Peer Review File

Article information: https://dx.doi.org/10.21037/cco-22-119

Reviewer comments

Hepatocellular carcinoma is the most common primary liver cancer and the 3rd leading cause of cancer death worldwide. Treatment options include surgical resection, liver transplantation, image-guided percutaneous locoregional options and systemic therapies. In the manuscript "Image-Guided Percutaneous Locoregional Therapies for Hepatocellular Carcinoma", authors reviewed indications, complications, and outcomes of locoregional therapies for hepatocellular carcinoma.

Couple questions are required to be answered before it will be accepted.

(1) Whether the Image-Guided Percutaneous Locoregional Therapies could be applied for the treatment of hepatic metastases?

Reply 1: Thank you for your comment. Image-guided percutaneous locoregional therapies are indeed applied for the treatment of hepatic metastases, especially for colorectal cancer metastases. However. this review article is focused on HCC and not metastatic disease. We will add a sentence mentioning the utilization of LRT in metastatic disease.

Percutaneous ablation of liver metastases from colorectal cancer is routinely performed in oligometastatic patients. Ablation of secondary liver lesions due to non-colorectal cancers (such as neuroendocrine, thyroid, breast, …) may also be a treatment option in selected patients with liver-only or oligometastatic disease (Crocetti et al, CVIR 2020).

Transarterial embolization (TAE) and chemoembolization (TACE) are options for treatment of hepatic metastases from neuroendocrine tumor, colorectal cancer, or uveal melanoma (Gaba et al, JVIR 2017). Other drugs may then be used, such as irinotecan in colorectal cancer metastases. TAE and TACE may sometimes be performed in selected patients with limited progressive disease unresponsive to systemic therapy and liver-dominant metastases from other cancers (such as soft tissue sarcomas, gastrointestinal stromal tumor, breast carcinoma, and gynecologic malignancies).

Transarterial radioembolization (TARE) is a treatment option for liver metastases from colorectal cancer (Garin et al, CVIR 2022; Mulcahy et al, J Clin Oncol 2021) and from neuroendocrine tumor (de Mestier et al, Rev Endocr Metab Disord. 2017). More recently, studies reported outcomes of TARE for secondary liver tumors from other malignancies, such as ovarian (Lacayo et al, JVIR 2021) or breast cancers (Schatka, Cancers 2021).

Intra-arterial hepatic infusion is another image-guided percutaneous locoregional therapy that can be offered for colorectal metastases treatment (Kwan et al, Cancers 2021).

References:

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Changes in the text:

Page 3 line 22: Image-guided percutaneous locoregional therapies has been proven to be safe and effective in treating hepatic metastases, especially for colorectal cancer metastases but also in neuroendocrine, thyroid, lung and breast. However, the focus of this review is HCC and therefore only treatment options for HCC will be reviewed here.

(2) In the introduction, it was proposed to add related reference (DOI: 10.21037/tcr.2019.09.15) about the TACE for Hepatocellular Carcinoma.

Reply 2: Thank you for your advice. The reference "Xiang H, Xiong B, Li H, Zhao C, Zhang Z, Ma C, Zheng C, Luo C, Qiu H, Yao Y, Hu H, Zhao H, Long Q, Zhou J, Chen C, Ma Y. Comparison of liver function and safety in hepatocellular cancer patients treated with DEB-

TACE and cTACE: a multi-center, retrospective cohort study. Transl Cancer Res. 2019 Sep;8(5):1950-1964. doi: 10.21037/tcr.2019.09.15. PMID: 35116944; PMCID: PMC8799233" has been added in the introduction.

Changes in the text:
Page 2, last line, reference has been added.

(3) Whether there were adverse events in the Image-Guided Percutaneous Locoregional Therapies for Hepatocellular Carcinoma?

Reply 3: Thank you for your comment. Every locoregional therapy can have adverse events. We have listed the main complications of these techniques in each section.

Changes in the text:
No change in the text. Complications are presented in each section.

(4) Whether there were differences of curative effect between MWA and RFA for HCC?

Reply 4: Both RFA and MWA are thermal-ablation techniques that induce lesion coagulative necrosis. They are mainly used to ablate small HCC lesions, typically <3–5 cm. More data with RFA are currently available, as MWA is a newer technology (Habibollahi, et al, Cancers 2020). Although to our knowledge, there are no clear data supporting that MWA is superior or equivalent to RFA, it is commonly accepted that MWA allows larger ablation than monopolar RFA, allowing then to treat lesions even larger than 5 cm (Abdelaziz et al, Scand J Gastroenterol. 2015). The 2022 BCLC update indeed suggests that MWA technique is potentially the best ablative option for the treatment of 2 cm < HCC < 4 cm (Reig et al, J Hepatol 2022). Furthermore, whereas the ablation zone may be limited with RFA due to "heat-sink effect" through adjacent vessels (Nault et al, J Hepatol 2018), MWA demonstrates less susceptibility to this effect and has been shown to be effictive and safe in treating HCC tumors adjacent to large vessels (Huang et al, Eur J Radiol 2014). These are the reasons why MWA is increasingly replacing RFA for HCC ablation in current clinical practice.

References:

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Changes in the text:

Page 6 line 3: The following statement has been added:

Both RFA and MWA are thermal-ablation techniques that induce lesion coagulative necrosis. They are mainly used to ablate small HCC lesions, typically <3–5 cm. More data with RFA are currently available, as MWA is a newer technology (27). To our best knowledge, there are no clear data supporting that MWA is superior or equivalent to RFA, however it is commonly accepted that MWA allows larger ablation than monopolar RFA, allowing then to treat lesions even larger than 5 cm (23). The 2022 BCLC update indeed suggests that MWA technique is potentially the best ablative option for the treatment of 2 cm < HCC < 4 cm (6). Furthermore, whereas the ablation zone may be limited with RFA due to "heat-sink effect" through adjacent vessels, MWA demonstrates less susceptibility to this effect and has been shown to be effective and safe in treating HCC tumors adjacent to large vessels (28). These are the reasons why MWA is increasingly replacing RFA for HCC ablation in current clinical practice.

(5) What were your good suggestions for the optimal treatment options for HCC? Please state in the conclusion.

Reply 5: Thank you. The optimal treatment depends on the type and extent of liver tumor involvement.

Overall, in our opinion, percutaneous ablation remains the best locoregional therapy for small single HCCs < 2-3 cm or in the presence of less than 3 nodules < 3 cm, whereas radioembolization is particularly interesting for larger single nodules, in the case of unilobar disease or in the presence of a nodule not accessible to ablative treatment. The role of TAE/ TACE remains multinodular disease, especially when super selective therapy is possible. The role of these therapies is much more limited in cases of tumor thrombosis, diffuse and infiltrative disease, with nevertheless, possible good results obtained by radioembolization in the presence of tumor thrombosis.

Changes in the text:

Page 20 line 15. The sentence "Overall, in our opinion, percutaneous ablation remains the best locoregional therapy for small single HCCs < 2-3 cm or in the presence of less than 3 nodules < 3 cm, whereas radioembolization is particularly interesting for larger single nodules, in the case of unilobar disease or in the presence of a nodule not accessible to ablative treatment. The role

of TAE/TACE remains multinodular disease, especially when super selective therapy is possible. The role of these therapies is much more limited in cases of tumor thrombosis, diffuse and infiltrative disease, with nevertheless, possible good results obtained by radioembolization in the presence of tumor thrombosis." has been added in the conclusion.