Basis and prospects of radiotherapy combined with high-intensity focused ultrasound ablation (Review)

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Abstract. Radiotherapy (RT) and high-intensity focused ultrasound (HIFU) are important local treatments for solid tumors; however, they have notable limitations. RT can damage the surrounding normal tissues and vascular system, limiting the maximum dose that can be safely delivered to the tumor, and potentially contributing to local recurrence. Furthermore, RT courses are typically protracted and cannot easily be repeated in the same field. The efficacy of RT is also reduced in radioresistant cells, such as those in hypoxic niches or in specific cell cycle phases. By contrast, HIFU achieves non-invasive tumor ablation through focused thermal energy while sparing adjacent tissues. However, its use is restricted to tumors without air or bone in the ultrasound path, such as those in the liver or prostate. Currently, HIFU is primarily used for palliation and cannot eradicate subclinical diseases. Its optimal integration with other modalities remains unknown. A synergistic combination of RT and HIFU has been proposed to overcome these limitations. Preclinical studies have indicated that HIFU can effectively target radioresistant tumor regions, whereas RT can reduce tumor volume and alter the tumor microenvironment, thereby enhancing subsequent HIFU ablation. Some clinical research on cancer, including hepatocellular carcinoma and pancreatic, prostate and bone metastases, suggests that this combined approach can improve outcomes such as pain relief, local control and survival, with a manageable safety profile. The present review summarizes the fundamental rationale and accumulates clinical evidence supporting the combined use of RT and HIFU, and discusses the current challenges and future directions for this integrated approach.

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1. Introduction

Radiotherapy (RT) is the cornerstone of modern oncology and plays an indispensable role in the curative and palliative treatments of various solid tumors, including head and neck, early-stage lung and prostate cancer. Current evidence-based medical data indicate that ~50% of patients with cancer benefit from RT during their treatment journey, further underscoring its pivotal role in multidisciplinary cancer care (1). The advent of precision technologies, such as intensity-modulated RT (IMRT) and stereotactic body RT (SBRT), has enabled more accurate tumor irradiation (2). Despite these technical advances, the efficacy of RT remains constrained by the tolerance of the surrounding normal tissues, which limits dose ceilings and increases the risk of local recurrence (3). Furthermore, RT has limited efficacy against biologically radioresistant cell populations (such as hypoxic cells) (4), and generally cannot be repeated within previously irradiated areas (5).

High-intensity focused ultrasound (HIFU) has emerged as a well-recognized non-invasive ablative modality. By extracorporeally focusing acoustic energy to induce localized coagulative necrosis via precise thermal ablation (≥60˚C) at a focal point, tumor destruction can be achieved with minimal

damage to the intervening tissues (6). This non-ionizing approach offers a distinct therapeutic advantage for tumors in acoustically accessible organs such as the liver, kidney and prostate, as it enables precise, non-invasive ablation while preserving organ function (7). However, the clinical utility of HIFU is limited by physical and biological constraints. The presence of air or bone along the ultrasound path impedes energy delivery and precludes the treatment of thoracic or bowel-adjacent lesions (8). Furthermore, HIFU does not eliminate subclinical lesions when used as a therapeutic modality. Consequently, its efficacy is often limited to localized or palliative treatments. To achieve better therapeutic outcomes, combining HIFU with radiotherapy or systemic therapy is often necessary (9).

Notably, the limitations of RT and HIFU do not overlap. The former primarily faces challenges in radiobiology and radiophysics, whereas the latter is constrained by the physical and anatomical limitations of the ultrasound pathway. The non-overlapping nature of these limitations provides a solid theoretical foundation for the combined application of both therapies. Preclinical studies have indicated the synergistic effects of combined therapy: HIFU effectively ablates radiation-resistant tumor regions, whereas RT reduces lesion volume and alters tumor microarchitecture (for example, by decreasing intratumoral blood flow), potentially enhancing subsequent HIFU efficacy (10-12). In addition to direct tumor cell killing, this combination therapy may also effectively modulate antitumor immune responses by altering the tumor microenvironment; for example, radiotherapy has been shown to reduce blood perfusion and induce microvascular damage, while HIFU (particularly mechanical HIFU) disrupts the collagen matrix and releases damage-associated molecular patterns (DAMPs) that promote T-cell activation. These complementary alterations may therefore open new avenues for immunotherapy combinations (7,11,13).

Based on this rationale, clinical research on the combination of RT and HIFU continues to advance. The present review aims to integrate the existing basic research evidence and clinical study data to determine if this combined treatment approach should be supported. Specifically, it includes details on the independent limitations of both therapies, analyzes the potential underlying mechanisms of the synergistic effects, evaluates the clinical efficacy of combined RT and HIFU for various malignant tumors, and explores the current challenges and future directions of combined treatment strategies.

2. Limitations of RT

The clinical application of RT is limited by several critical factors in radiophysics, radiobiology and the clinical environment. The primary limitation stems from radiation damage to normal tissues. To control tumors, radiation must penetrate the surrounding healthy tissues, inevitably causing acute or chronic radiation injury to vital organs such as the skin, mucous membranes, lungs and spinal cord, while suppressing the hematopoietic system (14). The fundamental cause of these side effects is the existence of a clear upper limit to the radiation dose that normal organs and tissues can tolerate, known as the 'organ at risk (OAR) dose limit,' which is a primary concern for clinical radiation oncologists. This limit prevents the safe administration of sufficiently high curative doses for numerous tumors, particularly those that are large or located in challenging anatomical positions, thereby increasing the risk of local residual disease or recurrence (15). Furthermore, the cumulative radiation dose delivered to normal tissues progressively increases with each subsequent RT session. This makes multiple RT treatments (retreatment) at the same site clinically challenging and high-risk, markedly limiting local treatment options for patients with recurrence (16).

Secondly, the intrinsic resistance of certain tumor cells to radiation is an inherent limitation of RT. Among the various resistance mechanisms, the resistance of hypoxic cells represents one of the most classic biological mechanisms. DNA radicals generated by ionizing radiation require the stabilizing effect of oxygen molecules (O_2) to effectively induce DNA damage (17). The widespread presence of hypoxic zones within solid tumors markedly reduces the sensitivity of cells in these areas to radiation. These hypoxic zones often require radiation doses two to three times higher than those required in well-oxygenated areas to achieve equivalent killing effects, making them primary sites for post-treatment recurrence (18,19). Persistent hypoxia can arrest cells in the G_1 phase of the cell cycle, reducing the effects of RT on these cells (20). Cellular cycle heterogeneity results in distinct radiation resistances. Cells at different phases of the cell cycle demonstrate vastly different sensitivities to radiation; mitotic phase (M phase) cells are the most sensitive, whereas DNA synthesis phase (S phase) cells exhibit marked resistance. Tumor cell proliferation is not synchronized, indicating that during any single irradiation session, a proportion of cells will invariably be in a relatively resistant phase, enabling sustained survival (21).

Finally, RT also has limitations with respect to its clinical implementation. Precision RT techniques, such as IMRT and image-guided RT, often involve complex workflows. CT simulations and meticulous target delineation for complex treatment planning require specialized expertise and time. Furthermore, the use of immobilization devices such as thermoplastic masks contributes to patient discomfort. In clinical practice, a standard course of curative RT typically requires continuous treatment for several weeks, administered daily without interruption (excluding weekends and holidays in most cases). This poses challenges for the currently strained medical resources, patient and family compliance, and patient quality of life (22).

3. Limitations of HIFU

HIFU, a non-invasive localized thermal ablation technique, has unique advantages in treating various benign and malignant tumors. However, this method also has several limitations. The most fundamental constraint stems from the physical limitations encountered along the ultrasound path, as its core principle relies on the predictable transmission and focusing of ultrasound within the tissue. Consequently, strong reflections or scattering along the acoustic pathway severely impede treatment efficacy. Gases within the lungs and intestines generate intense acoustic reflections, causing the majority of ultrasound energy to be reflected before reaching the target lesion and preventing penetration. This renders lung cancer within the thoracic cavity and abdominal tumors obscured by intestinal

gas physically inaccessible for HIFU treatment (23). Irregular high-density tissues, such as bone, cause severe acoustic scattering, which not only markedly attenuates energy but also impairs ultrasound focusing. This makes treating lesions adjacent to or behind the bone extremely challenging, thereby compromising efficacy assessment (24). These physical limitations strictly confine HIFU indications to solid organs with favorable acoustic pathways and no gas or bone obstruction, such as the liver, kidneys, prostate and uterus (6,8). Furthermore, the volume ablated in a single session is limited to a small area around the focal point. For larger tumors, multiple sessions with multiple focal points arranged in a grid-like pattern are required to cover the entire tumor and complete the treatment. Consequently, during HIFU treatment, overlapping or uneven heat distribution may leave residual lesions within the tumor, thereby increasing the risk of local recurrence (25).

Second, the interaction between the internal tumor characteristics and heat conduction processes adds complexity to the treatment. Although thermal ablation itself does not depend on cellular oxygenation status, tumor heterogeneity directly affects the efficacy of HIFU treatment. In regions with a rich blood supply, persistent perfusion accelerates local heat dissipation (thermal diffusion), potentially preventing temperatures from being sustained above the threshold required for complete protein denaturation (typically >60˚C). This creates 'danger zones' within the tumor where ablation is incomplete (26). More critically, HIFU is a localized ablation modality that relies on imaging and physician judgment, and its therapeutic scope is limited to visually detectable tumor regions; it cannot fully address subclinical infiltrates and metastases that are only visible under a microscope (27). This fundamental characteristic limits the curative potential of HIFU as a stand-alone treatment for most clinically significant malignancies, which inherently carry the risk of metastasis. Consequently, the primary therapeutic role of HIFU is to achieve localized lesion control and palliative symptom relief.

Currently, according to authoritative domestic and international cancer diagnosis and treatment guidelines (9,28), HIFU remains primarily used as a palliative or local salvage therapy, such as in patients with advanced disease to relieve tumor compression or in those with local recurrence after curative RT. However, the combination of HIFU with other antitumor therapies has not yet been fully explored. For instance, there is a lack of high-quality evidence-based medical data or authoritative consensus guidelines regarding the optimal timing and sequence for combining HIFU with different antitumor therapies, such as RT, chemotherapy or immunotherapy, are lacking (29,30). This area requires further investigation of HIFU treatment.

4. Basis of combined RT and HIFU

The combination of RT and HIFU has multiple scientific applications. First, it enables better utilization of spatial positioning to achieve complementary effects between the two treatments, while reducing their respective side effects. RT targets the gross tumor volume (GTV) visible on imaging and the potential subclinical infiltration area [clinical target volume (CTV)] (31). Conversely, HIFU, a non-invasive ablation modality, is strictly limited to effectively treating the visually identifiable GTV (32). Therefore, the combined approach theoretically enables RT to control the subclinical infiltration around the tumor, whereas HIFU further enhances the tumoricidal effects of RT within the tumor itself. This complementarity has unique advantages at specific anatomical locations. For instance, tumors in the abdominal cavity near the gastrointestinal tract face limitations; HIFU can only partially treat these areas owing to intestinal air obstruction, whereas RT is restricted by OAR dose constraints for the stomach. As shown in Fig. 1, the proximity of tumors to the stomach makes it difficult for RT to deliver a curative dose directly to the tumor body. A combination of HIFU therapy can enhance the efficacy. The region above the tumor (area A), free from air obstruction along the ultrasound path, is suitable for HIFU treatment, whereas the region below the tumor (area B), obstructed by gas, cannot receive effective HIFU therapy (33). Although curative doses cannot be delivered to the tumor itself, RT can precisely cover the entire tumor region (GTV), including area B and the subclinically infiltrated area (CTV), compensating for the physical limitations of HIFU. Fig. 2 demonstrates that for tumors insensitive to RT, such as primary hepatocellular carcinoma, soft-tissue sarcomas and pancreatic cancer, HIFU can non-invasively ablate the visually detectable GTV, enhancing local tumor destruction. HIFU is ineffective against subclinically infiltrated areas within the CTV, whereas RT can deliver therapeutic doses to both the GTV and the CTV simultaneously. This resolves the inability of HIFU to address potential tumor infiltration zones (34).

As aforementioned, the efficacy of RT is severely limited by the effects of hypoxia. Hypoxic regions exhibit two to three times greater resistance to radiation, and cells within these areas frequently become sites of recurrence (35). However, the tumor cell-killing mechanism of HIFU does not depend on the oxygen concentration. Instead, it effectively eliminates hypoxic cell clusters resistant to RT through multiple mechanisms, including inducible coagulative necrosis via high-temperature effects (≥60˚C), mechanical effects and cavitation-induced irreversible tumor cell damage (36). Furthermore, cells in the synthesis phase (S-phase) of the cell cycle are relatively insensitive to RT. Although no studies have directly demonstrated the specific killing effect of HIFU on S-phase cells, the thermal and mechanical effects of HIFU enable broad tumor cell destruction, potentially including cells in the S phase (37,38). Preliminary RT can effectively shrink tumors and reduce their blood supply (39), preventing heat dissipation during subsequent HIFU treatment due to abundant tumor perfusion, thereby enhancing therapeutic efficacy (40). Conversely, prior HIFU treatment can reduce the tumor burden and potentially improve oxygenation in residual tumors, creating favorable conditions for subsequent RT (36,41).

Both RT and HIFU have been demonstrated to induce immunogenic cell death (ICD) (42). Specifically, RT triggers endoplasmic reticulum stress and reactive oxygen species accumulation, and dysregulates autophagy through ionizing radiation, thereby promoting antigen exposure or the release of DAMPs, such as high-mobility group box 1 (HMGB1) and adenosine triphosphate (ATP), from tumor cells, which activate immune responses (43,44). Similarly, HIFU induces tumor cell necrosis/apoptosis through thermal effects (>60˚C) or mechanical cavitation, releasing DAMPs [such as HMGB1,

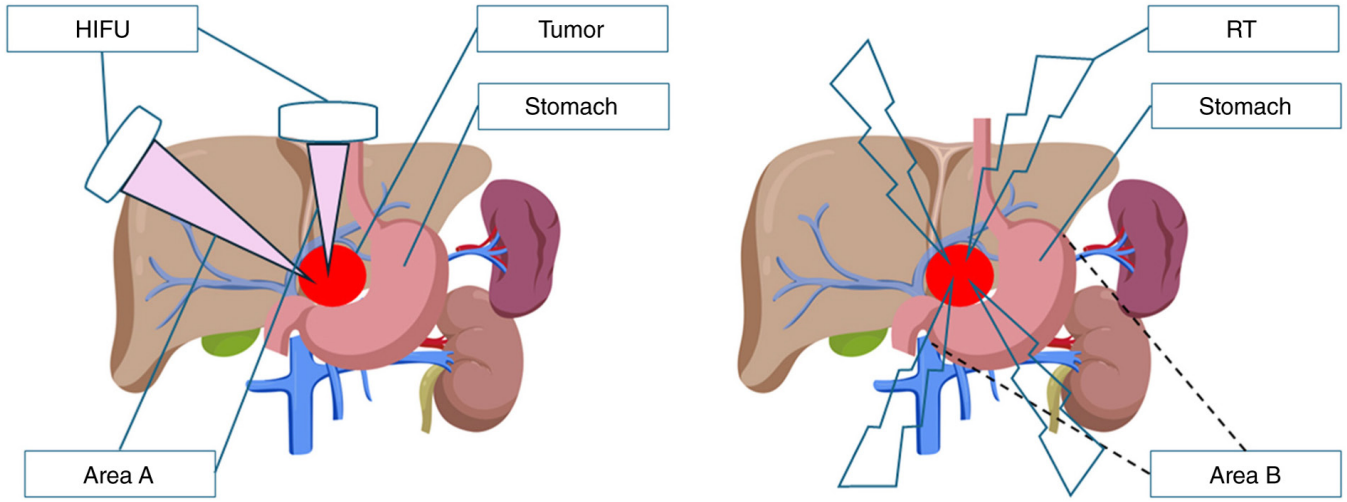

Figure 1. Combined RT and HIFU in the treatment of tumors. A schematic diagram demonstrating the complementary roles of HIFU and RT for a tumor adjacent to the stomach. HIFU, high-intensity focused ultrasound; RT, radiotherapy.

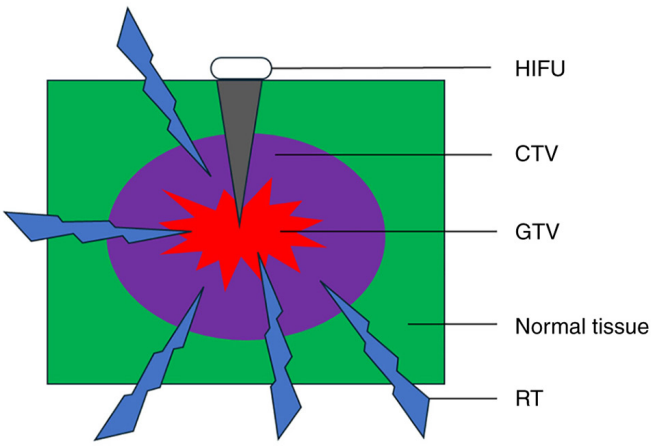

Figure 2. Schematic diagram of RT combined with HIFU. Illustrative comparison of treatment volumes: HIFU ablates only the GTV, while RT covers both the GTV and the CTV. HIFU, high-intensity focused ultrasound; CTV, clinical target volume; GTV, gross tumor volume; RT, radiotherapy.

heat shock protein 70 (HSP70) and ATP]. The triggered ICD promotes dendritic cell (DC) maturation and T-cell infiltration, reversing immunosuppression and even generating distant effects (11,45-49). Although RT and HIFU can independently induce immunogenic cell death and modulate the tumor microenvironment, their mechanisms are complementary. RT induces cytoplasmic double-stranded DNA (dsDNA) accumulation, activates the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) pathway, and subsequently induces type I interferon production. Concurrently, irradiated tumor cells release HMGB1, which binds to Toll-like receptor 4 (TLR4) on DCs, promoting antigen cross-presentation via the myeloid differentiation primary response 88 adaptor protein (50,51). These two pathways converge to drive DC maturation and $CD8^+$ T-cell priming. The thermal effects of HIFU can induce the release of HMGB1 and the membrane translocation of HSP70/HSP90, thereby activating the TLR4 signaling pathway (52). Importantly, the mechanical effects of HIFU (resulting in more immunogenically intact tumor antigens) trigger an earlier and more abundant release of HMGB1 accompanied by a potent release of dsDNA. Consequently, TLR4 activates the cGAS-STING pathway (53,54). Therefore, the combination of RT and HIFU can synergistically activate the cGAS-STING and TLR4 pathways, thereby enhancing the activity of these two signaling axes and boosting anti-tumor immunity (Fig. 3). Cirincione *et al* (55) systematically compared the differential effects of both therapies on tumor DAMP release, DC activation and T-cell responses, suggesting that combination therapy may synergistically enhance anti-tumor immune responses (55). However, further preclinical studies are required to validate these hypotheses.

5. Clinical studies of combined RT and HIFU

In recent years, a combination of RT and HIFU has been increasingly adopted in clinical practice for various solid tumors. However, relevant clinical studies have not consistently emerged. As shown in Tables I and II, most studies in this area are retrospective, involve small sample sizes and were conducted at a single center. These study designs are subject to inherent biases (such as selection bias) and heterogeneity in treatment protocols (for example, variation in radiation dose, HIFU parameters and sequencing). Currently, there is a lack of high-quality large-scale prospective clinical studies on RT combined with HIFU to improve the level of evidence-based medicine for these combined treatment approaches. Therefore, we emphasize that prospective multicenter trials are urgently required to validate these preliminary findings. In hepatocellular carcinoma, earlier small-sample studies demonstrated that HIFU combined with RT exhibited good safety profiles, with objective response rates and 1-year survival rates reaching >80% (56,57). Ma *et al* (58) demonstrated that HIFU combined with SBRT for hepatocellular carcinoma resulted in notable clinical improvement at 3 months, marked reductions in AFP and CA19-9 levels, and a substantial decrease in Child-Pugh scores according to the Child-Pugh classification system (59). For unresectable large hepatocellular carcinomas (typically >5 cm), single-modality local therapy often fails to

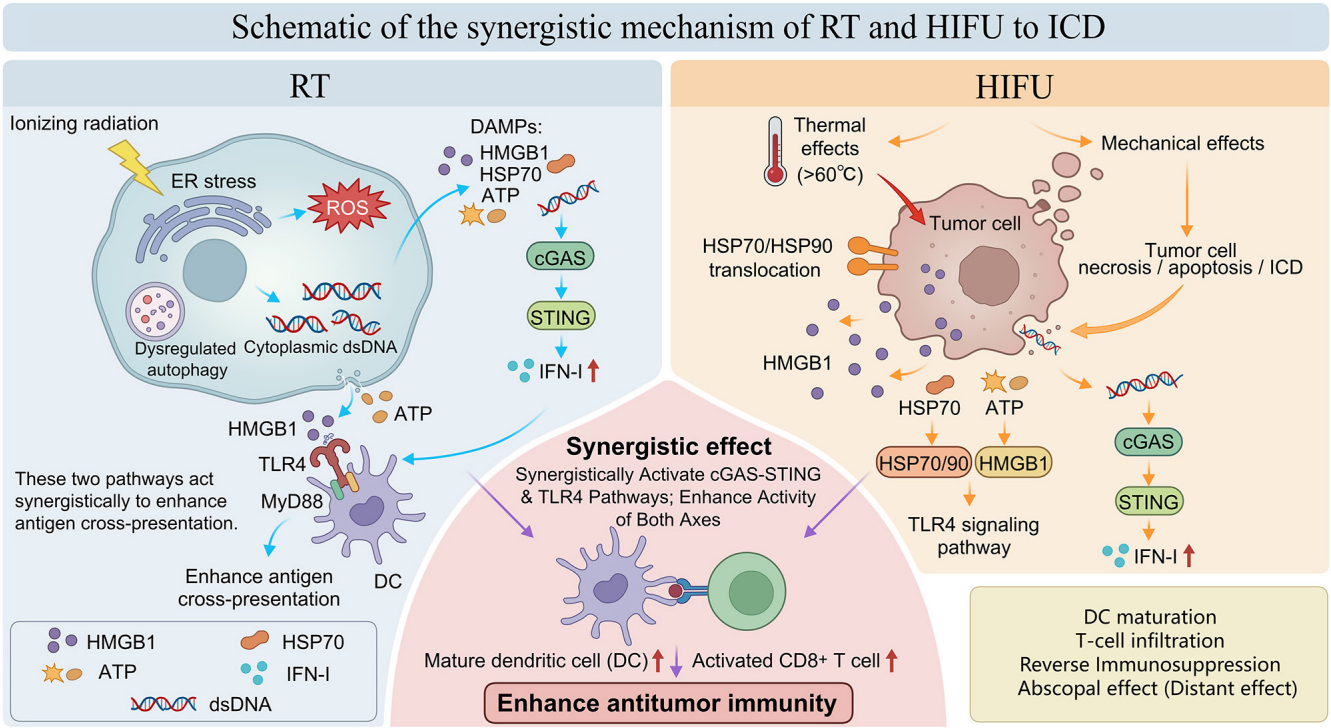

Figure 3. Schematic illustration of the synergistic molecular mechanisms of RT and HIFU in inducing ICD. RT activates the cGAS-Sting pathway and the TLR4 pathway via double-stranded DNA and HMGB1, while HIFU activates both pathways simultaneously through thermal effects and the release of DAMPs. Their synergistic action promotes DC maturation, T-cell infiltration, and antitumor immune responses. HIFU, high-intensity focused ultrasound; RT, radiotherapy; DAMPs, damage-associated molecular patterns; ICD, immunogenic cell death; DC, dendritic cell.

achieve optimal efficacy. Another retrospective study directly compared the efficacy of SBRT, combined HIFU and SBRT, and SBRT alone in large hepatocellular carcinoma. The results demonstrated superior outcomes in the combination therapy group across tumor response rates and survival benefits, without increased treatment-related toxicity (60).

Refractory pain is a clinical manifestation of advanced pancreatic cancer. Numerous retrospective studies in China have demonstrated that HIFU combined with RT yields favorable efficacy and safety, with response rates >60% (61-63). Clinical symptom relief, particularly pain relief, can be quantified at >80% and can outperform RT alone. This approach also improves appetite and body weight, while reducing CA19-9 and CEA levels (64). Li (65) indicated that HIFU combined with RT further enhanced NK T cell and $CD4^+$ T cell-mediated antitumor immune responses, enabling more effective tumor cell destruction. Clinical research by Li *et al* (66) confirmed that the combined use of HIFU and RT markedly alleviated pain in most patients, with longer-lasting relief compared with HIFU alone. Furthermore, no serious adverse reactions occurred during or after the combined application of HIFU and RT.

In prostate cancer, numerous clinical studies have explored the combination of HIFU and RT for treating prostate cancer. However, most of these studies are retrospective or cohort studies that were conducted in China with relatively small sample sizes. The clinical research reported by Yao *et al* (67) demonstrated that HIFU combined with three-dimensional conformal RT achieved an efficacy rate >90% for treating prostate cancer, which was notably higher than that in the RT-only group, while also improving local tumor control rates. Compared with RT alone, the combination group also exhibited a marked reduction in RT-induced bone marrow suppression and radiation-induced inflammation (including radiation proctitis and cystitis), establishing it as an effective local treatment for locally advanced prostate cancer without surgical indications. Wu *et al* (68) further demonstrated that HIFU combined with RT achieved good local tumor control and enhanced patient immune cells. Internationally, particularly in France, numerous high-quality, large-sample systematic reviews and meta-analyses of prostate-related topics have been published. Although these studies only retrospectively analyzed prostate cancer recurrence after HIFU or RT and added to the efficacy and toxicity of other treatments, they provided some evidence for the potential feasibility of combining RT and HIFU as dual therapies (10,69).

Regarding bone metastases, an ongoing international, multicenter, phase III randomized controlled trial named the 'FURTHER Trial' is currently underway (ClinicalTrials.gov registration number NCT04307914; trial registration date: January 13, 2020) (70). The FURTHER Trial (ClinicalTrials.gov NCT04307914) is an ongoing phase III randomized controlled trial evaluating the combination of radiotherapy and focused ultrasound for pain palliation in patients with bone metastases. In the study by Bartels *et al* (71), 6 patients with bone metastases were treated using RT combined with HIFU. All the patients showed good tolerance to the combined treatment. In total, 5 out of the 6 patients had a pain relief reaction 7 days after the end of the combined treatment, and the pain response was stable at 60% during the 4-week follow-up. A summary of clinical studies on HIFU combined with RT is presented in Table I.

Table I. Summary of clinical studies on high-intensity focused ultrasound combined with radiotherapy.

First author, year	Site	Study design	Efficacy outcomes	Safety	(Refs.)
Jin *et al*, 2011	Liver	Feasibility	mOS time, 18 months; 1-year survival rate, 74.1%	Good safety profile	(56)
Jing, 2015	Liver	Cohort	3-, 6- and 12-month survival rates, 93.62, 78.72 and 57.45%, respectively (higher than radiotherapy alone)	Lower incidence of nausea/vomiting vs. radiotherapy alone	(57)
Ma *et al*, 2019	Liver	Observational	Clinical symptoms and tumor markers markedly decreased	No notable difference in liver function	(58)
Shi *et al*, 2020	Pancreatic	Retrospective	Tumor markers decreased; complete pain relief rate, 89%	Good safety profile	(61)
Zhuang *et al*, 2010	Pancreatic	Retrospective	Tumor markers decreased; complete pain relief rate, 57.14%	No obvious adverse reactions	(62)
Du *et al*, 2012	Pancreatic	Cohort	Objective response rate, 63.64%; clinical benefit rate, 95.45%; 2-year survival rate, 50%; mOS time, 17.6 months	Not reported	(63)
Cui *et al*, 2018	Pancreatic	Observational	Objective response rate, 52.17%; clinical benefit rate was notably higher than that in the radiotherapy-alone group	Good safety profile	(64)
Li, 2017	Pancreatic	Cohort	Enhanced antitumor immunity mediated by NK-T cells and $CD4^+$ T cells	Not reported	(65)
Yao *et al*, 2011	Prostate	Observational	Efficacy rate: >90%; enhanced immune cell activity	Notably lower radiation proctitis and myelosuppression vs. radiotherapy alone	(67)
Wu *et al*, 2012	Prostate	Retrospective	High local control rate; enhanced immune cell activity	Not reported	(68)
Bartels *et al*, 2021	Bone metastasis	Phase I/II prospective	High pain relief rate and long duration of stability	Good safety profile	(71)

mOS, median overall survival; NK, natural killer.

In addition to studies investigating the concurrent combination of RT and HIFU, several clinical trials have documented HIFU as a salvage modality in cases of RT failure and recurrence, among which research on prostate cancer is predominant. Systematic reviews encompassing >1,000 patients have indicated that salvage HIFU can provide effective oncological control after RT, with reported 5-year overall survival and incontinence rates of ~85 and 30%, respectively (72,73). Prospective registry studies have further substantiated this role, demonstrating acceptable midterm oncological outcomes (74,75). The keys to patient selection are pre-salvage PSA levels and biopsy characteristics, which serve as predictors of treatment response (76). The available evidence indicates that salvage HIFU is an effective and safe local treatment option for prostate cancer after recurrent RT. Jin *et al* (77) (2020) reported preliminary experience using HIFU to treat 24 residual lesions in 20 patients with hepatocellular carcinoma who had previously undergone SBRT. This study demonstrated the feasibility and safety of this sequential approach. For the treated lesions, HIFU achieved an ablation rate of 75.8±18.2%, with a complete ablation rate of 70.8%. The median overall survival time was 21 months, with a 1-year survival rate of 76.2%. Critically, no serious HIFU-related adverse events were reported and postprocedural liver function remained stable (77). Preliminary clinical analysis suggests that HIFU is a feasible and safe local treatment option for patients with residual hepatocellular carcinoma after RT (78). An early clinical analysis indicated that HIFU is a feasible, safe and effective salvage treatment to achieve a local pathological complete response in patients with cervical cancer and post-RT residual lesions (79). A summary of relevant clinical studies on salvage HIFU therapy following RT is presented in Table II.

Table II. Summary of clinical studies on salvage HIFU for post-radiotherapy residual/recurrent tumors.

First author, year	Site	Study design	Efficacy outcomes	Safety	(Refs.)
Sobhani *et al*, 2024	Prostate	Narrative review	Salvage HIFU as an effective local salvage option	Not reported	(72)
Maestroni *et al*, 2021	Prostate	Systematic review	5-year overall survival rate: 85.2%	Not reported	(73)
Baco *et al*, 2014	Prostate	Prospective two-center	Median follow-up 16.3 months; PFS rates at 12, 18 and 24 months, 83, 64 and 52%, respectively	Severe incontinence, 8% (4/48); pad-free rate, 75% (36/48)	(74)
Siddiqui *et al*, 2017	Prostate	Prospective registry	Median bRFS time, 63 months; 5-yr OS rate, 88%; CSS rate, 94.4%	Fistula and severe incontinence rates, 3.7% each	(75)
Dason *et al*, 2018	Prostate	Retrospective	Median 2- and 5-year RFS rates, 66.3 and 51.6%; undetectable PSA nadir was the sole predictor of improved RFS	Good safety profile	(76)
Jin *et al*, 2020	Liver	Feasibility	mOS time, 21 months; 1-year survival rate, 76.2%; ablation rate, 75.8±18.2%	Good safety profile	(77)
Su, 2015	Liver	Preliminary analysis	Marked reduction in AFP level and tumor size	Good safety profile	(78)
Yang *et al*, 2009	Cervix	Retrospective	Pathological complete response rate, 100% (14/14)	Good safety profile	(79)

HIFU, high-intensity focused ultrasound; mOS, median overall survival; RFS, recurrence-free survival; PSA, prostate-specific antigen; CSS, cancer-specific survival; bRFS, biochemical recurrence-free survival.

Notably, among the studies listed in Tables I and II, considerable heterogeneity was observed in the treatment sequence (RT before HIFU vs. HIFU before RT) and radiation dosage (ranging from conventional fractionation to SBRT). No study has systematically compared different sequences or dose levels, highlighting the urgent need for standardized protocols in future trials.

6. Prospects of combined RT and HIFU

The combination of HIFU and RT as two antitumor treatment modalities not only enhances tumor-killing efficacy but also modulates systemic and local antitumor immune responses. However, these studies were largely based on small sample sizes, and have not thoroughly addressed key clinical parameters, such as optimal treatment sequencing and dose optimization. Regarding treatment sequencing, the optimal sequence of RT and HIFU remains undefined and may depend on tumor characteristics. For hypoxic or radioresistant tumors, HIFU before RT can debulk the tumor, improve oxygenation and enhance radiosensitivity. Conversely, for tumors located near air-filled organs (such as the bowel), upfront RT may shrink the tumor and create a more favorable acoustic window for the subsequent HIFU. These two sequences may differentially affect the tumor immune microenvironment. Therefore, future clinical trials should include sequencing as a stratification factor. Combining RT with HIFU may allow radiation dose de-escalation (for example, reducing the total dose by 20-30%) while achieving equivalent local control, thereby lowering toxicity to organs at risk. For large or radioresistant tumors, standard RT doses can be maintained while adding HIFU to ablate the residual hypoxic cells; however, the underlying mechanistic basis remains unexplored. For instance, animal studies could be conducted to verify whether combining RT and HIFU, both of which have demonstrated antitumor immune activation effects, enhances their combined immune-activating capacity and whether this combination produces stronger 'distant effects.' These areas represent promising directions for future studies.

Traditional RT often induces tissue fibrosis, thereby impairing the HIFU acoustic pathways. Tissue along the HIFU treatment pathway that has previously received ≥45 Gy of RT is also a clear contraindication for HIFU. This fibrotic effect is dose-dependent and region-specific. Tissues receiving ≥45 Gy are at markedly higher risk of developing dense fibrosis, which can increase ultrasound attenuation, distort focusing, and raise the risk of skin or subcutaneous burns during subsequent HIFU (28,80). Therefore, when conventional RT is used before HIFU, careful assessment of the acoustic pathway is mandatory. FLASH RT is one of the most revolutionary advances in radiation oncology. First reported by Favaudon *et al* (81) in 2014, FLASH RT was used to irradiate mouse lungs at ultra-high dose rates (>40 Gy/sec). This approach achieved tumor control equivalent to conventional dose rates and significantly reduced

the pulmonary radiation injury. This phenomenon is termed the 'FLASH effect'. Subsequent studies validated this protective effect in various normal tissues, including the brain, intestines and skin (82-84). Therefore, replacing conventional RT with FLASH RT in combination therapy may fundamentally overcome this bottleneck, allowing patients to receive curative-dose RT without losing the option of subsequent HIFU treatment.

7. Summary

In the era of personalized cancer treatment, the selection of local therapies requires continuous learning and exploration by clinicians. Radiotherapy and HIFU have unique advantages; however, they have distinct limitations. Notably, their combination offers complementary benefits. HIFU enhances the tumor-killing efficacy of RT (for example, by overcoming resistance in hypoxic cells or S-phase cells), whereas while RT can address subclinical latent lesions that HIFU cannot directly treat. Combination therapy protocols integrating RT and HIFU are increasingly being adopted in clinical practice, although most related studies are retrospective and small-sample clinical investigations. Multiple studies have demonstrated the immune-activating effects for both RT and HIFU. This warrants further mechanistic research to explore whether their combination can synergistically alter the tumor immune microenvironment. Novel RT techniques such as FLASH RT have demonstrated tissue-sparing effects. Combining FLASH RT with HIFU is promising for overcoming the bottleneck in which high-dose RT for superficial tumors causes acoustic channel sclerosis, thereby precluding HIFU treatment. We anticipate that future advancements will yield additional combined local treatment strategies to benefit patients.

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Availability of data and materials

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Authors' contributions

LLF was responsible for conceptualization, funding acquisition and writing the original draft. XYY was responsible for conceptualization, review and editing, and writing the original draft. JL reviewed and edited the manuscript. YL performed the literature search, data extraction and project administration, and contributed to the drafting and critical revision of the manuscript. YXB was responsible for the design and creation of the figures, and writing the original draft. XM reviewed and edited the manuscript. LY and FG contributed to the critical review and editing of the manuscript. GF performed the literature search and data extraction, and reviewed and edited the manuscript. QLS was responsible for funding acquisition, and reviewing and editing the manuscript. XBD was responsible for conceptualization, study design, supervision, and manuscript review. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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