Application Progress of High Intensity Focused Ultrasound in Advanced Liver Cancer

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ABSTRACT High intensity focused ultrasound is a safe, noninvasive, accurate, and repeatable treatment modality that has received extensive attention in tumor therapy. Liver cancer, a malignant tumor of the digestive tract, has high incidence, insidious onset, high recurrence rate, and poor prognosis, and effective treatment methods are still lacking. High intensity focused ultrasound therapy provides a novel mechanism and a new method for the treatment of liver cancer. When combined with arterial interventional therapy, ablation therapy, radiotherapy, and systemic therapy, the efficacy is significantly improved, benefiting more patients. This paper reviews the basic principles of high intensity focused ultrasound therapy and discusses its efficacy and combined treatment effects for advanced liver cancer.

INDEX TERMS Ablation therapy, Advanced liver cancer, Comprehensive treatment, High intensity focused ultrasound, Interventional therapy, Radiotherapy, Sensitizer.

I. INTRODUCTION

Liver cancer is a malignant tumor arising from the liver, including primary and secondary types. Globally, the incidence of primary liver cancer is severe, ranking sixth in incidence and third in cancer-related deaths [1]. In China, the situation is also concerning. According to data from the National Cancer Center, in 2022 there were 367,700 new cases of primary liver cancer, ranking fourth among all cancers, and 316,500 deaths, ranking second after lung cancer [2]. These data highlight the major threat of liver cancer to public health in China. Currently, surgical resection remains the first-line treatment for liver cancer, but early symptoms are subtle, and many patients are already at an advanced stage at diagnosis, missing the opportunity for surgery [3]. Only about 20%–30% of patients are eligible for surgery, and the postoperative recurrence rate is as high as 50%–70%. For patients who lose the chance for surgery, treatments such as ablation, transarterial interventional therapy, radiotherapy, and systemic therapy can be used [4]. However, these methods have limitations for primary and secondary liver cancer, and new treatment approaches are urgently needed [5]. High-intensity focused ultrasound (HIFU) is a noninvasive method that mainly causes tissue damage through the synergistic effects of heat and mechanical action, achieving therapeutic goals [6]. It can be used to treat uterine fibroids, breast cancer, liver cancer, pancreatic cancer, and other diseases [7]. Therefore, summarizing the principles of HIFU and its research progress in advanced liver cancer may provide new ideas for clinical treatment and benefit more patients.

II. PRINCIPLE OF HIGH-INTENSITY FOCUSED ULTRASOUND

The therapeutic mechanism of HIFU relies on the excellent penetrating ability of ultrasound in biological tissues. Using imaging technology to precisely locate the lesion, ultrasound waves generated by a specific transducer are focused on the target area, producing a series of biological effects such as thermal effect, mechanical effect, and cavitation. This results in coagulative necrosis of the tissue while preserving the integrity of surrounding healthy tissues, ultimately achieving noninvasive treatment [8].

III. HIGH-INTENSITY FOCUSED ULTRASOUND MONOTHERAPY

After years of development, HIFU technology has been increasingly used in clinical practice with remarkable results, especially in the treatment of advanced liver cancer. Many studies have shown that liver cancer patients can benefit from HIFU, with prolonged survival and improved quality of life. Wang et al. [9] performed a meta-analysis of 188 liver cancer patients treated with HIFU and 224 treated with transarterial chemoembolization (TACE). The results showed no differences in 1-year overall survival, disease stability, disease progression, or postoperative complications between HIFU and TACE, while HIFU showed higher 6-month and 2-year overall survival rates. Several studies have indicated that HIFU has unique advantages in treating liver cancer in difficult locations or unresectable liver cancer [10]. Chen et al. [11] retrospectively analyzed 144 patients with liver cancer and portal vein tumor thrombus treated with HIFU. The median overall survival was 14 months, and the 6-month and 1-year cumulative survival rates were 79.0% and 58.6%, respectively. Most adverse reactions were mild (e.g., skin edema, local pain) and resolved after symptomatic treatment, demonstrating benefits for patients with advanced liver cancer. Xiao et al. [12] found that HIFU can stimulate the tumor immune microenvironment, enhancing therapeutic efficacy, and when combined with immune checkpoint inhibitors, chemotherapy, or radiotherapy, it further increases the immune effect. However, due to individual differences (e.g., tumor location, size, fat layer thickness, ribs, respiratory motion), some patients still do not achieve the desired effect with HIFU alone [13]. Blood perfusion is another important factor affecting HIFU ablation efficiency [14]. The liver has a dual blood supply (hepatic artery and portal vein), making it highly vascularized.

During HIFU treatment, abundant blood flow can remove part of the heat, affecting heat deposition in the tumor and reducing energy deposition, thereby lowering ablation efficiency. Increasing power may increase complications such as fever, pain, skin burns/edema, nausea/vomiting, peripheral nerve injury, and intestinal injury. Therefore, how to safely and effectively improve HIFU ablation outcomes has been a focus of HIFU research, and modifying the physicochemical properties of the target tissue (e.g., by physical or chemical means) is a hot topic [15]. Approaches include combining HIFU with ablation therapy, radiotherapy, transarterial interventional therapy, systemic therapy, and ultrasound sensitizers.

IV. COMBINATION THERAPIES

A. COMBINATION WITH ABLATION THERAPY

Percutaneous ethanol injection (PEI) is a widely used ablation agent with high safety, particularly suitable for lesions in high-risk areas such as near the hepatic hilum, gallbladder, and gastrointestinal tract [4]. It causes rapid dehydration, protein coagulation, and necrosis of cancer cells and their vessel walls, occluding vessels around the tumor and leading to ischemic necrosis of the tumor tissue [16]. Qiao et al. [17] combined PEI with HIFU to treat rabbits bearing VX2 tumors. The tumor necrosis rate in the combination group was 90.27%, compared to 63.55% in the PEI alone group, indicating that PEI combined with HIFU effectively improves ablation necrosis. Zou et al. [18] randomized 40 patients with small liver cancer in special high-risk locations into a PEI+HIFU group and a HIFU alone group. The combination group showed significantly larger ablation volume and higher ablation rate than the HIFU alone group under the same power, with lower average irradiation time and power, and significantly lower irradiation energy per unit volume of tumor, as well as fewer complications. Ma et al. [19] divided 122 liver cancer patients into a HIFU+WMA group and a HIFU alone group. The overall survival and progression-free survival in the combination group were 31.44±4.29 months and 26.29±5.11 months, respectively, significantly better than the HIFU alone group (25.63±5.19 months and 20.41±4.89 months, $P<0.05$), without increasing adverse reactions. These studies indicate that HIFU combined with ablation therapy has better efficacy and does not increase adverse events, meriting further investigation.

B. COMBINATION WITH INTERVENTIONAL THERAPY

Transarterial interventional therapy can be divided into hepatic arterial infusion chemotherapy (HAIC), transarterial chemoembolization (TACE), transarterial embolization (TAE), and transarterial radioembolization (TARE) based on embolization techniques. Among these, TACE is the most commonly used, primarily relying on the direct cytotoxic effect of chemotherapeutic drugs and embolization of the main feeding vessels to induce ischemic necrosis of tumor cells [20]. Chang et al. [21] investigated the efficacy of TACE combined with HIFU for primary hepatocellular carcinoma. The objective response rate was 82.4% in the combination group versus 66.2% in the HIFU alone group ($P<0.05$), and the combination group had longer progression-free survival and significantly lower serum alpha-fetoprotein levels. Liu et al. [22] studied HIFU combined with TACE for advanced primary liver cancer and found that the combination treatment significantly inhibited tumor progression, enhanced the expression of tumor suppressor genes, reduced pain, and improved quality of life. Hu et al. [23] performed a meta-analysis of 488 patients with advanced liver cancer (232 treated with TACE alone, 262 with TACE+HIFU) and showed that the combination therapy significantly enhanced tumor response and improved survival. These findings indicate that HIFU combined with interventional therapy benefits liver cancer patients, greatly prolonging survival without increasing side effects, and thus the antitumor value should be emphasized clinically.

C. COMBINATION WITH RADIOTHERAPY

Radiotherapy includes external beam and internal radiation, killing tumor cells by directly or indirectly causing DNA double-strand breaks [24]. Jin et al. [25] explored the feasibility of HIFU for residual hepatocellular carcinoma after stereotactic body radiotherapy (SBRT). Twenty patients with 24 residual lesions after SBRT received HIFU ablation. The median survival was 21 months, the tumor ablation rate was 75.8%±18.2%, and no severe HIFU-related adverse events were observed, suggesting that HIFU can safely and effectively ablate residual HCC after SBRT. Xu et al. [26] randomized 60 patients with advanced liver cancer into an observation group (gamma knife + HIFU) and a control group (gamma knife alone). The observation group had a higher response rate and lower post-treatment ALT and AST levels than the control group, with no difference in adverse reaction rates, indicating that the combination therapy is effective and does not increase adverse events.

D. COMBINATION WITH SYSTEMIC THERAPY

Systemic therapy includes molecular targeted therapy, immune checkpoint inhibitors, traditional Chinese medicine (TCM), antiviral therapy, and supportive care. Wu et al. [27] demonstrated that sorafenib combined with HIFU was superior to HIFU alone in inhibiting the growth of HepG2 liver cancer xenografts in mice, reducing the expression of HIF-2α and VEGFA and microvessel density, indicating that the combination not only destroys tumor cells but also inhibits the release of key cytokines, thereby suppressing tumor proliferation. Yang et al. [28] studied HIFU combined with anti-PD-1 immunotherapy for liver metastases. The combination relieved tumor-related pain and partially prevented further growth of local and systemic tumors, with a disease control rate of 78.6%. However, clinical studies combining HIFU with molecular targeted or immunotherapy are still limited and require further exploration.

Combining the holistic regulation of TCM with the precise targeting of HIFU integrates local treatment and systemic regulation, merging modern medicine with traditional wisdom to combat cancer, prolong survival, reduce complications, and improve quality of life [29]. Chen et al. [30] discussed the efficacy of Peiyuan Guben decoction combined with focused ultrasound ablation for primary liver cancer. Patients receiving HIFU plus TCM showed significantly lower serum AFP, CA19-9, AST, and ALT levels, as well as lower vascular endothelial growth factor and osteopontin, compared to those receiving HIFU alone, indicating that the combination reduces tumor markers, improves liver function, and inhibits tumor angiogenesis. Ju et al. [31] used staged oral and external TCM combined with HIFU for primary liver cancer and found that the therapy significantly reduced the number of enemas, protected digestive function, and improved quality of life. Meng et al. [32] investigated the attenuation and synergy of Hugan Buzu formula combined with oxaliplatin in hepatocellular carcinoma-bearing nude mice. The combination group showed significantly reduced tumor volume and weight ($P<0.01$) and increased red blood cell, white blood cell, and platelet counts ($P<0.05$), indicating that Hugan Buzu formula not only inhibits tumor growth but also alleviates oxaliplatin-induced hematologic toxicity. In summary, the combination of HIFU and TCM deserves further investigation and promotion.

E. COMBINATION WITH SYNERGIZING AGENTS

HIFU relies on a transducer to focus ultrasound on the lesion, depositing energy in the target area to induce tumor necrosis. Ultrasound sensitizers can alter the properties of the target area, facilitating energy deposition and enhancing HIFU ablation. Therefore, exploring efficient and safe sensitizers is of great importance. Zhang [33] developed a multifunctional thermotherapy sensitizer because HIFU alone often yields poor thermal effects. In mouse subcutaneous and liver cancer models, this sensitizer induced programmed cell death and maintained a balance between diffusion and deposition within the tumor, thereby triggering a potent antitumor immune response and expanding the thermal ablation zone, offering a new approach for combining thermotherapy sensitization with immune activation. Xiong et al. [34] studied the effect of HIFU combined with B7-H3-targeted microbubbles (T-MBs) on mouse liver cancer. The T-MBs+HIFU group showed better tumor ablation and growth inhibition, as well as gradually enhanced antitumor immune response, compared to HIFU alone. Guo et al. [35] investigated the effect of HIFU combined with microbubbles on primary liver cancer and peripheral blood T lymphocytes. The addition of microbubbles significantly increased the number of peripheral blood T lymphocytes in patients ($P<0.05$), suggesting that microbubbles may enhance antitumor immunity. Wang et al. [36] evaluated the efficacy of lauromacrogol for rabbit liver cancer, confirming that lauromacrogol can kill liver cancer cells, inhibit proliferation, and has little effect on normal liver tissue. Cao et al. [37] injected lauromacrogol or ethanol into rabbit VX2 liver cancer models under ultrasound guidance and found that lauromacrogol was more effective and safer than ethanol in killing tumor cells and inhibiting tumor growth, demonstrating the potential of lauromacrogol for liver cancer treatment. Ding et al. [38] combined lauromacrogol with HIFU to ablate healthy rabbit liver and found a synergistic effect compared to HIFU alone. However, whether the combination of HIFU and lauromacrogol improves overall treatment outcomes for patients with advanced liver cancer needs further clinical exploration.

V. CONCLUSION AND OUTLOOK

HIFU is a noninvasive treatment modality with the advantages of safety, no incision, high precision, and repeatability. Many studies have shown that combining HIFU with transarterial interventional therapy, radiotherapy, TCM, etc., not only does not increase adverse reactions but also effectively prolongs survival and improves quality of life, and has unique advantages in treating tumors in special locations. However, challenges remain: the ablation focal zone cannot completely cover the entire tumor in one session; respiratory motion, ribs, and adipose tissue affect precise targeting; and the quantitative relationship between ultrasound irradiation dose and therapeutic effect is still uncertain. With the development of artificial intelligence, computer technology, and imaging technology, HIFU will receive advanced technical support, continuous innovation, and play a more significant role in the comprehensive treatment of patients with advanced liver cancer, benefiting many patients.

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