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ORIGINAL ARTICLE

Analysis of efficacy and safety of TACE in combination with RFA and MWA in the treatment of middle and large primary hepatic carcinoma

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Summary

Purpose: *To compare and explore the efficacy and safety of transcatheter arterial chemoembolization (TACE) in combination with radiofrequency ablation (RFA) and microwave ablation (MWA) in the treatment of middle and large primary hepatic carcinoma.*

Methods: *A retrospective analysis was made on 75 patients with middle and large hepatic carcinoma (tumor diameter ≥3 cm) receiving TACE in combination with thermal ablation therapy in our hospital from January 2012 to January 2015, with hepatic function Child-Pugh class A and B. Forty-one cases received TACE+RFA, while 34 cases received TACE+MWA. Patients in both groups were followed up to observe the short-term efficacy, 3-year survival rate, alpha fetoprotein (AFP), indexes of hepatic function and incidence of adverse reactions.*

Results: *No statistical differences was noted in preoperative general conditions between the two groups of patients. The results showed 28 cases of complete response (CR) and 13 cases of partial response (PR) in the TACE+RFA group, and 29 cases of CR and 5 cases of PR in the TACE+MWA group. The difference in the short-term efficacy between two groups was not significant (p>0.05). With tumor diameter 3-5 cm, there was no statistically significant difference in the efficacy between the two groups (p>0.05), and with tumor diameter over 5 cm, the efficacy in TACE+MWA group was significantly better than that in TACE+RFA group (p=0.041). After treatment, the level of AFP in both groups was decreased in different degrees but without statistical significance (p>0.05). The levels of ALT and AST of hepatic functions in both groups increased after treatment. The postoperative average levels of ALT and AST in the TACE+RFA group were 85.90±49.02 U/L and 113.53±56.54 U/L, respectively, which were significantly lower than those in the TACE+MWA group (138.62±69.04 U/L and 178.03±104.50 U/L; p<0.05). During follow-up, the 1-, 2- and 3-year cumulative survival rates in the TACE+RFA group were 68.30, 36.60 and 14.60%, and those in TACE+MWA group were 79.40, 53.00 and 38.20%. The tumor-free survival rates in the TACE+RFA group were 53.70, 29.30 and 12.20%, and those in TACE+MWA group were 58.80, 38.20 and 29.40%. The difference in survival rate between two groups had no statistical significance (p>0.05). The differences in postoperative adverse reactions and follow-up conditions between two groups were not statistically significant (p>0.05).*

Conclusions: *The difference in the short-term efficacy between the TACE+RFA and TACE+MWA group in the treatment of middle and large primary hepatic carcinoma had no statistical significance. When the tumor size was over 5 cm, the efficacy in TACE+MWA group was better than that in TACE+RFA group. There were no obvious differences in 1-year cumulative survival rate and tumor-free survival rate between the two groups, but postoperative liver function damage in the TACE+RFA group was lighter than that in TACE+MWA group.*

Key words: *efficacy, microwave ablation, primary hepatic carcinoma, radiofrequency ablation, safety, transcatheter arterial chemoembolization*

Introduction

Hepatocellular carcinoma (HCC) is featured with occult onset, high malignant grade and rapid disease progression, and 70% of the patients are in the middle and advanced stage when treated [1,2].

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Transcatheter arterial chemoembolization (TACE) can effectively control tumor growth and improve prognosis, which has become the first choice for the treatment of unresectable HCC [3,4]. In recent years, thermal ablation therapy, represented by radiofrequency ablation (RFA) and microwave ablation (MWA), has developed rapidly and become an important minimally invasive treatment means of HCC because of its safety and efficacy. Clinical practice proved that its effect is equivalent to that of surgery in the treatment of small hepatic carcinoma (<3 cm), so it has become the first-line treatment method for hepatic carcinoma, However, it has poor efficacy on middle and large hepatic carcinomas (>3 cm), with low complete necrosis rate and high recurrence rate [5-7]. The comprehensive treatment mode of TACE in combination with thermal ablation can achieve better treatment results in middle and large hepatic carcinomas compared with single treatment mode, with a reliable safety. Currently, it is the most commonly-used non-surgical method in the clinical treatment of hepatic carcinoma, the efficacy of which is significant[8].

In this study a retrospective analysis was made on the application of TACE combining RFA and MWA in the treatment of middle and large hepatic carcinomas to compare their efficacy and safety, thus providing a clinical basis for selecting proper treatment method for middle and advanced hepatic carcinoma patients that have lost the surgery opportunity. This study was approved by the Ethics Committee of the hospital and all treatment methods were agreed by the patients and relatives who signed informed consent.

Methods

Research objectives

General materials

A total of 75 non-surgical HCC patients receiving TACE in combination with ablation in our hospital between January 2012 and January 2015 were selected. There were 41 cases with 53 lesions in the TACE+RFA group, including 30 males and 11 females aged 39-75 years (mean 56.94±8.77). The mean tumor diameter was 4.8±2.7 cm and there were 34 cases with a diameter of 3-5 cm and 7 cases with a diameter >5 cm. The tumor was on the liver surface in 21 cases, close to great vessels in 7 cases, close to gallbladder in 2 cases and close to diaphragm in 11 cases. Preoperative hepatic function grading showed 26 cases in Child-Pugh class A and 15 cases in Child-Pugh class B. The preoperative level of AFP was ≥400 ng/mL in 23 cases and <400 ng/mL in 18 cases. There were 34 cases with 41 lesions in the TACE+MWA group, including 27 males and 7 females

Table 1. Demographics and general clinical data of all studied patients

Data	*TACE+RFA group*	*TACE+MWA group*	*p value*
	(n=41) *n (%)*	*(n=34)* *n (%)*	
Gender (Male/Female)	30/11	27/7	0.595
Age (years), mean±SD	56.94±8.77	58.09±10.22	0.602
Number of tumors			0.767
1	31 (75.6)	28 (82.4)	
2	8(19.5)	5(14.7)	
3	2(4.9)	1(2.9)	
Size of tumors (cm)			0.886
3-5	34 (82.9)	26 (76.5)	
>5	7 (17.1)	8 (23.5)	
Tumors adjacent to			0.886
Liver surface	21(51.2)	17 (50)	
Large blood vessel	7 (17.1)	8 (23.5)	
Gallbladder	2 (4.9)	1 (3.0)	
Diaphragm	11 (26.8)	8 (23.5)	
Child-Pugh class			0.685
A	26 (63.4)	20 (58.8)	
B	15 (36.6)	14 (41.2)	
AFP (ng/mL)			0.985
≥400	23 (56.1)	19 (55.9)	
<400	18 (43.9)	15 (44.1)	

TACE:Transcatheter arterial chemoembolization; RFA:Radiofrequency ablation; MWA:Microwave ablation; AFP:alpha fetoprotein

aged 41-76 years (mean 58.09±10.22). The mean tumor diameter was 5.3±2.3 cm and there were 26 cases with a diameter of 3-5 cm and 8 cases with a diameter >5 cm. The tumor was on the liver surface in 17 cases, close to great vessels in 8 cases, close to gallbladder in 1 case and close to diaphragm in 8 cases. Preoperative hepatic function grading showed 20 cases in Child-Pugh grade A and 14 cases in Child-Pugh grade B. The preoperative level of AFP was ≥400 ng/mL in 19 cases and <400 ng/mL in 15 cases (Table 1).

Inclusion and exclusion criteria

Inclusion criteria: patients diagnosed with primary hepatic carcinoma according to the definite pathological report; patients with nodular lesions with rich blood supply detected using two or more imaging methods; patients whose liver tumor size was ≥ 3 cm; patients without extrahepatic metastasis and cancer embolus in main portal vein and the left and right branches; patients in Child-Pugh class A and B; and patients without surgery or interventional therapy and without other severe diseases.

Exclusion criteria: patients with diffuse hepatic carcinoma or metastasis in other organs; patients with severe liver cirrhosis; patients with moderate or large amount of ascites; patients with severe disturbances of blood coagulation or bleeding tendency; and patients with a history of biliary infection or hepatic abscess 2 months before treatment.

Treatment methods

All patients were admitted to the hospital after definite diagnosis, and were subjected to routine examinations, such as routine blood tests, hepatic and renal function, coagulation function and AFP. Then TACE was performed once. After local anesthesia via 2% lidocaine, 6F sheath catheter, 5F pigtail catheter and Yashiro catheter were successfully inserted via the right femoral artery, followed by abdominal aortography, superior mesenteric artery radiography and celiac trunk angiography to observe the main branches of hepatic artery, intrahepatic lesions and blood flow in the main portal vein trunks. If a single lesion was located in the hepatic lobe on one side, more than two lesions were concentrated in the hepatic lobe on one side, or the feeding arterial branch of the lesion could be clearly found, the catheter should be inserted into the feeding artery of the hepatic lobe or lesion (n=43). If the lesion occurred in the hepatic lobe on both sides, the catheter should be inserted only into the common hepatic artery (n=32). After the catheter was in place, 50 mL of 100 mg oxaliplatin and normal saline were injected first, and then 20-30 mL mixed suspension of 40 mg epirubicin and ultra-fluid lipiodol were slowly injected for embolism under fluoroscopic guidance. The injection dose was determined based on the deposition of lipiodol and whether there was backflow or wrong embolism. Finally, gelatin sponge particles or PVA (Cook) were injected, and the embolism continued until the blood supply of the lesion was reduced by more than 95% as shown in angiography.

After 2 weeks, RFA or MWA were performed using radiofrequency interstitial tumor ablation (RITA) instrument or MTc-3cMWA instrument under the CT positioning. The multi-needle multi-point MWA or single-needle multi-point RFA was adopted. Before operation, morphine and hemocoagulase were given for analgesia and hemostasis, and the venous access was established. During operation, vital signs were monitored using multi-functional monitor. In RFA, the power was set at 150 W and temperature at 105°C, and the opening scope of multi-stage needle and ablation time were determined according to the size of lesion. In MWA, the intraoperative output power was set at 50-80 W, and the ablation time was determined according to the scope of lesion. The CT plain scan was performed every time after ablation to observe the defect scope as well as the therapeutic goal and scope. The tumor and normal liver tissues at 1 cm around it should be covered, and the ablation was performed again for tumor uncovered in the defect scope.

Observation indexes

Determination of efficacy: All patients underwent enhanced CT scan (Toshiba Xpress/SX) before operation and at 1 month after combined treatment. The enhancement of intrahepatic lesions in the arterial phase indicated that there was still blood supply in the tumor and combined treatment should be continued, which was deemed as partial response (PR). The opposite situation indicated that there was no blood supply in the tumor, which was deemed as complete response (CR). After that, patients were reviewed once every 2 months.

Laboratory examinations: Routine blood tests, serum AFP and hepatic and renal function examinations were performed on d 1 before operation, and d 3, week 1 and 2 after operation. Patients were reviewed once every 2 months after treatment, and once every 3 months after 1 year.

Postoperative adverse reactions and complications were observed and recorded. Patients were followed up for 3 years to estimate the cumulative survival and tumor-free survival rates of patients.

Statistics

SPSS 13.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical processing. W test showed that detected indexes in this study were normally distributed. Continuous variables were presented as mean ± standard deviation, and the variance was homogeneous according to Levene test. The independent t-test sample was used for comparison of numerical data, and chi-square test was used for categorical data. $P<0.05$ suggested that the difference was statistically significant.

Results

Short-term efficacy in TACE+RFA group and TACE+MWA group

The efficacy was evaluated using the results of enhanced liver CT scan 1 month after treatment according to the Response Evaluation Criteria in Solid Tumors (RECIST) issued by the National

Cancer Institute (NCI). There were 28 cases of CR and 13 cases of PR in the TACE+RFA group and 29 cases of CR and 5 cases of PR in the TACE+MWA group (p>0.05). When the tumor diameter was 3-5 cm, there were 25 cases of CR and 9 cases of PR in the TACE+RFA group and 23 cases of CR and 3 cases of PR in the TACE+MWA group (p>0.05). When the tumor diameter was larger than 5 cm, there were 3 cases of CR and 4 cases of PR in the TACE+RFA group and 6 cases of CR and 2 cases of PR in the TACE+MWA group, so the efficacy in the TACE+MWA group was superior to that in the TACE+RFA group (p=0.041; Table 2).

Laboratory examination indexes in TACE+RFA group and TACE+MWA group

After treatment, the AFP level decreased from 990.23±677.54 ng/mL to 510.71±422.39 ng/mL in the TACE+RFA group and from 1170.41±745.98 ng/mL to 380.65±311.06 ng/mL in the TACE+MWA group (p>0.05). On d 2 after operation, the levels of ALT and AST in both groups increased in different degrees. The level of ALT increased from 65.44±33.70 U/L to 85.90±49.02 U/L in the TACE+RFA group and from 70.55±39.04 U/L to 113.53±56.54 U/L in the TACE+MWA group. The level of AST increased from 87.90±56.91 U/L to 138.62±69.04 U/L in the TACE+RFA group and from 97.22±60.15 U/L to 178.03±104.50 U/L in the TACE+MWA group. There were statistically significant differences between the two groups (p=0.026, p=0.043), suggesting that the liver function damage of patients in the TACE+MWA group after operation in this study was more severe than that in the TACE+RFA group (Table 3).

Comparison of survival rate between TACE+RFA group and TACE+MWA group

A total of 75 patients in both groups were followed up for 3 years. The overall survival time

Table 2. Clinical efficacy of the two studied groups

Parameters	*TACE+RFA group*	*TACE+MWA group*	x^2	*p value*
	(n=41) *n (%)*	*(n=34)* *n (%)*		
CR	28 (68.3)	29 (85.3)	2.945	0.086
PR	13 (31.7)	5 (14.7)		
Tumors 3-5cm			0.014	0.230
CR	25(73.5)	23 (88.5)		
PR	9(26.4)	3 (11.5)		
Tumors >5cm			4.144	0.041
CR	3 (42.9)	6 (75.0)		
PR	4 (57.1)	2 (25.0)		

TACE:Transcatheter arterial chemoembolization; RFA:Radiofrequency ablation; MWA:Microwave ablation; CR:Complete Response; PR:Partial Response

Table 3. The laboratory indexes before and after operation in the two studied groups

Parameters	*TACE+RFA group*	*TACE+MWA group*	*p value*
	n=41 *Mean±SD*	*n=34* *Mean±SD*	
AFP (ng/mL)			
Preoperative	990.23±677.54	1170.41±745.98	0.277
Postoperative	510.71±422.39	380.65±311.06	0.140
ALT (U/L)			
Preoperative	65.44±33.70	70.55±39.04	0.545
Postoperative	85.90±49.02	113.53±56.54	0.026
AST (U/L)			
Preoperative	87.90±56.91	97.22±60.15	0.494
Postoperative	138.62±69.04	178.03±104.50	0.043

TACE:Transcatheter arterial chemoembolization; RFA:Radiofrequency ablation; MWA:Microwave ablation; AFP:alpha fetoprotein; ALT:Alanine aminotransferase; AST:Aspartate aminotransferase

of 41 patients in the TACE+RFA group was 5-36 months with a mean of 18±9 months, including 13 cases with survival time <1 year, 13 cases with survival time of 1-2 years, 9 cases with survival time of 2-3 years, and 6 cases with survival time >3 years. The 1-, 2- and 3-year cumulative survival rates were 68.30% (28/41), 36.60% (15/41) and 14.60% (6/41), respectively. The overall survival time of 34 patients in the TACE+MWA group was 7-36 months with an average of 20±7 months, and including 7 cases with survival time <1 year, 9 cases with survival time of 1-2 years, 5 cases with survival time of 2-3 years, and 13 cases with survival time >3 years. The 1-, 2- and 3-year cumulative survival rates were 79.40% (27/34), 53.0% (18/34) and 38.20% (13/34), respectively. The 1-, 2- and 3-year tumor-free survival rates were 53.70%, 29.30% and 12.20% in the TACE+RFA group, and 58.80%, 38.20% and 29.40% in the TACE+MWA group, respectively. No statistically significant difference was found in the comparison of survival rates between the two groups (p>0.05; Table 4).

Adverse reactions and follow-up data

After ablation, transient decrease in blood pressure and increase of dyspnea occurred in 1 patient in the TACE+MWA group which were alleviated spontaneously after fluid infusion and oxygen inhalation for about 15 min. All patients suffered of abdominal pain, nausea, vomiting, fever and other adverse reactions in different degrees, and symptoms were improved after symptomatic treatment. In follow-up there was 1 case of intra-abdominal hemorrhage, 3 cases of ascites, 5 cases of gastrointestinal variceal rupture hemorrhage, 8 cases of tumor recurrence, and 1 case of bone metastasis in the TACE+RFA group. There was 1 case of intrahepatic hematoma, 2 cases of intra-abdominal hemorrhage, 1 case of portal vein thrombosis, 5 cases of ascites, 3 cases of gastrointestinal variceal

Table 4. Overall survival and recurrence free survival of the two studied groups

Parameters	*TACE+RFA group*	*TACE+MWA group*	*p value*
	(n=41) %	*(n=34)* %	
Overall survival			0.073
1 year	68.30	79.40	
2 years	36.60	53.00	
3 years	14.60	38.20	
Recurrence free survival			0.143
1 year	53.70	58.80	
2 years	29.30	38.20	
3 years	12.20	29.40	

TACE: Transcatheter arterial chemoembolization; RFA: Radiofrequency ablation; MWA: Microwave ablation

Table 5. Operation-related complications and follow up data of the two studied groups

Parameters	*TACE+RFA group*	*TACE+MWA group*
	(n=41) *n*	*(n=34)* *n*
Fever	31	29
Gastrointestinal reactions	34	30
Intrahepatic hematoma	0	1
Intraperitoneal hemorrhage	1	2
Portal vein thrombosis	0	1
Ascites	3	5
Variceal bleeding	5	3
Recurrence	8	5
Bone metastases	1	0

TACE: Transcatheter arterial chemoembolization; RFA: Radiofrequency ablation; MWA: Microwave ablation

rupture hemorrhage, 5 cases of tumor recurrence and no case of bone metastasis in the TACE+MWA group. No statistically significant differences in the comparisons of adverse reactions and follow-up between the two groups were noted (p>0.05) (Table 5).

Discussion

In recent years, the incidence rate of hepatic carcinoma in many countries has been increased dramatically, especially in China. According to epidemiological data, the incidence rate of hepatic carcinoma in China ranks 1st in the world, accounting for approximately 55% of the total incidence of hepatic carcinoma in the world. Besides, the incidence rate of hepatic carcinoma ranks 3rd in all cancers in China, and its total mortality rate ranks 2nd and even 1st in rural areas [9].

Most patients with primary hepatic carcinoma are in the mid-late stage when diagnosed, or cannot be operated due to insufficient liver reserve function. Minimally-invasive techniques, such as TACE and local thermal ablation, have provided new treatment opportunities for such patients, and they have become important treatment means for hepatic carcinoma, whose safety and effectiveness are widely recognized [10,11]. In TACE, the cannula is inserted via the femoral artery using the Seldinger technique, the catheter is inserted into the feeding artery of tumor ultra-selectively or selectively under fluoroscopic guidance, the chemotherapy drug and embolizing agent are mixed into emulsion and injected into the blood vessel, and the tumor vessel is obstructed due to the blocking effect of embolizing agent, ultimately leading to necrosis of tumor tissues due to ischemia. As a kind of local minimally-invasive treatment technique of hepatic carcinoma, TACE is characterized by small trauma, high safety, small toxic and side effect, etc. However, the complete necrosis rate of medium-large lesions in the treatment with TACE alone is low, the adverse reactions caused by repeated TACE and chemotherapy drugs will aggravate liver function damage, and the efficacy of TACE on hypovascular tumor is often unsatisfactory [12,13]. In recent years, a great progress has been made in the treatment of tumors with local ablation. Although there are various ablation methods and different mechanisms, tumor lesions can be positioned accurately and ablated under the guidance of imaging equipment. Currently, the commonly used methods of local ablation are RFA and MWA. RFA has a definite efficacy on small hepatocellular carcinoma with a tumor diameter <3 cm, which has been included into the National Comprehensive Cancer Network (NCCN) Guidelines [14,15]. However, it is limited by the ablation range, the blood flow inside the tumor can take away most of the heat, so the local temperature cannot meet the requirement, leading to residual tumor, and its treatment effect on larger hepatic carcinoma is poor. Compared with RFA, MWA has been more and more widely used in the treatment of hepatic carcinoma because of its higher efficiency and larger ablation range [16,17]. In the treatment of large hepatic carcinoma, TACE combined with local ablation, because of its significant synergistic effect, can act supplementarily to the inactivation of residual lesions with embolism and unsatisfactory lipiodol deposition and hypovascular lesions after TACE of large hepatic carcinoma, thus further enhancing the therapeutic effect and improving the treatment outcome of larger hepatic carcinoma, which has become the development trend of multidisciplinary synthetic treatment of hepatic carcinoma [18,19]. In this study, the efficacy, survival rate and safety of TACE combined with RFA and MWA in the treatment of medium-large primary hepatic carcinoma were compared, so as to provide a clinical basis and reference for selecting appropriate therapeutic methods for middle-advanced hepatic carcinoma patients who have lost the opportunity of operation.

In this study, it was found that there was no statistically significant difference in the comparison of short-term efficacy between the two groups. The difference in the efficacy was not statistically significant between the two groups when the tumor diameter was 3-5 cm, but the efficacy in the TACE+MWA group was significantly superior to that in the TACE+RFA group when the tumor diameter was larger than 5 cm. Some studies have demonstrated that MWA has a larger ablation range, and multiple microwave needles can work simultaneously to result in a larger area of ablation than single sequential ablation. With the prolongation of treatment time of RFA, there will be carbonized changes in surrounding tissues, and with the increase of carbonized degree, it is difficult for RFA range to increase with the extension of ablation time [20]. Therefore, multi-needle MWA has a better efficacy than RFA on larger tumors, especially those with a diameter of more than 5 cm.

After treatment, AFP levels in both groups decreased in different degrees, but without statistically significant difference. ALT and AST levels in both groups increased after treatment, and the increase degrees in the TACE+MWA group were higher than those in the TACE+RFA group, indicating that the liver function damage of patients in the TACE+MWA group after operation was more se-

vere than in the TACE+RFA group. The possible reason is their mechanism of action. The multi-stage needles in RFA transmit high-frequency current to surrounding tissues, the ions in tissues vibrate and are heated by rubbing, coagulation necrosis occurs in local cancer tissues, and the peripheral area solidify into a reaction zone, thus effectively controlling the ablation range [21]. The heating effect of microwave on biological tissues is the integrated result of ion heating and coupler heating, which is characterized by high power, high temperature-rise efficiency and quick heating. Besides, it is not affected by the drying and carbonization of liver tissues, and a lot of tissues will be damaged within a short time, which is faster than RFA. Comparatively, it is inferior to RFA in controlling the defect scope. However, the above-mentioned liver function damage is only manifested within a short time after operation, and it can be improved after liver-protecting treatment. Therefore, if the patient has severe liver cirrhosis and poor liver compensatory ability, more attention should be paid to strengthening the liver-protecting treatment after MWA.

No statistically significant differences in the cumulative survival rate and tumor-free survival rate were found between the two groups during the 3-year follow-up, and the incidence of adverse reactions after operation also displayed no statistically significant difference, suggesting that the two combined treatments have a similar effect on the survival rate of patients, and both of them are safe and effective.

There were many shortcomings in this study. For example, the research sample size was too small. To study the efficacy of the two combined treatments, more clinical research objects should be included for data analysis in a large sample size. In this study, only the short-term efficacy and 3-year survival rate were analyzed, but the mental and psychological factors of patients with middle-advanced hepatic carcinoma after treatment were not focused on, and the quality of life and subjective feelings of patients after operation were not studied via follow-up. Whether there is a difference in the effect on quality of daily life between the two combined treatments still needs further exploration and research. It is expected that the multi-center clinical research on TACE combined with thermal ablation therapy can provide more accurate references for clinical decision-making, and benefit middle-advanced hepatic carcinoma patients who have lost the opportunity of operation.

Conclusions

There was no statistically significant difference in the comparison of total short-term efficacy between the TACE+RFA and TACE+MWA group in the treatment of middle-large primary hepatic carcinoma. When the tumor diameter was larger than 5 cm, the efficacy in the TACE+MWA group was dramatically superior to that in the TACE+RFA group. No significant differences were found in the 1-year cumulative survival rate and tumor-free survival rate between the two groups, but the liver function damage in the TACE+RFA group after operation was lighter than that in the TACE+MWA group.

Conflict of interests

The authors declare no conflict of interests.

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