

Application and Research Progress of Radiotherapy in Unresectable Hepatocellular Carcinoma

Chunrou Qin, Kehe Chen

Youjiang Medical University for Nationalities, Baise, Guangxi, China

Abstract: Unresectable hepatocellular carcinoma (uHCC) accounts for 70%-80% of newly diagnosed hepatocellular carcinoma (HCC) cases, presenting significant clinical challenges in treatment. Conventional therapies such as transarterial chemoembolization (TACE) or systemic approaches (targeted/immunotherapy) have shown limited efficacy, with a 5-year survival rate below 15%. Recent advancements in precision radiotherapy technologies (stereotactic body radiation therapy [SBRT], proton/heavy ion therapy) combined with synergistic exploration of immunotherapy and targeted therapies have transformed radiotherapy from a palliative to a curative modality. This systematic review examines the technological progress, core clinical applications, challenges, and controversies in uHCC radiotherapy over the past five years, while outlining future research directions to inform clinical practice and scientific inquiry.

Keywords: Liver Tumor; Hepatocellular Carcinoma; Radiotherapy; Radiotherapy Techniques.

1. Foreword

1.1. Epidemiology of HCC and Definition of uHCC

Hepatocellular carcinoma (HCC) is the sixth most common malignant tumor globally. According to GLOBOCAN data from 2023, its annual new cases reached 865,000, with 759,000 deaths, and China contributed nearly 50% of the global new cases and deaths [1]. HCC has an insidious onset, and approximately 70% of patients are initially diagnosed as uHCC due to tumor invasion of major blood vessels (such as portal vein thrombosis/PVTT), multiple intrahepatic metastases, extrahepatic oligometastases, or decompensated liver function (Child-Pugh B/C stage) [2]. According to the BCLC staging, uHCC includes BCLC B/C stage and some BCLC A stage cases that are inoperable due to comorbidities, with extremely poor prognosis. The median overall survival (OS) with simple TACE treatment is only 12-14 months, and the objective response rate (ORR) with targeted therapy (such as sorafenib, lenvatinib) or immunotherapy (such as atezolizumab, sintilimab) is less than 20%, with a 5-year survival rate of <15% [3-4].

1.2. Historical Development and Current Status of Radiotherapy in HCC Treatment

Radiotherapy was once considered a "contraindication" for HCC due to the liver's radiation sensitivity and the low tolerable dose for normal liver tissue (average whole liver dose <30 Gy). However, with advancements in image-guided radiotherapy (IGRT), dose-conformal algorithms (such as VMAT), and biological effect modulation, radiotherapy has evolved from a palliative pain management approach to a critical local treatment for uHCC. In recent years, landmark studies have demonstrated that SBRT achieves a local control rate (LC)>90% for small-volume uHCC, proton therapy can safely treat large-volume or PVTT-type HCC, and radiotherapy combined with immunotherapy shows potential for "off-boost effects" [5-7]. This article will review technological advancements, clinical applications, and future directions in this field.

2. Advances in Radiotherapy Technology: Precision and Multimodal Fusion

2.1. Stereotactic Body Radiotherapy (SBRT): A Revolution in High-Dose, Fractionated Treatment

SBRT delivers high-dose radiation (≥ 100 Gy BED) in single or 3-5 fractions, achieving highly conformal tumor dosing through multi-field coplanar/non-coplanar irradiation while minimizing exposure to surrounding normal tissues. Its core technologies include: Target definition: Using enhanced CT/MRI fusion or PET-CT combined with tumor motion tracking (e.g., respiratory gating or real-time monitoring) to expand the internal target volume (ITV), followed by external expansion to 5-8 mm for the planning target volume (PTV). Dosimetric advantages: A single fraction of 8-12 Gy (total 48-60 Gy/5 fractions) with <15% normal liver V30 (≥ 30 Gy volume) results in <5% severe radiation-induced liver damage (RILD) [8]. A 2022 multicenter Korean study (n=327) demonstrated SBRT achieved 92% 1-year local control (LC) for ≤ 10 cm uHCC, with median OS of 18.6 months (no statistically significant difference from surgery, 19.2 months, P=0.72) [9]. Indications expanded: From early-stage HCC to large-volume (>5 cm) or hilar tumors. In 2023, Japanese researchers reported that SBRT combined with TACE for 6-10 cm uHCC increased 1-year LC to 89% (compared to 78% with SBRT alone), suggesting that locally advanced tumors can benefit from "radiation sensitization" [10].

2.2. Volume Modulated Anamorphic Tomography (VMAT): Dynamic Optimization of Dose Distribution

VMAT dynamically adjusts radiation intensity within a 360° range through gantry rotation and dose rate modulation, achieving more uniform target coverage while minimizing exposure to healthy tissues. Compared to traditional 3D conformal radiotherapy (3D-CRT), it demonstrates significantly improved efficiency, reducing treatment time to 5-

10 minutes and enhancing patient compliance. Furthermore, optimized radiotherapy dosing was observed in a 2023 Taiwanese study involving 120 uHCC patients. The VMAT group showed significantly lower normal liver V30 (11.2% vs 18.5%) and gastric V15 (8.7% vs 15.3%) compared to the 3D-CRT group ($P < 0.05$), with superior 2-year local control (85% vs 72%) and overall survival (OS) (16.8 vs 12.4 months) [11]. For hilar or inferior vena cava adjacent tumors, VMAT avoids spinal cord and kidneys through non-coplanar fields. A 2024 single-arm trial demonstrated 81% 2-year local control for hilar uHCC with only 2% grade 3 toxicity [12].

2.3. Proton and Heavy Ion Therapy: Dual Advantages of Physical and Biological Effects

Proton therapy leverages the Bragg peak property to concentrate over 90% of radiation dose in the tumor target area, followed by a sharp dose drop, significantly reducing exposure to the liver and surrounding organs (stomach, duodenum). Heavy ion therapy (e.g., carbon ions) demonstrates higher relative biological effectiveness ($RBE \approx 2.5-3.0$), delivering stronger cytotoxicity against hypoxic tumor cells. The 2024 multicenter Phase II trial in South Korea (NCT03186385) enrolled 85 uHCC patients (median tumor size 6.2 cm, 23% with PVTT), with a median follow-up of 24 months. The 1-year local control (LC) rate reached 94%, while grade 3+ toxicity (primarily fatigue and thrombocytopenia) occurred in only 3% of cases. Subgroup analysis revealed a 2-year overall survival (OS) of 38% in patients with PVTT (compared to 15% in the TACE-only group) [13], indicating significant efficacy with acceptable side effects. In 2023, the Heidelberg Ion Therapy Center in Germany reported that carbon ion therapy achieved a 3-year OS of 41% for large-volume uHCC (> 10 cm, $n=42$), significantly outperforming photon radiotherapy (28%, $P=0.03$) with a RILD incidence rate of 7% (compared to 15% in the photon group) [14]. This mechanism may be attributed to heavy ions inducing stronger immunogenic cell death (ICD).

3. Core Application Scenarios of Radiotherapy in uHCC

3.1. Radical Transformation Therapy for Locally Advanced uHCC

For locally advanced uHCC, particularly when combined with PVTT or intrahepatic metastases without distant dissemination, radiotherapy serves as the primary treatment modality. By ablating tumors locally, reducing tumor size, or eliminating PVTT, it creates favorable conditions for surgical resection.

3.1.1. Combined PVTT and uHCC: Radiotherapy with TACE

PVTT is an independent factor for poor prognosis in uHCC (with a median OS of only 3-6 months) [15]. Radiotherapy can directly act on the tumor thrombus, and combined with TACE can synergistically control intrahepatic lesions. In the 2022 China multicenter study ($n=156$), the median OS in the SBRT (50 Gy/5 times) combined with TACE group reached 16.3 months, with a 1-year conversion to surgery rate of 18% (compared to 5% in the TACE-only group), and a RILD incidence of 4% (related to Child-Pugh classification) [16]. Another Japanese study ($n=92$) using VMAT combined with sorafenib for hilar PVTT-type uHCC achieved a 3-year OS of 32% (vs 15% in the sorafenib-only group), suggesting that

radiotherapy can overcome hemodynamic impairments caused by PVTT [17].

3.1.2. Hepatic Metastatic uHCC: "Tumor-Reducing Radiotherapy" Combined with Systemic Therapy

For uHCC patients with ≥ 3 intrahepatic lesions without distant metastases, SBRT serves as a tumor reduction modality to alleviate tumor burden. Data from the 2023 MD Anderson Cancer Center in the United States demonstrated that SBRT (48 Gy/4 fractions) combined with atezolizumab and bevacizumab (ATEZO/BEV) for 4-6 intrahepatic lesions (≤ 5 cm each) achieved a median progression-free survival (PFS) of 10.2 months (6.8 months with systemic therapy alone), with overall response rate (ORR) increasing from 22% to 41% [18]. Mechanistically, radiation-induced tumor antigen release enhances the immune response to systemic therapy.

3.2. Local Control and Survival Extension of HCC with Oligotransplantation

For uHCC patients with oligometastases (≤ 5 extrahepatic metastases, such as lung, lymph node, or adrenal), combining SBRT for metastatic lesions with primary tumor treatment significantly prolongs PFS. A 2023 international multicenter retrospective study ($n=214$) demonstrated a 1-year local control rate of 91% with SBRT for metastases, achieving a median PFS of 12.4 months (vs. 6.8 months with systemic therapy alone). Subgroup analysis showed the most significant benefit in lung metastasis patients (median PFS 14.1 months vs. 5.2 months), likely due to the immunomodulatory effects of low-dose radiation in the lungs [19]. Another French study ($n=87$) evaluating SBRT combined with PD-1 inhibitors for adrenal oligometastases reported a 2-year OS rate of 58% (vs. 32% with systemic therapy alone), suggesting that radiotherapy can enhance the remote effects of immunotherapy [20].

3.3. Radiotherapy Combined with Immunotherapy: Synergy from "Local" to "Systemic"

Radiotherapy triggers 'immunogenic cell death' (ICD), which releases damage-associated molecular patterns (DAMPs). These DAMPs activate dendritic cells (DCs) to present antigens, recruit CD8+ T cells to infiltrate the tumor microenvironment (TME), and synergize with immune checkpoint inhibitors (ICI) to enhance anti-tumor immunity.

3.3.1. Mechanism Exploration: Radiotherapy Reconstructs TME

Basic research demonstrates that SBRT (8 Gy \times 3) induces PD-L1 expression in HCC cells (up to 3-5 times higher) and significantly enhances CD8+ T cell infiltration (2.1 times more than in radiotherapy-only groups) [21]. Single-cell sequencing further reveals that after radiotherapy, the proportion of M1-type macrophages in the tumor microenvironment (TME) rises from 12% to 35%, while myeloid-derived suppressor cells (MDSC) decrease from 28% to 15%, indicating reversal of the immunosuppressive state [22].

3.3.2. Clinical Studies: From Phase II to Phase III Exploration

In a Phase II trial ($n=40$) published in JCO in 2022, the combination of SBRT (50 Gy/5 fractions) with pembrolizumab achieved a 45% overall response rate (ORR) (RECIST 1.1) for uHCC, with a median overall survival (OS) of 21.6 months. Four cases (10%) demonstrated extrahepatic

lesion regression (off-boost effect) [23]. Updated data from the 2024 ASCO meeting revealed significantly better outcomes for patients with PD-L1 CPS $\geq 10\%$ (ORR 62% vs 28%, $P=0.02$), highlighting the need for biomarker-guided stratified therapy [24]. Another Phase I/II study evaluating radiotherapy combined with bispecific antibodies (e.g., EGFR \times CD3) for uHCC showed an initial ORR of 58% without increased grade ≥ 3 toxicity [25], providing insights for novel immunotherapy combination strategies.

4. Challenges and Controversies: From "Technically Feasible" to "Precise and Safe"

4.1. Prediction and Management of Radiation-Induced Liver Damage (RILD)

RILD (radiation-induced liver disease) is the primary limitation of radiotherapy, categorized into classical (elevated liver enzymes with ascites/hepatic encephalopathy) and subclinical (only imaging abnormalities). Its occurrence is closely related to the normal liver volume, baseline liver function (Child-Pugh score, ALBI index), and radiation dose.

4.1.1. Prediction Model: From Experience to Imaging Omics

In 2023, the European Organization for Research and Treatment of Cancer (EORTC) developed a CT imaging-based RILD prediction model that integrates liver parenchymal heterogeneity (entropy), portal blood flow (CT perfusion parameters), and clinical indicators (Child-Pugh B grade), achieving an AUC of 0.89 to identify high-risk patients (probability $>20\%$) [26]. A domestic MRI-based T2 mapping model also demonstrated predictive efficacy for RILD (AUC=0.85) [27].

4.1.2. Clinical Management: Dose-Limiting and Intervention Strategies

Current clinical guidelines recommend maintaining normal liver V30 $<10\%$ and V20 $<20\%$ to reduce the risk of radiation-induced liver disease (RILD) [28]. For high-risk patients (e.g., Child-Pugh B grade), fractionated radiotherapy can be implemented by replacing 4-5 Gy \times 10 sessions with 6-8 Gy \times 5 sessions to minimize single-dose exposure. Concurrently, using polyene phosphatidylcholine antioxidants in combination with ursodeoxycholic acid during radiotherapy to improve cholestasis may reduce grade 3 RILD incidence to $<3\%$ [29]. Additionally, early intervention for hepatic dysfunction is advised. When ALT/AST levels exceed three times the upper limit of normal (ULN), prompt corticosteroid therapy (e.g., prednisone 0.5 mg/kg/day) can reverse subclinical RILD.

4.2. Individualized Radiotherapy Guided by Biomarkers

Currently, there is a lack of clear prognostic biomarkers. A 2022 study in China showed that the clearance rate of circulating tumor DNA (ctDNA) 4 weeks after SBRT treatment was positively correlated with PFS (HR=0.32, $P=0.01$), which can serve as an efficacy monitoring indicator [30]. Meanwhile, studies have demonstrated that patients with abundant CD8 $^+$ T cell infiltration show better responses to radiotherapy combined with immunotherapy (ORR 58% vs 22%, $P=0.003$) [31]. Some scholars pointed out that HCC with TP53 mutation type has lower sensitivity to SBRT (LC 78% vs 92%, $P=0.04$), suggesting the possibility of combining targeted therapy [32].

5. Outlook: The Future from "Local Treatment" to "Systematic Regulation"

5.1. Multimodal Imaging-Guided Precision Radiotherapy

Future radiotherapy will rely on MRI or PET-CT fusion imaging to achieve dynamic target tracking. By monitoring tumor movement in real-time through 4D-MRI, the PTV expansion range can be reduced from 8 mm to 5 mm, minimizing exposure to normal tissues. Additionally, SUV values based on PET or diffusion-weighted imaging (DWI) parameters from MRI will help distinguish high-metabolism regions, enabling 'dose gradient' irradiation.

5.2. Deep Synergy between Radiotherapy and Novel Immunotherapy

Studies have demonstrated that combining radiotherapy with EGFR/CD3 bispecific antibodies or HER2-ADC can enhance tumor-specific T-cell recruitment. Research indicates that proton radiotherapy pretreatment eliminates immune suppressor cells (e.g., Treg) and improves CAR-T cell infiltration efficiency in solid tumors. Furthermore, radiotherapy combined with DNA methyltransferase inhibitors (e.g., 5-fluorouracil) enhances tumor antigen expression and dendritic cell maturation.

5.3. Precision Stratified Therapy based on Multi-omics

By integrating genomic data (TP53 and TERT mutations), transcriptomic profiles (PD-L1 expression), imaging data (tumor heterogeneity), and clinical parameters (Child-Pugh score and AFP), we developed predictive models to guide treatment strategies: SBRT for high-risk patients versus conventional fractionated radiotherapy for low-risk patients. In combination regimens, PD-L1-positive patients are prioritized for immunotherapy (ICI), while VEGF-high patients receive anti-angiogenic agents.

6. Conclusion

Breakthroughs in precision radiotherapy technologies (SBRT, proton/heavy ion) and their synergies with immunotherapy and targeted therapies have significantly expanded the treatment options for uHCC. Radiotherapy not only achieves high local control rates but also activates systemic immunity by reshaping the tumor microenvironment (TME), delivering survival benefits to uHCC patients. Future research should validate optimal regimens through large-scale randomized controlled trials (RCTs) and explore biomarker-guided personalized strategies to promote standardized and precision radiotherapy applications in uHCC.

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