CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
http://doi.org/10.5281/zenodo.2658482

Available online at: http://www.iajps.com *Research Article*

HEPATIC RESECTION FOR HEPATOCELLULAR CARCINOMA IN PATIENTS WITH PORTAL HYPERTENSION: A LONG-TERM BENEFIT COMPARED WITH TRANSARTERIAL CHEMOEMBOLIZATION AND THERMAL ABLATION

[1]Dr Rimsha Marryiam,[2]Dr Sehrish Ijaz,[3]Dr Mahwish Majeed.

[1]WMO,THQ Thal MNSH,Layyah., [2]WMO,RHC Chawinda,Sialkot., [3]WMO,THQ Thal MNSH,Layyah.

Article Received: February 2019 **Accepted:** March 2019 **Published:** April 2019

Abstract:

Hepatocellular carcinoma (HCC), in its very early stage, is heterogeneous both in terms of liver function (i.e., presence or absence of portal hypertension, model for end-stage liver disease score, Child-Pugh score 5 or 6, bilirubin level) and tumour characteristics (i.e., location, alpha-fetoprotein values, pathological features such as micro-vascular invasion, tumour grade and satellitosis). Existing evidence in comparing different curative options for patients with very early HCC is poor due to small sample sizes and lack of solid subgroup analyses. Large observational studies are available, with the potential to identify effective interventions in different subgroup of patients and to discover which treatments work ''in a real world setting''. These studies suggest some important treatment selection strategies in very early HCC patients. According to extent of liver resection, and liver function, percutaneous ablation or liver resection are the recommended first line therapies in these patients. Laparoscopic surgery (resection or ablation) is the preferable strategy when the tumour is in the surface of the liver or close to extra-hepatic organs. Due to scarce donor resources and competition with patients at high transplant benefit (HCC patients unsuitable for non-transplant radical therapies and non-HCC patients with decompensated cirrhosis), transplantation is recommended only as second line therapy in patients with very early stage HCC in case of tumour recurrence or liver failure after ablation or liver resection.

Keywords: *Very early hepatocellular carcinoma; Evidence based treatment; personalized approach; Ablation; Liver transplantation; Liver resection.*

Corresponding author:

Rimsha Marryiam,

WMO,THQ Thal MNSH,Layyah.

QR code

Please cite this article in press Rimsha Marryiam et al., ***Hepatic Resection For Hepatocellular Carcinoma In Patients With Portal Hypertension: A Long-Term Benefit Compared With Transarterial Chemoembolization And Thermal Ablation.,*** *Indo Am. J. P. Sci, 2019; 06(04).*

INTRODUCTION:

Liver cancer is the sixth most frequent cancer and the second most frequent cause of cancer related death worldwide. The incidence and mortality of hepatocellular carcinoma (HCC) in 2008 was 65,000 and 60,240, respectively, in Europe compared with 21,000 and 18,400, respectively, in the United States (US). Of particular concern is that both the incidence and mortality of HCC are increasing worldwide. In fact, it is estimated that by 2020 the number of cases in Asia and Europe and the US will reach 128,000, 78,000 and 27,000, respectively. The prognostic classification of patients with HCC is complex, since any prognostic scheme has to account for both the background liver disease and the tumour itself. The management of HCC has significantly improved over the last decade related to a better knowledge of the natural history, improvements in staging systems and treatment algorithms, as well as emerging therapeutic options. One of the most reliable and widely adopted methods for staging HCC is the Barcelona Clinic Liver Cancer (BCLC) system, which stratifies patients according to the characteristics of the tumour, underlying liver disease and performance status. According to this system, the presence of an asymptomatic single nodule 62 cm, in the absence of vascular invasion or extra-hepatic disease, and in the presence of well-compensated cirrhosis is defined as very early stage HCC (BCLC stage 0). In recent years, largely due to improved surveillance programs in the cirrhotic population, more patients are being diagnosed with very early HCC. Although some of these patients may benefit from alcohol injection or transarterial chemoembolization (TACE), here we focus on the three treatment modalities considered to represent the best potential curative options for patients diagnosed with very early HCC [6]: liver resection (LR), liver transplantation (LT), and radiofrequency ablation (RFA). In general, patients with very early HCC who are treated with any of these strategies can have excellent recurrence-free and overall survival outcomes compared with patients who have more advanced tumors. In the last decade, the concept of ‘‘evidence based management” of patients with HCC has been introduced to define therapeutic strategies or algorithms derived from comparative studies evaluating treatment efficacy. Following the traditional pyramid of evidence based medicine (EBM), the best evidence is based on data obtained from randomized clinical trials (RCTs) or meta-analyses of RCTs. However, in the absence of RCTs, some treatment protocols have also been established based on the results of observational and cost-effectiveness studies.

The concept of EBM continues to change over recent years, however, and the quality of data should be considered only in light of a more dynamic EBM paradigm. For example, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group has now replaced the traditional EBM pyramid and allows observational studies to be upgraded (or RCTs downgraded) along the evidence pyramid. Moreover, systematic reviews are omitted from the pyramid (i.e., in the revised pyramid, systematic reviews are a lens through which evidence is viewed/applied).

Along with these changes, many experts worldwide now strongly support the use of observational studies and evidence derived from ‘‘big data” to develop and validate individual prognostic prediction and treat

COMPARATIVE EFFICACY STUDIES OF PATIENTS WITH VERY EARLY HCC UNDERGOING CURATIVE THERAPIES:

Clinical Trials:

There are only a few randomised control trials that investigate curative options for patients with HCC, and all focus solely on the comparison of LR vs. RFA. Among the six RCTs (Table 1), three studies demonstrated a superiority of LR over RFA in terms of overall survival, while the other three reported comparable results with either therapy.

Table 1. Randomized clinical trials comparing LR and RFA in HCC patients.

Author	Tumor characteristics	CPT class	OS	DFS	Major complications	*p* value OS/DFS
Chen, 2006			4 yr	5 yr		n.s./n.s.
Resection (n = 90)	Single, ⩽5 cm	A	64%	52%	55%*	
RFA (n = 71)	Single, ⩽5 cm	A	68%	46%	4%	
Lu, 2006			3 yr	5 yr		n.s./n.s.
Resection (n = 54)	Within Milan criteria	A	86%	82%	11%	
RFA/MWA (n = 51)	Within Milan criteria	A	87%	51%	8%	
Huang, 2010 [10]			5 yr	5 yr		0.001/0.017
Resection (n = 115)	Within Milan criteria	A/B: 106/9	76%	51%	32%*	
RFA (n = 115)	Within Milan criteria	A/B: 110/5	70%	29%	5%	
Feng, 2012			3 yr	3 yr		n.s./0.027
Resection (n = 84)	⩽2 nodules, ⩽4 cm	A/B: 43/41	75%	62	21%*	
RFA (n = 84)	⩽2 nodules, ⩽4 cm	A/B: 39/45	67%	46	9%	
Fang, 2014			3 yr	3 yr		n.s./n.s.
Resection (n = 60)	⩽3 nodules, ⩽3 cm	A/B-C*: 43/17	78%	41%	28%*	
RFA (n = 60)	⩽3 nodules, ⩽3 cm	A/B-C*: 32/23/5	83%	47%	5%	
Liu H, 2016			5 yr	5 yr		0.007/0.02
Resection (n = 100)	Within Milan criteria	A/B: 98/2	62%	48%	23%*	
RFA + TACE (n = 100)	Within Milan criteria	A/B: 96/4	46%	36%	11%	

RFA, radiofrequency ablation; MWA, microwave ablation; CP, Child-Pugh; DFS, disease-free survival; OS, overall survival; n.s., not significant.
* *p* value <0.05 in the comparison between groups.

Of note, these trials were designed to detect relatively large differences in survival among patients with early HCC being treated by resection vs. ablation. In turn, these RCTs were likely underpowered and suffered from a small sample size to detect smaller differences in survival among the treatment groups. Moreover, enrolment criteria for these trials were heterogeneous in terms of tumour characteristics, liver function, and treatment procedures (i.e., RFA or microwave ablation were used in one trial, RFA plus TACE were used in another trial), thus making it difficult to interpret the data. The small sample size also made it difficult to examine subgroups to identify potential prognostic factors or identify whether one treatment might be superior to another (e.g., microwave vs. radiofrequency). Another important limit was that all of these RCT studies were solely conducted in Asia/China, thereby limiting the generalization of the results to the rest of the world. To mitigate some of the problems associated with these studies due to small sample size, meta-analyses of the RCT data have been performed. In one such meta-analysis, Qi et al. reported that LR was superior to RFA in terms of recurrence-free and overall survival. In contrast, LR had a higher incidence of post-operative complications compared with RFA. A separate study by Wang et al. similarly noted that LR was superior to RFA among patients with very early HCC, however LR was associated with a higher morbidity. Unfortunately, to date, there are no RCTs that directly compare LT with LR or RFA.

Retrospective matched comparisons:

In addition to the handful of prospective trials, numerous retrospective studies that compared LR vs. RFA or vs. LT for HCC have been published. Comparing the efficacy of different therapeutic modalities such as LT, LR, and RFA for HCC using retrospective data can be problematic. In particular, many of these studies suffer from selection bias and confounding by indication. Patients treated with RFA are usually older, have slightly worse liver function and most importantly, an increase in associated comorbidities (which contraindicate LR). In an attempt to simulate RCTs (i.e., comparative efficacy studies) and mitigate the inherent selection bias characteristic of retrospective studies, many investigators have adopted specific statistical techniques (i.e., case-matching, propensity score analysis, etc.) in an attempt to compare more homogeneous groups of patients.

Several recent studies that specifically sought to compare LR and RFA for patients with very early stage HCC. Of note, three studies reported a similar overall survival and disease-free survival among patients treated with either LR or RFA; in contrast, one study reported better overall survival among patients undergoing RFA, especially for centrally located tumours. With regards to recurrence free survival (RFS), while most studies have noted a comparable RFS, two studies have reported a superior RFS for LR compared with RFA. The majority of studies demonstrated that LR had a significantly higher complication rate than RFA. Since much of the data on this topic have been published recently, no robust meta-analyses have yet been carried out. In general, however, data from retrospective studies have largely confirmed the results derived from the RCT subgroup meta-

analyses that LR was associated with better disease-free survival (DFS) than RFA for very early stage HCC patients, but LR has a higher postoperative morbidity.

The BCLC algorithm does allow for an exception to this new treatment proposal in patients who are considered potential candidates for LT (based on patient's age and presence of comorbidities). These patients, in fact, are recommended to undergo LR because, unlike other local therapy treatment options, the pathological examination of the resected tumour allows for the identification of patients at high risk of tumour recurrence (i.e., those who have the presence micro vascular invasion or additional nodules in the surgical specimen). For these patients, the BCLC proposes a policy of ''ab initio" or preventive LT.

The evidence to support this approach is, however, poor and based on a small single centre observational study without external validation. Moreover, it is well known that the rate of micro vascular invasion increases according to the tumour size, with an incidence of only 20–25% in very early HCC. Of note, since clinically relevant portal hypertension (PH) and high bilirubin levels are associated with high mortality and morbidity following LR, very early HCC patients with these clinical features of liver decompensating is considered non-respectable. In these patients, percutaneous ablation or primary LT are considered more appropriate first line therapies.

Comparative effectiveness studies of patients with very early HCC undergoing curative therapies

Large observational studies have the potential to identify effective interventions among different subgroup of patients and to delineate which treat approaches may work in a ''real world" setting. In contrast, traditional randomized trials (or retrospective studies simulating a RCT) typically provide efficacy data for the ''average" patient only. Recently, health institutions and laws have incorporated comparative effectiveness research as a scientific mechanism to help improve health care. It is likely that the amount of observational research will continue to increase, especially with studies that involve the statistical analysis of large administrative databases and electronic medical records (i.e., big data). HCC, in its very early stage, is heterogeneous both in terms of liver function (i.e., presence or absence of PH, model for end-stage liver disease score, Child-Pugh score 5 or 6, bilirubin level) and tumour characteristics (i.e., location, alpha-fetoprotein values, pathological features such as micro vascular invasion, tumour grade and satellitosis).

Tumour location, need for extensive or complex liver resection, local donor resources and waiting list pressure are some examples of the important variables that need to be considered among patients with HCC. In turn, such variables can confound and complicate the clinical picture, contributing to why trials in this setting are challenging and likely will never totally inform treatment decisions for individual patients. The nuanced and individual context of each case also explains why strict treatment algorithms are often not followed in clinical practice in a large proportion of patients worldwide. For these reasons, the evidence for the personalized approach derives not only from RCTs but also from large cohort studies that may reflect the actual clinical setting and allow for generalization of results due to the high numbers of patients included in most studies.

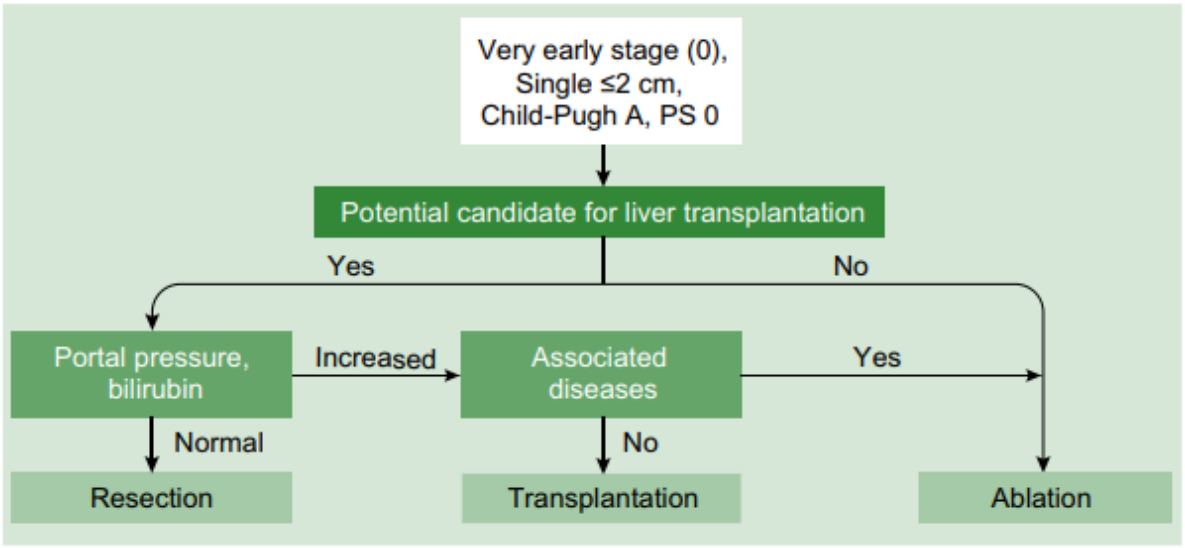

Figure 1

Well-designed observational studies can offer compelling evidence to define the main prognostic factors within each treatment group (i.e., tumour size or location for the ablation group, liver dysfunction for the resection group). The results of prognostic studies, therefore, may be used for a qualitative assessment of treatment effectiveness in different subgroups of patients with very early HCC. Large observational studies can sometimes be transformed into quantitative comparative analyses by using specific statistical simulation/modelling strategies. The robustness of these studies typically depends on the strength of the survival model used to predict individual survival in different treatment groups. The higher the prognostic power of multivariate survival models, the higher the intrinsic statistical evidence of the simulation results. Simulation studies may also be based on solid data from the literature, such as meta-analyses. Furthermore, simulation studies may include other outcome measures such as quality of life and costs.

Liver transplantation for very early HCC:

The first decision rule in the BCLC algorithm is whether the patient is a potential candidate for LT (Fig. 1). As noted above, LT is generally considered the best treatment modality for HCC, as it extirpates both the tumour within the liver as well as the remaining oncogenic cirrhotic tissue caused by the underlying pathology. The disparity between scarce organ donors and the increased number of patients on the waiting list is the main limitation of LT. This crucial limit of LT requires the adoption of specific allocation principles. There are at least two possible bases for organ allocation: medical urgency and utility. A utility-based system would assign priority in accordance with expected post-transplant outcomes. Based on utility, therefore, patients with very early HCC should receive the highest priority for LT because these patients have the lowest risk of post-transplant HCC recurrence. Conversely, under a medical urgency-based allocation system, patients with worse waiting list outcomes are given higher priority or transplantation. This is what actually happens in many countries worldwide for non HCC patients prioritized according to the model for end-stage liver disease (MELD) score.

According to this principle, very early stage HCC represents the category of HCC patients with the lowest survival benefit from LT. Based on this consideration; LT remains a second line treatment for patients with very early HCC. The main benefit of LT is the treatment of recurrence after LR or RFA. Several authors have recently used the results of multivariate survival analyses to compare the outcome of HCC patients with and without LT. The survival benefit of LT in HCC patients was strongly influenced by liver function and availability of alternative therapies. Patients with the highest benefit from LT were those patients without the option of receiving a radical alternative therapy (for example BCLC B patients) or those with decompensated cirrhosis (Child-Pugh class C). Some authors have

also specifically demonstrated that, from a transplant benefit point of view, LT should be contraindicated in patients with respectable HCC, particularly when the tumour is single and the patient has a low MELD score.

The evidence suggests three important considerations:

1) Comparative ‘‘efficacy” studies have shown that LR offers better DFS than RFA at the price of higher postoperative morbidity. This finding is an average result obtained in underpowered comparative studies. In larger comparative ‘‘effectiveness” studies the difference in DFS translates into a significantly higher long-term survival after LR compared with RFA among well-selected patients with very early HCC.

2) Laparoscopic ablation is an important therapeutic procedure available in real life clinical practice ignored by current guidelines. The minimal invasive approach has the potential to overcome some limits of percutaneous ablation particularly in patients with very early HCC in ‘‘high risk locations” (i.e., surface or partially exophytic lesions closed to abdominal organs).

3) Based on the transplant benefit principle, LT has the lowest survival benefit among patient with very early HCC compared with patients who have HCC that is more advanced according to the BCLC stages.

CONCLUSION:

Based on these considerations, LR is probably justified as first line therapy in very early HCC only when the risk of postoperative LD is comparable to that of non-resection approaches. According to recent evidence, an optimal postoperative result can be obtained among very early HCC patients using a minor LR in the absence of clinically relevant PH and with a MELD score 69. Among patients with PH, optimal results are better achieved with a laparoscopic minor LR.

REFERENCES:

1. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11
2. Lafaro KJ, Demirjian AN, Pawlik TM. Epidemiology of hepatocellular carcinoma. Surg Oncol Clin N Am 2015; 24:1–17
3. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 2001;35:421–430
4. Bruix J, Sherman M. Practice guidelines committee, American association for the study of liver diseases. Management of hepatocellular carcinoma. Hepatology 2005;42:1208–1236.
5. European Association for the Study of the LiverEuropean Organisation for Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908–943.
6. Bruix J, Reig M, Sherman M. Evidence-based diagnosis, staging, and treatment of patients with hepatocellular carcinoma. Gastroenterology 2016;150:835–853.
7. Murad MH, Asi N, Alsawas M, Alahdab F. New evidence pyramid. Evid Based Med 2016. http://dx.doi.org/10.1136/ebmed-2016-110401, [pii: ebmed-2016- 110401].
8. Van Poucke S, Thomeer M, Heath J, Vukicevic M. Are randomized controlled trials the (G)old Standard? From clinical intelligence to prescriptive analytics. J Med Internet Res 2016;18:e185.
9. Genta RM, Sonnenberg A. Big data in gastroenterology research. Nat Rev Gastroenterol Hepatol 2014;11:386–390.
10. Chen MS, Li JQ, Zheng Y, et al. A prospective randomized trial comparing percutaneous local ablative.