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Integrating the new systemic treatment landscape and surgical therapy in hepatocellular carcinoma

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ABSTRACT

The treatment landscape of hepatocellular carcinoma has evolved rapidly within the last decade. Minimally-invasive techniques have reached a new level of safety, affording surgeons to pursue more aggressive treatment strategies to ultimately improve oncological outcomes. These procedures have been increasingly applied to treat patients with more progressed tumors and in select case even patients with advanced stage disease confined to the liver. Concomitantly, a dramatic increase in research into immunotherapy has altered the treatment paradigm in advanced disease stages, where the emerging treatment regimens can provide durable responses in a subset of the patient population for whom prognosis is dramatically improved. These treatments are now tested in early-stage disease to address the pressing unmet need of high recurrence rates after resection and in intermediate stage to complement the proven efficacy of intraarterial embolization in delaying progression. This review provides an in-depth discussion of these trends and describes how the treatment landscape has already changed and which impediments remain.

Keywords: Hepatocellular carcinoma, surgery, liver, chemotherapy, immunotherapy, systemic therapy

INTRODUCTION

Hepatocellular carcinoma (HCC) remains a leading cause of cancer-related mortality globally. Despite improved screening programs and refined understanding of pathogenesis and risk factors, incidence rates are on the rise with ~1.000.000 new cases expected annually starting in 2025 (1,2). As a unique feature in clinical oncology, both staging and treatment allocation are dictated by the Barcelona Clinic Liver Cancer (BCLC) criteria that distinguish between very early (0), early (A), intermediate (B) and advanced stage disease (C) taking into account tumor morphometrics (size and number of nodules) as well as liver function and general health, accounted for by ECOG performance score (3). Historically, curative treatment approaches have been applied almost exclusively in patients with early or very early-stage disease. The underlying rationale for this notion, as advocated by guidelines, is to pursue ideal patient selection in order to ensure optimal outcomes (4,5). When rigorously applied, surgical resection for patients with early stage tumors can provide a median overall survival (mOS) of approximately five years although recurrence rates remain high at 50-70% within the same time period (6). Optimal candidates can be considered for liver transplantation (LT) which can improve outcomes further, providing five year mOS of ~70% while reducing recurrence rates to 10-20% after five years (7).

1st Trend: The Extension of Operative Indication

Improving the outcomes of patients with HCC has been the subject of substantial clinical and translational efforts involving several specialities in the treatment algorithm of this disease. Regarding surgical therapies, advances have been mostly based on a technical level. Refined surgical techniques and in particular minimally-invasive procedures have enabled clinicians to push the limits considerably in terms of extending indications. Patients with a higher risk profile, resections which entail a higher degree of difficulty and patients with more progressed tumors are nowadays amenable to resection (8-10). Several retrospective studies have validated this strategy as surgery has been able to provide improved outcomes compared to alternative treatments that these patients would have otherwise

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defaulted to (11-13). The benefits provided by these technical advances have encouraged surgeons to extend indications beyond early-stage disease and increasingly consider those patients with multinodular or even advanced stage disease for resection. Indeed, in patients with intermediate stage disease amenable to resection, surgical treatment conveyed a marked improvement in 1-,3- and 5- year survival rates compared to TACE (71%, 42%, and 33% vs. 54%, 24%, and 16%) as shown in a high-impact metaanalysis (14). Concerning patients with macrovascular invasion, emerging evidence, predominantly from Asia, have supported a role of liver resection in selected patients (15,16). A registry study from the US reporting outcomes of >11.000 patients has lead to similar results; resection -when feasible- is associated with a strong benefit in mOS compared to systemic therapy (21.4 vs. 8.1 months). Certainly these data should be interpreted cautiously given the evident selection bias (17). Even more recently, robotic surgery has been increasingly performed in hepatobiliary surgery and has been shown to be non-inferior to standard laparoscopy although longer learning curves have been reported (18-20). However, this approach has key innate advantages; first, it affords the operating surgeon increased stability. Second, with the improved instrumental flexibility, high stability, and tremor filtration, it is particularly effective in a narrow situs. Magnified 3-d vision further increases the precision of surgical maneuvers, which makes the robotic approach particularly effective in hilar dissection (Figure 1). Isolated resections of liver segment I, the caudate lobe, are traditionally procedures hardly amenable to laparoscopy, whereas the properties of the robotic platforms enable surgeons to conduct this challenging resection strictly minimally-invasively. Figure 1 shows preoperative imaging from a 61-year-old male with biopsy-proven HCC in CP A cirrhosis outside of Milan criteria. The patient subsequently underwent robotic-assisted Segment I resection at our center.

Overall, these minimally-invasive procedures have been demonstrated to elicit a major reduction in morbidity while retaining high-quality oncologic outcomes (21). A recent metaanalysis, reporting outcomes of 6812 patients, has substantiated these notions; laparoscopic resection for HCC was associated with a significantly reduced morbidity and 30 day mortality [odds ratio (OR) 0.42; 95% CI 0.34-0.52 and OR 0.32; 95% CI 0.16-0.66] while achieving similar rates in R0 resection (22). Moreover, a large French multicenter study has highlighted

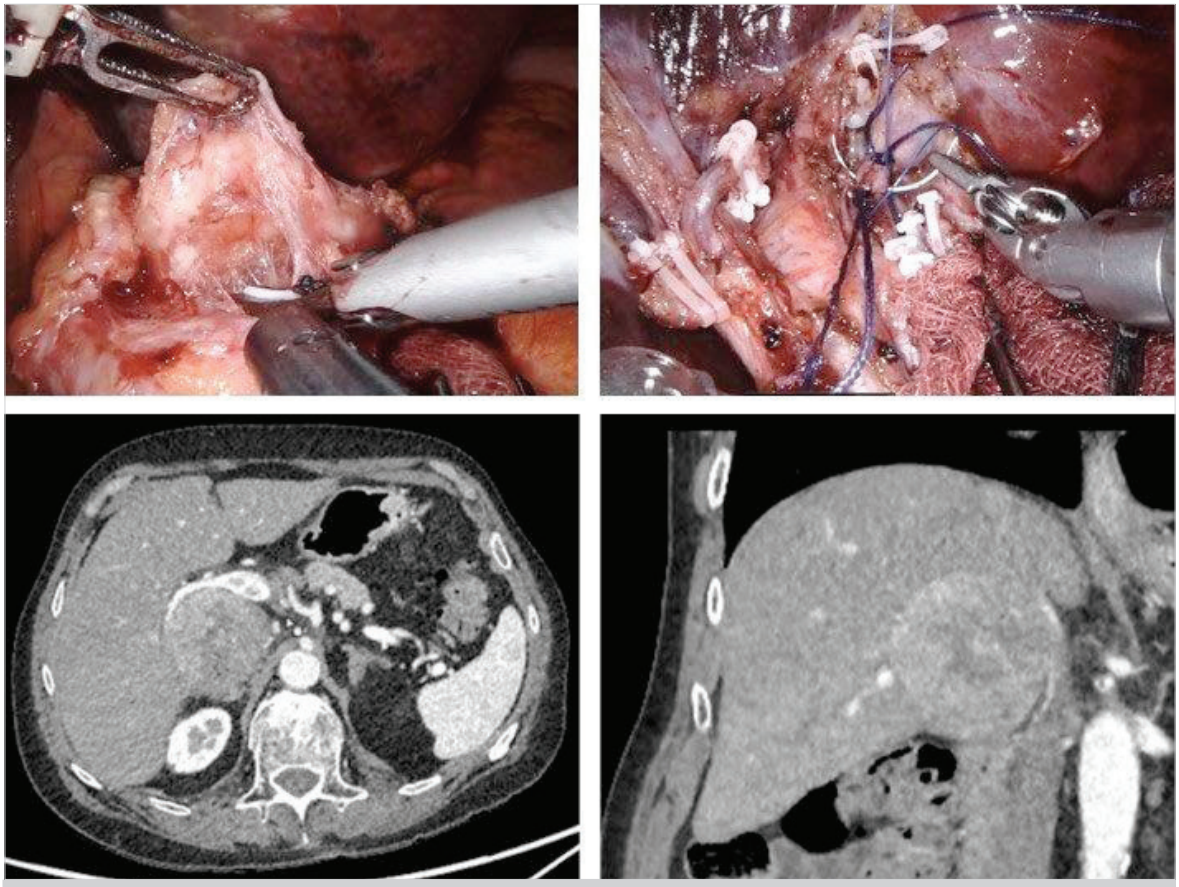

Figure 1. Top two panels: Hilar dissection using the robotic approach. Bottom two panels: Isolated biopsy-proven HCC in the caudate lobe prior to robotic-assisted segmentectomy.

the positive impact of laparoscopy on reducing the chance of post-hepatectomy liver failure (PHLF) (23).

These trends have been able to ameliorate the detrimental impact of organ scarcity on LT in HCC, where especially patients with compensated hepatic function are increasingly considered for resection as a definite treatment option. LT, on the other hand, is more and more reserved for patients where dismal liver function precludes resection or those where it offers a greater survival advantage compared to resection or intraarterial therapies.

Overall, this represents the first major trend in the clinical space; the extension of operative indication, heralded by technological advances and an improved understanding of morbidity risk. Excitingly, this trend is set to coalesce with the other major development in hepatocellular carcinoma; a fast-paced development of systemic therapy strategies.

2nd Trend: Extending Systemic Treatment Beyond Advanced Stage Disease

For the better part of the past two decades, the treatment of advanced stage HCC has been mostly limited to the use of receptor-tyrosine kinase inhibitors (TKI) that have been able to provide a modest survival benefit for a broad proportion of the patient population. In case of sorafenib, the first approved TKI, OS was extended by three months in both the SHARP and the AP trials (24,25). Likewise, lenvatinib, regorafenib and cabozantinib have provided similarly narrow benefits for patients (26-28). Within the past three years, however, treatment of advanced stage HCC has undergone a paradigm shift. As across cancer types, the use of immune checkpoint inhibitors (ICI) has revolutionized clinical care. Contrary to outcome patterns after TKI treatment, response patterns after ICI are highly heterogeneous; Indeed, only a proportion of the patient population exhibits radiological objective response (OR), where an outstanding survival advantage is achieved, whereas the majority of patients exhibit either stable disease or primary progressive disease (29). The size of the patient subset responding to ICI is variable across cancer type and guides whether single-agent ICI is a viable treatment option in a given field. In case of HCC, OR rates (ORR) are between 15-20% after single-agent anti-PD1 (30,31) but can be enhanced through combinatorial therapies; the combination of anti-PD-L1 atezolizumab and anti-VEGF bevacizumab has been demonstrated to elicit a mOS of beyond 19 months in patients with advanced stage and is now considered the standard of care (32). Dual ICI combination durvalumab and tremelimumab has also increased survival relative to sorafenib and represents an alternative in frontline (33). Further trials have investigated the viability of these combination treatments such as COSMIC312 and LEAP002 investigating cabozantinib + atezolizumab and lenvatinib + pembrolizumab, respectively (34,35). Although similar survival data was achieved, these trials have failed to meet their primary endpoint, in part due to unexpectedly well performing control arms. The central underpinning of the success of combination treatments has been the extension of the immune sensitive population through establishing a more ICI-conducive tumoral microenvironment by the auxiliary drug (36,37).

The treatment landscape of advanced HCC is thus proven to be highly dynamic at this point and efforts are shifting towards leveraging the established efficacy of these drugs in earlier disease stages to address major unmet needs that have prevailed for decades. In case of early stage disease, it is sought to reduce recurrence rates after resection or local percutaneous ablation which remain high at 50-70% after five years (38). Second, in intermediate stage disease, TACE is firmly established as the standard of care and has been virtually unchallenged in this position (39). Here ICIs have been increasingly tested as either standalone or complementary to TACE to prolong survival. To provide a better understanding of these trends the following sections will elucidate in more detail where these trends intersect, what the bottlenecks are and how the treatment landscape may change in the long run.

Reducing Recurrence Rates After Resection and Ablation

Adjuvancy

Reducing recurrence rates after resection and ablation remains a critically unmet need. The success of ICI-based systemic treatment in advanced stage HCC has imposed several investigations into its potential applications in earlier disease stages. The rationale behind this trend is that the efficacy of checkpoint inhibitors might be particularly pronounced in early-stage disease, where the tumor burden is still contained and malignant cells have acquired limited immune evasion mechanisms. As a cautionary tale, the same rationale has failed before, where the success of the TKI sorafenib has failed to elicit a meaningful benefit in an adjuvant setting and likewise brivanib which could not adjuvantly augment the efficacy of TACE (40,41). Interestingly, before the onset of checkpoint inhibitors, the only notable trial that reported a positive outcome in HCC that was designed for adjuvancy was a trial testing cellular immunotherapy by means of autologous cytokine-induced killer cells. The authors reported a significantly prolonged RFS although concerns regarding imbalanced study arms have hindered the adoption of these results by guidelines (42). The results, however, underscored the potential of immunotherapy to reduce recurrence rates following resection and ablation and may have contributed to the evolving treatment landscape of today.

The standard of care treatment for advanced HCC, anti-VEGF bevacizumab and anti-PD-L1 atezolizumab, convey a marked improvement in OS, PFS and objective response rates compared

to single-agent ICI and its success has prompted investigations in early disease stages to test its potential adjuvantly. Recently, results from IMbrave050 have been reported, where 668 patients were randomized to receive either active surveillance or atezolizumab + bevacizumab (43). At the first interim analysis, the primary endpoint of improving recurrence-free survival (RFS) was met, as treatment improved 12-month RFS from 65% to 78%. Expectedly, data for OS are immature at this point due to low frequency of events after a median follow-up of 17.4 months. Analysis of the Kaplan-Meier curves on RFS reveals a clear and early separation of the curves within the first year after treatment which leads to the reported 12-month RFS data. However, a convergence is observed in the subsequent period, when treatment is halted, which requires further long-term analysis. Given the trend, it remains unclear whether there will be any difference in two-year RFS, which would indicate the study regimen to delay early recurrence rather than preventing it in the first place. In HCC, recurrence within the first two years after resection are generally considered the results of remaining micrometastases whereas recurrence beyond that interval is regarded as a de-novo tumor, drawing into question the suggested duration of treatment. Given the high-crossover rate for those patients developing recurrence and the high rates of non-cancer specific mortality in HCC, it appears unlikely that a separation in OS curves will be observed in the future. Considering that RFS is unequivocally recommended as the primary endpoint for adjuvant trials in HCC, it is reasonable to assume that if a difference in RFS is maintained in follow-up analyses, atezolizumab and bevacizumab will be adopted by guidelines as the adjuvant treatment option of choice for those patients at high risk to develop recurrence. (As defined by the study protocol; 1 tumor >5 cm, >3 tumors, microvascular invasion, minor macrovascular invasion Vp1/Vp2 or Grade 3/4) (44). Further ongoing phase III RCTs testing adjuvant pembrolizumab (KEYNOTE-937), nivolumab (CHECKMATE 9DX), duvalumab ± bevacizumab (EMERALD 2) and toripalimab (JUPITER 04) are currently underway and will clarify the role of ICI in adjuvancy within the coming years.

Neoadjuvancy

The backbone of the current innovation in this setting is clearly based on checkpoint inhibitors. Strikingly, the application of these drugs to reduce recurrence rates might be most appropriate in a neoadjuvant setting: herein, the presence of the tumor can be leveraged as a priming load for antigen-presenting and ICI-boosted immune effector cells to convey antitumoral immunity and thus contain tumor growth or even induce necrosis prior to resection (Figure 2). This would render potential

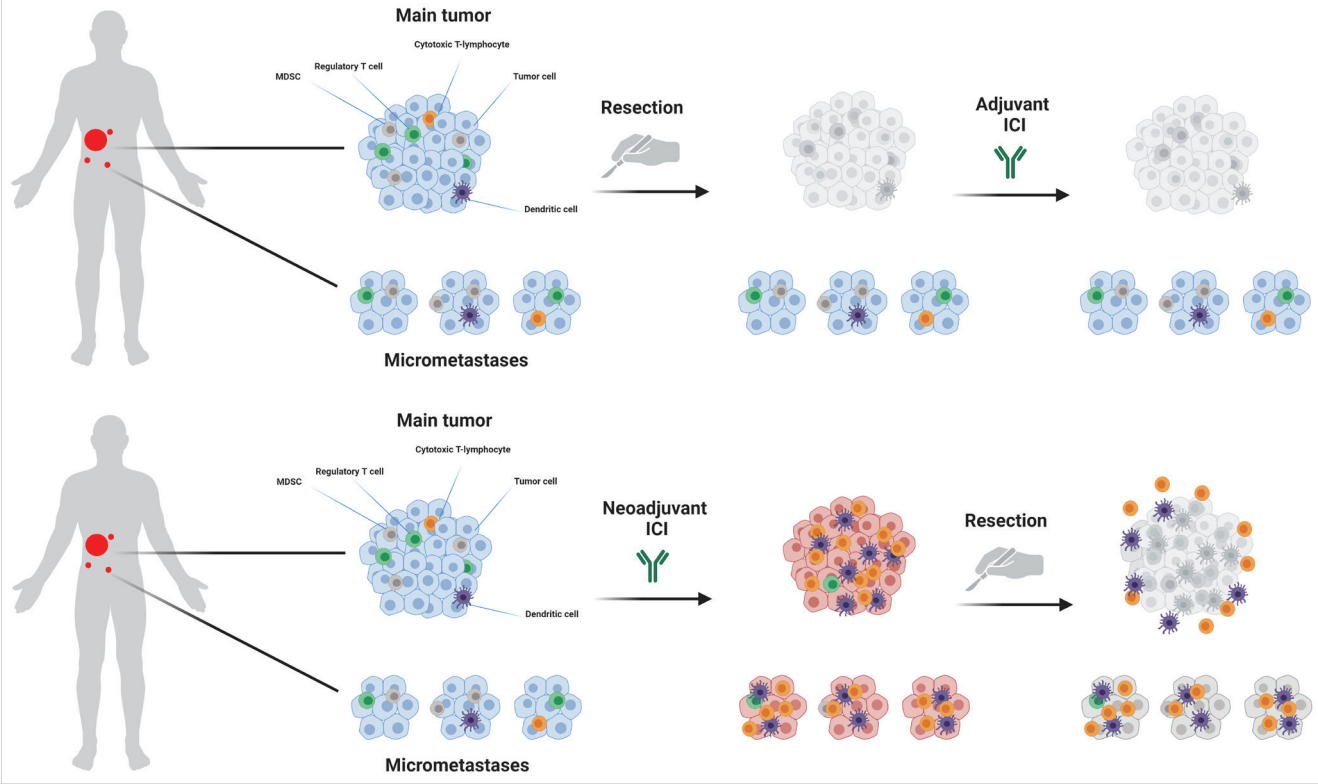

Figure 2. Adjuvant treatment with checkpoint-inhibitor based regimen might be less effective due to lacking induction of tumor-specific T cells and failure to eliminate micrometastasis leading to relapse (top panel). Neoadjuvant ICI, contrarily, may leverage the tumor as a priming load for effective antigen-presentation to induce effective immunosurveillance following resection.

micrometastases less viable following resection or ablation and empower T cells to conduct more effective immunosurveillance following resection. This hypothesis has been tested in tumors with more extensive history of ICI application such as melanoma where reports have found that neoadjuvant treatment leads to a more robust immune response with increased tumor-specific T cells (45). The neoadjuvant study design offers further advantages compared to a strictly adjuvant concept: investigators can assess response to treatment not just via imaging but also through histology, including the expansion of T cell infiltrates, tertiary lymphoid structures, which can be hubs of antitumoral immune response, and tumor cell viability. Pooled analysis from clinical trials in melanoma has shown that pathological assessment of response correlated with recurrence-free survival where patients with major pathological response (MPR= 70% tumor cell necrosis) having significantly longer RFS and disease-free survival (DFS) (46). Whether or not a patient displays MPR in the resection specimen may also guide clinical decision making regarding adjuvancy. In this scenario, patients with progression or only marginal tumor necrosis may not benefit from further postoperative treatment.

This would collaterally address a key caveat of ICI treatment, which is substantial heterogeneity in terms of response and the lack of clinically applicable biomarkers. From a research perspective, a neoadjuvant approach can also provide researchers with a unique opportunity to improve our grasp of the tumoral microenvironment and factors dictating response and resistance to treatment.

In HCC, neoadjuvancy is not yet integrated in routine clinical practice but very recently several high-quality studies have provided invaluable preliminary evidence of its feasibility. Kaseb et al. have reported a phase II study, where patients were randomized to receive either nivolumab (anti-PD1) every two weeks or nivolumab every four weeks + ipilimumab every six weeks (anti-CTLA4) for up to four doses prior to resection (47). Out of 20 patients undergoing resection, six had MPR in the specimen, with five of these patients developing complete tumor necrosis. The patients displaying MPR in turn, did not develop recurrence during the follow-up, whereas 50% of the remaining patients did, underscoring the potential of MPR as a surrogate endpoint in this clinical setting. Marron et al. have reported on the use of anti-PD1 agent cemiplimab in a further phase II study, where patients received two cycles of treatment for a total of six weeks prior to resection and eight further cycles following resection (48). The authors have found that 35% of patients had at least 50% of tumor cell necrosis and linked this with the rise of $CD8^+$ T cells from pre-treatment biopsies compared to the resection specimen. Transcriptomic analysis revealed several gene expression signatures related to Interferon-y signalling and active antigen presentation to be markedly enhanced among responding patients. In a further phase II trial, Xia et al. have reported on the perioperative use of apatinib (TKI) + camrelizumab (anti-PD1), which was able to elicit at least major pathological response in 4/18 patients (49). Nanostring-based transcriptome analysis also demonstrated inflammatory signalling and an intact antigen-presentation machinery to be enriched among responders.

More investigations in this field are currently underway (Table 1) with preliminary findings already reported that build on the available data from the published trials (50-52). With evidence building up and a refined grasp of predictors of response and resistance to ICI, the field is moving towards a point where biomarker-driven precision oncology in a neoadjuvant setting may be attainable in the mid-term.

Table 1. Selected phase II/III trials aimed at reducing recurrence rate in early stage HCC

Trial	Study Arm	Design	Primary Endpoint	High Recurrence Risk Only	Phase	Estimated Enrolment
PREVENT-2	Tislelizumab + Lenvatinib	Adjuvant	RFS	Yes	III	200
EMERALD-2	Duvalumab + Bevacizumab	Adjuvant	RFS	Yes	III	908
KEYNOTE-937	Pembrolizumab	Adjuvant	RFS	No	III	950
DaDaLi	Sintilimab + Bevacizumab	Adjuvant	RFS	Yes	III	246
SHR-1210-III-325	Camrelizumab + Rivoceranib	Adjuvant	RFS	Yes	III	687
JUPITER 04	Toripalimab	Adjuvant	RFS	No	III	402
CheckMate 9DX	Nivolumab	Adjuvant	RFS	Yes	III	545
JS001-020-Ib-HCC	Toripalimab + Lenvatinib	Neoadjuvant	MPR	No	II	40
NCT03916627	Cemiplimab	Neoadjuvant + adjuvant	MPR	No	II	73
NEOTOMA	Duvalumab + Tremelimumab	Neoadjuvant + adjuvant	Safety	No	II	28
NeoLeap-HCC	Pembrolizumab + Lenvatinib	Neoadjuvant + adjuvant	MPR	No	II	43
TALENT	Tislelizumab/Tislelizumab + Lenvatinib	Neoadjuvant + adjuvant	DFS	No	II	80

RFS: Recurrence-free survival, MPR: Major pathological response, DFS: Disease-free survival.

Enhancing The Efficacy of Intraarterial Therapies in Intermediate Stage

Transarterial chemoembolization is the stalwart treatment of intermediate stage HCC after it was established through a landmark metaanalysis by Llovet and Bruix in 2002 (39). Since then, however, little progress has been made, with the improvement in OS observed in the interval being mostly due to the success of post-progression therapies in the form of TKIs and ICI. Combination treatments trying to utilize the effectiveness of TKI together with TACE were futile and failed to show a meaningful survival benefit (53,54). Encouragingly, the onset of ICI is set to impact this disease stage as well. The rationale behind combining immunotherapy with intraarterial treatment appears sound; due to tumor cell necrosis evoked by TACE, a plethora of tumoral neoantigens are released that may be recognized by dendritic cells and thus function as a priming load for the immune system, which can then be boosted by ICI to exert antitumoral cyotoxicity. Moreover, locoregional treatments have been demonstrated to modulate immune properties within the tumor by repressing infiltrations of immunosuppressive T cells, particularly FOXP3 + regulatory T cells that have been implicated in immune evasion (55). The same rationale has been applied to earlier disease stages by combining radiofrequency ablation with ICI as well. Early experiences were published in 2017 when Duffy et al. reported feasibility through 32 patients receiving tremelimumab and undergoing either RFA or TACE. The combination interestingly provided higher response rates even outside the ablated zone supporting the notion that systemic treatment may augment locoregional strategies and vice versa. Further studies built on this premise and demonstrated that TACE + anti-PD1 may provide a survival benefit to either standalone treatment in intermediate and advanced stage, respectively (56,57). Similar results have been reported for transarterial radioembolization (TARE) which was able to elicit a response rate of 30.6% when combined with nivolumab compared to 20% as monotherapy (58). Recently, de la Torre et al. have reported on a phase II study also testing TARE + nivolumab in 42 patients, where an ORR of 41.5% was achieved and four patients were downstaged to subsequently undergo potentially curative liver resection.

Certainly, further evidence is needed to clarify the potential synergy between ICI and locoregional treatments. To this end, a recent press release has announced that the phase III EMERALD-1 study has met its primary endpoint of prolonging PFS in the interim analysis. In this trial 616 patients with unresectable HCC were randomized to receive either durvalumab + bevacizumab + TACE or TACE alone. Data regarding efficacy and safety are eagerly awaited as this combination could potentially represent a new standard of care for patients with intermediate stage HCC.

Several further trials testing TACE combined with single-agent ICI as well as doublets and triple therapies are currently ongoing with results expected within the next three years. A paradigm shift in the treatment of unresectable HCC would go beyond a simple change in the definitive treatment. Indeed, augmenting intraarterial strategies will likely have ramifications for patients on the waitlist for LT, where TACE is routinely applied as a bridging therapy to contain tumor growth. In this regard, preliminary evidence has been made available in recent years. Tabrizian et al. have reported on the feasibility of using ICI as a bridging therapy in a small series of nine patients from Mount Sinai (59). Herein, no rejections after LT were noted, a critical issue since ICI raise the risk of acute rejection when given after LT. Moreover, a third of patients developed at least 90% tumor necrosis following the bridging therapy. Clearly, several questions remain unanswered such as the timing of therapy with regard to LT and whether or not immunosuppressive regimens need to be adjusted accordingly.

Downsizing Through Systemic Therapy

Advanced stage disease remains the key domain of systemic treatment, where the application of checkpoint inhibitor-based combination treatment has driven a marked improvement in outcomes with tangible benefits for the patients. However, outcomes remain highly heterogeneous and a significant reduction in tumor burden as accounted for by the ORR is reached in approximately a third of patients, whereas the majority of patients exhibit stable disease and primary progression is observed in ~20% of the population (32). As a key feature of these novel treatments, response is sustained for a median duration of 18 months (60). In this interval, the reduction in tumor burden may open up therapeutic avenues with potentially curative treatments that the patients were previously not eligible for. For these select patients, the benefits conveyed by either resection or even transplantation is still attainable despite having previously advanced stage disease. Since approval of the current standard of care atezolizumab + bevacizumab or alternatively durvalumab and tremelimumab is relatively new, limited data is available on long term outcomes in patients achieving response and currently no consensus exists for pursuing potentially curative treatments in these patients. One small phase Ib study assessed the ability of cabozantinib and nivolumab to downsize irresectable non-metastatic HCC so that resection would be technically feasible and conducive from an oncologic perspective (61). A total of 15 patients were enrolled, most of whom had either multinodular disease or macrovascular invasion as initial contraindications towards surgery. Of those, 13 eventually underwent surgery, with one patient declining the procedure and one dropping out due to insufficient liver remnant function. 5/13 patients displayed MPR or complete pathologic response, whereas only

1/13 patients exhibited OR via imaging when using RECIST 1.1 criteria. This discrepancy underscores another disputed area in the field, where imaging criteria are simply morphometric readouts whereas histology workup can account for tumor cell viability and thereby provide a more granular picture of drug efficacy. This poses a challenge in clinical practice where routine serial biopsies after treatment are not available and recognizing a point in time where the tumor might be susceptible to anatomical targeting (i.e. ablation or resection) is thus entirely reliant on imaging. The biomarker analysis of the above-mentioned study highlighted the ability of the TKI cabozantinib to strengthen antitumor T cell responses, hence complementing the co-administered ICI nivolumab. Expectedly, the combination heavily enhanced the inflammatory infiltrate within the tumor in responding patients, where tumor cells accounted for ~30% of all cells within the specimen compared to 75% in non-responders. Despite these encouraging data, it has to be acknowledged that there is a paucity of trials exploring this highly important clinical setting and most evidence to date is derived from retrospective series. Zhang et al. reported about 224 patients receiving systemic treatment due to irresectable disease between 2019 and 2022. Twenty-six were deemed resectable after systemic treatment, for the most part featuring a TKI in combination with a checkpoint inhibitor as well as either TACE or hepatic artery infusion therapy (HAIC). Disease control in this patient population was 100%, with an ORR of 77% and all patients were still alive after a median follow up of 13 months (62). Further small series support the conclusion that for a proportion of patients with irresectable or advanced stage disease, ICI-based combo treatments may offer a path towards subsequent potentially curative treatments (63,64). It has to be mentioned that this path is currently very narrow and the vast majority of patients undergoing systemic treatment for advanced stage disease will at some point progress and receive 2nd and 3rd line therapy. However, given the improving grasp of determinants of response and resistance to systemic treatments in HCC, as well as the introduction of further drugs aimed at overcoming resistance, it is reasonable to hypothesize that this patient subset could expand in the coming years (65-68). For respective patients the line embedded in staging and treatment allocation that separates palliative and curative intent can hopefully blur through those trends.

CONCLUSION

Recent years have seen a steady improvement in outcomes for patients with HCC across disease stages. Two key developments have driven this trend; first is the refinement of anatomical approaches with new surgical techniques that enable to push the limits in terms of indications while maintaining acceptable safety outcomes. To this end, minimally-invasive resections have been adopted as the default treatment for early stage HCC by several high-volume centers globally, while liver transplantation, as a modality dependent upon a limited resource, is increasingly reserved to treat either younger patients or those with compromised hepatic function. Likewise, the therapeutic armamentarium of percutaneous ablative techniques has increased with techniques such as microwave ablation challenging radiofrequency ablation as the mainstay for very early-stage tumors and new modalities emerging to add layers of complexity to treatment allocation. The second major development has been the changing treatment paradigm in advanced stage fuelled by a drastic increase in both clinical and translational research. While further tyrosine kinase inhibitors have been established, the onset of checkpoint inhibitor-based immunotherapy has revolutionized systemic therapy. The ripple effects of new systemic treatment combinations are already seen in earlier disease stages, where their efficacy is utilized to reduce recurrence rates after resection or ablation and augment established intraarterial therapies to delay progression. Critically, these treatments have teased out a yet small patient population with progressed tumors that may undergo curative-intent treatment options after successful downsizing. Unfortunately, the near absence of clinically applicable predictive biomarkers to maximize the effectiveness of drug deployment remains a glaring unmet need. Likely, further development of synergistic combinations and their precision-oncology based application across disease stages will shape the trial landscape of this decade.

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BÜTÜNLEYİCİ DERLEME-ÖZET
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Hepatoselüler karsinomda yeni sistemik tedavi seçenekleri ve cerrahinin tedavi planına entegrasyonu

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ÖZET

Hepatoselüler karsinom tedavisi son on yılda hızlı bir şekilde gelişmiştir. Minimal invaziv teknikler güvenle uygulanmaya başlanmış ve cerrahların onkolojik başarıyı geliştirmek için daha agresif tedavi stratejileri izlemelerine olanak sağlamıştır. Bu ameliyatlar, ilerlemiş tümörleri olan hastaları ve hatta bazılarında karaciğerle sınırlı ileri evre hastalığı olan hastaları tedavi etmek için giderek daha fazla uygulanmaktadır. Buna paralel olarak, immünoterapi araştırmalarındaki dramatik gelişmeler, ortaya çıkan yeni tedavi rejimleriyle prognozu önemli ölçüde iyileştirmekte ve hasta popülasyonunun bazı alt kümelerinde kalıcı yanıtlar sağlayabilmektedir. Bu nedenle ileri hastalık evrelerindeki tedavi paradigması değiştirmektedir. Bu tedaviler erken evre hastalıkta, rezeksiyon sonrası yüksek nüks oranlarını önlemek, orta evrelerdeyse intraarteriyel embolizasyonun kanıtlanmış etkinliğini tamamlamak ve ilerlemeyi geciktirmek amacıyla denenmektedir. Bu derleme, bu trendlerin derinlemesine bir tartışmasını sunmakta ve günümüzde tedavi planlarının nasıl değiştiğini ve önümüzde hangi engellerin kaldığını açıklamaktadır.

Anahtar Kelimeler: Hepatoselüler karsinom, cerrahi, karaciğer, kemoterapi, immünoterapi, sistemik tedavi

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