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Contents

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Contents

ABOUT COVER

AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

INDEXING/ABSTRACTING

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LETTER TO THE EDITOR

Conversion therapy for unresectable hepatocellular carcinoma: Advances and challenges

Yan-Fei He

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Abstract

Recently, the *World Journal of Gastrointestinal Oncology* published an article entitled "Pathologically successful conversion hepatectomy for advanced giant hepatocellular carcinoma after multidisciplinary therapy: A case report and review of the literature", in which the authors shared their successful experience with complete surgical resection after multidisciplinary conversion therapy. The study by Chu *et al* demonstrates the great challenges that the advanced hepatocellular carcinoma (HCC) poses to surgical oncology, reveals the complexity of conversion therapy for unresectable HCC, emphasizes the important role of a multidisciplinary management model in conversion therapy, and enriches our understanding of the dynamics of personalized treatment for different patients. At present, conversion therapy is a hot research topic in the treatment of unresectable HCC, which has brought new hope to many patients with moderately advanced HCC. However, there are still many urgent problems to be solved in conversion therapy. Here, we would like to further discuss the advances and challenges of conversion therapy for unresectable HCC with the authors and the general readers.

Key Words: Unresectable hepatocellular carcinoma; Conversion therapy; Challenges; Advances; Advanced hepatocellular carcinoma; Targeted therapy; Immunotherapy

Core Tip: This letter reviews recent advances in conversion therapy for hepatocellular carcinoma (HCC), comparatively describes the characteristics of different conversion programs, addresses current challenges in conversion therapy, highlights the complexity of conversion therapy for moderately advanced HCC, and emphasizes the importance of a multidisciplinary, team-based management model, and provides valuable insights into the treatment of unresectable HCC.

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TO THE EDITOR

Primary hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, with an incidence rate ranked sixth among malignancies and a cause of death ranked third, second only to lung and colorectal cancer[1], and due to its high grade and rapid progression, the 5-year survival rate of patients is only 18%[2]. Currently, surgical resection is still the first choice for the treatment of HCC. More than 10 years ago, Ba *et al*[3] reported a case of a giant HCC with a diameter of more than 30 cm and a weight of more than 10 kg that was completely resected. Liver surgery has developed rapidly with the deepening knowledge of liver anatomy and physiology, the introduction of new techniques, and the increased experience of the surgical team, and the indications for liver resection are expanding and becoming more complex. Not coincidentally, we searched the reference citation analysis database[4] for relevant articles in the cutting-edge field in the past two years, studies proved that the application of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) technique is safe and feasible for the treatment of giant HCC larger than 10 cm[5]. The prognosis of these two cases is encouraging. Unfortunately, not all patients with giant HCC are as fortunate as the above two patients. Due to the insidious onset of HCC and the lack of specific clinical manifestations in the early stage, approximately 70% of patients with HCC miss the optimal time for surgery at the time of diagnosis, despite the continuous updating of HCC diagnosis and treatment techniques in recent years[6]. Equally distressing is the fact that there is no broad consensus on the treatment of this type of giant HCC.

In recent years, targeted therapy and immunotherapy have made significant progress in the field of HCC, and some patients with unresectable HCC have had their tumors reduced in size and stage during systemic therapy and have been offered the opportunity to undergo surgery after their tumors have been converted from unresectable to resectable status. Recently, I read with interest the article published by Chu *et al*[7] in the *World Journal of Gastrointestinal Oncology* in March 2024, which is a high-quality and representative case report, and its special feature is that the patient with advanced giant HCC was completely accepted for surgical resection after 21 months of multiple conversion therapy, and the postoperative pathology results showed complete response, and the references cited in the article are accurate and novel, and this report provides valuable insights into conversion therapy for unresectable HCC. I believe that the report of Chu *et al*[7] on the successful surgical resection of giant HCC after conversion therapy with multidisciplinary teamwork will be highly appreciated by readers, especially those in the field of surgery.

Although conversion therapy as an emerging tool has made breakthrough progress in surgical oncology[8,9], a consensus has not yet been reached in the field of HCC, and there are still many problems and challenges in conversion therapy, for example, how to grasp the optimal timing of surgery after conversion? If the conversion fails, what should be the subsequent management? Here, this editorial reviews the recent advances in conversion therapy for unresectable HCC and discusses the current acute conflicts facing conversion therapy for HCC.

CONNOTATION OF CONVERSION THERAPY FOR HCC

Conversion therapy usually refers to the treatment process in which patients who are considered to have too high surgical risk or unresectable tumors at initial diagnosis due to tumor stage, surgical technique, or insufficient future liver remnant (FLR) after resection are converted to a treatment process in which it is technically possible to achieve safe radical resection of the tumors after systematic, local, and other treatments. Conversion therapy for HCC is an important treatment modality for unresectable HCC to achieve downstaging, conversion resection, control tumor progression, and improve survival rate.

The history of conversion therapy for HCC can be traced back to the 1970s[10], nearly 50 years of research have shown that patients with HCC who have undergone conversion resection can have a 5-year postoperative survival rate of 50% to 60%, which is similar to that of early HCC after surgery[11-13]. The reasons for unresectable HCC can be divided into two levels. One level is unresectable from a surgical point of view, including the patient's inability to tolerate surgical trauma due to systemic disease, liver dysfunction, or inadequate FLR. The other is technically resectable, but the postoperative outcome is not better than non-surgical treatment and is considered unresectable from an oncologic or biological point of view. The goal of conversion therapy is to eliminate these two causes, achieve the conversion of HCC from unresectable to resectable, prolong the progression-free survival of patients, and improve the overall survival rate.

PROGRAMS FOR CONVERSION THERAPY FOR HCC

Currently, there are numerous and lack of uniformity in the conversion therapy programs for unresectable HCC, and Table 1[14-43] describes various conversion therapy options in detail. In general, in recent years, targeted therapy and immunotherapy have been a major breakthrough to traditional treatment, and trying the combined application of multiple therapeutic means is the trend in the conversion therapy of unresectable HCC, as well as the future direction of translational therapy research.

EVALUATION OF CONVERSION THERAPY FOR HCC

The primary factor in evaluating the efficacy of conversion therapy is the objective remission rate, with more refined measures including the rate of disease progression, time to remission, duration and depth of remission, and the incidence of adverse events. A lower disease progression rate means that fewer patients experience tumor progression during conversion therapy. A shorter time to remission helps reduce the duration of exposure to conversion therapies, which in turn reduces the incidence of adverse events. A longer duration of remission means a longer window, which is important for selecting the optimal timing of resection and adjusting preoperative status. A deeper remission means a higher probability of tumor shrinkage and downstaging, which facilitates subsequent treatment. A lower incidence of adverse events contributes to improved surgical safety.

CHALLENGES OF CONVERSION THERAPY FOR HCC

Population selection

The Chinese expert consensus on conversion therapy for HCC (2021 edition)[44] states that patients with surgically unresectable China liver cancer staging (CNLC) Ia, Ib, and IIa HCC and surgically resectable and unresectable CNLC-IIb and IIIa HCC are the target population for conversion therapy. The term "unresectable" includes both surgically and oncologically unresectable. Thus, there are huge differences in the tumors and general conditions of patients with HCC who need to undergo conversion therapy, and how to determine which patients are the most suitable for conversion therapy is still a difficult problem today.

Selection of treatment programs

The extent, rate, and duration of tumor response, as well as organ-specific tumor response, are important factors that influence treatment decisions. There is no consensus on which conversion therapy regimen to choose, and in general, conversion therapy regimens should be based on patient characteristics, tumor biology, and treatment goals. As Chu *et al* [7] emphasize in their article, the involvement of a multidisciplinary team throughout the patient's care, the development of an individualized treatment plan, long-term follow-up, and the balancing of the risks and benefits of different therapeutic interventions are key to the success of conversion therapy.

Timing of surgery

At present, there is no uniform standard for the selection of the timing of surgery; in principle, it should be considered from the perspective of both tumor response and surgical safety. Most studies concluded that after conversion therapy, patients with HCC of all stages can undergo surgical resection if there is no distant metastasis and the tumor extent and margin can meet the technical requirements for complete resection. The efficacy of conversion therapy should be evaluated by radiological imaging every 4-8 weeks after the start of conversion therapy, and treatment-sensitive patients have a chance of successful conversion in 3-7 cycles. Specifically, for technically resectable CNLC-IIb and IIIa patients, surgical resection can be considered if the tumor achieves objective remission according to the modified revised evaluation of the efficacy of solid tumor therapy criteria or if the tumor achieves a stable state for 3-4 months after conversion therapy; for technically unresectable patients, surgical resection should be performed at the earliest possible time once surgical resectability criteria are met.

Follow-up of conversion therapy

In general, patients with unresectable/advanced HCC should be categorized according to the outcome of conversion therapy.

Failure of conversion and tumor progression: The goal of these patients at this time is no longer tumor resection, but to strive for prolonged survival, so it is recommended to switch to other first-line treatment options or drug combinations, or directly use second-line treatment options. It is worth noting that conversion therapy does not contradict the current conventional treatment strategy for advanced HCC, and even if the conversion is not successful, the survival expectancy of patients will not be greatly affected.

Tumor partial remission or stable disease but not successfully down staged: These patients have no chance of surgery, but if the general condition of the patient allows, the duration of conversion therapy is shorter, and there is no obvious drug resistance, the current treatment can be continued to be maintained or intensified for 6-12 months, and regular

Table 1 Hepatocellular carcinoma conversion therapy programs

Program			Definition	Applicable population	Mechanism	Advantage	Disadvantage
Local therapy	TACE		The use of iodized oil as a carrier and chemotherapeutic drugs mixed into an emulsion is injected into the blood-supplying arteries of the tumor, then the corresponding arteries are embolized with embolic agents, resulting in ischemia and necrosis of the tumor	Patients with unresectable HCC with vascular invasion	Chemotherapeutics and embolic agents are injected through the hepatic artery into the tumor-nourishing artery, providing a synergistic effect of vascular occlusion and local chemotherapy, resulting in tumor necrosis[14]	Long drug metabolism time, strong local tumor-killing effect, high reproducibility, and fewer systemic side effects[15]	Periportal inflammatory adhesions and increased risk of intraoperative bleeding
	TARE		Selective transcatheter and intra-arterial injection of micron-sized particles containing radioisotopes (mostly ^{90}Y) to treat moderately advanced HCC[16-18]	HCC patients with less than 50% liver involvement	Tumor ischemia and necrosis are caused by blocking the tumor's nutrient blood vessels, while local radiotherapy kills the tumor with glass microspheres containing radioactive substances	Prolongs the time to tumor progression, shrinks tumors, and promotes healthy liver proliferation	Risk of peptic ulcer and biliary injury
	HAIC		Anti-cancer drugs and embolization agents are injected directly into the tumor tissue using catheter technology to kill the tumor cells	Patients with combined arteriovenous fistula and portal vein cancer thrombus[19,20]	The continuous infusion of chemotherapeutic agents through the hepatic artery allows the chemotherapeutic agents to accumulate in high concentrations in the tumor and have a constant effect on the tumor cells	It can significantly increase the concentration of the drug in the targeted tumor, with a low incidence of adverse events and less trauma	It is less effective in patients with large and numerous tumors
	PVE		Atrophy of the embolic lobe and compensatory hyperplasia of the non-embolic lobe of the liver by selective embolization of the portal vein branches and alteration of portal blood flow	Patients who are not resectable due to lack of adequate FLR	Selective embolization of portal vein branches induces hyperplasia in the rest of the liver	It can shorten the duration of conversion therapy and has fewer postoperative complications	Residual liver hyperplasia takes a relatively long time and may increase the rate of tumor growth
	ALPPS		Liver resection was divided into two operations and two stages. In the first operation, the liver was divided into the expected resected portion and the expected preserved portion, the liver tissue between the two was isolated, and the branch of the portal vein on the expected resected side was ligated	Giant HCC with extensive tumor invasion and inadequate FLR after resection	The surgery is divided into two stages, in the first stage, the liver with invasion is isolated from the normal liver, and the affected portal vein is ligated, after the liver on the healthy side grows to a sufficient size, in the second stage, the liver on the affected side is completely resected	It rapidly induces proliferation in the rest of the liver and minimizes the risk of tumor progression	Patients have to undergo two complex and traumatic surgeries
	Radiotherapy		Treatment of localized HCC with high-energy radiation[21]	Patients with combined portal vein thrombosis or macrovascular invasion in advanced HCC	Kill tumor cells with ionizing radiation	It causes the cancerous embolus to shrink or disappear, effectively controlling the tumor and improving the long-term effect of surgical resection [22]	Limited range, high requirements for tumor sensitivity, and may cause damage to normal tissue
	Ablation therapy	Chemical ablation	A local treatment in which a chemical ablative agent is injected directly into the tumor, causing degeneration and necrosis of the tumor cells[23,24]	HCC patients with cancer foci near high-risk hilar, gallbladder, and gastrointestinal sites	Denaturing and necrotizing tumor cells using chemical ablators	Safe, minimally invasive, and fast recovery	Inability to destroy potential circulating tumor cells
		Physical ablation	Tumor tissue is heated or frozen using specific physical techniques to induce	Patients with solitary HCC without vascular,	The application of heat results in necrosis of the tumor tissue	The surgery is simple and less invasive, with a shorter	There is a heat sink effect that can damage

			coagulation and freeze-thaw necrosis[25-28]	biliary, or adjacent site involvement		recovery time	surrounding tissue
		Irreversible electroporation	By disrupting cellular homeostasis with short but powerful electric fields, causing irreversible cell damage, tumor cells die naturally[29]	HCC is located where vital extracellular matrix, blood flow, and nerves need to remain	Tumor cell membranes are disrupted by electrical impulses, resulting in apoptotic cell necrosis	There is no heat sink effect, and tumors close to ducts and nerve sites can be killed without damaging blood vessels and nerves	Conductivity has a high impact on the local environment. It is susceptible to the presence of residual tumor tissue
Systemic therapy	Chemotherapy		Chemotherapy alone to treat tumors[30]	Advanced and relatively limited HCC without severe cirrhosis	Kill cancer cells by interfering with their growth and division process	Safe and tolerable	Low conversion rate
	Target therapy		Targeting of specific cancer-causing sites at the cellular molecular level[31-33]	Primary HCC with multiple liver metastases and vascular invasion	The drug enters the body and specifically selects oncogenic sites to bind to and act on, causing tumor cell-specific death	Kill tumor cells specifically without damaging surrounding normal tissue	It is necessary to find a clear therapeutic target with limited applicability
	Immunotherapy		By directly or indirectly increasing the body's immunoreactive cells, regulating tumor immune-related signaling pathways or vascular growth factors, inhibiting angiogenesis, and delaying tumor cell proliferation[34-38]	Patients with tumors invading large blood vessels, distant metastases, poor hepatic function, and those who cannot tolerate surgery	By enhancing host immune activity and immune recognition, it strengthens the body's immune response to tumors, weakens tumor immune escape, and inhibits or kills tumor cells	Highly targeted, high specificity, and low side effects	Lengthy conversion time and immune-related hepatitis
Combination therapy	Dual therapy	Targeted combined immunotherapy	Targeted drugs and immunotherapy work together to kill cancer cells	Patients with associated portal and vena cava cancer embolism	Targeted drugs select specific tumor targets to kill tumor cells while stimulating the body's immune response and enhancing the anti-tumor immune response	Synergistic effect and high converting efficiency[39,40]	Risk of immune-mediated inflammation
		TACE combined RFA	Combination TACE with percutaneous RFA [41]	HCC with intrahepatic, portal vein, or distant metastatic disease	Based on the blockage of most of the tumor's blood supply, the remaining small lesions are precisely ablated, resulting in the complete destruction of the tumor tissue	The high temperature generated by the radiofrequency ablation needle after embolization is more concentrated and sustained at the tumor site, and tumor tissue is more thoroughly destroyed	The presence of adjacent vessels and invasive tumor growth may result in inadequate ablation
	Triple therapy	TACE combined with ICI and TKI	Combination of TACE, targeted therapy, and immunotherapy[42]	Patients with intermediate-stage HCC (CNLC IIb stage) or multiple lesions	Positive reinforcing feedback effects on the hypoxic and immunosuppressive microenvironment	High conversion efficiency and fewer grade 3 to 4 adverse events	Low efficacy in non-viral HCC
		HAIC combined with ICI and TKI	Combination of HAIC, targeted therapy, and immunotherapy[43]	HCC patients with portal vein thrombosis	Block tumor blood vessels and competitively inhibit tumor cell proliferation	Strong synergistic effect and long-lasting anti-tumor response	Heterogeneity was high and trial data were limited

HCC: Hepatocellular carcinoma; FLR: Future liver remnant; TACE: Transcatheter arterial chemoembolization; HAIC: Hepatic artery infusion chemotherapy; PVE: Portal vein embolization; ALPPS: Associating liver partition and portal vein ligation for staged hepatectomy; TARE: Trans-arterial radioembolization; RFA: Radiofrequency ablation; ICI: Immune checkpoint inhibitor; TKI: Tyrosine kinase inhibitor; CNLC: China liver cancer staging.

review and evaluation[44].

Tumor remission and successful conversion: Surgical resection or even radical resection can be performed in these patients, and resection of resectable extrahepatic metastatic lesions should be performed at the same time[44].

COMPLICATIONS OF CONVERSION THERAPY FOR HCC

The complexity of patients undergoing conversion therapy and the complexity of post-conversion surgical resection compared to conventional HCC resection, which includes dealing with extrahepatic metastases in addition to conventional resection of the primary focus, adequate margins, resection of vascularized cancer plugs, and preservation of adequate functional residual liver volume, as well as dealing with the potential impact of different conversion therapies on surgical treatment, not surprisingly, these factors combined with the high intensity of conversion therapy may expose patients to a higher risk of complications. As noted by the authors[7], common complications include hypertension, diarrhea, thrombocytopenia, hypothyroidism, and dermatitis, most of which can be managed with medication. However, some serious complications, such as ALPPS with 8%-9% 90-day mortality[45], possible bile leakage in 20% of cases[46], postoperative liver failure[47], immunotherapy-induced immune-associated hepatitis[48], and prolonged postoperative incisions, require close attention and prompt management by the treatment team. There are few studies on recurrence and metastasis after conversion therapy; however, postoperative recurrence rates as high as 70% have been reported[49]. In addition, the syndrome caused by abdominal decompression after surgical resection of giant HCC must also be taken seriously by clinicians[3].

LIMITATIONS OF CONVERSION THERAPY FOR HCC

Conversion therapy for HCC also has limitations. First, the definition of unresectable HCC is subjective, resulting in patients with HCC who would not otherwise require conversion therapy not receiving surgical treatment. Second, the population benefiting is small, with only 8%-18% of patients with preoperatively unresectable HCC able to successfully achieve tumor conversion and undergo surgical resection[14]. Third, tumor progression and metastasis may occur during conversion. Fourth, as mentioned above, there are no standardized criteria for the selection of conversion regimens, which may result in higher rates of perioperative mortality and postoperative liver failure if the regimen is not selected appropriately. In addition, there is clearly room for improvement in areas such as health insurance, drug potency, adverse effects and management, and access to liver transplantation.

CONCLUSION

The report by Chu *et al*[7] provides valuable insights for further research into individualized treatment strategies for customized giant HCC. This letter reviews the study by Chu *et al*[7] details the various conversion therapy programs for unresectable HCC, and provides insight into the many challenges currently facing conversion therapy. The authors' study and this editorial encourage further research into all aspects of conversion therapy for unresectable HCC. Although there are a number of real-world successes, these are still predominantly small-sample, retrospective cohort studies and the small amount of available evidence does not fully answer these questions, with the expectation that more large-sample, multicenter, long-term, clinically controlled studies will gradually shed light on them.

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