

SPECIFIC COMMENTS TO AUTHORS

General comments: This study is a single-institutional retrospective review of 522 patients with liver cancer treated with transarterial chemoembolization (TACE). The authors evaluated therapy-related pain of patients within 24 hours after TACE. As a result, 97 (16.7%) of these patients had moderate to severe pain. Blood vessel invasion, TACE history, drug-eluting beads TACE, and previous history of abdominal pain after TACE were significant predictors for moderate to severe pain following TACE. On the basis of the outcomes, they made out the predictive model to manage more suitably acute pain of patients treated with TACE. This article is interesting and well written. Actually, their work does not contribute to improved prognosis of patients, but the evaluation of quality of life is an important issue. It will give useful information to physicians. However, there are some problems that the authors should clarify and revise as mentioned in the specific comments below.

Specific comments:1. **Materials and methods, Patients** In this study, performance status was included in inclusion criteria, but is not included in Table 2. Why was it? Wasn't this a significant predictor for pain?

Answer: The inclusion criteria are actually the same as those for the indication of TACE. Thus, instead, we have included a detailed description of the exclusion criteria. Performance status may be a significant predictor for pain, but we did not look into the data, and now that the research is over there is no way to go further, so I have added discussion of this to the section on the limits of the study (p. 7 & p. 14).

2. **Materials and methods, Chemoembolization procedure** Dezocine (5 mg) was used as an analgesic during surgery. Were there no patients who more and/or other type of analgesics were used to relieve increased pain during TACE? If any, didn't it affect the results of pain following TACE? Does "perfusion chemotherapy" mean systemic

(intravenous) chemotherapy?

Answer: Very few patients had pain during surgery and need additional painkillers, but this has been added to the exclusion criteria (MATERIALS AND METHODS, p. 7).

“Perfusion chemotherapy” does not mean systemic (intravenous) chemotherapy, but arterial perfusion.

3. Materials and methods, Analysis, 1st paragraph The pain scores were recorded 0, 2, 4, 6, 12, and 24 h after TACE.” Was the greatest score through the overall time defined as a pain score in each patient? Please clarify it.

Answer: Yes. I have added this information to the revised manuscript (p. 8).

4. Discussion Do the authors think that there was no relationship between the total dose of chemotherapeutic agents administered for TACE and the pain score? If possible, I suggest discussing this matter.

Answer: Some studies show that the total dose of chemotherapeutic agents administered for TACE is related to the pain score. In this study, the chemotherapy drugs used were pirarubicin hydrochloride administered at a dose of 30 mg for traditional TACE and 60 mg for DEB-TACE, and that may be one of the reasons why postembolization pain was worse for DEB-TACE. I have added this point to the revised manuscript (p. 13).

5. Table 1 Please add a unit to “Dose of Lipiodol”.

Answer: I have added this information to the revised manuscript (p. 20).

6. Table 2 Does “recurrence” mean recurrence after surgery? Does “Non-multiple” mean solitary? Were diffusely extended tumors defined as “Multiple”? Please write what HCC, ICC, and PVA show in full in the footnote of this table.

Answer: “recurrence” means recurrence after surgery. I have added this information (Tables 2 and 3).

“Non-multiple” means fewer than 3 tumors, multiple means 3 or more tumors including diffusely extended tumors. I have added this information (Tables 2 and 3).

I have defined HCC, ICC, and PVA in full in the footnotes of Tables 2 and 3.

7. Table 3 What is a definition of “Invasion of blood vessels”? Were both hepatic vein and portal vein included? Up to their first or second branch? Please specify it in the text. “Postoperative analgesics” was not significant variable for pain. Does this mean that analgesics were not selected in accordance with the grade of pain?

Answer:

7.1 Invasion of blood vessels means portal vein tumor thrombosis (PVTT). Primary liver cancer has a great propensity to invade the portal venous system, which leads to PVTT. PVTT is found in the trunk or branches of the portal vein, and TACE is considered if the portal vein trunk is not completely blocked or portal collateral circulation is already present in the hepatic hilar region. I have specified this in the Discussion (p. 12).

7.2 Postoperative analgesics refer to **prophylactic analgesics**, including NSAIDs or weak opioids. prophylactic analgesics was no significant variable for pain . It might be that the efficacy of these analgesics was relatively weak, and the prevention effect of moderate and severe pain was relatively weak. Therefore, some scholars suggest that strong opioids should be used to prevent TACE pain.

When pain occurred, analgesics were selected in accordance with the grade of pain; tramadol or morphine is usually selected for moderate or severe pain, but these analgesics were not included in our study.