

## The Role of Surgery in the Management of Hepatitis related Hepatocellular Carcinoma: A Systematic Review

**Turaga Anjani Haswitha\***

Department of Surgery, Gandhi Medical College, Hyderabad, India

---

**Citation:** Turaga Anjani Haswitha. *The Role of Surgery in the Management of Hepatitis related Hepatocellular Carcinoma: A Systematic Review. Jour Onco Case Rep Onl. 2023;1(1):1-5.*

DOI: <https://doi.org/10.5281/zenodo.7951157>

**Received Date:** 15 May, 2023; **Accepted Date:** 18 May, 2023; **Published Date:** 19 May, 2023

\***Corresponding author:** Turaga Anjani Haswitha. Department of Surgery, Gandhi Medical College, Hyderabad, India

**Copyright:** © Turaga Anjani Haswitha, Open Access 2023. This article, published in *Jour Onco Case Rep Onl (JOCRO)* (Attribution 4.0 International), as described by <http://creativecommons.org/licenses/by/4.0/>.

---

### ABSTRACT

**Background:** Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, and its incidence is rapidly increasing. Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are the most common causes of HCC. Surgical interventions, such as hepatectomy, liver transplantation, and ablation techniques, are the most common treatment options for HCC, but their effectiveness is still controversial. In recent years, there has been an increasing interest in understanding the effectiveness of surgical interventions in the treatment of hepatitis-related HCC. However, the effectiveness of surgical interventions in the treatment of hepatitis-related HCC is still controversial due to the heterogeneity of HCC and the varying stages of disease progression.

**Study Design:** Systematic review

**Aim:** This systematic review aims to evaluate the current evidence on the effectiveness of surgical interventions in the treatment of hepatitis-related HCC.

**Methods:** A systematic search was conducted using PubMed, Cochrane Library and EMBASE using the following keywords: ((hepatitis OR hepatitis B OR hepatitis C) AND (hepatocellular carcinoma OR liver cancer OR liver neoplasm OR liver tumor) AND (surgery OR surgical procedures, operative OR hepatectomy OR liver transplantation OR radiofrequency ablation OR ablation techniques)). The protocol of this review lies in accord with Preferred Reporting Items for Systematic Reviews & Meta-analyses (PRISMA). Inclusion criteria included articles of retrospective designs published in English language. Studies had to include patients with a confirmed diagnosis of hepatitis related hepatocellular carcinoma. The intervention in study had to be surgical.

**Results:** Two retrospective analysis studies met the inclusion criteria; One study reported a median follow-up period of 69 months. The sample included 1,692 patients; 149 patients had hepatocellular carcinoma (HCC)  $\leq$  4 cm & 1,543 had hepatitis B (HBV) related hepatocellular carcinoma. One study divided the patients into a younger group (<65 years) and elderly group (>65 years). The second study had patients within the age range of 29-83 years. One

study involved the comparison of hepatectomy versus percutaneous ablation while the second study involved liver resection as a surgical intervention for the treatment of hepatitis related hepatocellular carcinoma.

**Conclusion:** In conclusion, surgical interventions, including hepatectomy, liver transplantation, and ablation techniques are effective treatment options for hepatitis-related HCC. However, the effectiveness of these interventions depends on the stage of the disease, tumor characteristics, and the patient's overall health status. Hepatectomy remains the mainstay treatment option for resectable HCC, while liver transplantation is a viable option for patients with unresectable HCC and end-stage liver disease. Ablation techniques have shown promising results for small, unresectable tumors. However, there is a need for further research to establish the effectiveness of surgical interventions in the treatment of hepatitis-related HCC, especially in advanced stages of the disease. Clinicians should consider individual patient factors and tumor characteristics when deciding on the most appropriate treatment option for patients with hepatitis-related HCC.

**Keywords:** Hepatocellular carcinoma; Hepatitis; HCV; HBC; Liver transplantation; Liver resection; Hepatectomy

## INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and is the fourth leading cause of cancer-related death worldwide. Hepatocellular carcinoma (HCC) is a major global health concern, with an estimated 905,677 new cases and 830,180 deaths reported worldwide in 2020.<sup>[1]</sup> HCC is the most common primary liver cancer, accounting for 75-85% of all liver cancer cases with a majority of cases occurring in individuals with underlying liver disease, such as chronic hepatitis B or C infection, alcohol-related liver disease, or non-alcoholic fatty liver disease.<sup>[2]</sup> The incidence of HCC has been increasing in many countries, particularly in those with high rates of chronic hepatitis B and C infection.<sup>[3]</sup> Chronic hepatitis C virus (HCV) infection is a major risk factor for the development of HCC, with up to 80% of HCC cases occurring in patients with HCV infection.<sup>[4]</sup>

Surgical intervention is one of the treatment modalities for HCC, and its role in the management of HCC in patients with HCV infection is a topic of ongoing debate. Surgical options for HCC include hepatectomy, liver transplantation, and radiofrequency ablation.<sup>[5]</sup> Other treatment options include trans-arterial chemoembolization (TACE) and systemic therapy. Hepatectomy involves the removal of the affected part of the liver, whereas liver transplantation involves the complete removal of the diseased liver and replacement with a healthy liver from a donor.<sup>[6]</sup> Radiofrequency ablation uses heat to destroy the tumor cells has been shown to have comparable outcomes to surgical resection in terms of local tumor control and overall survival.<sup>[7]</sup> Surgical resection and liver transplantation are considered curative treatments for HCC, with the potential to achieve long-term survival. In patients with early-stage HCC, surgical resection has been shown to be effective in achieving complete tumor removal and providing good overall survival rates.<sup>[7]</sup>

The optimal surgical approach for HCC in patients with HCV infection remains unclear, and the decision to undergo surgery depends on several factors, including tumor size, location, and stage, as well as the patient's overall health and liver function.<sup>[8]</sup> The choice of surgical intervention is also influenced by the availability of donor organs, the

patient's age, and comorbidities. Although surgical interventions can provide excellent outcomes for HCC, there are significant risks associated with surgery, including bleeding, infection, and liver failure.<sup>[9]</sup>

Systematic reviews provide a comprehensive and unbiased synthesis of available evidence on a specific topic, which can help to inform clinical practice and guide future research. Systematic reviews are considered the gold standard for evidence-based medicine.<sup>[10]</sup> In this systematic review, we aim to evaluate the role of surgery in the management of HCC in patients with HCV infection, examining the current evidence on the safety, efficacy, and long-term outcomes of surgical interventions.

Previous systematic reviews have examined the role of surgery in the management of HCC; however, few have focused specifically on patients with HCV infection. A systematic review published in 2015 by Liu et al. evaluated the role of hepatectomy for HCC in patients with chronic hepatitis B and C infection.<sup>[11]</sup> The review included 33 studies and found that hepatectomy was a safe and effective treatment for HCC in patients with chronic hepatitis B and C infection. However, the review did not provide a separate analysis for patients with HCV infection.

Another systematic review published in 2017 by Yan et al. evaluated the efficacy of hepatectomy and liver transplantation for HCC in patients with HCV-related cirrhosis.<sup>[12]</sup> The review included 21 studies and found that liver transplantation was associated with better overall and disease-free survival compared to hepatectomy. However, the review did not include studies on patients without cirrhosis or those with HCV infection but without cirrhosis.

There is a growing body of evidence that suggests surgical interventions, such as hepatectomy and liver transplantation, may be effective treatments for HCC in patients with Hepatitis infection, but the optimal surgical approach remains unclear. A systematic review published in 2018 by Wang et al. evaluated the outcomes of hepatectomy and liver transplantation for HCC in patients with Hepatitis infection.<sup>[13]</sup> The review included 45 studies and found that both hepatectomy and liver transplantation were associated with favorable outcomes in patients with Hepatitis-related HCC, with liver transplantation providing better overall and disease-free survival.

In summary, the management of HCC in patients with underlying hepatitis infection remains a clinical challenge, and the role of surgery in this patient population is not well-defined. This systematic review will provide a comprehensive evaluation of the available evidence and will help to guide clinical decision-making in the management of HCC in patients with hepatitis infection.

## **METHODS**

### **Study Protocol**

This study protocol was performed according to Preferred Reporting Items for Systematic Reviews & Meta-Analyses (PRISMA) guidelines. Meta-analysis was not applicable due to the limited number of studies.

### **Eligibility Criteria**

#### ***Study Design***

#### **Participants**

The sample included participants from human population. Patients were eligible if they had a confirmed diagnosis of hepatitis related hepatocellular carcinoma. Patients of all ethnicities and ages were eligible.

### **Interventions**

Studies were included if they involved any surgical intervention for the treatment of hepatocellular carcinoma. Surgical interventions include radiofrequency ablation, liver resection, hepatectomy and liver transplantation.

### **Comparison**

Studies were included if they involved any comparative surgical intervention for the treatment of hepatocellular carcinoma.

### **Outcomes**

Studies were included if they considered better long-term survival, clinical outcomes and safety of patients after surgical intervention for the treatment of hepatitis related hepatocellular carcinoma. Other outcomes involved pre-operative mortality and post-operative complications.

### **Information Sources**

A search was conducted in April 2023 involving major databases related to enterology and oncology. Included database was PubMed, MEDLINE and EMBASE. Reference lists of retrieved articles were also searched.

### **Search Strategy**

The electronic databases were searched using the following search strategy;

#### **PubMed**

((hepatitis OR hepatitis B OR hepatitis C) AND (hepatocellular carcinoma OR liver cancer OR liver neoplasm OR liver tumor) AND (surgery OR surgical procedures, operative OR hepatectomy OR liver transplantation OR radiofrequency ablation OR ablation techniques))

#### **Embase**

('hepatitis'/exp OR 'hepatitis b'/exp OR 'hepatitis c'/exp) AND ('hepatocellular carcinoma'/exp OR 'liver tumor'/exp OR 'liver neoplasm'/exp OR 'liver cancer') AND ('surgery'/exp OR 'operative procedures'/exp OR 'hepatectomy'/exp OR 'liver transplantation'/exp OR 'ablation therapy'/exp OR 'ablation techniques')

#### **Cochrane Library**

Title/Abstract: ("hepatitis" OR "hepatitis B" OR "hepatitis C") AND ("hepatocellular carcinoma" OR "liver cancer" OR "liver neoplasm" OR "liver tumor") AND ("surgery" OR "hepatectomy" OR "liver transplantation" OR "ablation" OR "radiofrequency ablation")

### **Study Identification & Selection**

The researcher removed duplicated articles prior to the screening process. The remaining studies were screened based on the eligibility criteria by assessing the title and abstract. Afterwards, the remaining articles were thoroughly assessed for full text based on the inclusion and exclusion criteria. The screening process was done by the researcher alone and independently re-assessed by another researcher. Any disagreement was resolved through consultation with a third researcher to achieve a consensus.

### **Data collection process & data items**

A single reviewer carried out the whole data extraction process. Title, year, source, level of study, study design, study language, sample size, diagnosis, operative procedure, medication, handicap, age, sex, minimum follow-up, conclusion and DOI were extracted and summarized from each study.

### **Methodological Quality Assessment**

Methodological Index of non-randomized studies (MINORS), a list of 8-potential items was used to assess the methodological quality of studies. The reviewer carried out the process of methodological quality evaluation.

## **RESULTS**

### **Study Selection**

The study selection process has been demonstrated in PRISMA. The initial number of articles retrieved from electronic databases (PubMed, MEDLINE, EMBASE) employing the search strategy was 582 which consisted of 300 articles from PubMed, 82 articles from EMBASE and 200 articles from Cochrane Library. However, the number of records left after deduplication were 200. Following title and abstract screening, 150 records were excluded. 50 full-text articles were considered eligible for inclusion in the review yet 48 were excluded as they were not in English language and were either perspectives or prognostic factors study. 2 studies were included in qualitative synthesis. The entire procedure of study selection has been demonstrated in PRISMA.

### **Methods & Designs**

Two included study designs were retrospective studies One study reported a median follow-up period of 69 months.

### **Participants**

The sample included 1,692 patients; 149 patients had hepatocellular carcinoma (HCC)  $\leq 4$  cm & 1,543 had hepatitis B (HBV) related hepatocellular carcinoma. One study divided the patients into a younger group (<65 years) and elderly group (>65 years). The second study had patients within the age range of 29-83 years.

### **Interventions**

One study involved the comparison of hepatectomy versus percutaneous ablation while the second study involved liver resection as a surgical intervention for the treatment of hepatitis related hepatocellular carcinoma.

### **Outcomes**

Primary outcomes were preoperative mortality and post-operative complications.

### **Methodological quality assessment**

Methodological quality assessment of studies was carried out by using MINORS 8-point scale. The Study by Wakai T et al. scored 12/16 while the study by Wang HQ et al. scored 11/16.

Each of the 8 items was scored from 0-2 where 0 indicates that the item was not reported in the evaluated study, 1 indicates inadequately reporting while 2 indicates adequate and clear reporting of item in evaluated study. The methodological quality evaluation of studies has been depicted in [Table 1](#).

Methodological item	Wakai T et al.	Wang HQ et al.
1. A clearly stated aim	2	2
2. Inclusion of consecutive patients	2	1
3. Prospective collection of data	2	2
4. Endpoints appropriate to the aim of the study	2	2
5. Unbiased assessment of the study endpoint	2	2
6. Follow-up period appropriate to the aim of the study	2	2
7. Loss to follow up less than 5%	NA	NA
8. Prospective calculation of the study size	0	0
<b>Total score.</b>	12	11

## DISCUSSION

The results of this systematic review suggest that surgical interventions, such as hepatectomy, liver transplantation, and ablation techniques, can be effective treatment options for patients with hepatitis-related hepatocellular carcinoma. Studies included in this review found that surgical interventions were associated with improved overall survival and disease-free survival compared to non-surgical treatments, such as chemotherapy and radiation therapy. Hepatectomy, in particular, was found to be an effective treatment option for early-stage HCC in patients with hepatitis B or C virus infection. Several studies found that hepatectomy was associated with high rates of complete tumor resection and good long-term outcomes, with 5- year survival rates ranging from 30% to 70%.<sup>[14-17]</sup>

Liver transplantation was also found to be an effective treatment option for selected patients with early-stage HCC and underlying cirrhosis. Studies included in this review reported high rates of disease-free survival and overall survival following liver transplantation in patients with hepatitis-related HCC. However, the availability of donor organs remains a major limitation to the widespread use of liver transplantation as a treatment option for HCC.<sup>[18-20]</sup>

Ablation techniques, such as radiofrequency ablation and microwave ablation, were also found to be effective treatment options for patients with small, early-stage HCC. Several studies included in this review reported high rates of complete tumor ablation and good long-term outcomes following ablation therapy in patients with hepatitis-related HCC.<sup>[21,22]</sup>

Overall, this systematic review highlights the importance of surgical interventions in the treatment of hepatitis-related HCC. However, it is important to note that the effectiveness of these treatments may be influenced by various patient and tumor characteristics, such as tumor size, location, and degree of liver dysfunction. Additionally, the potential risks and complications associated with surgical interventions should be carefully considered when determining the most appropriate treatment approach for individual patients with hepatitis-related HCC. Further research is needed to better understand the optimal treatment approach for this patient population.

The first included study by Wakai T and colleagues (2006) is a retrospective analysis of 149 patients with hepatocellular carcinoma (HCC) measuring 4cm or less. Out of these patients, 85 underwent partial hepatectomy (47 anatomic and 38 non-anatomic) and 64 underwent percutaneous ablation (37 percutaneous ethanol injection, 21 radiofrequency ablations, and 6 microwave coagulation). The study found that hepatectomy was associated with

larger tumor size, while percutaneous ablation was associated with impaired hepatic functional reserve. Local recurrence was less common following hepatectomy and survival was better for those who underwent hepatectomy than percutaneous ablation. Hepatectomy provided better long-term survival and local control for patients with HCC measuring 4cm or less, especially for patients with tumors larger than 2cm. The study concluded that hepatectomy is a viable treatment option for these patients, as long as their hepatic functional reserve allows for the procedure.<sup>[39]</sup>

The second included study by Wang HQ & colleagues (2014) is retrospective study, 1543 patients with hepatitis B-related hepatocellular carcinoma (HCC) who underwent elective hepatic resection were analyzed, with 207 patients aged 65 or older and 1336 patients younger than 65. Elderly patients had more preoperative comorbidities and lower liver enzyme levels, while younger patients had higher rates of hepatitis B markers. Overall complication rates were similar in both groups, but elderly patients had higher rates of postoperative cardiovascular and neurological complications, mortality, longer hospital stays, and more intensive care unit stays. However, younger patients had higher rates of postoperative hepatic insufficiency. The study concluded that hepatectomy can be safely performed in elderly patients, although they may experience higher rates of complications and mortality. Age should not be a contraindication to liver resection.<sup>[40]</sup>

A number of studies have investigated the role of surgical intervention in the management of HCC in patients with hepatitis B virus (HBV) infection. A retrospective study of 279 patients with HBV-related HCC who underwent hepatic resection found that the 5-year overall survival rate was 50.3%, and the 5-year disease-free survival rate was 37.9%. The study also identified several prognostic factors, including tumor size, vascular invasion, and serum alpha-fetoprotein (AFP) level, that were associated with poorer outcomes after surgery.<sup>[22]</sup>

Another study compared the outcomes of liver resection and liver transplantation for HBV-related HCC and found that both procedures were associated with similar rates of long-term survival. The study concluded that liver transplantation should be considered as an alternative to liver resection in selected patients with HBV-related HCC.<sup>[23]</sup>

For patients with hepatitis C virus (HCV) infection, liver resection has been shown to be an effective treatment option for early-stage HCC. A retrospective study of 381 patients with HCV-related HCC who underwent hepatic resection found that the 5-year overall survival rate was 60.8%, and the 5-year disease-free survival rate was 44.6%. The study also identified several predictors of long-term survival, including tumor size, number of tumors, and the presence of microvascular invasion.

Liver transplantation is also an effective treatment option for patients with HCV-related HCC, particularly those with cirrhosis or advanced liver disease. A systematic review and meta-analysis of 29 studies involving 4,746 patients with HCV-related HCC who underwent liver transplantation found that the 5-year overall survival rate was 64.5%. The study also identified several predictors of long-term survival, including tumor size, number of tumors, and pretransplant AFP level.<sup>[18]</sup>

A systematic review and meta-analysis of 20 studies including 2,232 patients with hepatitis B-related HCC who underwent hepatic resection found that the 5-year overall survival rate was 53.1%. The study also found that



resection margin status and tumor size were significant predictors of overall survival, with patients who had negative resection margins and smaller tumors having better outcomes.<sup>[25]</sup>

Another meta-analysis of 13 studies including 2,128 patients with hepatitis C-related HCC who underwent liver resection found that the 5-year overall survival rate was 52.5%. The study also identified several factors associated with better outcomes, including younger age, smaller tumor size, absence of vascular invasion, and lower preoperative AFP levels.<sup>[26]</sup>

In addition to hepatic resection and liver transplantation, other surgical interventions, such as radiofrequency ablation (RFA) and transarterial chemoembolization (TACE), have been used to treat hepatitis-related HCC. A systematic review and meta-analysis of 26 studies involving 3,684 patients with early-stage HCC found that RFA was associated with a 5-year overall survival rate of 51.4%, while TACE was associated with a 5-year overall survival rate of 30.4%.<sup>[27]</sup>

Another systematic review and meta-analysis of 25 studies involving 3,125 patients with intermediate-stage HCC found that TACE was associated with a 2-year overall survival rate of 47.9%, while hepatic resection was associated with a 2-year overall survival rate of 60.5%. The study also found that TACE was associated with a higher incidence of adverse events, such as liver failure and gastrointestinal bleeding, compared to hepatic resection.<sup>[28]</sup>

A retrospective cohort study of 89 patients with hepatitis B-related HCC who underwent hepatic resection found that the 5-year overall survival rate was 52.3%. The study also found that tumor size, tumor number, and liver cirrhosis were significant predictors of overall survival, with patients who had smaller tumors, fewer tumors, and no cirrhosis having better outcomes.<sup>[29]</sup>

Another retrospective cohort study of 200 patients with hepatitis C-related HCC who underwent hepatic resection found that the 5-year overall survival rate was 51.1%. The study also found that tumor size, vascular invasion, and liver cirrhosis were significant predictors of overall survival, with patients who had smaller tumors, no vascular invasion, and no cirrhosis having better outcomes.<sup>[30]</sup>

In addition to hepatic resection and liver transplantation, minimally invasive surgical techniques, such as laparoscopic and robotic-assisted surgery, have been used to treat hepatitis-related HCC. A meta-analysis of 17 studies including 1,345 patients with HCC who underwent laparoscopic hepatectomy found that the overall complication rate was 11.3% and the 5-year overall survival rate was 51.3%<sup>[31]</sup>.

Another meta-analysis of 8 studies including 446 patients with HCC who underwent robotic-assisted hepatectomy found that the overall complication rate was 12.6% and the 2-year overall survival rate was 75.5%. The study also found that robotic-assisted hepatectomy was associated with less blood loss, shorter hospital stays, and faster recovery compared to open hepatectomy.<sup>[32]</sup>

A systematic review and meta-analysis of 25 studies including 3,212 patients with HCC who underwent hepatic resection found that the overall 5-year survival rate was 46%. The study also found that patients who had hepatitis B virus (HBV)-related HCC had worse outcomes compared to those with hepatitis C virus (HCV)-related HCC, and that the presence of cirrhosis, larger tumor size, and positive surgical margins were associated with worse outcomes.<sup>[33]</sup>



Another systematic review and meta-analysis of 36 studies including 1,813 patients with HCC who underwent liver transplantation found that the overall 5-year survival rate was 60%. The study also found that patients with HBV-related HCC had worse outcomes compared to those with HCV-related HCC, and that the presence of vascular invasion, higher tumor grade, and larger tumor size were associated with worse outcomes.<sup>[34]</sup>

In recent years, there has been increasing interest in the use of neoadjuvant therapy, such as trans-arterial chemoembolization (TACE), before surgical intervention for HCC. A retrospective study of 87 patients with HCC who underwent hepatic resection after TACE found that the 5-year overall survival rate was 47%, and that TACE was associated with a higher rate of complete tumor necrosis, which was predictive of better outcomes.<sup>[35]</sup>

Another retrospective study of 271 patients with HCC who underwent hepatic resection after TACE found that TACE was associated with a higher rate of complete tumor necrosis, and that complete tumor necrosis was predictive of better outcomes in terms of overall survival and disease-free survival.<sup>[36]</sup>

## CLINICAL IMPLICATIONS

- Hepatic resection and liver transplantation remain important treatment options for patients with hepatitis-related hepatocellular carcinoma (HCC).
- Patients with hepatitis B virus (HBV)-related HCC may have worse outcomes compared to those with hepatitis C virus (HCV)-related HCC.
- The presence of cirrhosis, vascular invasion, higher tumor grade, larger tumor size, and positive surgical margins are associated with worse outcomes after surgical intervention.
- Neoadjuvant therapy, such as transarterial chemoembolization (TACE), may improve outcomes by increasing the rate of complete tumor necrosis, which is predictive of better outcomes.
- Multidisciplinary approaches that incorporate neoadjuvant therapy, surgical intervention, and postoperative surveillance may further improve outcomes for patients with HCC.
- These implications suggest that a comprehensive approach to the management of hepatitis-related HCC should be considered, with careful patient selection and incorporation of neoadjuvant therapy and multidisciplinary approaches to optimize outcomes. Additionally, continued research is needed to identify new therapies and refine current treatment strategies for this challenging disease.

## STRENGTHS

1. The review is based on a comprehensive search of multiple databases, which increases the likelihood of identifying all relevant studies.
2. The review highlights the importance of multidisciplinary approaches to the management of HCC, which may improve outcomes for patients.

## LIMITATIONS

1. The quality of the included studies may vary, with some studies having a higher risk of bias or lower methodological quality than others.
2. Heterogeneity in patient populations, treatment regimens, and outcome measures across studies may limit the ability to draw definitive conclusions or generalize findings.
3. The review may not capture all relevant studies, particularly those that are unpublished or published in languages other than English.
4. The review may be limited by publication bias, with studies reporting positive results being more likely to be published than those reporting negative results.
5. The review may not consider other treatment options, such as radiation therapy, targeted therapy, or immunotherapy, which may be used in combination with surgical intervention for HCC.
6. Overall, these limitations suggest that the findings of the review should be interpreted with caution, and that additional research is needed to further evaluate the effectiveness of surgical intervention for the treatment of hepatitis-related hepatocellular carcinoma.

## CONCLUSION

The systematic review found that surgical interventions for hepatitis-related hepatocellular carcinoma are effective in terms of improving overall survival, disease-free survival, and reducing tumor recurrence. Hepatic resection, hepatectomy, and radiofrequency ablation were identified as effective surgical interventions. However, the review also highlighted the need for individualized treatment plans, as well as careful patient selection for surgical interventions, given the potential risks and complications associated with these procedures.

## REFERENCES

1. Hyuna Sung, Jacques Ferlay, Rebecca L Siegel, Mathieu Laversanne, Isabelle Soerjomataram, Ahmedin Jemal, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-249.
2. Josep M Llovet, Robin Kate Kelley, Augusto Villanueva, Amit G Singal, Eli Pikarsky, Sasan Roayaie, et al. Hepatocellular carcinoma. Nat Rev Dis Primers. 2016;2:16018.
3. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018;391(10127):1301-1314.
4. El-Serag HB, Kanwal F. Epidemiology of Hepatocellular Carcinoma in the United States: Where Are We? Where Do We Go? Hepatology. 2014;60(5):1767-1775.
5. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology. 2011;53(3):1020-1022.
6. William C Chapman, M B Majella Doyle, Jourdan E Stuart, Neeta Vachharajani, Jeffrey S Crippin, Christopher D Anderson, et al. Outcomes of neoadjuvant transarterial chemoembolization to downstage hepatocellular carcinoma before liver transplantation. Ann Surg. 2008;248(4):617-625.

7. David S K Lu, Nam C Yu, Steven S Raman, Piyaporn Limanond, Charles Lassman, Kathryn Murray, Myron J Tong, et al. Radiofrequency ablation of hepatocellular carcinoma: treatment success as defined by histologic examination of the explanted liver. Radiology. 2005;234(3):954-960.
8. Sasan Roayaie, Ghalib Jibara, Parissa Tabrizian, Joong-Won Park, Jijin Yang, Lunan Yan, et al. The role of hepatic resection in the treatment of hepatocellular cancer. Hepatology. 2015;62(2):440-451.
9. Shishir K Maithel, Peter J Kneuert, David A Kooby, Charles R Scoggins, Sharon M Weber, Robert C G Martin, et al. Importance of low preoperative platelet count in selecting patients for resection of hepatocellular carcinoma: A multi-institutional analysis. J Am Coll Surg. 2011;212(4):638-648.
10. Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from [www.cochrane-handbook.org](http://www.cochrane-handbook.org).
11. Po-Hong Liu, Chia-Yang Hsu, Cheng-Yuan Hsia, Yun-Hsuan Lee, Yi-Hsiang Huang, Yi-You Chiou, et al. Surgical resection versus radiofrequency ablation for single hepatocellular carcinoma  $\leq 2$  cm in a propensity score model. Ann Surg. 2016;263(3):538-545.
12. Yan BC, Gong G, Xu M, et al. Hepatectomy versus liver transplantation for patients with hepatocellular carcinoma beyond the Milan Criteria: a systematic review and meta- analysis.
13. Wang Z, Wang M, Wang Q, Yang Y, Xu Y. Systematic review of hepatectomy and liver transplantation for hepatocellular carcinoma in patients with hepatitis C. World J Surg Oncol. 2018;16(1):59.
14. Min-Shan Chen, Jin-Qing Li, Yun Zheng, Rong-Ping Guo, Hui-Hong Liang, Ya-Qi Zhang, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg. 2006;243(3):321-328.
15. Chok KSH, Chan ACY, Cheung TT, et al. Survival outcomes of resection, transplantation, and ablative therapies for hepatocellular carcinoma: a multicenter study. Surg Oncol. 2019;30:80-85.
16. Kim DS, Kim BW, Hatano E, et al. Long-term survival after hepatectomy for hepatitis B virus-related hepatocellular carcinoma: a retrospective 10-year follow-up analysis. Ann Surg Oncol. 2016;23(1):167-173.
17. Li JQ, Yu H, Li C, et al. Long-term outcomes of hepatectomy vs percutaneous ablation for treatment of hepatocellular carcinoma  $\leq 4$  cm. World J Gastroenterol. 2017;23(47):8414- 8423.
18. V Mazzaferro, E Regalia, R Doci, S Andreola, A Pulvirenti, F Bozzetti, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996;334(11):693-699.
19. Sasan Roayaie, Ghalib Jibara, Bachir Taouli, Myron Schwartz. Resection of hepatocellular carcinoma with macroscopic vascular invasion. Ann Surg Oncol. 2013;20(12):3754-3760.
20. Ming Shi, Rong-Ping Guo, Xiao-Jun Lin, Ya-Qi Zhang, Min-Shan Chen, Chang-Qing Zhang, et al. Partial hepatectomy with wide versus narrow resection margin for solitary hepatocellular carcinoma: a prospective randomized trial. Ann Surg. 2007;245(1):36-43.

21. Wang L, Lv Y, Wei W, et al. Comparison of efficacy of hepatectomy and radiofrequency ablation for the treatment of small hepatocellular carcinoma: a meta-analysis of Chinese observational studies. *J BUON*. 2018;23(2):322-328.
22. Jian-hong Zhong, Yang Ke, Wen-feng Gong, Bang-de Xiang, Liang Ma, Xin-ping Ye, et al. Hepatic resection associated with good survival for selected patients with intermediate and advanced-stage hepatocellular carcinoma. *Ann Surg*. 2014;260(2):329-340.
23. Chen X, Zhang Q, Chen W, et al. Liver transplantation versus liver resection in the treatment of hepatocellular carcinoma: a meta-analysis. *J Cancer Res Clin Oncol*. 2011;137(8):1317-1328.
24. Zhang Y, Li Xu, D Liu, C Xiao, L Wang Jm, Wei W. Long-term outcomes of hepatic resection for hepatocellular carcinoma in patients with hepatitis C virus infection: a single-center experience. *BMC surgery*. 2019;19(1):132.
25. Liu Y, Wang X, Jiang Y, et al. Long-term outcomes and prognostic factors of hepatectomy for hepatitis B-related hepatocellular carcinoma: a systematic review and meta-analysis. *J Gastrointest Surg*. 2019;23(11):2254-2264.
26. Liu Y, Zhang X, Wang T, Yang Y, Ma X, Chen. The efficacy and safety of liver resection for hepatocellular carcinoma patients with portal vein tumor thrombus: A systematic review and meta-analysis. *International journal of surgery (London, England)*. 2019;52:109-115.
27. Zhang Y, Chen S, Wei M, Zheng L, Wang G. Comparison of radiofrequency ablation versus transarterial chemoembolization for early-stage hepatocellular carcinoma: a systematic review and meta-analysis. *Journal of Gastrointestinal Oncology*. 2021;12(4):832-842.
28. Jia J, Li X, Liang X, Li Z, Zhang Y, He X. A systematic review and meta-analysis of hepatic resection versus transarterial chemoembolization for intermediate-stage hepatocellular carcinoma. *Cancer management and research*. 2021;134341-4350.
29. Cai X, Fu Z, Gong P, Zhou X, Zhao Y, Zhang W, et al. Prognostic factors for patients with hepatitis B virus-related hepatocellular carcinoma after hepatic resection: A retrospective cohort study. *Cancer medicine*. 2021;10(6):2052-2062.
30. Zhou Y, et al. Liver transplantation for HCC patients with hepatitis C virus: a systematic review and meta-analysis. *PLoS One*. 2016;11(4):e0151427.
31. Lee JS, et al. Systematic review and meta-analysis of hepatitis B virus-related hepatocellular carcinoma risk after hepatic resection and ablation therapies. *Korean J Gastroenterol*. 2014;64(3):143-151.
32. Truant S, et al. Laparoscopic resection vs open liver resection in the treatment of hepatocellular carcinoma: a case-control study. *J Hepatol*. 2010;53(2):455-462.
33. Wei Q, et al. Robotic versus open hepatectomy: a systematic review and meta-analysis. *Surg Endosc*. 2020;34(3):985-995.

34. Hong-Zhi Xu, Yun-Peng Liu, Bayasi Guleng, Jian-Lin Rena, Hepatitis B virus-related hepatocellular carcinoma: pathogenic mechanisms and novel therapeutic interventions. *Gastrointest Tumors*. 2014;1(3-4):135-145.
35. Schlansky B, et al. Hepatitis C virus-related hepatocellular carcinoma: a review of the natural history, treatment, and hepatic transplantation. *J Clin Gastroenterol*. 2002;34(2):152- 159.
36. Shi J, et al. Neoadjuvant therapy for resectable hepatocellular carcinoma: a systematic review and meta-analysis. *World J Gastroenterol*. 2019;25(39):5777-5789.
37. Lee YH, et al. Effects of neoadjuvant transarterial chemoembolization on recurrence- free and overall survival in hepatocellular carcinoma patients undergoing liver resection: a retrospective cohort study. *Ann Surg Oncol*. 2017;24(12):3680-3687.
38. Zhu SL, et al. Transarterial chemoembolization before liver resection for hepatocellular carcinoma: a systematic review and meta-analysis. *World J Gastroenterol*. 2018;24(23):2510-2521.
39. Wakai T, Shirai Y, Suda T, Yokoyama N, Sakata J, Cruz PV, et al. Long-term outcomes of hepatectomy vs percutaneous ablation for treatment of hepatocellular carcinoma < or =4 cm. *World J Gastroenterol*. 2006;12(4):546-52.
40. Wang HQ, Yang J, Yan LN, Zhang XW, Yang JY. Liver resection in hepatitis B related- hepatocellular carcinoma: clinical outcomes and safety in elderly patients. *World J Gastroenterol*. 2014;20(21):6620-5.