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Review

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Emerging data on immune checkpoint inhibitors in the neoadjuvant and adjuvant setting for patients with hepatocellular carcinoma

Samantha M. Ruff, Timothy M. Pawlik

Department of Surgery, Division of Surgical Oncology, The Ohio State University Wexner Medical Center and James Comprehensive Cancer Center, Columbus, OH 43210, USA.

Correspondence to: Prof. Timothy M. Pawlik, Department of Surgery, Division of Surgical Oncology, The Ohio State University Wexner Medical Center and James Comprehensive Cancer Center, 395 W. 12th Ave., Suite 670, Columbus, OH 43210, USA. E-mail: tim.pawlik@osumc.edu

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Abstract

Hepatocellular carcinoma (HCC) is a form of liver cancer that commonly arises in patients with chronic liver disease. Patients who present with early-stage disease, even after curative intent resection or ablation, are likely to develop local recurrence or metastatic disease. Chronic inflammation disrupts the tightly relegated immune system of the liver, making it more susceptible to carcinogenesis. In turn, research has focused on leveraging immunotherapy for these patients. This approach has primarily been accomplished through immune checkpoint inhibitors, which are monoclonal antibodies that inhibit immune checkpoints and restore T cells' activity against cancer cells. The IMbrave150 and HIMALAYA trials established immunotherapy as the first-line treatment for patients with advanced HCC. Therefore, there has been interest in expanding the indications for immunotherapy among patients with HCC to the neoadjuvant and adjuvant settings. Furthermore, locoregional therapies, like radiation therapy, may be able to prime the tumor microenvironment and make it more susceptible to immunotherapy, thereby improving response to treatment. We herein review recent research and clinical trials focused on the use of immunotherapy in the neoadjuvant and adjuvant setting for patients with HCC.

Keywords: Surgery, hepatocellular carcinoma, immunotherapy, radiation therapy, neoadjuvant therapy

INTRODUCTION

Hepatocellular carcinoma (HCC) is a form of primary liver cancer that often arises in patients with chronic liver disease or cirrhosis. The liver maintains the body's homeostasis and fulfills several roles, including the filtration of waste from the blood. As such, the liver must maintain an immune environment that tolerates dietary and bacterial products while also recognizing pathogens or toxins that require an inflammatory response. Chronic inflammation of various etiologies (e.g., hepatitis, alcohol abuse) disrupts this tightly relegated immune system. Eventual remodeling and fibrosis combined with immune cell exhaustion can make the liver susceptible to carcinogenesis[1].

Given the unique role of the immune system in the development of HCC and the absence of effective systemic therapies, research has focused on leveraging immunotherapy. Treatment of patients with HCC has largely involved immune checkpoint inhibitors, which are monoclonal antibodies that restore T cells' activity against cancer cells[2]. The IMbrave150 trial evaluated sorafenib *vs.* atezolizumab and bevacizumab in patients with advanced HCC[3]. Atezolizumab/bevacizumab conferred a survival advantage over sorafenib [12 month overall survival (OS) 67.2% *vs.* 54.6%, respectively]. This was a landmark trial that established atezolizumab/bevacizumab as first line therapy for patients with advanced HCC according to the Barcelona Clinic Liver Cancer (BCLC) guidelines [Figure 1][4]. Additionally, the HIMALAYA trial demonstrated that tremelimumab and durvalumab conferred a survival benefit compared with sorafenib (36-month OS 30.7% *vs.* 20.2%, respectively) for patients with advanced HCC[5]. As such, the combination of tremelimumab/durvalumab is also now approved as first-line therapy.

When diagnosed early, surgery and/or transplantation are the most effective treatments. Unfortunately, even after a successful oncologic resection, many patients will develop local recurrence or distant metastatic disease[4]. Recurrent disease may represent disseminated micrometastatic disease that was present at the time of resection or a de novo primary tumor from the persistent chronic liver disease. Given that immunotherapy has proven to be successful in prolonging the survival in advanced HCC, there is interest in expanding its indications to the neoadjuvant and adjuvant settings. Furthermore, locoregional therapies, like radiation therapy, may be able to prime the liver tumor microenvironment and make it more susceptible to immunotherapy, thereby improving response to treatment[6]. We herein review recent research and clinical trials focused on the use of immunotherapy in the neoadjuvant and adjuvant setting for patients with HCC.

SURGICAL INDICATIONS FOR HCC

Patients with no portal hypertension, adequate liver function, appropriate future liver remnant (FLR), and anatomically resectable tumors should undergo surgical evaluation[4,7]. Individuals with no major vascular invasion and solitary tumors are ideal. Surgery can be performed in patients with multifocal disease or with major vascular invasion, but should be performed on a case-by-case basis. However, these indications remain somewhat controversial, given the elevated risk of postoperative recurrence[7-10]. According to the Japan Society of Hepatology Clinical Practice Guidelines (JSH-HCC), patients with up to three nodules can be considered for resection[11]. On the other hand, the BCLC guidelines recommend transplantation or ablation for multifocal disease[4]. Extra-hepatic metastases (including distant nodes) or inadequate FLR are considered absolute contraindications to surgery[7].

IMMUNE CHECKPOINTS AND IMMUNE CHECKPOINT INHIBITORS

Immune checkpoints are membrane-bound proteins that bind receptors on T cells to regulate the immune system. Physiologically, immune checkpoints suppress immune cell autoreactivity to prevent the immune system from attacking cells indiscriminately[12]. Cancer cells can manipulate this system by upregulating the

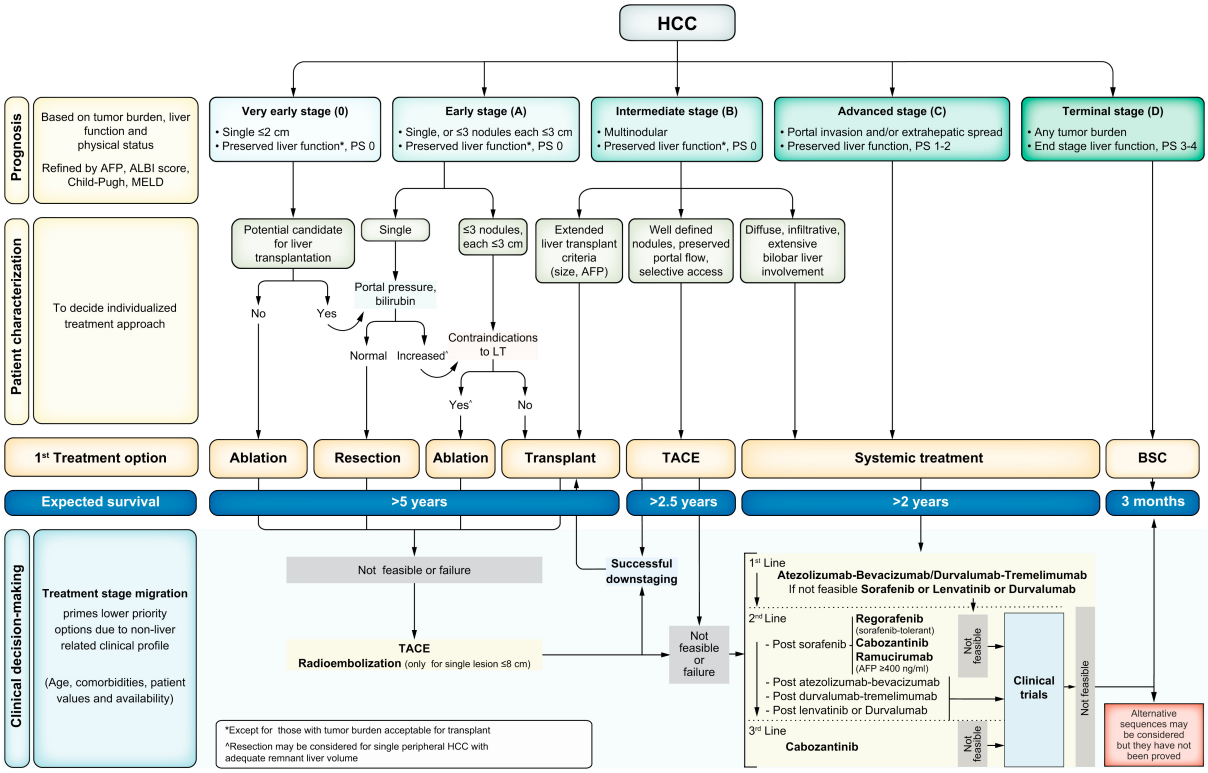

Figure 1. The BCLC system establishes a prognosis in accordance with the 5 stages that are linked to first-line treatment recommendation. The expected outcome is expressed as the median survival of each tumor stage according to the available scientific evidence. Individualized clinical decision-making, according to the available data on November 15, 2021, is defined by teams responsible for integrating all available data with the individual patient's medical profile. Note that liver function should be evaluated beyond the conventional Child-Pugh staging. AFP: alpha-fetoprotein; ALBI: albumin-bilirubin; BCLC: Barcelona Clinic Liver Cancer; BSC: best supportive care; ECOG-PS: Eastern Cooperative Oncology Group performance status; LT: liver transplantation; MELD: model of end-stage liver disease; TACE: transarterial chemoembolization. Figure reprinted with copyright permission from reference[4].

expression of inhibitor proteins and downregulating stimulatory proteins[2]. This process leads to T cell exhaustion, decreased helper cytokines, and suppression of immune cell proliferation[13]. Through this mechanism, cancer cells can evade the immune system and continue to proliferate. Immune checkpoint inhibitors (ICI) block these interactions and restore T cell antitumor function. It remains unclear, however, if ICIs also exert a larger effect on the homeostasis of the body. The events following immune checkpoint blockade and why only some patients respond to therapy are still poorly understood. Given the complexity of the immune system and its larger regulatory role in the body, this area of research still requires more investigation[14]. ICIs have more tolerable side effects compared with traditional chemotherapy[2].

There are two main immune checkpoints most frequently targeted: CTLA-4 and PD-L1 [Figure 2]. The B7 ligand on antigen-presenting cells (APCs) binds the CD28 T cell receptor to establish a pro-inflammatory state. However, when B7 binds the CTLA-4 receptor on T cells, B7 is sequestered and T cell expansion is inhibited[16,17]. In response to pro-inflammatory cytokines, PD-L1 on somatic cells binds the PD-1 receptor on immune cells. This process suppresses T cell migration, proliferation, and cytotoxin secretion[18-20]. Targeting these immune checkpoints with ICIs can be efficacious when treating solid tumors.

UPFRONT THERAPY

There are multiple rationales for upfront therapy among patients with HCC. Patients with initially

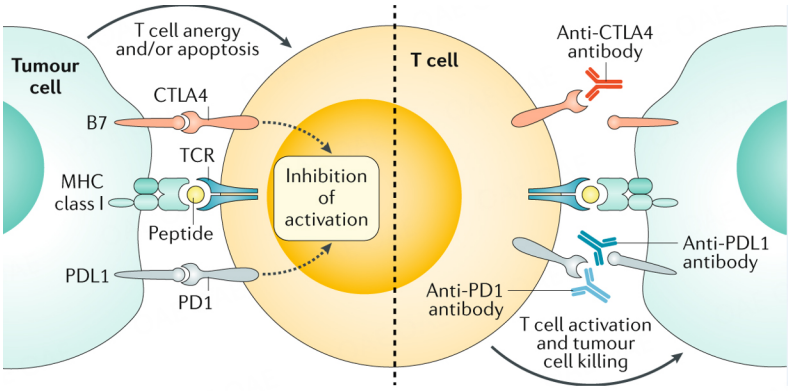

Figure 2. Endogenous peptides are processed and presented on major histocompatibility complex (MHC) class I molecules on the surface of all human cells, including cancer cells. The peptide-MHC complex is recognized by T cell receptors (TCRs). The response of the T cell is fine-tuned by a range of co-inhibitory or co-stimulatory signals. The ligands CD80 and CD86 of the B7 family of membrane-bound ligands can bind to the co-stimulatory CD28 and, especially in activated T cells, to cytotoxic T lymphocyte antigen 4 (CTLA4). Similarly, membrane-bound programmed cell death 1 ligand 1 (PDL1) and programmed cell death 1 ligand 2 (PDL2) can engage programmed cell death 1 (PD1), leading to T cell anergy and/or apoptosis. Monoclonal antibodies that bind to either the inhibitory receptors on T cells or their cognate ligands on cancer cells antagonize inhibitory signaling and enable T cell activation and cytotoxic tumor cell killing. This figure was reprinted with copyright permission from reference[15].

unresectable or locally advanced disease can be downstaged and made eligible for surgery or liver-directed therapies. After resection, the only remaining neoantigens are from micro-metastatic disease. However, in the preoperative setting, the tumor is still *in vivo*, which provides more neoantigens to prime the T cells and enhances the effects of immunotherapy. In addition, preoperative therapy may allow for assessment of tumor response on pathology after surgery, which can guide future treatment decisions.

Neoadjuvant immunotherapy for resectable HCC

Kaseb *et al.* reported a randomized trial for patients with resectable HCC[21]. Patients received either perioperative nivolumab (PD-1 inhibitor, n = 13) or combination of perioperative nivolumab and ipilimumab (CTLA-4 inhibitor, n = 14). The primary endpoint for this study was safety; both cohorts had acceptable toxicity levels and tolerated the treatments. The median progression free survival in the nivolumab *vs.* nivolumab/ipilimumab cohort was 9.4 months and 19.53 months, respectively. Interestingly, three patients in each arm had > 70% tumor necrosis on pathology. The ongoing PRIME-HCC trial is a phase I trial evaluating the safety of nivolumab and ipilimumab in patients with early-stage HCC[22]. On preliminary analysis, nivolumab/ipilimumab was demonstrated to be safely administered in the neoadjuvant setting without delaying liver resection; the disease control rate was 92% and an objective response rate of 23%. On interim analysis, nine patients had undergone an operation and had pathology available for analysis. Seven of these patients had achieved a pathologic response, two of whom had a complete pathologic response (NCT03682276). Similar to other trials, there was discordance between radiologic and pathologic response, which indicated that the methods used to measure response may need to be adjusted when assessing immunotherapy in clinical trials.

Marron *et al.* published a single-arm phase II trial that studied neoadjuvant cemiplimab (PD-1 inhibitor) in 21 patients with resectable HCC[23]. Among 20 patients who underwent surgery, four had significant tumor necrosis (defined as > 70% necrosis on pathology specimen) and three patients had a partial response. There were no grade 4 or 5 events. Xia *et al.* published a single-arm phase II trial evaluating the use of neoadjuvant camrelizumab (PD-1 inhibitor) with apatinib (VEGF inhibitor) among patients with resectable HCC[24]. Among 18 patients who completed neoadjuvant therapy, 17 were able to undergo a surgical resection; one-

year recurrence free survival was 53.85%. While limited, the data for neoadjuvant ICIs for patients with resectable HCC appears to be promising and should be the focus of future studies.

Upfront immunotherapy for unresectable HCC

For patients with unresectable HCC, upfront systemic therapy could potentially downstage or "convert" these patients to resectable disease. Recent retrospective studies demonstrate that while this may only apply to a small cohort of patients, the long-term benefits are still unclear[25,26]. In a study of 63 patients with unresectable HCC who received first-line systemic therapy of a tyrosine kinase inhibitor (lenvatinib or apatinib) and PD-1 inhibitor (pembrolizumab or camrelizumab), ten individuals were able to proceed to an R0 resection within 3.2 months of initiation of therapy[27]. Six of these patients achieved a complete pathologic response. At a median follow up time of 11.2 months, one patient had died from immune-related adverse events, eight had no disease recurrence, and one had tumor recurrence. A retrospective study of patients with HCC and major vascular invasion who underwent upfront tyrosine kinase inhibitor and PD-1 inhibitor systemic therapy demonstrated that salvage surgery could be effective[28]. Among ten patients who met inclusion criteria, eight individuals were able to undergo surgery; 12-month recurrence free survival was 75%.

Ho *et al.* performed a single-arm phase I trial that evaluated the feasibility of first-line cabozantinib (tyrosine kinase inhibitor) and nivolumab in 15 patients with locally advanced or borderline resectable HCC, defined as solitary tumors > 5 cm, unilateral multifocal disease (> 3 tumors or one tumor > 3 cm), bilateral disease, or high risk features (tumor > 3 cm with macrovascular invasion)[29]. Twelve patients underwent a margin negative resection and five (42%) had a major pathologic response. Specimens that demonstrated a pathologic response also had an increase in T effector cells and other critical changes to the immune microenvironment. The data suggest that if patients can be downstaged to resectable disease with immunotherapy, the role of surgical resection and ablative therapy for patients with advanced HCC will expand.

ADJUVANT THERAPY

Despite curative intent surgery or ablation, 5-year recurrence ranges from 70%-80%[30]. Residual micrometastatic disease in the liver may be disseminated or still be present at the time of ablation or resection. In addition, recurrent disease may represent a new primary tumor in the persistent background of chronic liver disease. In turn, adjuvant therapy may treat micrometastatic disease and/or help prevent progression of de novo tumors.

Adjuvant immunotherapy

The IMbrave050 study was a randomized controlled phase III trial comparing surveillance to adjuvant atezolizumab and bevacizumab after curative intent resection or ablation[31]. Currently, this is the only published trial evaluating adjuvant ICIs for HCC. Patients in this study had "high risk" HCC defined by number of tumors, tumor size, vascular invasion, and/or poorly differentiated tumors. While the final results are not yet published, the trial had accrued 334 patients in each arm. On interim analysis presented in 2023, with a median follow-up of 17.4 months, the trial met its primary endpoint and demonstrated improvement in recurrence-free survival with adjuvant atezolizumab/bevacizumab (hazard ratio 0.72, $P = 0.012$)[32]. Of note, IMbrave050 did not demonstrate a difference in overall survival. This finding could be attributed to the high cross-over rate in the trial. Additionally, at the time of interim analysis, the overall survival data were immature, with only a 7% event rate. As such, long-term follow-up will lend more insight. Several ongoing phase III trials are evaluating the use of adjuvant immunotherapy for HCC following curative intent resection or ablation [Table 1]. Given the unique immune microenvironment of

Table 1. Ongoing phase III trials evaluating adjuvant immunotherapy for patients with HCC

Trial name	Experimental arm	Comparison arm	Patient population	Primary outcome	Trial number
	Atezolizumab/bevacizumab	Active surveillance	High-risk HCC and able to undergo curative intent surgery or ablation	Recurrence-free survival	NCT04102098
EMERALD-2	Durvalumab/bevacizumab	Durvalumab monotherapy or Placebo	High-risk HCC and able to undergo curative intent surgery or ablation	Recurrence-free survival	NCT03847428
CheckMate 9DX	Nivolumab	Placebo	High-risk HCC and able to undergo curative intent surgery or ablation	Recurrence-free survival	NCT03383458
KEYNOTE-937	Pembrolizumab	Placebo	HCC and able to undergo curative intent surgery or ablation	Recurrence-free survival, overall survival	NCT03867084
	Camrelizumab/rivoceranib	Active surveillance	High-risk HCC and able to undergo curative intent surgery or ablation	Recurrence-free survival	NCT04639180

the liver and the success of immunotherapy in patients with advanced HCC, this is an intriguing area of investigation.

COMBINATION OF LOCOREGIONAL THERAPY AND IMMUNOTHERAPY

Locoregional therapies, like ablative therapy or trans-arterial chemoembolization (TACE), can induce a peripheral immune response[33-36]. Locoregional therapy results in immunogenic cell death, which allows the tumor to essentially act as an *in situ* tumor vaccine. In contrast to standard apoptosis, immunogenic cell death releases damage-associated molecular patterns (DAMPs), which are phagocytized by dendritic cells and presented as antigens to T cells. This stimulates downstream secretion of interleukin-2 (IL-2), causing T cell expansion. These tumor-specific T cells seek out and kill cancer cells[37-39]. This process may restore the antitumor effects of the immune system. However, this immunomodulatory effect is transient, which explains why recurrence rates after ablative therapies can range from 50%-70%[6]. Upregulated immune checkpoint molecules, pro-inflammatory state of the tumor microenvironment, and increase in intratumoral T cell infiltration caused by locoregional ablative therapies may enhance the efficacy of ICIs and make the tumor and/or micrometastatic disease more susceptible to systemic therapy [Figure 3]. This synergistic effect between locoregional therapy and immunotherapy is currently being explored in early phase trials.

Studies evaluating combination immune checkpoint inhibitors and locoregional therapy

Duffy *et al.* were the first to evaluate the use of tremelimumab and radiofrequency ablation or TACE in 32 patients with advanced HCC[41]. The locoregional treatment was performed on day 36, early in the course of tremelimumab therapy. The authors demonstrated a 26% overall response rate (ORR). More importantly, they saw an increase in intra-tumoral $CD8^+$ T cells on biopsy of the tumors not treated with locoregional therapies. These data demonstrated that ablation could improve tumor immunogenicity and enhance the adjuvant effects of ICIs. Guo *et al.* published a phase II trial evaluating the use of sintilimab (PD-L1 inhibitor) and TACE among patients with HCC who had either BCLC stage A disease that exceeded the Milan criteria or BCLC stage B disease[42]. Among 60 patients in the study, 51 underwent surgery. Among surgical patients, median progression-free survival was not reached and 12-month progression-free survival was 76%. There was a complete pathologic response in 14% of surgical patients. These data demonstrated that neoadjuvant sintilimab with TACE for high-risk HCC may confer a survival benefit.

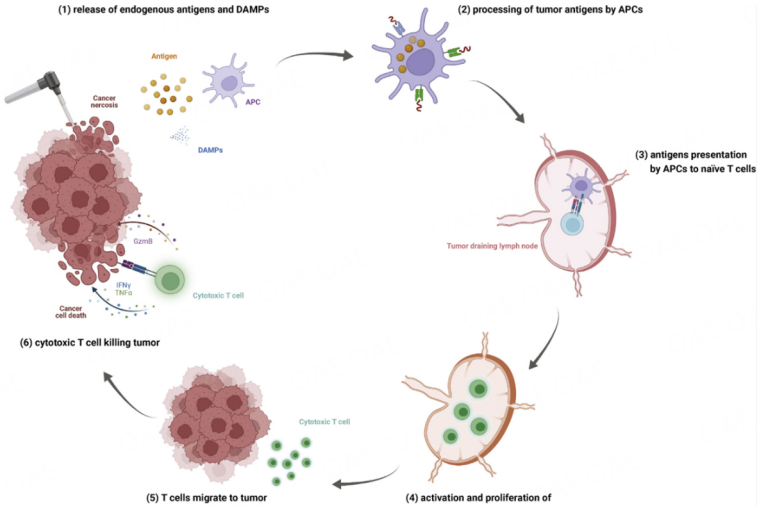

Figure 3. Overview of cancer immunity cycle in post-locoregional therapy. Locoregional therapies generate cytotoxic $CD8^+$ T cells that enhance the destruction of local and systemic cancers. Tumor destruction by locoregional therapy results in the release of several tumor antigens that can be processed by antigen-presenting cells and presented to naive T cells through major histocompatibility complex (MHC) class I molecules. The simultaneous release of DAMPs induces an adaptive immune response. Tumor-specific cytotoxic T cells were activated and proliferated in the lymph nodes, and then migrated into the circulatory system. APC: antigen-presenting cells; DAMPs: damage-associated molecular patterns; IFN-γ: interferon-gamma; Gzmb: granzyme B; TNF-α: tumor necrosis factor-alpha. Figure reprinted with copyright permission from reference[40].

In a retrospective study, surgery alone was compared with neoadjuvant triple therapy (Lenvatinib (tyrosine kinase inhibitor), PD-1 inhibitor, and TACE) followed by surgery for patients with high-risk HCC[43]. Triple therapy cohort had improved 12- and 24-month overall survival (100% and 85.7%, respectively) *vs.* surgery alone (73.7% and 48.7%, respectively). After propensity score matching, the same effect was noted for disease-free survival. In turn, the data strongly suggested that neoadjuvant Lenvatinib, PD-1 inhibitor, and TACE with surgical resection conferred a survival benefit over patients who underwent surgery alone. There is currently a prospective trial studying the use of Lenvatinib, sintilimab, and radiation therapy in the neoadjuvant setting for patients with HCC and portal vein thrombus (NCT05225116) and another trial evaluating neoadjuvant tislelizumab (PD-1 inhibitor) with radiation therapy in patients with resectable HCC (NCT05185531).

CONCLUSION AND FUTURE DIRECTIONS

Surgical resection remains the cornerstone of therapy for primary HCC. Many patients recur either due to micrometastatic disease at the time of surgery, or due to *de novo* disease that develops post-resection. While the risk of recurrence has been correlated with tumor-specific factors (grade, differentiation, lymph node status, tumor size, microvascular invasion, *etc.*), recurrence can occur in a range of patients independent of tumor features. As such, a combination of surgery and systemic therapy has increasingly been recommended to mitigate the risk of recurrence. Given the success of ICI for metastatic HCC, research has focused on immunotherapy in the neoadjuvant and adjuvant setting. In the upfront setting, ICI can potentially downstage unresectable tumors, allow for assessment of tumor response on postoperative pathology, and be more efficacious due to the presence of the *in vivo* tumor and increase in neoantigens. In the adjuvant setting, ICI may target micrometastatic disease or prevent tumorigenesis. In addition, the immunomodulatory effect of ablative or chemoembolization therapies on the tumor microenvironment may enhance the efficacy of ICIs.

Of note, a number of patients with HCC do not respond to ICIs. As such, considerable work is still needed in the laboratory setting using RNA sequencing and other approaches to help define changes in the immune microenvironment to identify subsets of patients who will best respond to ICIs. This is an exciting field and future large, multicenter clinical trials evaluating ICI are necessary to define the role of this therapeutic approach for patients with HCC.

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Author Contributions

Contributed to the concept, writing, and editing of this manuscript: Ruff SM, Pawlik TM

Availability of data and materials

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Conflicts of interest

Both authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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