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Reply to: “Adjuvant medications that improve survival after locoregional therapy.”

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We thank Dr. Jiang for the interest in our paper [1], where we showed that aspirin was associated with improved survival when taken at the time of initial embolization for HCC.

Before embolization, the aspirin and non-aspirin groups showed no difference in AJCC stage, Child Pugh score, etiology of underlying liver disease, ECOG performance status, Charlson comorbidity index, or prior therapy (sorafenib or liver resection). This is not surprising, because aspirin is taken for reasons unrelated to the HCC diagnosis, such as pain or cardiovascular disease.

After embolization, the aspirin group showed significantly improved survival. In addition, there were differences in subsequent therapy after completing the initial treatment. When comparing the aspirin versus non-aspirin groups using the Fisher exact test, the aspirin group was more likely to receive additional ablation (21% vs 8%, $p=0.009$) embolization (60% vs 39%, $p=0.01$) and radioembolization (5% vs 0%, $p=0.02$), but no difference in subsequent liver resection (0% vs 2%, $p=1$). To evaluate whether these differences were due to the increased survival in the aspirin group allowing them to survive long enough to receive additional therapy, we also examined additional procedures in just the first year after initial embolization, in patients who survived at least one year. In the first year after initial embolization, the aspirin group was more likely to receive additional embolization (65% vs 36%, $p=0.01$) but there was no difference in subsequent ablation (13% vs 6%, $p=0.2$), radioembolization (0% vs 0%, $p=1$), or liver resection (0% vs 3%, $p=1$). We do not have complete data on subsequent liver transplantation, because those patients were referred to a transplant center.

Based on these data, it appears that aspirin taken at the time of initial embolization for HCC is associated with an increase in subsequent ablation and radioembolization, which is related to the patients surviving long enough to receive additional therapies. In addition, the aspirin group was more likely to receive additional embolization, possibly because they were more likely to remain candidates for additional embolization in the first year after initial

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embolization. Future studies should examine whether aspirin affects response to embolization or time to progression after embolization, and the exact mechanism for improved survival after embolization.

Starting HCC patients on aspirin 81 mg daily before TACE or TAE might be beneficial, based on the evidence presented in our paper [1], another retrospective study showing improved survival when combining aspirin and TACE for HCC [2], a retrospective study showing that aspirin reduces both the risk of developing HCC and the risk of death from chronic liver disease [3], and randomized trials showing that aspirin decreases the risk of death from various adenocarcinomas [4]. Caution should be exercised if the patient has peptic ulcer disease, high risk of bleeding, or another contraindication to aspirin. Combining aspirin and TACE or TAE should be further evaluated in a randomized trial.

References

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