-treat group (70.4±10.2 years vs. 58.7±5.9 years, $P < 0.001$). The most common primary cause for cirrhosis and HCC in the study population was Hepatitis C in both groups (63.2% in definitive LRT group versus 77.2% in the wait-and-not-treat group). MELD score and alpha-fetoprotein levels were similar in both groups while the patients in definitive

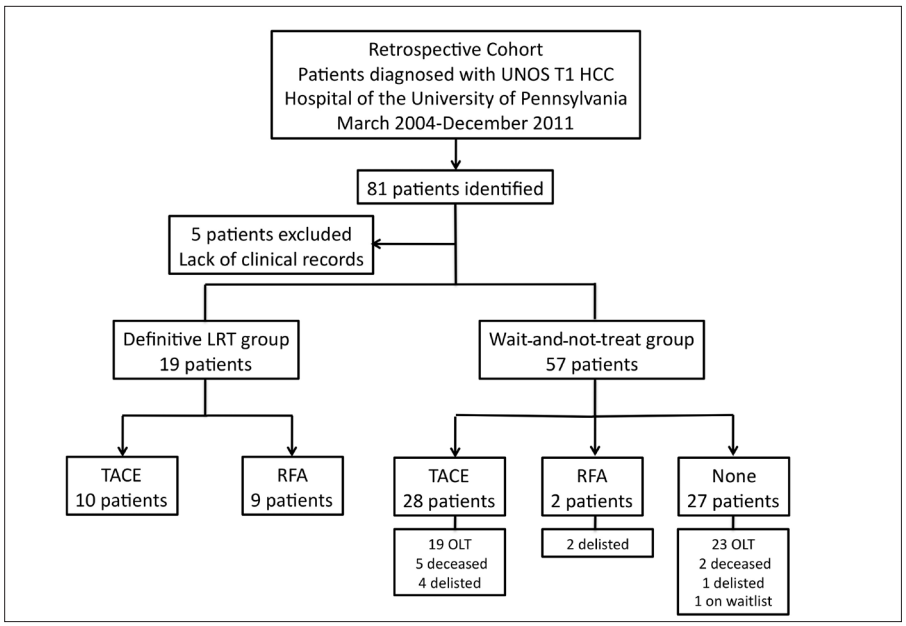

Figure 1. Flowchart of the study population. UNOS, United Network for Organ Sharing; HCC, hepatocellular carcinoma; LRT, locoregional therapy; TACE, transcatheter arterial chemoembolization; RFA, radiofrequency ablation; OLT, orthotopic liver transplantation

Table 1. Patient characteristics at the time of HCC diagnosis

	Definitive LRT	Wait-and-not-treat	*P*
Age (years)	70.4±10.2	58.7±5.9	<0.001*
Female gender	9 (47.4)	12 (21.1)	0.026*
Primary diagnosis			
HCV	12 (63.2)	44 (77.2)	0.420
HBV	0 (0)	2 (3.5)	
Alcoholic cirrhosis	2 (10.4)	5 (8.8)	
NASH	3 (15.8)	3 (5.3)	
Cryptogenic cirrhosis	1 (5.3)	2 (3.5)	
AIH	1 (5.3)	1 (1.7)	
Total bilirubin (mg/dL)	1.1±0.7	1.8±1.9	0.120
MELD score	11.1±4.0	11.8±4.5	0.550
AFP (ng/mL)	69.9±191.8	42.5±81.2	0.384
Child-Pugh score	6.2±1.4	7.2±1.9	0.048*

Data are presented as n (%) or mean±standard deviation.
HCC, hepatocellular carcinoma; LRT, locoregional therapy; HCV, hepatitis C virus; HBV, hepatitis B virus; NASH, nonalcoholic steatohepatitis; AIH, autoimmune hepatitis; MELD, model for end-stage liver disease; AFP, alpha-fetoprotein.
*Statistically significant difference.

LRT group had slightly lower Child-Pugh scores (7.2±1.9 vs. 6.2±1.4, $P = 0.048$).

Fig. 1 shows a flowchart of the patient population and Table 2 lists the tumor and treatment characteristics. Patients in the definitive LRT group (19 patients) received either TACE (10 patients, 52.6%) or RFA (9 patients, 47.4%) as primary treatment. The primary reason for LT ineligibility was the presence of comorbidities in 6 patients, advanced age (>70 years) in 9 patients, substance abuse in 2 patients, social issues in 1 patient and personal preference in 1 patient. During the follow up period, repeat LRT was performed in 9 patients in the definitive LRT group (5 patients due to local recurrence within treatment zone and in 4 patients to treat new foci of HCC).

Among the patients listed for LT, 7 patients passed away while on the waitlist, 7 patients were removed from the waitlist and 42 patients were transplanted. One patient is still awaiting LT. The primary reason for waitlist removal was worsening comorbidities in 3 patients, HCC progression in 3 patients and moving to another state in 1 patient. Table 3 lists the characteristics of patients who had disease progression beyond T2 while on the waitlist. Cause of death while on the waitlist were sepsis in 2 patients, gastrointestinal (GI) bleeding in 1 patient, the development of metastatic HCC in 1 patient, acute respiratory failure in 1 patient, and unknown in 1 patient, while 1 patient passed away during liver transplantation in the operating room. While waitlisted, 30 out of 57 patients received bridging LRT (Fig. 1 and Table 2). The mean time to LT from HCC diagnosis was 18.5±16.1 months for patients receiving bridging LRT versus 12.3±15.5 months for the rest of the patients in this group ($P = 0.214$). Type of primary LRT in the wait-and-not-treat group was either TACE (28/30 patients, 93.3%) or RFA (2/30 patients, 6.7%).

Survival rates at 1, 2, 3 and 5 years were 89.4%, 70.5%, 53.3% and 33.3% for the definitive LRT group compared with 87.7%, 82.5%, 78.9% and 68.4% for the patients in the wait-and-not-treat group. Survival rate was significantly greater for the patients in the wait-and-not-treat group (Mantel-Cox test, $P = 0.013$). Mean survival for definitive LRT group at the end of 5 years was 34.3±6.0 months with a median of 30.3 months (95% CI, 5.7–55 months) compared with 48.7±2.6 months for the wait-and-not-treat group, respectively (median not reached since survival rate was higher than 50% in this group throughout the study). Fig. 2 demonstrates the Kaplan-Meier curve for the survival analysis. Cause of death among waitlisted patients was metastatic HCC in 5 patients, end-stage renal failure in 1 patient, liver failure in 1 patient, unknown cause in 4 patients, in addition to the patients who passed away while awaiting LT. In the definitive LRT group, the cause of death was metastatic HCC in 3 patients, liver failure in 3 patients, unknown in 2 patients and gastrointestinal bleeding in 1 patient.

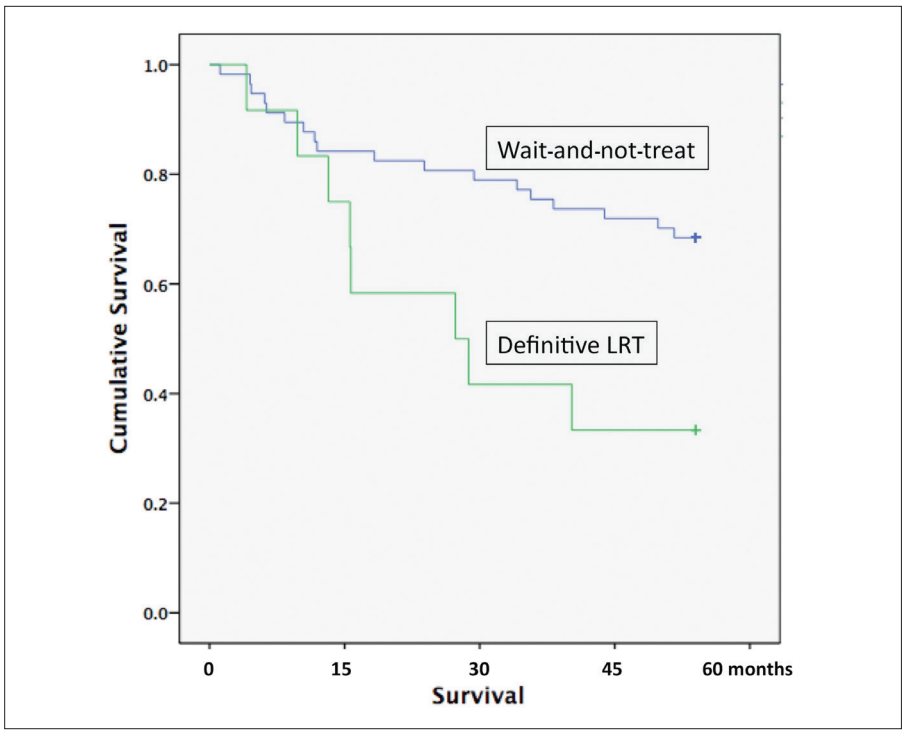

Figure 2. Kaplan-Meier curve for HCC patients treated with definitive LRT compared with LT waitlisted patients with T1 stage HCC managed by wait-and-not-treat approach. At the end of 5-year follow up, patients in the wait-and-not-treat group had markedly improved survival (34.3±6.0 months compared with 48.7±2.6 months, Mantel-Cox test, $P = 0.013$).

Table 2. Tumor and treatment characteristics for patients who underwent LRT based on treatment group

	Definitive LRT	Wait-and-not-treat	*P*
Number of patients treated	19 (100)	30 (52.6)	<0.001*
Largest lesion diameter at diagnosis (cm)	1.7±0.4	1.4±0.2	0.004*
Largest lesion diameter at LRT (cm)	1.7±0.4	2.3±0.8	0.004*
Number of lesions at LRT	1.0±0.0	1.5±0.8	0.011*
Type of primary LRT			<0.001*
TACE	10 (52.6)	28 (93.3)	
RFA	9 (47.4)	2 (6.7)	
Time to LRT (months)	4.5±6.8	8.6±5.3	0.025*
Patients with multiple LRT sessions	9 (47.3)	7 (12.3)	0.003*
Number of LRT sessions	1.6±0.8	1.3±0.4	0.023*

Data are presented as n (%) or mean±standard deviation.
LRT, locoregional therapy; TACE, transcatheter arterial chemoembolization; RFA, radiofrequency ablation.
*Statistically significant difference.

Discussion

Treatment protocol for patients with veHCC varies depending on availability of the LT. In countries where LT is less often performed, surgical resection and RFA are usually the treatments of choice. Several studies in the past have looked into the outcomes of patients undergoing RFA or surgical resection and have documented comparable survival rates between both methods (18–20). A recent meta-analysis published in Cochrane library by Majumdar et al. (23) found that RFA overall is associated with higher rates of local recurrence and cancer-related mortality, but surgery is associated with a higher risk of serious perioperative adverse events. On the other hand, this meta-analysis could not find any difference in overall survival and all-cause mortality rates.

In countries where LT is a viable option, it is the preferred treatment for HCC as it results in higher long-term survival rates (8, 9). However, the limited number of available organs and a growing number of patients with HCC on the LT waitlist has led to complicated organ allocation policy that gives priority to patients at higher risk of disease progression, precluding most HCC patients from liver transplantation (10). Since March 2004, patients with veHCC are not eligible to receive MELD exception points at the time of listing due to the low risk of short-time disease progression beyond T2 stage (11). After this major organ allocation policy change, many patients with veHCC underwent watchful waiting with repeat imaging every 3 months until tumor progression beyond T1 stage, which allows for MELD exception points and provides additional waitlist priority (17). At this point, LRT would be the ideal treatment since prior studies have documented effectiveness of LRT in preventing drop-outs from waitlist (15, 16). In our study, we have evaluated the long-term survival of patients with veHCC on an intention-to-treat basis. Our findings confirmed a high long-term (5-year) survival rate of about 70% for patients treated with watchful waiting until disease progression to T2 stage, and then bridging them to LT with TACE or RFA if expected to be on waitlist for more than another 6 months. These numbers are comparable to prior studies reporting a 5-year survival rate of about 70%–75% for patients within Milan criteria (including both UNOS T1 and T2) treated with LT (8, 9). Our findings confirm that this approach does not result in a lower long-term survival or unexpectedly high waitlist drop-out due to disease progression beyond T2 stage, as this was only seen in three patients (3/57, 5.3%). Only a few studies have evaluated the short and intermediate-term outcomes of patients treated using this approach. In a retrospective study performed by Mehta et al. (17), the outcomes of wait-and-not-ablate approach (no ablation until disease progression to UNOS T2 stage) were investigated in 114 patients with veHCC with RFA as the LRT method of choice. This study confirmed

Table 3. Characteristics of the patients who progressed beyond T2 stage on waitlist

Patient	Age (years)	Lesion size at diagnosis (cm)	AFP (ng/mL)	MELD	CPS	Time to progression (months)	Tumor burden at delisting
1	59	1.2	5	9	5	20	2.2 cm tumor and metastatic lymphadenopathy
2	61	1.2	29.3	10	5	11.6	25 lesions largest measuring 8.4 cm
3	63	1.5	23	13	9	21.7	3 lesions measuring 2.0, 2.4, and 3.7 cm

AFP, alpha-fetoprotein; MELD, model for end-stage liver disease; CPS, Child-Pugh score.

a very low tumor size growth (median of 0.14 cm/month) and very low risk of disease progression beyond T2 stage on follow-up (4.4% at 6 months and 9% at both 12 and 24 months). They reported 1- and 3-year survival rates of 94.5% and 75.5%. Our study had few differences with this study, most importantly having a definitive LRT arm for comparison, longer follow-up (5 years vs. 3 years) and use of TACE or RFA as the LRT technique compared with only RFA in their study. Despite these differences, overall survival at the end of 3 years was about the same (78% in our study compared with 75% in the study by Mehta et al.) (17), which suggests comparable efficacy of TACE versus RFA in bridging veHCC patients to LT when they progress to T2 stage.

Our study also included 19 patients who underwent definitive LRT as they were ineligible for LT, mostly due to old age or comorbidities. As expected, 3- and 5-year survival was markedly lower in this group compared to waitlisted patients (53% and 33% compared with 78% and 68% at the end of 3- and 5-year follow-up). Previous studies comparing surgical resection to RFA reported 3- and 5-year overall survival of 80.3%–87.7% and 67.4%–72% (18–20); however, these studies included patients who were significantly younger and may have had less comorbidity. For example, the mean age of the patients undergoing RFA in the study performed by Peng et al. (20) was 52.1 years compared with 70.4 years in our study, and therefore a direct comparison is impossible.

The current study has a number of limitations. First, the process of patient selection, assignment to LRT and selection between RFA and TACE is not controlled due to retrospective nature of the study. Second, the environment of the study being a tertiary referral center may affect the findings and not reflect the overall experience elsewhere. Third, patients in the definitive LRT group were older and had more comorbidities, which limits the comparison. Fourth, due to small sample size in subpopulations, effectiveness of TACE and RFA cannot be compared.

In conclusion, these findings point towards the effectiveness of wait-and-not-treat method in managing patients with veHCC until disease progression to T2 stage followed by bridging to LT by TACE or RFA with high 5-year survival rates approaching 70%. Patients treated using wait-and-not-treat approach had significantly better 3- and 5-year survival compared with patients treated with definitive LRT; however, comparison between the two groups was limited due to fundamental differences in patient population regarding age and comorbidities.

Conflict of interest disclosure

Dr. Soulen received grants and personal fees from Guerbet, grants from BTG International, personal fees from Merit Medical, personal fees from Sirtex medical, personal fees from Terumo medical, personal fees from Bayer/Onyx, outside the submitted work. Dr. Nadolski received grants from Guerbet, LLC, grants from Teleflex Medical, grants from Bard, personal fees from Teleflex Medical, outside the submitted work. The rest of the authors have nothing related to disclose.

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