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Review Article

Advances in Research Based on Different Strategies to Improve Resistance to Radiotherapy in Cervical Cancer

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Abstract

Radiotherapy is one of the important means of treatment for cervical cancer, however, radio-inflammation and tumor radiotherapy resistance caused by high-dose radiotherapy seriously affects the compliance and success rate of patient treatment. In recent years, many studies have reported that radiotherapy combined with sensitizers, thermotherapy, targeted therapy, immunotherapy, and other strategies can effectively improve the radiosensitivity of cervical cancer cells and promote the killing effect of rays on tumor cells, which is crucial to the clinic. This article provides an overview of the signaling pathways involved in cervical carcinogenesis and systematically describes the mechanisms affecting resistance to radiotherapy in cervical cancer and the different strategies to improve resistance to radiotherapy. In addition, the predictive modalities of radiotherapy sensitivity in cervical cancer are summarized to develop new ideas and provide a reliable theoretical basis and systematic scientific reference for cervical cancer patients troubled by the presence of radiotherapy resistance in the course of radiotherapy.

Keywords: Cervical cancer; Radiotherapy; Sensitizer; Thermotherapy; Mechanism

Introduction

Currently, cervical cancer is still the malignant tumor with the highest incidence rate in the female reproductive tract [1,2]. The National Comprehensive Cancer Network (NCCN) and the International Federation of Gynecology and Obstetrics (FIGO) guidelines for standard treatment of cervical cancer state that cervical cancer with surgical access should be treated with radical cervical cancer surgery and that postoperative adjuvant therapy should be used depending on whether or not there is a combination of high-risk factors after surgery. External irradiation +/- chemotherapy for inoperable patients [3]. In addition, the World Health Organization launched the Global Cervical Cancer Elimination Strategy initiative [4]. To achieve this goal, it is necessary not only to provide vaccination coverage and promote standardized screening for cervical cancer but also to improve standardized diagnosis and treatment of cervical cancer patients. However, the development of medical services in many countries is not balanced. Most patients have advanced disease at diagnosis and can only receive radical or palliative radiation [5]. Therefore, it is important to study the sensitivity of radiotherapy for cervical cancer thoroughly and to clarify the mechanisms by which different strategies improve the resistance to radiotherapy for cervical cancer.

Signaling Pathways Associated with Cervical Cancer

Several studies have found that signaling pathways such as RANKL/RANK, MAPK, and Hippo promote cervical carcinogenesis by affecting the proliferation and migration of cervical cancer cells, cycle regulation, and the expression of oncogenic proteins [6]. The treatment of cervical cancer by targeting and regulating signaling pathways may become an effective therapeutic strategy.

RANKL/RANK Signaling Pathway

NF-κB receptor activator (RANK) and its ligand RANKL were initially identified as osteoclast differentiation factors and regulatory molecules for interacting with T cells and dendritic cells [7]. *SHANG, et al.* [8] showed that high levels of mRANKL/RANK expression in cervical cancer lesions play an important role in the malignant proliferation of cervical cancer cells. Furthermore, in cervical precancerous lesions, high RANKL expression often leads to a poor prognosis in certain cancers by modulating cancer cell characteristics and altering anti-tumor immune responses [9]. It has also been reported in the literature that the RANKL/RANK pathway is a key signal that promotes progesterone-driven [10]. Deletion of RANK or pharmacological inhibition of RANKL reduces breast cancer susceptibility gene 1 (Brca1) mutations in mice by regulating stem cell number and proliferation and acts as a treatment for breast cancer [11,12]. However, further research is urgently needed to see if anti-RANKL therapy can be used in cervical cancer.

MAPK Signaling Pathway

MAPK (mitogen-activated protein kinase) mainly consists of three signaling pathways, ERK, p38 MAPK, and JNK, and plays an important role in complex cellular programs, such as proliferation, differentiation, development, and inflammatory responses [13,14]. *WENG, et al.* [15]. demonstrated that zinc finger protein 488 could promote cervical cancer cell proliferation and cycle progression. Knockdown of zinc finger protein 488 caused upregulation of p-ERK level, and the addition of ERK inhibitor effectively reversed the activation of ERK signaling pathway and cell proliferation ability, thus confirming that zinc finger protein 488 induces cervical carcinogenesis through ERK signaling pathway. CHENG, et al. [16] found that the activated p38 MAPK signaling pathway promoted apoptosis, inhibited cell proliferation and increased apoptotic protein-caspase 3 expression in cervical cancer HeLa cells. In addition, activation of the JNK pathway can also mediate proliferation inhibition and promote mitochondrial apoptosis in cervical cancer HeLa and Siha cells [17]. Because the occurrence of cervical cancer is related to the MAPK signaling pathway, there have been many reports in the literature that Chinese medicine monomers can inhibit the proliferation and migration of tumor cells, regulate the cell cycle, and down-regulate the expression of oncogenic proteins through the mechanisms of regulating the MAPK signaling pathway, to achieve the goal of treating cervical cancer [18-20].

Hippo Signaling Pathway

Hippo signaling has been reported to control organ size by regulating cell proliferation, apoptosis and stem cell self-renewal [21-24]. The Hippo pathway prevents tumorigenesis by limiting the expression of the downstream effector molecule YAP [25,26]. *CHEN, et al.* [27] found that miR-200a-3p differentially regulates the proliferation and metastasis of cervical cancer cells in an HPV-associated manner, and its mediated alteration of YAP function also differentially affects the tumor cell fates of HPV-negative and HPV-positive cervical cancers. In addition, down-regulation of large tumor suppressor kinase 1 (LATS1) protein expression is involved in cervical carcinogenesis by activating YAP and entering the nucleus to form a transcriptional complex with TEA structural domain transcription factors, which in turn blocks apoptosis, induces cell proliferation, and other processes [28]. It has been found that rhizophorin plays an important role in inhibiting the migration and proliferation of cancer cells by its unique antioxidant, anti-inflammatory and anticancer bioactivities [29]. *JU, et al.* [30] demonstrated that rhizopodophyllin inhibited migration, invasion and proliferation of HPV-positive cervical cancer cells, and the mechanism may be related to the down-regulation of the YAP/TAZ signaling pathway.

Radiotherapy Resistance and Sensitization Methods in Cervical Cancer

Fundamentals of Radiotherapy

Radiotherapy is one of the three major means of treating tumors, which kills tumors by damaging the DNA of tumor cells through ionizing radiation produced by various rays [31]. Specifically, radiation produces chemical and biological changes inside the cell through energy release, thereby damaging the DNA, proteins, and cellular structure of the cancer cell. It can not only directly damage the genetic material of cancer cells, leading to cell death or loss of dividing ability, but also indirectly damage cancer cells by generating free radicals and oxidative stress, causing damage to important biomolecules and structures of cancer cells, which in turn leads to apoptosis or inability of cancer cells to divide and proliferate normally. It has also been reported that radiation can have an inhibitory effect on the blood supply and neovascularization of cancer cells [32]. It is important to note that radiation does not only affect cancer cells only, but normal tissues may also experience varying degrees of inflammatory response, impaired cellular function, fibrosis, and other adverse effects.

Mechanisms of Radiotherapy Resistance

Although radiation therapy has a certain therapeutic effect on tumors, however, its efficacy is limited by tumor recurrence and metastasis after radiotherapy, and the mechanism is still unclear [33]. It is now generally accepted that radiotherapy resistance of tumor cells is an important factor in tumor recurrence and metastasis after radiotherapy, which is closely related to the tumor microenvironment, inactivation of apoptosis pathway, and

enhanced DNA damage response, etc (Figure 1). For example, the microenvironment around the tumor may affect the tumor's response to radiotherapy; tumor cells are more sensitive to radiotherapy during the mitotic phase; and tumor cells have a strong DNA repair ability and can effectively repair the damage caused by radiotherapy [33]. In addition, tumor cell heterogeneity, genetic mutations, and the overall health of the patient may affect the efficacy of radiation therapy [34].

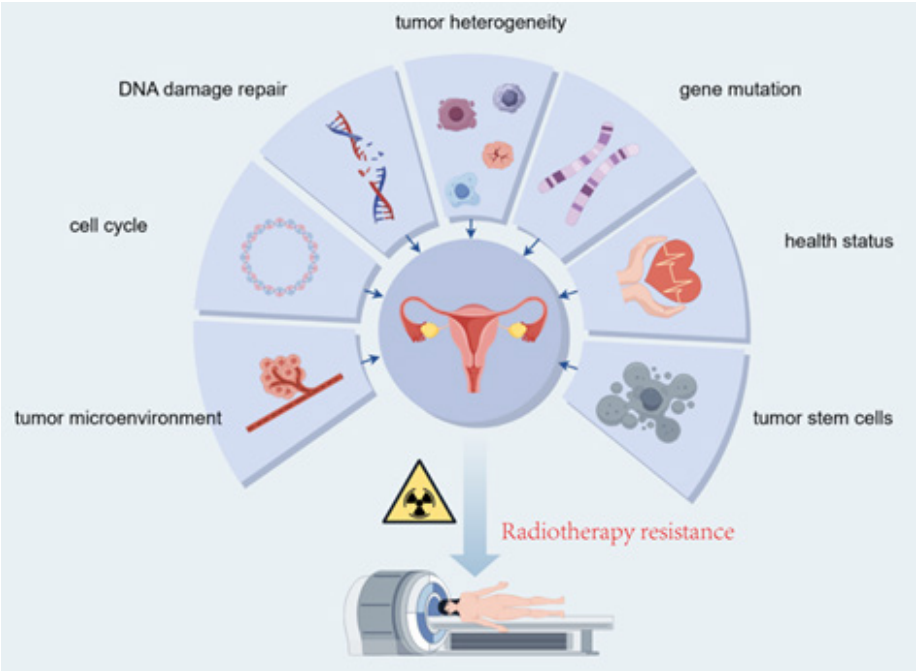

Figure 1: Radiotherapy resistance in cervical cancer patients is affected by tumor microenvironment, cell cycle, DNA damage repair, tumor heterogeneity, gene mutation, tumor stem cells and patient health status.

Tumor microenvironment: Studies have shown that the microenvironment of oxygen deprivation, neovascularization, and immune cell infiltration plays an important role in radioresistance in cervical cancer [35]. In addition, fibrosis or immunosuppression, among others, may lead to decreased efficacy. Among them, hypoxia is an important regulator of tumor growth with profound effects on the biological behavior and malignant phenotype of cancer cells. It mediates the effects of cancer treatments such as chemotherapy, radiotherapy and immunotherapy through complex mechanisms and is closely associated with poor prognosis in patients with various cancers [36].

In a hypoxic environment, the resistance of tumor cells to radiation can be increased 2-3 times. It was found that hypoxia-inducible factor 1α (HIF-1α) up-regulation enhances radiotherapy resistance of cervical cancer cells by regulating downstream target genes and proteins, such as vascular endothelial growth factor (VEGF) [37]. HIF-1α knockdown enhances radiosensitivity of Hela cervical cancer cells [38]. Secondly, hypoxia destabilizes free radicals produced by the indirect action of radiation, which in turn causes limited and mostly reparable DNA damage [36]. In addition, cervical cancer radioresistance is also closely related to immune cells in the tumor microenvironment. High levels of tumor-associated neutrophils can lead to radioresistance in cervical cancer cells, which seriously affects patient prognosis [37]. Thus, a better understanding of the unique microenvironmental interactions of tumors will hopefully lead to the development of new cervical cancer therapies to reduce radioresistance.

Cell cycle: The cell cycle is divided into four phases: G1 (growth phase before DNA synthesis), S (DNA replication/synthesis), G2 (final preparation for division), and M (mitosis). Tumor cells in different cell cycle time phases have different sensitivities to radiation. The G1/S and G2/M phase checkpoints have been reported to respond to disruption or damage by blocking the cell cycle [39]. For example, radiation-induced DNA damage induces a G1/S phase checkpoint, which in turn induces G1/S phase cell arrest through signaling pathways such as ATM/p53 and ATM/checkpoint kinase 2, which promotes DNA damage repair and ultimately leads to radiation therapy resistance [33].

Knockdown of RSF-1, an identified tumor biomarker highly expressed in many human cancers, effectively inhibits cell proliferation and promotes apoptosis in a variety of cancer cells [40-42]. *TAN, et al.* [43] demonstrated that RSF-1 siRNA combined with radiation inhibited cell viability redistributed the cell cycle, and induced apoptosis in HeLa and SiHa cells, which in turn enhanced radiotherapy sensitivity. In addition, aspirin aggravated radiotherapy resistance by decreasing G2/M phase cellular regulatory proteins, leading to G2/M phase arrest in SiHa cells of cervical cancer, which likewise enhanced radiotherapy sensitivity [44]. Recent studies have pointed out that cancer cells when subjected to radiation damage, trigger own DNA breaks by activating the expression of caspase-activated DNA enzymes, which promote G2 phase arrest during cell division and buy time for radiation treatment-induced DNA damage [45]. Therefore, targeting the G2 cycle checkpoint pathway may be a potential way to improve the efficacy of radiotherapy.

DNA damage repair: Certain tumor cells have been reported to have a strong DNA repair capacity, which can effectively repair the damage caused by radiotherapy and is one of the key factors affecting the effect of radiotherapy [33]. It has been found that when radiation passes through genetic material, the deposition of energy triggers extensive DNA damage. Typically, this type of damage occurs in the form of double-strand breaks (DSBs), single-strand breaks, base damage, and interstrand cross-links, with the most deleterious being DSBs [46]. DNA damage repair proteins such as PARP-1, DNA-dependent protein kinase (DNA-PK), and radiation-sensitive protein 51 (RAD51) are potential targets for sensitization to radiotherapy [47-49]. In addition, *WANG, et al.* [50] found that the application of the chaperone protein heat shock protein 90 (Hsp90) inhibitor PU-H71 could effectively block DNA damage repair by inhibiting the activity of the catalytic subunit of DNA-PK and prolonging the expression time of RAD51, thus improving the sensitivity to radiotherapy in HeLa and SiHa cells that had acquired radiation resistance. Therefore, targeting key regulators in the DNA damage repair pathway to reduce tumor cell tolerance to radiotherapy by interfering with the DNA damage repair regulatory system is an important method to improve the therapeutic efficacy of cervical cancer.

Radiotherapy Sensitization Methods for Cervical Cancer

Radiotherapy resistance is a major cause of treatment failure and poor prognosis in cervical cancer [51]. In recent years, with the in-depth study of radiotherapy resistance mechanism, various radiotherapy sensitization methods have emerged and become a research hotspot in the field of radiotherapy for cervical cancer. For example, studies on the combination of immune checkpoint inhibitors and radiotherapy have shown that activation of the immune system can make tumor cells more susceptible to radiotherapy; radiosensitizers can inhibit the DNA repair mechanisms of tumor cells, thereby increasing the effectiveness of radiotherapy; and specific biomarkers can be identified through genomic analysis to optimize radiotherapy regimens for individualized treatment [52].

Radiotherapy combined with sensitizers: Although radiotherapy is one of the important means of cancer treatment at present, however, the complications caused by high-dose radiotherapy, such as radioinflammation, radioactive skin injury, peripheral blood decline, tumor radioresistance, etc., have seriously affected the patient's adherence to treatment and success rate [53]. It has been found that drugs such as resveratrol, paclitaxel, curcumin, genistein, and opponent can be used as sensitizers for radiotherapy, and play an important role in clinical tumor radiotherapy by inducing apoptosis of cervical cancer HeLa cells, affecting angiogenesis and repair of DNA damage, and effectively improving the radiosensitization of tumor cells, and facilitating the killing effect of rays on tumor cells (Table 1).

Inducing apoptosis in HeLa cells: Studies have found that increasing intracellular reactive oxygen species (ROS) levels, inhibiting key genes, and suppressing the cell cycle are different mechanisms by which radiotherapy sensitizers work, and among them, selectively increasing the ROS production rate in cancer cells is the most direct and effective way to improve the efficacy of radiotherapy [66,67]. Ganoderic acid T (GAT), a typical triterpene in Ganoderma lucidum, is highly cytotoxic to cancer cells. Previous studies have reported that GAT inhibits cell proliferation in human cervical cancer cells by inducing G1-phase blockade and can cause cytotoxicity in various tumor cells [68, 69]. *SHAO, et al.* [54] demonstrated that GAT induced apoptosis by γ-irradiation by increasing the level of ROS in cervical cancer cell line HeLa. It was also confirmed that GAT induced necrotic apoptosis with apoptosis in a dose-dependent manner under certain radiation conditions, and that the death status of HeLa cells changed from apoptosis to necrotic apoptosis when the concentration of GAT was increased. In addition to GAT, curcumin, the main active ingredient of turmeric, and resveratrol, a resveratrol extract, have significantly induced apoptosis in HeLa cells, and can be used as effective sensitizers for radiation therapy [53, 55].

Table 1: Different mechanisms by which radiotherapy combined with sensitizers improves resistance to radiotherapy in cervical cancer.

Sensitizer		Mechanism	Ref
Ganoderic acid T	Inducing apoptosis in HeLa cells	Increased intracellular ROS levels in HeLa cells	[54]
Curcumin		via the caspase-dependent apoptotic pathway	[53]
Resveratrol		Anti-inflammatory and antioxidant	[55]
Baicalein		Inactivation of JAK2/STAT3 signaling pathway upregulates miR-183 and inhibits cell viability and EMT	[56]
Indisulam		Inhibits the expression of splicing factor RBM39 and up-regulates the pro-apoptotic protein TAp73 and down-regulates the expression of apoptosis-suppressing factor ΔNp73 in human HeLa cells	[57]
Picrasidine injection		Enhance immune function and reduce toxic side effects	[58]
Apatinib	Influencing angiogenesis	Dephosphorylation mechanism inhibits the activity of key signaling molecules of VEGFR2 pathway and JAK2/STAT3 signaling pathway in SiHa and HeLa cells	[59]
Recombinant human vascular endothelial inhibitor		Significantly reduced serum tumor markers and VEGF-A levels	[60]
Bevacizumab		Targeted inhibition of VEGF signaling	[61]
Glyburide sodium	DNA damage repair	Reduction of radiotherapy-induced compensatory increase in regulatory T cell Foxp3 levels	[62]

Nirapani		Enhanced radiotherapy-induced HeLa cytotoxicity	[47]
Rucapari		Targeted inhibition of DNA repair enzymes (PRAP)	[63]
Polyethylene glycolized platinum nanoflower complexes		Amplification of gamma-ray-induced killing of Hela cells	[64]
Exosomes transporting miR-22		Inhibition of MYCBP expression, resulting in decreased expression of hTERT	[65]

Baicaleins are one of the most abundant flavonoids in Xanthophylls and are of interest because of their wide range of biological activities. LEI, et al. [56] demonstrated in in vitro experiments that baicalein intervened in X-ray-treated cervical cancer HeLa cells to improve radiotherapy sensitivity. The mechanism is that baicalein inhibited cell viability and EMT, and induced cell apoptosis of Hela cells, through upregulating miR-183 via inactivation of the JAK2/STAT3 signaling pathway. Indisulam, a splicing-regulated sulfonamide, has demonstrated antitumor activity in many tumors. Researchers used Indisulam to treat human HeLa cells, and the results showed that low concentrations of Indisulam combined with X-rays or 12C6+ ion beams enhanced the radiosensitivity of HeLa cells, suggesting that Indisulam could be used as a new type of cervical cancer radiation therapy drug in the clinic [57]. In addition, Picrasidine injection has the antitumor synergistic effect of chemotherapeutic drugs and reduces chemotherapy resistance in tumors [58]. In chemotherapy for cervical cancer, *CUO, et al.* [70] demonstrated that Picrasidine injection increased chemosensitivity, improved chemotherapeutic efficacy, prolonged progression-free survival, and increased clinical benefit.

Influencing angiogenesis: Preclinical Study Shows Improved Tumor Control with Combination of Radiotherapy and Anti-Angiogenic Therapy and Progress in Unraveling the Complex Mechanisms by Which VEGF Inhibitors Enhance the Response to Radiotherapy [71]. Apatinib is an inhibitor of tyrosine kinase activity that highly selectively inhibits vascular endothelial growth factor receptor 2 (VEGFR2) and has demonstrated a favorable safety profile and positive therapeutic effects in the treatment of a variety of solid tumors. It has been confirmed that Apatinib inhibits the activity of key signaling molecules of the VEGFR2 pathway and JAK2/STAT3 signaling pathway in SiHa and HeLa cells through dephosphorylation mechanism, suppresses the proliferation of malignant tumor cells and neovascularization, and then increases the sensitivity of tumor cells to radiotherapy [59]. A randomized controlled study by *SHU, et al.* [60] analyzed the recent efficacy of 91 patients with locally advanced squamous carcinoma of the uterine cervix treated with simultaneous radiotherapy with or without recombinant human vascular endothelial inhibitor (VEI) and found that the combination of recombinant human VEI significantly increased the complete remission rate, and significantly reduced the serum tumor markers and VEGF-A levels. HUA, et al. [61] demonstrated that bevacizumab in combination with radiotherapy is a safe and tolerable treatment for patients with refractory cervical cancer and can improve their survival. Due to the rapid tumor regression, high three-year survival rate, locoregional recurrence-free survival rate, and distant metastasis-free survival rate, this combination therapy is likely to become a first-line option in clinical practice. Of note, although antiangiogenesis promotes tumor normalization and helps improve radiotherapy efficacy. However, the efficacy of this combination is variable and many questions remain about how best to use both modalities to achieve optimal response and minimal toxicity. An important limiting factor is that, unlike some other targeted therapies, antiangiogenic agents are not used in selected patient populations because biomarkers for identifying responders have not yet been identified [71].

DNA damage repair: In addition to anti-angiogenesis, DNA damage repair is one of the mechanisms of resistance to radiotherapy in cervical cancer, many drugs combined with radiotherapy can achieve the effect of sensitization to radiotherapy by affecting DNA damage repair. In terms of sensitization to radiotherapy for cervical cancer, *LI, et al.* [62] found through a mouse transplantation tumor model of cervical cancer that glycosaminidazole sodium could enhance the efficacy of radiotherapy, and at the same time reduce the compensatory increase in the level of regulatory T-cells Foxp3 induced by radiotherapy, and decrease the response to radiotherapy. However, levels of the T cell activation inhibitor immunoglobulin variable structural domain (VISTA) may increase substantially during the treatment of both, and the combination of VISTA inhibitors may increase antitumor responses. *XUE, et al.* [47] found that olaparib combined with radiotherapy significantly enhanced radiotherapy-induced cytotoxicity in cervical cancer HeLa. This combination strategy showed prominent inhibition of tumor growth in mice, thus establishing the radiosensitizing activity of niraparib. *SAHA, et al.* [63] compared four inhibitors of DNA damage repair in radiotherapy for cervical cancer and found that, compared with the other three drugs (ataxia telangiectasia and Rad3-related kinase inhibitor, cell cycle CHK1 inhibitor, and cell cycle regulator egg WEE1 kinase inhibitor), the molecularly targeted (PARP) inhibitor of DNA damage repair, rucaparib, had the radiosensitization sensitizing effect was the strongest. Thus, DNA damage response inhibition is a promising strategy to both improve the effectiveness of current treatments and protect the kidney from cisplatin-induced toxicity.

In recent years, it has been found that a suitable drug delivery vehicle can maximize the concentration of sensitizing drugs in the tumor and thus effectively enhance the sensitivity of cervical cancer cells to radiotherapy. Polyethylene glycolated platinum nanoflower complexes synthesized by *Yang, et al.* [64] amplified γ-radiation-induced killing of cervical cancer cell line Hela cells, and the radiosensitization ratio could be increased by 23%. In addition to synthetic drug delivery systems, exosomes, as natural drug delivery carriers, can also be used for radiosensitization. It has been found that exosomes carrying miR-22 can enhance the radiosensitization of cervical cancer cells by inhibiting the expression of c-Myc Binding

Protein (MYCBP), leading to a decrease in the expression of human Telomerase Reverse Transcriptase (hTERT) [65]. Although the above radiotherapy combined with Chinese and Western medicines and delivery systems can effectively inhibit radiotherapy resistance and improve radiotherapy sensitivity in cervical cancer patients, its application is limited by side effects. Therefore, balancing the sensitization efficacy and its side effects is still a major challenge for chemotherapeutic agents to be used in cervical cancer radiotherapy sensitization.

Radiotherapy combined with thermotherapy: Tumor thermotherapy refers to the application of different physical factors such as radiofrequency, microwave, ultrasound, laser, and so on to increase the temperature of tumor tissue or body, using high temperature to kill and its secondary effects to treat tumors. In 1930, radiologist Kristian Overgaard first tried to treat tumors with the combination of thermotherapy and radiotherapy and found that compared with radiotherapy alone, the effect of thermal radiation is better in controlling the tumors [72]. Because thermotherapy can effectively kill tumor cells and play a sensitizing effect to improve the effect of radiotherapy, and at the same time reduce the toxic side effects of chemotherapy and radiotherapy, it is called "green therapy" by the international medical community [73]. Thermal therapy sensitizes cells to radiotherapy by degrading proteins associated with DNA damage repair in a time-dependent manner [74,75]. *CREZEE, et al.* [76] showed that potential synergistic mechanisms of hyperthermia include inhibition of DNA repair, selective killing of radiation-resistant hypoxic tumor tissue, and increased radiosensitivity through enhanced tissue perfusion, each of which exhibits different dose-effect relationships, different optimal time intervals, and different optimal sequences between radiotherapy and hyperthermia. Further studies found that the mechanism by which thermotherapy degrades DNA damage repair proteins is transient and that longer time intervals result in less radiosensitization. Preclinical studies have shown that the radiosensitizing effect of hyperthermia is significantly reduced at time intervals as short as 1-2 h between radiotherapy and hyperthermia, but clinical evidence is limited [77,78]. Short Intervals Between External Beam Radiotherapy (EBRT) and Thermal Therapy Are Associated with Lower Risk of Field Recurrence and Better Overall Survival in Women with Advanced Cervical Cancer [79]. However, some scholars believe that the time interval is not an independent risk factor affecting the prognosis of chemoradiotherapy in patients with cervical cancer, and they believe that chemoradiotherapy intervals of 4h or less and then shorter intervals do not affect clinical outcomes.

It has been noted that acute hypoxia alone has no significant effect on cellular response to heat therapy under well-defined nutritional conditions [80-82]. However, prolonged hypoxia or chronic hypoxia increases cellular sensitivity to heat [80, 83]. This because that thermal therapy can increase the sensitivity of cells in hypoxic areas to radiotherapy by increasing the increase in oxygen perfusion through reoxygenation [73]. Mild whole-body heating significantly alters the tumor microenvironment in human head and neck tumor xenograft models by decreasing interstitial hydraulics and hypoxia in the tumor while increasing microvascular perfusion [84]. In addition, other mechanisms of sensitization by heat therapy have been reported in other studies. Mildly elevated body temperature reduces tumor interstitial fluid pressure and hypoxia and enhances the efficacy of radiotherapy in a mouse tumor model [85]. High temperature induces chromatin trapping of factors involved in dna repair and replication, enhancing the sensitivity of cancer cells to dna damage therapy [86].

Currently, radiotherapy combined with concurrent cisplatin chemotherapy is the standard of care for women with locally advanced cervical cancer [87]. However, thermal radiotherapy is the best evidence-based, well-tolerated alternative to concurrent radiotherapy with a more significant reduction in toxicities and side effects, and is expected to be an alternative for patients with contraindications to cisplatin and those who cannot tolerate cisplatin radiotherapy [88]. Although the addition of thermotherapy to radiotherapy regimens has significant benefits for malignant tumors, the criteria for combining thermotherapy with radiotherapy have not yet been standardized, and there is a lack of large-scale clinical trials to confirm its efficacy and safety. Therefore, the efficacy of chemoradiotherapy in terms of sequence, temperature level, treatment duration, and the time interval between radiotherapy and thermotherapy should be thoroughly investigated, and it is expected to be widely applied to the treatment of cervical cancer and other cancers in clinical practice.

Other Joint Strategies: Some new advances have also been made in research to optimize simultaneous radiotherapy using new radiotherapy techniques. EMBRACE-I [89] was designed to evaluate the local control rate and recurrence rate of tumors after radiotherapy combined with magnetic resonance-guided image-guided adaptive brachytherapy (IGABT). It was found that the 5-year local control rate was 92%, the overall survival (OS) rate was 74%, and the progression-free survival (PFS) rate was 68%. The 5-year cumulative incidence of grade 3-5 adverse events was 6.8% for genitourinary, 8.5% for gastrointestinal, and 5.7% for vaginal. The results suggest that magnetic resonance-guided IGABT for locally advanced cervical cancer is effective and has a manageable risk. These results also represent a positive breakthrough in the treatment of locally advanced cervical cancer and may be used as a benchmark for clinical practice and all future studies. In addition, extensive localized lesions or a narrow vagina may interfere with brachytherapy for cervical cancer. *COBUSSEN, et al.* [90] attempted to combine IGABT and 3D-printed interpolated templates, which effectively solved this problem and provided a practical solution to achieve individualized treatment.

At the same time, simultaneous radiotherapy combined with molecular targeted therapy, immunotherapy, and other research has also been a hot spot of research in recent years. The RTOG0417 trial [91] was a study to evaluate the efficacy and safety of bevacizumab in combination with concurrent radiotherapy for the treatment of locally advanced cervical cancer. The results showed high 3-year OS and local control rates in the concurrent radiotherapy group combined with bevacizumab. The ENGOT-cx11/GOG-3047/KEYNOTE-A18 study [92] evaluated the efficacy of pembrolizumab

in combination with radiochemotherapy for high-risk locally advanced cervical cancer. Results Pabolizumab in combination with radiotherapy significantly improved overall survival in patients with locally advanced cervical cancer, as well as the results of the first interim analysis, support this immunoradiotherapy strategy as a new standard of care for this population.

The value of adjuvant radiotherapy after radical simultaneous radiotherapy for locally advanced cervical cancer has been controversial. *ZHONG, et al.* [93] conducted a meta-analysis to validate the role of consolidation chemotherapy after simultaneous radiotherapy in bulky and locally advanced cervical cancer. The results suggested that the OS rate and PFS rate of the group receiving adjuvant chemotherapy after simultaneous radiotherapy (CCRT+CT) were superior to that of the group receiving simultaneous radiotherapy alone (CCRT). In contrast, the recently published findings of the adjuvant chemotherapy After radiotherapy as primary treatment for locally advanced cervical cancer versus radiotherapy alone (OUTBACK) trial were inconsistent [87]. The OUTBACK trial found that the administration of adjuvant chemotherapy with carboplatin and paclitaxel after standard cisplatin radiotherapy for unselected locally advanced cervical cancer increased short-term toxicity and did not improve overall survival. This result suggests that adjuvant chemotherapy should not be routinely given after simultaneous radiotherapy for locally advanced cervical cancer, and the role of adjuvant chemotherapy after radical radiotherapy needs to be further explored.

In conclusion, improvements in radiotherapy technology and targeted immunotherapy have opened up new modalities for the treatment of locally advanced cervical cancer, but the current level of clinical evidence is low, with limited enhancement of efficacy, and the combination of these tools for optimal diagnostic and treatment modalities awaits higher-quality studies to provide higher levels of evidence.

Predictive Modalities of Sensitivity to Radiotherapy for Cervical Cancer

For patients with locally advanced cervical cancer, simultaneous radiotherapy is now considered the standard of care [94]. However, due to the heterogeneity of cervical cancer tumors and individual differences in patient sensitivity to radiotherapy, there would be some blindness if radiotherapy were administered to all patients. Timely, rational, and accurate assessment of the therapeutic response to radiotherapy not only helps to predict the outcome of patients but also lays the foundation for adaptive radiotherapy. In adaptive radiotherapy, the radiotherapy plan can be modified repeatedly during the fractionation period to maintain optimal target coverage and minimize radiotherapy-related side effects [95]. More importantly, the prediction of radiotherapy sensitivity will help clinicians to adjust the treatment strategy of patients promptly, so that patients who are insensitive to radiotherapy will not miss the best treatment opportunities.

Based on molecular diffusion properties, diffusion-weighted MRI (DW-MRI) noninvasively assesses treatment response by providing excellent tissue contrast, and efficacy adjudication is straightforward, allowing close follow-up of cancer treatment to be used as a predictive and monitoring biomarker for response to radiotherapy treatment in cervical cancer patients [96]. Plasma metabolomic analysis has been reported to be widely used for biomarker discovery and identification of cancer-specific metabolic pathways. The results of *Eiji, et al.* [97] suggest that the metabolite profiles of patients with cervical cancer may be an important indicator for differentiating these patients from healthy cohorts, and may also be useful for predicting sensitivity to radiotherapy, and could be used as a predictive biomarker for the diagnosis of cervical cancer and radiation sensitivity. *Sushma, et al.* [98] the demonstrated that apoptosis index can be used as a predictive marker of radiosensitivity in cervical cancer, and also pointed out that there is a correlation between apoptosis and its related biomarkers, membrane fluidity, superoxide dismutations, and changes in intracellular calcium levels of the enzyme. Table 2 summarizes the biomarkers associated with predicting sensitivity to radiotherapy in cervical cancer. In conclusion, by predicting the sensitivity of cervical cancer in radiotherapy with the help of certain means, screening whether patients benefit from radiotherapy, accurately stratifying patients with different sensitivities, and choosing the most effective treatment plan, it helps to realize the precision treatment of cervical cancer.

Table 2: Biomarkers associated with predicting sensitivity to radiotherapy in cervical cancer.

Biomarker	Biological Description	Significance	Ref
HIF-1 and VEGFR	Hypoxia Inducible Factor (HIF) and Vascular Endothelial Growth Factor	Mechanisms for predicting preoperative radiotherapy sensitivity in patients with locally advanced cervical cancer	[99]
SCC-Ag Series	SCC-Ag, squamous cell carcinoma antigen	Elevated Pre-Treatment SCC-Ag Levels Predict Treatment Failure and Selection of Adjuvant Therapy in Pelvic Radiotherapy Patients	[100]
ZNF582 Methylation	Zinc finger protein	Predicting the sensitivity of neoadjuvant radiotherapy for cervical adenocarcinoma	[101]
miR-100-5p	microRNA (microRibonucleic Acid)	Predicting the sensitivity of locally advanced cervical cancer to simultaneous radiotherapy	[102]
Metabolite profile	Polyunsaturated fatty acids, nucleic acids and arginine metabolism	Indicators that distinguish healthy cohorts of cervical cancer patients can also be used to predict radiotherapy sensitivity	[97]
PD-L1 status	Programmed cell death ligand 1	Predictive Prognostic Markers for Carbon Ion (C-ion) Radiation Therapy (CIRT) in Cervical Cancer	[103]

Serological marker	C-reactive protein, lactate dehydrogenase, nutritional indices	Predicting postoperative radiotherapy-chemotherapy-thermal therapy combinations	[104]
Apoptotic index	____	Predicting the prognosis of radiotherapy in patients with stage III cervical cancer	[98]

Summary and Outlook

Radiotherapy resistance to cervical cancer is an important factor affecting its treatment effect. In recent years, as the research on radiotherapy resistance in cervical cancer is being deepened, the research on radiotherapy combined with sensitizers, thermotherapy, molecular targeted therapy, and immunotherapy has made great progress in enhancing the sensitivity of radiotherapy. However, a large number of basic studies are needed to explore the specific mechanisms of combination strategies to increase radiotherapy sensitivity before they can be applied to the clinic. In addition, the combination strategies should be standardized to avoid the waste of research resources, and more importantly, the effects and risks of treatments with different strategies should be fully evaluated to ensure the safety of combination therapy. Different combination strategies to enhance radiotherapy resistance are expected to be widely used in clinical practice in the future so that more cervical cancer patients can benefit and improve their healing.

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CX-C: Data management, Data analysis, Manuscript writing, Project development. YX: Manuscript writing, Project development. ZH-L: Conception and design. JH-Z: Project development, Conception and design. YL-W: Project development, Conception and design. The manuscript's published form was approved by all authors after they had read it.

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Data Availability

No datasets were generated or analysed during the current study.

Clinical Trial Number

Not applicable.

Declarations

Competing Interests

The authors declare no competing interests

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Footnotes

Cixiang Chen and Yan Xu are contributed equally to this work.

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