Pelizzaro *et al. Hepatoma Res* 2024;10:44
DOI: 10.20517/2394-5079.2024.107

Hepatoma Research

Review

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Hepatocellular carcinoma recurrence after liver transplantation: risk factors, targeted surveillance and management options

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How to cite this article: Pelizzaro F, Ferrarese A, Gambato M, Zanetto A, Russo FP, Germani G, Senzolo M, Rizzato MD, Soldà C, Vitale A, Gringeri E, Cillo U, Burra P. Hepatocellular carcinoma recurrence after liver transplantation: risk factors, targeted surveillance and management options. *Hepatoma Res* 2024;10:44. https://dx.doi.org/10.20517/2394-5079.2024.107

Received: 24 Aug 2024 **First Decision:** 9 Oct 2024 **Revised:** 12 Oct 2024 **Accepted:** 18 Oct 2024 **Published:** 25 Oct 2024

Academic Editor: Hirayuki Enomoto **Copy Editor:** Ting-Ting Hu **Production Editor:** Ting-Ting Hu

Abstract

Hepatocellular carcinoma (HCC) represents a well-recognized indication for liver transplantation (LT), with improving graft and patient survival rates due to medical and surgical advancements over time. Despite the implementation of selection criteria to ensure the highest transplant benefit, post-LT recurrence of HCC is not uncommon and is often associated with poor outcomes. Therefore, a post-transplant surveillance strategy appears to be a cost-effective approach, particularly in the early post-surgery period when the recurrence rate is high. Although specific guidelines are still lacking, emerging strategies tailored to pre-transplant tumor history and explant pathology show promise. Moreover, new immunosuppressive therapy schemes and aggressive management of post-transplant medical complications can be implemented to reduce the risk of cancer recurrence. Finally, multimodal oncological strategies are increasingly used to improve survival even after cancer recurrence. This paper reviews the evidence on HCC recurrence after LT, providing insights into risk factors, targeted surveillance, and management strategies.

Keywords: Liver transplantation, liver cancer, tumor recurrence, surveillance

INTRODUCTION

The landscape of liver transplantation (LT) is rapidly changing in terms of indications, outcomes, available organs, and medical and surgical advancements[1]. Over the last few decades, hepatocellular carcinoma (HCC) became a solid indication for LT, leading to a steady increase in the number of patients undergoing transplantation for this indication in most transplant programs worldwide. This trend is due to multiple factors, including a reduction in end-stage liver disease patients with active hepatitis B and C, a steady increase in new HCC diagnoses, and excellent post-transplant survival outcomes. Consequently, the selection of HCC patients for LT has been refined over time, with a wise expansion of the selection criteria[2-4]. Among treatments for HCC, LT can provide the largest survival benefit[5].

HCC recurrence represents a cornerstone in the natural history of transplanted patients. The recurrence rate is about 16%, more frequent within three years after transplantation[6-8]. In the landmark study by Mazzaferro *et al.*, 8% of patients after four years of follow-up developed tumor recurrence[2,9], but further studies reported a recurrence rate of 10%-16% in patients within Milan criteria based on pre-transplant imaging data[10-14]. The risk of HCC recurrence seems closely related to the tumor burden at the time of transplant, and it increases proportionally as the patients exceed the Milan criteria[15]. Most recurrences (66%) are extrahepatic, mainly in the lungs, bones, adrenal glands, peritoneum, soft tissues, and central nervous system[6,16-19]. As expected, tumor recurrence significantly impairs post-transplant prognosis, with a median survival of about two years after diagnosis.

Given the great number of patients being transplanted for HCC and the wise expansion of transplant criteria, it seems appropriate to implement strategies to reduce the risk of recurrence and adopt active post-LT surveillance strategies to capture any recurrence as soon as possible[16,20]. Moreover, it is of utmost importance to establish multimodal strategies (surgical, radiological, oncological) to treat the recurrence itself, both intra- and extrahepatic[21,22].

In this review, we will first analyze the prognostic factors of post-LT HCC recurrence and then provide insights specifically into targeted surveillance and multimodal treatment.

PREDICTING HCC RECURRENCE

LT in HCC patients should be offered after balancing the survival benefit derived from the transplant (i.e., transplant benefit) with the risk of tumor recurrence (i.e., transplant utility)[23]. Post-LT HCC recurrence has a detrimental effect on the prognosis of patients transplanted for this indication and on the postoperative outcome. Thus, approaches for rapidly identifying patients at high risk of post-LT recurrence are urgently needed.

Several factors have been identified as predictors of post-LT recurrence, including tumor-related characteristics (e.g., tumor burden, biomarkers, tumor biology), transplant procedures, and post-transplant management (e.g., immunosuppression) [Figure 1]. Tumor-specific variables have been incorporated in several pre-transplant selection criteria and prognostic models to expand the pool of possible candidates to LT, possibly maintaining an acceptable risk of post-transplant recurrence and without disadvantaging non-HCC patients on the waiting list [Table 1]. Moreover, post-LT variables have also been included in some post-transplant prognostic models. Although intriguing, the role of donor characteristics and recipient gender as risk factors for tumor recurrence remains controversial and requires further exploration[42,43]. To enhance our ability to predict post-LT HCC recurrence, a valuable tool could be the combination of pre- and post-transplant risk factors in predictive models with artificial intelligence and machine learning[44]. Some preliminary experiences demonstrate that machine learning models could accurately stratify

Table 1. Proposed pre-transplant selection criteria and prediction models

Model name (year)	Design	Variables			Performance
		tumor burden	Biomarker	Other criteria	
Milan criteria (1996)[2]	Prospective single-center study	Single tumor > 5 cm or ≤ 3 tumors ≤ 3 cm	-	No vascular invasion or lymph nodes	5-year OS: 85% 5-year RFS: 92%
UCSF criteria (2001)[24,25]	Retrospective evaluation of prospectively collected data, single center[24] Prospective single-center study[25]	Single nodule ≤ 6.5 cm or 2-3 nodules ≤ 4.5 cm and total tumor diameter ≤ 8 cm	-	No vascular invasion	5-year OS: 75.2% in[24] 5-year RFS 80.9% in[25]
Padua criteria (2004)[26,27]	Retrospective evaluation of prospectively collected data, single center[26] Prospective single-center study [27]	Any size or number of tumors	-	No vascular invasion/extrahepatic spread No poorly differentiated tumor (grade III and IV)	5-year OS: 75% 5-year RFS: 92% In[27] 1-, 3- and 5-year ITT survival rates were: 95%, 85% and 79% in Milano out 84%, 69% and 69% in Milano in
Seoul criteria (2007)[28]	Retrospective single-center study	Tumor size (≤ 3, 3.1-5, 5.1-6.5, > 6.5 cm) and number (1, 2-3, 4-5, > 5)	AFP (≤ 20, 20.1-200, 200.1-1,000, > 1,000 ng/mL)	-	Score 3-6 (transplantable): 3-year RFS: 87% 3-year OS: 79% Score 7-12 (non-transplantable): 3-year RFS: 31% 3-year OS: 38%
SMC criteria (2007)[29]	Retrospective single-center study	Tumor size ≤ 5 cm	AFP level ≤ 400 ng/mL	-	Within criteria: 5-year DFS: 88.4% 5-years OS: 86.8% Outside criteria: 5-year DFS: 42.1% 5-year OS: 23.3%
Up-to-7 criteria (2009)[15]	Retrospective multicenter study	Sum of the largest tumor size and number of lesions < 7	-	-	5-year OS: 71.2% (beyond Milano and within up-to-7 criteria)
AFP-French model (2012)[30]	Retrospective multicenter study (training + validation cohorts)	Tumor size (≤ 3, 3-6, > 6 cm) and tumor number (1-3, ≥ 4)	$\log_{10}$(AFP) Simplified version: AFP level (≤ 100, 100-1,000, > 1,000 ng/mL)	-	Training cohort Low-risk (score ≤ 2) 5-year recurrence rate: 13.4% 5-year OS: 69.9% High-risk (score > 2) 5-year recurrence rate: 45.3% 5-year OS: 40.8%
AFP/TTD criteria (2012)[31]	Retrospective multicenter study	Total tumor diameter ≤ 8 cm	AFP ≤ 400 ng/mL	-	Recurrence rate (43 months of FU): In criteria: 4.9% Outside criteria: 33.0% 5-year DFS similar compared to Milan criteria: 74.4% *vs.* 72.9%
TTV/AFP model (2015)[32]	Prospective multicenter study	Total tumor volume < 115 cm^3	AFP < 400 ng/mL	No macrovascular invasion; no extrahepatic disease	4-year DFS: 68.0% 4-year OS: 74.6% (beyond Milano and within TTV/AFP)

TRAIN score (2016)[33]	Retrospective evaluation of prospectively collected data, two centers (training + validation cohorts)	-	AFP slope ≥ 15 ng/mL/month	Radiological response to locoregional treatment (mRECIST) NLR ≥ 5 at liver transplant Length of waiting time (months)	In criteria (score < 1) 5-year ITT survival analysis: 67.5% 5-year recurrence rate: 8.9% Outside criteria (score ≥ 1) 5-year ITT survival analysis: 23.5% 5-year recurrence rate: 30.0%
Extended Toronto criteria (2016)[34]	Prospective single-center study	Any size or number of tumors	-	No vascular invasion; no extrahepatic disease No cancer-related symptoms (weight loss > 10 kg and or ECOG ≥ 1 in 3 months) No poorly differentiated tumors	Beyond Milano and within ETC: 10-year risk of recurrence: 33% (*vs.* 15% for Milano in) 10-year survival: 50% (*vs.* 60% for Milano in)
Pre-MORAL score (2017)[35]	Prospective single-center study	Largest tumor size > 3 cm	Maximum AFP > 200 ng/mL Preoperative NLR ≥ 5	-	5-year RFS: Low-risk group (score 0-2): 98.6% Medium-risk group (score 3-6): 69.8% High-risk group (score 7-10): 55.8% Very high-risk group (score > 10): 0% (1-year RFS 17.9%)
EurHeCaLT transplant benefit model (2017)[36]	Retrospective multicenter study	Single tumor > 5 cm or ≤ 3 tumors ≤ 3 cm (Milano in) considered as a negative factor	AFP ≥ 1,000 ng/mL considered as a negative factor	Considered as negative factors: MELD ≤ 13 CR or PD after locoregional treatment (mRECIST)	Transplant benefit: 3-4 negative factors: 0 months (no benefit) 2 negative factors: 20 months (small benefit) 1 negative factor: 40 months (moderate benefit) 0 negative factors: 60 months (large benefit)
HALT-HCC score (2017)[37]	Retrospective single-center study	Hypotenuse between lesion number and lesion size (TBS)	ln(AFP)	MELD-Na	Risk equation: 1.27*TBS + 1.85*ln(AFP) + 0.26* MELD-Na 5-year OS: Quartile 1: 78.7% Quartile 2: 74.5% Quartile 3: 71.8% Quartile 4: 61.5%
NYCA score (2018)[38]	Retrospective evaluation of prospectively collected data, multicenter	Maximum tumor size (0-3, 4-6, > 6) and maximum tumor number (1, 2-3, ≥ 4)	AFP response (max to final)	-	5-year RFS: Low-risk (score 0-2): 90% Acceptable risk (score 3-6): 70% High-risk (score ≥ 7): 42%
Metroticket 2.0 model (2018)[39]	Retrospective evaluation of prospectively collected data, multicenter (training, internal and external validation cohorts)	Tumor number and size of the largest tumor†	AFP (< 200, 200-400, 400-1000, > 1000 ng/mL) †	-	5-year RFS: within criteria 89.6% *vs.* beyond criteria 46.8% 5-year OS: within criteria 79.7% *vs.* beyond criteria 51.2% (with a tumor-specific survival of 93.5% within *vs.* 55.6% beyond)
Metroticket 2.0 + mRECIST criteria (2020)[40,41]	Retrospective evaluation of prospectively collected data, multicenter	Tumor number and size of the largest tumor	AFP (< 200, 200-400, 400-1,000, > 1,000 ng/mL)	Radiological response to neoadjuvant therapies (mRECIST criteria)	5-year HCC-related death: CR: 3.1% PR/SD: 9.6% PD: 13.4% In comparison to Metroticket 2.0, the inclusion of radiological response resulted in the reclassification of 9.4% of patients who died from

	HCC-related death within 5 years from LT

[†]Criteria for transplantability: HCC with up-to-7 criteria if AFP < 200 ng/mL; HCC within up-to-5 criteria if AFP 200-400 ng/mL; HCC within up-to-4 criteria if AFP 400-1,000 ng/mL [considering as up-to-7, to 5 and to 4 the maximum allowed sum of size (cm) and number of tumors derived in any given HCC before transplantation, whether or not preceded by neoadjuvant therapies]. OS: Overall survival; RFS: recurrence-free survival; AFP: alpha-fetoprotein; DFS: disease-free survival; TTD: total tumor diameter; TTV: total tumor volume; FU: follow-up; mRECIST: modified response evaluation criteria in solid tumors; NLR: neutrophils-to-lymphocytes ratio; ETC: extended Toronto criteria; MELD: model for end-stage liver disease; CR: complete response; PD: progressive disease; TBS: tumor burden score; UCSF: University of California San Francisco.

transplanted patients for their probability of HCC recurrence[45,46], but further studies are needed.

Tumor burden

Traditional transplant eligibility criteria relied only on tumor morphological characteristics (number and size of liver lesions) as determined by pre-LT imaging. It has been demonstrated that morphologic parameters are associated with microvascular invasion and poor differentiation[47], both of which are predictors of HCC recurrence after LT. The paradigm of morphologic selection criteria is represented by the Milan criteria[2], which became the benchmark for LT candidate selection and the comparator for other proposed criteria.

However, growing evidence suggests that these criteria may be excessively restrictive, leading to the exclusion of a subgroup of patients who could also benefit from LT. Therefore, other criteria have been proposed, with outcomes comparable to those of the Milan criteria. The use of the University of California San Francisco (UCSF) criteria (single nodule ≤ 6.5 cm or 2-3 nodules ≤ 4.5 cm with a total tumor diameter ≤ 8 cm) led to a favorable 5-year survival rate of 75.2% and a post-LT recurrence rate of 11.4%[24,25]. The "up-to-seven" criteria [the limit for transplantability is 7 as the sum of the diameter (cm) of the largest tumor and the number of nodules][15] demonstrated post-LT survival results comparable to those of patients meeting the Milan criteria[48,49].

As mentioned above, the further outside the Milan criteria, the greater the risk of recurrence[15,24,25,39]. However, patients with an initial tumor burden beyond morphologic criteria who meet transplant eligibility criteria through downstaging treatments (locoregional, surgical or systemic therapies) have similar post-LT outcomes in terms of HCC recurrence as compared to patients who were within criteria at presentation[50-52]. By contrast, tumors progressing despite locoregional treatments exhibit worse outcomes after LT, mainly related to aggressive tumor biology[53-55]. Therefore, downstaging represents an additional stratification tool in the selection of patients for LT because it merges morphologic and biologic features[50]. While the Milan criteria are often used as the endpoint of downstaging protocols, the upper limits of tumor burden for downstaging remain controversial[56]. Obviously, the greater the initial tumor burden that we bring back within the transplantability limits through downstaging, the higher the transplant benefit for the patient[57]. Among the available downstaging therapies, immunotherapy may have a role but additional data are necessary to estimate the risk of rejection after transplant[58].

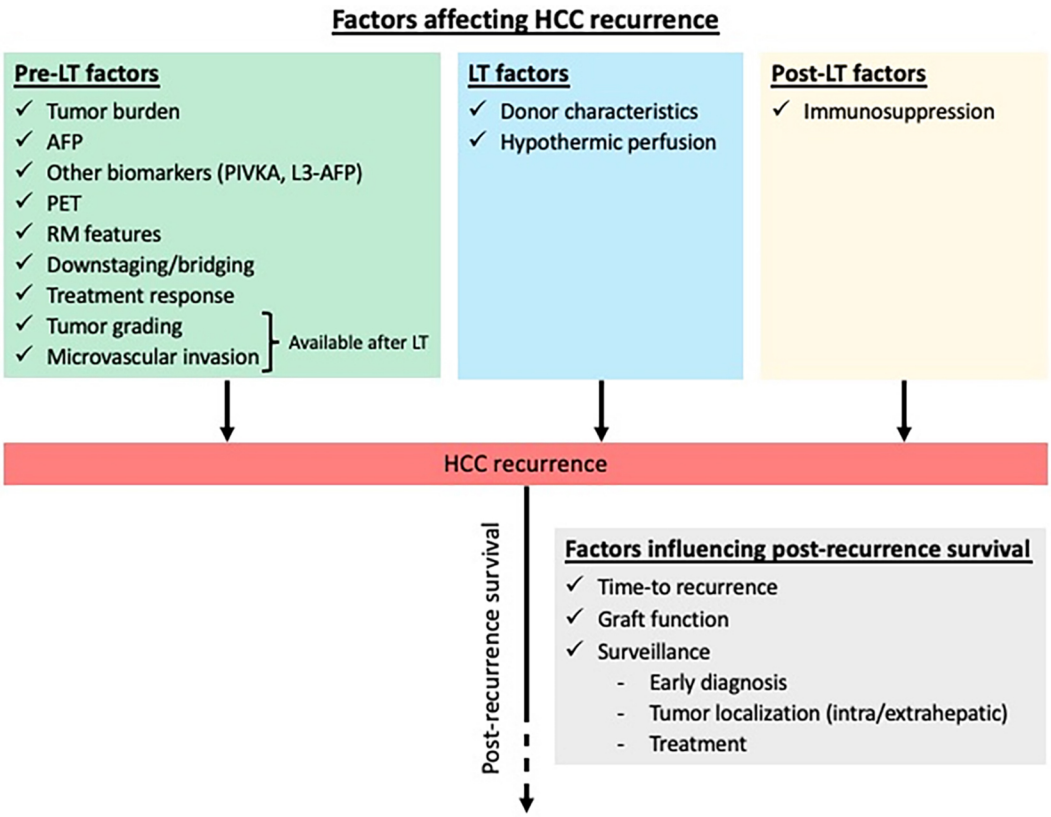

Figure 1. Factors affecting HCC recurrence (pre-LT, LT and post-LT variables) and factors influencing post-recurrence survival. HCC: Hepatocellular carcinoma; PIVKA: protein induced by vitamin K absence; AFP: alpha-fetoprotein; PET: positron emission tomography; RM: risk management; LT: liver transplantation.

Despite advances in cross-sectional imaging in recent decades, the staging of HCC through radiologic investigations is far from being perfect. Under-staging of HCC at imaging still occurs in 25%-30% of patients, especially after multiple locoregional procedures[59-62], and misdiagnosis (no HCC found on explant) has been reported in 11%-25% of cases[63,64].

Alpha-fetoprotein and other biomarkers

Alpha-fetoprotein (AFP) is a powerful prognostic and predictive biomarker for HCC patients. In the LT setting, it accurately predicts the risk of drop-out from the waiting list, the probability of post-LT recurrence, and the overall survival (OS). It has been largely evaluated both as a static and dynamic biomarker as a surrogate of tumor biology. An association between AFP levels before transplantation and post-LT mortality has been shown, with progressively worsening outcomes as the levels increase, starting from values as low as 16-20 ng/mL[65-67]. Therefore, AFP has been included in many prognostic models. However, the cut-off values that can accurately predict the risk of post-LT HCC recurrence differ significantly among these models[29-32,36,67-73] [Tables 1 and 2].

Other biomarkers, such as neutrophils to lymphocytes ratio (NLR), AFP-L3 and des-γ-carboxyprothrombin (DCP), have been correlated with tumor biology and have been considered for inclusion in pre-transplant prognostic models[19,77,78]. A recent prospective cohort study demonstrated that AFP-L3 and DCP outperformed AFP in the prediction of HCC recurrence after LT. Moreover, the combination of AFP-L3 ≥ 15% and DCP ≥ 7.5 predicted 61.1% of HCC recurrences, whereas HCC only recurred in 2.6% of patients

Table 2. Post-transplant prognostic models

Model name	Design	Variables			Performance
		Tumor burden	Biomarker	Histologic criteria	
Parfitt *et al.* and Aziz *et al.* (2007)[40,41]	Retrospective single-center study	Tumor size ≥ 3 cm	-	Microvascular invasion Satellitosis Giant/bizarre cells > 25% visible at low power	Recurrence in: Low-risk (score 0-4): 4.3% Intermediate-risk (score 7-7.5): 28.5% High-risk (score 10-14): 50.0% At the cut-off of 3.5: AUROC = 0.8, sensitivity 80%, specificity 79%
Decaens *et al.* (2011)[74]	Retrospective single-center study (training and validation cohorts)	Number of nodules (1, 2-3, ≥ 4) and maximal diameter of the largest nodule (≤ 2, 2-3, 3-5, > 5 cm)	-	Tumor differentiation (well, moderate, poor)	Training cohort: AUROC = 0.65 (95%CI: 0.59-0.71) 5-year tumor-free survival: 60.2% with a score < 4 and 36.4% with a score ≥ 4 (P < 0.0001) Validation cohort: AUROC = 0.63 (95%CI: 0.50-0.76) 5-year tumor-free survival: 82.8% with a score < 4 and 50.0% with a score ≥ 4 (P < 0.0001)
UCLA nomogram (2015)[19]	Retrospective evaluation of prospectively collected data, single-center	Within Milano/downstaged to Milano *vs.* Milano out Maximal radiological tumor diameter	AFP NLR Total cholesterol	Microvascular invasion Tumor grade	C statistic of 0.85 (95%CI: 0.82-0.89) Nomogram predicting 1-, 3- and 5-year recurrence risk for any individual patient with HCC
Post-Moral (2017)[35]	Retrospective evaluation of prospectively collected data, single-center	On explant pathology: Largest size > 3 cm Tumor number > 3	-	Vascular invasion Tumor grade	5-year RFS: Low-risk group (score 0-2): 97.4% Medium-risk group (score 3-6): 75.1% High-risk group (score 7-10): 49.9% Very high-risk group (score > 10): 22.1%
RETREAT score (2018)[65,66]	Retrospective cohort study	Explant largest viable tumor diameter + number of viable tumor (0 *vs.* 1-4.9 *vs.* 5-9.9 *vs.* > 10)	AFP at LT (0-20 *vs.* 21-99 *vs.* 100-999 *vs.* > 1,000 ng/mL)	Presence of microvascular invasion	3-year recurrence risk: Score 0: 1.6% Score 1: 5.0% Score 2: 5.6% Score 3: 8.4% Score 4: 20.3% Score ≥ 5: 29.0%
R3-AFP score (2022)[75]	Retrospective multicenter study (training and validation cohorts)	Number of nodules (1-3 *vs.* ≥ 4) Major nodule diameter (≤ 3 *vs.* 3-6 *vs.* > 6 cm)	Last AFP available before LT (≤ 100 *vs.* 101-1,000 *vs.* > 1,000 ng/mL)	Microvascular invasion Grading > II	Risk of recurrence at 5 years: R3-AFP = 0: 5.5% (95%CI: 3.5-8.7) R3-AFP = 1-2: 15.1% (95%CI: 11.3-20.1) R3-AFP = 3-6: 39.1% (95%CI: 32.4-46.7) R3-AFP score > 6:73.9% (95%CI: 59.7-86.3)
RELAPSE score (2023)[76]	Retrospective multicenter study (training and validation cohorts)	Maximum tumor diameter (per-log SD)	Pre-LT maximum AFP, (per-log SD) Neutrophil-lymphocyte ratio (per-log SD)	Vascular invasion (none, microvascular, macrovascular) Differentiation (well, moderate, poor, necrotic/no viable tumor)	Prediction of HCC recurrence risk: Training cohort: C-statistic = 0.78 (95%CI: 0.75-0.80) Internal validation cohort: C-statistic =

	0.76 (95%CI: 0.72-0.79)

AUROC: Area under the receiver operating characteristic curve; AFP: alpha-fetoprotein; NLR: neutrophils-to-lymphocytes ratio; RFS: recurrence-free survival; LT: liver transplantation.

without this dual positivity[79].

Available serum biomarkers are useful in predicting HCC recurrence after LT, so they have been integrated into prognostic tools to refine the prediction of HCC recurrence after LT. However, their accuracy is not excellent, so they cannot be used as a single factor but must be integrated with other tumor characteristics, such as radiological and biological features. Novel biomarkers under investigation should be more accurate than those currently being used, easy to use and reliable in different care settings.

Explant features predicting HCC recurrence

The presence of microvascular invasion on the explanted liver is strongly associated with HCC recurrence and worse prognosis after LT[40,80] [Table 2]. The likelihood of vascular invasion strongly correlates to the disease burden, with greater incidence in lesions > 5 cm[47,81] and in patients with multifocal disease[82]. Very high AFP levels (> 1,000 ng/mL)[81] and positive uptake on positron emission tomography[83] have also been associated with the presence of microvascular invasion. This tumor feature cannot be used as a stratification tool before transplant because it cannot be reliably assessed prior to LT due to the very low sensitivity of tumor biopsies for its detection[84].

Similarly, poorly differentiated tumor grade has been identified as a risk factor for post-LT HCC recurrence [Table 2]. In most cases, tumor biopsy is not performed for diagnostic purposes, thus limiting the possibility of integrating information regarding tumor differentiation into selection criteria and pre-transplant prognostic models. Transplanting only patients with well-differentiated tumors may confer very good survival rates after transplantation, minimizing cancer recurrence[26,27,34]. However, evaluating tumor biology through liver biopsy should take into account sampling bias, intratumoral heterogeneity, and finally, a poor concordance between pre-operative tumor histology and explant pathology[85,86]. Therefore, although tumor differentiation should theoretically be considered a robust predictor of post-transplant neoplastic disease recurrence, the aforementioned issues often prevent its universal application.

POST-TRANSPLANT HCC SURVEILLANCE

Planning an adequate surveillance program and appropriate management of HCC recurrence depends on understanding the timing and pattern of recurrence. To be cost-effective, post-LT surveillance should cover the majority of recurrences and use imaging modalities capable of evaluating anatomical sites where recurrences typically occur. Most HCC recurrences occur within 2-3 years after LT[12,13,20,87-89], although later recurrences (after 5 years from LT and, anecdotally, beyond 20 years after transplantation) have been described[13,90,91]. Consistent data show that earlier recurrence correlates with worse prognosis, likely due to more aggressive biology[20,90].

Retrospective data suggest that surveillance provides a survival benefit by increasing the likelihood of curative-intent retreatment, thus reducing post-recurrence mortality[92]. However, there are few studies on the optimal tests and their schedule, and no randomized trials have proven the cost-effectiveness of different surveillance protocols and their prognostic impact. Despite the absence of solid scientific evidence, there is broad consensus that periodic contrast-enhanced imaging and periodic AFP evaluation should be performed post-LT. The European Guidelines do not yet provide advice on the best surveillance follow-up for patients transplanted for HCC[93]. The American Association for the Study of Liver Diseases (AASLD) and The International Liver Transplantation Society (ILTS) Guidelines acknowledge that a fixed surveillance algorithm has not yet been validated but propose a reasonable scheme with chest-abdomen CT scans every 6 months for the first 3 years after transplant, possibly combined with serum AFP measurement[94,95]. However, the post-LT surveillance landscape is not homogeneous across Transplant Centers. A survey of many US LT Centers reported significant heterogeneity in the frequency, duration, and discontinuation of surveillance protocols. Moreover, surveillance protocols are tailored to risk stratification in only a minority of cases, and the schedule is rarely modified according to the expected risk of HCC recurrence[96].

Given the locations and patterns of HCC recurrence, standard surveillance strategies are based on chest and abdomen cross-sectional imaging [either contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI)]. Since recurrences frequently occur outside the liver, an ultrasound-based surveillance approach focused only on the graft seems inadequate for accurate postoperative follow-up. Although bones are commonly affected by HCC recurrence, routine bone scans are not recommended, unless there is a suspicion[84]. Due to its low cost and ease of determination, AFP is usually monitored in post-transplant surveillance, whereas other biomarkers (e.g., AFP-L3%, DCP) are not yet routinely used for this purpose[97,98].

Regarding the surveillance schedule, a 6-month interval between imaging investigations seems reasonable[84], as shorter intervals do not appear to provide additional benefit[99]. Since most cancers recur within 3 years after LT, a duration of at least 3 years is generally recommended for surveillance[84,94,95,100]. Most transplant programs discontinue surveillance 5 years after LT due to the low probability of recurrence thereafter, but strong recommendations are not possible due to the lack of data on the best and cost-effective surveillance length.

Refinement of surveillance: who deserves to be surveilled after LT?

Several post-transplant scores have been developed to predict HCC recurrence. These scores usually include tumor burden, tumor grade, and the presence or absence of microvascular invasion [Table 2]. Most of these scores also incorporate AFP or other biomarkers. To refine surveillance strategies after LT, these models help identify patients at high risk of tumor recurrence, allowing for the development of personalized follow-up schedules.

The first prognostic models included only HCC characteristics observed in explant histopathology. For example, the score proposed by Parfitt *et al.* and Aziz *et al.*, which combines four histological tumor variables (size ≥ 3 cm, microvascular invasion, satellitosis, and giant/bizarre cells > 25% visible at low power), demonstrated good predictability of recurrence (a cut-off value of ≥ 3.5 has a sensitivity of 80% and a specificity of 79%)[40,41]. Tumor burden (number and size of tumors) and tumor differentiation have been combined by Decaens *et al.* in a score that discriminates patients according to their risk of HCC recurrence (5-year tumor-free survival: 82.8% with score < 4 and 50.0% with a score ≥ 4)[74]. However, both models lacked management guidance based on recurrence risk.

Similarly, Agopian *et al.* proposed a prognostic nomogram including several variables (tumor within Milan/downstaged to Milan *vs.* outside Milan, maximal radiological tumor diameter, AFP, NLR, total cholesterol, tumor grade, vascular invasion) to predict 1-, 3-, and 5-year recurrence probability (c-statistic of 0.85, 95%CI: 0.82-0.89). However, it was not useful for stratifying patient surveillance[19].

Conversely, the post-MORAL scoring system (based on tumor size > 3 cm, the number of tumors > 3 on explanted liver, tumor grading, and vascular invasion) accurately stratified patients according to recurrence risk (c-statistic 0.88, 95%CI: 0.83-0.93)[35]. This system identifies four groups based on 5-year recurrence-free survival (RFS), ranging from 97.4% in the low-risk group (score 0-2) to 22.1% in the very high-risk group (score > 10), providing a valuable tool to tailor surveillance according to predicted recurrence risk. The combo-MORAL score, which combines pre-MORAL and post-MORAL models, further improves accuracy (c-statistic 0.91, 95%CI: 0.87-0.95)[35].

Mehta *et al.* formally proposed tailoring the surveillance protocol according to their model's estimated risk of recurrence[64]. They developed the RETREAT score, combining three parameters (serum AFP at LT, presence of microvascular invasion, and the sum of the largest viable tumor diameter and the number of viable tumors on explant) to obtain a scoring risk from 0 to > 5[65]. This score was externally validated in the United Network for Organ Sharing (UNOS) dataset and in European centers[66,101,102]. The score adequately categorized patients according to recurrence risk (3-year recurrence risk from 1.6% to 29% with RETREAT scores from 0 to ≥ 5)[66]. Based on this score, surveillance regimens were tailored: no surveillance for patients with a score of 0; surveillance every six months for two years post-LT for patients with a score of 1-3; every six months for five years for those with a score of 4; and strict surveillance (every 3-4 months) for the first two years followed by semestral surveillance for patients with the highest scores (≥ 5)[66].

Recently, the Recurrence Risk Reassessment (R3)-AFP score was developed based on the number of nodules, size of the largest nodule, microvascular invasion, tumor grading, and the last pre-LT AFP value. It was validated in a large international cohort[75]. This model stratified patients into four categories of 5-year recurrence risk: very low-risk (R3-AFP = 0 points: 5.5%; 95%CI: 3.5-8.7), low-risk (R3-AFP = 1-2 points: 15.1%; 95%CI: 11.3-20.1), high-risk (R3-AFP = 3-6 points: 39.1%; 95%CI: 32.4-46.7), and very high-risk (R3-AFP > 6 points: 73.9%; 95%CI: 59.7-86.3). Compared to the RETREAT score, this model showed similar discriminatory power and it is likely more applicable in real-life clinical practice since it includes patients beyond the Milan criteria for pre-LT imaging.

The most recent post-LT predictive score, RELAPSE, was proposed and validated in an American/European collaborative study using machine learning models[76]. Including the maximum pre-transplant AFP value, immediate pre-LT NLR, tumor size, vascular invasion, and tumor differentiation at explant pathology, the RELAPSE score showed a good prediction of HCC recurrence (c-statistic 0.78) in a large multicenter UNOS database. It demonstrated similar performance in a European validation cohort (AUC 0.74-0.77)[76].

Using a post-LT prediction model for personalized postoperative surveillance appears reasonable, though these scores have not been derived from prospective studies. Many questions remain unanswered, such as the approach for patients with incidental HCC at explant and the optimal time to discontinue surveillance. Artificial intelligence, which can explore complex, nonlinear relationships between patient and HCC-specific variables, may help answer these questions, especially when applied with innovative techniques exploring tumor biology in more depth[26,103,104]. Recent papers have preliminarily explored this topic, identifying several machine learning algorithms capable of improving the predictive accuracy of the conventional models currently in use. However, some key points remain to be clarified, such as the

applicability of these models in real life and some intrinsic issues of artificial intelligence, such as overfitting[103,105,106].

STRATEGIES FOR PREVENTING HCC RECURRENCE

Type of immunosuppression and risk of HCC recurrence

The immunosuppressive regimen is a factor influencing the reappearance of HCC after a transplant, as the immune system is a major defense against cancer. Tacrolimus and cyclosporine [Calcineurin inhibitors (CNIs)] are the backbone of an immunosuppression schedule, but they impair the immune surveillance system, thus creating a permissive environment for the growth of cancer cells/micrometastases. Preclinical data demonstrated that CNIs promote tumor growth and cancer progression[107,108]. The tumor doubling time of Recurrent HCC after LT in patients receiving immunosuppression with cyclosporine and steroids has a lower doubling time compared to the growth rate of recurrent tumors after liver resection[109]. Additionally, CNI therapy, especially if high circulating levels of the drug are maintained in the early post-transplant period, is associated with an increased risk of post-LT malignancies and HCC recurrence[110-113].

The mammalian target of rapamycin inhibitors (mTORi) sirolimus and everolimus have both immunosuppressive and antiangiogenic activities. They inhibit T cell proliferation, regulate cell proliferation and apoptosis signaling, and modulate vascular endothelial growth factor (VEGF) - mediated pathways. Several retrospective studies and meta-analyses have demonstrated that using sirolimus in immunosuppressive regimens, compared to CNIs, is beneficial in terms of reducing HCC recurrence[114-122]. Toso *et al.* demonstrated improved OS for patients managed with sirolimus-based immunosuppressive therapy[117], whereas Yanik *et al.* showed reduced cancer-specific mortality and HCC recurrence in patients receiving sirolimus[118]. A systematic review of 3,666 patients transplanted for HCC showed that mTORi-containing regimens significantly reduce the risk of HCC recurrence compared to CNI (13.8% *vs.* 8.0%; $P < 0.001$)[121]. Another systematic review and meta-analysis confirmed these data[122,123].

A phase III trial showed that sirolimus therapy, added 6 weeks after transplantation, benefited OS in patients transplanted within the Milan criteria (i.e., low-risk patients). However, this positive effect was not maintained over time, as there were no differences in long-term RFS and OS between the two groups[124]. This benefit seemed to be highest in younger patients (< 60 years), those treated with sirolimus for ≥ 3 months, and those with AFP ≥ 10 ng/mL[125].

Regarding everolimus, a study on 192 patients with HCC undergoing LT did not show an association between this drug and tumor recurrence[126]. A monocentric retrospective study showed that patients receiving everolimus and CNIs had significantly longer time-to-recurrence and OS compared to patients receiving CNIs alone[127]. In another retrospective study, patients on everolimus showed a reduced risk of recurrence (7.7% *vs.* 16.9%; $P = 0.002$), and everolimus usage had an independent positive impact on the risk of transplant recurrence[128]. Stratifying patients according to pre-LT tumor burden, it seems that everolimus reduces the risk of recurrence in patients transplanted beyond the Milan criteria compared to tacrolimus (5.9% *vs.* 23.1%; $P = 0.22$), but not in patients transplanted within Milan (2.9% *vs.* 2.1%; $P = 0.1$)[129]. Further evidence on the role of everolimus in reducing post-LT recurrence risk is forthcoming, as a trial evaluating tacrolimus and everolimus versus tacrolimus and mycophenolate mofetil is currently ongoing[130].

How to choose immunosuppression on the basis of the risk of HCC recurrence

The aforementioned studies demonstrate the direct correlation between CNI and HCC recurrence, and the potential inverse correlation between mTORi and cancer reappraisal. Clinically, there are two possible alternatives: reduce the dose of CNI without increasing the risk of rejection, or replace CNIs with other

immunosuppressors (e.g., mTORi), maintaining a very low risk of rejection. The first option is based on the link between high doses of CNI (usually in the early post-transplant phase) and HCC development, and involves the simultaneous introduction of CNI and mTOR inhibitors at low doses. The second option suggests the possibility of introducing a CNI-free therapy using mTORi from the beginning. A recent meta-analysis has shown that the early introduction of everolimus seems effective, with a satisfactory safety profile[131].

The optimal immunosuppressive therapy that minimizes the risk of HCC recurrence and improves survival has not yet been determined. The immunosuppression regimen should probably be personalized based on the individual risk of post-LT tumor recurrence. Despite the lack of solid evidence and while awaiting stronger data from prospective randomized trials, an mTOR inhibitor-based immunosuppressive algorithm may be pursued in patients perceived to be at high risk, especially if relevant risk factors for everolimus/sirolimus side effects (e.g., proteinuria, dyslipidemia) are absent[95,132-134].

Adjuvant therapy

Despite several proposed schemes[17], there is no evidence to support the use of adjuvant systemic chemotherapy to prevent post-LT HCC recurrence, and this strategy is currently not recommended. Indeed, HCC is recognized as a chemoresistant tumor. Initially, adjuvant treatment with sorafenib, a multi-tyrosine kinase that showed significant improvement in the survival of patients with advanced HCC, appeared to be potentially useful. Among the 14 patients included in a phase I trial with sorafenib at a maximum dose of 200 mg twice daily, one death and only four recurrences were registered after a median follow-up of 32 months[135]. However, the potential utility of sorafenib in the post-LT setting was not confirmed, even though all available data come from small single-center studies and case series. In a small group of patients with explant features at high risk of tumor recurrence, adjuvant therapy with sorafenib did not halt the risk of postoperative tumor recurrence nor improve postoperative survival[136]. The lack of benefit with sorafenib after LT mirrors what was found in patients at high risk for recurrence after resection or ablation receiving adjuvant sorafenib[137]. A meta-analysis including three prospective and five retrospective studies (including not only sorafenib but different oncological treatments) did not show any benefit in terms of HCC recurrence rate[138].

Lenvatinib has not been prospectively tested in the adjuvant setting and only few small retrospective studies and case series are available[139-141]. A small case series showed acceptable drug safety and patient tolerance but did not show any significant reduction in HCC recurrence[141]. *Guo et al.* demonstrated that in patients transplanted beyond the Milan criteria, adjuvant lenvatinib was an independent protective factor for tumor recurrence and reduced the rate of early recurrence (< 2 years) after LT (15.8% *vs.* 33.3%; $P = 0.04$), but in patients receiving the adjuvant treatment, the OS was comparable to that of the control group[139].

Recently, immune-checkpoint inhibitors (ICIs) became the standard of care treatment in unresectable HCC and the combination of atezolizumab and bevacizumab has been tested in the adjuvant setting for patients at high risk of recurrence after surgery and ablation, demonstrating potential benefit[142]. Currently, no prospective studies have investigated in depth the potential adjuvant role of ICIs after transplantation. However, the risk of acute rejection and potential graft loss raises concerns about the safety of these drugs in transplanted patients, in case of overt cancer recurrence and even more in the adjuvant setting[143].

MANAGEMENT OF POST-TRANSPLANT RECURRENCE

The detailed analysis of all possible treatments for patients with post-transplant HCC recurrence goes beyond the scope of this review. However, it is useful to provide some insights into therapeutic strategies.

The first aspect concerns the patient's clinical conditions and performance status, which allow a clear distinction between the choice of therapeutic options and palliative care. Secondly, the location of the recurrence (intra- *vs*. extrahepatic, single *vs*. multisite) represents essential elements for choosing the correct therapeutic option.

In patients with a single nodule or oligometastatic intrahepatic recurrence, surgery or interventional radiology procedures can be considered. Surgery can include both resection and ablation, depending on the location and number of lesions and the functionality of the transplanted liver. Few studies have demonstrated a significant increase in median survival in those who underwent surgery compared to those receiving non-surgical therapy and those who received best supportive care[17,144]. Therefore, whenever feasible, surgery should be pursued.

One small, single-center retrospective study comparing patients who underwent resection *vs*. ablation demonstrated similar outcomes in terms of RFS[145]. It should be noted that the laparoscopic approach is challenging in such cases and that immunosuppression may delay wound repair and increase the risk of postoperative surgical site infection. Trans-arterial chemoembolization can be considered an option in patients with multinodular disease, especially those with bilobar (i.e., unresectable) involvement, similar to what is usually proposed in pre-LT patients. There are few data available on the efficacy of this technique and it may face greater technical difficulties compared to the pre-transplant phase, especially in the case of complex arterial reconstructions at the time of transplant.

Regarding extrahepatic metastases, few data are available on surgical treatment for lung metastases. A recent series from South Korea showed good outcomes after lung surgery (mainly wedge resection) in 52 patients, with a median of 1.7 years of RFS after metastasectomy. Notably, more than half received adjuvant chemotherapy and experienced further recurrence after lung surgery[146].

Patients with multiple metastases, deemed not resectable, both inside and outside the liver, may receive systemic therapy. This option should be weighed against possible side effects, patient performance status, and comorbidities. Moreover, patients' and family members' expectations should be considered in the decision-making process. Few data are available for sorafenib as a first-line treatment[147,148], lenvatinib as a first-line treatment (median OS of 14.5 months)[149], and regorafenib as a second-line treatment after sorafenib (median OS of 12.9 months and 38.4 months for the sorafenib initiation)[150].

These data suggest that OS is acceptable, even in the second line, and that there are no significant safety concerns. However, it is possible that these studies, often with retrospective design, consider highly selected patients with excellent performance status and relatively favorable baseline characteristics. Few data have already investigated ICIs in post-transplant HCC recurrence, with the aforementioned concerns. A recently published individual patient data meta-analysis examining the impact of pre-LT ICIs on the subsequent risk of rejection showed a 26% rejection rate after transplant, suggesting that a washout period between chemotherapy and transplant may be necessary[151]. Therefore, this rate is expected to be even higher when immunotherapy is applied in the postoperative setting. Determining which patients may safely receive immunotherapy post-LT, and where this therapy should be placed (first- *vs*. second-line therapy)[152] remain gray areas to date. Therefore, these drugs should not be used outside of well-designed controlled studies[153]. A possible future development in the treatment of post-LT recurrence is the use of target T cell therapy against HCC cells. In particular, some preliminary and exploratory studies evaluated the treatment of patients with HBV-related HCC recurrences with HBV-specific T cell receptor-redirected T cells; these cells demonstrated the ability to target extrahepatic metastases[154]. The use of immunosuppressive drug-resistant

T cells for the immune therapy of post-LT recurrences can improve the efficacy of these treatments[155]. Beyond being complex in its delivery, the efficacy and safety of this therapeutic option will require to be tested in large randomized clinical trials.

CONCLUSIONS

The recurrence of HCC remains a concern in the LT setting despite significant improvements in patient selection and downstaging treatments. There is still much work to be done in this area.

Multiple models with good accuracy have been proposed for stratifying the risk of post-transplant recurrence, and they deserve universal application within various transplant programs. Specifically, the ability to stratify risk based on clinical and histological factors should allow clinicians to create tailored surveillance programs and guide the choice of the most appropriate immunosuppression regimen. However, the long-term benefits of these surveillance programs are still to be understood, though they have been proven to be cost-effective, especially within the first five years post-transplant.

The second ambitious goal is to significantly increase survival in patients with post-transplant HCC recurrence, which currently averages around 24 months from diagnosis. Achieving this requires new, preferably prospective, studies comparing multimodal therapeutic strategies, especially in light of new oncological treatments.

A multidisciplinary approach should be pursued after every diagnosis of HCC recurrence. A thorough discussion within the local/oncological transplant board can ensure the best surgical and oncological care based on disease presentation, graft function, and patient performance status. This approach can pave the way for innovative oncotherapies being tested in such patients, involve dedicated surgeons to treat metastases in specific body areas, and provide comprehensive counseling and psychological support to patients and their families.

DECLARATIONS

Acknowledgments

Graphical abstract created with BioRender.com.

Authors' contributions

Conceptualized and designed the review: Pelizzaro F, Ferrarese A, Burra P
Wrote, reviewed, and edited the manuscript: Pelizzaro F, Ferrarese A, Burra P
Reviewed the manuscript for intellectual content: Gambato M, Zanetto A, Russo FP, Germani G, Senzolo M, Rizzato MD, Soldà C, Vitale A, Gringeri E, Cillo U
Approved the final version for submission: All authors

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

Burra P is an Associate Chief Editor of *Hepatoma Research*, Cillo U and Vitale A are Editorial Board members of *Hepatoma Research*, Zanetto A, Ferrarese A, and Pelizzaro F are Junior Editorial Board

members of *Hepatoma Research*. The other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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