Review

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Neoadjuvant therapies in resectable hepatocellular carcinoma: Exploring strategies to improve prognosis

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SUMMARY Hepatocellular carcinoma (HCC), a challenging malignancy, often necessitates surgical intervention, notably liver resection. However, the high recurrence rate, reaching 70% within 5 years post-resection, significantly impacts patient outcomes. Neoadjuvant therapies aim to preoperatively address this challenge, reducing lesion size, improving surgical resection rates, deactivating potential micro-metastases, and ultimately lowering postoperative recurrence rates. This review concentrates on advances in research on and clinical use of neoadjuvant therapies for HCC, with particular attention to the use of immune checkpoint inhibitors (ICIs) targeting programmed cell death-1 (PD-1), programmed cell death ligand-1 (PD-L1), and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4). Ongoing clinical studies exploring immunotherapy combined with a tyrosine kinase inhibitor (TKI), interventional therapy, radiotherapy, and other modalities offer promising insights into overcoming resistance to monotherapies. In summary, neoadjuvant therapies hold significant promise in terms of improving the prognosis for patients with HCC and enhancing long-term survival, particularly through innovative combination strategies.

Keywords immunotherapy, targeted therapy, recurrence, clinical trials, endpoint, response

1. Introduction

Liver cancer remains a global health challenge, and its incidence is steadily rising worldwide (*1,2*). Estimates are that by 2025, over a million individuals annually will be affected by liver cancer (*3*). Hepatocellular carcinoma (HCC) accounts for approximately 90% of liver cancer cases and is the most prevalent subtype. The primary methods for treating HCC involve surgical interventions, including liver resection (LR) and liver transplantation (LT). LT faces challenges due to organ scarcity and a prolonged waiting time, leading to patients being dropped from the waiting list due to tumor progression. Studies conducted across multiple centers in China, Italy, Japan, and the United States suggest that the likelihood of achieving a cure through resection is comparable to transplantation when the dropout rate exceeds 20% (*4*). Moreover, factors such as cancer thrombus formation, microvascular infiltration, a tumor diameter exceeding 5 cm, poor tumor differentiation, narrow surgical margins (< 1.0 cm), multifocal tumors, satellite nodules, and lymph node metastasis contribute to early recurrence following curative LR (*5-7*). Global liver cancer guidelines (as shown in Table 1), including those from the European Association for the Study of the Liver (EASL) (*8*), Barcelona Clinic Liver Cancer (BCLC) (*9*), American Association for the Study of Liver Diseases (AASLD) (*10*), National Comprehensive Cancer Network (NCCN) (*11*), China (*12*), Japan Society of Hepatology (JSH) (*13*), Korean Liver Cancer Association-National Cancer Center (KLCA-NCC) (*14*), and Indian National Association for the Study of the Liver (INASL) (*15*), indicate a recurrence rate of 10–40% after LT. Furthermore, 70% of patients with HCC experience recurrence within 5 years post-LR, with early recurrence (< 2 years) constituting 60–70% of recurrent cases. Postoperative recurrence of HCC poses a significant challenge to cure, resulting in low survival rates for patients (*16,17*). Therefore, the identification of effective approaches to reduce postoperative recurrence and enhance the curative resection rate is of paramount importance.

Traditionally, adjuvant therapy refers to postoperative treatment aimed at consolidating the surgical intervention's role in eliminating residual tumor cells. However, concerns persist regarding the effectiveness and safety of postoperative adjuvant therapy for HCC. For instance, postoperative sorafenib therapy following

Table 1. Global overview of indications, postoperative recurrence, and post-recurrence treatment strategies for hepatocellular carcinoma

Area (year) (*Ref.*)	Indications for LR	Recurrence rate after LR	Management of recurrence after LR	Indications for LT	Recurrence rate after LT	Management of recurrence after LT
Europe						
EASL (2018)(*8*)	solitary or < 3 cm × 2–3 nodules, portal hypertension (-), preserved LF, PS = 0	5-year recurrence rate of 70%. 60–70% of recurrences occur within the first 2 years.	adjuvant therapy after LR is not recommended	solitary or < 3 cm × 2–3 nodules, portal hypertension (-), preserved LF, PS = 0;	13%	preoperative NAT, including bridging and downstaging therapy, is recommended for patients eligible for LT.
BCLC (2022)(*9*)	solitary or ≤ 3 cm × 2–3 nodules, preserved LF, PS = 0;	5-year recurrence rate of 70%.	LRT; LT in patients with successful downstaging treatment; systemic therapy in patients with VI, EHM, or inappropriate TACE.	solitary or ≤ 3 cm × 2–3 nodules, preserved LF, PS = 0; multiple nodules, preserved LF, PS = 0	5-year recurrence rate 10–15%.	LRT; LT in patients with successful downstaging therapy; systemic therapy in patients with VI, EHM, or inappropriate TACE.
America						
AASLD (2023)(*10*)	solitary or ≤ 3 cm× 2–3 nodules, preserved LF, PS = 0;	5-year recurrence rate of 50–70%	remedial LT within the Milan criteria; LRT for localized recurrence beyond Milan criteria, and LT in patients with successful downstaging; systemic therapy in patients with VI, EHM, TACE is inappropriate, or advanced recurrence HCC.	solitary or ≤ 3 cm × 2–3 nodules, preserved LF, PS = 0; multiple nodules, preserved LF, PS = 0	10–15%	LRT LT in patients with successful downstaging treatment; systemic therapy in patients with VI, EHM, or inappropriate TACE.
NCCN (2023)(*11*)	Child-Pugh A/B, adequate FLR, solitary, portal hypertension (-); limited and resectable multifocal; major VI+; initially unresectable HCC that responds to therapy	5-year recurrence rate exceeds 70%	postoperative adjuvant therapy	solitary, Child-Pugh A/B, Adequate FLR, portal hypertension (-); tumor characteristics marginally outside of the UNOS criteria downstaged to within criteria	18–40%	NAT is recommended for patients eligible for LT;pre-LT NAT reduces postoperative recurrence rates
Asia						
China (2022)(*12*)	Child-Pugh A/B, PS = 0–2, solitary ≤ 5 cm (Ia); solitary > 5 cm or ≤ 3 cm × 2–3 nodules (Ib); > 3 cm × 2–3 nodules (IIa); ≥ 4 nodules (IIb); VI+ (IIIa);	5-year recurrence rate of 40–70%	Depending on the characteristics of the recurrent tumor, re-surgical resection, ablation therapy, interventional therapy, radiation therapy, or systemic anti-tumor therapy can be chosen; aggressive radical resection can be considered for patients with postoperative pure peritoneal metastases.	Child-Pugh A/B, PS = 0–2, solitary ≤ 5 cm; Child-Pugh A/B, PS = 0–2, solitary > 5 cm or ≤ 3 cm × 2–3 nodules; Child-Pugh A/B, PS = 0–2, > 3 cm × 2–3 nodules; Child-Pugh C, PS = 3–4.	5-year recurrence rate 33.7%.	early postoperative withdrawal or hormone-free regimens and reduced dosage of calcium-modulated phosphatase inhibitors in the early postoperative period after LT reduce tumor recurrence rates
JSH (2021)(*13*)	Child-Pugh A/B, ≤ 3 cm × 1–3; Child-Pugh A/B, > 3 cm × 1–3; Child-Pugh A/B, VI+;	Annual recurrence rate exceeds 10%, and 5-year recurrence rate is 70–80%. More than 90% of the initial recurrence occurs within the liver.	If recurrence occurs within the liver, treatment is considered based on the amount of liver remnant and LF. The treatment strategy is essentially the same as for the first treatment: surgical resection or, if resection is difficult, RFA, TARE, or systemic therapy	Child-Pugh C, within Milan or 5-5-500 criteria, age ≤ 65 years;	1-year recurrence rate 9.9%, 3-year recurrence rate 16.1%.	surgical resection or systemic therapy if resection is difficult.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; BCLC, Barcelona Liver Cancer; CTP, Child–Turcotte–Pugh score; EASL, European Association for the Study of the Liver; EBRT, external beam radiation therapy; EHM, extrahepatic metastases; HCC, hepatocellular carcinoma; INASL, Indian National Association for Study of the Liver; JSH, Japanese Society of Hepatology; KLCA-NCC, Korean Liver Cancer Association (KLCA) and National Cancer Center (NCC) Korea; FLR, future liver remnant; LF, liver function; LR, liver resection; LRT, locoregional therapy; LT, liver transplantation; NAT, neoadjuvant therapy; NCCN, US National Comprehensive Cancer Network; PS, performance status; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; TKI, tyrosine kinase inhibitor; UNOS, United Network for Organ Sharing; VI, vascular or bile duct invasion.

Table 1. Global overview of indications, postoperative recurrence, and post-recurrence treatment strategies for hepatocellular carcinoma (continued)

Area (year) (*Ref.*)	Indications for LR	Recurrence rate after LR	Management of LR recurrence	Indications for LT	Recurrence rate after LT	Management of LT recurrence
KLCA-NCC (2022)(*14*)	solitary ≤ 2 cm; solitary > 2 cm; ≤ 2 cm × 2–3 nodules; solitary ≤ 2 cm, VI+; >2 cm, ≤ 3 nodules; solitary > 2 cm, VI+;	5-year recurrence rate of 50–60%	selection of treatment regimen based on time to recurrence, residual LF, functional status, and size, location, and number of recurrent tumors	2 cm < solitary < 5 cm; multiple ≤ 2 cm; multiple > 2 cm;	8–20%	retreatment selected based on the timing of recurrence, LF, exercise status, size, location, and number of recurrent tumors.
INASL (2023)(*15*)	solitary < 5 cm, or ≤ 3 cm × 2–3 nodules (within Milan criteria), preserved LF (CTP ≤ 6), PS = 0; VI and/or EHM, moderately preserved LF (CTP ≤ 8), PS ≤ 2;	5-year recurrence rate of 70%, and intrahepatic recurrence rate of 68–98%.	TACE, TARE, or SBRT as adjuvant therapy in INASL-BCLC stage B patients TARE, SBRT or resection as adjuvant therapy in INASL-BCLC stage C1 patients	solitary or multiple nodules ≥ 5 cm (beyond Milan criteria), moderately preserved LF (CTP ≤ 8), PS ≤ 1; end stage LF (CTP ≥ 9);	15%	multimodal therapy; oligo-recurrence is resectable in one or two organs, surgical resection if R0 resection is feasible; ablation alone or combined with LRT.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; BCLC, Barcelona Liver Cancer; CTP, Child–Turcotte–Pugh score; EASL, European Association for the Study of the Liver; EBRT, external beam radiation therapy; EHM, extrahepatic metastases; HCC, hepatocellular carcinoma; INASL, Indian National Association for Study of the Liver; JSH, Japanese Society of Hepatology; KLCA-NCC, Korean Liver Cancer Association (KLCA) and National Cancer Center (NCC) Korea; FLR, future liver remnant; LF, liver function; LR, liver resection; LRT, locoregional therapy; LT, liver transplantation; NAT, neoadjuvant therapy; NCCN, US National Comprehensive Cancer Network; PS, performance status; RFA, radiofrequency ablation; SBRT, stereotactic body radiation therapy; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; TKI, tyrosine kinase inhibitor; UNOS, United Network for Organ Sharing; VI, vascular or bile duct invasion.

resection or ablation did not improve overall survival (OS) or disease-free survival (DFS) (*17*). In contrast to adjuvant radiotherapy, neoadjuvant radiotherapy has shown potential in improving long-term survival for patients (*18*). Considering current perspectives, early metastases often exist at the time of diagnosis, even when conventional imaging or standard diagnostic methods may not detect them. Therefore, neoadjuvant therapy (NAT), as a preoperative treatment approach, has garnered increasing attention (as shown in Figure 1). In the context of HCC, NAT presents an opportunity to reduce tumor staging and prevent early recurrence.

As many patients exhibit impaired liver function at the baseline, preserving the future liver remnant by shrinking tumors may expand the population eligible for surgery or ablation. NAT can inactivate potential micrometastases, enhance surgical resection outcomes, and reduce postoperative recurrence rates. It can also reduce lesion size, offering a chance for R0 surgical resection in potentially operable cases, thus increasing the surgical resection rate. According to the EASL (*19*), INASL (*15*), and KLCA-NCC (*14*) guidelines, the concept of NAT extends to LT, potentially lowering patients to the Milan criteria or expanding the transplant criteria.

This review specifically discusses NAT, which is intended to eliminate residual hidden cancer cells after resection and provide a means to explore the biological characteristics of tumors, for resectable HCC. For instance, the pathological response to NAT can offer prognostic information and guide the selection of adjuvant treatment regimens. Research on NAT deepens our understanding of the mechanisms of HCC pathogenesis and progression, it fosters the discovery of more effective strategies for treating HCC, and it positively influences the standardized implementation of NAT.

2. Surgical resection alone *vs.* NAT followed by surgical resection in resectable HCC

The fundamental principles for patients with HCC undergoing LR are as follows: (1) Completeness: thorough removal of the tumor with no residual tumor at the margins; (2) Safety: preservation of an adequate volume of functional liver tissue to ensure compensatory liver function postoperatively, reduce surgical complications, and lower mortality rates (*12*). However, determining resectability is a complex issue. In 2023, Japanese experts conducted relevant studies on the concept of resectability in HCC (*20*). Referring to the concept of classifying pancreatic cancer, resectability in HCC is categorized into resectable, potentially resectable, and unresectable. Unresectable HCC (uHCC) is defined as a disease with distant metastasis or the inability to achieve macroscopically radical resection (*21*). The residual liver indocyanine green clearance rate (ICG-Krem) and major vessel infiltration were

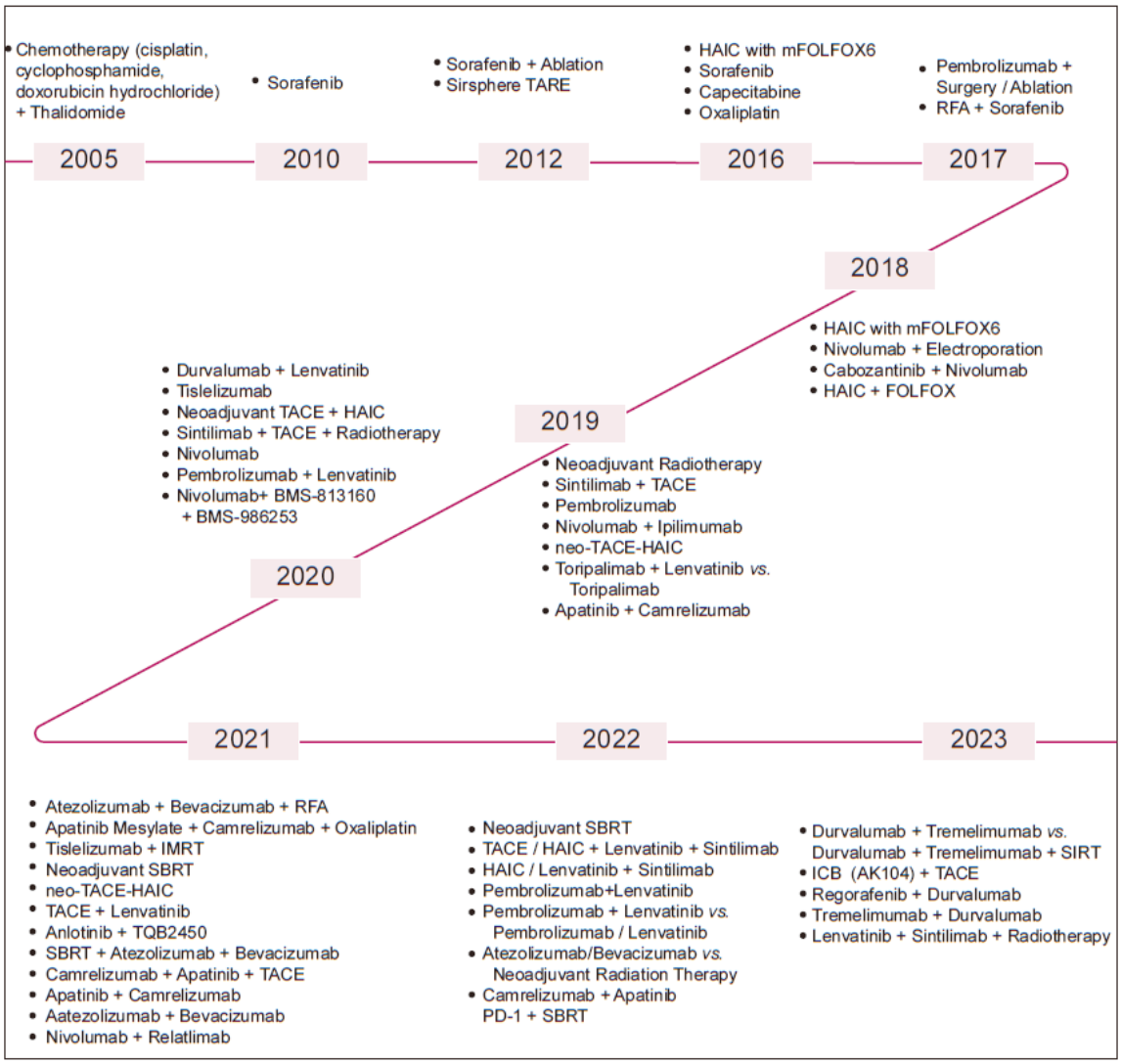

Figure 1. Evolution of clinical research on neoadjuvant therapy in hepatocellular carcinoma. The figure delineates the historical progression of neoadjuvant therapy protocols utilized in clinical studies on hepatocellular carcinoma, showcasing the emergence of novel treatment modalities over time.

selected as determinants for potentially resectable HCC, defining potentially resectable HCC as a high-risk group with clinically relevant liver failure after LR assessed with ICG-Krem and/or HCC with major vessel infiltration (*21,22*). Major vessel infiltration is defined as involvement of Vp2-Vp4 and/or Vv2-Vv3 (*23*). ICG-Krem = preoperative ICG clearance rate × future liver remnant volume (FLRV) / total liver volume (TLV). According to studies and relevant guidelines (*21,22,24*), ICG-Krem < 0.03 is defined as uHCC, ICG-Krem < 0.05–≥ 0.03 is defined as potentially resectable HCC, and the rest are classified as resectable HCC. Chinese experts have implemented a more detailed classification of uHCC, identifying two primary types (*25*). The first type is characterized by surgical unresectability, encompassing patients who are unable to endure surgical trauma due to factors such as their general condition, liver function, and insufficient FLRV. The second type of uHCC is technically resectable but effectiveness cannot be achieved compared to non-surgical treatment after resection, rendering it oncologically/biologically unresectable.

In patients with resectable HCC, those who underwent NAT before surgery have significantly improved survival rates and outcomes compared to those underwent surgery alone. Findings from a multicenter randomized controlled clinical trial involving 208 patients with resectable HCC in stage III revealed that patients in the neoadjuvant hepatic arterial infusion chemotherapy (HAIC) group had markedly higher 1-year, 2-year, and 3-year OS rates (92.9%, 78.6%, and 63.5%, respectively) in contrast to the surgery-alone group (79.5%, 62.0%, and 46.3%, respectively) (p = 0.016) (*26*). In another multicenter phase III clinical trial involving 487 patients with resectable HCC, those who underwent neoadjuvant HAIC had significantly higher 1-year, 2-year, and 3-year OS rates (97.7%, 86.3%, and 77.1%, respectively) compared to the surgery-alone group (90.0%, 80.9%, and 70.6%, respectively) (p = 0.032) (*27*). A retrospective analysis of 100 high-risk

patients with resectable HCC at various centers indicated that patients who received triple NAT consisting of lenvatinib, anti-programmed cell death-1 (PD-1) antibody, and transcatheter arterial chemoembolization (TACE) had a significantly improved DFS and OS compared to the surgery-alone group. The OS rates at 6, 12, 18, and 24 months in the NAT group were 100.0%, 100.0%, 100.0%, and 85.7%, respectively, whereas the surgery group's OS rates were 92.1%, 73.7%, 53.9%, and 48.7%, respectively ($p < 0.001$) (*28*). Moreover, the NAT group had markedly superior DFS rates at 6, 12, 18, and 24 months (82.2%, 66.95%, 48.8%, and 48.8%, respectively) compared to the surgery-alone group (41.92%, 28.34%, 27.05%, and 22.99%, respectively) ($p = 0.003$) (*28*). In patients with Chinese Liver Cancer (CNLC) stage IIb-IIIa resectable HCC, those who underwent NAT with camrelizumab plus apatinib for 1 year had significantly higher OS rates than the surgery-alone group (100% *vs.* 74.2%) ($p = 0.023$). In addition, the NAT group had a substantially lower 1-year recurrence rate than the surgery-alone group (42.9% *vs.* 64.0%, $p = 0.050$) (*29*). In the subset of HCC patients with a single tumor, the 1-year recurrence rate in the surgery-alone group was notably higher compared to the NAT group (71.0% *vs.* 25.0%, $p = 0.022$) (*29*).

NAT results in enhanced OS and DFS outcomes, particularly in patients with massive resectable HCC (≥ 10 cm). A 10-year retrospective analysis over the period from 2004 to 2014 revealed that patients with massive resectable HCC (≥ 10 cm) who underwent neoadjuvant TACE had a significantly improved median OS compared to the surgery-alone group (32.8 months *vs.* 22.3 months , $p = 0.035$) and a better DFS (12.9 months *vs.* 6.4 months, $p = 0.016$) (*30*). In patients with resectable HCC and portal vein tumor thrombus (PVTT), the neoadjuvant radiation therapy group had significantly improved 6-month, 12-month, 18-month, and 24-month OS rates (89.0%, 75.2%, 43.9%, and 27.4%, respectively) compared to the surgery-alone group (81.7%, 43.1%, 16.7%, and 9.4%, respectively) ($p < 0.001$) (*31*). Moreover, the corresponding DFS rates for the neoadjuvant radiation therapy group at 6, 12, 18, and 24 months (56.9%, 33.0%, 20.3%, and 13.3%, respectively) were superior to those of the surgery-alone group (42.1%, 14.9%, 5.0%, and 3.3%, respectively) ($p < 0.001$) (*31*). Among patients with HCC and PVTT, the neoadjuvant folinic acid, fluorouracil, and oxaliplatin (FOLFOX)-HAIC treatment group had significantly higher 1-year, 3-year, and 5-year OS rates (94.9%, 78%, and 66.4%, respectively) compared to the surgery-alone group (84.6%, 47.6%, and 37.2%, respectively) ($p < 0.001$) (*32*). In addition, the neoadjuvant FOLFOX-HAIC group had superior 1-year, 3-year, and 5-year recurrence-free survival (RFS) rates (88.7%, 56.2%, and 38.6%, respectively) compared to the surgery-alone group (84.9%, 38.3%, and 22.6%, respectively) ($p = 0.002$) (*32*).

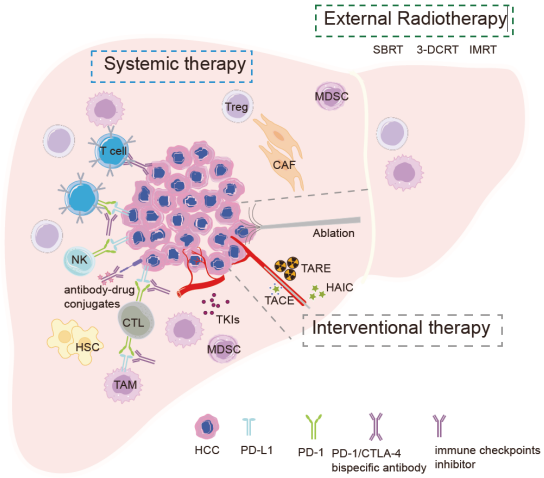

Figure 2. Schematic representation of neoadjuvant therapeutic mechanisms in hepatocellular carcinoma (HCC). Current neoadjuvant therapeutic strategies for HCC are characterized by the predominant utilization of interventional, radiation, and systemic modalities, with a discernible escalation in the prevalence of combination therapies within these treatment paradigms. Interventional approaches are exemplified by transarterial chemoembolization (TACE) and hepatic arterial infusion chemotherapy (HAIC). Radiation therapies include transarterial radioembolization (TARE), stereotactic body radiation therapy (SBRT), 3-dimensional conformal radiotherapy (3-DCRT), and intensity-modulated radiation therapy (IMRT). Systemic treatments predominantly involve tyrosine kinase inhibitors (TKI) and immune checkpoint inhibitors (ICI). An observable trend is the increasing adoption of diverse combination strategies among these therapeutic modalities.

3. NAT strategies prior to LR in HCC

One of the key objectives of NAT in resectable HCC is to enhance overall efficacy and prevent early postoperative metastasis. In addition, NAT functions as a biological assay to evaluate the feasibility of surgery and the tumor's responsiveness to treatment. The choice of an optimal NAT regimen is pivotal, given its substantial impact on patient prognosis. Through a thorough examination of current studies, as depicted in Figure 2, primary neoadjuvant strategies for HCC before LR encompass interventional therapy, radiation therapy, systemic treatment, and combination therapy.

3.1. Interventional therapy

The utilization of neoadjuvant TACE was initially reported by Monden *et al.* in 1989 (*33*). A retrospective analysis from 1990 to 1995 subsequently revealed that the 5-year DFS rate was 51.0% for the group that underwent TACE treatment two or more times preoperatively, 35.5% for the group that underwent TACE treatment once preoperatively, and 21.4% for the group that underwent no preoperative TACE treatment. The average DFS for these groups were 66.4 months, 22.5 months, and 12.5 months, respectively, suggesting a significant improvement in patient prognosis with preoperative TACE neoadjuvant therapy (*34*). In

2009, a study investigated the impact of preoperative TACE on the surgical outcomes of patients with resectable large HCC (diameter ≥ 5 cm). Although not statistically significant, the preoperative TACE group had a seemingly better DFS and OS than the control group (*35*). In 2010, a retrospective analysis of Korean patients with resectable HCC compared the survival outcomes of patients who received preoperative TACE treatment with those who underwent LR alone. The study, involving 1,530 patients with HCC, indicated that patients who underwent TACE before resection had similar 1-year, 2-year, and 5-year OS rates compared to those who did not receive preoperative treatment (p = 0.11) (*36*). However, patients in the preoperative TACE group had lower rates of DFS (*36*). In 2014, findings from a single-center study in China, encompassing 183 patients who received neoadjuvant TACE and 405 patients who underwent LR alone, had similar 1-year, 3-year, and 5-year OS rates (p = 0.739) (*37*). A phase III clinical study involving seven centers in China revealed that neoadjuvant FOLFOX-HAIC could improve the prognosis for patients with resectable BCLC A/B stage HCC beyond the Milan criteria. The disease control rate (DCR) in the NAT group reached 97.4% (*27*). A safety assessment indicated that neoadjuvant HAIC treatment was relatively safe, with rates of surgery-related adverse events (AEs) being similar between the NAT and control groups (p = 0.265) (*27*). Another phase III clinical trial, conducted between 2016 and 2020 at five hospitals in China, yielded comparable results. Patients in the NAT group had significantly better 6-month, 12-month, and 18-month PFS rates (77.6%, 50.4%, and 47.4%, respectively) than patients in the control group (52.7%, 42.8%, and 34.8%, respectively) (p = 0.017) (*26*). Preoperative ^{90}Y transarterial radioembolization (TARE) has demonstrated benefits in increasing the functional residual liver volume (*38*). Findings from a clinical study in 2023 revealed that patients with locally advanced HCC treated with ^{90}Y-selective internal radiation therapy (SIRT) before LR had a significantly improved 5-year OS and RFS compared to those underwent early LR (5-year OS 69.0% *vs.* 47.5%, p = 0.048; 5-year RFS 53.5% *vs.* 27.0%, p = 0.047) (*39*). Moreover, the 5-year OS and RFS in the NAT group were comparable to those of patients who underwent early LR (5-year OS 69.0% *vs.* 62.6%, p = 0.475; 5-year RFS 53.5% *vs.* 39.0%, p = 0.736) (*39*).

3.2. Radiation therapy

Preoperative treatment with ^{131}I-lipiodol has been found to lead to a reduction in serum alpha-fetoprotein (AFP) levels by more than 50% in 70% of patients (*40*). Out of 34 patients from whom postoperative tumor tissue samples were obtained, 25 displayed an objective response or tumor necrosis exceeding 90% (*40*). The RFS rates of the patients at 1, 2, and 3 years after surgery were 94%, 48%, and 48%, respectively (*40*).

Compared to the surgery-alone group, preoperative neoadjuvant three-dimensional conformal radiotherapy (3-DCRT) significantly reduced the recurrence rate and HCC-related mortality in patients with HCC and main portal vein thrombus (*41*). A clinical trial in 2018 indicated that preoperative SIRT can improve outcomes in patients with cirrhotic HCC; a major pathological response (MPR) was achieved postoperatively in 80% of patients treated with neoadjuvant radiotherapy and a pathological complete response (pCR) was achieved in 40% (*42*). In 2019, a study indicated that neoadjuvant 3-DCRT significantly reduced HCC-associated mortality and recurrence rates compared to surgery alone in patients with resectable HCC and PVTT (hazard ratio (HR): 0.35 *vs.* 0.45, $p < 0.001$) (*31*).

In 2020, a study indicated that preoperative treatment with SIRT facilitated the recruitment/activation of effector immune cells within the tumor. This resulted in a significant increase in tumor-infiltrating lymphocytes (TILs), CD4(+) T cells, CD8(+) T cells, and granzyme B (GZB) compared to patients in either the surgery-alone group or the group undergoing TACE preoperatively (*43*). A 2021 clinical study indicated a 65.3% 5-year OS rate for patients receiving neoadjuvant radiation therapy, compared to 46.6% in the surgery-alone group. In addition, the study found that neoadjuvant radiation therapy was significantly associated with improved OS (HR 0.549; p = 0.023) (*44*). In 2022, a phase II clinical trial investigated the use of neoadjuvant intensity-modulated radiotherapy (IMRT) for centrally located HCC. Results revealed notable outcomes, with 1-year, 3-year, and 5-year OS rates of 94.6%, 75.4%, and 69.1%, respectively. The DFS rates were 70.3%, 54.1%, and 41.0%, with a median DFS of 45.8 months. Moreover, an MPR was achieved in 34.2% of patients, and a pCR was achieved in 13.2% (*45*).

3.3. Systemic therapy

The advent of tyrosine kinase inhibitors (TKIs) marks a new era in systemic therapy for HCC, and sorafenib, which is a NAT, has exhibited a favorable safety profile in patients with resectable HCC (*46*). In recent years, immunotherapy has emerged as a prominent area of research for the treatment of HCC, and its main mechanisms include induction of immune responses, promotion of immunogenicity, regulation of immune responses, recruitment of cytotoxic immune cells, stimulation of cytotoxic T cell proliferation, reduction of immune tolerance, and other related factors. Extensive research is currently being conducted on monotherapy immunotherapy, and specifically immune checkpoint inhibitors (ICIs) that target PD-1, programmed cell death ligand-1 (PD-L1), and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4).

As an example, the PD-1-targeting antibody

cemiplimab is used in NAT for patients with resectable HCC, yielding an R0 resection rate of 95.2%. Notably, a pCR with over 70% necrosis was observed in 20% of patients, and an MPR with 50–70% necrosis was observed in 15% (*47*). Following NAT with toripalimab, 80% of patients (8/10) underwent LR, with an incidence of MPR of 20% (*48*). In patients with resectable HCC receiving monotherapy with nivolumab, an MPR was achieved in approximately 33% (*49*).

3.4. Combination therapy

Combination therapy has shown promise in enhancing the efficacy of HCC treatment compared to monotherapy, making it a prospective approach to address the challenge of resistance to monotherapy as more clinical trials are conducted.

(1) Anti-PD-1 antibody combined with TKIs

In a study of 24 patients with resectable HCC receiving NAT with tislelizumab combined with lenvatinib, 17 patients (70.8%) underwent R0 resection, a pCR was achieved in 17.6%, and an MPR was achieved in 35.3% (necrosis >70%) (*50*). After undergoing NAT with nivolumab combined with cabozantinib, R0 resection was successfully performed in approximately 85.7% of patients. In addition, an MPR or a cPR was observed in 41.7% of tumor specimens (*51*). In the NAT group receiving toripalimab combined with lenvatinib, all 8 patients underwent surgical resection, and immunohistochemical analysis of tumor tissue infiltration revealed increased T-cell infiltration in responsive tumor tissue compared to non-responsive tumor tissue (*48*).

(2) Anti-PD-1 antibody combined with a vascular endothelial growth factor receptor (VEGFR) antagonist

In HCC patients with a high risk of recurrence, NAT combining camrelizumab and apatinib resulted in a favorable pathological response. In a study focusing on patients with resectable HCC with a high risk of recurrence, a 100% R0 surgical resection rate was achieved in those who underwent NAT with camrelizumab combined with apatinib (*52*). A MPR was observed in 38.5% of those patients, and a pCR was noted in 7.7%. Another clinical trial involving HCC patients with an intermediate to high risk of recurrence reported that approximately 89% of patients successfully underwent LR after receiving camrelizumab combined with apatinib, with a corresponding MPR rate of 46.2% in patients who underwent LR (*53*). In patients who underwent NAT with camrelizumab combined with apatinib, the LR rate was 94.4%, the MPR rate was 29.4% (5/17), and the pCR rate was 5.9% (1/17) (*54*).

(3) Anti-PD-1 antibody combined with anti-CTLA-4 antibody

In patients with resectable HCC, the combination of nivolumab and ipilimumab in NAT resulted in a significantly improved median PFS compared to nivolumab monotherapy (19.53 months *vs.* 9.4 months) (*49*). In patients who received combination NAT, the MPR rate was 27% (*49*). However, the incidence of grade 3–4 AEs with combination therapy was higher than that observed with nivolumab alone (43% *vs.* 23%) (*49*). Following NAT with ipilimumab combined with nivolumab, the DCR was 95%, and the MPR rate was 56% (*55*). In an ongoing phase II randomized controlled clinical trial, a pCR was achieved in approximately 25% of patients receiving neoadjuvant immunotherapy with nivolumab combined with ipilimumab (*56*).

4. Predictive biomarkers for NAT response and prognosis in HCC

Identifying robust biomarkers to predict NAT response and prognosis is pivotal to guiding treatment selection, optimizing intervention timing, and assessing surgical outcomes in HCC. Despite the evolving landscape of NAT for HCC, the scarcity of extensively validated biomarkers capable of reliably predicting efficacy and surgical success remains a challenge. Figure 3 provides an overview of biomarkers associated with treatment and prognosis in advanced HCC, serving as a foundation for an expanded exploration of NAT-related biomarkers in HCC.

4.1. Circulating biomarkers

Several studies have underscored the utility of changes in AFP levels as surrogate biomarkers, reflecting both systemic and local treatment responses throughout

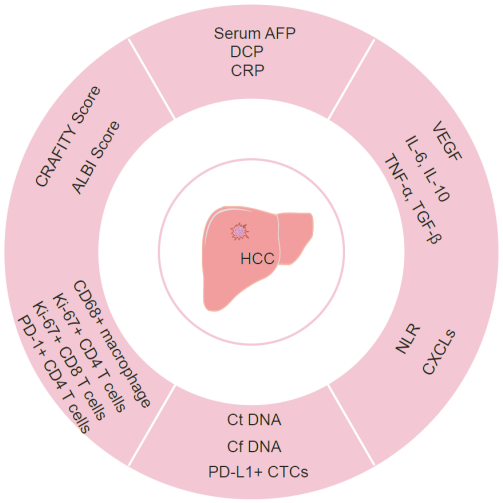

Figure 3. Overview of biomarkers associated with treatment and prognosis in hepatocellular carcinoma (HCC). Referencing studies on biomarkers associated with treatment and prognosis in advanced HCC provides valuable insights to further expand clinical research on neoadjuvant therapy (NAT) biomarkers in HCC. This includes circulating biomarkers such as serum AFP, DCP, CRP, the ALBI score, CRAFITY score, VEGF, IL-6, IL-8, IL-10, TGF-β, TNF-α, NLR, and CXCL9 and tumor microenvironment-related biomarkers such as Ki-67+ CD4 T cells and CD8 T cells, PD-1+ CD4 T cells, and CD68 macrophages. Liquid biopsy components consist of ctDNA, cfDNA, and circulating tumor cells (CTCs).

various stages of HCC treatment. Specifically, an early AFP response, defined by a >20% decline in serum AFP levels within the initial 4 weeks of treatment compared to baseline, has emerged as an independent predictor associated with a prolonged OS and PFS in advanced HCC treated with ICI (*57*).

Monitoring AFP levels during atezolizumab plus bevacizumab (Atez/Bev) treatment is essential for real-time assessment and treatment optimization. In a prospective multicenter study, researchers defined optimal thresholds for AFP response in patients with uHCC who received Atez/Bev treatment. An AFP response of 50% or more and 20% or more was associated with the objective response rate (ORR) and the DCR, respectively. Both responses were also associated with PFS (*58*). The phase Ib GO30140 study proposed using AFP criteria at 6 weeks to identify responders and disease controllers for Atez/Bev treatment (*59*). AFP thresholds delineated in the study, involving a decline of at least 75% and a rise of no more than 10% from the baseline at 6 weeks, were used to discern responders to Atez/Bev and disease controllers, respectively. In HCC patients with AFP levels exceeding 20 ng/mL, a decrease of ≥20% in AFP at 3 weeks can predict the tumor prognosis in patients undergoing Atez/Bev treatment. Combining this with the albumin-bilirubin (ALBI) score enhances the accuracy of prognostic discrimination (*59*).

The CELESTIAL phase III study established that maintaining AFP levels without an increase from the baseline at 8 weeks serves as the most reliable predictor for prolonged OS and PFS in patients with advanced HCC treated with cabozantinib (*60*). Outcomes from the REACH and REACH-2 phase III trials revealed that patients treated with ramucirumab had a prolonged OS when manifesting an AFP response, defined as a reduction of at least 20% from the baseline (*61*). Ramucirumab treatment was considered suitable for patients with AFP levels of at least 400 ng/ml (*61*). In patients with a baseline AFP level of ≥10 ng/mL, an AFP response (defined as a reduction of ≥10% from the baseline) may have a significant effect on the treatment outcomes of patients with HCC who underwent lenvatinib therapy. For patients with an AFP level <10 ng/mL, the baseline ALBI score and the change in ALBI score from the baseline to the one-month post-treatment estimate could play a crucial role in determining treatment response (*62*).

The C-reactive protein and alpha-fetoprotein in immunotherapy (CRAFITY) score, derived from a multicenter retrospective study in Japan, is designed to predict treatment outcomes and treatment-associated AEs among patients with diverse stages of HCC undergoing Atez/Bev therapy. Patients with an AFP level ≥ 100 ng/mL and C-reactive protein (CRP) ≥ 1 mg/dL received a CRAFITY score of 1 (*63*). Concurrently, a multicenter retrospective study in Europe, in line with the Japanese study, found that the CRAFITY score correlated with patient survival and radiographic response during PD-(L)1 immunotherapy (*64*). In Japan, another retrospective multicenter study, encompassing 426 patients with HCC treated with Atez/Bev, established the mALF score based on a baseline mALBI grade of 2b or 3 (HR 2.36, $p = 0.002$) and AFP ≥ 100 ng/ml (HR 2.61, $p < 0.001$). This study validated the mALF score's robust predictive capability for survival in patients undergoing Atez/Bev treatment for HCC (*65*). A retrospective analysis evaluating disease response rate and changes in AFP and des-gamma-carboxy prothrombin (DCP) levels at 1, 2, 3, and 6 weeks, respectively, suggested that an AFP/DCP ratio of 1.4 or higher at 3 weeks may serve as an early predictor for advanced HCC treated with Atez/Bev (*66*). Studies indicated that changes in the Response Evaluation Criteria in Solid Tumors (RECIST), AFP, and DCP can be scrutinized for early response assessment in HAIC (*67*). Within clinical trials of neoadjuvant FOLFOX-HAIC therapy, a logistic regression model integrating AFP and CRP resulted in enhanced precision in predicting neoadjuvant FOLFOX-HAIC response, boasting a sensitivity of 72.2% and specificity of 72.4% (*32*).

In a phase II clinical study evaluating pembrolizumab for uHCC, Lynn *et al.* identified a correlation between reduced efficacy of pembrolizumab treatment and higher plasma levels of transforming growth factor-beta (TGF-β) (≥ 200 pg/mL) in patients (*68*). Moreover, elevated serum interleukin 6 (IL-6) (> 18.49 pg/mL) was linked to diminished clinical benefits, defined as achieving complete or partial remission or disease stabilization for ≥6 months, in patients receiving Atez/Bev for uHCC (*69*). Patients with a lower baseline IL-6 levels had increased response rates and prolonged PFS and OS following Ate/Bev treatment compared to those with elevated baseline IL-6 levels (*70*).

HCC patients with elevated serum IL-10 levels exhibit a substantial suppression of peripheral blood lymphokine-activated killer (LAK) and natural killer (NK) cell activity (*71*). In a prospective study, patients with serum IL-10 levels exceeding 1 pg/mL had a shorter OS (5.0 months *vs.* 14.9 months; $p < 0.0001$), and the IL-10 level emerged as an independent prognostic factor (HR 1.824; $p = 0.0005$) (*72*). In a multicenter phase II pilot study, researchers identified baseline levels of IL-6 at 8.58 pg/mL and IL-8 at 57.9 pg/mL as effective thresholds for predicting OS in uHCC patients treated with sorafenib (*73*). Baseline IL-6 and IL-8, with their respective cut-off values, can serve as predictors for ORR based on modified RECIST (mRECIST) in a subset of 42 patients with available follow-up imaging (IL-6, 46.6% *vs.* 19.2%, $p = 0.007$; IL-8, 50.0% *vs.* 17.4%, $p = 0.011$) (*73*). Moreover, plasma IL-8 and tumor necrosis factor-alpha (TNF-α) levels may serve as predictors of response to sorafenib in uHCC patients during early treatment (5–10 days) (*74*).

The pre-treatment assessment of serum vascular

endothelial growth factor (VEGF) levels has emerged as a promising prognostic biomarker for ablative interventions in HCC. Patients with serum VEGF levels surpassing 240 pg/mL had diminished OS and RFS rates (*75*).

The neutrophil-to-lymphocyte ratio (NLR) is instrumental in evaluating the effectiveness of neoadjuvant TACE therapy (*76*). Notably, patients with a high NLR (≥ 1.6) within the TACE plus sequential resection cohort had a markedly lower 5-year OS rate compared to those with a low NLR (78.4% *vs.* 100%, $p = 0.027$) (*76*). Robust evidence supports the pivotal role of NLR in predicting outcomes of Atez/Bev therapy in HCC patients. As a predictive marker for Atez/Bev response in HCC, pre-treatment NLR was significantly lower in patients in whom disease control was achieved compared to that in patients experiencing disease progression (2.47 *vs.* 4.48, $p = 0.013$). Moreover, patients with NLR ≤ 3.21 had a significantly superior PFS compared to those with NLR > 3.21 ($p < 0.0001$) (*77*). In a separate study, the observed difference in cumulative OS at 2, 4, 6, and 8 months between patients with low (< 3.0) and high NLR (≥ 3.0) in HCC patients treated with Atez/Bev was statistically significant ($p = 0.001$) (*78*). Nonetheless, there were no statistically significant differences in the response to combination therapy between patients with a low and high NLR (*78*). In terms of AEs, notable differences were noted in immune-related liver injury, decreased appetite of any grade, proteinuria of at least grade 3, and AEs of any other grade between patients with a low and high NLR (*78*).

Recent findings have elucidated the optimal threshold for NLR-2c initiation at the outset of the second therapeutic course in patients with uHCC who underwent Atez/Bev treatment, identifying it as 1.97 (*79*). Notably, patients with an NLR-2c < 1.97 had a superior OS and PFS compared to those with NLR-2c ≥ 1.97 (*79*). In a cohort of Japanese patients with HCC treated with Atez/Bev, a baseline NLR ≥ 3 emerged as the exclusive independent factor associated with highly progressive disease (*80*). A German study corroborated NLR > 3.2 as the most critical predictor of poorer ORR and PFS (*81*). Moreover, a multicenter international retrospective cohort study independently established NLR ≥ 5 as a predictor of inferior survival outcomes (*82*).

A study conducted in Japan has validated the potential of serum chemokine C-X-C motif ligand 9 (CXCL9) as a predictive indicator for early disease progression after Atez/Bev treatment (*83*). The research established that the optimal serum CXCL9 threshold for predicting early disease progression in uHCC treated with Atez/Bev is 333 pg/mL, with a sensitivity of 60.0% and specificity of 92.3%. Patients with lower serum CXCL9 levels (< 333 pg/mL) had a higher likelihood of early disease progression, accompanied by a significantly shorter median PFS compared to those with higher levels (126 days *vs.* 227 days, $p = 0.0084$). Notably, patients exhibiting an objective response to lenvatinib displayed notably lower baseline serum CXCL9 levels than those without an objective response (*83*).

4.2. Tumor microenvironment (TME)-related biomarkers

As an immune organ housing a diverse array of immune cells, the liver is particularly prone to developing immunotherapy tolerance. Early recurrent HCC displays reduced levels of T regulatory cells (Tregs) and elevated levels of dendritic cells (DCs) and CD8(+) T cells in comparison to primary HCC (*84*) . An immunohistochemical examination of human HCC tissues has revealed that PD-L1 is preferentially expressed in CD68 macrophages within the TME. Among patients undergoing nivolumab treatment, 3 out of 8 had a positive response to anti-PD-1 therapy. Responders had a higher proportion of Ki-67+ CD4 and CD8 T cells in their blood compared to non-responders (*85*). The greater the number of cells expressing CD68 and PD-L1 in the tumor, the more favorable the response to multikinase inhibitors in patients with HCC (*86*). In patients receiving neoadjuvant treatment with camrelizumab in combination with apatinib, tumor immune microenvironment (TIME) cell infiltration, particularly of DCs, was observed to be more favorable in responding tumors than in non-responding tumors (*54*). A recent study has indicated that patients with a higher baseline frequency of PD-1+ CD4 cells are more likely to exhibit positive responses to anti-CTLA4 therapy, including trastuzumab (*87*). Moreover, studies integrating single-cell and spatial transcriptomics data have found that the structural composition of the tumor immune barrier within the TME may also influence the efficacy of immunotherapy (*88*).

4.3. Liquid biopsy

In patients with HCC, the levels of circulating tumor DNA (ctDNA) are correlated with tumor size, extrahepatic spread, and vascular infiltration. Liquid biopsy, utilizing ctDNA and circulating tumor cells (CTCs), has emerged as a promising method for predicting treatment response and prognosis. In a phase II study involving camrelizumab plus apatinib for HCC treatment, ctDNA played a crucial role in predicting pathological response and RFS (*54*). A Japanese study explored the potential for cell-free DNA (cfDNA)/ctDNA in peripheral blood to serve as a biomarker with which to predict treatment response in patients with uHCC treated with Atez/Bev (*89*). The study revealed that elevated cfDNA levels pretreatment were linked to lower response rates and a shorter PFS and OS. Telomerase reverse transcriptase (TERT) mutations in peripheral blood cfDNA and serum AFP levels ≥400 ng/mL were identified as independent predictors of poor OS following Atez/Bev treatment (*89*). These factors provide

a basis for stratifying patients undergoing Atez/Bev therapy based on prognosis (*89*).

A phase II study indicated that ctDNA can serve as a predictor of pathological response and relapse following treatment with camrelizumab and apatinib (*54*). Patients in whom a pCR/MPR was achieved at the baseline had a higher mutation burden compared to patients in whom a pCR/MPR was not achieved (6 mutations *vs.* 2.5 mutations, $p = 0.025$). There was a noticeable trend towards a shorter RFS in ctDNA-positive patients after adjuvant therapy compared to ctDNA-negative patients (*54*). The clinical predictive significance of mutations in the human TERT (hTERT) promoter in free DNA for the treatment of advanced HCC has been established. Responders who had peak DNA levels within one week of TKI initiation had a significantly improved PFS compared to non-responders ($p = 0.004$). The extent of mutant DNA changes after TACE was significantly correlated with tumor volume ($p < 0.001$) (*90*).

CTCs are regarded as ideal biomarkers due to their cancer-specific characteristics. PD-L1+ CTCs can serve as an independent predictor of OS ($p = 0.010$). Patients with PD-L1+ CTCs have a worse OS compared to those lacking PD-L1+ CTCs (14.0 months *vs.* not achieved, $p = 0.001$) (*91*). In patients with HCC treated with anti-PD-1/PD-L1, the presence of PD-L1+ CTCs was strongly associated with a favorable treatment response (*91,92*). Specifically, in patients with uHCC receiving a combined regimen of IMRT, anti-PD-1 antibodies, and antiangiogenic drugs, those with PD-L1+ CTC counts below 2 have a prolonged ORR and OS in comparison to patients with counts above 2 (ORR: 56. 5% *vs.* 16.7%, $p = 0.007$; OS: not reached *vs.* 10.8 months, $p = 0.001$) (*93*).

5. Ongoing clinical studies on preoperative NAT for HCC

In the current landscape of global clinical trials exploring neoadjuvant locoregional therapy for HCC, various treatment modalities take precedence, including TACE-HAIC (FOLFOX), (oxaliplatin, leucovorin, and 5-fluorouracil) mFOLFOX6-TAI, FOLFOX-HAIC, and (cisplatin, doxorubicin hydrochloride, and thalidomide) PLADOTH-TACE (as shown in Table 2A). Ongoing clinical trials of NAT for HCC also involve sorafenib monotherapy, sorafenib combined with capecitabine and oxaliplatin, and lenvatinib in conjunction with TACE (as shown in Table 2B). In addition, ongoing studies into neoadjuvant radiation therapy for HCC are outlined in Table 2C. Neoadjuvant immunotherapy studies, both as monotherapy and as combination therapy, constitute a significant focus (as shown in Table 3). Combination therapies are broadly categorized into two- and three-agent combinations. Noteworthy combinations involve anti-PD-1 antibodies paired with interventional therapy, radiation therapy, VEGFR antagonists, VEGF/VEGFR monoclonal antibodies, anti-CTLA-4 antibodies, C-C chemokine receptor 2/5 (CCR2/5) inhibitors, or anti-IL-8 antibodies. Triple NAT options include combinations of anti-PD-L1 antibodies with VEGF/VEGFR monoclonal antibodies and interventional therapy, anti-PD-1 antibodies with VEGFR antagonists and chemotherapeutic agents, anti-PD-L1 antibodies with radiation therapy and interventional therapy, anti-PD-L1 antibodies with anti-CTLA-4 antibodies and radiation therapy, anti-PD-1 antibodies with VEGFR antagonists and radiation therapy, and anti-PD-L1 antibodies with TKIs and radiation therapy.

In a phase 1b study evaluating neoadjuvant cabozantinib and nivolumab in patients with locally advanced or borderline resectable HCC, an R0 resection was achieved in 85.7% of patients (12/14) who completed NAT (*51*). A pathological examination revealed a MPR with over 90% tumor necrosis in 42% of patients (5/12). Immunoassays revealed a significant enrichment in the spatial arrangement of T effector cells, tertiary lymphoid structures, and CD138+ plasma cells and B cells in responders compared to non-responders (*51*).

6. Appropriate research endpoints

In the context of current clinical research paradigms, as delineated in Tables 2 and 3, the primary research endpoints in neoadjuvant local chemotherapy clinical trials encompass OS, PFS, and event-free survival (EFS), with a study duration spanning 3-5 years. For neoadjuvant TKI monotherapy or combination therapy, key endpoints include significant pathologic response, the surgical resection rate, and DFS in a study, conducted over a period of 56 days to 1 year. In neoadjuvant radiotherapy trials, primary endpoints consist of OS, the dropout rate, and treatment-related adverse events (trAEs) according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0), with a study period ranging from 3 months to 1 year. Neoadjuvant immunotherapy with ICIs is characterized by a comprehensive set of primary research endpoints, including OS, RFS, EFS, pCR, MPR, DFS, significant tumor necrosis (STN), ORR, the resection rate, delayed surgery rate, immune-related AEs (irAEs, CTCAE v5.0), and lesion reduction >10% (RECIST v1.1), in a study over a period of 6 weeks to 4 years.

In phase III clinical studies, the primary endpoint emphasis is on OS and RFS. Phase II studies commonly use RFS, STN, ORR, MPR, the tumor response rate (mRECIST), time to recurrence, time to progression, resection rate, and DFS as primary endpoints. Phase I studies prioritize the assessment of AEs, irAEs, the number of patients completing preoperative treatment and undergoing surgical intervention, recurrence rate, ORR, and pathological response.

Treatment with TKIs has been found to be associated with a reduced probability of tumor shrinkage, whereas

Table 2A. Clinical trials investigating neoadjuvant locoregional chemotherapy for hepatocellular carcinoma

Research phase	Treatment	Disease	Number of cases	Treatment modality	Primary endpoint	Time window	NAT duration	Interval from NAT completion to surgery	NCT number	Region
III	mFOLFOX6-TAI	HCC with PVTT	230	NAT	OS	5 years	N/A	N/A	NCT03368651	China
III	mFOLFOX6-TAI	resectable HCC beyond Milan criteria	344	NAT	OS	5 years	N/A	N/A	NCT03851913	China
III	FOLFOX-HAIC	resectable HCC beyond Milan criteria	252	NAT	OS	5 years	4 cycles	N/A	NCT03469479	China
II	PLADOTH-TACE	resectable HCC	47	NAT/AT	1.EFR 2.OS	N/A	N/A	N/A	NCT00276705	UK
N/A	TACE-HAIC(FOLFOX)	resectable HCC	320	NAT	PFS	3 years	N/A	N/A	NCT04777942	China
N/A	TACE-HAIC(FOLFOX)	resectable HCC	280	NAT	PFS	3 years	N/A	N/A	NCT04424043	China
N/A	TACE-HAIC(FOLFOX)	HCC with PVTT	320	NAT	PFS	3 years	N/A	N/A	NCT04181931	China

Table 2B. Ongoing clinical trials on neoadjuvant treatment of hepatocellular carcinoma with tyrosine kinase inhibitors

Research phase	Treatment	Disease	HCC stage/liver function	Number of cases	Treatment modality	Primary endpoint	Time window	NAT duration	Interval from NAT completion to surgery	NCT number	Region
II	Sorafenib	resectable HCC	Child-Pugh B/C	36	NAT	1.Antiangiogenic effects 2.Significant pathological changes	on day 50 and at 3 months after surgery	4 weeks	7 days	NCT01182272	France
II	Sorafenib, capecitabine, oxaliplatin	resectable HCC	Child-Pugh A	15	NAT	Resectability	at the end of cycle 4 (each cycle is 14 days)	56 days		NCT03578874	Hong Kong
N/A	TACE+lenvatinib	resectable HCC	CNLC III, Child-Pugh A/B	164	NAT	DFS	1 year			NCT04961138	China

Table 2C. Ongoing clinical trials on neoadjuvant radiotherapy for hepatocellular carcinoma

Research phase	Treatment	Disease	HCC stage/liver function	Number of cases	Treatment modality	Primary endpoint	Time window	NAT duration	Interval from NAT completion to surgery	NCT number	Region
III	Radiotherapy	HCC with PVTT	Child-Pugh A/B	214	NAT	OS	1 year	N/A	4 weeks	NCT04025437	China
I	SBRT	resectable HCC	Child-Pugh 0/A	30	NAT	Drop-out rate	5 months	N/A	4-6 weeks	NCT04587739	France
I	SBRT	resectable HCC	BCLC A, Child-Pugh A/B	15	NAT	trAE (CTCAE v5.0)	3 months after surgery	N/A	N/A	NCT05598060	China

Abbreviations: AE, adverse event; AT, adjuvant therapy; BCLC, Barcelona Clinic Liver Cancer; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DFS, disease-free survival; EFR, event-free survival; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; mFOLFOX6, infusional oxaliplatin, calcium folinate, and 5-FU; N/A, not applicable; NAT, neoadjuvant therapy; OS, overall survival; PFS, progression-free survival; PLADOTH, cisplatin, doxorubicin hydrochloride, and thalidomide; PR, partial response; PVTT, portal vein tumor thrombus; RECIST, Response Evaluation Criteria in Solid Tumors; SBRT, stereotactic body radiotherapy; TACE, transcatheter arterial chemoembolization; TAI, transarterial chemoinfusion; TARE, transarterial radioembolization; 3D, three-dimensional; trAE, treatment-related adverse event.

Table 3. Ongoing clinical trials on neoadjuvant immune checkpoint inhibitors for hepatocellular carcinoma

Research phase	Treatment	Disease	HCC stage/liver function	Number of cases	Treatment modality	Primary endpoint	Time window	NAT duration	Interval from NAT completion to surgery	NCT number	Region
III	TACE/HAIC combined with lenvatinib+sintilimab	resectable HCC	BCLC B/C	90	NAT	RFS	1 year	N/A	3 months from start	NCT05250843	China
III	Camrelizumab combined with apatinib	resectable HCC	CNLC Ib/IIa/IIb/IIIa	130	NAT/AT	RFS	3 years	4 weeks	≥ 1 week	NCT05613478	China
II	Pembrolizumab+ surgery/ ablation	resectable HCC	BCLC 0/A	50	NAT/AT	RFS	1 year	once	N/A	NCT03337841	Japan
II	Tislelizumab+IMRT	resectable HCC	BCLC 0/A	30	NAT	RFS	2 years	N/A	N/A	NCT04850157	China
II	Apatinib+camrelizumab+oxaliplatin	resectable HCC	BCLC 0/A	15	NAT	MPR#	2 years	N/A	N/A	NCT04850040	China
II	Tislelizumab	resectable HCC	BCLC A/B	80	NAT	DFS	1 year	4 weeks	2 weeks	NCT04615143	China
II	Immune-checkpoint blockade therapy (AK104) combined with TACE	resectable HCC	BCLC A/B	54	NAT	MPR#	2 years	4 weeks	N/A	NCT05578430	China
II	Cemiplimab+SBRT	resectable HCC	BCLC A/B/C	73	NAT/AT	STN	Upon surgery	N/A	N/A	NCT03916627	USA
II	Cemiplimab	resectable HCC	BCLC A/B/C	73	NAT/AT	STN	Upon surgery	N/A	N/A	NCT03916627	USA
II	Cemiplimab+fianlimab	resectable HCC	BCLC A/B/C	73	NAT/AT	STN	Upon surgery	N/A	N/A	NCT03916627	USA
II	Sintilimab+TACE+radiotherapy	resectable HCC	BCLC B/C	10	NAT	EFS	4 years	N/A	N/A	NCT04653389	China
II	Apatinib+camrelizumab	resectable HCC	BCLC B/C	78	NAT/AT	RFS	1 year	7 weeks	N/A	NCT04930315	China
II	Nivolumab+ipilimumab	resectable HCC	BCLC B/C	40	NAT	Tumor shrinkage**	4 years	6/12 weeks	N/A	NCT03510871	China
II	Aatezolizumab+bevacizumab	resectable HCC	BCLC B/C	45	NAT	pCR	6 months	4 weeks	N/A	NCT04954339	South Korea
II	Regorafenib+durvalumab	resectable HCC	Child-Pugh A Child-Pugh A	27	NAT	ORR	16 weeks	3 weeks	1 week	NCT05194293	USA
II	Nivolumab	Potentially resectable HCC	Child-Pugh A	20	NAT	pRR	After surgery (normally 6 weeks after the start of nivolumab)	5 weeks	2 weeks	NCT05471674	Hong Kong
II	Pembrolizumab+lenvatinib	resectable HCC	Child-Pugh A	43	NAT/AT	MPR*	24 weeks	9 weeks	1week	NCT05389527	China
II	Pembrolizumab+lenvatinib *vs.* pembrolizumab/lenvatinib alone	resectable HCC	Child-Pugh A	60	NAT	MPR#	4 months	6/4/6 weeks	N/A	NCT05185739	UK
II	Atezolizumab/bevacizumab *vs.* neoadjuvant SBRT	HCC with PVTT	Child-Pugh A	70	NAT	proportion of LR	17 weeks	10 weeks/10 days	N/A	NCT05137899	Canada

Abbreviations: AE, adverse event; AT, adjuvant therapy; BCLC, Barcelona Clinic Liver Cancer; CNLC, China Liver Cancer Staging System; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DFS, disease-free survival; EFS, event-free survival; HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; HKLC, Hong Kong Liver Cancer staging system; IMRT, intensity modulated photon therapy; irAE, immune related adverse event; MPR, major pathological response; MPR$^{\#}$, defined as <10% viable tumor within resection; MPR*, defined as ≥ 50% necrosis pathologically in the resected specimen; mRECIST, modified Response Evaluation Criteria in Solid Tumors; N/A, not applicable; NAT, neoadjuvant therapy; ORR, objective response rate; OS, overall survival; pCR, pathologically complete response; PFS, progression-free survival; pPR, pathological partial response; PR, partial response; pRR, pathological response rate; PVTT, portal vein tumor thrombus; RECIST, Response Evaluation Criteria in Solid Tumors; RFS, relapse-free survival; SBRT, stereotactic body radiotherapy; STN, significant tumor necrosis; SIRT, selective internal radiation treatment; TACE, transcatheter arterial chemoembolization; TAI, transarterial chemoinfusion; trAE, treatment-related adverse event; UICC, Union for International Cancer Control classification system.

Table 3. Ongoing clinical trials on neoadjuvant immune checkpoint inhibitors for hepatocellular carcinoma (continued)

Research phase	Treatment	Disease	HCC stage/liver function	Number of cases	Treatment modality	Primary endpoint	Time window	NAT duration	Interval from NAT completion to surgery	NCT number	Region
II	Tremelimumab+durvalumab	resectable HCC	Child-Pugh A	28	NAT/AT	AE	4 years	5 weeks	N/A	NCT05440864	Spain
II	Nivolumab	resectable HCC	N/A	36	NAT	(1) MPR# (2) STN	2 years	5 weeks	N/A	NCT04123379	USA
II	Nivolumab+BMS-813160 (CCR2/5 inhibitor)	resectable HCC	N/A	36	NAT	(1) MPR# (2) STN	2 years	5 weeks	N/A	NCT04123379	USA
II	Nivolumab+BMS-986253 (anti IL-8)	resectable HCC	N/A	36	NAT	(1) MPR# (2) STN	2 years	5 weeks	N/A	NCT04123379	USA
Ib/II	Anlotinib hydrochloride +TQB2450	resectable HCC	BCLC A/B	20	NAT	(1) pCR (2) ORR	6 months	N/A	N/A	NCT04888546	China
I/II	Ipilimumab/ipilimumab+nivolumab	resectable HCC	Child-Pugh A	32	NAT	(1) Delay to surgery (2) trAE	(1) 89 days (2) 127 days	/6 weeks	N/A	NCT03682276	UK
I	Durvalumab+tremelimumab *vs.* durvalumab+tremelimumab+SIRT	resectable HCC	BCLC 0/A	20	NAT /AT	AE (at least one grade 3-5 trAE according to CTCAE v5.0)	18 months	4 weeks	3 weeks/24 days	NCT05701488	USA
I	SBRT+atezolizumab+bevacizumab	resectable HCC	BCLC A/B	20	NAT	AE (grade 3-4 trAE according to CTCAE v5.0)	6 months	6 weeks	6-8 weeks	NCT04857684	USA
I	Pembrolizumab	resectable HCC	BCLC B	45	NAT	(1) Recurrence rate (2) Number of CD8+ Ki67+ T cells in tumor	2 years after operation	one dose	4 weeks	NCT04224480	Singapore
I	Lenvatinib+sintilimab+radiotherapy	HCC with PVTT	BCLC C	20	NAT	(1) AE (2) Number of patients who complete surgery	5 years	N/A	N/A	NCT05225116	China
I	Tislelizumab+SBRT	resectable HCC	N/A	20	NAT	(1) Delay to surgery (number of patients experiencing a surgical delay of 6 weeks or longer) (2) ORR (3) pCR, pPR, MPR (4) irAE (CTCAE v5.0)	(1) 92 days (2) 1 day before LR (3) 1 month after LR (4) 2 months after LR	N/A	N/A	NCT05185531	China

Abbreviations: AE, adverse event; AT, adjuvant therapy; BCLC, Barcelona Clinic Liver Cancer; CNLC, China Liver Cancer Staging System; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DFS, disease-free survival; EFS, event-free survival; HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; HKLC, Hong Kong Liver Cancer staging system; IMRT, intensity modulated photon therapy; irAE, immune related adverse event; MPR, major pathological response; MPR$^{\#}$, defined as <10% viable tumor within resection; MPR*, defined as ≥ 50% necrosis pathologically in the resected specimen; mRECIST, modified Response Evaluation Criteria in Solid Tumors; N/A, not applicable; NAT, neoadjuvant therapy; ORR, objective response rate; OS, overall survival; pCR, pathologically complete response; PFS, progression-free survival; pPR, pathological partial response; PR, partial response; pRR, pathological response rate; PVTT, portal vein tumor thrombus; RECIST, Response Evaluation Criteria in Solid Tumors; RFS, relapse-free survival; SBRT, stereotactic body radiotherapy; STN, significant tumor necrosis; SIRT, selective internal radiation treatment; TACE, transcatheter arterial chemoembolization; TAI, transarterial chemoinfusion; trAE, treatment-related adverse event; UICC, Union for International Cancer Control classification system.

Table 3. Ongoing clinical trials on neoadjuvant immune checkpoint inhibitors for hepatocellular carcinoma (continued)

Research phase	Treatment	Disease	HCC stage/liver function	Number of cases	Treatment modality	Primary endpoint	Time window	NAT duration	Interval from NAT completion to surgery	NCT number	Region
I	Nivolumab *vs.* nivolumab +relatlimab	resectable HCC	N/A	20	NAT	Number of patients who complete surgery	4 years	N/A	N/A	NCT04658147	USA
N/A	HAIC/lenvatinib+sintilimab	resectable HCC	Child-Pugh A	60	NAT	DFS	1 year	7 weeks	N/A	NCT05621499	China
N/A	Camrelizumab+apatinib+TACE	resectable HCC	BCLC B/C	290	NAT	EFS	3 years	3 weeks	2-4 weeks	NCT04521153	China

Abbreviations: AE, adverse event; AT, adjuvant therapy; BCLC, Barcelona Clinic Liver Cancer; CNLC, China Liver Cancer Staging System; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DFS, disease-free survival; EFS, event-free survival; HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; HKLC, Hong Kong Liver Cancer staging system; IMRT, intensity modulated photon therapy; irAE, immune related adverse event; MPR, major pathological response; MPR#, defined as <10% viable tumor within resection; MPR*, defined as ≥ 50% necrosis pathologically in the resected specimen; mRECIST, modified Response Evaluation Criteria in Solid Tumors; N/A, not applicable; NAT, neoadjuvant therapy; ORR, objective response rate; OS, overall survival; pCR, pathologically complete response; PFS, progression-free survival; pPR, pathological partial response; PR, partial response; pRR, pathological response rate; PVTT, portal vein tumor thrombus; RECIST, Response Evaluation Criteria in Solid Tumors; RFS, relapse-free survival; SBRT, stereotactic body radiotherapy; STN, significant tumor necrosis; SIRT, selective internal radiation treatment; TACE, transcatheter arterial chemoembolization; TAI, transarterial chemoinfusion; trAE, treatment-related adverse event; UICC, Union for International Cancer Control classification system.

ICIs may result in unconventional radiologic response patterns, such as delayed responses or pseudoprogression, initially appearing as an increased tumor burden and later transforming into radiologic shrinkage (*94*). This poses a challenge to the use of conventional response criteria such as RECIST v1.1 (*95*) and mRECIST (*96*). RECIST v1.1, for instance, fails to account for complete pathologic necrosis of HCC with lipiodol deposition as a result of conventional TACE (*97*). In addition, the mRECIST criteria necessitate subtraction imaging for an accurate assessment of complete pathologic necrosis (*98*).

Immunotherapy-related imaging tumor response assessment criteria, such as immune-related response criteria (irRC) (*99*), immune-related RECIST (irRECIST) (*100*), immune RECIST (iRECIST) (*101*), immune-modified RECIST (imRECIST) (*102*), and intra-tumoral RECIST (itRECIST) (*103*), are designed to measure treatment response or disease progression in patients who underwent immunotherapy, and the use of those criteria shows promise (as shown in Table 4). A recent proposal by Japanese researchers regarding combination therapy involving systemic and local therapies outlined clinical complete response (cCR) criteria (*104*): (1) Attainment of a complete response (CR) according to the mRECIST/RECIST v1.1 criteria assessed with CT/MRI, and (2) Attainment of a CR indicated according to three tumor markers (AFP, vitamin K absence II (PIVKA-II), and AFP bound to Lens culinaris agglutinin (AFP-L3)) that have remained continuously normalized for more than 6 weeks.

Determining the optimal duration of therapeutic intervention is a crucial consideration within the clinical landscape. Ordinarily, cemiplimab is used as a neoadjuvant within a concise 22-day protocol (*47*), while the administration of nivolumab as a neoadjuvant, whether as a monotherapy or in conjunction with ipilimumab, entails a more protracted 6-week regimen (*49*). A point worth noting is that there is a discernible inverse correlation between the duration of treatment administered to patients before surgery and the subsequent pathological response rate. The main goals of NAT are reducing the risk of recurrence by eliminating micro-metastatic disease that cannot be detected by imaging and facilitating treatment of the primary tumor through cytoreductive surgery. Given these goals, the primary reason for using NAT is to stimulate an immune response against micro-metastatic disease rather than directly killing the tumor. Consequently, interventions of a shorter duration may offer comparable benefits while potentially mitigating the risk of preoperative irAEs that could compromise planned surgical procedures. According to the Chinese expert consensus and related studies, NAT should typically last 1.5–3 months, with a maximum duration of 4 months. The goal of this therapy is to achieve the surgical objective as soon as possible, regardless of whether the lesion has shrunk or not (*25*).

Table 4. Radiological assessment criteria for tumor response

Criteria (*Ref.*)	RECIST v1.1 (*95*)	mRECIST (*96*)	irRC (*99*)	irRECIST (*100*)	iRECIST (*101*)	imRECIST (*102*)	itRECIST (*103*)
Lesion definition	Uni-dimensional, largest diameter	Uni-dimensional, enhancing tumor	Bi-dimensional	Uni-dimensional	Uni-dimensional, largest diameter	Uni-dimensional	Uni-dimensional
Target lesions	Measurable (> 10 mm), largest lesions; Lymph node ≥ 15 mm in short axis	Measurable (> 10 mm), largest lesions with arterial-phase enhancement; Lymph node ≥ 20mm in short axis at the porta hepatis	Measurable (≥ 5 × 5 mm), 15 lesions	Measurable (> 10 mm), largest lesions	Measurable (> 10 mm), largest lesions; Lymph node ≥ 15mm in short axis	Measurable (> 10 mm), largest lesions; Lymph node ≥ 15 mm in short axis	Measurable (> 10 mm), largest lesions
Number of targets	Five (two per organ)	Five (two per organ)	Five (per organ)	Five (two per organ)	Five (two per organ)	Five (two per organ)	Ten (five injected, five not injected)
Complete Response	Disappearance of all target lesions; Lymph node with short axis < 10 mm	Disappearance of any intra-tumoral arterial enhancement in all target lesions	Disappearance of all target lesions	Disappearance of all target lesions	Disappearance of all target lesions; Lymph node with short axis < 10mm	Disappearance of all target lesions	Disappearance of all target lesions
Partial Response	≥ 30% decrease in sum of maximum diameter of target lesions	≥ 30%decrease in sum of maximum diameter of enhancing target lesions	≥ 50% decrease from the baseline	≥ 30% decrease from the baseline	≥ 30% decrease in sum of maximum diameter of target lesions	≥ 30% decrease from the baseline	≥ 30% decrease for injected lesions, ≥ 30% decrease for not injected lesions
Progressive Disease	≥ 20% increase in sum of diameters and at least 5 mm absolute increase in sum and/or new lesions	≥ 20%increase in sum of diameters of enhancing target lesions and/or new lesions	≥ 25% increase from the nadir	≥ 20% increase from the nadir (≥ 5 mm)	iUPD; iCPD	≥ 20% increase from the nadir (≥ 5 mm)	≥ 20% increase from the nadir (≥ 5 mm)
Confirmation of Progressive Disease	Not applicable	Not applicable	At least 4 weeks	4-12 weeks	4-8 weeks	At least 4 weeks	4-12 weeks

Abbreviations: iCPD, immune-confirmed progressive disease, Confirmed progression with increase in sum of measures ≥ 5 mm; imRECIST, immune-modified RECIST; iRECIST, immune RECIST; irRC, immune-related response criteria; irRECIST, immune-related RECIST; itRECIST, intra-tumoral RECIST; iUPD, immune-unconfirmed progressive disease, ≥ 20% increase in sum of diameters and at least 5 mm absolute increase in sum; mRECIST, modified RECIST; PD, Progressive Disease; RECIST, Response Evaluation Criteria in Solid Tumors.

7. Challenges with NAT for LR in HCC

The potential drawbacks associated with NAT involve significant challenges, as evinced by a phase II clinical trial that evaluated the perioperative efficacy and safety of camrelizumab in combination with apatinib for resectable HCC (*54*). Despite the notable pathological response observed in resected specimens, a substantial proportion of patients completing NAT - 89% (16/18) - experienced AEs. Of particular concern, 16.7% (3/18) of patients experienced grade 3 or higher AEs, necessitating a dose adjustment of apatinib in 5.6% (1/18) of patients due to high blood pressure. Moreover, 11.1% (2/18) of patients required preoperative steroid therapy to deal with severe liver dysfunction or a severe rash. There were additional challenges preoperatively, with 38.8% (7/18) of patients experiencing post-hepatectomy grade A liver failure, 16.7% (3/18) developing postoperative bile leakage, 11.1% (2/18) requiring blood transfusions, and 5.6% (1/18) reporting chest tightness. These findings underscore the intricate balance between efficacy and potential complications associated with NAT, emphasizing the need for comprehensive efforts through expanded clinical research (as shown in Figure 4).

For early-stage HCC, the efficacy of NAT in improving patient survival and reducing cancer recurrence remains uncertain. There are concerns regarding the risks of tumor progression during NAT and the potential for delayed curative surgery due to AEs during treatment. Neoadjuvant immunotherapy in particular carries the possibility of reactivating the hepatitis B virus in patients (*105*). Addressing the challenges associated with potential delayed tumor responses and the chemotherapy-free interval (CFI) during NAT is paramount. Moreover, clinical predictors to distinguish patients who may derive optimal benefits from NAT need to be promptly identified. The absence of a standardized definition for MPR in HCC adds complexity, and its prognostic significance remains unclear. The lack of validated biomarkers predicting surgical success further contributes to the existing challenges. There is still considerable heterogeneity in the selection of a treatment plan among different cancer centers. Additional clinical evidence is needed to guide decisions on whether patients who underwent NAT should proceed to immediate surgery upon disease progression or opt for delayed surgery.

8. Prospects for NAT

In the evolving landscape of clinical trials, advances in research are gradually revealing more efficacious NAT options for HCC. Treatment decisions for patients with HCC should be collaboratively determined through a multidisciplinary team (MDT) approach involving surgery, oncology, radiation therapy, pathology, interventional radiology, and other specialties. This ensures the formulation of optimal treatment strategies and enhances overall patient survival rates. NAT plays a pivotal role in bolstering local control, targeting latent micrometastases in the early stages of the disease, facilitating preoperative recovery, and enhancing the probability of completing multimodal treatment. The assessment of response post-NAT furnishes valuable

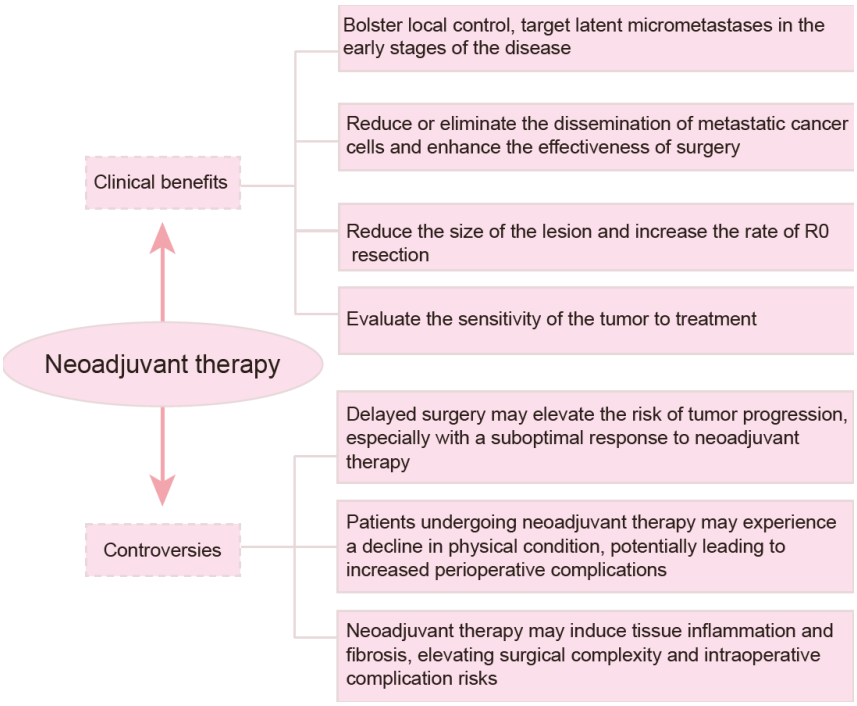

Figure 4. Clinical benefits and controversies of neoadjuvant therapy in hepatocellular carcinoma (HCC).

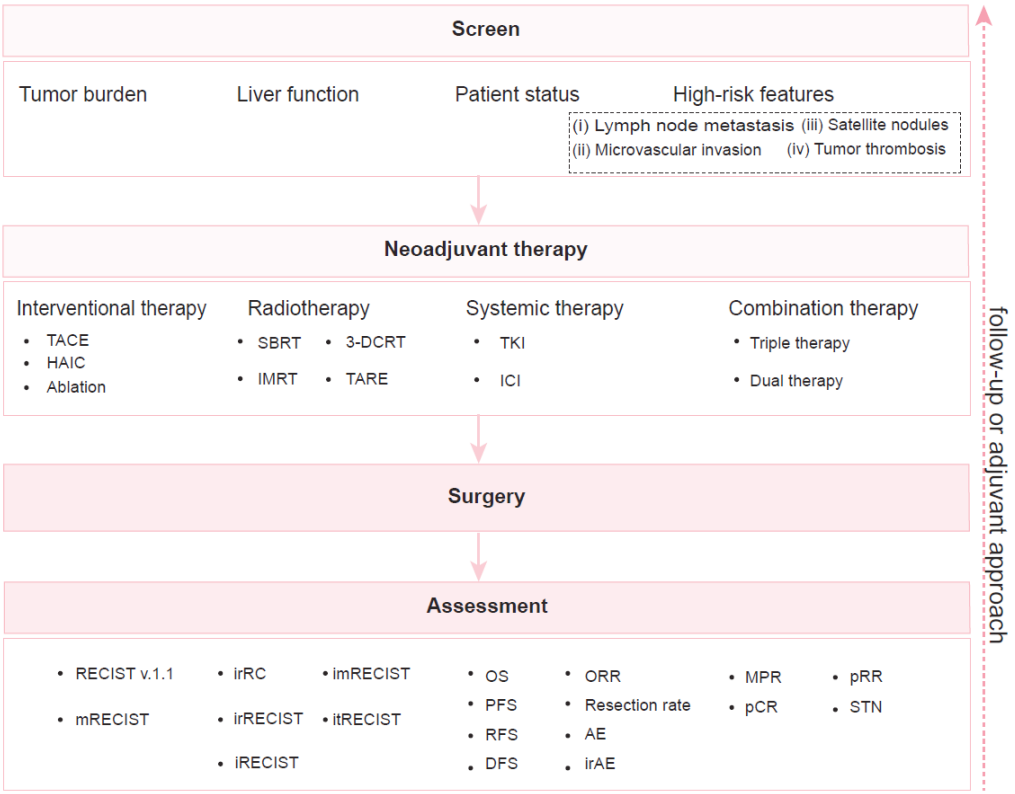

Figure 5: Recommended paradigm for neoadjuvant therapy in hepatocellular carcinoma (HCC). A comprehensive assessment, incorporating patient tumor burden, hepatic function, patient status, and high-risk features, is advocated for the identification of resectable hepatocellular carcinoma patients who may benefit from neoadjuvant therapy (NAT). NAT encompasses interventional, radiation, systemic, and combination modalities. Subsequent to the completion of neoadjuvant treatment, the next step involves surgical intervention. Postoperative evaluation should include a holistic approach, integrating imaging studies, biomarkers, pathological response, disease status, and adverse events. A thorough assessment should be performed and a subsequent adjuvant therapeutic strategy should be formulated in a multidisciplinary collaborative framework, followed by diligent follow-up.

insights into planning subsequent treatments. Preliminary outcomes show promise, but further research is needed to delineate the optimal duration of treatment, to validate pertinent endpoints, and to identify biomarkers that can adeptly help to decide treatments.

In summary, NAT for HCC has significant advantages in improving pCR, MPR, ORR, DFS, and OS. NAT for HCC represents a paradigm shift in the treatment of HCC (as shown in Figure 5), requiring multidisciplinary collaboration for assessing disease and deciding treatment. In addition, the incorporation of immunotherapy in NAT poses new challenges regarding endpoints of radiological, pathological, and clinical research. Therefore, further research is essential to enhancing treatment options guided by biomarkers, to determining the optimal duration of treatment, and to ultimately improving survival time and the quality of life for patients with HCC.

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