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ORIGINAL RESEARCH

Hypofractionated Low-Dose Radiotherapy Combined with Immune Checkpoint Inhibition in Metastatic Solid Tumors

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Background: The combination of radiotherapy and immunotherapy can bring benefits to patients, especially advanced patients. However, conventional radiotherapy brings about great adverse reactions. How about the hypofractionated low-dose radiotherapy?

Materials and Methods: In this retrospective cohort study, we included 32 patients with metastatic solid tumors treated with hypofractionated radiotherapy combined with an immune checkpoint inhibitor. Patients underwent radiotherapy of 4Gy/Fx on day 1, 3, and 5, and received single-drug immunotherapy of PD-1 inhibitor on day 2. We evaluated the following outcomes: objective response rate (ORR), disease control rate (DCR), change of nonirradiated and irradiated lesions, quality of life, and symptom improvement.

Results: Among the 32 patients, the ORR was 9.4% (3/32) and the DCR was 56.25% (18/32). Hypofractionated radiotherapy combined with immunotherapy showed a remarkable efficacy of local control on metastatic tumor patients. Local masses irradiated in two patients (6.25%) were complete remission, partial response rate was 37.5% (12 patients), and 56.25% was stability (18 patients). Out of those 18 patients, 15 patients had the local masses shrank more or less. The ORR of local control reached 43.75%, and its DCR was 100%. In addition, the intratumor necrosis rate was 44.4% in the SD patients. Median progression-free survival was 3.8 months (95%Cl: 2.2–5.4). By treating the local mass, the symptoms of most patients were alleviated, and the quality of life was improved.

Conclusion: Our retrospective analysis revealed that hypofractionated radiotherapy combined with immunotherapy was effective in local control, it also relieved clinical symptoms and improved quality of life. The adverse effect rate was low. However, the incidence of abscopal effects was low either. This mode was suitable for the palliative treatment and expected to improve survival for patients with metastatic tumors.

Keywords: hypofractionated radiotherapy, low-dose radiotherapy, immune checkpoint inhibitors, metastatic tumors

Introduction

Since the 20th century, the treatment of tumors has advanced by leaps and bounds. In recent years, more advanced therapies—such as targeted therapy, anti-angiogenesis therapy, and immunotherapy—have emerged. Cancer immunotherapy has become more widespread recently. This therapy targets immune checkpoints; suppressing programmed death 1 (PD-1) or programmed death L1 (PD-L1) to reactivate immunity, recognize tumor antigens, and kill tumor cells. However, single-drug therapy has not yet achieved the desired effect. Chemotherapy,

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radiotherapy, and surgery are the main methods of cancer treatment; thus, combined treatments have recently been explored. One such efficacious combination therapy is radiotherapy combined with immunotherapy, which works by stimulating tumor antigens and other mechanisms of action. For example, in the Pacific study, patients with stage III unresectable non-small cell lung cancer (NSCLC) significantly improved the progression-free survival (PFS) and overall survival (OS) by durvalumab treatment following concurrent radiotherapy and chemotherapy. In addition, the treatment retained the patient's quality of life.[1] The KEYNOTE-001[2] study has shown that before pembrolizumab treatment, patients receiving radiotherapy had better PFS and OS than patients who did not receive radiotherapy. Radiotherapy combined with immunotherapy can bring benefits to patients, especially hypofractionated radiotherapy (eg SBRT) in addition to the possibility of abscopal effects, the benefits for the treatment of tumors may be greater (more clinical trials detail in Table 4).

The combination of radiotherapy and immunotherapy can bring benefits to patients with abscopal effects, including advanced patients. However, in the combination therapy, the divided dose, total dose, combination method, and timing of radiotherapy are still unclear and not uniform.[3] Most scholars believe that hypofractionated radiotherapy (such as stereotactic radiotherapy) is a better choice for combined immunotherapy, but in current clinical trials, the individualized radiotherapy plan—the fractional dose and the total dose are affected by the location, size and type of tumor, which may affect the judgment of immune-strengthening effect. This article retrospectively analyzed the short-term clinical efficacy of the uniform fractional and total dose of radiotherapy-combined immunotherapy for metastatic tumors.

Materials and Methods

We recruited 32 patients (20 male, 12 female) from the Cancer Center of the Second People's Hospital of Changzhou who received hypofractionated low-dose radiotherapy (12 Gy/3 fractions) combined with immunotherapy. The patients were from 29 to 85 years old (median: 60 years old). The patients' disease distribution is as such: melanoma, 4 cases; rectal cancer, 2 cases; lung cancer, 9 cases; pancreatic cancer, 8 cases; gastric cancer, 6 cases; breast cancer, 1 case; liver cancer, 2 cases. All patients were at stage IV and are being treated as follows: 5 patients with first-line treatment; 2 patients with second-line treatment; 25 patients with third-line treatment and above. Performance status (PS) scores ranged from 0 to 2

Table 1 Patient and Tumor Characteristics

Characteristics	No. of Patients (%)
Stage of tumor	
IV	32 (100)
Gender	
Men	20 (62.5)
Women	12 (37.5)
Oncology type	
Lung cancer	9 (28.13)
Rectum cancer	2 (6.25)
Melanoma	4 (12.5)
Breast cancer	1 (3.13)
Gastric cancer	6 (18.75)
Pancreatic cancer	8 (25)
Liver cancer	2 (6.25)
Treatment line	
2	7 (21.88)
≥ 3	25 (78.12)
Performance status score	
0–1	15 (46.88)
2	17 (53.12)
Number of metastasis lesions	
1	5(15.62)
2	7(21.88)
≥3	20(62.5)
Metastasis sites	
Brain	7(21.88)
Liver	15(46.88)
Lung	12(37.5)
Previous therapy	
Radiotherapy	6(18.75)
Immunotherapy	0
Molecular alteration	
EGFR	3(9.37)
HER-2	1(3.13)
KRAS	1(3.13)
Unknown	22(68.75)
Expression of PD-L1	NA
0	5(15.62)
<1%	2(6.25)
1%-50%	1(3.13)
>50%	1(3.13)
Unknown	23(71.88)

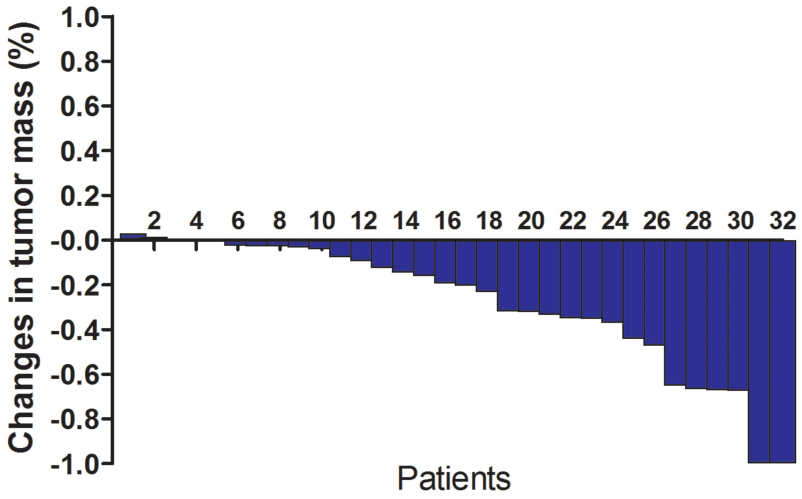

Figure 1 Waterfall plot for the changes in the tumor mass after radiotherapy.

points. The median follow-up time was 6 months (Table 1).

Patients were treated with a combination treatment plan that radiotherapy on day 1, 3, and 5; and single-drug immunotherapy on day 2. PD-1 inhibitors were given according to indications. The metastatic mass that could be evaluated by computerized tomography (Siemens) was delineated as gross tumor volume (GTV). The planning gross tumor volume (PGTV) was the GTV extroverted by 0.5 cm. Hypofractionated low-dose and volume intensity-modulated radiotherapy was required and get approved by physicist. The PGTV was given 4 Gy in a single fraction, 3 fractions in total, making up a total dose of 12 Gy. The biologically effective dose (BED) was equivalent to 16.7 Gy.

We used Elekta Infinity linear accelerator as the radiotherapy platform. The treatment planning system was Elekta (Monaco). The effectiveness of our treatment was evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 standards. The size of the lesion irradiated and non-irradiated would be measured, respectively. We also evaluated the tumor's liquefactive necrosis by the CT value.

Symptom relieves were evaluated based on the comparison of the clinical symptoms after treatment. Tumor marker item by sera diagnosis was compared to evaluate the changes of each case. If the tumor marker was within the normal range, we considered that it made no sense. Quality of life improvement was assessed by the qualities of life scale (QLQ-C30). Adverse reactions were evaluated based on the classification of immune and radiotherapy adverse reactions.

The peripheral blood T cell subsets were measured 1 week before radiotherapy and 1 month after radiotherapy, using the cellular immunochip method, at the Department of Pathology of our hospital. All statistical analyses were performed by SPSS22.0 software. The correlation between tumor relief and peripheral blood T cell subsets was analyzed by Pearson correlation.

Results

Local Response After Radiotherapy and Efficacy Evaluation on Patients

Hypofractionated low-dose radiotherapy combined with immunotherapy for metastatic tumors showed significant efficacy in local control. Two patients experienced complete remission of the local tumors irradiated: one of the remission lesions was located in the left lung of a small cell lung cancer patient, and the other one was the brain metastasis of a breast cancer patient. Twelve patients (37.5%) experienced partial remission of local mass. Eighteen patients (56.25%) were evaluated as having stable disease (SD), but the tumors of 15 patients were smaller than before (not achieving partial response). The ORR after radiotherapy reached 43.75%, and DCR was 100% (Figure 1). In addition, among these SD patients, half of the patients (44.4%) showed intra-tumor necrosis (evaluated by CT). ORR on included non-irradiated lesions was 11.54% (3 of 26) and DCR was 65.38% (17 of 26). Six patients have no non-irradiated lesions (Table 2)

Table 2 Comparison of Volume Change of Lesion Post-Radiation

Patients	Tumor Type	Immunotherapy	Treatment Line	Irradiated Lesion	Relative Change Ratio*	
					Irradiated Lesion	Non-Irradiated Lesion
1	NSCLC	Nivolumab	2	Lung tumor	−67.2%	−37.4%
2	NSCLC	Pembrolizumab	2	Lung tumor	−16.3%	NA
3	NSCLC	Toripalimab	2	Lung tumor	−100.0%	−3.2%
4	NSCLC	Nivolumab	2	Lung tumor	−19.6%	−2.4%
5	NSCLC	Sintilimab	2	Lung tumor	−23.4%	−1.5%
6	NSCLC	Sintilimab	4	Lung tumor	−2.7%	NA
7	SCLC	Camrelizumab	3	Enterocoelia metastasis	−67.5%	−34.1%
8	SCLC	Nivolumab	3	Enterocoelia metastasis	−33.6%	−21.4%
9	SCLC	Sintilimab	3	Lung tumor	−65.2%	−12.5%
10	Liver cancer	Camrelizumab	3	Liver tumor	−66.7%	NA
11	Liver cancer	Camrelizumab	4	Liver tumor	−32.3%	−2.1%
12	Melanoma	Toripalimab	3	Liver metastasis, celiac lymph nodes	−35.4%	−3.0%
13	Melanoma	Toripalimab	2	Inguinal lymph nodes	−35.1%	−1.2%
14	Melanoma	Toripalimab	3	Inguinal lymph nodes	1.4%	32.5%
15	Melanoma	Pembrolizumab	3	Inguinal lymph nodes	−20.5%	36.1%
16	Breast cancer	Toripalimab	5	Brain metastasis	−100.0%	−12.5%
17	Gastric cancer	Sintilimab	3	Gastric tumor	−44.4%	−32.5%
18	Gastric cancer	Toripalimab	3	Retroperitoneal lymph node	−37.2%	1.0%
19	Gastric cancer	Sintilimab	3	Liver metastasis	−3.5%	5.1%
20	Gastric cancer	Sintilimab	2	Gastric tumor	−47.3%	31.0%
21	Gastric cancer	Sintilimab	3	Liver, celiac lymph nodes	−31.9%	21.5%
22	Gastric cancer	Sintilimab	3	Liver metastasis	0.0%	36.5%
23	Pancreatic cancer	Toripalimab	3	Liver metastasis	−14.8%	−1.2%
24	Pancreatic cancer	Camrelizumab	3	Liver metastasis, celiac lymph nodes	3.0%	5.0%
25	Pancreatic cancer	Sintilimab	3	Pancreas tumor, liver metastasis	0.0%	NA
26	Pancreatic cancer	Sintilimab	3	Pancreas tumor	−12.5%	20.5%
27	Pancreatic cancer	Camrelizumab	3	Liver metastasis, celiac lymph nodes	−3.0%	21.4%
28	Pancreatic cancer	Toripalimab	3	Pancreas tumor	0.0%	24.0%
29	Pancreatic cancer	Sintilimab	3	Pancreas tumor	−9.5%	NA
30	Pancreatic cancer	Toripalimab	3	Pancreas tumor	−4.2%	37.5%
31	Carcinoma of the rectum	Sintilimab	3	Retroperitoneal lymph node	−2.9%	−2.4%
32	Carcinoma of the rectum	Sintilimab	4	Enterocoelia metastasis	−7.7%	NA

Note: *Relative Change Ratio= Dmax (post-radiation − before-radiation)/before-radiation×100%.
Abbreviation: Dmax, sum of the largest diameters of lesions.

However, in the retrospective analysis, we had observed that the local efficiency of hypofractionated low-dose radiotherapy combined with immunotherapy for metastatic tumors was prominent. By evaluating the short-term effectiveness, we found that 0 patient achieved complete remission, 3 patients (who had lung cancer, liver cancer, and gastric cancer) experienced partial remission, 15 patients experienced stable disease, while 14 patients experienced disease progression. The objective response rate (ORR) was 9.4%, and the disease control rate (DCR) was 56.25%. The systemic efficacy was consistent with the clinical benefits of immunotherapy in most clinical trials. The median progres-

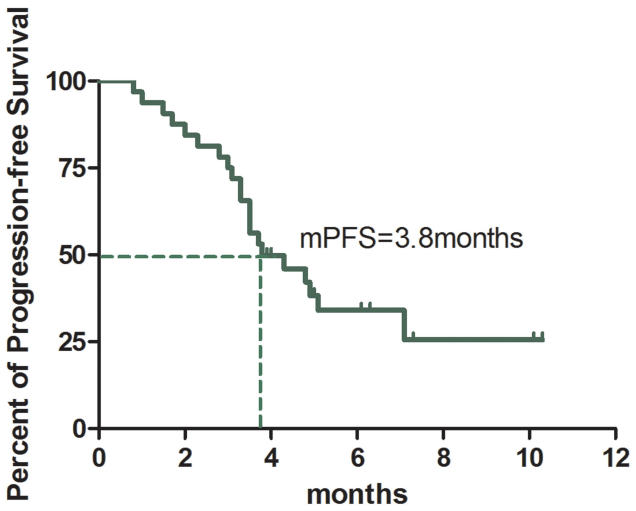

Figure 2 Kaplan–Meier graph for the progression-free survival in patients (n=32).

sion-free survival (mPFS) was 3.8 months (95%Cl: 2.2–5.4) (Figure 2). Overall survival (OS) has not been observed.

Symptoms, Quality of Life and Tumor Index on Patients

By treating local masses, the symptoms of most patients were relieved, and the quality of life was improved. The masses selected for local radiotherapy include all solid masses that may cause patients' symptoms (pain, numbness, obstruction, etc.). Of the 32 patients, 25 patients (78.13%) experienced symptom relief. As for the quality of life before and after treatment, 26 patients improved their quality of life, and the median maintenance time was about 3.6 months.

Each patient underwent a full set of tumor index tests (CEA, AFP, CA125, CA199, CA153, CA50, CA724, NSE, CY211). The tumor indexes of 56.25% of patients (18/32) decreased more or less after combination therapy.

Changes in Peripheral Blood T Cell Subsets

Among the T cell subsets, $CD4^+$ T cells, $CD8^+$ T cells, and the ratio of ($CD4^+/CD8^+$ T cells) were analyzed by the Pearson correlation analysis. There was no significant correlation between all measures and local tumor shrinkage ($P>0.05$).

Adverse Reactions of Radiotherapy and Immunotherapy

Two patients had serious adverse reactions of grade III and above, one had autoimmune myocarditis that resulted in death, and the other one had interstitial pneumonia. Adverse reactions of the remaining patients were all below grade II including fatigue, diarrhea, autoimmune hepatitis, and rash (Table 3).

A Typical Case of a Patient with Hepatocellular Carcinoma

We wish to share a typical case of hepatocellular carcinoma in our department. A 65-year-old patient with massive hepatocellular carcinoma with intrahepatic metastasis and portal tumor thrombus. The first-line treatment was transhepatic arterial chemoembolization (TACE) with pirarubicin + retitripse + sorafenib. The second-line treatment was a PD-1 inhibitor (carilizumab) + radiotherapy for liver

Table 3 Toxicity During Radiotherapy and Immunotherapy

Toxicity	Number of Patients(%)				
	I–II	III	IV	V	All Grade
Fatigue	7(21.8)	0	0	0	7(21.8)
Diarrhea	6(18.75)	0	0	0	6(18.75)
Leukopenia	4(12.5)	0	0	0	4(12.5)
Myocarditis	0	0	1(3.12)	0	1(3.12)
Pneumonia	1(3.12)	1(3.12)	0	0	2(6.25)
Hypothyroidism	5(15.62)	0	0	0	5(15.62)
Hyperthyroidism	0	0	0	0	0
Thrombocytopenia	1(3.12)	0	0	0	1(3.12)
Acute liver injury	4(12.5)	0	0	0	4(12.5)
Rash	5(15.62)	0	0	0	5(15.62)

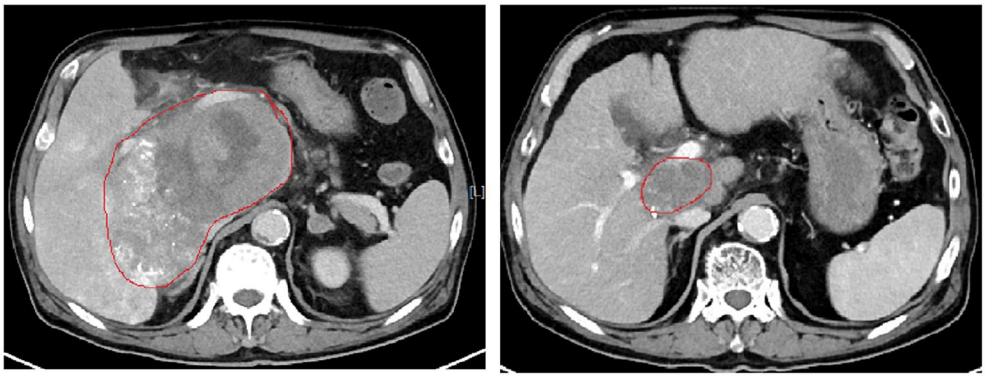

Figure 3 Change of the mass in CT after radiotherapy.

mass (12 Gy/3 fractions). All of the lesions in the liver were irradiated, including portal tumor thrombus. After treatment, the tumor size was significantly reduced, reaching PR (Figure 3), and the tumor index alpha-fetoprotein (AFP) decreased from >1000 ng/mL to the normal range.

Discussion

Immunotherapy is a new treatment modality. Various immune checkpoint inhibitors have been developed recently, they have shown significant benefits in many tumors; therefore, they have become well-received, especially in combination with chemotherapy, radiotherapy, and/or anti-angiogenesis agents.[4–6]

Tumor metastasis and recurrence are the main reasons leading to treatment failure, lower quality of life, and death. The tumor's ability to escape the immune system is one of the important causes of tumor metastasis and recurrence. The mechanism mainly includes the following events: (1) The tumor is chronically affected during the development process. It gradually loses or hides its tumor-specific antigen (TSA) and tumor-associated antigen (TAA), such as MHC-1: the incidence of MHC-1 loss is high, as much as 100% in metastatic lymph nodes of prostate cancer and 85% in primary foci.[7] The loss of tumor antigen is one of the reasons why tumor-infiltrating lymphocytes cannot recognize or kill tumor cells. (2) In the process of tumor development, the tumor itself releases some factors, such as PGE-2, IL-16, VEGF, and TGF-β among others. These factors induce that: the development of dendritic cells (DCs) to inhibit antigen-presenting cells (APC), the aggregation of bone-marrow-derived suppressor cells (MDSC) to the malignant tumor edge, and immunosuppression. MDSCs inhibit the function of T cells and DCs through various pathways, such as secretion of indolamine 2,3-dioxygenase (IDO) and arginase. (3) While the tumor produces the above immunosuppressive factors, it induces the activation of FOXP3 + Treg cells, directly or indirectly by the secretion of cytostatic factors (eg TGF-p, IL-10), DCs function and $CD8^+$ or $CD28^+$ CTL cell activity inhibition. The activity of FOXP3 in Treg cells brings important immunosuppressive effects, one of which is to inhibit the activity of DCs and cytotoxic T cells. All the above changes occur in the local microenvironment of the tumor. In addition to these immune factors, changes in the tumor microenvironment also have an impact on tumor immune changes and the outcome of tumor treatment, for example, hypoxia stimulates Treg cell activation and local immune suppression.[8] Although both APC and immune effector cells like cytotoxic T cells exist, the immune effect depends on the T cell receptor (TCR) and other co-regulatory receptors (CD28, CD80, or CD86). In recent years, studies have found that tumor immune response and immunosuppression have a significant relationship with signal transmission at immune checkpoints. Immune checkpoints control the activation and suppression of T cells by APC.

Radiotherapy combined with immunotherapy has become more prevalent in research. Due to gene mutations, malignant tumor cells and normal tissue cells differ in the expression of many antigens. Clinical trials (Phase Ⅰ and Ⅱ) have shown that the efficacy of anti-tumor vaccines correlates significantly with the number of tumor-associated antigens.[9] The expression of tumor-associated antigens and the production of new tumor antigens can be promoted by radiotherapy, which would subsequently activate anti-tumor immune responses. However, tumors can inhibit antigen presentation. Among them, $CD8^+$ T cells recognize the key molecule MHC-1 expressed on all nucleated cells,

yet in tumor cells, the expression of MHC-1 decreases significantly.[10] Radiotherapy up-regulation the expression of MHC-1 molecules effectively, which would in turn promote the maturation and invasion of DC to the tumor.[11] Studies have shown that immature DC inhibits the proliferation of T lymphocytes, which suppresses the anti-tumor immune response in turn. Tumor cells also inhibit the maturation of APC by releasing multiple inhibitors, thus promoting tumor growth.[12] Radiotherapy causes DNA damage and tumor cell immunogenicity. Both conventional split irradiation and high-dose split irradiation can produce tumor immunogenicity. Fractionated radiotherapy concurrent with immune inhibitors can achieve long-term tumor control in Dovedi's report.[13] Abscopal effect was observed in the trials of immunotherapy-combined high-dose radiotherapy (12–20Gy/1fraction) in tumor-bearing mice, which suppressed the growth of the unirradiated lesion. The combined treatment induced persistent systemic anti-tumor immune response in tumor-bearing mice model studies.[14,15] Based on the abscopal effect of radiotherapy (especially SBRT), high-dose radiotherapy can induce some responses of the immune system, involving the promotion of antigen cross-presentation in exhausted lymphonodus by tumor-specific antigen of MHC complexes and infiltration of T cell in tumor.[16] Expressions of PD-1 and CD137 in $CD8^+$ tumor-infiltrated lymphocytes were also promoted by radiotherapy in tumor-bearing mice. The combined treatment of PD-1 inhibitors with radiotherapy and CD137 inhibitors enhanced the out-field response.[17] Another report showed that radiotherapy followed by an immune inhibitor (PD-1) promoted the ratio of $CD8^+$/Treg and expression of PD-L1 in tumor cells significantly. It suppressed tumor growth, resulting in a long survival in the mice model of non-small cell lung cancer.[18] Meanwhile, radiotherapy-combined PD-L1 inhibitors could suppress the MDSCS and T_{reg} in a tumor mouse model, and increase the $CD8^+$ T cells. The treatment inhibited the growth of tumor.[19] However, the effects of hypofractionated and conventional irradiation on immunity are completely different. In addition, the conclusions of a lot of pre-clinical trials on the optimal segmentation model during radiotherapy combined with immunotherapy are different. In a melanoma animal experiment combined with T cell immunotherapy, single large-dose radiotherapy is more effective than conventional split radiotherapy.[20] Meanwhile, in another animal experiment of lymphoma combined with TLR7 agonist, the radiotherapy dose of 10 Gy/fraction showed an absolute advantage over the 2 Gy × 5 fraction mode.[21] On the other hand, hypofractionated radiotherapy has an adverse effect, resulting in a significant promotion in transforming growth factor-β (TGF-β).[22] TGF-β can regulate the proliferation and function of $CD8^+$ T cell and affect $CD4^+$ T cells to adopt a regulatory phenotype (Treg), resulting in an adverse effect on the antitumor immune response induced by radiation. Furthermore, preclinical study indicates that high-dose radiation (12 Gy in a single fraction) upregulates PD-L1 expression, depending on IFN-γ produced by $CD8^+$ T cells.[13,14] An increase in PD-L1 expression binds to its receptor PD-1, which enhances the suppression of immune response, resulting in resistance to high-dose radiotherapy. Post-radiation lesions can increase the expression of chemoattractant stromal cell-derived factor 1, C-X-C chemokine receptor type 4, and colony-stimulating factor 1 (CSF-1), thus enhancing infiltration of tumor-associated macrophage (TAM).[23–25] Accordingly, tumor growth, invasion, and metastasis are promoted by increased TAMs and result in a poor prognosis.[26] Research by Barsoumian et al indicated that it was necessary to treat metastatic tumors by checkpoint inhibitor combined radiotherapy, which included high-dose radiation for the primary lesion and low-dose radiation for the metastatic lesions. Low-dose radiation could favor M1 macrophage polarization, enhance NK cell infiltration, and reduce TGF-β, resulting in the promotion of the antitumor outcomes.[27] Yin et al got the same result.[38] At present, it is not clear whether different radiotherapy fraction modes can achieve the same bioequivalent dose, and whether the different fraction modes in animal experiments have the same effect as the conventional fraction and hypofraction in the clinical application. The optimal total dose of radiotherapy required for combined immunotherapy is also one of the problems that needs urgent attention. It is necessary to induce an effective anti-inflammatory response and activate a specific anti-tumor immune response.[28] Studies have shown that a higher dose of radiotherapy is beneficial to promote T cell clustering and tumor antigen expression, but simultaneously stimulates the proliferation of Treg.[29]

At present, most clinical trials use SBRT combined with immune checkpoint inhibitors. In the trials of PEMBRO-RT (Phase 2) and MDACC (Phase 1/2),[34,35] advanced NSCLC patients were divided into two groups; one is immunotherapy (pembrolizumab) with radiotherapy group, and the other is immunotherapy alone group. The outcomes of the combination arm were better, but not significantly (Table 4). Interestingly, Theelen et al made a pooled analysis of two random trials,[37] they found that

Table 4 Landmark Trials of Radiotherapy Combined with PD-1/PD-L1 Inhibitors for the Treatment of Cancer

Trials	Study	Tumor Stage	Patients	PD-1/PD-L1 Inhibitor	Radiotherapy Plan	Arms	ORR	PFS	OS	Adverse Effect(3–5)
KEYNOTE001[30]	Phase I	Stage IV Advanced (NSCLC)	97	Pembrolizumab 10 mg/kg q2w or 2 mg/kg q2w or 10 mg/kg q3w	Previously received any radiotherapy	Pembrolizumab with a history of radiotherapy vs pembrolizumab alone	NR	mPFS: 4.4 vs 2.1; p = 0.019	mOS: 10.7 vs 5.3; p = 0.026	Treatment-related pulmonary toxicity 13% vs 1%
NCT02621398[31]	Phase I	Stage III (NSCLC)	21	Pembrolizumab 100 mg q3w or 200 mg q3w	Chemoradiotherapy (60 Gy/30fractions)	Concurrent chemoradiotherapy + Pembrolizumab	NR	mPFS (pembro 100mg): 18.7 m; mPFS (pembro 200mg): 21m	mOS: 29.4m	NR
NCT02608385[32]	Phase I	Metastatic solid tumors	79	Pembrolizumab 200 mg q3w	SBRT 30 to 50 Gy in 3 to 5 fractions	SBRT(multisite) +Pembrolizumab	13.2%	mPFS 3.1m	mOS: 9.6m	Dose-limiting toxicity rate: 9.7%
NCT02303990[33]	Phase I	Metastatic solid tumors	24	Pembrolizumab 200 mg q3w	First half: 8 Gy × 3; second half in each stratum: 17 Gy × 1	Pembrolizumab +hypofractionated radiotherapy	12.5%	NR	NR	17%
MDACC Trial[34]	Phase I/2	Stage IV (NSCLC)	72	Pembrolizumab 200 mg/kg q3w	12.5 Gy ×4fractions; 3 Gy × 15 fractions	Pembrolizumab +SBRT vs Pembrolizumab	22% vs25%; P=0.99	mPFS 9.1 vs 5.1; p = 0.52 mPFS 20.8 vs 4.6; p = 0.004(low PD-L1 expression)	NR	8.3%
PEMBRO-RT[35]	Phase 2	Stage IV (NSCLC)	92	Pembrolizumab 200 mg/kg q3w	8 Gy × 3 fractions	Pembrolizumab +SBRT vs Pembrolizumab	36% vs18%; p= 0.07	mPFS 6.6 vs 1.9; p = 0.19	mOS:15.9 vs 7.6; p= 0.16	NR
LUNG14-179[36]	Phase 2	Stage III (NSCLC)	92	Pembrolizumab 200 mg q3w for up to 1 year	59–66.6Gy	Concurrent chemoradiation with consolidation pembrolizumab	NR	mPFS 18.7m	mOS:35.8m, The 1-, 2-, and 3-year OS estimates were 81.2%, 62.0%, and 48.5%	17.4%
PACIFIC[1]	Phase 3	Stage III (NSCLC)	709	Durvalumab 10mg/kg q2w for up to 12months	Previously definitive chemoradiotherapy	Durvalumab + previous chemoradiotherapy vs placebo + previous chemoradiotherapy	28.4% vs.16.0%; p <0.001	mPFS 16.8 vs 5.6; p < 0.001	mOS 23.2 vs 14.6; p < 0.001	29.9%vs26.1%

the best out-of-field response rate (pembrolizumab alone group versus combination group) was 19.7% versus 41.7%, and the best abscopal disease control rate was 43.4% versus 65.3%. mPFS was 4.4 months versus 9.0 months, and mOS was 8.7 months versus 19.2 months. SBRT combined pembrolizumab significantly promoted outcomes in advanced NSCLC.

However, due to the limitation of normal organs irradiated, the fraction and total dose cannot be standardized. From the previous clinical trials, immunotherapy combined with a high-dose and low-dose radiation promotes the outcomes in advanced NSCLC. Similarly, this article reviewed the efficiency of hypofractionated radiotherapy (same fractions and total doses) combined immunotherapy for patients with metastatic tumors in our department. In this study, 15 patients were evaluated as having stable disease. Fourteen patients showed disease progression. The ORR was 9.4% and the DCR was 56.25%. The systemic efficiency is similar to the benefits of immunotherapy in most clinical trials. However, through retrospective analysis, we found that two patients experienced complete remission of the local tumors irradiated. Twelve patients experienced partial remission of the local mass, while 18 patients had a stable local mass, of which 15 patients had local tumor shrinkage of varying degrees. The responses of local tumor irradiated were as follows: CR, 6.25%; PR, 37.5%; SD, 56.25%; PD, 0%. The ORR of local mass after radiotherapy was 43.75%, while DCR was 100%. In addition, among these patients who had stable disease, half of the patients showed intra-tumor necrosis (evaluated by CT), reaching 44.4%.

We have observed that the hypofractionated low-dose radiotherapy combined with immunotherapy for metastatic tumors had a significant local benefit, and the mPFS achieved 3.8 months. Because the follow-up time was limited, the sustained remission time of local lesions and survival benefits have not been observed. By the control of local mass, the symptoms of most patients were reduced and the quality of life was improved. 78.13% of patients (25/32) experienced symptom relief. Assessment of quality of life revealed that 26 patients improved their quality of life, and the median maintenance time was about 3.6 months.

In this study, the radiation therapy was given in a unified dose and fraction for all patients (4 Gy for single, a total dose of 12 Gy in 3 fractions, the effective biological dose of this dose is about 16.7 Gy, which is equivalent to one-third of the usual palliative radiotherapy dose for bone metastases or brain metastases). Considering the tolerated dose of normal organs, it is almost suitable for most tumors of all organs. The benefit of immunotherapy alone is limited, and it can be enhanced by radiotherapy. The benefits of radiotherapy combined with immunotherapy were not significant in ORR and PFS, similar to the PEMBRO-RT and MDACC trials. The abscopal effect rate was also low. But the treatment effectively controlled the local mass, highlighting the in situ immune effects of hypofractionated radiotherapy on tumors. There were also some limitations to this retrospective study. Whether local control can bring long-term benefits or not? Further follow-up and randomized controlled clinical trials are needed. In terms of short-term efficiency, this radiotherapy mode is especially suitable for the treatment of patients with multiple lesions, poor general condition, and those who are limited by normal tissue exposure. It provides a new mode for tumor treatment in such patients. It is also conducive to study the mechanism of radiotherapy combined with immunotherapy in clinical trials and provides new ideas for the clinical trials of combined treatment.

Abbreviations

PD-1, programmed death 1; PD-L1, programmed death L1; NSCLC, non-small cell lung cancer; PFS, progression-free survival; OS, overall survival; PS, performance status; GTV, gross tumor volume; PGTV, planning gross tumor volume; BED, biologically effective dose; RECIST, Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; mPFS, median progression-free survival; DCR, disease control rate; TACE, transhepatic arterial chemoembolization; AFP, alpha-fetoprotein; TSA, tumor-specific antigen; DCs, dendritic cells; TAA, tumor-associated antigen; APC, antigen-presenting cells; MDSC, marrow-derived suppressor cells; IDO, indolamine 2.3-dioxygenase; TCR, T cell receptor; SBRT, stereotactic body radiation therapy.

Data Sharing Statement

All data generated or analyzed during this study are available from the corresponding author Hua Jiang upon reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of the Affiliated Changzhou No.2 People's Hospital of Nanjing Medical University. The number of the ethical approval was [2019]KY049-01. All participants provided written

informed consent and the procedures were conducted in accordance with the principles of the Declaration of Helsinki.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest for this work.

References

1. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III Non-small-cell lung cancer. *N Engl J Med*. 2017;377(20):1919–1929. doi:10.1056/NEJMoa1709937
2. Leighl NB, Hellmann MD, Hui R, et al. Pembrolizumab in patients with advanced non-small-cell lung cancer (KEYNOTE-001): 3-year results from an open-label, phase 1 study. *Lancet Respir Med*. 2019;7(4):347–357. doi:10.1016/S2213-2600(18)30500-9
3. Teng F, Kong L, Meng X, Yang J, Yu J. Radiotherapy combined with immune checkpoint blockade immunotherapy: achievements and challenges. *Cancer Lett*. 2015;365(1):23–29. doi:10.1016/j.canlet.2015.05.012
4. De Lima Lopes G, Wu YL, Sadowski S, et al. P2.43: pembrolizumab vs platinum-based chemotherapy for PD-L1+ NSCLC: phase3, randomized, open-label KEYNOTE-042 (NCT02220894). *J Thoracic Oncol*. 2016;11(10):S244–S245. doi:10.1016/j.jtho.2016.08.114
5. Gillison ML, Blumenschein G, Fayette J, et al. CheckMate 141: 1-year update and subgroup analysis of nivolumab as first-line therapy in patients with recurrent/metastatic head and neck cancer. *Oncologist*. 2018;23(9):1079–1082. doi:10.1634/theoncologist.2017-0674
6. Reck M, Mok TSK, Nishio M, et al. Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label Phase 3 trial. *Lancet Respir Med*. 2019;7(5):387–401. doi:10.1016/S2213-2600(19)30084-0
7. Blades RA, Keating PJ, Mcwilliam LJ, George NJ, Stern PL. Loss of HLA class I expression in prostate cancer: implications for immunotherapy. *Urology*. 1995;46(5):681–687. doi:10.1016/S0090-4295(99)80301-X
8. Ben-Shoshan J, Maysel-Auslender S, Mor A, Keren G, George J. Hypoxia controls CDd+CD25+regulatory T-cell homeostasis via hypoxia-inducible factor-Ialpha. *Eur J Immunol*. 2008;38(9):2412–2418. doi:10.1002/eji.200838318
9. Walter S, Weinschenk T, Stenzl A, et al. Multipeptide immune response to cancer vaccine IMA901 after single-dose cyclophosphamide associates with longer patient survival. *Nat Med*. 2012;18(8):1254–1261. doi:10.1038/nm.2883
10. Marincola FM, Jaffee EM, Hicklin DJ, Ferrone S. Escape of human solid tumors from T-cell recognition: molecular mechanisms and functional significance. *Adv Immunol*. 2000;74:181–273. doi:10.1016/s0065-2776(08)60911-6
11. Zeng J, See AP, Phallen J, et al. Anti-PD-1 blockade and stereotactic radiation produce long-term survival in mice with intracranial gliomas. *Int J Radiat Oncol Biol Phys*. 2013;86(2):343–349. doi:10.1016/j.ijrobp.2012.12.025
12. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. *Nature*. 2011;480(7378):480–489. doi:10.1038/nature10673
13. Dovedi SJ, Adlard AL, Lipowska-Bhalla G, et al. Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. *Cancer Res*. 2014;74(19):5458–5468. doi:10.1158/0008-5472.CAN-14-1258
14. Deng L, Liang H, Burnette B, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. *J Clin Invest*. 2014;124(2):687–695. doi:10.1172/JCI67313
15. Park SS, Dong HD, Liu X, et al. PD-1 restrains radiotherapy-induced abscopal effect. *Cancer Immunol Res*. 2015;3(6):610–619. doi:10.1158/2326-6066.CIR-14-0138
16. Sharabi AB, Nirschl CJ, Kochel CM, et al. Stereotactic radiation therapy augments antigen-specific PD-1-mediated antitumor immune responses via cross-presentation of tumor antigen. *Cancer Immunol Res*. 2015;3(4):345–355. doi:10.1158/2326-6066.CIR-14-0196
17. Rodriguez-Ruiz ME, Rodriguez I, Garasa S, et al. Abscopal effects of radiotherapy are enhanced by combined immunostimulatory mAbs and are dependent on CD8 T cells and crosspriming. *Can Res*. 2016;76(20):5994–6005. doi:10.1158/0008-5472.CAN-16-0549
18. Herter-Sprie GS, Koyama S, Korideck H, et al. Synergy of radiotherapy and PD-1 blockade in Kras-mutant lung cancer. *JCI Insight*. 2016;1(9):e87415. doi:10.1172/jci.insight.87415
19. Gong XM, Li XF, Jiang T, et al. Combined radiotherapy and anti-PD-L1 antibody synergistically enhances antitumor effect in non-small cell lung cancer. *J Thorac Oncol*. 2017;12(7):1085–1097. doi:10.1016/j.jtho.2017.04.014
20. Suzuki Y, Mimura K, Yoshimoto Y, et al. Immunogenic tumor cell death induced by chemoradiotherapy in patients with esophageal squamous cell carcinoma. *Cancer Res*. 2012;72(16):3967–3976. doi:10.1158/0008-5472.CAN-12-0851
21. Dovedi SJ, Melis MH, Wilkinson RW, et al. Systemic delivery of a TLR7 agonist in combination with radiation primes durable antitumor immune responses in mouse models of lymphoma. *Blood*. 2013;121(2):251–259. doi:10.1182/blood-2012-05-432393
22. Sharabi AB, Lim M, DeWeese TL, Drake CG. Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy. *Lancet Oncol*. 2015;16(13):e498–509. doi:10.1016/S1470-2045(15)00007-8
23. Spiotto M, Fu YX, Weichselbaum RR. The intersection of radiotherapy and immunotherapy: mechanisms and clinical implications. *Sci Immunol*. 2016;1(3):EAAG1266. doi:10.1126/sciimmunol.aag1266
24. Wang SC, Yu CF, Hong JH, Tsai CS, Chiang CS. Radiation therapy-induced tumor invasiveness is associated with SDF-1-regulated macrophage mobilization and vasculogenesis. *PLoS One*. 2013;8(8):e69182. doi:10.1371/journal.pone.0069182
25. Xu J, Escamilla J, Mok S, et al. CSF1R signaling blockade stanches tumor-infiltrating myeloid cells and improves the efficacy of radiotherapy in prostate cancer. *Cancer Res*. 2013;73(9):2782–2794. doi:10.1158/0008-5472.CAN-12-3981
26. Ruffell B, Chang-Strachan D, Chan V, et al. Macrophage IL-10 blocks CD8+ T cell-dependent responses to chemotherapy by suppressing IL-12 expression in intratumoral dendritic cells. *Cancer Cell*. 2014;26(5):623–637. doi:10.1016/j.ccell.2014.09.006

27. Barsoumian HB, Ramapriyan R, Younes AI, et al. Low-dose radiation treatment enhances systemic antitumor immune responses by overcoming the inhibitory stroma. *J Immunother Cancer*. 2020;8(2): e000537. doi:10.1136/jitc-2020-000537
28. Formenti SC, Demaria S. Combining radiotherapy and cancer immunotherapy: a paradigm shift. *J Natl Cancer Inst*. 2013;105 (4):256–265. doi:10.1093/jnci/djs629
29. Schaue D, Ratikan JA, Iwamoto KS, McBride WH. Maximizing tumor immunity with fractionated radiation. *Int J Radiat Oncol Biol Phys*. 2012;83(4):1306–1310. doi:10.1016/j.ijrobp.2011.09.049
30. Shaverdian N, Lisberg AE, Bornazyan K, et al. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of nonsmall-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial [published correction appears in Lancet Oncol. 2017 Jul;18(7): e371]. *Lancet Oncol*. 2017;18 (7):895–903. doi:10.1016/S1470-2045(17)30380-7
31. Jabbour SK, Berman AT, Decker RH, et al. Phase 1 trial of pembrolizumab administered concurrently with chemoradiotherapy for locally advanced non-small cell lung cancer: a nonrandomized controlled trial. *JAMA Oncol*. 2020;6(6):848–855. doi:10.1001/jamaoncol.2019.6731
32. Luke JJ, Lemons JM, Karrison TG, et al. Safety and clinical activity of pembrolizumab and multisite stereotactic body radiotherapy in patients with advanced solid tumors. *J Clin Oncol*. 2018;36 (16):1611–1618. doi:10.1200/JCO.2017.76.2229
33. Maity A, Mick R, Huang AC, et al. A Phase I trial of pembrolizumab with hypofractionated radiotherapy in patients with metastatic solid tumours. *Br J Cancer*. 2018;119(10):1200–1207. doi:10.1038/s41416-018-0281-9
34. Welsh J, Menon H, Chen D, et al. Pembrolizumab with or without radiation therapy for metastatic non-small cell lung cancer: a randomized phase I/II trial. *J Immunother Cancer*. 2020;8(2): e001001. doi:10.1136/jitc-2020-001001
35. Theelen WSME, Peulen HMU, Lalezari F, et al. Effect of pembrolizumab after stereotactic body radiotherapy vs pembrolizumab alone on tumor response in patients with advanced non-small cell lung cancer: results of the PEMBRO-RT phase 2 randomized clinical trial. *JAMA Oncol*. 2019;5(9):1276–1282. doi:10.1001/jamaoncol.2019.1478
36. Durm GA, Jabbour SK, Althouse SK, et al. A phase 2 trial of consolidation pembrolizumab following concurrent chemoradiation for patients with unresectable stage III non-small cell lung cancer: Hoosier cancer research network LUN 14-179. *Cancer*. 2020;126 (19):4353–4361. doi:10.1002/cncr.33083
37. Theelen WSME, Chen D, Verma V, et al. Pembrolizumab with or without radiotherapy for metastatic non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Respir Med*. 2020. doi:10.1016/S2213-2600(20)30391-X
38. Yin L, Xue J, Li R, et al. Effect of low-dose radiation therapy on abscopal responses to hypofractionated radiation therapy and anti-PD1 in mice and patients with non-small cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2020;108(1):212–224. doi:10.1016/j.ijrobp.2020.05.002