

SURVEILLANCE AND MANAGEMENT OF POST-TRANSPLANT HEPATOCELLULAR CARCINOMA RECURRENCE

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Summary

Hepatocellular carcinoma (HCC) is one of the leading indications for liver transplantation (LT) worldwide, yet tumour recurrence after LT remains a major limitation to long-term survival. Recurrence occurs in 6-20 % of transplant recipients and is most commonly detected within two to three years after transplant. Early recurrence (< 24 months) has a median post-recurrence survival of 10-13 months. In the absence of universal guidelines, clinicians must navigate a complex landscape of risk factors, prognostic scores, surveillance schedules and therapeutic options. This review synthesises current evidence, including recent consensus statements and clinical trials, to provide a comprehensive, practice-oriented guide for clinicians managing post-transplant HCC recurrence. We describe the pathophysiological mechanisms of recurrence, discuss patient- and tumour-specific risk factors, detail prognostic scoring systems, present risk-stratified surveillance algorithms, review immunosuppression and adjuvant therapies, and outline management strategies for intrahepatic and extrahepatic recurrence. We also highlight future directions in imaging, biomarkers, systemic therapy and precision immunosuppression.

Key words: hepatocellular carcinoma, surveillance, liver transplantation, immunosuppressive therapy

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INTRODUCTION

Liver transplantation offers the best chance of cure for patients with HCC who are unsuitable for resection or ablation. Over the last two decades the proportion of liver grafts allocated to HCC has increased dramatically, driven by advances in surgical technique, improvements in organ preservation and an expansion of eligibility criteria¹. In Western countries, HCC now accounts for 22–32% of adult transplant indications¹. Despite strict selection policies such as the Milan criteria and adoption of down-staging protocols, recurrence remains a formidable challenge². Tumour recurrence is estimated to occur in 8–20% of LT recipients, and recurrence accounts for up to half of all deaths after HCC transplantation^{3,4}. The natural history of recurrence is heterogeneous: early recurrence (< 24 months) typically indicates residual micrometastatic disease or aggressive biology and portends a median survival of 10–13 months; late recurrence (> 24 months) may reflect *de novo* tumour development or slower-growing clones and carries a better prognosis^{3,5}. With the advent of living donor transplantation, expansion beyond Milan criteria⁶,

and increasing use of locoregional therapies as bridging or down-staging modalities⁷, the spectrum of patients receiving LT has broadened, making individual risk prediction and tailored surveillance ever more important^{4,8}. This review aims to provide a detailed, evidence-based overview of post-transplant HCC recurrence. We begin by outlining the mechanisms that underlie recurrence, followed by an in-depth discussion of epidemiology and patterns of relapse. We then review the diverse array of risk factors – including tumour biology, recipient and donor characteristics, and immunosuppressive regimens^{3,4,6-12} – and summarise validated prognostic models¹³⁻¹⁶. Next, we present practical surveillance strategies, incorporating risk-stratified schedules and imaging modalities. We discuss the impact of immunosuppression and evaluate the evidence for adjuvant therapies. Management of recurrence is covered in detail, including surgical, locoregional and systemic options¹⁷. Finally, we highlight future directions in biomarker discovery, machine learning and immunotherapy.

MECHANISMS AND PATHOPHYSIOLOGY OF RECURRENCE

Understanding the mechanisms driving recurrence is crucial for developing preventative and therapeutic strategies. Recurrence arises from two principal mechanisms.

Residual micrometastatic disease

Despite complete radiological response and adherence to selection criteria, small numbers of viable tumour cells may persist in the liver or disseminate systemically prior to LT. These micrometastases can evade detection by imaging and survive during the perioperative period. Factors promoting their survival include neoangiogenesis, resistance to hypoxia and immune evasion^{1,4}.

De novo tumour formation

The chronically inflamed cirrhotic milieu, metabolic syndrome and viral hepatitis may predispose the graft to *de novo* tumorigenesis¹. After LT, continued exposure to carcinogenic factors (viral recurrence, alcohol, non-alcoholic steatohepatitis) and prolonged immunosuppression may facilitate oncogenesis. Dysregulation of immune surveillance by calcineurin inhibitors (CNIs), overactivation of the mTOR pathway and alterations in gut microbiota further contribute to oncogenic signalling^{4,18-20}.

At the molecular level, aggressive HCC clones often display epithelial-mesenchymal transition, vascular endothelial growth factor (VEGF) pathway activation, microvascular invasion (MVI) and overexpression of stemness markers. Circulating tumour cells (CTCs) and circulating tumour DNA (ctDNA) have been detected in a

subset of patients prior to LT and correlate with recurrence risk¹. The immunosuppressive microenvironment after LT – characterised by depletion of cytotoxic T cells, expansion of regulatory T cells and myeloid-derived suppressor cells – may permit tumour outgrowth. A detailed understanding of these pathways has spurred interest in mTOR inhibitors, which possess antiproliferative and antiangiogenic properties, and in immunotherapies that can restore immune surveillance^{4,18,19,21}.

EPIDEMIOLOGY AND PATTERNS OF RECURRENCE

Incidence and timing

Meta-analyses and registry studies consistently report recurrence rates of 8-20%. The risk of recurrence correlates with tumour burden at the time of transplant and increases proportionally as selection criteria are expanded^{2,3,6}. Most recurrences occur within the first two to three years after LT: 60-75% of recurrences are detected in this period. Late recurrences (> 5 years) are rare (< 10%), but long-term surveillance is still advocated due to occasional late metastases^{3,5}. The median time to recurrence differs by pattern: solitary intrahepatic recurrences arise after a median of 20.6 months^{3,4}, while extrahepatic solitary recurrences appear after 11 months. These temporal patterns inform surveillance intensity.

Anatomical distribution

Recurrence is predominantly extrahepatic. Autopsy and imaging series report that 50-60% of recurrences are solely extrahepatic; 30-40% involve both hepatic and extrahepatic sites; and only 15-40% are confined to the graft. The lungs are the most frequent site (40-60%), followed by bone (25-30%), adrenal glands (~10%), lymph nodes (~10%), peritoneum (~10%) and brain (~4%). Intrahepatic recurrences may present as nodular lesions, vascular invasion or biliary tract infiltration. Recognising the typical distribution is essential to design surveillance protocols and to plan surgical or ablative therapy^{3,5}.

Risk factors for recurrence

Risk factors for post-transplant HCC recurrence can be broadly categorised into tumour-related factors, recipient and donor factors, and treatment-related factors. Table 1 summarises major predictors identified in observational studies and meta-analyses.

Tumour-related factors

Tumour burden

Exceeding the Milan criteria (single tumour ≤ 5 cm or up to three tumours each ≤ 3 cm) remains one of the strongest

Table 1. Major risk factors for post-transplant HCC recurrence.

Category	Risk factors	Notes
Tumour-related	Tumour > 5 cm; multifocal disease (> 3 nodules); macrovascular invasion; poor differentiation; microvascular invasion; satellite nodules; elevated AFP; elevated DCP; poor response to locoregional therapy	Exceeding the Milan criteria increases recurrence; down-staging responders have lower risk
Recipient factors	Advanced age; obesity; metabolic syndrome; diabetes; hepatitis C or B infection; high MELD score; immunological status	Comorbidities may influence recurrence
Donor/graft factors	Donor age > 60 years; steatotic or extended criteria donor grafts; living donor transplantation; prolonged cold ischemia	Impact on recurrence is modest but present
Immunosuppression	High tacrolimus or cyclosporine trough levels; prolonged steroid use; lack of mTOR inhibitor	CNIs promote tumour growth; mTOR inhibitors may reduce recurrence
Biological markers	High neutrophil-to-lymphocyte ratio; high platelet-to-lymphocyte ratio; high D-dimer; presence of circulating tumour cells	Emerging biomarkers; prospective validation needed

AFP: alpha feto-protein; CNIs: calcineurin inhibitors; DCP: des-gamma-carboxy-prothrombin; MELD: model for end-stage liver disease; mTOR: mammalian target of rapamycin.

predictors of recurrence. Extended criteria such as the University of California San Francisco (UCSF), University of Toronto, and Kyoto criteria allow for larger or more numerous tumours but increase recurrence rates. Large tumours (> 5 cm), multifocal disease (> 3 nodules) and presence of macrovascular invasion are associated with recurrence rates up to 50%^{8,9}.

Histopathology

Poorly differentiated tumours and MVI are independent predictors of recurrence. MVI is present in 15–45% of explants and is associated with early, aggressive recurrence. Satellite nodules and sarcomatoid features also portend a worse prognosis^{4,20}.

Serum biomarkers

Elevated AFP (> 400 ng/mL) at listing or at the time of LT correlates with recurrence and poorer survival. Dynamic AFP response to locoregional therapy provides additional prognostic information: declining AFP suggests effective tumour control whereas rising AFP despite therapy indicates aggressive biology. Other biomarkers such as des-gamma-carboxy prothrombin (DCP), lectin-reactive AFP, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio and D-dimer have been associated with recurrence^{4,22}.

Response to bridging/down-staging therapies

Tumour progression or lack of response to trans-arterial chemoembolisation (TACE), radioembolisation, or thermal ablation before LT is associated with increased recurrence risk. Conversely, complete necrosis on explant histology predicts very low recurrence rates^{7,22}.

Recipient and donor factors

Older recipient age, obesity, metabolic syndrome, diabetes

mellitus, hepatitis C or B co-infection, and advanced liver fibrosis at the time of transplant have been linked to recurrence^{4,19}. Donor factors include advanced donor age, fatty liver, extended criteria donor grafts and prolonged cold ischemia time. Living donor LT may confer a slightly higher recurrence risk compared with deceased donor LT, possibly due to smaller graft size and shortened wait times. The interplay between donor and recipient genetics (e.g., Patatin-like phospholipase domain-containing protein 3 [PNPLA3] polymorphisms) is an emerging area of research⁴.

Immunosuppression and treatment-related factors

The type and intensity of immunosuppression profoundly influence recurrence risk. High exposure to CNIs promotes tumour growth by inhibiting anti-tumour immunity and enhancing transforming growth factor- β signalling^{4,18}. Several studies demonstrate a dose-dependent relationship between tacrolimus trough levels and recurrence; early tapering of CNIs is recommended. mTOR inhibitors such as sirolimus and everolimus inhibit angiogenesis and cell proliferation; observational studies suggest they reduce recurrence rates^{18,21}. In a meta-analysis, recurrence occurred in 13.8% of CNI-treated patients versus 8% of mTORi-treated patients. The benefit appears greater in high-risk recipients, though randomised data are lacking. Steroid maintenance beyond 3–6 months may increase recurrence; rapid tapering is therefore advocated. Finally, post-transplant antiviral therapy for hepatitis B or C reduces recurrence by minimising oncogenic viral replication^{4,18}.

Prognostic models and risk stratification

Prognostic models integrate multiple risk factors to estimate recurrence risk and guide surveillance intensity. The

most widely used models include the post-MORAL score, combo-MORAL score, RETREAT score, R3-AFP score and the RELAPSE score. These models differ in the variables incorporated and the timing of application (pre- vs post-transplant), but all strive to discriminate low- from high-risk patients.

Post-MORAL and combo-MORAL scores

The post-MORAL score, developed by Halazun and colleagues, uses explant pathology variables—largest tumour > 3 cm, tumour number > 3, poor differentiation and MVI—to stratify patients¹⁴. Scores range from 0 to > 10. In the original cohort, 5-year recurrence-free survival decreased from 97.4 % (score 0–2) to 22.1 % (score > 10). The combo-MORAL score integrates pre-LT variables (AFP, tumour size, neutrophil-to-lymphocyte ratio) with explant findings, improving discrimination (c-statistic 0.91 vs 0.88)¹⁴.

RETREAT score

The RETREAT (Risk Estimation of Tumor Recurrence After Transplant) score is widely used because it relies on readily available post-transplant variables: AFP at LT, presence of MVI and the sum of the largest viable tumour diameter plus number of viable tumours¹³. Scores range from 0 to > 7. Validation studies show 3-year recurrence rates of 1.6% for score 0, 4.1% for score 1, 12% for score 2, 25% for score 3, 34% for score 4 and 29% for scores > 5. The score informs surveillance: low-risk patients (score 0) may require minimal surveillance; intermediate-risk patients (scores 1–3) benefit from six-monthly imaging for two years; high-risk patients (score 4) undergo five years of six-monthly imaging; and very high-risk patients (scores > 5) warrant intensive surveillance every 3–4 months for two years, then six-monthly thereafter (Tab. II)^{8,13}.

R3-AFP, RELAPSE and other models

The R3-AFP model (also known as the AFP model for recurrence) incorporates the number of tumours (> 3), largest tumour diameter (> 3 cm), presence of MVI and the final pre-LT AFP level to categorise patients into very low (R3-AFP ≤ 2), low (3–4), high (5–6) and very high risk (> 6) groups²³. Five-year recurrence rates range from 5.5 % in the very low-risk group to 73.9 % in the very high-risk group. The model is easier to apply because it does not require explant pathology, making it suitable for pre-LT counselling and listing decisions.

The RELAPSE score, proposed by Agopian and colleagues, uses seven variables (tumour burden, AFP, viral status, response to locoregional therapy, waitlist time, donor age and ischemia time) to predict recurrence. It stratifies patients into low, intermediate and high risk, with 5-year recurrence rates of roughly 5–20% and 40%¹⁵, respectively. Machine-learning algorithms are being developed to refine these models by incorporating genomic, radiomic and immunologic data¹.

Surveillance strategies

Active surveillance aims to detect recurrence early, when curative therapies are feasible. Despite the lack of uniform guidelines, consensus has emerged for risk-adapted surveillance that balances detection yield with cost and radiation exposure. Surveillance should be multidisciplinary and incorporate both clinical assessment (symptoms, physical exam), laboratory testing (AFP and other biomarkers) and cross-sectional imaging^{5,8}.

Imaging modalities

Computed tomography (CT)

Multiphasic CT of the chest, abdomen and pelvis is the cornerstone of surveillance. Contrast-enhanced CT detects most intrahepatic and extrahepatic metastases; it is widely available and cost-effective^{5,17}. However, repeated CT exposes patients to ionising radiation and may miss small peritoneal or bone metastases.

Magnetic resonance imaging (MRI)

Gadoxetic acid-enhanced MRI offers superior sensitivity for small intrahepatic lesions, particularly in the liver graft. Diffusion-weighted imaging improves lesion detection. MRI is preferred for patients with impaired renal function or contrast allergies. Whole-body MRI may detect bone metastases but is more time-consuming and expensive.

Positron emission tomography (PET)

18F-FDG PET/CT has limited sensitivity for well-differentiated HCC but may detect extrahepatic or poorly differentiated lesions. Dual-tracer PET using FDG and 11C-acetate improves detection but is not widely available. PET is reserved for equivocal cases.

Ultrasound

Ultrasound is inexpensive and widely used for screening cirrhotic patients but is inadequate for post-transplant surveillance due to limited sensitivity for deep or small lesions.

Bone scintigraphy and brain MRI

These modalities are not routinely employed in surveillance but should be considered when patients develop bone pain, neurologic symptoms or when other imaging suggests metastasis⁵.

Risk-adapted surveillance schedules

Table II outlines a proposed surveillance schedule based on the RETREAT score. This algorithm aligns with recommendations from the International Liver Cancer Association (ILCA) and the International Liver Transplantation Society (ILTS), which advise six-monthly cross-sectional

Table II. Proposed surveillance algorithm based on RETREAT score.

RETREAT score	Recurrence risk at 3 years	Recommended surveillance
0	1.6%	Clinical review and AFP every 6-12 months; imaging optional
1-3	4-25%	AFP and chest/abdominopelvic CT or MRI every 6 months for 2 years; annually thereafter
4	34%	AFP and CT/MRI every 6 months for 5 years; consider whole-body MRI or PET annually
≥ 5	≥ 29%	Intensive surveillance with AFP and CT/MRI every 3-4 months for 2 years, then every 6 months; include chest, abdomen and bone imaging; consider PET/MRI and bone scans

imaging and AFP measurement for intermediate-risk patients and more frequent imaging (every 3-4 months) for high-risk patients. Surveillance beyond five years may be individualised based on risk factors, comorbidities and patient preferences^{8,24-26}.

IMMUNOSUPPRESSION AND ADJUVANT THERAPIES

Optimising immunosuppression

Immunosuppressive regimens should balance rejection prevention with oncological control. Early reduction of CNIs is recommended, with target tacrolimus trough levels ≤ 5 ng/mL by 3-6 months^{4,18}. Introduction of mTOR inhibitors (sirolimus or everolimus) is considered in patients with high recurrence risk or in those who develop *de novo* malignancies. mTOR inhibitors may be started *de novo* at day 0 in high-risk recipients or converted from CNIs at 1-3 months in stable patients. In kidney transplant cohorts, mTOR inhibitors reduce cancer incidence compared with CNIs; analogous benefits are inferred for LT recipients^{19,22}. Steroids should be tapered rapidly and discontinued within 3-6 months. Antiviral therapy (direct-acting antivirals for hepatitis C, nucleos(t)ide analogues for hepatitis B) should be maintained to minimise viral replication and associated carcinogenesis⁴.

Adjuvant therapies

Several pharmacologic agents have been evaluated as adjuvant therapy to reduce recurrence after LT:

- **Tyrosine-kinase inhibitors (TKIs).** Sorafenib and lenvatinib inhibit VEGF and other kinases. Randomised trials of sorafenib or lenvatinib as adjuvant therapy after LT did not demonstrate a significant reduction in recurrence or improvement in survival. Adverse events were common, leading to early discontinuation²⁷.
- **Immunotherapy.** Immune-checkpoint inhibitors (ICIs) targeting programmed death-1 (PD-1) and cytotoxic T-lymphocyte antigen-4 (CTLA-4) have revolutionised advanced HCC treatment^{28,29}. However, their use in transplant recipients carries a high risk of acute

rejection. Case series and retrospective analyses report rejection rates of 20-29% and graft loss in several patients^{9,10}. Current consensus guidelines advise against routine adjuvant ICI therapy outside clinical trials. Experimental strategies include high-dose tacrolimus combined with PD-1 blockade and adoptive T-cell transfer, but these remain investigational^{11,12}.

- **Other agents.** mTOR inhibitors may be considered "adjuvant" due to their anti-tumour properties and are routinely used in high-risk patients. The role of metformin, statins, and aspirin is being investigated but evidence is insufficient to recommend their use^{4,18}.

Management of recurrence

Management depends on the pattern and extent of recurrence and should be individualised by a multidisciplinary transplant oncology team. Curative intent therapy is pursued whenever feasible.

Intrahepatic recurrence

Surgical resection

For patients with good performance status and preserved graft function, partial hepatectomy is the treatment of choice. Retrospective studies report median post-recurrence survival of 20-27 months, with 5-year survival rates up to 50% in selected cases. Anatomical resection of segments containing the tumour maximises oncological margins. Repeat LT is rarely performed because of organ scarcity and high recurrence risk^{17,26}.

Thermal ablation

Radiofrequency ablation (RFA) or microwave ablation is an alternative for lesions ≤ 3 cm or for patients unfit for surgery. Outcomes approach those of resection for small tumours. Stereotactic body radiotherapy (SBRT) offers a non-invasive option for tumours up to 5 cm; local control rates exceed 70%^{17,26}.

Trans-arterial therapies

For multinodular intrahepatic recurrence or vascular invasion, TACE or Yttrium-90 radioembolisation provides palliative benefit. Altered hepatic arterial anatomy after

Table III. Therapeutic options by recurrence pattern.

Recurrence pattern	Therapy	Evidence and outcomes
Solitary intrahepatic	Surgical resection; RFA/microwave ablation; SBRT	Resection yields median survival 20–27 months; ablation comparable for ≤ 3 cm lesions
Multinodular intrahepatic or vascular invasion	TACE; Y-90 radioembolisation; systemic therapy	Palliative; technical complexity due to altered anatomy
Oligometastatic extrahepatic (e.g., lung, bone)	Metastasectomy; SBRT	Lung metastasectomy yields ≈ 1.7 years recurrence-free survival
Disseminated/unresectable	Systemic therapy (sorafenib, lenvatinib, regorafenib, cabozantinib, ramucirumab); clinical trials	Median OS ≈ 12 –15 months; combination ICI + anti-VEGF regimens are promising but experimental
Immunosuppression adjustment	CNI minimisation; initiation of mTOR inhibitors; steroid withdrawal	Reduces recurrence risk; prospective trials are limited
Emerging therapies	Adoptive T-cell transfer; neo-adjuvant or adjuvant immune modulation; radio-immunotherapy	Preclinical and early clinical data suggest potential benefit; safety in transplant recipients unproven

CNI: calcineurin inhibitors; ICI: immune checkpoint inhibitors; OS: overall survival; RFA: radiofrequency ablation; SBRT: stereotactic body radiation therapy; TACE: trans-arterial chemo-embolization; VEGF: vascular endothelial growth factor.

LT poses technical challenges, and careful angiographic evaluation is required. Drug-eluting bead TACE may reduce systemic toxicity³⁰.

Extrahepatic and disseminated recurrence

Oligometastatic recurrence

Isolated pulmonary or osseous metastases may be treated with metastasectomy or SBRT. Lung metastasectomy yields a recurrence-free survival of about 1.7 years. Surgical resection of adrenal or brain metastases is reserved for highly selected cases^{17,26}.

Disseminated recurrence

When disease is widespread, systemic therapy is the mainstay. First-line treatment historically consisted of sorafenib; lenvatinib provides non-inferior survival and better response rates²⁷. In the general (non-transplant) HCC population, combination immunotherapy with atezolizumab plus bevacizumab improved median overall survival (OS) to 19.2 months with a 27% response rate, and durvalumab plus tremelimumab (STRIDE) achieved OS 16.4 months^{28,29}. These regimens are under investigation as post-LT therapies but are currently contraindicated outside clinical trials due to rejection risk. Second-line options include regorafenib, cabozantinib and ramucirumab. Median OS with sequential TKI therapy is approximately 12–15 months²⁷. Participation in clinical trials is encouraged.

Adjustment of immunosuppression at recurrence

Upon diagnosis of recurrence, immunosuppression should be minimised. Tacrolimus doses are reduced to trough levels ≤ 3 ng/mL; steroids are discontinued; and

mTOR inhibitors are introduced or increased. If systemic therapy is initiated, potential drug–drug interactions with immunosuppressants must be monitored¹⁸. The possible options to be considered for adjustment of immunosuppressive therapy are summarised in Table III and IV.

FUTURE DIRECTIONS

The management of post-transplant HCC recurrence is poised to evolve substantially in coming years. Key avenues include:

- **Biomarker discovery.** Circulating tumour DNA, micro-RNAs, exosomes and tumour-educated platelets show promise as non-invasive markers of minimal residual disease. Integration of liquid biopsy with imaging may allow earlier detection and guide adjuvant therapy^{1,12,29}.
- **Radiomics and artificial intelligence.** Machine-learning algorithms that analyse imaging features can predict tumour biology and recurrence risk, potentially refining prognostic models. Radiomics may identify subtle patterns of recurrence not visible to the human eye^{1,5}.
- **Precision immunosuppression.** Novel agents targeting co-stimulatory pathways or cytokine signalling may allow fine-tuning of graft tolerance while preserving anti-tumour immunity. High-dose tacrolimus combined with PD-1 blockade has demonstrated antitumour activity without rejection in preclinical models^{10–12}.
- **Combination systemic therapies.** The success of atezolizumab plus bevacizumab and durvalumab plus tremelimumab in unresectable HCC has spurred exploration of combinatorial regimens. Trials assessing TKIs

Table IV. Overview of systemic therapies for recurrent HCC after LT.

Class	Agents	Key targets	Outcomes in general HCC population	Considerations post-LT
Tyrosine-kinase inhibitors	Sorafenib, lenvatinib, regorafenib, cabozantinib	RAF/MEK/ERK, VEGFR, FGFR, KIT, RET	Sorafenib improves OS vs placebo (~10.7 months vs 7.9 months) in advanced HCC; lenvatinib non-inferior to sorafenib; regorafenib improves OS in sorafenib-progressed patients; cabozantinib improves OS after sorafenib	Well tolerated post-LT; monitor for hand-foot syndrome, hypertension and interactions with CNIs
Anti-angiogenic monoclonal antibodies	Bevacizumab, ramucirumab	VEGF-A (bevacizumab), VEGFR-2 (ramucirumab)	In combination with atezolizumab, bevacizumab improves OS to 19.2 months with 27 % response; ramucirumab improves OS in patients with AFP $\geq$ 400 ng/mL	Risk of bleeding and impaired wound healing; limited post-LT data
Immune-checkpoint inhibitors	Atezolizumab, nivolumab, pembrolizumab, durvalumab, tremelimumab	PD-L1/PD-1 (atezolizumab, nivolumab, pembrolizumab), CTLA-4 (tremelimumab)	Combination atezolizumab + bevacizumab and STRIDE regimen extend OS beyond 19 months	High risk of acute rejection (20-29 %); restricted to clinical trials
mTOR inhibitors	Sirolimus, everolimus (used as immunosuppressants)	mTOR C1 pathway	Reduce recurrence when used instead of CNIs	Routinely used to minimise CNI exposure; careful monitoring for proteinuria and dyslipidaemia
Emerging therapies	Adoptive T-cell transfer, oncolytic viruses, cancer vaccines	Tumour-specific antigens, tumour microenvironment	Early phase trials show immunologic activity; unknown OS benefit	Investigational; require immunological monitoring

CNIs: calcineurin inhibitors; CTLA-4: cytotoxic T lymphocyte associated antigen-4; ERK: extracellular signal-regulated kinase; FGFR: fibroblast growth factor receptor; KIT: tyrosine kinase protein c_KIT (CD117); LT: liver transplantation; MEK: mitogen-activated extracellular signal-regulated kinase; mTOR: mammalian target of rapamycin; OS: overall survival; PD: programmed death; PD-L1: programmed death ligand -1; RAF: rapidly accelerated fibrosarcoma; RET: rearranged during transfection gene; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor.

plus ICIs or dual ICIs as neoadjuvant therapy before LT or as treatment for recurrence after LT are underway. Careful patient selection, immunological monitoring and early recognition of rejection will be paramount^{27,28};

- **Adoptive cell therapies and vaccines.** Engineering of donor-derived or third-party T cells to target tumour antigens, possibly modified to resist CNIs, holds promise. Vaccines targeting tumour-associated antigens (e.g., GPC3, AFP) are being evaluated for adjuvant therapy^{10,12}.

CONCLUSIONS

HCC recurrence after liver transplantation remains a formidable challenge, affecting up to one fifth of recipients and accounting for a substantial proportion of post-transplant mortality¹. Recurrence arises from residual micrometastatic disease and *de novo* carcinogenesis in the

context of immunosuppression^{4,25}. Risk factors include tumour burden, poor differentiation, microvascular invasion, elevated AFP, recipient/donor characteristics and high CNI exposure⁴. Prognostic models such as post-MORAL, combo-MORAL, RETREAT, R3-AFP and RELAPSE stratify patients and guide surveillance^{26,31}. Risk-adapted surveillance – combining AFP measurement and cross-sectional imaging – enables early detection, allowing surgical or ablative therapies for intrahepatic and oligometastatic recurrence. Minimising CNIs and incorporating mTOR inhibitors may reduce recurrence risk^{4,18,21}. Tyrosine-kinase inhibitors remain the backbone of systemic therapy; immune-checkpoint inhibitors show promise but carry high rejection risk²⁶⁻²⁸. Future progress will depend on multimodal strategies integrating biomarkers, imaging and precision immunosuppression, coupled with clinical trials evaluating novel therapies^{11,12,29}. A multidisciplinary approach is essential to optimise outcomes for this complex patient population.

Conflict of interest statement

The authors declare no conflict of interest.

Author contributions

VG: conceived the overall structure of the manuscript, performed the literature review, and drafted the initial version; MS: critically revised the text, supervised the preparation of the final version, and approved it for submission as corresponding author.

All authors have read and approved the final manuscript.

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