**Revisão - Revisor A**

Agradecemos ao Revisor A pelos comentários e questões que coloca. Em seguida, respondemos às questões colocadas.

Métodos:

**Comentário 1:** *A decisão pela realização de TACE foi tomada numa reunião multidisciplinar de decisão terapêutica, envolvendo Hepatologistas, Cirurgiões e Radiologistas? Se sim, isto deveria ser referido.*

**Resposta:** Sim. Esta informação foi acrescentada na secção Métodos: “The decision of which patients should perform TACE procedures was made in a weekly multidisciplinary team meeting that included surgeons, hepatologists and radiologists.”

**Comentário 2:** *A população de estudo deveria ter sido melhor caracterizada, nomeadamente quanto à etiologia da hepatopatia.*

**Resposta:** A caracterização da população quanto à etiologia da hepatopatia foi acrescentada na secção métodos:

“The most frequent cause of cirrhosis was alcohol-related liver disease, which accounted for 44% of the patients (121 patients). Other common cause of cirrhosis was viral infection: there were 50 patients (18%) with hepatitis C virus (HCV) infection alone and 51 patients (18%) with both HCV infection and alcohol abuse. There were also 12 patients (4%) with cirrhosis related to hepatitis B virus (HBV), 3 patients with both HBV virus infection and alcohol abuse, 4 patients with HBV plus HCV infection and one patient with all these three factors combined (HBV + HCV + alcohol abuse). Hemochromatosis was the cause of cirrhosis in 3 patients, and there were also 3 patients with hemochromatosis plus alcohol abuse and one patient with hemochromatosis and HCV infection. Non Alcoholic Fatty Liver Disease (NASH) was the cause of cirrhosis in 5 patients and there were also 4 cases of cryptogenic cirrhosis and one case of auto-immune cirrhosis. Three patients with non-cirrhotic livers on biopsy developed HCC. There were 14 clinical charts in which the cause of cirrhosis was not clear.”

**Comentário 3:** *Há dúvidas no follow-up dos doentes. Foram contabilizados os doentes que podem ter sofrido síndrome pós-embolização (PES) após a alta e que recorreram a outras instituições? Assim, a incidência de PES pode ter sido subestimada. Esta limitação é referida da discussão mas o Material e Métodos deveria ter contemplado isto, nomeadamente com uma consulta de seguimento.*

**Resposta:** Todos os doentes mantiveram consulta de seguimento em Cirurgia Hepato-biliar no Centro. Todos os doentes realizaram consulta de follow-up 1 e 3 meses após o procedimento. Este dado foi também acrescentado na secção Métodos: **“**The patients submitted to TACE procedures maintained a follow-up medical appointment in our centre with a hepatobiliary surgeon and all of them had an appointment one and three months after the procedure.

Foi também reformulada esta informação na discussão: “But if, for example, a patient had recurred to another institution with symptoms of PES in the post-procedural period, we would not have access to that information if the surgeon did not register it in the clinical chart in the usual follow-up appointment (one/three months after the procedure).”

**Comentário 4:** *É referido que dois doentes tiveram PES e “hepatite”. Qual a definição para esta complicação? Elevação assintomática das aminotransferases ou compromisso da função hepatocelular?*

**Resposta:** A definição foi a elevação assintomática das aminotransferases (esta informação foi acrescentada na secção resultados, quando é fornecida a informação relativa às varias complicações observadas):

“two patients had PES and hepatitis (asymptomatic elevation of aminotransferases)”

Resultados:

**Comentários:** *As tabelas deveriam ter legendas mais completas. A leitura da legenda das tabelas deve ser auto-suficiente.*

**Resposta:** Acrescentámos pontos que consideramos importantes nas legendas das tabelas para a sua correcta compreensão:

**“TABLE 1:** Transarterial chemoembolization complications **–** This table indicates the number of complications observed after TACE procedure, the corresponding percentage for the total number of complications and also the percentage for the total number of procedures. Some patients had more that one of the complications listed.

**TABLE 2:** Categorical variables: Chi-square (Pearson)/Fisher test – This table shows the proportion of procedures in each category for both cases and controls, the respective percentage and the p-value of Pearson/Fisher tests. A p-value less than 0.05 was considered statistically significant.

**TABLE 3:** Continuous variables: T-test for independent samples – In this table we can see the media ± standard deviation for the continuous variables in the cases and control groups and the p-value of T-test for independent samples. A p-value less than 0.05 was considered statistically significant.

**TABLE 4:** Multivariate logistic regression – This table shows the results for multivariate logistic regression, namely the Odds Ratio, the confidence interval and p-values. A p-value less than 0.05 was considered statistically significant.”

Discussão:

**Comentário:** *A associação entre PES e o sexo feminino merecia outra análise mais cuidada. Quais os factores que podem justificar? Influências hormonais? Etiologia diferente de hepatopatia nos sexos?*

**Resposta:** Acrescentámos alguns pontos à discussão:

**“**Our results showed that female gender is related with a higher risk of PES and this association was confirmed in Multivariate logistic regression. This finding was also pointed out in a previous study by Siriwardana *et al*.2 Another study by Wang *et al*.18 also showed that female gender correlates with a higher incidence of postprocedural nausea, particularly in premenopausal women.18 In that study, they found no statistically significant difference in the incidences of nausea and vomiting between male over 50 years and female patients who have entered menopause, a finding that raised the suspicion that these association could be due to hormonal causes, namely the oestradiol level. However, in our study, all women included both in the cases and control groups were postmenopausal, so this explanation is not applicable. Another aspect that would be interesting to investigate is the potential influence of the body mass index (BMI), which is general inferior in female patients. It was not possible to investigate this association in the present study since it is a retrospective study and the necessary data (height and weight) was not present in the clinical charts. We could also consider the possibility of this association being related with other confounding factors that can differ between genders, like the cause of cirrhosis.”

Conclusões:

**Comentário:** *Na análise multivariada, apenas o sexo feminino foi factor de risco para PES. Este facto deveria ser reforçado. Os restantes factores de risco indicados (dose de doxorrubicina e tamanho do maior nódulo) não foram confirmados.*

**Resposta:** Esta informação foi acrescentada, com ligeira reformulação da Conclusão:

**“**With this study, we found that female gender is related to a higher incidence of PES. This association was the only one that was further confirmed in multivariate logistic regression. The reason for this association is not yet understood and deserves future investigation.

We also found that the administration of a dose of doxorubicin above 75 mg is associated with a higher risk of developing PES. This finding may be helpful for decision making in clinical practice, whenever it is possible to avoid a higher dose without compromising the efficacy of the treatment. The size of the largest nodule treated was also associated with the risk of development of PES after TACE for HCC treatment.

Age, Child-Pugh and MELD scores, number of nodules, embolization of the cystic artery, use of additional embolics, previous TACE procedures and segmental portal vein thrombosis were not related to the development of PES.”

Figuras:

**Comentário:** *O material de sutura descrita poderá corresponder a clips metálicos ou agrafos de sutura de encerramento da ansa digestiva da hepaticojejunostomia. Não deverão ser descritos como “material de sutura da anastomose biliodigestiva”.*

**Resposta:** Esta legenda foi corrigida – “Computed Tomography scan showing the presence of metallic suture staples of hepaticojejunostomy.”