29828-Answering Reviewers

Thank you for the reviews. We have responded to all the reviewers as detailed below. We have made all the changes recommended by the reviewers.

Reviewer 00032726

Nowadays, liver cancer has become a difficult problem in the world. Operation sometimes cannot work efficiently because of various reasons. Other kind of treatment which can replace operation are inevitable. Radiotherapy, a kind of potential treatment, may play its role with the development of hardware and software. However, in clinical practice, using radiotherapy faces lots of problems and difficulties, as it mentioned in this article. So this review which provides information for the practical implementation is of immense value. Although this study promotes us to think deeply about how to take advantage of radiotherapy, there are several flaws or questions that should be addressed before further consideration. (1) The table should be created to intuitively show the theme which is a summary of hepatocellular carcinoma radiotherapy studies. The table is too complicated. (2) I personally recommend to merge those three figures into one.

Answering Reviewer 00032726

1) We agree that the table is complicated and we kept the data to a minimum yet provided the reader with sufficient details to compare trials. The table represents one of the most complete reviews in the literature. We have removed the range from the median follow up and median tumor diameter columns to make the table easier to read.

   As World Journal guidelines indicate that large tables will be online only, we can include a shorter two page table for the paper itself. This is attached below if the editors wish to have two tables (one for the paper and a more complete version for online availability).

Source, year	Number of patients	% of Child-Pugh B patients	Median tumor diameter (range) cm	Dose (range) / Number of fractions	Median follow up interval in months	1 year OS	2 year LC	Toxicity
Yamashita, 2015	79	11%	2.7 cm	48 Gy (40-60)/4-10	21	53% at 2 year	40%	gr3-4: 4.6% gr2: 2.3%
Huertas, 2015	77	14.3%	2.4 cm	45 Gy/3	12	81.8	99%	14.9%
Zhong, 2014	72	26%	13.1 cm	35.6 Gy/12	18	56%	NR	gr1-2:5.6% liver gr1-2:9.8% gastrointestinal
Lo, 2014	53	NR	4.3 cm	40 Gy/4-5	13.1	70.1 %		RILD 9.4%
Sanuki, 2014	63	16%	2.6 cm	35-40 Gy/5	31.1	100 %	95%	gr3: early: 16% late: 21% gr4-5: 0%
Bujold, 2013	102	0%	9.9 cm	24-54 Gy (36)/6	31.4	75%	74%	gr3: 21% gr4: 2.9% gr5: 6.9%

Yoon, 2013	93	26%	2 cm	45 Gy (30-60)/3-4	25.6	86.0 %	94.8% * (2yr)	gr3: 4.3% gr4: 1.0% gr5: 1.0%
Jang, 2013	108	10%	3.0 cm	51 Gy (33-60)/3	30	83%*	87%	gr3: 6.5% gr4: 1.9% gr5: 0%
Jung, 2013	92	26%	Vol: 8.6 cc	45 Gy (30-60)/3-4	25.7	86.9 %	92.1% (3yr)	gr≥3: 7%
Bibault, 2013	75	11%	3.7 cm	40-45 Gy /3	10	78.5 %	89.8%	gr3: 4% gr4: 1.3% gr5: 0%
Sanuki, 2013	185	15%	CP-A: 27 cm CP-B: 24 cm	CP-A: 40 Gy /5 CP-B: 35 Gy /5	24	95%	93% (2 yr)	gr5: 1.1%
Andolino , 2011	60	40%	3.1 cm	CP-A: 30-48 Gy /3 CP-B: 24-48 Gy /5	27	82%*	90% (2 yr)	gr3: 35% gr4: 1.7% gr5: 0%

2) The three figures have been changed (see reviewer below) and merged as requested in to figure 2.

Reviewer 00058381

Major Comment: According to the ESPS (and to the reviewer invitation by e-mail) this manuscript is considered for the World Journal of Hepatology. However, in their article (page 1 and page 4), the authors write that it is intended for the World Journal of Gastrointestinal Oncology. Of course, the World Journal of Radiology is also an option. Minor Comments: Page 5, second sentence: "…the estimated numbers of cases of colorectal cancer, primary liver, and intrahepatic bile duct cancers will be 132,700 and 35,660, respectively, in 2015." One number is missing here ("estimated numbers of cases of colorectal cancer, primary liver, and intrahepatic bile duct cancers" -> three numbers) and it would be better, in this context, to speak of colorectal liver metastases rather than of "colorectal cancer". Page 11, last paragraph, fifth sentence: "…number of fraction are low" -> please correct this part of the sentence.

Answering Reviewer 00058381

1) Have changed Page 1 and 4 to reflect that this paper has been 'accepted with revisions' to the World Journal of Hepatology. We would be happy if this were to be published in either the World Journal of Hepatology or World Journal of Radiology, and would leave this to the discretion of the World Journal editors.
2) This sentence has been amended to clarify that this is a common and increasing cancer. "According to Surveillance, Epidemiology, and End Results (SEER) statistics, the estimated numbers of cases of liver cancer (including intrahepatic bile duct cancers) will be 35,660 in 2015 representing the second largest annual increase in incidence amongst all cancers." Colorectal incidence has been removed.
3) The sentence highlighted by the reviewer on page 11 has been removed as it was not integral to the paragraph.

Reviewer 01560036

Nice and useful review

Answering Reviewer 01560036

Thank you for review.

Reviewer 00182276

It is a very clear overview about radiotherapy of the liver primary and scondary malignancies. There are listed gating techniques. I guess that counting the future remnant liver capacity according to surgical planning the PTV could remain a bit larger. So the target will be always in the irradiated volume. The liver can revoover very well within very short period. There are a few correction remained in the manuscript. Following careful minor revision I highly recommend for publication.

Answering Reviewer 00182276

Thank you for review. Changes recommended within the document as comments have been made.

Reviewer/Editor Comments from the manuscript comment section

Thank you for asking me to review the manuscript by Lock et al, entitled `Strategies to tackle the challenges of external beam radiotherapy for liver tumors.'

The authors have reviewed the role of radiotherapy in the management of patients with hepatocellular carcinoma and colorectal carcinoma-derived liver metastases. The review is highly technical with great detail on potential strategies for improving precision of the delivered radiation and recent advancements in delivery. The written English and grammar is good.

I have the following comments:

Major

1. *The sections on delivery of radiation are strongly written with practical guidance for management. The initial sections on which patients might benefit from external radiotherapy are less strong. I think there needs to be a much stronger statement that significant evidence has been generated over recent years to support the use of radio-frequency ablation, hepatic resection, trans-arterial embolization and sorafenib in HCC. There is no such data for radiotherapy with a collection of single centre observational studies. Until a prospective randomized trial emerges to support the use of radiation, it will continue to have little role in patient management. This is a shame, as it could have an important role.*

   Response: We agree with the reviewer that surgery, RFA, TACE and sorafenib have made the following change to the paragraph on page 6, increased the emphasis on radiotherapy's reliance on case series data and added a paragraph on page 16. "There have been significant advances in the options available for hepatocellular carcinoma beyond surgery with level 1 evidence of an overall survival benefit for sorafenib, radiofrequency ablation and TACE. Patient selection for sorafenib consists of patients with vascular invasion and/or extra-hepatic metastasis expected to live beyond 3 months based on a single randomized controlled trial. TACE has been shown in two randomized controlled trials and one metaanalysis to improve survival at two years. Subsequent metaanalysis has added to the controversy indicating no improvement. However, there are no prospective randomized studies to inform clinical practice beyond radiofrequency ablation, sorafenib, TACE and surgery. This makes selection of appropriate patients subject to interpretation of the evidence. For radiotherapy there is no prospective randomized trial, and we must rely on interpretation of multiple studies reporting case series data with variable patient inclusion, treatment and length of follow-up (Table 1)." Also page 6 "For radiotherapy there is no prospective randomized trial, and we must rely on interpretation of multiple studies reporting case series data with variable patient inclusion, treatment and length of follow-up (Table 1)". If the editors wish us to address a more comprehensive comparison of treatments by level of evidence for liver cancer, we would be happy to submit such an article.

2. *There is no description of what external radiation is actually used for in HCC: bony and spinal mets where it is usually (temporarily) effective.*

   Response: The reviewer highlights the use of radiation for hepatocellular carcinoma that has metastasized to regions such as the spine and bone. Clearly various disciplines have strongly held beliefs on the use of various modalities; radiation is being investigated as a potential alternative for primary liver treatment. This paper addresses theevidence-based strategies to implement a radiation liver program. The literature primarily discusses radiation for the liver itself and is the focus of this paper.

3. *I think that a review such as this should at least in passing describe the emerging role for SIRT / Y90 in HCC. This could be the best circumstantial evidence for radiation of HCC available. There are clearly some dramatic responders to SIRT, who could benefit from external radiation at a fraction of the cost.*

   Response: We agree with the reviewer that the use of Y90/SIRT may play an important role in liver cancers; however, this paper focused on 'external beam' radiotherapy only as is indicated in the title of the paper "Strategies to tackle the challenges of **external beam radiotherapy** for liver tumors**".** Strategies for implementation of a radionuclide program or a comparison of clinical outcomes with radionuclides would represent a separate papers; we would be happy to submit such a paper if the editors so wish. To further address the issue we have added a paragraph on page 16 that mentions radionuclides such as Y90/SIRT in passing as requested. See also next point.

4. *It would be nice to discuss some future trends such as the development of radiosensitizers such as inhibitors of autophagy, nimorazole and cetuximab. The combination of arterially embolised sensitizer followed by external radiation could be especially powerful in targeting tumour deposits.*

   Response: To address this issue and the point above, we have added a new paragraph on page 16. "Future Trends: Patients with primary or secondary liver cancer are growing in incidence and have a rising mortality rate. Current management with RFA, TACE, sorafenib and surgery often are not possible or result in moderate improvements. Therefore, patients and their physicians must seek alternatives or combination of

treatments. In addition to external beam radiation, work in the use of radionuclides, radiosensitizers (such as inhibitors of autophagy), epigenetic agents, liquid biopsies to better select patients, and immune modulation are exciting avenues of investigation. As for external beam radiotherapy, our review suggests that radiotherapy can be implemented safely and with high local control rates. In the future, we will continue to refine our technique and patient selection, but appropriate multidisciplinary randomized trials need to be completed before radiation can become a standard of care."

Minor

1. *Introduction, 1st paragraph: `the estimated numbers of cases of colorectal cancer, primary liver, and intrahepatic bile duct cancers will be 132,700 and 35,660, respectively, in 2015'. They list 3 cancers and then only give 2 figures. Is this prevalence? Which country are they talking about? Please spell out that this is US data from the NCI.*

   Response: thank you for noting this detail. We have addressed this point by changing the sentence to read "According to Surveillance, Epidemiology, and End Results (SEER) statistics, the estimated numbers of cases of liver cancer (including intrahepatic bile duct cancers) will be 35,660 in 2015 representing the second largest annual increase in incidence amongst all cancers in the United States"

2. *Similarly, `surgical extirpation could result in 5-year overall rates of 25-40%[2]'. Rates of what? Overall survival? Progression-free survival?*

   Response: we have added the word 'survival' to clarify this sentence

3. *Introduction, manuscript pdf p6, 2nd paragraph: `Patient selection for sorafenib consists of patients with vascular invasion and/or extra-hepatic metastasis expected to live beyond 3 months based on a single randomized controlled trial.' I have to disagree with most of this. Sorafenib can be given to any patient with HCC, that earlier treatment options are not suitable for, or patients who have progressed despite other treatment options. It tends to be given for patients with extensive disease within or without the liver, including patients with portal vein invasion. The evidence for its use is based upon 2 trials: the SHARP trial (PMID: 18650514) and the Asia-Pacific study (PMID: 19095497).*

Response: The sentence mentioned directly lists the inclusion criteria for a single study (SHARP). However, the reviewer raises a good point and we realize that many clinicians have extrapolated care beyond the exact SHARP and Asia-Pacific trials. Therefore, we have added both trials for references purposes and clarification. In addition, we have used the reviewer's exact wording in adjusting this sentence. It does not change the purpose of the sentence, and makes the change recommended by the reviewer. "Patient selection for sorafenib is limited to patients with HCC, that earlier treatments options are not suitable, or patients who have progressed on other treatments. This tends to be patients with extensive disease within or outside the liver, including patients with portal vein invasion based on two randomized controlled trials"

4. *Introduction pdf p6, `…European Association of Study of Liver (EASL) provides recommendations for radiation with and without alternative treatments based on stage, resectability, and burden of disease[15,16]. For early unresectable disease, recommendations include TACE plus radiation'. I think this is bending the truth somewhat; the EASL guidelines state: `The benefits of external three-dimensional conformal radiotherapy have only been tested in uncontrolled investigations [302]. There is no scientific evidence to recommend these therapies as primary treatments of HCC and further research testing modern approaches is encouraged.' You should re-phrase this paragraph to avoid confusion.*

   Response: The reviewer raises a very good point and we have removed this sentence and the following sentence completely to avoid confusion.

5. *Introduction, p7, `are those with tumor vein thrombosis'. Likely you mean portal vein thrombosis.*

   Response: correction has been made

6. *Figure 1 is not the most convincing HCC that I have ever seen. Could we have a tumour that convincingly washes in and then washes out?*

   Response: a new image has been selected (figure 2) and a new figure (figure 1) has been added to better demonstrate the concept described in the paragraph as requested by this reviewer and reviewer number one.