

1. Eligibility criteria for downstaging and the definition of downstaging determined the success rate of downstaging treatment. The authors need to analyze the outcomes accordingly to clarify the effectiveness of different downstaging protocol.

Unfortunately many research didn't provide detailed information about the unresectability of HCC. EASL-EORTC Clinical practice Guidelines(CPG) presented patient with solitary tumors and very well-preserved liver liver function,defined as normal bilirubin with either hepatic venous pressure gradient \leq 10mmHg or platelet count \geq 100000 as good candidate for resection. Furthermore anatomical resections defined are also recommended. What's more, patients are considered not suitable for surgery when they have insufficient FLR, portal vein thrombosis,portal invasion, multinodular tumors, extrahepatic metastases , unsatisfied ICG-R15. In fact, in some research we have searched, HCC are not unresectable at first, and many of them provide no details about why it is unresectable.

Our view is coincident with Law WY, and we quote one of his table to add weight to our view.As we can see, there is no definite definition of unresectability.

TABLE 1. *Studies on salvage surgery after tumor downstaging for unresectable HCC*

Study	Patients receiving downstaging regimen (n)	Reason of unresectability	Downstaging agent
Sitzmann et al. 1993 ⁴⁵	Unknown	Distant metastases; four segments disease; major vessels involvement	Combined radiotherapy (external beam/ ¹³¹ I-labeled antiferritin) and chemotherapy
Majno et al. 1997 ⁴²	49	Unknown	TACE
Fan et al. 1998 ⁴¹	360	Tumors were too bulky for resection; tumors were situated centrally at the hepatic hilus	TACE
Meric et al. 2000 ⁴⁶	25	Proximity to major vessels; liver cirrhosis	HAI
Clavien et al. 2002 ⁴⁷	5	Extensive bilobar tumor; large solitary tumor; proximity of major vessels	HAI
Lau et al. 2004 ⁴⁴	270	Distant metastases; extensive bilobar tumor; major vessel involvement	Chemoimmunotherapy; intra-arterial ⁹⁰ Y microspheres; sequential therapy
Tang et al. 2004 ⁴³	1085	Unknown	HAL/HAI alone; HAI+HAL; HAI + HAL + radioimmuno-therapy/radiotherapy

Given that downstaging, we previously think tumor downstaging is from T3 to T2 based on UNOS criterion. But here we give downstaging a new definition: make resection possible,that is when tumor is downstaged after conversion therapy ,it increases it resectability, not just based on UNOS

2. The authors presented different methods to evaluate residual liver volume, liver function and liver stiffness. The advantage and shortcomings of these methods should be analyzed and discussed.

According to the opinion reviewer,we have added some advantages and shortcomings in the assay.

3. The authors proposed that salvage surgery should be performed after TACE when (1) after CR both in radiology and AFP; (2) PVT has disappeared as confirmed radiologically and no extrahepatic metastasis occurs; and (3) corresponds to the Makuuchi criteria. The criteria is hard to reach when the tumor size is > 5 cm, or when major vascular invasion presents. The author should provide the possibility of successful downstaging under such criteria.

4. Viable tumors during pathological examination is frequent after TACE, even in radiological

complete response tumors. The authors suggest removing the tumors even after TACE. If this is true, TACE procedure without increasing the residual liver volume cannot increase the resectability of HCC. More evidence and clear explanation for this suggestion is recommended.

Answer: For question 3 and 4, We carefully assess the assay and renew our conclusion. we considered that not all patients undergo salvage surgery after TACE, especially those who achieve CR with respect to necrosis. The rationality might be that patients achieving CR in terms of radiologic necrosis actually have no or few viable tumor cells which potentially induce tumor recurrence, resulting in better survival. We also think that the subsequent salvage time after TACE to be the time when patients achieve PR in radiology, because considerable quantity of tumor cell still active in liver and resection is expected to remove the viable tumor cell in order to prolong the DFS.

In the future, more effort should be put on the following to evaluate the timing for salvage surgery: (1) diminishment of large hepatocellular carcinoma. (2) future liver remnant. (3) disappearance of PVT or MVI. (4) margin with tumor clearance >2cm.

5. The increased liver volume after portal vein embolization (PVE) is not proportional to the improvement of liver function. Decision for safe liver resection after PVE should be different from that in patients without PVE. The authors reviewed criteria for successful liver resection both after PVE and without PVE. They suggested liver resection is safe when FLR is >25%. The conclusion is not fully supported by the references.

We have refresh our search and conclusion. the majority of assays mixed the safe cutoff with PVE with safe cutoff without PVE and only few assays taking a close look at what the safe cutoff of FLR after PVE it is. Possible reasons is elucidated by [52] [43], which indicated the immediate post-operative liver function per unit of volume in patients with PVE is better than those without PVE. Two large studies have confirmed the 20% FLR as safe cutoff for surgery [44, 47]. we refresh the conclusion: FLR is usually used for evaluation of the appropriate surgery time; surgery may be safe when FLR is >20% for normal livers after PVE. Other predictive parameter like GR, KGR are treated as an effective supplementary to the assessment. Tc-99m-GSA scintigraphy might be a good candidate to accurately evaluate the salvage surgery time

6. The authors recommended SIRT “for patients with insufficient FLR, vital structures invaded by tumors or a heavy tumor burden”. Other downstaging treatments can also be used under the same circumstances. The authors did not define the specific role of SIRT.

We search for assays again. We found that Y-90 RE didn't distinguish itself compared with other conversion therapy. In terms of FLR, PVE is superior to RE. According to our search, y-90 RE is considered when patients are contraindicated for PVE or vital structure is likely to get invaded because of tumor progression. In terms of those who only needs adequate FLR, PVE is prior to RE. More studies are expected to test the efficiency of Y-90 RE as conversion therapy.

7. In theory, sequential TACE and PVE provide a safe and effective method of HCC downstaging. The authors need to clarify the eligibility criteria in compares with TACE or PVE only.

Studies on TACE+PVE is rare. We have found that compared with PVE, TACE + PVE is able to

induce higher rate of hypertrophy and tumor necrosis. Compared with TACE, TACE+PVE features higher rate of hypertrophy, and there are few studies on the difference in terms of tumor necrosis. Peter has reported: 48.3% of patients with IAT+PVE had either a partial or complete response based on EASLD criteria on cross-sectional imaging, compared with a mean tumour necrosis of 50% to 60% in patients with IAT alone. We think that it need more research to demonstrate its efficiency.

8. The full text of PLF should be supplied.

PLF is changed into PHLF post hepatectomy liver failure

9. Spelling errors are found in this article. English editing is necessary.

We have check out the assay and modify it.

10. The manuscript of Zhang et al. presents several important problems, so that an initial comment about their aim is difficult to be done. They did not insert the page number, therefore it was difficult to trace the comments. The title is cryptic since it is explained neither what is the purpose of the manuscript nor that it is a review. The abstract summarize and reflect the work described in the manuscript. In the abstract there are plenty of abbreviations that are not defined. In the first line of the abstract they report that the manuscript is a review, but they should specify the type of review (in this case they presented a narrative review). Once again, in the first line it is not clear what the authors mean for "The aim of this review was to investigate conversion therapy ..". The first paragraph of the methods should be rewritten "Conversion therapy and salvage surgery were briefly defined and then we proceed to the literature retrieval of these topics". The preoperative types of liver volume and function assessment are just the summary of common parameters or scores known in the literature. This should be not considered a search but merely a list.

First, we have insert page number. The purpose of our review is to review the conversion therapy for initially unresectable hepatocellular carcinoma(HCC) patients and the possible timing for subsequent salvage surgery, which is correlated to the title: For initially unresectable hepatocellular carcinoma: conversion therapy and the possible timing for subsequent salvage surgery: a narrative review. We also add some full text to the abbreviation in the abstract. Our types of review is narrative review. And we have modify the sentence: Conversion therapy and salvage surgery were briefly defined and then we proceed to the literature retrieval of these topics.

10. The preoperative types of liver volume and function assessment are just the summary of common parameters or scores known in the literature. This should be not considered a search but merely a list.

A: we have deleted the sentence.

11. In the following sentence (line 10-11) the authors probably meant that they provided a careful search of conversion therapies and salvage surgery strategies reported in the literature. The key words are not correctly listed. For example “Hepatocellular carcinoma; Initially; Unresectable” should be substituted with “Unresectable hepatocellular carcinoma”

KEY words has been modified. “unresectable hepatocellular carcinoma” , “hepatectomy” , “conversion therapy” , “resection” , “salvage surgery” and “downstaging”

12. The manuscript adequately describes the background and present status while the aim is not well explained. In addition, the following sentence is repetitive and should be removed “It has been reported that initially unresectable HCC patients undergoing conversion therapy followed by salvage surgery have a 5-year survival rate of 57%, comparable to the rate in patients who underwent liver resection immediately after presenting with resectable tumors[8]” .

We have removed the sentence.

13. The methods describing the procedure used to select papers from the literature are very insufficient.

A pubmed search was undertaken from 1987 to 2017 to identify articles using the key words “unresectable hepatocellular carcinoma” , “hepatectomy” , “conversion therapy” , “resection” , “salvage surgery” and “downstaging” . Additional studies were investigated through a manual search of the references from the articles. The main and widely used conversion therapies and the subsequent salvage surgery time were discussed in detail. Two members of our group independently performed the literature search and data extraction.

The research objectives are achieved by the experiments used in this study. However, the contributions that the study has made for research progress in this field is limited by the nature of the paper. The manuscript interprets the findings highlighting the key points clearly and logically. The findings and their applicability/relevance to the literature are stated in a clear and definite manner. Part of the discussion is reported in the results section where the authors make comments on the various techniques used. Apart from authors’ comments the issue treated is of relevance to clinical practice. Figures should be improved (the figure is hardly legible). Tables are sufficiently good. References are appropriate. The style, language and grammar are accurate, but there are many typographical mistakes (words not followed by space). As far as the research methods and reporting, the authors did not insert the PRISMA 2009 Checklist

1. title

we have changed it in to "Conversion therapy and suitable timing for subsequent salvage surgery for initially unresectable hepatocellular carcinoma: what is new?"

2. In the Abstract –Results section- the authors report the definition of Conversion

Therapy that is not mentioned in the manuscript.. In the following paragraph the definition of conversion therapy should be added. I would suggest "Therapy that may render some unresectable tumors surgically approachable and may also contribute to better outcome. (Advances in systemic therapy for hepatocellular carcinoma. James J. Harding, ... Ghassan K. Abou-Alfa, in Blumgart's Surgery of the Liver, Biliary Tract and Pancreas, 2-Volume Set (Sixth Edition), 2017).

We have added the definition of conversion therapy and used the citation. The definition is

"It is usually defined as the therapy that render some unresectable tumor surgical approachable in an attempt to improve the outcome of patients"

3. Introduction: "Thus, hepatectomy is currently the first-line curative therapy, but only 10% to 30% of lesions are resectable at the time of diagnosis." Where is the reference ????

The reference is from lancet^[1]. And we have changed the 10-30% into about 30%.

4.The last sentence of the introduction, defining the aims, should be similar to that of the abstract, which stars "To review ...".

We have changed it into “To review the selection of conversion therapy and the following suitable salvage surgery time, we conduct the review of current literatures.”

5. I suggest to move the three paragraph following the introduction (pre-operative assessment, liver volume tests and liver function tests, which are not included in the aims) after the “Conversion therapy for initially unresectable HCC” paragraph, since they correspond exactly to the first point (1) assessment of the patient’s condition, including tumor stage, liver function, FLR, and body tolerance.

We have applied the suggestion.

6. In the paragraph dedicated to TACE, in the first part dedicated to the description of the technique, I would add the reference “Facciorusso A et al. Transarterial chemoembolization: Evidences from the literature and applications in hepatocellular carcinoma patients. World J Hepatol 2015;7:2009-19.”

We have added the citation.

7. The initial part of the discussion is too negative. It should be better to suggest some concept that are reported by the same authors about the factors to consider for the assessment of resectability. The sentence should be changed as following: “Firstly, the definition of unresectable is still subjective once T1 and T4 stages are excluded. However, the distribution of the nodules to both hepatic lobes, the presence of high alpha-feto levels, and the vascular involvement are substantial tumoral parameters that help in the

evaluation of resectability beside residual liver function and patients general conditions.

Moreover, the limit of unresectability depends on the level of the hospital and the experience of the operator or their expertise in surgery.”

We have used your suggestion.

1 Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *The Lancet* 2003; **362**(9399): 1907-1917 [DOI: 10.1016/s0140-6736(03)14964-1]