Reviewer’s report

Title: Intra-arterial ethanol embolization augments response to TACE for treatment of HCC with portal venous tumor thrombus

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Reviewer: Daniel Sze

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Review: BMC Cancer

Ethanol Delivery for Portal Vein Tumor Invasion using Cone Beam Computed Tomography: A Pilot Study

BCAN-D-17-00753

Title: Unclear what "ethanol delivery" entails. Cone Beam CT is already standard of care for TACE and other liver-directed therapies, and this is not a new application. Consider changing to "Intra-arterial ethanol embolization augments response to TACE for treatment of HCC with portal venous tumor thrombus."

Abstract: Needs grammatical editing throughout

Keywords: remove "transcatheter ethanol delivery"

Background:

Page 5 Line 8 5th most common in incidence, 2nd most lethal

Page 5 Line 18 Precipitation of bleeding is from exacerbation of portal hypertension, and is not limited to esophageal and gastric varices. Gastropathy, rectal and duodenal varices are other common complications. In addition, ascites is a common complication.

Page 5 Line 43 What is the benefit from sorafenib? Cite statistics.

Page 5 Line 48 Add background and reference that PVTT was formerly considered a contraindication to TACE

Page 5 Line 54 Avoid abbreviations like "IHL" that are not standard.

Page 6 Line 13 Specify intraarterial, since other applications have involved intraportal
"transcatheter ethanol delivery (TED)" is too vague and nonstandard. Consider changing to "intraarterial ethanol embolization."

Methods:

Unclear - the control arm consisted of eligible patients who refused ethanol embolization?

What is the definition of "optimal coagulation and liver function"?

Child class B could be INR of 5 or bilirubin of 20, which are certainly not optimal coagulation or liver function.

Which typical features? Consider using a standard system such as LIRADS, OPTN, or AASLD

Why limit to 18 cm?

Criterion 9 states patients must refuse sorafenib, but criterion 11 states they must have already been treated by sorafenib and failed - mutually exclusive?

Procedure:

Spell out FPD and all other abbreviations at first usage

If feeding artery was treated with ethanol until occlusion, how could they embolize with gelatin sponge particles? The artery was already occluded. Figure 2 appears to show gelatin sponge embolization of the parent artery, not the PVTT feeding arteries.

How did authors limit gelatin sponge particles to 0.2-0.5 mm size? Fragmentation through a 3-way stopcock yields a much wider assortment of sizes.

No analgesia or sedation?

How did the authors decide who needed repeat treatment? Interval imaging? Original PVTT size or extent? Original dose of ethanol? Lipiodol uptake by CBCT? How many patients underwent repeat treatment?

What tradition? What dose and concentration of epirubicin? What was the epirubicin dissolved in? What ratio of epirubicin solution to lipiodol? What maximum doses of epirubicin and lipiodol? Was gelatin sponge or other embolic mixed with epirubicin/lipiodol emulsion? What was the angiographic endpoint?

This paragraph is unclear and needs to be rewritten. If the PVTT-feeding artery could not be catheterized, how was "mixture injected in PVTT-feeding artery?" Was TACE performed to stasis distal to small tortuous feeding arteries, followed by proximal injection of ethanol? Call out Figure 2.
Page 10 Line 56   How did the authors catheterize the "distal outflow vein?" Navigate through the PVTT from the arterial end? Direct percutaneous portal access? If blood is flowing away from the PVTT in the vein, how did the authors make the gelatin sponge stay in the vein? The figure illustrates embolizing the artery that feeds the outflow vein, not the outflow vein itself.

Page 11 Line 21   Port? What port? Did all these patients have intraarterial ports placed? If so, where was the infusion site - proper hepatic artery? This is certainly not "traditional TACE."

Page 11 Line 54   Grading system would benefit from a figure and drawings, and additional details. For instance, grade is recanalization - recanalization of what? How complete? If a right lobe PVTT previously protruded into the main PV and retracted after treatment to allow recanalization of the main and left PV but the right PV is still completely occluded, is that grade 3? For grade 2, what degree of decrease is enough? In addition to diameter, is retraction of length measured? Likewise for grade 0, what if diameter is stable but length is increased? Certainly a response system is needed, but the described system is inadequately detailed.

Page 12 Line 24   What if lesion diameter decreased but there was still enhancing tumor?

Results:

Page 13 Line 5    Maximum of 50 mg epirubicin, or did all patients receive same dose regardless of tumor size? What volume lipiodol for TACE?

Page 13 Line 16  Did all patients undergo CT 2-7 days after treatment? If so, this should be described in Methods.

Page 13 Line 38  Use consistent significant digits.

Page 13 Line 60  Consider using a standard of toxicity, such as CTCAE v. 4.03, and SIR or CIRSE standards of procedural complications.

Page 14 Line 24  Stable disease should not be included as "response." Objective response is CR + PR. Adding SD is "Disease control rate."

Page 14 Line 29  What is "clinical response rate?" Other response described in this paragraph is radiographic response, not clinical response. Does clinical response mean response by the PVTT grading proposed on page 11?

Discussion:

Page 14 Line 54  What were the results of TED for HCC in reference 16?
Stage of disease should have been described in Methods. No new data should be presented in the Discussion. Table 1 does not support claim that test patients had more advanced disease.

TACE+TED OS was higher, but TACE alone OS was far lower than other figures published in the literature. Why?

What is meant by control of ethanol doses? Amount of ethanol? Distribution of ethanol?

Well performed CT and MRI with dynamic imaging provides good flow information. The CTs in the figures appear to be performed with poor contrast bolus and too early timed arterial phase, so it may be true that CT and MRI performed at the authors' institution do not provide good flow information. Contrast-enhanced US can also provide very good PVTT diagnosis. Catheter angiography and CACT should not be relied upon for diagnostic purposes in this day and age.

The advantages of using CACT for liver-directed therapies has been well documented, and the superficial and incomplete description here could easily be replaced by a few good references.

Many authors use other ratios. Why not use lower concentration of lipiodol?

In PVTT, often there is hepatofugal flow in the affected PV, and administration of lipiodol/ethanol passing through sinusoids would result in nontarget portal embolization. The references they describe here are not pertinent.

Any evidence that it diffuses within tumor cells? Previous paragraph just wrote on mechanism of action of ethanol on vascular endothelium. Authors should not make claim of diffusion unless they have proof or references.

Why include one sentence on angiogenesis? Did they study this? Are they proposing that angiogenesis is a factor in TED?

Limitations:

Ethics of randomizing vs sorafenib? Need to review published results of sorafenib. Is repeated TACE cheaper than sorafenib?

Table 1

Cirrhosis, ascites can be graded rather than be binary.

Was tumor size distribution normal? If not, should use median, not mean
"Angiography of PVTT feeding-artery" is not normally reported, and I am not sure what these numbers mean

Table 3

Adverse events should be graded from 0 to 5, not binary.

Figure 2

How does the port fit in to this procedure?

Figure 3

A3: Arterial phase image is very early and does not show PVTT enhancement. Aorta is not very enhanced, suggesting weak bolus.

B2: Any evidence of arteriportal shunting?

C: Any followup imaging of response? Did lipiodol wash out of PVTT faster than from intraparenchymal tumor?

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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I recommend additional statistical review

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