Annals of Hepatology 27 (2022) 100654

Contents lists available at ScienceDirect

Annals of Hepatology

journal homepage: www.elsevier.es/annalsofhepatology

Concise review

Management of hepatocellular carcinoma recurrence after liver transplantation

Parul D. Agarwal*, Michael R. Lucey

Division of Gastroenterology and Hepatology, Department of Medicine, University of Wisconsin School of Medicine and Public Health, 1685 Highland Avenue, Suite 4224, Madison, WI 53705, United States

ARTICLE INFO

Article History:
Received 14 September 2021
Accepted 30 November 2021
Available online 17 December 2021

Keywords:
(In addition to title)
Alpha fetoprotein
Ablation
Trans-arterial chemoembolization
Chemotherapy

ABSTRACT

Despite careful selection for liver transplantation (LT) of patients with hepatocellular carcinoma (HCC), HCC may still recur after LT and is frequently associated with dismal outcome. Tumor factors, including serum alpha-fetoprotein (AFP), the presence of microvascular invasion, tumor grade/differentiation, and largest tumor size are amongst the most important predictors of recurrence after transplantation. The nature of recurrence can be highly variable, but often presents with extra-hepatic involvement. As such, management of patients with HCC can be challenging, and consensus guidelines are lacking. Curative options, with surgery or ablation, which may be applicable in patients with isolated intra-or extrahepatic metastases, offer the best chance for improved long-term outcome in patients with HCC recurrence after transplantation. Most patients with recurrence have unresectable disease, and may benefit from palliative treatments, including intra-arterial therapies and/or systemic therapy.

1. Introduction

Almost all patients with hepatocellular carcinoma (HCC) have simultaneous cirrhosis. Liver transplantation (LT) is the best curative treatment modality for cirrhotic patients with HCC as they are simultaneously treated for both their cancer and their underlying liver disease, thereby eradicating the risk of future HCC development by replacement of the pro-oncogenic fibrotic liver. However, the process of LT evaluation aims at triaging patients with HCC, and selecting those with low risk for recurrence [1]. The landmark study by Mazzaferro in 1996 established deceased donor orthotopic liver transplantation as an effective treatment option for patients with HCC, with long-term survival comparable to patients transplanted for non-oncological indications [2]. Indeed, HCC is a growing indication for liver transplantation, accounting for 15-50% of all liver transplants performed in most centers. Despite strict adherence to accepted selection criteria for transplantation, and refinements in allocation policy over the past two decades, HCC still recurs in 6-18% of patients post-OLT, and is associated with significantly lower survival in these patients compared to those without recurrence [3].

Recurrence of HCC is the greatest additional risk to survival that candidates with HCC incur when compared to their peers without HCC. In the broadest sense, recurrence of HCC is reflective of the 'biology' of the cancer. Aggressive HCCs, in contrast to indolent tumors, display rapid growth and incursion into vascular and lymphatic spaces. In the United States, this phenomenon has been recognized in the UNOS rules requiring an interval of observation on the transplant waiting list for patients with HCC, before they become eligible for exceptional MELD allocation points. This waiting period allows the 'aggressive HCC' declare itself, at which point the patient can be removed from the list. In this review we will concentrate on the post-transplant period, while recognizing that transplantation occurs within a continuum of care of the patient with HCC. Events prior to transplantation, including the waiting interval and tumor-directed therapy, will not be covered herein.

Recurrence may be early, i.e. within 2 years from transplantation, or late (> 2 years from transplantation). In a review of the US national database, malignancy, largely representing recurrent HCC, was an important medium interval cause of death, accounting for only 5.3% of deaths within the first year post-LT, but increasing to 20% in the 1- to 5-year interval, and 14% after 5 years [4]. In published literature, the median time to HCC recurrence after LT is 13 months, with early recurrence carrying a poor prognosis with median survival of only 12.2 months [3]. Recurrence in this timeframe is thought to be related to micro-metastases either before or at the time of hepatectomy or engraftment of circulating cancer cells. Late recurrence, in

Abbreviations: HCC, Hepatocellular carcinoma; LT, Liver transplantation; AFP, Alpha fetoprotein; TACE, Trans-arterial chemoembolization; mTOR, Mammalian target of rapamycin

* Corresponding author.
E-mail address: pagarwal@medicine.wisc.edu (P.D. Agarwal).

https://doi.org/10.1016/j.aohep.2021.100654

contrast, is associated with better long-term survival, and is thought to be related to delayed engraftment of latent or indolent cancer cells [5]. In some instances, occurrence of HCC may stem from *de novo* HCC development in the allograft, although this usually occurs in the background of recurrent chronic viral hepatitis. The majority of transplant recipients with HCC recurrences present with extra-hepatic involvement, most often the lungs, bone, adrenal glands, peritoneal lymph nodes and rarely the brain [6].

2. Risk factors for HCC recurrence

Several predictors for tumor recurrence have been reported, analysis of which may help identify those patients at highest risk for recurrence after transplantation. Although different prognostic models vary, studies have determined that tumor-related factors including elevated serum alpha-fetoprotein (AFP) at transplant, presence of micro- or macrovascular invasion, poor tumor grade/differentiation and larger tumor diameter are all associated with increased risk for recurrence after transplantation. Often, these tumor characteristics may not be accurately determined until explant pathology is available as up to 60% of patients who fit strict radiological criteria are incorrectly staged [7]. In addition to these tumor characteristics, other pre-and post-transplant factors likely affect risk for recurrence. Pre-operative biopsy of the tumor is associated with a small, but significant, risk of seeding and micro-metastasis. Post-transplantation, the type and burden of immunosuppression may also contribute to the risk of HCC recurrence. At present, there are no established practices to anticipate tumor recurrence after transplantation using circulating biomarkers such as circulating tumor cells or cell-free DNA or on the basis of the etiology of the underlying liver disease.

While there are no well-established protocols for surveillance of HCC recurrence after liver transplantation, it is a widely accepted practice to obtain surveillance imaging, with contrast-enhanced CT or MRI, at regular intervals for the first 2-3 years after transplantation [8]. Furthermore, for patients who had an elevated AFP associated with their HCC diagnosis prior to LT, serial AFP determinations are useful to track post-LT. A rising AFP in a patient who had a prior elevated AFP should prompt a careful search for recurrence, including in extrahepatic sites mentioned above. Use of prognostic scores, such as the Risk Estimation of Tumor Recurrence After Transplantation (or RETREAT score) may help stratify those patients at higher-risk for recurrence and individualize their surveillance strategy [9]. RETREAT score ranges from 0-8, with decreased post-LT survival at 3 years in patients with increasing RETREAT scores [9]. (Table 1)

3. Management of HCC recurrence

HCC recurs after transplantation in 6-16% of patients, and is often associated with poor long-term survival. Currently, there are no established consensus guidelines regarding the management of HCC recurrence post-transplantation. However, given the heterogeneity of HCC recurrence, as well as the various treatment options available, management of HCC recurrence is best individualized. This is often accomplished utilizing a multidisciplinary team approach, or 'tumor board', which includes transplant hepatology, surgery, diagnostic and interventional radiology and oncology [10]. Potential treatment options include those with curative intent, including surgical resection or ablation, and palliative options including intra-arterial therapies (chemo- and radioembolization), and/or systemic chemotherapy.

4. Curative treatments

Curative treatment with surgical resection should be considered first-line for management of recurrent HCC. Published literature confirms that patients amenable to resection with curative intent have significantly longer survival compared to those with unresectable disease [11]. It is important to note that there is an inherent selection bias in this cohort of patients undergoing surgery, who also tend to have isolated recurrence with normal allograft function and good performance status. Unfortunately, only a minority (10-30%) of patients with recurrent HCC present with isolated hepatic or extra-hepatic metastases deemed amenable for resection. In patients not deemed suitable for resection, but with isolated recurrence, curative treatment with thermal ablation can be also be considered. It should be noted that resection, or ablation, of HCC recurrence may be compromised by high rates of recurrence, with need for re-treatment [11].

Table 1
The elements of the 'Risk Estimation of Tumor Recurrence After Transplantation' or RETREAT score, and score points allocated based on the predictors of HCC recurrence [9].

Predictor	RETREAT points
Serum AFP at LT (ng/mL)	
0-20	0
21-99	1
100-999	2
>1000	3
Presence of Microvascular Invasion	2
Sum of largest diameter of viable tumor (cm) and number of viable tumors on explant	
0	0
1-4.9	1
5-9.9	2
>10	3

5. Intra-arterial therapies

For patients with multifocal hepatic recurrence, not amenable to resection or ablation, intra-arterial therapies with trans-arterial chemoembolization (TACE) or radioembolization with yttrium-90 (Y90) may be considered. TACE may pose technical challenges due to changes in the post-transplant hepatic arterial anatomy, such as stenosis or kinks. There also remains concern for inducing biliary ischemia especially with less selective embolization, such as lobar treatment, and lack of collateral vascularization. Despite these concerns, higher complication rates related to TACE have not been reported in the literature [12]. Radioembolization with yttrium-90 has also been performed in patients with recurrent HCC without adverse effects [13]. On the basis of the individualized assessment per the multidisciplinary board, some patients are selected for combinations of locoregional therapies, such as thermal ablation and TACE.

6. Systemic chemotherapy

The majority of patients, especially those with early recurrence of HCC, present with widespread metastatic disease, which warrants use of systemic chemotherapy. Unfortunately, HCC is a chemotherapy-insensitive tumor and studied chemotherapeutic agents, including doxorubicin, 5-Fluorouracil and platinum-based agents, have demonstrated little efficacy [14]. Sorafenib, an oral multi-kinase inhibitor, was approved in 2008 for advanced stage HCC and is the first-line chemotherapy treatment for patients with systemic spread [15]. Published reports indicate better outcomes in patients with recurrent HCC treated with sorafenib compared to those managed with only best supportive care [16]. Second-line therapy with regorafenib has also been published in case series [17]. With regards to immunotherapy, significant concerns remain for their utilization in the post-transplant setting related to risk of precipitating graft rejection with immune activation. While a small retrospective case-control match study suggested possible benefit of sorafenib as adjuvant

therapy in high-risk patients after transplantation, a phase III double blinded placebo-controlled trial failed to show any benefit in HCC recurrence of adjuvant therapy after curative treatment with ablation or resection [18–19]. Thus, there is currently no role for any studied chemotherapeutic agent for adjuvant use post-transplantation.

7. Immunosuppression management

High burden of immunosuppression in the early post-transplant period, particularly with calcineurin inhibitors, such as cyclosporine and tacrolimus which are often the foundation of the post-transplant anti-rejection regimen, may also contribute to increased risk for HCC recurrence [20–22]. This is thought to be related to direct inhibition of the immune system, thereby hindering detection and eradication of circulating cancer cells. Immunosuppression regimens consisting of mammalian target of rapamycin (mTOR) inhibitors, such as sirolimus and everolimus, which have anti-neoplastic properties *in vitro* and *in vivo*, have also been hypothesized to reduce rates of HCC recurrence. Unfortunately, a prospective phase III multi-center randomized trial failed to show any benefit in HCC recurrence rates in transplant recipients treated with sirolimus compared to sirolimus-free regimens [23]. Use of both sorafenib and sirolimus, which may have a synergistic effect, has also been proposed in patients with recurrent HCC, however there is currently insufficient evidence to recommend this broadly.

Conclusion

HCC recurrence after liver transplantation occurs in a significant number of patients, despite adherence to strict selection criteria, and can be challenging to manage. The nature of recurrence is heterogenous, and can range from isolated intra- or extrahepatic metastases to widely disseminated disease. Curative treatment should be sought if feasible, and may prolong survival. For unresectable patients, multiple palliative options are available including intra-arterial therapy and systemic chemotherapy, and multidisciplinary approach to individualize HCC-specific care would be ideal.

Financial support and sponsorship

None.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Conflicts of interest

All authors declared that there are no conflicts of interest.

References

[1] Martin P, DiMartini A, Feng S, Brown Jr. R, Fallon M. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the study of liver diseases and the American Society of Transplantation. Hepatology 2014;59:1144–65.
[2] Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Montalto F, et al. Liver Transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693–9.
[3] De'Angelis N, Landi F, Clotilde Carra M, Azoulay D. Management of recurrent hepatocellular carcinoma after liver transplantation: a systematic review. World J Gastroenterol 2015;21:11185–98.
[4] Daniel KE, Eickhoff J, Lucey MR. Why do patients die after a liver transplantation? Clin Transpl 2017:31e12906.
[5] Toso C, Cader S, Mentha-Dugerdil A, Meeberg G, Majno P, Morard I, et al. Factors predicting survival after post-transplant hepatocellular carcinoma recurrence. J Hepatobil Pancreat Sci 2013;20:342–7.
[6] Fernandez-Sevilla E, Allard MA, Selten J, Golse N, Vibert E, Sa Cunha A, et al. Recurrence of hepatocellular carcinoma after liver transplantation: is there a place for resection? Liver Transpl 2017;23:440–7.
[7] Kaihara S, Kiuchi T, Ueda M, Oike F, Fujimoto Y, Ogawa K, et al. Living-donor liver transplantation for hepatocellular carcinoma. Transplantation 2003;75(3 suppl): S37–40.
[8] Sapisochin G, Bruix J. Liver transplantation for hepatocellular carcinoma: outcomes and novel surgical approaches. Nat Rev. Gastro 2017;14:203–17.
[9] Mehta N, Dodge JL, Roberts JP, Yao FY. Validation of the prognostic power of the RETREAT score for hepatocellular carcinoma recurrence using the UNOS database. Am J Transpl 2018;18:1206–13.
[10] Agarwal PD, Phillips P, Hillman L, Lucey MR, Lee F, Mezrich JD, Said A. Multidisciplinary management of hepatocellular carcinoma improves access to therapy and patient survival. J Clin. Gastroenterol. 2017;51:845–9.
[11] Valdivieso A, Bustamante J, Gastaca M, Uriarte JG, Ventoso A, Ruiz P, et al. Management of hepatocellular carcinoma after liver transplantation. Transpl Proceed 2010;42:660–2.
[12] Zhou B, Shan H, Zhu KS, Jiang ZB, Guan SH, Meng XC, et al. Chemoembolization with lobaplatin mixed with iodized oil for unresectable recurrent hepatocellular carcinoma after orthotopic liver transplantation. J Vasc Interv Radiol 2010;21:333–8.
[13] Rivera L, Giap H, Miller W, Fisher J, Hillebrand DJ, Marsh C, et al. Hepatic intra-arterial infusion of yttrium-90 microspheres in the treatment of recurrent hepatocellular carcinoma after liver transplantation: a case report. World J Gastroenterol 2006;12:5729–32.
[14] Lee JO, Kim DY, Lim JH, Seo MD, Yi HG, Oh DY, et al. Palliative chemotherapy for patients with recurrent hepatocellular carcinoma after liver transplantation. *J Gastroenterol Hepatol* 2009;24:800–5.
[15] Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. SHARP investigators study group. Sorafenib in advanced hepatocellular carcinoma. N. Engl J Med. 2008;359(4):378–90.
[16] Sposito C, Mariani L, Germini A, Flores Reyes M, Bongini M, Grossi G, et al. Comparative efficacy of sorafenib versus best supportive care in recurrent hepatocellular carcinoma after liver transplantation: a case control study. J Hepatol 2013;59:59–66.
[17] Lavarone M, Invernizzi F, Czauderna C, Sanduzzi-Zamparelli M, Bhoori S, Amaddeo G, et al. Preliminary experience on safety of regorafenib after sorafenib failure in recurrent hepatocellular carcinoma after liver transplantation. Am J Transplant 2019;19:3176–84.
[18] Saab S, McTiguq M, Finn RS, Busuttil RW. Sorafenib as adjuvant therapy for high-risk hepatocellular carcinoma in liver transplant recipients: feasibility and efficacy. Exp Clin Transplant 2010;8:307–13.
[19] Bruix J, Takayama T, Mazzaferro V, Chau GY, Yang J, Kudo M, et al. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomized double-blind, placebo-controlled trial. Lancet Oncol 2015;16:1344–54.
[20] Rodriguez-Peralvarez M, Tsochatzis E, Naveas MC, Pieri G, Garcia-Caparros C, O'Beirne J, et al. Reduced exposure to calcineurin inhibitors early after liver transplantation prevents recurrence of hepatocellular carcinoma. J Hepatol 2013;59:1193–9.
[21] Vivarelli M, Cucchetti A, Piscaglia F, La Barba G, Bolondi L, Cavallari A, et al. Analysis of risk factors for tumor recurrence after liver transplantation for hepatocellular carcinoma: key role of immunosuppression. Liver Transpl 2003;11:497–503.
[22] Vivarelli M, Cucchetti A, La Barba G, Ravaioli M, Del Gaudio M, Lauro A, et al. Liver transplantation for hepatocellular carcinoma under calcineurin inhibitors: reassessment of risk factors for tumor recurrence. Ann Surg 2008;248:857–62.
[23] Geissler EK, Schnitzbauer AA, Zulke C, Lamby PE, Proneth A, Duvoux C, et al. Sirolimus use in liver transplant recipients with hepatocellular carcinoma: a randomized multicenter, open-label phase 3 trial. Transplantation 2016;100:116–25.