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REVIEW

Immunotherapy Plus Radiotherapy for the Treatment of Sarcomas: Is There a Potential for Synergism?

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Abstract: Soft tissue sarcoma (STS) is a highly heterogeneous malignant tumor derived from mesenchymal tissue. Advanced STS has a poor response to the current anti-cancer therapeutic options, with a median overall survival of less than two years. Thus, new and more effective treatment methods for STS are needed. Increasing evidence has shown that immunotherapy and radiotherapy have synergistic therapeutic effects against malignant tumors. In addition, immunoradiotherapy has yielded positive results in clinical trials for various cancers. In this review, we discuss the synergistic mechanism of immunoradiotherapy in cancer treatment and the application of this combined regimen for the treatment of several cancers. In addition, we summarize the existing evidence on the use of immunoradiotherapy for the treatment of STS and the relevant clinical trials that are currently ongoing. Furthermore, we identify challenges in the use of immunoradiotherapy for the treatment of sarcomas and propose methods and precautions for overcoming these challenges. Lastly, we propose clinical research strategies and future research directions to help in the research and treatment of STS.

Keywords: PD-1 inhibitor, PD-L1 inhibitor, immune checkpoint inhibitor, radiotherapy, sarcoma, immunoradiotherapy

Introduction

Soft tissue sarcoma (STS) is a highly heterogeneous (more than 70 subtypes) malignant tumor derived from mesenchymal tissue.[1–3] Although the incidence of STS is low, hundreds of thousands of advanced STS cases are recorded worldwide each year. Chemotherapy is the most effective treatment for advanced STS, with the response rate of only 15–20%.[4,5] This poor efficacy resulting in a median overall survival of less than two years.[6–8] Therefore, new therapeutic options are needed for the effective treatment of advanced STS.

Immunotherapies are treatments that kill tumor cells by activating or promoting the body's anti-tumor immunity.[9,10] At present, the widely used immunotherapies in clinical practice include programmed death receptor-1 (PD-1)/programmed death protein ligand-1 (PD-L1) inhibitors and cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitors, and the new types of immunotherapy include adoptive cellular therapies and cancer vaccines.[11,12] PD-1/L1 and CTLA-4 inhibitors have promising efficacy (with a response rate of 10–28%) in the treatment of a few pathological subtypes of STS (undifferentiated pleomorphic sarcoma, dedifferentiated liposarcoma, alveolar soft part sarcoma and angiosarcoma), and their efficacy in the treatment of other subtypes of STS are limited.[11,13–15] Among approaches of adaptive cellular therapies, only engineered T-cell receptor (TCR) therapy has achieved remarkable efficacy in synovial sarcoma, with a response rate of over 50%.[16,17] The efficacy of adoptive cellular therapies in other subtypes of STS are limited.[11] Similarly, cancer vaccines only have promising efficacy in synovial sarcoma and myxoid/round cell liposarcoma.[18] Overall, the efficacy of immunotherapy alone in STS is disappointing. Increasingly combined therapies have been used to improve the efficacy of immunotherapy for malignant tumors and achieve synergistic sensitization.[19–21] Among these combined treatment strategies, the combination of immunotherapy and radiotherapy (immunoradiotherapy) has been extensively studied and is expected to have significantly improved treatment effects on malignant tumors, including STS.[22–26]

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In this review, we summarize the synergistic mechanism of immunoradiotherapy for the treatment of various malignant tumors, the clinical research on and progress in the application of immunoradiotherapy for the treatment of various malignant tumors, the existing evidence on the use of immunoradiotherapy for the treatment of STS, and key ongoing clinical trials. In addition, we propose clinical research strategies and future research directions to help in the research and treatment of STS.

Process of Anti-Tumor Immunity

Tumor immune response is a dynamic process of interaction between anti-tumor and pro-tumor immune responses. Anti-tumor immune cells include natural killer (NK) cells, dendritic (DC) cells, T cells (including cytotoxic CD8+ T cells and effector CD4+ T cells), and M1 phenotype tumor-associated macrophages (TAMs).[27,28] Pro-tumor immune cells mainly include myeloid-derived suppressor cells (MDSCs), regulatory T (Treg) cells, TAMs (M2 phenotype), cancer-associated fibroblasts (CAFs), and group 2 innate lymphoid cells.[28–30] Non-cellular factors (cytokines, chemokines, metabolites) related to tumor immunity can also be divided into anti-tumor and pro-tumor factors.[28,31]

The anti-tumor immune response, which mainly occurs in the tumor microenvironment (TME), is basically the recognition and killing of tumor cells.[32–34] Tumor cells that produce various immune antigens are first recognized by NK and DC cells. Activated NK cells not only initiate cytotoxic reactions to directly kill tumor cells, but also secrete a variety of anti-cancer cytokines to recruit, stimulate, and regulate a variety of anti-tumor immune cells to further activate the anti-tumor immune response.[35,36] After DC cells are activated by tumor antigens or NK cells, they mainly activate CD8+ T cells to induce anti-tumor immune responses of specific cytotoxic T lymphocytes (CTL], enhance the activities of NK cells and CD4+ T cells, and improve the anti-tumor immune response through various mechanisms.[37,38] After CD4+ T cells are activated by the activated DC cells, they can directly recognize and kill some tumor cells; recruit and activate more NK cells, DC cells, and CD8+ T cells; and enhance the ability of CTL to kill tumor cells.[39] Finally, CD8+ T cells are activated into CTL, becoming the main force that kills tumor cells.[40,41] This anti-tumor immune response process is negatively regulated by MDSCs, Treg cells, TAMs (M2 phenotype), and CAFs.[29,30,42]

Effects of Radiotherapy on Anti-Tumor Immunity

Radiotherapy is a local treatment for tumor lesions. The effect of radiotherapy on tumor immunity is mainly limited to the local TME of target tumor lesions.[43,44] In addition, the promotion and inhibition of the effects of radiotherapy on anti-tumor immune responses are entire processes and dynamic changes that occur in the TME of target lesions (Figure 1).[45] Radiotherapy may promote or inhibit anti-tumor immune responses depending on the total radiation dose and fractionations administered.[25,46]

There are several mechanisms underlying the promotion of anti-tumor immune response using radiotherapy. First, radiotherapy leads to a decrease in the number of tumor cells. Data from studies of many cancers suggest that a smaller tumor burden is associated with better treatment outcomes of immunotherapy.[47] The decrease in the tumor volume and the number of tumor cells caused by radiotherapy can reduce the pressure on the anti-tumor immune system and reduce the chances of tumor cell mutation and immune escape. Second, radiotherapy leads to stress and apoptosis (immunogenic death) of some tumor cells, resulting in the deposition of a large number of different types of tumor immune antigens on the tumor cell surface and in the TME. These antigens promote the activation and expansion of NK and DC cells, ultimately leading to the production of a large number of activated CD8+T cells for the achievement of an anti-tumor immune response.[24,48–50] Third, radiotherapy enhances the expression and secretion of anti-tumor immune-related cytokines, chemokines, and growth factors, thereby activating and enhancing anti-tumor immune response.[22,25,51] Furthermore, radiotherapy can induce the normalization of blood vessels in tumor tissues and increase the permeability of local blood vessels to anti-tumor immune cells, thus increasing the infiltration density of immune cells in the TME.[25,45] Other mechanisms behind the effect of radiotherapy on anti-tumor immune response have not been fully explored. For example, it has been reported that radiotherapy can reduce the abundance of tumor-induced erythroid progenitor cells in a manner dependent on interferon and CD8+ T cells, thereby inhibiting tumor growth.[52] In addition, radiation-induced exosomes can stimulate or inhibit anti-tumor immune responses through a series of mechanisms, such as metastasis of tumor antigens.[25]

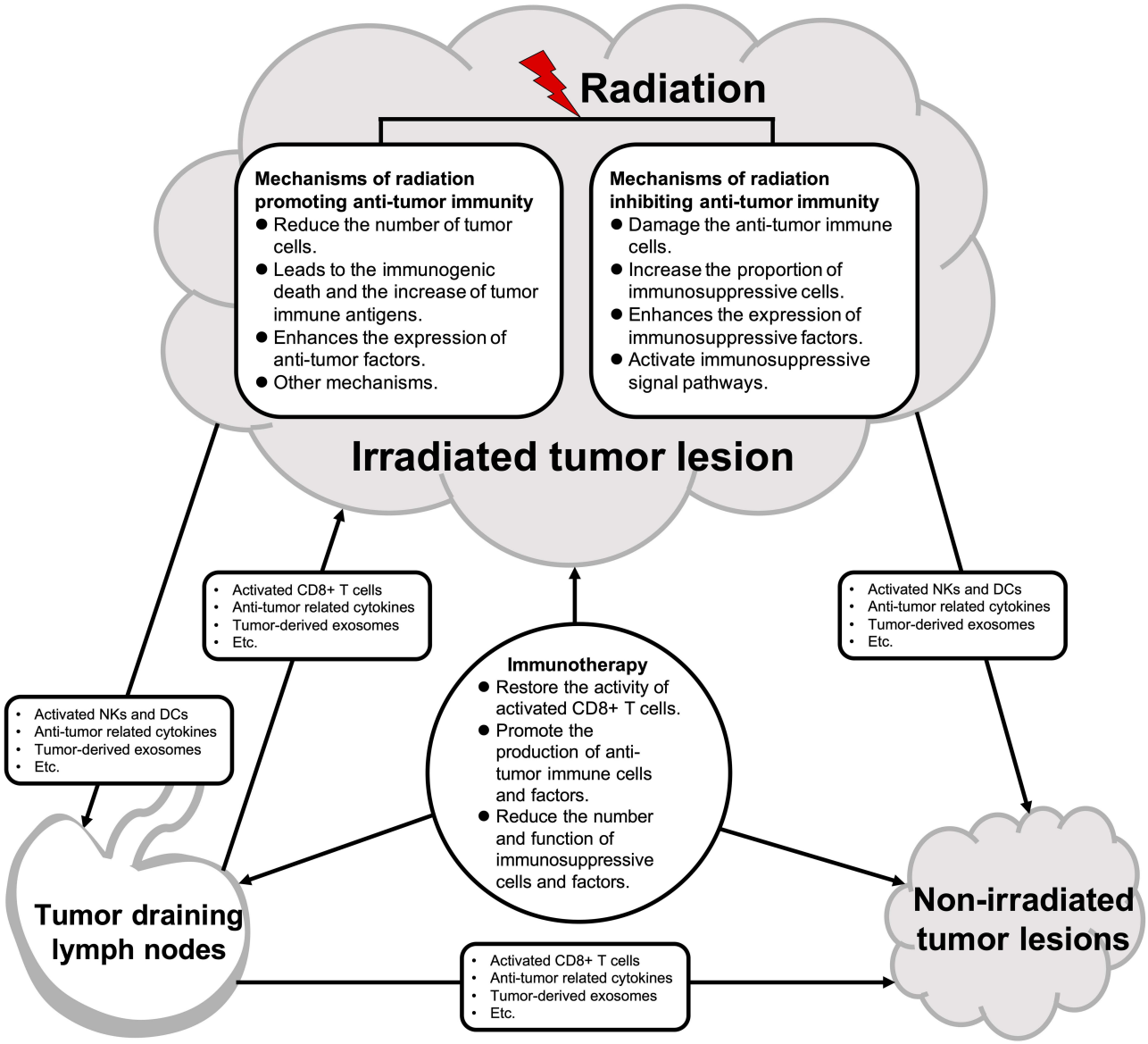

Figure 1 Mechanisms of radiotherapy and immunotherapy effect on the anti-tumor immune response system. The promotional and inhibitory effects of radiotherapy on the anti-tumor immune response system are full processes, with dynamic changes occurring in the irradiated tumor lesion. Radiotherapy may promote or inhibit anti-tumor immune responses depending on the total radiation dose and fractionations administered. The activated natural killer cells (NKs) and dendritic (DCs), anti-tumor related cytokines and tumor-derived exosomes produced by irradiated tumor lesion can directly or through tumor drainage lymph nodes (TDLNs) affect the non-irradiated tumor lesions, and finally induce the abscopal effect. TDLNs play an important role in anti-tumor immune response. The activated NKs and DCs, anti-tumor related cytokines and tumor-derived exosomes produced by irradiated tumor lesion can stimulate the production of CD8+ T cells and anti-tumor cytokines in TDLNs, thereby generating anti-tumor immunity against tumor lesions throughout the body. The addition of immunotherapy can activate the anti-tumor immune response of irradiated tumor lesions, TDLNs, and non-irradiated tumor lesions throughout the body.

In some cases (usually at large radiation doses), radiotherapy will inhibit the anti-tumor immune response in the TME of the irradiated lesion (Figure 1). The mechanisms underlying this effect are as follows: 1) damage to anti-tumor immune cells in the irradiated TME, resulting in a reduction of the number of cells and impairment of their functions;[22,25] 2) increase in the numbers and proportions of immunosuppressive cells, such as MDSCs, Treg cells, TAMs (M2 phenotype), CAFs, and tumor-associated neutrophils (N2 phenotype) in the irradiated local TME;[25,53] 3) induction of high expression of anti-tumor immunosuppressive cytokines and chemokines in the local TME;[22,25,54] and 4) activation of the immunosuppressive signaling pathway (including the PD-1/L1 pathway), which inhibits the anti-tumor activity of CD8+ T cells.[55,56]

In addition to its influence on the anti-tumor immune response in the local TME of the irradiated lesion, radiotherapy can also induce the abscopal effect (Figure 1). The abscopal effect is a phenomenon seen when irradiation at a distinct anatomic site induces a systemic antitumor response throughout the body.[57,58] The abscopal effect describes the shrinkage of unirradiated tumors that occurs concurrently with irradiated tumors in patients with multiple tumors. The basic principle of the abscopal effect is that the activated NK cells, DC cells, and CTL, as well as related non-cellular factors in the local TME of the target lesion, circularly move to the tumor tissue at the non-irradiated site to produce an anti-tumor effect.[59,60] Therefore, the main agents that drive the occurrence of the abscopal effect include CTL, NK cells, and cytokines that promote anti-tumor immunity activated in irradiated lesions.[61,62] Traditionally, these drivers are believed to migrate through the blood system to distant non-irradiated lesions. Recent research shows that tumor-draining lymph nodes (TDLN) and tumor-derived exosomes play key roles in the abscopal effect. TDLN are essential for effective anti-tumor immunity induced by radiotherapy. TDLN promote effective anti-tumor immune response by inducing the infiltration of CD8+T cells and increase in M1 phenotype TAMs. The loss of bilateral TDLN weakens the enrichment and cytotoxicity of CD8+T cells, leading to the weakening of the anti-tumor response induced by radiotherapy.[63] Another mechanism underlying the abscopal effect is the immunomodulatory effect of tumor-derived exosomes. Tumor-derived exosomes contain genetic material and immunosuppressive molecules. These exosomes may carry these signals to distant locations and interact with other immune cells, leading to abscopal effects.[22,25] Theoretically, when a target lesion is irradiated, the cytokines and immune cells in the whole body, including distant non-irradiated lesions, will also change; thus, the incidence of abscopal effects can reach 100%.[22] However, in clinical practice, the incidence of abscopal effects with clinical efficacy is low. This shows that the majority of abscopal effects are subclinical.[64–66] Thus, the "radscopal" technique was proposed to improve the abscopal effect of radiotherapy. The radscopal technique refers to the enhancement of the anti-tumor effect on the whole body through the administration of low-dose radiotherapy for treatment of multiple additional lesions based on conventional radiotherapy for target lesions.[67] Conventional radiotherapy may produce powerful immunosuppressive factors, whereas low-dose radiotherapy can reprogram and reactivate the TME, thus increasing the incidence of the abscopal effect.[22,67]

In summary, the effect of radiotherapy on the TME is two-sided; that is, it can promote or inhibit anti-tumor immune responses. The dose and fractionation of radiotherapy and the pathological classification of the tumor are key factors in the promotion or suppression of anti-tumor immunity.

Synergistic Mechanisms of Immunoradiotherapy

Immunotherapy can produce a series of synergistic effects when administered in combination with radiotherapy. These synergistic effects occur in irradiated and non-irradiated tumor lesions (Figure 1). The synergistic mechanisms of immunoradiotherapy are as follows: 1) restoration of the anti-tumor activity of activated CD8+ T cell;[68] 2) promotion of the production of more anti-tumor immune factors and T cells;[69] and 3) reduction in the numbers and functions of Treg cells and other immunosuppressive cells and factors and increase in the ratio of CD8+ T cells to Treg cells, ultimately leading to the extension of the killing ability to tumor cells.[68,70,71]

In summary, recent preclinical studies have demonstrated that immunoradiotherapy has great synergistic potential. The generation of this synergistic effect depends on the radiotherapy dose and fraction mode, as well as the timing and sequence of immunotherapy administration.[72,73] However, the treatment responses of different pathological types of tumors vary significantly.[68]

Efficacy of Immunoradiotherapy for Different Cancers

There are several potential synergistic mechanisms of immunoradiotherapy. However, these mechanisms are meaningful only when significant efficacy is achieved in clinical practice. Some representative clinical trials on the use of immunoradiotherapy for the treatment of some cancers have been completed (Table 1). Some of these trials achieved promising efficacy.

The results of a Phase 1 clinical trial reported in 2018 showed that multisite stereotactic body radiation therapy (SBRT) (30–50 Gy in three to five fractions to 2–4 lesions), followed by pembrolizumab, is well tolerated and has acceptable toxicity in patients with advanced solid tumors.[78] To our knowledge, this was the first report of multisite

Table 1 Representative Clinical Trials on Immunoradiotherapy for the Treatment of Different Cancers

Positive/ Negative Results	Year of Publication	Type of Cancer	Trial Phase	Treatment	Clinical Outcomes	References
Positive	2022	Oligometastatic ccRCC	I/ II	SABR (single fraction of 20 Gy, or ten fractions of 3 Gy) to all metastatic sites and pembrolizumab.	SABR and short-course pembrolizumab for oligometastatic ccRCC was well tolerated, with excellent local control. Durable responses and encouraging PFS were observed, warranting further investigation.	[74]
	2022	Metastatic CRPC	II	SABR (single fraction of 20 Gy to one or two lesions) + avelumab.	Avelumab with SABR demonstrated encouraging activity and acceptable toxicity in treatment-refractory metastatic CRPC.	[75]
	2021	Immunotherapy-naive metastatic NSCLC	II	Pembrolizumab alone or with radiotherapy (24 Gy in three fractions or 50 Gy in four fractions or 45 Gy in 15 fractions).	Adding radiotherapy to pembrolizumab significantly increased responses and outcomes in patients with metastatic NSCLC.	[76]
	2021	Metastatic MSS CRC and PDAC	II	Nivolumab + ipilimumab and radiotherapy (24 Gy in three fractions to one lesion).	This study provides proof of the concept of combining radiation with immune checkpoint blockade in immunotherapy-resistant cancers.	[77]
	2018	Advanced solid tumors	I	SBRT to 2–4 lesions at doses that ranged from 30 to 50 Gy in three to five fractions + pembrolizumab.	Multisite SBRT followed by pembrolizumab was well tolerated with acceptable toxicity. Additional studies on the clinical benefit and predictive biomarkers of combined multisite SBRT and PD-1–directed immunotherapy are warranted.	[78]
Negative	2022	Metastatic NSCLC refractory to previous PD(L)-1 therapy	II	Durvalumab + tremelimumab alone or with low-dose (0.5 Gy delivered twice per day, repeated for 2 days during each of the first four cycles of therapy) or hypofractionated radiotherapy (a total of 24 Gy delivered in three 8-Gy fractions during the first cycle only).	Radiotherapy did not increase response to combined PD-L1 plus CTLA-4 inhibition in patients with NSCLC resistant to PD(L)-1 therapy.	[79]
	2022	Pretreated mRCC	II	SBRT to a lesion at a dose of 10 Gy in three fractions and nivolumab.	No sufficient evidence that suggests that nivolumab in combination with SBRT provides an added benefit in the treatment of pretreated mRCC.	[80]
	2022	Advanced Merkel cell carcinoma	II	Nivolumab + ipilimumab alone or with SBRT (24 Gy in three fractions to at least one tumor site).	Addition of SBRT did not improve the efficacy of combined nivolumab and ipilimumab.	[81]
	2022	Refractory metastatic pancreatic cancer	II	SBRT of 15 Gy with nivolumab or nivolumab/ipilimumab.	The contribution from SBRT is unknown.	[82]

(*Continued*)

Table 1 (Continued).

Positive/ Negative Results	Year of Publication	Type of Cancer	Trial Phase	Treatment	Clinical Outcomes	References
	2021	Metastatic or recurrent HNSCC	II	Nivolumab or nivolumab + SBRT (9 Gy in three fractions) to one lesion.	The authors found no improvement in response and no evidence of an abscopal effect with the addition of SBRT to nivolumab in unselected patients with metastatic HNSCC.	[83]

Abbreviations: ccRCC, clear cell renal cell carcinoma; CRC, colorectal cancer; CRPC, castration-resistant prostate cancer; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; HNSCC, head and neck squamous cell carcinoma; mRCC, metastatic renal cell carcinoma; MSS, microsatellite stable; NSCLC, non-small-cell lung cancer; PDAC, pancreatic ductal adenocarcinoma; PD(L)-1, programmed death receptor-1/programmed death protein ligand-1; PFS, progression-free survival; SABR, stereotactic ablative body radiosurgery; SBRT, stereotactic body radiotherapy.

SBRT combined with immunotherapy. The results of a new clinical trial showed that multisite stereotactic ablative body radiosurgery (SABR) (single fraction of 20 Gy or 10 fractions of 3 Gy to all metastatic sites) and short-course pembrolizumab for the treatment of oligometastatic clear cell renal cell carcinoma is well tolerated and has excellent local control. These findings support the synergistic anti-tumor activity of immunoradiotherapy.[74] Several other representative clinical trials on the safety and efficacy of immunoradiotherapy for the treatment of multiple malignancies involved the use of PD-1 inhibitors combined with single-lesion radiation.[75–77,84] Although the synergistic anti-tumor effect of immunoradiotherapy was believed to have been achieved in these trials, no significant abscopal effect was observed in these studies.

Several recent key clinical trials on immunoradiotherapy have yielded negative results (Table 1). In these clinical trials, immunotherapy was used in combination with various forms of radiotherapy for the treatment of different cancers. However, no abscopal effect or evidence of synergy was observed.[79–83] There are several possible reasons for these findings. The mode of radiotherapy, number of target lesions irradiated, dose and fraction of radiotherapy, and timing of immunotherapy administration may have important effects on the results. However, several clinical trials on the use of different radiotherapy modalities in combination with immunotherapy for the treatment of different cancers are currently ongoing.[22]

There are two strategies to achieve synergy between radiotherapy and immunotherapy. The first strategy is to achieve an abscopal effect by irradiating a lesion using radiotherapy while simultaneously administering immunotherapy. The other strategy is to achieve synergistic effects by administering low-dose radiation to as many lesions as possible while simultaneously administering immunotherapy. However, regarding the irradiation of a single tumor lesion, no truly significant abscopal effect has been achieved using immunoradiotherapy in completed clinical trials with large sample sizes (Table 1). Consequently, the achievement of the abscopal effect using immunoradiotherapy remains elusive. It is relatively feasible to achieve synergistic effects by delivering low doses of radiation to as many lesions as possible.

Current Research Evidence on Sarcomas

Currently, radiotherapy is only recommended for preoperative or postoperative treatment of locally resectable STS to reduce the rate of recurrence.[85–88] Immunotherapy is marginalized and is only considered to have some efficacy against a few sarcoma subtypes.[87,89,90] This, together with the rarity of STS, ultimately leads to a scarcity of studies on the effect of immunoradiotherapy on STS compared to other cancers. However, some preclinical studies have preliminarily clarified the effect of radiotherapy on the TME of STS. Radiotherapy first affects TME by damaging cancer cells via direct breakage of DNA and the generation of reactive oxygen species.[22] The immunogenic cell death of the damaged cancer cells affects the behavior of immune cells.[25,72] Cellular response driven by DNA damage also changes the immunogenicity of these irradiated cancer cells.[54] Radiotherapy can also effectively increase the quantity and density of activated CD8+ T cells and PD-L1+ macrophages in sarcomas.[91–94] The change in the TME of sarcomas induced by

preoperative radiotherapy is related to the incidence of postoperative metastasis.[92] Although radiotherapy can induce an increase in the number of tumor-infiltrating lymphocytes in sarcoma tissues, it also upregulates the expression of various immunosuppressive factors, including PD-L1.[91,92,94,95] PD-1 blockade and radiotherapy successfully repolarize myeloid cells in sarcomas, transforming the immunosuppressive TME to pro-anti-tumor immune response.[93] In addition, immunoradiotherapy can effectively increase the number of B cells in TME,[94,96] and B cells are associated with survival and therapy response in STSs.[97–99]

Some clinical reports have indicated the existence of an abscopal effect related to radiotherapy in different sarcomas.[100,101] Immunoradiotherapy seems to achieve the abscopal effect more frequently in sarcomas that that of radiotherapy.[102–104] In a clinical case series, three patients with undifferentiated pleomorphic sarcoma, one with intimal sarcoma and one with chondroblastic sarcoma, concurrently received SBRT and pembrolizumab at ten sites of metastatic lesions. The expected high rates of local control in tumors treated using SBRT were observed. Two patients demonstrated either an enhanced local tumor regression or a possible abscopal effect.[105] In the abovementioned clinical reports, most of the patients with pathological subtypes of sarcoma, including pleomorphic sarcoma, clear cell sarcoma, unclassified round cell sarcoma, and alveolar soft part sarcoma, were highly sensitive to immunotherapy or radiotherapy.[106,107] This suggests that the population that most likely to benefit from immunoradiotherapy are those with subtypes of sarcomas that are sensitive to immunotherapy and/or radiotherapy, such as those with UPS or synovial sarcoma. Because UPS is a subtype of sarcoma that is sensitive to both radiotherapy and PD-1 inhibitor therapy;[11,12] Synovial sarcoma is a subtype of sarcoma that is sensitive to both radiotherapy and adaptive cellular therapy or cancer vaccine.[17,18,108–110]

The authors of these clinical case reports claim that radiotherapy has an abscopal effect on sarcomas. However, the results of research on other malignant tumors show that it is unrealistic to attempt to produce an abscopal effect by irradiating a single lesion. It is relatively feasible to achieve synergistic effects with immunoradiotherapy by the administration of low-dose radiation to as many lesions as possible. However, there is no research evidence or report on achieving the synergistic therapeutic effects of immunoradiotherapy by irradiating multiple STS lesions.

The use of predictive biomarker could be extremely helpful in stratifying patients for their risk and for their propensity to effectively responds to immunotherapy, thereby increasing therapeutic options for selected patients and reducing unnecessary side effects. A series of studies have demonstrated that higher tumor infiltrating immune cell infiltrates, sarcoma immune class E, tertiary lymphoid structure, neutrophil-to-lymphocyte ratio, immune-related adverse event are predictive biomarkers of survival in patients with STS who received immunotherapy.[111–113] However, there are currently no reports of predictive biomarkers related to the immunoradiotherapy of STSs.

Ongoing Trials on Immunoradiotherapy for Sarcomas

Several clinical trials on the use of immunoradiotherapy for the treatment of STSs have been registered at clinicaltrials.gov and are currently ongoing (Table 2). Most of these trials are focused on the perioperative management of resectable STSs; only one study is focused on advanced STSs. The immunotherapeutic drugs used in these clinical trials include atezolizumab, durvalumab, ipilimumab, nivolumab, pembrolizumab, and tremelimumab. Conventional high-dose radiotherapy is the primary irradiation method used in these studies. The completion of these clinical trials will further validate the synergistic efficacy of different immunotherapeutic agents combined with radiotherapy for the treatment of sarcomas. This is a necessary step towards improving treatment outcomes for patients with STS. However, the research evidence obtained so far indicate that the designs of these clinical trials have obvious limitations. The major problems and drawbacks of these trials are as follows: 1) no specific sarcoma subtype was selected; 2) no solid theoretical and preclinical basis for the trial; 3) the effects of irradiation dose and fraction, as well as the number of irradiated lesions, were not considered; 4) evaluation was limited to perioperative treatment and did not include the verification of the abscopal effect in advanced disease; 5) the influence of the time of administration of immunotherapy agents was not considered; and 5) the influence of adjuvant drugs was not considered.

Discussion

In this review, we discuss the synergistic mechanisms of immunoradiotherapy for the treatment of cancers. To our knowledge, this is the first review of the possible synergistic mechanism of immunoradiotherapy for cancer treatment, the

Table 2 Ongoing Clinical Trials on Immunoradiotherapy for Soft Tissue Sarcomas

Estimated Study Completion Date	NCT Number	Trial Phase	Indication	Intervention	Number of Patients
2027	NCT03548428	II	Oligometastatic STS	SBRT (3 to 5 fractions depending on tumor size) + atezolizumab	103
2025	NCT03463408	I	Resectable STS	Standard of care radiation + nivolumab and ipilimumab	14
2025	NCT03092323	II	High-risk STS	Conventional radiotherapy (50 Gy in 25 fractions) + pembrolizumab	126
2025	NCT03915678	II	Advanced STS	Radiotherapy (27–60 Gy in 3–5 fractions) + atezolizumab and BDB001	247
2025	NCT04420975	I	Resectable STS	Radiotherapy (5 fractions) + nivolumab and BO-112	20
2023	NCT03474094	II	Operable localized STS	Conventional radiotherapy (50 Gy in 25 fractions) + atezolizumab	69
2023	NCT03338959	II	High-risk STS	Radiotherapy + pembrolizumab	26
2022	NCT03116529	II	High-risk STS	Conventional radiotherapy (50 Gy in 25 fractions) + durvalumab and tremelimumab	35
2022	NCT03307616	II	Recurrent or resectable undifferentiated pleomorphic sarcoma or dedifferentiated liposarcoma	Radiotherapy (5 fractions) + nivolumab and ipilimumab	32

Abbreviations: NCT number, registration number at https://clinicaltrials.gov; SBRT, stereotactic body radiotherapy; STS, soft tissue sarcoma.

effectiveness of the combined regimen for the treatment of several cancers, the evidence of efficacy of immunoradiotherapy for the treatment of STSs, and key ongoing clinical trials. Immunoradiotherapy has achieved positive results in the treatment of a variety of cancers. This may be an important breakthrough in the treatment of several cancers. However, application of immunoradiotherapy for STS is still in the preliminary validation stage. Existing research evidence indicate that immunoradiotherapy has a promising effect on some subtypes of STS, especially those subtypes sensitive to immunotherapy and/or radiotherapy. Such as UPS or synovial sarcoma. However, there is limited relevant evidence or ongoing clinical trials on this.

To improve the therapeutic effects on STS, the study of immunoradiotherapy for STS needs to be more in-depth and detailed (Figure 2). Several problems need to be addressed in future clinical studies. First, the sarcoma subtypes that are more responsive to combination therapy should be determined. The radiosensitivity of tumor cells, percentage of interstitial cells, structure of angiogenesis, and mode of metastasis for each type of sarcoma vary. This leads to a considerable difference in the responses of sarcoma subtypes to immunotherapy and radiotherapy. Therefore, it is necessary to study the therapeutic response of each sarcoma subtype to immunoradiotherapy.[46] Second, the number of irradiated lesions is a key factor in immunoradiotherapy for STS. As previously mentioned, there are two irradiation methods for possibly achieving synergy between radiotherapy and immunotherapy. One strategy is to irradiate one lesion hoping to produce abscopal effects to shrink other non-irradiated lesions. Another strategy is to irradiate as many lesions as possible. According to the results of the studies discussed in this review, the latter approach is more feasible. Third, according to results of existing research, different radiation doses or fractions lead to completely different or even reverse immune responses. Therefore, it is necessary to study the effects of different total doses and fractions of radiation on immunoradiotherapy for STS. Fourth, attention should be paid to the timing of the administration of immunotherapy drugs, which has a significant impact on the effect of the therapy.[73,114] If the timing of administration is inappropriate, the number of anti-tumor immune cells activated by the immunotherapeutic agent may be reduced by radiotherapy or the anti-tumor immune response activated by radiotherapy may not be synchronized with immunotherapy, resulting in poor anti-tumor efficacy. Fifth, a combination of additional treatments could be considered. As previously mentioned,

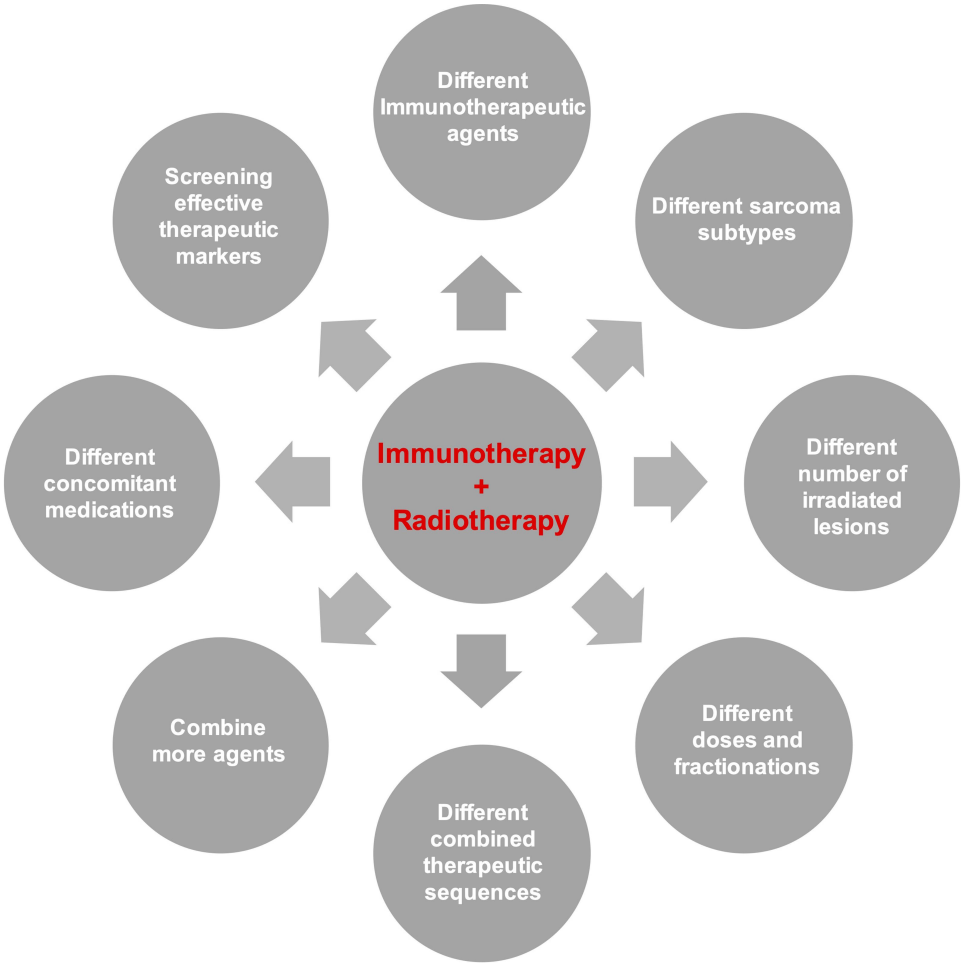

Figure 2 Problems need to be addressed in future mechanisms and clinical studies on immunoradiotherapy in soft-tissue sarcomas.

radiotherapy results in a 100% abscopal effect.[22] However, this effect is so weak that it rarely occurs in clinical practice. Therefore, immunoradiotherapy combined with other systemic treatments, such as chemotherapy, is worthy of exploration. Sixth, attention should be paid to the influence of concomitant use of medications. Many drugs have been preliminarily proven to inhibit the efficacy of immunotherapy.[115] Therefore, the influence of concomitant use of drugs should be considered in detail when designing clinical trials on immunoradiotherapy for STS. Finally, therapeutic markers require further study.

In conclusion, immunoradiotherapy has shown synergistic effects in the treatment of some cancers (such as renal cell carcinoma, prostate cancer, colorectal cancer, pancreatic adenocarcinoma and lung cancer). However, there is still no overwhelmingly positive evidence of these effects in completed clinical trials. In addition, studies on immunoradiotherapy for the treatment of sarcomas are in the preliminary stages, and immunoradiotherapy may benefit patients with subtypes of sarcomas that are sensitive to immunotherapy and/or radiotherapy. Although there are problems that still need to be studied, there is no denying that immunoradiotherapy is a promising treatment for STSs.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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