

# World Journal of *Gastroenterology*

*World J Gastroenterol* 2018 August 21; 24(31): 3469-3566



**EDITORIAL**

- 3469 Locoregional therapy response in patients with hepatocellular cancer waiting for liver transplantation: Only selection or biological effect?

*Lai Q, Di Martino M, Lucatelli P, Mennini G*

**REVIEW**

- 3472 *Helicobacter pylori*: A foodborne pathogen?

*Quaglia NC, Dambrosio A*

- 3488 Hepatitis B virus infection: Defective surface antigen expression and pathogenesis

*Wu CC, Chen YS, Cao L, Chen XW, Lu MJ*

- 3500 Immunometabolism: A novel perspective of liver cancer microenvironment and its influence on tumor progression

*Zhang Q, Lou Y, Bai XL, Liang TB*

**MINIREVIEWS**

- 3513 Osteoporosis in primary biliary cholangitis

*Danford CJ, Trivedi HD, Papamichael K, Tapper EB, Bonder A*

- 3521 Ubiquitin-proteasome system and oxidative stress in liver transplantation

*Alva N, Panisello-Roselló A, Flores M, Roselló-Catafau J, Carbonell T*

**ORIGINAL ARTICLE****Basic Study**

- 3531 Stomach wall structure and vessels imaging by acoustic resolution photoacoustic microscopy

*Wang C, Lu YF, Cai CM, Xiang HZ, Zheng G*

- 3538 Clinical correlation of B7-H3 and B3GALT4 with the prognosis of colorectal cancer

*Zhang T, Wang F, Wu JY, Qiu ZC, Wang Y, Liu F, Ge XS, Qi XW, Mao Y, Hua D*

**Retrospective Cohort Study**

- 3547 Favorable clinical outcome of nonalcoholic liver cirrhosis patients with coronary artery disease: A population-based study

*Tsai MC, Yang TW, Wang CC, Wang YT, Sung WW, Tseng MH, Lin CC*

**Prospective Study**

- 3556 PillCamColon2 after incomplete colonoscopy - A prospective multicenter study

*Baltes P, Bota M, Albert J, Philipper M, Hörster HG, Hagenmüller F, Steinbrück I, Jakobs R, Bechtler M, Hartmann D, Neuhaus H, Charton JP, Mayershofer R, Hohn H, Rösch T, Groth S, Nowak T, Wohlmuth P, Keuchel M*

**ABOUT COVER**

Editorial board member of *World Journal of Gastroenterology*, Tamara Vorobjova, DA, PhD, Academic Research, Department of Immunology, Institute of Biomedicine and Translational Medicine, University of Tartu, Tartu 51014, Estonia

**AIMS AND SCOPE**

*World Journal of Gastroenterology* (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7<sup>th</sup>, 14<sup>th</sup>, 21<sup>st</sup>, and 28<sup>th</sup> each month. The *WJG* Editorial Board consists of 642 experts in gastroenterology and hepatology from 59 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, gastrointestinal imaging, gastrointestinal interventional therapy, gastrointestinal infectious diseases, gastrointestinal pharmacology, gastrointestinal pathophysiology, gastrointestinal pathology, evidence-based medicine in gastroenterology, pancreatology, gastrointestinal laboratory medicine, gastrointestinal molecular biology, gastrointestinal immunology, gastrointestinal microbiology, gastrointestinal genetics, gastrointestinal translational medicine, gastrointestinal diagnostics, and gastrointestinal therapeutics. *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

**INDEXING/ABSTRACTING**

*World Journal of Gastroenterology* (*WJG*) is now indexed in Current Contents<sup>®</sup>/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch<sup>®</sup>), Journal Citation Reports<sup>®</sup>, Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2018 edition of Journal Citation Reports<sup>®</sup> cites the 2017 impact factor for *WJG* as 3.300 (5-year impact factor: 3.387), ranking *WJG* as 35<sup>th</sup> among 80 journals in gastroenterology and hepatology (quartile in category Q2).

**EDITORS FOR THIS ISSUE**

Responsible Assistant Editor: *Xiang Li*  
Responsible Electronic Editor: *Yan Huang*  
Proofing Editor-in-Chief: *Lian-Sheng Ma*

Responsible Science Editor: *Xue-Jiao Wang*  
Proofing Editorial Office Director: *Ze-Mao Gong*

**NAME OF JOURNAL**  
*World Journal of Gastroenterology*

**ISSN**  
ISSN 1007-9327 (print)  
ISSN 2219-2840 (online)

**LAUNCH DATE**  
October 1, 1995

**FREQUENCY**  
Weekly

**EDITORS-IN-CHIEF**  
**Andrzej S Tarnawski, MD, PhD, DSc (Med),**  
**Professor of Medicine, Chief Gastroenterology, VA**  
Long Beach Health Care System, University of California, Irvine, CA, 5901 E. Seventh Str., Long Beach, CA 90822, United States

**EDITORIAL BOARD MEMBERS**  
All editorial board members resources online at <http://www.wjgnet.com/1007-9327/editorialboard.htm>

**EDITORIAL OFFICE**  
Ze-Mao Gong, Director  
*World Journal of Gastroenterology*  
Baishideng Publishing Group Inc  
7901 Stoneridge Drive, Suite 501,  
Pleasanton, CA 94588, USA  
Telephone: +1-925-2238242  
Fax: +1-925-2238243  
E-mail: [editorialoffice@wjgnet.com](mailto:editorialoffice@wjgnet.com)  
Help Desk: <http://www.f6publishing.com/helpdesk>  
<http://www.wjgnet.com>

**PUBLISHER**  
Baishideng Publishing Group Inc  
7901 Stoneridge Drive, Suite 501,  
Pleasanton, CA 94588, USA  
Telephone: +1-925-2238242  
Fax: +1-925-2238243  
E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
Help Desk: <http://www.f6publishing.com/helpdesk>  
<http://www.wjgnet.com>

**PUBLICATION DATE**  
August 21, 2018

**COPYRIGHT**  
© 2018 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

**SPECIAL STATEMENT**  
All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

**INSTRUCTIONS TO AUTHORS**  
Full instructions are available online at <http://www.wjgnet.com/bpg/gerinfo/204>

**ONLINE SUBMISSION**  
<http://www.f6publishing.com>

## Locoregional therapy response in patients with hepatocellular cancer waiting for liver transplantation: Only selection or biological effect?

Quirino Lai, Michele Di Martino, Pierleone Lucatelli, Gianluca Mennini

Quirino Lai, Gianluca Mennini, Department of General Surgery and Organ Transplantation, Sapienza University of Rome, Rome 00161, Italy

Michele Di Martino, Pierleone Lucatelli, Department of Radiology, Sapienza University of Rome, Rome 00161, Italy

ORCID number: Quirino Lai (0000-0003-1487-3235); Michele Di Martino (0000-0003-1504-1166); Pierleone Lucatelli (0000-0002-7448-1404); Gianluca Mennini (0000-0002-6412-6863).

Author contributions: Lai Q, Di Martino M, Lucatelli P and Mennini G conceived the study and drafted the manuscript; both authors approved the final version of the article.

Conflict-of-interest statement: The authors have no conflict of interest to declare.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Quirino Lai, MD, PhD, Academic Fellow, Academic Research, Doctor, Senior Lecturer, Department of General Surgery and Organ Transplantation, Sapienza University of Rome, Viale del Policlinico 155, Rome 00161, Italy. [lai.quirino@libero.it](mailto:lai.quirino@libero.it)  
Telephone: +39-34-93020126  
Fax: +39-6-499701

Received: May 18, 2018

Peer-review started: May 19, 2018

First decision: May 29, 2018

Revised: June 29, 2018

Accepted: July 16, 2018

Article in press: July 16, 2018

Published online: August 21, 2018

### Abstract

Locoregional treatments (LRT) represent a broad strategy used for reducing the risk of drop-off and contextually improving the survivals in patients with hepatocellular cancer receiving a liver transplantation (LT). However, it is not sufficiently clear if LRT are only a surrogate of tumor aggressiveness or if they consent a real benefit in terms of tumor stabilization. A recent study by Pommergaard *et al* reported the results from the European Liver Transplant Registry. Patients receiving LRT before LT had better 5-year survival rates respect to no-LRT cases (69.7% *vs* 65.8%;  $P < 0.001$ ). When the number of LRT was tested, one-to-two treatments were connected with improved survivals respect to no treatment [hazard ratio (HR) = 0.85 and 0.71, respectively]. The efficacy of LRT was also reported in the presence of larger tumors (HR = 0.78) and micro-macrovascular invasion (HR = 0.71). The results observed in the present study are partially in discordance with other analyses showing a detrimental effect of LRT. The main problem in the interpretation of these results is connected with the possible initial selection biases present in the studies. The most recent guidelines suggest to perform LRT before the transplant, but the level of evidence is typically low due to the absence of prospectively designed studies.

**Key words:** Allocation; Recurrence; Trans-arterial chemo-embolization; Radiofrequency ablation; Model for end-stage liver disease

© The Author(s) 2018. Published by Baishideng Publishing

Group Inc. All rights reserved.

**Core tip:** The role of locoregional treatments in the setting of hepatocellular cancer and liver transplantation is controversial. On one side, neoadjuvant approaches should consent a selection of tumor aggressiveness. On the other side, a real survival improvement thanks to the tumor ablation should be achieved. Recent evidences report an effective beneficial role of locoregional strategies in terms of survival and recurrence. However, several biases must be taken into account in these studies, due to the heterogeneous characteristics of treated *vs* untreated subjects. Further studies are need with the intent to clarify this important topic.

Lai Q, Di Martino M, Lucatelli P, Mennini G. Locoregional therapy response in patients with hepatocellular cancer waiting for liver transplantation: Only selection or biological effect? *World J Gastroenterol* 2018; 24(31): 3469-3471 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v24/i31/3469.htm> DOI: <http://dx.doi.org/10.3748/wjg.v24.i31.3469>

## INTRODUCTION

Liver transplantation (LT) represents the gold-standard treatment in patients with unresectable hepatocellular cancer (HCC) developed on underlying cirrhosis<sup>[1]</sup>. Unfortunately, LT represents a scarce resource, mainly due to the limited number of available donors<sup>[2]</sup>. Thus, in patients awaiting LT, disease burden may progress beyond the conventional LT criteria while on the waiting list<sup>[3]</sup>. Several strategies have been adopted with the intent to alleviate the risk of drop-out due to tumor progression: for example, Model for End-Stage Liver Disease (MELD) exception points are routinely used in several regions in the presence of T2 HCCs<sup>[4]</sup>. Another widespread strategy is the use of locoregional treatments (LRTs) as a neo-adjuvant strategy with the intent to bridge patients to LT<sup>[5]</sup> or downstage patients initially outside transplantation criteria<sup>[6]</sup>.

Response to LRT has been correlated with improved post-LT survival rates in several studies<sup>[7,8]</sup>. However, it is not sufficiently clear if LRTs are only a surrogate of tumor aggressiveness, efficaciously selecting patients with favorable tumor biology, or if they are beneficial concerning tumor stabilization, mainly in case of complete or partial response.

## STUDY ANALYSIS

In a recent Issue on Transplant International, Pommergaard *et al*<sup>[9]</sup> reported the results of a multicentric study based on the European Liver Transplant Registry (ELTR) and focused on the use of LRT in HCC patients undergoing LT. A total of 4978 patients (no LRT = 1406, 28.2%; LRT = 3572, 71.8%) were enrolled. As expected, the median waiting time was longer in the LRT group

(4 mo *vs* 1.7 mo;  $P < 0.001$ ) and the median MELD score was higher in the directly transplanted subjects (12 *vs* 10;  $P < 0.001$ ). Overall, patients receiving LRT before LT had better 5-year survival rates respect to no-LRT cases (69.7% *vs* 65.8%;  $P < 0.001$ ). When the different treatment types were investigated, the use of radiofrequency ablation (RFA) had the strongest association with an improved overall survival [hazard ratio (HR) = 0.51]. The beneficial effect was also observed in case of the combination of RFA and trans-arterial chemo-embolization (TACE) (HR = 0.74). Several sub-analyses were also done. As for the number of LRT performed, one-two treatments were connected with improved survivals respect to no treatment (HR = 0.85 and 0.71, respectively). On the opposite, three or more treatments showed no association (HR = 1.11).

When a subclass of HCCs being larger (> 3 cm) or with more nodules (> 5 lesions) was examined, LRT maintained their protective role for the risk of death (HR = 0.78). In this context, RFA, TACE or combined RFA + TACE all were significantly associated with improved survival (HR = 0.54, 0.81, and 0.60, respectively).

Stratifying the entire population according to the underlying liver status (cirrhosis *vs* non-cirrhotic liver), in case of HCC on cirrhosis LRT were also protective (HR = 0.86).

In the presence of pathological micro-macrovascular invasion, the effect of LRT was strong (HR = 0.71). Both RFA and TACE (HR = 0.54 and 0.69, respectively) were associated with improved survival.

## PERSPECTIVE

The role of LRT in the setting of HCC and LT has not been fully clarified, mainly in light of the potential detrimental effects of repetitive treatments. For example, a recent meta-analysis performed on 1122 TACE patients showed an increased risk of post-LT hepatic artery complications (odds ratio = 1.57;  $P = 0.02$ )<sup>[10]</sup>. Another study from the US performed on 3601 patients all meeting the Milan Criteria, showed that the increasing number of LRT significantly predicted post-LT recurrence (3 LRTs: HR = 2.1;  $P < 0.001$ ; 4 + LRTs: HR = 2.5;  $P < 0.001$ )<sup>[5]</sup>. Interestingly, LRT patients achieving complete response had superior 5-year recurrence-free survivals when compared with untreated cases or LRT subjects not achieving complete response (72% *vs* 69% *vs* 67%; respectively)<sup>[5]</sup>. The here described study performed on a large population of European HCC cases showed the beneficial role of LRT, mainly in case of RFA use. Moreover, the repetitive number of treatments was not connected with worse results. LRT maintained their protective role for the risk of death even when larger tumors or harmful clinical conditions like vascular invasion were investigated. It is difficult to definitively clarify if the LRT only select low-risk HCC, or if their ability of tumor burden zeroing should also have some impact regarding survival improvement. It is clear that

the response after LRT is a robust predictor of post-LT course. A recent large multicentric European study based on 2103 HCC patients identified the poor radiological response after LRT as one of the most important predictors for the risk of low intention-to-treat benefit after transplant<sup>[11]</sup>. Another multicentric European study performed on 276 cases all treated with LRT showed that an HCC-related remaining vital tissue in the main lesion  $\geq 2$  cm at pathological assessment after LT was a strong independent risk factor for post-LT recurrence (HR = 5.6;  $P < 0.001$ )<sup>[12]</sup>. All of these results have been positively recognized by the recent European Association for the Study of the Liver (EASL) guidelines, in which it is stated that “in LT candidates with HCC, the use of pre-transplant (neoadjuvant) loco-regional therapies is recommended if feasible, as it reduces the risk of pre-LT drop-out and aims at lowering post-LT recurrence - particularly when complete or partial tumour response are achieved”<sup>[13]</sup>. Unfortunately, although the strength of recommendation for this statement is strong, the scientific evidence is low, clearly underlining the lack of prospectively designed studies. More researchers are needed, with the intent to better explore the role of LRT concerning intention-to-treat survivals.

Moreover, we should remember the critical impact that local allocation rules and waiting time duration may play on the role and the effect of LRT. As an example, in the United States most HCC patients wait for at least six months from the diagnosis before having the opportunity to be transplanted. More studies also focused on these aspects are surely needed.

## REFERENCES

- 1 **Lai Q**, Lerut JP. Hepatocellular cancer: how to expand safely inclusion criteria for liver transplantation. *Curr Opin Organ Transplant* 2014; **19**: 229-234 [PMID: 24811435 DOI: 10.1097/MOT.000000000000085]
- 2 **Lai Q**, Melandro F, Levi Sandri GB, Mennini G, Corradini SG, Merli M, Berloco PB, Rossi M. Use of elderly donors for liver transplantation: has the limit been reached? *J Gastrointest Liver Dis* 2011; **20**: 383-387 [PMID: 22187704]
- 3 **Mehta N**, Heimbach J, Lee D, Dodge JL, Harnois D, Burns J, Sanchez W, Roberts JP, Yao FY. Wait Time of Less Than 6 and Greater Than 18 Months Predicts Hepatocellular Carcinoma Recurrence After Liver Transplantation: Proposing a Wait Time “Sweet Spot”. *Transplantation* 2017; **101**: 2071-2078 [PMID: 28353492 DOI: 10.1097/TP.0000000000001752]
- 4 **Marrero JA**, Kulik LM, Sirlin C, Zhu AX, Finn RS, Abecassis MM, Roberts LR, Heimbach JK. Diagnosis, Staging and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology* 2018; Epub ahead of print [PMID: 29624699 DOI: 10.1002/hep.29913]
- 5 **Agopian VG**, Harlander-Locke MP, Ruiz RM, Klintmalm GB, Senguttuvan S, Florman SS, Haydel B, Hoteit M, Levine MH, Lee DD, Taner CB, Verna EC, Halazun KJ, Abdelmessih R, Tevar AD, Humar A, Aucejo F, Chapman WC, Vachharajani N, Nguyen MH, Melcher ML, Nydam TL, Mobley C, Ghobrial RM, Amundsen B, Markmann JF, Langnas AN, Carney CA, Berumen J, Hemming AW, Sudan DL, Hong JC, Kim J, Zimmerman MA, Rana A, Kueht ML, Jones CM, Fishbein TM, Busuttil RW. Impact of Pretransplant Bridging Locoregional Therapy for Patients With Hepatocellular Carcinoma Within Milan Criteria Undergoing Liver Transplantation: Analysis of 3601 Patients From the US Multicenter HCC Transplant Consortium. *Ann Surg* 2017; **266**: 525-535 [PMID: 28654545 DOI: 10.1097/SLA.0000000000002381]
- 6 **Kulik L**, Heimbach JK, Zaiem F, Almasri J, Prokop LJ, Wang Z, Murad MH, Mohammed K. Therapies for patients with hepatocellular carcinoma awaiting liver transplantation: A systematic review and meta-analysis. *Hepatology* 2018; **67**: 381-400 [PMID: 28859222 DOI: 10.1002/hep.29485]
- 7 **Lai Q**, Nicolini D, Inostroza Nunez M, Iesari S, Goffette P, Agostini A, Giovagnoni A, Vivarelli M, Lerut J. A Novel Prognostic Index in Patients With Hepatocellular Cancer Waiting for Liver Transplantation: Time-Radiological-response-Alpha-fetoprotein-Inflammation (TRAIN) Score. *Ann Surg* 2016; **264**: 787-796 [PMID: 27429025 DOI: 10.1097/SLA.0000000000001881]
- 8 **Lai Q**, Avolio AW, Graziadei I, Otto G, Rossi M, Tisone G, Goffette P, Vogel W, Pitton MB, Lerut J; European Hepatocellular Cancer Liver Transplant Study Group. Alpha-fetoprotein and modified response evaluation criteria in solid tumors progression after locoregional therapy as predictors of hepatocellular cancer recurrence and death after transplantation. *Liver Transpl* 2013; **19**: 1108-1118 [PMID: 23873764 DOI: 10.1002/lt.23706]
- 9 **Pommergaard HC**, Rostved AA, Adam R, Thygesen LC, Salizzoni M, Gómez Bravo MA, Cherqui D, De Simone P, Boudjema K, Mazzaferro V, Soubrane O, Garcia-Valdecasas JC, Fabregat Prous J, Pinna AD, O’Grady J, Karam V, Duvoux C, Rasmussen A; European Liver and Intestine Transplant Association (ELITA). Locoregional treatments before liver transplantation for hepatocellular carcinoma: a study from the European Liver Transplant Registry. *Transpl Int* 2018; **31**: 531-539 [PMID: 29380442 DOI: 10.1111/tri.13123]
- 10 **Sneiders D**, Houwen T, Pengel LHM, Polak WG, Dor FJMF, Hartog H. Systematic Review and Meta-Analysis of Posttransplant Hepatic Artery and Biliary Complications in Patients Treated With Transarterial Chemoembolization Before Liver Transplantation. *Transplantation* 2018; **102**: 88-96 [PMID: 28885493 DOI: 10.1097/TP.0000000000001936]
- 11 **Lai Q**, Vitale A, Iesari S, Finkenstedt A, Mennini G, Spoletini G, Hoppe-Lotichius M, Vennarecci G, Manzia TM, Nicolini D, Avolio AW, Frigo AC, Graziadei I, Rossi M, Tsochatzis E, Otto G, Ettorre GM, Tisone G, Vivarelli M, Agnes S, Cillo U, Lerut J; European Hepatocellular Cancer Liver Transplant Study Group. Intention-to-treat survival benefit of liver transplantation in patients with hepatocellular cancer. *Hepatology* 2017; **66**: 1910-1919 [PMID: 28653750 DOI: 10.1002/hep.29342]
- 12 **Manzia TM**, Lai Q, Iesari S, Perera MTPR, Komuta M, Carvalheiro A, Shah T, Angelico R, Quaranta C, Nicolini D, Montalti R, Scarpelli M, Palmieri G, Orlacchio A, Vivarelli M, Angelico M, Lerut J, Tisone G. Impact of remnant vital tissue after locoregional treatment and liver transplant in hepatocellular cancer patients, a multicentre cohort study. *Transpl Int* 2018; Epub ahead of print [PMID: 29572974 DOI: 10.1111/tri.13153]
- 13 **European Association for the Study of the Liver**; European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *J Hepatol* 2018; **69**: 182-236 [PMID: 29628281 DOI: 10.1016/j.jhep.2018.03.019]

**P- Reviewer:** Bramhall S, Chiu KW, Inoue K, Koksai A, Ramsay MA, Therapondos G, Wang GY **S- Editor:** Gong ZM **L- Editor:** A **E- Editor:** Huang Y





Published by **Baishideng Publishing Group Inc**  
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA  
Telephone: +1-925-223-8242  
Fax: +1-925-223-8243  
E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
Help Desk: <http://www.f6publishing.com/helpdesk>  
<http://www.wjgnet.com>



ISSN 1007-9327

