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Review Article

Improving the Conversion Success Rate of Hepatocellular Carcinoma: Focus on the Use of Combination Therapy with a High Objective Response Rate

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Abstract

The high mortality rate in hepatocellular carcinoma (HCC) is partially due to the fact that a significant number of patients are diagnosed at an intermediate or advanced stage, with surgical treatment options unavailable. Conversion therapy, which involves both locoregional and systemic treatments, has the potential to downstage tumors in selected patients with initially unresectable HCC, thereby making surgical treatment a possibility and potentially increasing long-term survival. To optimize the conversion rate, it is necessary to maximize successful conversions and clearly define the target population for conversion treatment through a collaborative effort. In this review article, we summarize the clinical experience and evidence for conversion therapy in patients with 'potentially resectable' HCC from four perspectives: 1) defining the target population for conversion therapy, 2) selecting the appropriate conversion strategy, placing emphasis on the utilization of combination therapy that exhibits a significant objective response rate, 3) determining the timing and urgency of surgical resection, 4) promoting the adoption of a multidisciplinary team model. The authors are optimistic that with the continuous progress in treatment and a deeper understanding of HCC, the success rate of HCC conversion therapy will increase, and the overall survival of HCC patients will be prolonged.

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Keywords: Hepatocellular carcinoma; Conversion therapy; Conversion rate; Targeted population; Combination therapy.

Abbreviations: ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; anti-VEGF, anti-vascular endothelial growth factor; BCLC, Barcelona Clinic Liver Cancer; CNLC, China liver cancer staging; FLR, future liver remnant; HAIC, hepatic arterial infusion chemotherapy; HCC, hepatocellular carcinoma; ICIs, immune checkpoint inhibitors; MDT, multidisciplinary team; NAFLD, non-alcoholic fatty liver disease; ORR, objective response rate; pCR, pathological complete response; PVE, portal vein embolization; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; T+A, atezolizumab plus bevacizumab; TIME, tumor immune microenvironment; TKIs, tyrosine kinase inhibitors.

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Introduction

In 2020, hepatocellular carcinoma (HCC) ranked 6th in incidence and 3rd in mortality among all malignant tumors worldwide.[1] Despite the possibility of achieving long-term survival through curative treatments such as surgical resection, transplantation or ablation, a majority of patients in China are unfortunately diagnosed at an intermediate or advanced stage, resulting in only 30% being eligible for curative treatment and a 5-year survival rate of only 14.2%.[2] This lags behind other developed countries such as Japan, South Korea, Europe, and the United States.

However, advancements in drug treatment, local treatment, and concepts have made it possible to perform conversion treatment for patients who are initially diagnosed but cannot be resected. This transformation into a resectable lesion has proven to offer survival benefits, with some studies reporting a 5-year survival rate equal to that of initially resectable patients.[3]

Theoretically, the conversion success rate is equal to the number of successful conversions divided by the number of target conversions, multiplied by 100%. In order to improve the conversion rate, it is essential to not only maximize the number of successful conversions but also to accurately define the target population for conversion treatment. On one hand, optimization of conversion treatments is a widely discussed topic in clinical research, and various methods exist to enhance the outcome. On the other hand, defining the target population in a clear and uniform manner is equally important. Excluding patients with low or no conversion potential is crucial in this regard. This article delves into these two crucial aspects, drawing upon international literature and clinical experience, to shed light on how to improve the HCC conversion success rate (Fig. 1).

Defining the target population for conversion therapy

Definition of conversion therapy

The "Guidelines for the Diagnosis and Treatment of Hepa-

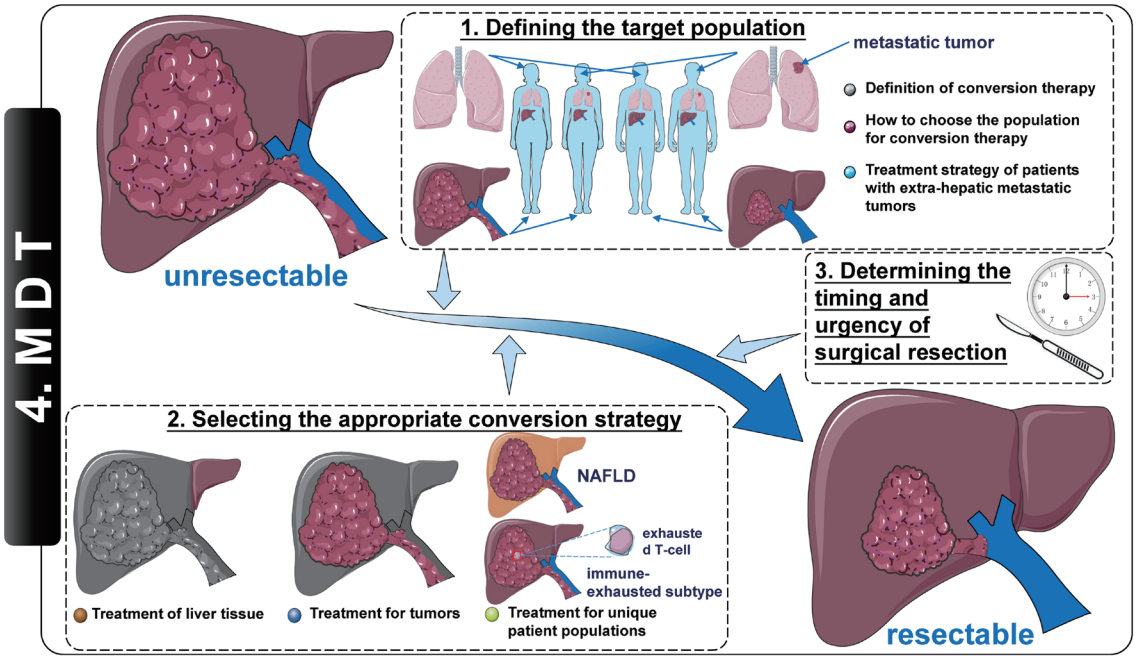

Fig. 1. Illustration for conversion therapy in patients with "potentially resectable" hepatocellular carcinoma from four perspectives. 1) defining the target population for conversion therapy, 2) selecting the appropriate conversion strategy, 3) determining the timing and urgency of surgical resection, and 4) promoting the adoption of a multidisciplinary team model. MDT, multidisciplinary team; NAFLD, non-alcoholic fatty liver disease.

tocellular Carcinoma (2021 Edition)"[4] and "Liver Cancer Conversion Therapy Chinese Expert Consensus (2021 Edition)"[5] succinctly state that it involves the transformation of unresectable HCC into resectable HCC, thereby enabling the complete removal of the tumor. The objective of conversion therapy is to attain a radical excision of the lesion.

How to choose the population for conversion therapy

However, the determination of the suitable patient population remains an area of contention. There are debates regarding the definition of inoperability, which currently encompasses both surgical and oncological considerations. Surgically unresectable HCC refers to inadequate liver volume (future liver remnant, FLR) or the impossibility of obtaining adequate cutting margins or achieving R0 resection. Oncologically unresectable HCC, on the other hand, refers to the inability to achieve optimal oncological outcomes after surgery, an effectiveness that is not as robust as that achieved through non-surgical treatments.[5] This standard remains a topic of debate and there is a lack of data-driven evidence as to whether surgery is a more advantageous approach than other modalities.

Additionally, the "China Expert Consensus on Conversion Therapy for Liver Cancer (2021 Edition)" designates patients with surgically unresectable China liver cancer staging (CNLC) stage Ia-IIa and those who are either surgically or oncologically unresectable CNLC stage IIb and IIIa as the intended recipients of conversion therapy.[5] It is not always feasible to extend this designation to all patients. Patients in the CNLC stage Ia, Ib, and IIa present with a limited number of tumors and thus hold considerable promise for conversion therapy. Conversely, patients with CNLC stages IIb and IIIa display a higher degree of heterogeneity and some may have forfeited both surgical resection opportunities and the possibility of being "potentially resectable" at diagnosis. For instance, the subgroup of intermediate-stage liver cancer defined as diffuse infiltrative and extensive bilateral lobar involvement in the updated 2022 Barcelona Clinic Liver Cancer (BCLC) guidelines is directly recommended for systemic therapy and may pose significant challenges in achieving successful conversion.[6] CNLC stage IIIa patients with Vp3/4 portal vein thrombosis are typically not considered "potentially resectable", but they are included in the ongoing TALENTop study to assess the feasibility of conversion therapy.[7] The final outcome of this study is required to affirm the success rate and clinical benefits of conversion therapy for this particular patient population.

In general, there is as yet no widely accepted criterion for determining "potentially resectable" cases, which tends to vary based on the clinician's experience. Thus, it is advisable to adopt a multidisciplinary team (MDT) approach in clinical practice to determine the status of "potentially resectable" and "no-conversion opportunity" status of patients and devise individualized treatment plans based on a comprehensive evaluation. This approach can help to increase the success rate of conversion therapy and optimize treatment options. For "potentially resectable" patients, the main evaluation standard during the conversion period should be the objective response rate (ORR) based on the RECIST 1.1 criteria, and aggressive, multi-modal treatments should be utilized to preserve liver function while maximizing the ORR. For "no-conversion opportunity" patients, the focus should shift to maximizing overall survival through anti-tumor treatments.

Treatment strategy of patients with extra-hepatic metastatic tumors

Some experts contend that those initially deemed unresectable yet still harboring the chance for curative treatment after intervention comprise the conversion population, and that CNLC stage IIIb patients with concomitant extrahepatic metastases, particularly oligometastases, represent an

ideal group for conversion therapy.[8,9] Advances in surgical techniques have made absolute surgical contraindications increasingly rare. A long-term study of 5,206 HCC patients with concurrent extrahepatic metastasis revealed a 5-year survival rate of 36% among those who met surgical criteria and underwent metastasis removal, compared to a mere 3% among those who did not receive removal, highlighting the potential for improved overall survival through removal.[10] This study only considers the surgical perspective and conversion therapy aims at converting unresectable original and/or metastatic lesions into resectable ones that can be surgically removed after comprehensive treatment. A study detailed nine patients with liver lesions deemed unresectable and concurrent extra-hepatic oligometastasis who underwent combinational target drug and immunotherapy and became eligible for surgery, resulting in the removal of both liver lesions and extrahepatic metastases.[11] Three of these patients achieved a pathological complete response (pCR), highlighting the potential benefit of simultaneous removal of liver and extrahepatic lesions post-conversion treatment, especially in the case of oligometastasis.

However, current research on surgical resection for patients with distant metastatic lesions primarily comes from small sample studies and lacks substantial evidence for treating these patients specifically. Although systemic treatment may render CNLC stage IIIb patients' hepatic and extrahepatic lesions surgically resectable, whether surgical treatment offers any oncological benefits remains to be determined through larger clinical studies.

In the medical community, it is widely recognized that patients with CNLC stage IIIb are deemed unresectable due to the biology of the tumor. Despite complete necrosis of the liver and metastatic lesions after systemic therapy, the risk of recurrence and metastasis persists. As a result, the survival benefits of surgical resection for these patients may not necessarily surpass those achieved through non-surgical treatment options.[12] The decision to choose surgery or continue with systemic treatment, possibly combined with local treatment, when considering conversion therapy for patients with concurrent liver metastasis is still being studied in ongoing clinical trials.

Selecting the appropriate conversion strategy

The field of conversion therapy encompasses a range of treatments aimed at both the liver tissue and the tumors. The primary objective of treatments that target the liver tissue, such as portal vein embolization (PVE) and associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), is to increase future liver remnant (FLR). On the other hand, treatments aimed at reducing the size of tumors and eliminating metastasis can be achieved through local therapies, systemic therapies, or a combination of both. Local therapies include modalities such as transarterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC), transarterial radioembolization (TARE), and radiotherapy. Systemic therapies encompass a broad range of approaches including tyrosine kinase inhibitors (TKIs), anti-vascular endothelial growth factor (anti-VEGF) agents, and immune checkpoint inhibitors (ICIs).

Treatment of liver tissue

The key to a successful surgical outcome is maintaining an adequate FLR. Conversion therapy aims to augment the FLR when it is inadequate. PVE is commonly used in clinical practice and has a high conversion rate of 60% to 80%, with low complication rates of 10% to 20%.[13] Nonetheless, the growth of FLR following PVE may take 4 to 6 weeks, during which up to 20% of patients may miss the surgical window due to either tumor progression or insufficient FLR growth.[14] Conversely, ALPPS offers rapid FLR augmentation within two weeks, reducing the risk of progression during the conversion period, with a conversion success rate of 95% to 100%.[15,16] However, ALPPS has a higher rate of perioperative complications compared to PVE.[17] Some researchers suggest choosing the approach based on the FLR-to-standard liver volume ratio, with ALPPS being chosen when the ratio is less than 30% and PVE when it falls between 30% and 40%.[16] Additionally, the integration of local or systemic therapy targeting the tumor, if liver function permits, during PVE or ALPPS transformation therapy can further increase the success rate of conversion.[18] It is also crucial to provide supportive treatment and complications management for CNLC stage II patients awaiting surgery to prevent the failure of conversion therapy due to perioperative complications.

Treatment for tumors

Achieving a high ORR according to RECIST 1.1 standards while preserving liver function is crucial for the success of tumor conversion therapy. Previous research has shown that the ceiling effect of ORR is difficult to overcome with single local or single targeted therapy or immunotherapy treatment.[19] Thus, a combination approach is necessary to overcome this limitation. The most frequently employed combination models are systemic-systemic and systemic-local, with the latter delivering a higher success rate in conversion and an increased ORR, by overcoming TKI resistance and immunological tolerance.

Systemic-systemic combination therapy

Monotherapy, whether targeted or immune-based, has limited success in terms of ORR, typically not exceeding 20%.[20] However, combination therapy has been shown to increase ORR through a synergistic effect. Studies have demonstrated the superiority of targeted therapy and ICI combinations, such as the "atezolizumab plus bevacizumab" (T+A) regimen reaching 27.3% ORR in the IMbrave150 study,[21] and the "lenvatinib plus permbrolizumab" combination with a 36% ORR in the Keynote524 study.[22] In China, the combination of "sintilimab plus a bevacizumab biosimilar"[23] and "camrelizumab with apatinib"[24] resulted in ORR of 20.5% and 34% respectively. Additionally, the combination of immunotherapy has shown promising results, with the "nivolumab plus ipilimumab"[25] achieving an ORR of 32% in the Checkmate040 study, and "tremelimumab plus durvalumab"[26] achieving an ORR of 24% in the Himalaya study. These findings emphasize the importance of systemic combination therapy in the treatment of HCC and its necessity in conversion therapy.

Local plus systemic treatment

The incorporation of local therapy can further enhance the ORR, conversion success rate, and reduce conversion time.[27] In the realm of liver cancer treatment, TACE was one of the earliest conversion therapies utilized, but it had some limitations. Its conversion success rate was relatively low, around 20%, and repeated TACE treatments could result in liver function deterioration and increase the risk of postoperative liver failure.[28]

The role of TARE as a conversion therapy for patients with unresectable HCC has been the subject of a comprehensive literature review by Cucchetti *et al*.[29] This review suggests that TARE can result in substantial tumor reduction and lead to the growth of the contralateral lobe. The complete re-

Table 1. Ongoing phase III clinical trials of interventional combination systemic therapy

	Treatment Plan	Registration Number	Name	Status
1	TACE + Durvalumab +/-Bevacizumab vs TACE	NCT03778957	EMERALD-1	ongoing
2	TACE + Lenvatinib + Pembrolizumab vs TACE	NCT04246177	LEAP 012	ongoing
3	TACE + Nivolumab +/-Ipilimumab vs TACE	NCT04340193	CheckMate 74W	ongoing
4	TACE + Nivolumab vs TACE	NCT04268888	TACE-3	ongoing
5	TACE + Atezolizumab + Bevacizumab vs TACE	NCT04712643	TALENTACE	ongoing
6	HAIC + H101 vs HAIC	NCT03780049	HCC-S032	ongoing
7	HAIC + Apatinib + Camrelizumab vs Apatinib + Camrelizumab	NCT05313282	TRIPLET-III	ongoing
8	TACE + Durvalumab + Tremelimumab +/- Lenvatinib vs TACE	NCT05301842	EMERALD-3	ongoing

TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy.

sponse rate for HCC patients receiving TARE was about 10%, with an ORR of 40%. Moreover, the contralateral hypertrophy reached up to 40%. A retrospective analysis over a 9-year period of patients treated with TACE or TARE also shows that TARE has several advantages, including an improved response rate, prolonged progression time, and decreased toxicity compared to TACE.[30] Additionally, TARE's capability to induce hypertrophy of the future liver remnant on the contralateral side may prove beneficial for patients who are potential candidates for resection with a small liver remnant.[31] The prospect of incorporating external beam radiotherapy with TACE as a downstaging strategy has also been evaluated, demonstrating that a combination regimen incorporating radiotherapy may represent a valuable adjunctive treatment option for patients with potentially resectable HCC.[32] However, it should be noted that TARE has yet to be widely adopted in some countries at this time, including China.

The limitations of TACE as a conversion therapy are partially addressed by HAIC. Several studies have demonstrated that FOLFOX-HAIC exhibits a high ORR, especially for patients with a high tumor burden and impaired liver function, where TACE treatment is less effective. The use of HAIC leads to rapid tumor shrinkage and significant regression of the tumor thrombus, improving the conversion success rate.[33,34] Additionally, HAIC has few adverse reactions, and patients are highly compliant and more confident in accepting subsequent treatments. Standardization of HAIC is also easier compared to TACE, facilitating its popularization and promotion. However, it should be noted that HAIC requires multiple treatments, often four or more courses, to achieve treatment goals. As such, combining systemic treatment with TACE or HAIC is expected to further enhance conversion efficiency.[8]

TACE or HAIC in combination with TKI has a demonstrated high ORR in previous clinical trials. The ORR of TACE combined with sorafenib in the TACTICS study was 71.3%,[35] while another study reported that the ORR of HAIC combined with sorafenib was 41.8%.[36] With the increasing use of ICIs, particularly the success of the IMbrave150 study, clinical trials combining TKI and ICI with interventional therapy have multiplied, leading to improved overall survival and ORR and an increased conversion success rate. A retrospective study revealed that the ORR of HAIC combined with lenvatinib and toripalimab (a PD-1 antibody) for the first-line treatment of advanced HCC was 59.2%.[37] In 2022, two updated trials investigating HAIC combined with TKI and ICI therapy from ASCO also produced favorable therapeutic results. The TRIPLET study's ORR of HAIC combined with "camrelizumab plus apatinib" was 66.7%, with a conversion success rate of 66.7%,[38] while the IBI305 study's ORR of HAIC combined with "sintilimab plus a bevacizumab biosimilar" was 70.96%.[39] Currently, the ORR of interventional therapy combined with TKI and ICI reported in clinical studies is commonly above 50%, signaling a new era for conversion therapy.

Despite the many combined treatment options available, there is no uniform consensus on the preferred combination. Numerous prospective clinical trials of interventional combined systemic treatment are still underway (Table 1). These results are expected to further improve the conversion success rate.

Treatment for unique patient populations

In general, a combination of interventional, TKI, and ICI therapies has the potential to increase the success rate of conversion. However, for specific patient populations, this combination may not necessarily lead to optimal efficacy. Particularly in the era of immunotherapy, the uniqueness of the tumor immune microenvironment (TIME) in some patients may render immunotherapy ineffective. Studies have shown that non-alcoholic fatty liver disease (NAFLD) induced HCC exhibits a poor response to immune therapy due to the accumulation of exhausted CD8+ T cells within the tumor.[40] Additionally, based on immune cell infiltration in the TIME, HCC can be classified into the inflamed class and the immune-tolerant class. The inflamed class can further be divided into the immune-active subtype and the immune-exhausted subtype.[41] Patients in the immune-tolerant class and the immune-exhausted subtype show a poor response to immune therapy, and it is recommended to avoid ICIs for these patients.

The precise method of converting liver tissue or tumor remains under exploration and it is unclear which approach yields the best conversion results. Nonetheless, an optimal conversion treatment plan should focus on maximizing FLR increase or tumor shrinkage and necrosis while minimizing liver function impact and adverse events, with the goal of reaching conversion resection standards in a timely manner.[42]

Determining the timing and urgency of surgical resection

The appropriate timing of surgical intervention after successful conversion therapy is a matter of debate in clinical practice, and it can have a substantial impact on the conversion success rate. Some believe that the survival benefits for patients after conversion therapy are related to the extent of lesion reduction, with greater lesion relief resulting in longer survival. As a result, it is recommended to perform surgical

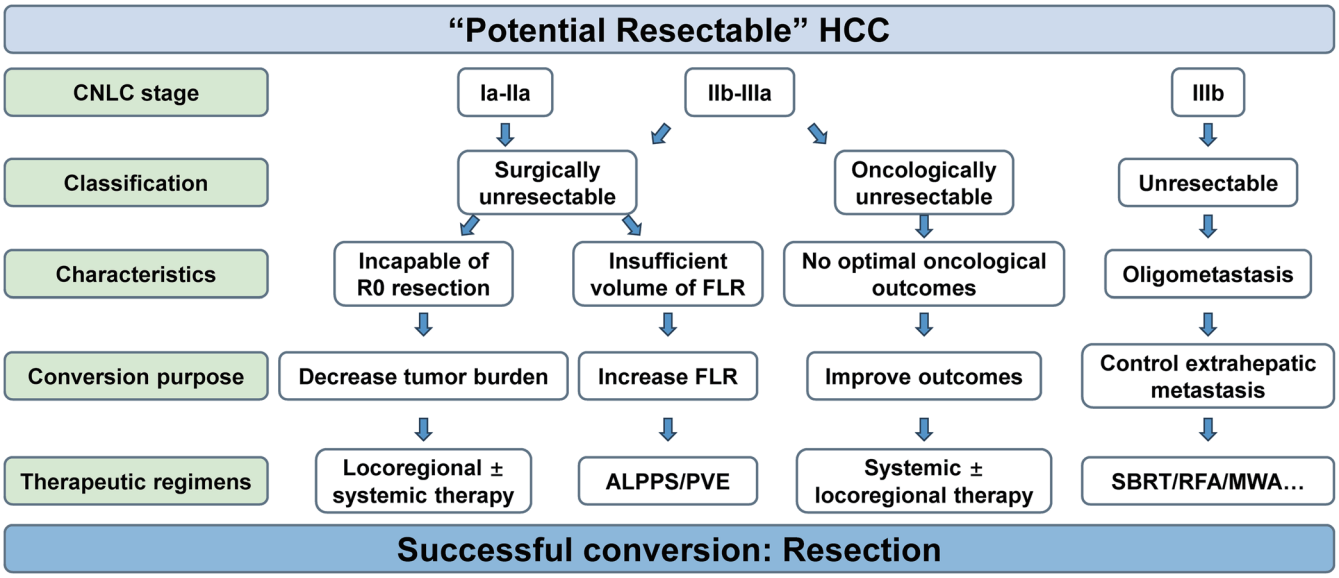

Fig. 2. A therapeutic algorithm of conversion therapy. HCC, hepatocellular carcinoma; CNLC, China liver cancer staging; FLR, future liver remnant; ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; PVE, portal vein embolization; SBRT, stereotactic radiotherapy; RFA, radiofrequency ablation; MWA, microwave ablation.

resection after the maximum therapeutic effect of conversion therapy has been achieved. Conversely, others argue that surgery should be performed as soon as the lesion is deemed surgically resectable after conversion, as waiting too long may result in the loss of surgical opportunities. At present, there is limited evidence to support the optimal timing of surgical resection, and different medical centers have varying approaches. However, to enhance the conversion success rate, it is advisable to move forward with surgery promptly to avoid missing surgical opportunities during the waiting period.[43]

Despite the improvement in HCC treatment efficacy, particularly through combination therapies, an increasing number of patients are showing radiologic CR or partial response. For instance, the ORR in the TACTICS study combining TACE with sorafenib and the "T+A" regimen in the IMbrave150 study were 71.3% and 27.3%, respectively. However, the proportion of patients undergoing surgical resection in these studies was only 2.1% and 1.5%, respectively. A substantial number of patients eligible for resection still choose to continue with systemic treatment, leading to a low conversion success rate.[21,35] Consequently, the necessity of further surgical resection in such conditions remains a matter of debate. Currently, the prevailing view is that even if radiologic CR is achieved through conversion therapy, further surgical resection is still necessary. A retrospective study showed that after TACE conversion, surgery or transplantation was performed in patients with radiologic CR up to 30%, but pCR was only 10%.[44] This indicates that even if radiologic CR is achieved, residual viable tumor cells may still be present and can cause future recurrence if not removed. Hence, for patients who receive the conversion treatment and achieve radiologic CR, it is recommended to undergo resection to increase the success rate of conversion therapy, reduce the risk of future recurrence, and ultimately benefit the patient's survival.[27]

Promoting the adoption of a multidisciplinary team (MDT) model

In the field of HCC treatment, a multidisciplinary approach, or MDT model, is essential. The complexity of the disease and the various therapeutic options necessitate collective decision-making and the development of personalized treatment plans. To ensure successful conversion therapy, the MDT model must facilitate effective communication and collaboration among its members. This requires a stable MDT with efficient communication channels. Implementing such efforts will enhance not only the conversion treatment process, but also the overall management of HCC patients.

Conclusion

The emergence of new treatments for HCC has emphasized the importance of conversion therapy in the management of the disease. Recently, Vitale *et al*. have introduced a novel variant of therapeutic hierarchy known as the converse therapeutic hierarchy.[45] In contrast to the conventional therapeutic hierarchy, which primarily focuses on the survival benefits of HCC treatments, the converse therapeutic hierarchy highlights the potential of systemic and locoregional therapies to improve the feasibility and effectiveness of radical therapies. Although further clinical trials are necessary to validate these findings, observational studies have indicated that this approach, combining locoregional therapy with systemic therapy, could potentially achieve a promising conversion rate to liver resection. This perspective challenges the traditional treatment hierarchy by recognizing the potential of systemic therapies to improve the biology of aggressive tumors and broaden the indications for radical therapies. Despite progress in HCC treatment, optimizing conversion therapy remains a challenge. The lack of a widely accepted standard for conversion therapy highlights the need for more extensive clinical studies. A multidisciplinary approach is essential in determining the best patient population for conversion therapy and customizing treatment plans. The careful selection of a combination therapy with a high overall response rate is crucial in improving the success of conversion. Additionally, we propose a therapeutic algorithm (Fig. 2), grounded in the most up-to-date knowledge, that could serve as a valuable

framework for optimizing conversion treatment in patients with HCC. The authors are optimistic that, as treatment options continue to develop and our understanding of HCC treatment grows, the success rate of conversion therapy for HCC will increase and the overall survival of HCC patients will be prolonged.

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Conflict of interest

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Author contributions

Conception and study design: QFC, NL, MZ; Investigation and data curation: QFC, SC; Methodology and formal analysis: QFC, SC; Interpretation of results: QFC, SC; Writing-original draft: QFC, SC; Writing-review and editing: QFC, MC, NL, MZ. All authors reviewed and approved the final draft.

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