Scientific Research Publishing

Journal of Biosciences and Medicines, 2025, 13(12), 374-385
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Conversion Therapy and Liver Regeneration in Liver Cancer

Xiaoqin Wu

School of Health Science and Engineering, University of Shanghai for Science and Technology, Shanghai, China
Email: wuxiaoqinxq@163.com

How to cite this paper: Wu, X.Q. (2025) Conversion Therapy and Liver Regeneration in Liver Cancer. *Journal of Biosciences and Medicines*, **13**, 374-385.
https://doi.org/10.4236/jbm.2025.1312028

Received: November 21, 2025
Accepted: December 21, 2025
Published: December 24, 2025

Abstract

This paper provides a narrative review of the primary modalities of conversion therapy for liver cancer, analyzes the characteristics and applications of different treatment approaches, and focuses on exploring the relationship between conversion therapy and liver regeneration, aiming to offer insights for optimizing conversion therapy strategies for liver cancer.

Keywords

Liver Cancer, Conversion Therapy, Liver Regeneration

1. Introduction

Liver cancer is one of the most common malignant tumors worldwide. Epidemiological data released by the China Cancer Center in 2022 indicate that liver cancer ranks fourth among the most common malignant tumors in China and is the second leading cause of cancer-related deaths [1]. Primary liver cancer is a malignant tumor originating from liver tissues, including Hepatocellular Carcinoma (HCC) derived from hepatocytes, Intrahepatic Cholangiocarcinoma (ICC) derived from bile duct cells, and combined Hepatocellular-Cholangiocarcinoma (cHCC-CCA) originating from both. Among these, HCC accounts for 75% - 85% of cases [2]. Liver cancer often has an insidious onset, and approximately 64% of patients in China are diagnosed at an intermediate or advanced stage (*i.e.*, CNLC stages IIb, IIIa, and IIIb) [3]. For these patients, factors such as large tumor size, multiple tumors, vascular invasion, distant metastasis, or insufficient liver function reserve often result in a low surgical resection rate and poor prognosis, making surgical resection unsuitable as the first-line treatment. Conversion therapy, through preoperative treatment, aims to downstage the tumor or improve liver function, thereby transforming unresectable cases into resectable ones and improving long-term

survival rates. Liver regeneration is a unique physiological function of the liver that promotes the restoration of liver tissue and function, and is closely related to surgical safety and patient prognosis. Therefore, investigating the relationship between conversion therapy and liver regeneration holds promise for further optimizing treatment strategies for liver cancer and providing a reference for clinical management.

2. Overview of Conversion Therapy for Liver Cancer

2.1. Basic Concept of Conversion Therapy for Liver Cancer

Conversion therapy is indicated for patients who are not candidates for upfront surgery due to factors such as high tumor burden, vascular invasion, or poor liver functional reserve. Its primary goal is to downstage the tumor clinically or improve liver function through preoperative treatment, thereby converting unresectable liver cancer into a resectable state and providing patients with an opportunity for surgical resection. The reasons for unresectability in liver cancer can be categorized into surgical and oncological factors. Surgical unresectability refers to the patient's inability to tolerate surgery, insufficient liver function, or inadequate future liver remnant volume. Oncological unresectability indicates that the efficacy of surgical resection is not superior to other treatment modalities [4]. The ultimate goal of conversion therapy is to prolong patient survival. Based on the reasons for unresectability, conversion therapy strategies encompass two main approaches: oncological conversion, which focuses on tumor shrinkage and downstaging through systemic or local therapies, and surgical condition-oriented conversion, which aims to create operable conditions by modulating liver tissue, such as with Portal Vein Embolization (PVE) or Associating Liver Partition and Portal Vein Ligation for Staged Hepatectomy (ALPPS) [5]. The ultimate goal of conversion therapy is to prolong patient survival by securing an opportunity for curative resection.

2.2. Major Modalities of Conversion Therapy for Liver Cancer

2.2.1. Systemic Therapy

Systemic therapy includes targeted therapy, immunotherapy, and systemic chemotherapy. Targeted therapy focuses on key genes and regulatory molecules, by designing drugs that target specific factors potentially leading to carcinogenesis. These targeted agents bind specifically to tumor cells, precisely acting on particular molecules or signaling pathways essential for tumor cell growth, thereby effectively inhibiting tumor proliferation and metastasis [6]. Immunotherapy utilizes the body's own immune system to recognize and attack tumor cells. It works by activating immune effector cells to kill tumor cells or by specifically inhibiting tumor growth and progression through anti-tumor immune responses [7], ultimately suppressing the advancement of liver cancer and extending patient survival. Systemic chemotherapy involves the use of anticancer drugs administered intravenously or orally to eliminate cancer cells. It works by interfering with DNA

replication or the cell division process of tumor cells, thereby killing rapidly proliferating cancer cells. As this approach is a non-discriminatory attack, it can also damage normal cells. However, the sensitivity of liver cancer to chemotherapeutic drugs is relatively low, and the efficacy of chemotherapy used alone is often unsatisfactory. Nevertheless, in specific cases, chemotherapy combined with other treatment modalities can produce synergistic effects, effectively shrinking tumors and achieving conversion resection.

2.2.2. Local Therapy

Local conversion therapies primarily include Transcatheter Arterial Chemoembolization (TACE), Hepatic Arterial Infusion Chemotherapy (HAIC), Selective Internal Radiation Therapy (SIRT), radiotherapy, and local ablation, among others. TACE involves the selective embolization of the tumor's feeding arteries using iodized oil or microspheres carrying chemotherapeutic agents. This induces ischemic necrosis of the cancer cells [8]. Its effects include tumor shrinkage, lesion disappearance, and liver volume increase. HAIC entails the direct infusion of chemotherapeutic drugs into the tumor-feeding arteries via a catheter placed into the hepatic artery. This method increases the local drug concentration around the lesion, enhances tumor drug uptake, and achieves effective intratumoral drug levels to inhibit tumor growth and progression [9]. SIRT, also known as radioembolization, involves injecting microspheres carrying radioactive isotopes into the tumor via the hepatic artery. These microspheres become lodged within the tumor vasculature, continuously releasing high-dose radiation from inside to destroy the tumor while causing minimal damage to the surrounding normal liver tissue [10]. Radiotherapy utilizes high-precision, high-dose radiation beams delivered from multiple external angles to focus on the tumor, directly damaging the DNA of tumor cells. Precise target delineation not only delivers a sufficient radiation dose to the lesion but also significantly protects surrounding healthy tissues [11], leading to reduced local recurrence rates and a lower incidence of adverse effects after radiotherapy. Local ablation techniques inactivate tumor cells in situ through physical means, resulting in coagulative necrosis of the tumor [12]. These include Radiofrequency Ablation (RFA), Microwave Ablation (MWA), and cryoablation (e.g., Argon-Helium Knife).

2.2.3. Surgically Guided Procedures

Surgical resection is the primary treatment modality associated with long-term survival for patients with liver cancer. Insufficient Future Liver Remnant (FLR) volume is a major surgical reason precluding resection. Currently, an FLR greater than 30% of the standard liver volume (or greater than 40% in patients with cirrhosis) is considered the safe threshold for performing surgical resection. To address insufficient liver volume, surgically guided procedures are employed to transform an inadequate FLR into a sufficient functional liver volume, thereby converting unresectable cases into resectable ones. PVE involves embolizing the portal vein branches feeding the tumor-bearing hemiliver. This induces compen-

satory hypertrophy of the future liver remnant, aiming to achieve sufficient functional liver volume to enable safe surgical resection of the tumor. The process of liver regeneration following PVE typically requires 4 - 6 weeks [13]. This relatively long timeframe carries the risk of tumor progression during the waiting period or inadequate hypertrophy of the FLR, potentially leading to missed surgical opportunities. ALPPS builds upon the concept of PVE. It involves surgical transection of the liver parenchyma in addition to portal vein ligation, which completely interrupts the collateral circulation between the liver lobes. This procedure rapidly induces hypertrophy of the intended liver remnant, often achieving the necessary liver volume within 1 - 2 weeks [14]. The degree of hypertrophy induced by ALPPS is significantly higher than that achieved with PVE. Furthermore, the shorter interval between the two surgical stages minimizes the risk of tumor progression.

2.3. Current Status of Conversion Therapy for Liver Cancer

Due to the strong heterogeneity of liver cancer, the efficacy of single-modality treatment is limited. Comprehensive therapy combining multiple modalities has become the development trend in conversion therapy. Common combination regimens include the combination of different systemic therapeutic agents and the combination of systemic therapy with local therapy. Targeted immunotherapy combines the principles of targeted therapy and immunotherapy. It utilizes targeted agents to modulate the tumor microenvironment and eliminate the immunosuppressive state, then synergizes with immunotherapy agents to further amplify the anti-tumor immune response, achieving a synergistic effect. In 2007, based on clinical research evidence from sorafenib [15], systemic therapy was first proven to provide survival benefits for patients with advanced HCC, thereby establishing its role in HCC treatment. Subsequently, successively approved drugs such as lenvatinib, regorafenib, donafenib, and bevacizumab have further enriched the options for targeted therapy in HCC. Immune Checkpoint Inhibitors (ICIs) work by blocking programmed cell death protein 1 (PD-1), its ligand PD-L1, and related pathways, thereby relieving T-cell immunosuppression and activating their ability to recognize and eliminate tumor cells [16], ushering in the era of immunotherapy for HCC. A series of ICIs, including atezolizumab, tislelizumab, and sintilimab, are now widely used in the treatment of intermediate and advanced HCC. However, due to the complex pathogenesis of HCC and the immunosuppressive tumor microenvironment, the conversion efficacy of Tyrosine Kinase Inhibitors (TKIs) and ICIs as monotherapies in HCC is limited. The Objective Response Rate (ORR) for sorafenib monotherapy is 12.4% [17], and the ORR for ICI monotherapy in HCC is 15% - 20% [18]. Furthermore, some patients develop acquired resistance after initial success with ICI treatment, posing a new challenge for HCC immunotherapy. Currently, the combination of TKIs and ICIs is the most commonly used strategy to enhance the efficacy of immunotherapy. In the study by Finn [19], the atezolizumab-bevacizumab ("T + A") regimen

achieved an ORR of 27.3%, higher than the 11.9% in the sorafenib control group, and the median Progression-Free Survival (PFS) in the study group was significantly longer than in the control group (6.8 months vs. 4.3 months). A study by Wang [20] showed that sintilimab combined with lenvatinib achieved an ORR of 66.7% (based on mRECIST criteria) and a conversion rate of 33%. Based on existing research, targeted-immunotherapy combinations yield higher ORRs and conversion rates compared to monotherapies. Local therapy combined with systemic therapy aims to achieve synergistic effects by integrating local and systemic treatments. Local therapy can directly reduce or eliminate tumor burden, while systemic therapy can inhibit micrometastases and delay recurrence; the combination further extends patient survival. A study on HAIC combined with donafenib and sintilimab for unresectable HCC [21] enrolled 36 patients, reporting ORRs of 58.3% (RECIST 1.1) and 80.6% (mRECIST), respectively, a conversion rate of 50%, and a 24-month Overall Survival (OS) rate of 59.6%. Gan [22] included 98 patients with unresectable HCC receiving TACE combined with lenvatinib and sintilimab. Within this group, the 37 potentially resectable patients achieved ORRs of 67.6% (RECIST 1.1) and 75.7% (mRECIST), respectively, a conversion rate of 40.5%, and a median PFS of 25 months, indicating that the combination of targeted therapy, immunotherapy, and local therapy leads to higher ORRs and conversion rates. Zhang [23] included 51 HCC patients who received PVE or PVE combined with TACE prior to hepatectomy. The resection rate in the simultaneous TACE + PVE group was significantly higher than in the sequential TACE + PVE group and the PVE-only group (100% vs. 82% vs. 67%), with longer median OS and Disease-Free Survival (DFS), suggesting that performing TACE and PVE simultaneously results in higher resection rates and improved survival. The comprehensive conversion therapy regimen needs to be individualized based on the patient's tumor characteristics, liver reserve function, and overall condition to maximize efficacy and minimize adverse effects.

3. The Process and Regulatory Mechanisms of Liver Regeneration

3.1. The Process of Liver Regeneration

Liver regeneration refers to the process by which the remaining liver cells, following partial resection or injury, undergo proliferation and differentiation under the coordinated regulation of a series of factors to restore normal liver volume and function [24]. Under normal circumstances, the liver possesses a remarkable capacity for regeneration. This repair and regeneration process constitutes a vital physiological response to hepatic injury. When the liver is damaged, various feedback signals stimulate the proliferation of hepatocytes, prompting these residual cells to transition from a quiescent state to a rapid growth state, thereby initiating the liver regeneration process to maintain normal liver function [25]. The process of liver regeneration primarily involves the regenerative proliferation of hepatic parenchymal cells and the reconstruction of liver tissue structure, regulated through

different mechanisms utilizing a variety of cytokines and growth factors within the body [26]. During hepatocyte proliferation, liver stem cells play a major role due to their stem cell characteristics, enabling them to proliferate and differentiate into functional hepatocytes. In cases of acute liver injury, the regeneration process is primarily driven by the proliferation of residual mature hepatocytes, whereas in chronic injury, it is driven by hepatic progenitor cells [27].

3.2. Regulatory Mechanisms of Liver Regeneration

The process of hepatocyte regeneration comprises three stages: the initiation phase, the proliferation phase, and the termination phase [28]. Under normal physiological conditions, hepatocytes are predominantly quiescent with low proliferative activity. Following partial hepatectomy or liver injury, Kupffer cells, among others, are activated and release Tumor Necrosis Factor-alpha (TNF-α) and Interleukin-6 (IL-6). IL-6 binds to its corresponding receptor, activating the STAT3 signaling pathway [29]. This activation enables quiescent hepatocytes to enter the cell cycle and prepare for proliferation, thereby initiating the liver regeneration process. The continuous release of cytokines such as Nitric Oxide (NO) and IL-6 stimulates Hepatic Stellate Cells (HSCs), leading to increased release of Hepatocyte Growth Factor (HGF) and Vascular Endothelial Growth Factor (VEGF). HGF binds to the c-Met receptor on the surface of hepatocytes, further activating downstream proteins like MAPK and triggering a cascade of reactions [30]. This drives hepatocytes to complete DNA synthesis and cell division, accelerating their proliferation and differentiation. VEGF promotes endothelial cell proliferation, angiogenesis, and increased vascular permeability, thereby propelling the liver regeneration process. Upon activation of the Wnt signaling pathway, the degradation of β-catenin protein is prevented, allowing it to enter the nucleus and regulate gene expression. This promotes hepatocyte repopulation and the restoration of liver lobule structure, and appropriately terminates the cell differentiation and regeneration process [31], preventing excessive hyperplasia. Concurrently, Transforming Growth Factor-beta (TGF-β) binds to its corresponding receptor, which can inhibit the division and proliferation of hepatocytes, thus terminating the liver regeneration process [32]. The process of liver regeneration is regulated by multidimensional factors, and its mechanisms are highly complex. Current clinical research in this area is still in a phase of ongoing exploration.

4. The Relationship between Conversion Therapy and Liver Regeneration in Liver Cancer

4.1. Impact of Conversion Therapy on Liver Regeneration

The various treatment modalities employed in conversion therapy for liver cancer, such as targeted therapy, immunotherapy, chemotherapy, and local therapies, induce changes in the liver and tumor microenvironment, thereby exerting varying degrees of influence on liver regenerative capacity. It should be noted that cirrhosis, as a significant factor in conversion therapy for liver cancer, constrains liver

regeneration capacity. It leads to issues such as reduced hepatocyte proliferative ability and disruption of signaling pathways associated with liver regeneration. Simultaneously, cirrhosis limits patient tolerance to conversion therapy, as hepatic dysfunction affects drug metabolism and increases the risk of toxicity. Specifically, while targeted therapeutic agents exert antitumor effects, their impact on liver regeneration is complex. Angiogenesis, a crucial process for tumor growth and metastasis primarily regulated by the VEGF pathway, provides nutrients and oxygen to tumor cells [33]. Targeted agents exert their anti-cancer effects by targeting various protein kinases involved in tumor cell proliferation and angiogenesis. Their inhibition of Vascular Endothelial Growth Factor Receptor (VEGFR) suppresses tumor angiogenesis. By remodeling the hepatic vascular network and improving the local liver microenvironment, they can create favorable conditions for liver regeneration. However, these drugs also often inhibit the Hepatocyte Growth Factor (HGF) and its receptor c-Met signaling pathway, which can impair hepatocyte proliferation and migration, thereby exerting an inhibitory effect on liver regeneration [34]. Immunotherapy activates the body's immune system to attack cancer cells, and its impact on liver regeneration is dual-edged. It can enhance immune function, clearing cancer cells and damaged hepatocytes, thereby creating a favorable environment for regeneration. By blocking the PD-1/PD-L1 signaling pathway, immune checkpoint inhibitors activate T-cell-mediated antitumor responses and can promote hepatocyte proliferation and liver regeneration. Nonetheless, a potential adverse effect of such immunotherapy is immune-mediated hepatitis [35], which causes hepatocyte injury and inhibits regeneration. This risk is compounded in patients with cirrhosis, as underlying hepatic dysfunction elevates the susceptibility to both TKI-associated liver damage and ICIs-induced immune hepatitis, further aggravating hepatic regeneration impairment. TACE induces tumor ischemia and necrosis by embolizing the tumor's blood supply and injecting chemotherapeutic drugs. However, it simultaneously induces local and systemic inflammation within the tumor microenvironment [36], causing some damage to normal liver tissue. This can lead to decreased liver function and suppressed regenerative capacity. TACE may also cause microcirculatory disturbances in the liver, affecting the nutrient supply to hepatocytes and the removal of metabolic waste products, further inhibiting liver regeneration. In patients with cirrhosis, complications such as post-embolization syndrome are more likely to occur after TACE, which exacerbates the suppression of liver regeneration. Radiotherapy, while killing tumor cells, also causes radiation damage to the surrounding normal liver tissue. High-dose radiotherapy can lead to hepatocyte apoptosis and necrosis [37], disrupting the normal liver structure and function and inhibiting regeneration. For patients with cirrhosis, the risk of radiation-induced liver disease is further increased. The changes in the liver and tumor environment caused by conversion therapy increase the incidence of liver injury and adverse reactions, leading to a higher rate of postoperative complications. As a key underlying condition, cirrhosis further impairs liver regeneration by constraining regenerative

capacity and limiting treatment tolerance.

4.2. The Role of Liver Regeneration in Conversion Therapy

Liver regeneration plays a critical role in conversion therapy for liver cancer, influencing the selection and implementation of treatment strategies. This is particularly relevant for cases deemed surgically unresectable due to insufficient liver function or inadequate Future Liver Remnant (FLR). Following partial hepatectomy or injury, hepatocytes rapidly proliferate, leading to compensatory hyperplasia of the remaining liver volume until sufficient functional liver volume is achieved, thereby converting an unresectable status to a resectable one [38]. During liver regeneration, improvements in hepatic blood circulation and metabolic function, along with enhanced systemic immune function, occur concurrently with tumor shrinkage and necrosis induced by conversion therapy. This creates favorable conditions for subsequent surgical resection. Robust liver regenerative capacity is a crucial safeguard for the successful implementation of conversion therapy. Whether it's chemotherapy, targeted therapy, or local therapy, each can cause a certain degree of liver injury. A strong regenerative ability facilitates rapid repair of hepatocytes, reducing the risk of post-treatment liver failure. For patients who undergo successful conversion and subsequent surgical resection, liver regenerative capacity also significantly impacts postoperative recovery. However, the cell proliferation mechanisms activated during liver regeneration may interact with tumor growth, potentially influencing the efficacy of conversion therapy. Growth factors (such as HGF, EGF, etc.) activated during liver regeneration, while promoting the proliferation of normal hepatocytes, might also stimulate the growth and invasion of tumor cells. This could lead to tumor recurrence or progression, thereby diminishing the effectiveness of conversion therapy. Furthermore, alterations in the liver microenvironment during regeneration, such as elevated levels of inflammatory factors and angiogenesis, might provide a more conducive environment for tumor cell growth, potentially increasing resistance to conversion therapy. It is noteworthy that in conversion strategies aimed at promoting future liver remnant hypertrophy, such as PVE, the postoperative hepatic regeneration process is relatively prolonged. During this period, insufficient hypertrophy of the future liver remnant or tumor progression may occur, potentially leading to the loss of surgical opportunity for the patient. Tumor progression or the development of treatment resistance during the waiting period following interventions like PVE represents one of the key limitations of conversion therapy. Therefore, while promoting liver regeneration to ensure treatment safety, effectively suppressing the abnormal proliferation of tumor cells is key to enhancing the efficacy of conversion therapy.

5. Discussion

Conversion therapy offers a new treatment direction for patients with intermediate and advanced liver cancer. The combined application of multiple treatment

modalities has significantly improved surgical resection rates and overall survival. Liver regeneration, as a core physiological function of the liver, is closely related to the safety and efficacy of conversion therapy. Conversion therapy can influence the process of liver regeneration through various mechanisms, while the capacity for liver regeneration not only determines a patient's tolerance to conversion therapy but may also affect its therapeutic outcome. Therefore, during the conversion therapy process, it is essential to integrate oncology objectives with the assessment of liver regenerative capacity. This integration aims to balance the tumor-killing effects of treatment with the protection of liver regeneration, while also preventing potential abnormal tumor proliferation during the regenerative process. This remains a significant challenge in clinical practice. Looking ahead, future efforts should focus on delving deeper into the molecular mechanisms by which conversion therapy affects liver regeneration and identifying key regulatory targets to provide a theoretical basis for drug development in conversion therapy. Comprehensive treatment strategies should be optimized to minimize liver damage while effectively inactivating tumors. Specific biomarkers (including multi-level markers from genomics, proteomics, radiomics, and physiology) need to be identified to establish a comprehensive evaluation system that can predict the efficacy of conversion therapy and liver regenerative capacity, enabling more precise patient stratification and treatment selection. Specific biomarkers—including genomic, proteomic, radiomic, and physiological indicators—should be screened to establish distinct immune cell profiles or tumor cell extrachromosomal DNA (ecDNA) signatures, thereby forming an integrated assessment system. Such a system aims to predict the efficacy of conversion therapy and evaluate liver regenerative capacity, enabling more precise patient stratification and treatment selection. With in-depth research into the relationship between conversion therapy and liver regeneration in liver cancer, treatment strategies will be continuously refined. This will enhance the success rate of conversion therapy and ultimately improve patient prognosis.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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