

Dear Editor of World Journal of Gastroenterology,

It is a pleasure for us to have our paper accepted for publication in your Journal.

We have carefully read all the comments from the reviewers about the manuscript.

Reviewer #1

Were there patients with symptoms who did not undergo endoscopy and may have had ulcers? How many patients were lost to follow up? Was there a symptom level that triggered endoscopy?

One of the most common adverse events after radioembolization are nausea and vomiting (20 – 32 %), after abdominal pain (23 – 56 %) and fatigue (54 – 61 %). They usually are mild and are successfully treated with medication (Sangro B. J Hepatol. 2012 Feb;56(2):464-73). As many patients have these symptoms, we only performed an endoscopy in those cases with severe or persistent symptoms despite of the medication.

None of the patients were lost during the follow up. They have different follow up periods because we evaluated a wide period of time, and the ulcers occurred in different moments.

Did any of the patients with ulcers have replaced left hepatic arteries from the left gastric artery in which the left hepatic artery was embolized through the left gastric following occlusion of gastric branches?

None of the patients in our series had this problem.

Were glass or resin microspheres used in this series?

We have used in all the procedures resin microspheres. It has now been specified in the manuscript (Material & Methods section).

Did any of the ulcer patients have premature occlusion of the treated artery allowing for retrograde administration of the agent?

One of the patients (patient 4) had a spasm of the treated artery that could lead to retrograde placement of the microspheres. This patient was treated by a double injection on the left and right hepatic arteries. Only half the prescribed dose could be injected into the left hepatic artery due to spasm, while the entire prescribed dose was injected into the right hepatic artery uneventfully. This is now described in the text.

Did retrospective review of the arteriography reveal residual extrahepatic supply?

A retrospective analysis of the arteriographies has been done. None of the studies had an extrahepatic deposit of contrast or collaterals in the planification angiography. It has now been specified in the paper (Discussion section).

Is there a potential for difference in incidence of ulcers in glass (less embolic) vs resin (more embolic) microspheres?

In series cited was there difference in ulcer incidence between the two agents?

Gastric ulcers result from the unnoticed presence of collateral vessels and therefore, they are much dependent on the experience of the interventional radiologist performing the procedure and on the site of injection. The higher number of studies reporting gastric ulcers after RE using resin microspheres is most likely due to the fact that glass microspheres are almost invariably delivered by a selective lobar or sublobar injection while resin microspheres are quite often injected into the proper hepatic artery (particularly for unresectable liver metastases). When glass microspheres were injected into the hepatic artery in an early series of HCC patients, 13.6% of them developed gastric ulcers (J Nucl Med 2000;41:1673). For resin microspheres, the Mount Sinai group reported an incidence of 2.6% among 270 RE-treated patients (Dig. Dis. Sci. 2010;55:2450). Furthermore, there are no controlled studies comparing the occurrence of gastrointestinal ulcers with either device.

It is also must to say that the pathophysiology of the ulcers is secondary to the radiation damage more than the embolization effect of the vessels (Carretero C. Am J Gastroenterol. 2007 Jun;102(6):1216-20).

Would be helpful to label findings on photographs.

We think that the figures are self-explanatory. If you consider that they need a specific labelling please let us know.

Reviewer #2

Overall, it is a well-written article. The only thing that should be mentioned is the relationship of the rate of the nontarget deployment of microspheres and the site of injection (lobar VS bilobar). Table 1 shows that in 4 out of 6 patients who had the complication, particle injection site was common or proper hepatic artery. This technical detail should be given in the 'radioembolization technique' and also should be discussed in the 'Discussion'. Seems like proximal injection increases the risk of extrahepatic deployment of the microspheres.

A comment about the site of injection and its possible role in the pathogenesis of the ulcers has been included in the manuscript (Radioembolization technique and Discussion sections).

We hope that we have answered all your questions and made a satisfactory point by point correction.

Yours sincerely,

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