Letter to the Editor

Reply to the commentary on "*The efficiency of pathological response after preoperative transcatheter arterial chemoembolization for microvascular invasion and early tumor recurrence in hepatocellular carcinoma*"

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We thank He *et al.* for their interest in our recent article (1) and for their thoughtful comments.

The first question raised by He *et al.* is on the total number of patients in the PSM cohort in *Table 1*, which they considered incorrect. In this study, we first analyzed the incidences of MVI in the groups of patients with or without preoperative TACE. Before PSM, there were 737 patients who received preoperative TACE, and 1,233 patients who did not receive preoperative TACE. After PSM, the numbers of patients with and without preoperative TACE in each of the 2 groups were 602. The incidences of MVI in the groups of patients with or without preoperative TACE were 37.5% (226/602), and 40.9% (246/602), respectively. The difference was not significant (37.5% *vs.* 40.9%, P=0.238). Next, we compared the incidences of MVI among patients with different necrosis areas, and patients without preoperative TACE before and after PSM, respectively. In the PSM cohort, there were 222 patients who had a pathological response (PR) area ≥90%, 420 patients who had a PR area between 60–90%, and 50 patients who had a PR area <60%, respectively. Therefore, the 602 patients in the PSM cohort were obtained from the PSM analysis of 737 patients with preoperative TACE and 1,233 patients without preoperative TACE, instead of 692 (222+420+50) as stated in the commentary by He *et al.* Furthermore, He *et al.* casted doubts on the 1:1 ratio in the PSM. We must admit that PSM has its limitations. As this study was a retrospective study, selection biases are inevitable. To minimize selection biases, the PSM method was used. However, PSM itself can also introduce selection biases when the effective sample size in a propensity analysis is small, as the statistical power of the study can be influenced. In our study, the sample size of patients without pre-operation TACE was twice that of the patients with preoperative TACE. Although a 1:1 match was used in this study, as clearly stated in the section of limitations, we mentioned that to minimize the biases introduced on selection of unobservable factors, relevant measurable variables were enrolled as much as possible (2). In this study, 21 variables associated with presence of MVI and prognosis were enrolled in the PSM which can partly improve the statistical power. In future, we shall recruit more patients to further verify the conclusions of our study.

The second question is on the errors in the article. After careful examination of *Tab. 3* (1), we found that the variable of "Microvascular Invasion (Presence *vs.* Absence)" in the variable column was missing, which could lead to data confusion in *Tab. 3*. We have added the information on the attached amended *Tab. 3* (*Table 1*). We are very appreciative of the authors in raising this question, and we are very sorry to the readers of this article for any inconvenience caused by the missing data.

For the third question raised by the authors, the early recurrence rates, and overall survival rates among patients

Table 1 Multivariable Cox regression analysis of early tumor recurrences (N=1,970)

Variable	Multivariable	
	HR (95% CI)	P
Preoperative TACE (yes *vs.* no)	–	–
Tumor number (multiple *vs.* single)	1.252 (1.126–1.596)	<0.001
Tumor size (≥5 *vs.* <5 cm)	1.765 (1.528–2.016)	<0.001
Satellite nodules (presence *vs.* absence)	1.077 (0.925–1.286)	0.365
Edmondson grade (III+IV *vs.* I+II)	1.118 (0.877–1.346)	0.295
Tumor capsule (non-complete *vs.* complete)	1.219 (0.999–1.518)	0.055
Liver cirrhosis (yes *vs.* no)	–	–
Age (≥60 *vs.* <60)	1.064 (0.897–1.169)	0.427
Gender (male *vs.* female)	–	–
Tumor margin (non-smooth *vs.* smooth)	1.177 (0.996–1.389)	0.062
HCV Ab (positive *vs.* negative)	–	–
HBV DNA (≥10,000 *vs.* <10,000 IU/mL)	–	–
TBIL (≥20 *vs.* <20 μmol/L)	–	–
ALT (≥40 *vs.* <40 U/L)	–	–
ALB (<40 *vs.* ≥40 g/L)	–	–
PLT (<100 *vs.* ≥100*10^9/L	–	–
AFP (≥400 *vs.* <400 ng/mL)	1.244 (1.077–1.426)	0.003
HbeAg (positive *vs.* negative)	–	–
HbsAg (positive *vs.* negative)	–	–
Microvascular invasion (presence *vs.* absence)	1.696 (1.508–2.009)	<0.001
Surgical margin (<1 *vs.* ≥1 cm)	1.053 (0.915–1.232)	0.469
Anatomical resection (no *vs.* yes)	1.058 (0.926–1.277)	0.416
Anti-virus treatment (yes *vs.* no)	0.792 (0.611–0.978)	0.035
PR	1	
PR area ≥90% *vs.* without preoperative TACE	0.742 (0.561–0.963)	0.032
PR area between 60–90% *vs.* without preoperative TACE	1.036 (0.869–1.119)	0.812
PR area <60% *vs.* without preoperative TACE	1.428 (1.095–1.929)	0.009
TACE sessions		
With single preoperative TACE session *vs.* without Preoperative TACE	–	–
With multiple preoperative TACE sessions *vs.* without Preoperative TACE	–	–

HR, hazard ratio; CI, confidence interval; TACE, transcatheter arterial chemoembolization; HCV Ab, hepatitis C virus antibody; HBV, hepatitis B virus; DNA, deoxyribonucleic acid; TBIL, total bilirubin; ALT, alanine aminotransferase; ALB, albumin; PLT, platelet; AFP, serum alpha-fetoprotein; HbeAg, hepatitis B e antigen; HbsAg, hepatitis B surface antigen; PR, pathological response.

with different PR areas and patients without preoperative TACE have been compared both before and after PSM. The 6-, 12-, and 24-month tumor recurrence rates in patients with tumor PR ≥90% who had preoperative TACE were significantly lower than those patients without preoperative TACE before and after PSM (both P<0.001 before and after PSM) (*Fig. 2A*,*2B*). In patients who had tumor PR between 60–90%, the corresponding tumor recurrence rates were comparable between the 2 groups of patients before and after PSM. In patients who had PR between 60–90% similar results were obtained between the 2 groups of patients (P=0.183 before PSM, and P=0.364 after PSM) (*Fig. 2C*,*2D*). However, patients with tumor PR <60%, the 6-, 12-, and 24-month tumor recurrence rates were significantly higher than those patients without preoperative TACE before and after PSM (P<0.001 before PSM, and P=0.042 after PSM) (*Fig. 2E*,*2F*). The 1-, 3-, and 5-year cumulative OS rates in patients with tumor PR ≥90% were significantly higher than those patients without preoperative TACE before and after PSM. (P<0.001 before PSM, and P=0.014 after PSM) (*Fig. 3A*,*3B*). For patients with tumor PR between 60–90%, the 1-, 3-, and 5-year cumulative OS rates were similar as those patients without preoperative TACE before and after PSM (P=0.259 before PSM, and P=0.604 after PSM) (*Fig. 3C*,*3D*). With tumor PR <60% the 1-, 3-, and 5-year cumulative OS rates of patients were significantly lower than those patients without preoperative TACE before and after PSM (P<0.001 before PSM, and P=0.045 after PSM) (*Fig. 3E*,*3F*).

It has well been reported that selective/superselective TACE to be able to obtain a higher rate of tumor necrosis than the conventional hemiliver or whole liver TACE (3,4). As a consequence, selective/superselective TACE should be carried out whenever technically feasible. In addition, the treatment regimen of chemoembolization can also affect the outcomes of TACE. A previous study has shown that a combination of cisplatin-Lipiodol emulsion and gelatin sponge particles is the most generally accepted method for chemoembolization (5). We used this method in our study and added 5-fluorouracil (1 g) and mitomycin C (20 mg) into the cisplatin-Lipiodol emulsion. This regimen of chemoembolization has also been used in two other studies (6,7). The impacts of dosages of chemo-agents and lipiodol, and sizes of gelatin sponges on tumor PR after preoperative TACE are unclear and they need to be further studied. In our study, the dosages of chemo-agents and lipiodol, and sizes of gelatin sponges were given based on tumor size, tumor number, tumor location, vascular condition of tumor feeding artery, patients' liver function, and presence or absence of accompanying liver cirrhosis.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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