

# Management of Hepatocellular Carcinoma Associated with NAFLD

Subjects: **Surgery**

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Non-alcoholic fatty liver disease (NAFLD) has gained attention due to its increasing prevalence worldwide becoming a global epidemic. The increasing incidence of NAFLD and the concurrent increase in the number of hepatocellular carcinoma (HCC) cases at a global level is a matter of concern. HCC has several risk factors, of which NAFLD and its associated metabolic disturbances—type 2 diabetes mellitus, obesity, and dyslipidemia—are of great interest due to their accelerating rise in incidence worldwide. There is a high amount of data derived from basic and clinical studies that reveal the molecular pathways that drive NAFLD-associated HCC. Based on these findings, new prevention, surveillance, and treatment strategies are emerging.

non-alcoholic fatty liver disease

hepatocellular carcinoma

management

hepatic resection

ablation

liver transplantation

transcatheter arterial chemoembolization (TACE)

systemic therapy

## 1. Introduction

Over the past few decades, liver cancer incidence and death have both been steadily increasing. With a total of 905,677 new cases reported in 2020, liver cancer constituted the sixth most prevalent cancer globally. Liver cancer still has a poor prognosis despite recent improvements. In terms of cancer-related deaths in 2020, liver cancer came in third with 830,180 fatalities <sup>[1]</sup>. HCC has several risk factors, of which NAFLD and its associated metabolic disturbances—type 2 diabetes mellitus, obesity, and dyslipidemia—are of great interest due to their accelerating rise in incidence worldwide <sup>[2]</sup>.

The therapeutic management of HCC is complex and, according to the recommendations of current guidelines, it requires a multidisciplinary team consisting of hepatologists, oncologists, and surgeons specialized in liver surgery and transplantation, as well as radiologists. However, data from the literature show that only half of patients diagnosed with HCC are subsequently evaluated by a multidisciplinary team. Currently, the treatment recommendations for HCC are based on the BCLC classification and do not differ from one etiology to another, but do take into consideration the presence of liver cirrhosis and consequently liver function <sup>[3]</sup>. Placing patients in a specific therapeutic strategy depends on the BCLC classification, taking into account patient heterogeneity, patient wishes, ongoing clinical trials, and local limitations. There are scarce data regarding both treatment modalities and

long-term survival in NAFLD-HCC, taking into consideration that these patients frequently have several comorbidities, such as type 2 diabetes mellitus, cardiovascular disease, and obesity. For instance, Wang et al. demonstrated that cirrhotic patients with type 2 diabetes and HCC have lower overall survival rates after curative hepatectomy compared to those without diabetes [4]. The authors concluded that diabetes may reduce the OS of HCC patients by exacerbating existing liver fibrosis, resulting in severe liver failure.

## 2. Hepatic Resection

In patients with HCC without liver cirrhosis and impaired liver function, hepatic resection represents the first option for treatment [5][6]. However, despite progress having been made in the last years in improving the survival rate in those with liver resection, the recurrence rate has not shown major changes. Research studies that assessed the overall survival (OS) and recurrence-free survival (RFS) in patients with NAFLD-associated HCC showed optimistic results (**Table 1**). It appears that OS at 5 years after liver resection for NAFLD-associated HCC ranges from 51.5% to 97%, whereas RFS at 5 years ranges from 36.3% to 66% [7][8][9][10][11][12][13]. However, there is an ongoing debate regarding the outcomes after resection in patients with NAFLD-associated HCC vs. other liver diseases. It appears that the presence of metabolic and cardiovascular comorbidities, which are often found in patients with NAFLD, has a negative impact on the OS after liver resection for HCC [14]. A meta-analysis that aimed to evaluate the outcome after hepatic resection for HCC in NAFLD vs. other liver diseases in approximately 7200 patients found a better RFS and OS in those with NAFLD [15]. Furthermore, a lower RFS was found in a study that compared NAFLD-associated HCC with HCV-related HCC (44.6% vs. 62.5%) [11]. Still, it is important to acknowledge that the high post-surgical mortality in patients with NAFLD is mainly due to the metabolic comorbidities, which should be carefully diagnosed and managed.

**Table 1.** Overall survival (OS) and recurrence-free survival (RFS) in patients with NAFLD-associated HCC after liver resection.

Ref.	Type of Study	Patients (n) and Characteristics	Overall Survival Rate *	Recurrence-Free Survival **
Koh et al. [16]	Retrospective	N = 996 HCC patients, 844 with non-NAFLD HCC and 152 with NAFLD HCC	70.1%	45.4%
Reddy et al. [17]	Retrospective	N = 214 HCC patients, 52 with NASH and 162 with HCV or ALD	59%	48%
Liang et al. [18]	Retrospective	N = 177 HCC patients, 75 with NASH and 102 with alcoholic or viral hepatitis	87%	51%
Vigano et al. [19]	Retrospective	N = 192 HCC patients, 96 with NASH and 96 with HCV	65.6%	37%
Billeter et al. [20]	Retrospective	N = 365 HCC patients, 62 with NASH and 303 with HCV	71.3%	36.3%

Ref.	Type of Study	Patients (n) and Characteristics	Overall Survival Rate *	Recurrence-Free Survival **
Yang et al. [21]	Retrospective	N = 1483 HCC patients, 96 with NAFLD HCC and 1387 with HBV HCC	51.4%	38.8%
Wakai et al. [22]	Retrospective	N = 225 HCC patients, 17 with NAFLD HCC, 61 with HBV, and 147 with HCV	59%	66%

; Glynn,

K.A.; Soerjomataram, I. Global burden of primary liver cancer in 2020 and predictions to 2040. *J. Hepatol.* 2022, 77, 1598–1606.

\* Five-year overall survival rate. \*\* Five-year recurrence free survival.

2. Younossi, Z.M.; Blissett, D.; Blissett, R.; Henry, L.; Stepanova, M.; Younossi, Y.; Racila, A.; Hunt, S.; Beckers, R. The economic and clinical burden of nonalcoholic fatty liver disease in the

United States and Europe. *Hepatology* 2016, 64, 1577–1586.

Radiofrequency ablation (RFA) is a non-surgical treatment method that is currently recommended in patients with stage 0 (tumors smaller than 2 cm) or A, according to the BCLC classification, with OS rates similar to resection [3].

3. Reig, M.; Forner, A.; Rimola, J.; Ferrer-Fàbrega, J.; Burrel, M.; Garcia-Criado, Á.; Kelley, R.K.; Galle, P.R.; Mazzaferro, V.; Salem, R.; et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. *J. Hepatol.* 2022, 76, 681–698.

Regarding NAFLD-associated HCC, a recent study that evaluated the OS rates in patients treated with RFA for HCC in NAFLD and other liver diseases reported no significant differences [2]. However, data from another study show that the presence of type 2 diabetes impairs the outcome after RFS, though metformin therapy has a positive impact on OS [23]. Despite the good efficacy and safety of microwave ablation of HCC, there are no data regarding the outcome in patients with NAFLD.

5. Trevisani, F.; D'Intino, P.E.; Morselli-Labate, A.M.; Mazzella, G.; Accogli, E.; Caraceni, P.;

Domericali, M.; De Nofali, S.; Roda, E.; Bernardi, M. Serum a-fetoprotein for diagnosis of

hepatocellular carcinoma in patients with chronic liver disease: Influence of hBsAg and anti-HCV status. *J. Hepatol.* 2001, 34, 570–575.

According to the European Liver Transplant Registry, the survival rate at 10 years after liver transplantation for HCC is 51%, irrespective of underlying etiology [24]. The current guidelines recommend liver transplantation as the first-line treatment for patients with HCC who do not meet the criteria for curative treatment.

6. Heidebrecht, J.K.; Kulik, L.M.; Finn, R.S.; Sirlin, C.B.; Abecassis, M.M.; Roberts, L.R.; Zhu, A.X.; Marrero, J.H.; Merz, J.A. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatology* 2018, 67, 359–380.

However, since many believe guidelines for the treatment of solid tumors are not applicable to liver transplantation, some studies have evaluated the outcomes of liver transplantation for HCC outside the Milan experience, with good results [26].

7. Koh, Y.X.; Tan, H.J.; Liew, Y.X.; Syn, N.; Teo, J.Y.; Lee, S.Y.; Goh, B.K.; Goh, G.B.; Chan, C.Y. There are several studies regarding long-term outcomes after liver transplantation in NAFLD-associated HCC. Liver resection for nonalcoholic fatty liver disease-associated hepatocellular carcinoma. *J. Am. Coll. Surg.* 2019, 229, 467–478.e1.

Table 2. The OS and RFS rates range from 59% to 88% and 48% to 68%, respectively [8][27][28][29][30][31]. Although some studies reported similar outcomes after liver transplantation for HCC in NAFLD and other etiologies [8][32], there are some studies that raised concerns regarding worse OS in those who had NAFLD-associated HCC.

8. Reddy, S.K.; Stein, J.; Chen, H.W.; De Matteo, D.J.; Cardinale, J.S.; Behari, A.; Humar, A.; Marshall, J.W.; Geller, D.A.; Tsung, A. Outcomes of curative treatment for hepatocellular carcinoma in nonalcoholic steatohepatitis versus hepatitis C and alcoholic liver disease. *Hepatology* 2012, 55, 1809–1819.

A comprehensive analysis from the European transplant registry, which included patients with liver transplantation for nonalcoholic steatohepatitis versus hepatitis C and alcoholic liver disease, reported similar outcomes for the three etiologies [25].

9. Liang, J.; Arizumi, S.-I.; Nakano, M.; Yamamoto, M. Diabetes mellitus and/or nonalcoholic steatohepatitis-related hepatocellular carcinoma showed favorable surgical outcomes after hepatectomy. *Anticancer Res.* 2019, 39, 5639–5643.

These differences could be attributed to different national listing and scoring systems. Overall, it seems that NAFLD has no significant impact on OS after liver transplantation for HCC compared to other causes of liver

10. Viganò, L.; Cacciari, S.; Cescon, M.; Fasola, G.; Capelli, P.; D'Ercole, A.; Torzilli, G.; Di Tommaso, D.; Giliardi, F.; Vecchiola, E.; et al. Curative resection for hepatocellular carcinoma in patients with metabolic syndrome: A multicenter matched analysis with HCV-related HCC. *J. Hepatol.* 2015, **63**, 1031–1039. [\[CrossRef\]](#)

Table 2. Overall survival (OS) and recurrence-free survival (RFS) in patients with NAFLD-associated HCC after

11. Billeter, A.T.; Müller, P.C.; Albrecht, T.; Roessler, S.; Löffler, M.; Lemekhova, A.; Mehrabi, A.;

Ref.	Type of Study	Patients (n) and Characteristics	Overall Survival Rate *	Recurrence-Free Survival	analysis.
1 Reddy et al. <a href="#">[17]</a>	Retrospective	N = 214 HCC patients, 52 with NASH and 162 patients with HCV or ALD	59%	48% at 5 years	Zhou,
1 Haldar et al. <a href="#">[33]</a>	Retrospective	N = 68,950 recipients, 1071 with NASH-HCC and 19,134 with HCC of other etiologies	68.6%	n/a	: A 320–
1 Wong C.R. et al. <a href="#">[34]</a>	Retrospective	N = 17,644 HCC patients, 406 patients with NAFLD, 1854 with HCV, 1342 with HBV, and 1024 with ALD	60%	n/a	for 5,
1 Rajendran et al. <a href="#">[35]</a>	Retrospective	N = 20,672 HCC patients, 2071 with NASH HCC and 18,601 with HCC of other etiologies	76.3%	n/a	of 1, 406,
1 Sadler et al. <a href="#">[4]</a>	Retrospective	N = 929 HCC patients, 60 with NASH and 869 with other etiologies	80%	68%	an, S.; noma in
1 Malik et al. <a href="#">[7]</a>	Retrospective	N = 17 NASH HCC patients	88% at 2.5 years	n/a	

nonalcoholic fatty liver disease. *Ann. Surg. Open* 2021, **2**, e065.

16. Tzartzeva, K.; Obi, J.; Rich, N.E.; Parikh, N.D.; Marrero, J.A.; Yopp, A.; Waljee, A.K.; Singal, A.G.

Surveillance imaging and alpha fetoprotein for early detection of hepatocellular carcinoma in patients with cirrhosis: A meta-analysis. *Gastroenterology* 2018, **154**, 1706–1718.e1.

Considering that nowadays there are numerous centers that offer liver transplantation beyond the Milan criteria,

17. Roberts, L.R.; Sirin, C.B.; Zaem, F.; Almasri, J.; Proken, J.; Heimbach, J.K.; Murad, M.H.; Mohammed, K.; Imaging for the diagnosis of hepatocellular carcinoma: A systematic review and meta-analysis. *Hepatology* 2018, **67**, 401–421. [\[CrossRef\]](#)

18. Zhang, J.; Yu, Y.; Li, Y.; Wei, L. Diagnostic value of contrast-enhanced ultrasound in

## 5. Neoadjuvant and Adjuvant Therapies

Currently, there is no recommendation for adjuvant and neoadjuvant therapies use in HCC management because of the low efficacy and poor safety profile of the agents studied until now. Although HCC has very high rates of recurrence after resection or ablation (up to 70% at 5 years after curative treatment), there has been no therapy

20. Xu, M.; Yang, D.; Lin, Y.; Chen, Y.; Ben, X.; Tian, G.; Deng, W.; Zhang, L.; Yan, W.; Xie, Y.; et al. Evaluating the efficacy of preoperative treatment of hepatocellular carcinoma with Ipemrolizumab, atezolizumab and durvalumab. *Front. Oncol.* 2022, **12**, 827. [\[CrossRef\]](#)

## 7. Systemic Therapy



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39. Lammer, J.; Malagari, K.; Vogl, T.; Pilleul, F.; Denys, A.; Watkinson, A.; Pitton, M.; Sergent, G.; Pfammatter, T.; Terraz, S.; et al. PRECISION V Investigators. Prospective randomized study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: Results of the PRECISION V study. *Cardiovasc. Interv. Radiol.* 2010, 33, 41–52.
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