



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 54634

Title: Radiofrequency combined with immunomodulation for hepatocellular carcinoma:
State of the art and innovations

Reviewer’s code: 03699961

Position: Peer Reviewer

Academic degree: PhD

Professional title: Professor

Reviewer’s Country/Territory: Japan

Author’s Country/Territory: United Kingdom

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Reviewer chosen by: AI Technique

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Reviewer performed review: 2020-02-11 14:21

Review time: 1 Day and 7 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input checked="" type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer’s expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input checked="" type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input checked="" type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input type="checkbox"/> General
			<input type="checkbox"/> No expertise
			Conflicts-of-Interest:
			<input type="checkbox"/> Yes
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SPECIFIC COMMENTS TO AUTHORS

Title: Radiofrequency combined with immunomodulation for hepatocellular carcinoma: State of the art and innovations Adriano Carneiro Costa, Mikael Sodergren, Kumar Jayant, Fernando Santa Cruz, Duncan Spalding, Madhava Pai, Nagy Habib

1) General Comments In this review article, the authors summarized the evidence that we have now in the combinatorial treatments of hepatocellular carcinoma using radiofrequency ablation and immunotherapy. Although the enough information is included, some of them are not along with guidelines and well-known facts in clinic. In addition, it is better to show how each evidence is confident. The followings are concerns that the authors may wish to consider:

2) Specific comments Major concerns: 1. The authors should indicate the evidence level of each study that is listed in the Table 1. 2. In the reference 30, a substantial number of cases were treated with not only RFA, but also cryoablation and/or TACE. The reference 30 is not a suitable manuscript in this review, in which the authors focus on RFA but on other locoregional treatments. Minor concerns: 1. American Association for the Study of Liver Diseases, The Japan Society of Hepatology, European Society for Medical Oncology, and European Association for the Study of Liver, all recommend the treatment using RFA for the patients with HCC of 3 cm or less in diameter and 3 nodules or less in number. HCCs over 3 cm should not be treated using RFA. 2. A reduction in HCV viral load after immunotherapy is too primitive to mention and out of focus in this review article. It is well known that the eradication of HCV does not significantly alter the recurrent rate at the first time after treatment of initial HCCs. The recurrence rate is getting lower at the second and later recurrences. 3. In terms of aflatoxins and aristolochic acid, it would be helpful if correspondent references are provided.



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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 54634

Title: Radiofrequency combined with immunomodulation for hepatocellular carcinoma:
State of the art and innovations

Reviewer's code: 00006459

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Academic degree: BSc, PhD

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Reviewer's Country/Territory: Australia

Author's Country/Territory: United Kingdom

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Reviewer performed review: 2020-02-18 03:54

Review time: 8 Days and 4 Hours

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language	(High priority)	<input checked="" type="checkbox"/> Anonymous
<input type="checkbox"/> Grade C: Good	polishing	<input type="checkbox"/> Accept	<input type="checkbox"/> Onymous
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of	(General priority)	Peer-reviewer's expertise on the
<input type="checkbox"/> Grade E: Do not	language polishing	<input checked="" type="checkbox"/> Minor revision	topic of the manuscript:
publish	<input type="checkbox"/> Grade D: Rejection	<input type="checkbox"/> Major revision	<input type="checkbox"/> Advanced
		<input type="checkbox"/> Rejection	<input checked="" type="checkbox"/> General
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			Conflicts-of-Interest:
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SPECIFIC COMMENTS TO AUTHORS

The topic of this review, improving treatment of hepatocellular carcinoma (HCC), is very important due to the low survival from HCC. It is logical that the new immunotherapies and indeed some other therapies will synergise with Radiofrequency Ablation (RFA), so it is important to evaluate such combination approaches, as is done here. This is a good review. It needs some improvements to structure, clarity and English expression. Most important is to largely confine the quoted data to HCC. The papers on colorectal cancer [CRC], refs 11 and 15, must be kept separate and made clear that they are on CRC. CAR-T and vaccines are mentioned, but need more detail to be understood. This review would be improved by adding sections commenting upon other methods that may or might synergise with RFA. I suggest mention of lytic virus anti-tumour therapy approaches. I suggest mention of potential future directions. For example, theranostics, such as with isotopes on FAP inhibitors that target tumour stroma [J Calais - Journal of Nuclear Medicine, 2020; Lindner, T., et al. (2019). "Targeting of activated fibroblasts for imaging and therapy." EJNMMI Radiopharmacy and Chemistry 4(1):16.] An image relevant to RFA would improve this review. For a broad GE audience, I suggest an explanation of when you would choose to use RFA versus TIPS. This would explain the place of RFA into context with HCC therapy as a whole. The abstract needs improved clarity and English. Also, The third page is the page most in need of improved English. Eg 'a way of antigen to the induction' and nearby sentences. Also, mid-page is a sentence that includes the word, 'evidence', but needs a reference cited. Page 6 and Table 1: 'number of white cells...' needs explanation of whether these WBC were intratumoral or in blood or other location. Page 8: near mid- page is a sentence ending, "carcinoma in mice." Please specify which reference (s) is relevant here.



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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 54634

Title: Radiofrequency combined with immunomodulation for hepatocellular carcinoma:
State of the art and innovations

Reviewer's code: 00054672

Position: Editorial Board

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Author's Country/Territory: United Kingdom

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SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION	PEER-REVIEWER STATEMENTS
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	<input type="checkbox"/> Accept	Peer-Review:
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SPECIFIC COMMENTS TO AUTHORS

In this review article Carneiro da Costa et al. summarized the published data regarding the combination of radiofrequency ablation (RFA) and immunotherapy for hepatocellular carcinoma. This is an important subject as the results and the outcomes of HCC treatments are far from optimal. RFA is a recommended method of treatment for small HCC (>3 cm) however it has been burdened with the progression/recurrence of the disease, therefore addition of immunotherapy is a promising attempt to improve the outcomes of HCC treatment as presented in this review based on the eight selected articles. This is a well-written review, and I would recommend it publication. However there are several minor remarks; data on HCV viral load are unnecessary and out of the scope of this manuscript; minor typing mistakes throughout the text should be corrected; throughout the text there are several references missing when referring to the specific data and should be added accordingly; references are not prepared according to the journal requirements.

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