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The Effect of Concurrent Stereotactic Body Radiation and Anti-PD-1 Therapy for Recurrent Metastatic Sarcoma

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Abstract

Patients diagnosed with metastatic sarcoma have limited options for achieving both local and distant tumor control. While SBRT can achieve local control, distant response rates remain low. There is limited evidence demonstrating the safety and efficacy for combining SBRT with concurrent PD-1 checkpoint blockade in metastatic sarcoma. In this prospective case-series, we examined five patients with metastatic sarcoma on pembrolizumab treated concurrently with SBRT from July 1, 2016–October 30, 2018. Acute and chronic toxicity were recorded using Common Terminology Criteria for Adverse Events (CTCAE, version 5.0). SBRT-treated tumor control was assessed using Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). With median follow-up of 14.9 months, three patients with undifferentiated pleomorphic sarcoma, one with intimal, and one with chondroblastic osteosarcoma received SBRT with concurrent pembrolizumab to 10 sites of metastatic disease. No grade 5 toxicities were observed. There was a single incidence of transient grade 4 lymphopenia which resolved without intervention. Grade 3 toxicities included anemia, thrombocytopenia, lymphopenia and colitis. One tumor demonstrated local progression after SBRT, and all others remained stable or with response. In conclusion, combining SBRT with PD-1 inhibition appeared to be safe in this patient population. Expected high rates of treated-tumor local control after SBRT were observed. Two of five patients demonstrated either enhanced local tumor regression, or possible abscopal effect.

INTRODUCTION

Soft-tissue sarcomas (STS) represent approximately 1% of all cancers in the U.S. Most STS patients present with metastatic disease frequently involving the lung. Metastasectomy and stereotactic body radiation therapy (SBRT) are possible local therapies demonstrating high rates of treated-tumor control (1, 2); however, many patients develop progressive

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metastatic disease, which underscores the importance of systemic control. Doxorubicin-based regimens demonstrate only 20–35% response rates and dose-intense regimens fail to provide an overall survival benefit (3). Therefore, other systemic therapies, such as programmed death-1 (PD-1) blockade, have recently been explored. While PD-1 blockade has demonstrated sustained objective responses in some selected sarcoma subtypes (e.g., undifferentiated pleomorphic), other subtypes fail to demonstrate meaningful response to single-agent immunotherapy (4, 5). The rationale for combining SBRT with anti-PD-1 therapy is to enhance both the local and systemic immune response. SBRT may cause massive cancer cell lysis releasing tumor-associated antigens and stimulating the translocation of calreticulin on the tumor cell surface (6). Calreticulin and tumor-associated antigens activate antigen-presenting cells, including macrophages and dendritic cells, to release pro-inflammatory cytokines and activate $CD8^+$ cytotoxic T cells against cancer cells (6, 7). This is consistent with preclinical murine models combining SBRT and anti-PD-1 therapy noting augmented $CD8^+$ T-cell activation resulting in higher rates of abscopal responses compared to either treatment modality alone (8, 9).

This finding encouraged oncologists to combine SBRT and anti-PD-1 therapy for metastatic disease. Published case studies and preclinical murine models have reported abscopal effects when combining SBRT with anti-PD-1 therapy (10, 11). In the current case-series, the safety and efficacy of SBRT were examined in five metastatic sarcoma patients who received concurrent uninterrupted anti-PD-1 therapy.

MATERIALS AND METHODS

Patient Selection

In this IRB-approved prospective study (study no. 201701826), five patients with metastatic sarcoma were investigated. These patients had received anti-PD-1 therapy concurrently with SBRT. Inclusion criteria included patients with biopsy-proven diagnosis of metastatic sarcoma, treatment with an anti-PD-1 agent prior to SBRT, and appropriateness for combination therapy as determined by sarcoma multidisciplinary tumor board. Exclusion criteria included patients with contraindications for ant-PD-1 therapy, contraindications to SBRT, patients who did not receive SBRT within 4 weeks of anti-PD-1 therapy, non-metastatic patients or those without a diagnosis of sarcoma, and patients who could not give consent to participate in the study. Patients were consented prospectively but evaluated after completing SBRT and pembrolizumab treatment. Of 10 lesions treated, seven were pulmonary metastases while three were located in the heart, the right retroperitoneum, or the left inguinal/pelvic lymph nodes.

SBRT and Pembrolizumab Delivery

Initial simulation for all pulmonary SBRT plans included 4D-CT scans to assess for tumor motion during various breathing phases. 4D-CT imaging and gating was performed as described elsewhere (12). Briefly, initial simulation for all SBRT plans included 4D-CT scans to account for tumor motion during various breathing phases. The 4D-CT datasets included 10 respiratory phases ranging from 20–100% inspiration to 0–80% expiration. Gross tumor volumes from the 100% inspiration, 0% expiration and full-expiration breath-

hold datasets were combined to create the internal target volume (ITV). Gating was implemented when tumor motion was >1 cm. The planning target volume (PTV) consisted of the ITV with a 5-mm margin. SBRT was delivered using a 7- or 10-MV flattening filter free linear accelerator in 3 to 5 fractions every other day. For non-pulmonary targets, simulation consisted of IV contrast-enhanced CT scan with or without PET. Pembrolizumab (200 mg IV) was administered every three weeks.

Toxicity and Treatment Response

Follow-up occurred one month after completion of SBRT and then every three months subsequently. Toxicity timing was classified as either “during SBRT”, within three months of completing SBRT, or greater than three months after completing SBRT. The primary end point was the safety and tolerability of the combination of SBRT with PD-1 blockade. Toxicities were scored using CTCAE version 5.0 (13, 14). CT imaging every 3–6 months after SBRT was used for treatment response assessment by RECIST version 1.1 criteria (15).

RESULTS

Patient/Tumor Characteristics

Five patients with a median follow-up of 14.8 months met inclusion criteria [three undifferentiated pleomorphic sarcoma (UPS), one intimal sarcoma and one chondroblastic osteosarcoma (Table 1)]. All patients had grade 2/3 disease according to the French Federation of Comprehensive Cancer Centers classification. Two patients had metastatic disease at presentation. The median age at diagnosis was 61 years old. Patients received a median of five cycles (range 1–13) of pembrolizumab prior to SBRT and eight cycles (range 1–24) after SBRT. PD-L1 tumor staining was >5–10% in two patients while PD-L1 immune cell staining was >5–10% in two other patients. Only one patient remains alive at the time of analysis.

Stereotactic Body Radiation Therapy

Among the five patients, 10 disease sites received SBRT: heart, lung (seven sites), right retroperitoneum, and left inguinal/pelvic lymph nodes. The median SBRT dose was 40 Gy (range 21–54 Gy) delivered over 3–5 fractions. Two patients received a second SBRT course to other metastatic sites while on pembrolizumab. Patient characteristics, number of pembrolizumab cycles and SBRT doses are shown in Table 1.

Toxicity

No treatment-related deaths were observed. One instance of transient grade 4 lymphopenia was observed, and six instances of grade 3 anemia, thrombocytopenia or lymphopenia were observed. No grade 3–4 toxicities required intervention. The most common grade 1–2 adverse events were fatigue (n = 5), lymphopenia (n = 5), nausea (n = 4), diarrhea (n = 2), pneumonitis (n = 2) and anemia (n = 2) (Tables 2 and 3). Three grade 1–2 toxicities required intervention: methylphenidate for fatigue (n = 1), prednisone taper for colitis (n = 1) and prednisone taper for symptomatic pneumonitis (n = 1). Descriptions of individual patient cases are provided below for clinical context.

Disease Control

SBRT of the 10 metastatic targets resulted in the following tumor control outcomes: five lesions with complete response, one lesion with partial response, three with stable disease, and one with progressive disease, by RECIST version 1.1 criterion. One out of five patients remained alive without distant progression for more than 18 months after SBRT.

Individual Patient Clinical Courses

Descriptions of patients' individual courses may be visually aided by referring to Fig. 1, where time 0 is defined as date of initial diagnosis.

Patient 1.—Patient 1 presented with undifferentiated high-grade pleomorphic sarcoma of the left atrium, with multifocal metastatic disease of the small bowel. He underwent surgical debulking of the cardiac primary and was started on pembrolizumab approximately one month later. Three days after cycle 1 of pembrolizumab Patient 1 was started on two concurrent conventionally fractionated radiation courses: one to the cardiac post-operative bed, and one to the metastatic disease of the small bowel. The post-operative bed of the primary received a single-fraction 5 Gy SBRT followed by 50.4 Gy in 28 fractions to both the post-operative bed, and to the abdominal metastatic disease in two separate fields. At cycle 9 of pembrolizumab treatment Patient 1 presented with hemoptysis and radiographic evidence of progression in the left lung/bronchus, and SBRT of 21 Gy in 3 fractions was delivered.

Five months later Patient 1 experienced recurrent hemoptysis (from a different location in the lung based on bronchoscopic exam) and was administered packed red blood cells. At this time, he experienced transient grade 4 lymphopenia (increased from a baseline of grade 2), which resolved spontaneously and exhibited no clinical symptoms. Nine months after SBRT, follow-up imaging demonstrated grade 1 pneumonitis adjacent to the radiation field. He remained asymptomatic and no intervention was required. The disease site in the left bronchus treated with SBRT remained stable through final follow-up, the patient continued to progress distantly and ultimately passed away approximately two years after initial diagnosis.

Patient 2.—Patient 2 presented with localized undifferentiated pleomorphic sarcoma of the left anterior thigh and received 50 Gy SBRT in 25 fractions prior to surgical resection of the primary approximately four months after initial diagnosis. Two months later, previously indeterminate pulmonary nodules progressed on follow-up imaging and pembrolizumab treatment was started. Patient 2 completed a total of 21 cycles of pembrolizumab and two courses of SBRT to three metastatic lesions in the lung. After the initial six cycles of pembrolizumab, the first SBRT course targeted two separate lesions in the RLL and LLL of the lung (Fig. 2, first two columns). After an additional seven cycles of pembrolizumab, a second course of SBRT to a third lesion in the RUL of the lung was delivered (Fig. 2, third column), and finally eight more cycles of pembrolizumab were administered. All SBRT courses were 40 Gy in 5 fractions.

Six weeks after Patient 2's first course of SBRT this patient developed grade 3 lymphopenia (criteria: absolute neutrophil count 200–500 per mm^3), which never resolved. The patient never demonstrated symptoms or opportunistic infections. Other WBC lineages remained within normal limits. Patient also developed grade 2 fatigue requiring methylphenidate for approximately nine months. Approximately 6–8 weeks after the second course of SBRT patient developed grade 1 pneumonitis by radiographic criteria in the field of SBRT. This resolved nine months later without intervention and there was no clinical change in the patients' baseline chronic dry cough.

All three lesions receiving SBRT achieved first partial response (6–12 weeks) and eventual complete response (6–12 months) status-post SBRT. Additionally, during both courses of SBRT, lesions adjacent to those receiving SBRT, which had previously been progressing and incidentally received >20 Gy, also demonstrated partial responses, as shown in Fig. 2. Pembrolizumab was eventually discontinued due to systemic progression, and the patient passed away approximately 2 years 9 months after initial diagnosis.

Patient 3.—Patient 3 presented with localized undifferentiated pleomorphic sarcoma of the left posterior thigh and received 50 Gy SBRT in 25 fractions prior to surgical resection of his primary approximately four months after initial diagnosis. Nine months later metastatic disease was identified in the lungs and the left inguinal and external iliac lymph nodes and the patient was started on pembrolizumab. The patient underwent a total of 13 cycles of pembrolizumab and two courses of SBRT to four lesions. After the initial five cycles of pembrolizumab, the first course of SBRT was administered to the left inguinal disease (21 Gy in 3 fractions). An additional two cycles of pembrolizumab were given, followed by a second course of SBRT to three separate pulmonary lesions in the RUL, inferior LUL and superior LUL, each to 54 Gy in 3 fractions. A cycle of pembrolizumab was administered the day after the first SBRT fraction and followed by an additional four cycles prior to discontinuation of this drug due to distant progression.

During the first course of SBRT to the inguinal region, Patient 3 suffered grade 1 diarrhea, fatigue, anemia and lymphopenia, all of which resolved without intervention <2 months post-SBRT. Similarly, after the second course of SBRT, grade 1 lymphopenia, anemia and fatigue were observed, which resolved without intervention <1 month later. Three months after this second course of SBRT to the three pulmonary lesions, symptomatic grade 2 pneumonitis in the radiation field was noted. The patient was administered prednisone followed by a prednisone taper with clinical resolution of pneumonitis in seven weeks, and radiographic resolution seven months from date of diagnosis of pneumonitis.

The left inguinal lesion that received SBRT remained stable throughout the remainder of the patient's course (15 months). Two pulmonary lesions in the LUL showed complete response by two months after SBRT and did not recur for the remaining 14 months of follow up. The RUL lesion also had complete response, but then recurred approximately 10 months after SBRT. The patient continued to progress distantly and died approximately 2 years, 8 months after initial diagnosis.

Patient 4.—This patient with high-grade undifferentiated pleomorphic sarcoma arising from the right perinephric tissue/retroperitoneum underwent a radical right nephrectomy with negative margins. PD-L1 tumor cell expression was <1% but was 10% positive on immune cell staining. Eight months after presentation, imaging demonstrated local recurrence in the nephrectomy bed as well as a metastatic lesion immediately posterior to the bladder. Ten days prior to initiating the first cycle of pembrolizumab treatment, these lesions measured 4.1 × 2.6 cm and 5.2 × 4.4 cm, respectively. After two cycles of pembrolizumab, the disease in the nephrectomy bed measured 6.6 × 3.0 cm while the disease posterior to the bladder had grown to 5.6 × 5.4 cm. The post-nephrectomy disease was treated with 24 Gy SBRT in 3 fractions with no significant dose delivered to the metastatic lesion adjacent to the bladder (<0.05 Gy). During SBRT, Patient 4 experienced grade 1 fatigue, diarrhea and nausea, as well as grade 2 lymphopenia. These adverse events resolved spontaneously less than one month after SBRT. Eight months after completion of SBRT, the disease in the nephrectomy bed demonstrated a complete response while the metastatic lesion adjacent to the bladder had decreased in volume by >50% (Fig. 3). Patient 4 was continued on pembrolizumab for a total of 26 cycles after which he developed grade 2 colitis. Enteric pathogen panel, *C. difficile*, and general infectious workup were negative. Pembrolizumab was discontinued and an oral daily prednisone taper was started at 100 mg with resolution of the symptoms within two weeks. At the time of manuscript preparation, the patient has been off pembrolizumab for two to three months without radiographical or clinical signs of recurrence.

Patient 5.—Patient 5 presented with metastatic chondroblastic osteosarcoma of the left pelvis and underwent two cycles of doxorubicin and cisplatin treatment, hemipelvectomy of the primary, and three cycles of topotecan and pazopanib. The latter was held due to grade 2 thrombocytopenia and pembrolizumab was initiated. After one cycle the patient received SBRT to one site of metastatic disease in the right middle lobe of the lung (30 Gy in 3 fractions). This was followed by one more cycle of pembrolizumab the day prior to his third fraction.

During the patient's SBRT course, grade 1 fever and fatigue as well as grade 2 anemia and lymphopenia (these were unchanged from his baseline) were noted. The patient was switched from pembrolizumab to gemcitabine after two cycles due to concerns for progression; two weeks after initiating gemcitabine, the patient developed grade 3 anemia, thrombocytopenia and lymphopenia. The lesion that received SBRT was identified as stable disease throughout the remainder of the patient's treatment course, but distant progression occurred and the patient died approximately 14 months after initial diagnosis.

DISCUSSION

In this case-series of patients with progressive disease on pembrolizumab alone, SBRT with concurrent pembrolizumab for metastatic sarcoma was found to be safe and effective in terms of treated-tumor control. SBRT resulted in stable disease to complete response in 90% of targeted lesions with the most common toxicities being minor hematologic deficiencies. To our knowledge, this study contains the largest series of sarcoma metastases treated with SBRT and concurrent pembrolizumab. With median follow-up of 14.8 months, the reported

90% treated-tumor control is in agreement with rates of local control from previously published studies of SBRT in sarcoma (16).

Because SBRT induces a variety of inflammatory reactions, oncologists remain hesitant to recommend SBRT while patients are receiving immunotherapy due to the risk of exacerbating potential adverse effects. Common toxicities associated with anti-PD-1 therapy include colitis, pneumonitis, rash and endocrinopathies (13). A retrospective study examining the combination of palliative radiation with either CTLA-4 or PD-L1 therapy failed to correlate adverse events with treatment site (17). More recently Luke *et al.* reported on their prospective experience using SBRT and pembrolizumab for two to four sites of metastatic disease. Reporting on 79 patients, 4%, 3% and 1% developed grade 3 pneumonitis, colitis, and hepatic toxicity after the combination. Meanwhile, 37% of patients demonstrated grade 1–2 respiratory, thoracic or mediastinal disorders (18). Similarly, two (40%) patients developed low-grade pneumonitis in our series, both in the field of SBRT. Endocrinopathies and hepatic toxicity were not observed in this small study. Other limitations of this study include its observational nature, short follow-up and small number of patients, which could mask low-incidence adverse events.

Patient 2, who presented with more than 20 lung metastases from undifferentiated pleomorphic sarcoma (UPS), received SBRT to 40 Gy in 5 fractions to three metastases and developed resolution of the nearby disease which incidentally received >20 Gy. Despite this tumor staining strongly for PD-L1, prior to SBRT the pulmonary metastasis continued to grow during five cycles of pembrolizumab. While radiation was effective for the treated tumor and the nearby tumors treated with lower dose therapy, outside of the radiation field, this patient's tumors continued to progress. Patient 2 did not demonstrate an abscopal response but tumors that received at least 20 Gy had a strong partial response.

While elevated tumoral PD-L1 expression has been shown to predict treatment response to PD-1 inhibitors in various cancers, SARC028 found that 30% of patients with UPS progress while on PD-1 therapy (4, 19). Radiation could change the tumor microenvironment to promote CD8 and CD4 T-cell infiltration. This is supported by a recent histological examination of 17 UPS tumor samples before and after irradiation, which appreciated greater immune cell infiltrate as well as higher tumoral PD-L1 expression after radiotherapy (20). Outside of the radiation field, this patient's tumors continued to progress.

Patient 4 demonstrated a possible abscopal response (Fig. 3). This patient received two cycles of pembrolizumab prior to the initiation of SBRT during which both the primary and a solitary metastatic lesion had grown from 4.1 × 2.6 cm to 6.6 × 3.0 cm for the primary, and from 5.2 × 4.4 cm to 5.6 × 5.4 cm for the metastatic lesion. One week after completion of SBRT to the recurrent primary lesion, it decreased in size to 3.7 × 2.6 cm while the metastatic lesion (which received <0.05 Gy) decreased to 5.5 × 4.2 cm. Eight months after completion of SBRT, the disease in the nephrectomy bed demonstrated a complete response while the metastatic lesion adjacent to the bladder had decreased in volume by >50%. This likely represents an abscopal response, although the possibility of a delayed systemic response might be considered. The results of SARC028 provide perhaps the best evidence as to the expected timeline of radiographic responses of sarcomas to PD-1 inhibitor

therapy (4). This does not support a high incidence of early radiographic pseudoprogression. While most patients would not have had radiographic assessment this early in their treatment course it remains difficult to ascertain definitively whether the metastatic lesion had an abscopal response or responded to PD-1 inhibition alone with a delayed response timing. At approximately 18 months post-SBRT, both the recurrent primary and the metastatic lesion remain stable with no radiographic or clinical evidence of distant failure. While multiple preclinical studies were able to produce abscopal responses at various radiation doses and fractionation schemes with checkpoint inhibitors, reproducing these results clinically has been challenging (21, 22). However, there is some evidence to suggest doses of 8–12 Gy per fraction may be ideal (10, 23).

Future/ongoing studies in the field include five active or recruiting phase I/II clinical trials for SBRT in the setting of metastatic sarcoma (NCT01949506, NCT03548428, NCT02561559, NCT02581384 and NCT04098887) (24-28). Two are specific to STS (24, 25), one to chondrosarcoma (28), and two allow for a variety of sarcoma subtypes (26, 27). One does not allow concurrent immunotherapy per protocol (28), three allow it but do not include immunotherapy as part of the protocol (24-26), and one randomizes patients to SBRT with or without concurrent atezolizumab (PD-L1 inhibitor) (27). Three trials are specific to SBRT for pulmonary metastases (24-26), and toxicity/adverse events/safety and tolerability are the primary outcomes for three (24, 26, 28) and secondary outcomes for another (27).

In conclusion, this study provides encouraging preliminary evidence for the safety of combining SBRT with PD-1 blockade in metastatic STS. With median follow-up of 14.8 months in this case-series, SBRT resulted in 90% treated-tumor control in agreement with rates of local control from previous studies (16) with acceptable toxicity. Larger prospective trials are needed to validate these results.

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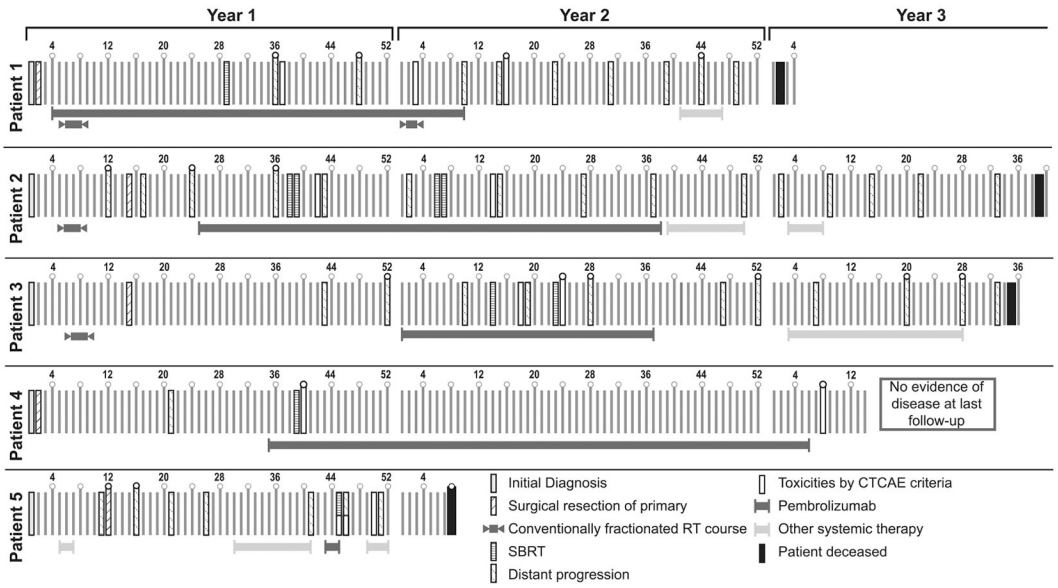

FIG. 1.

Individual patient time-course describing diagnosis, surgical resection, radiation treatment, pembrolizumab treatment, progression and death. Please see individual patient narratives for clinical context.

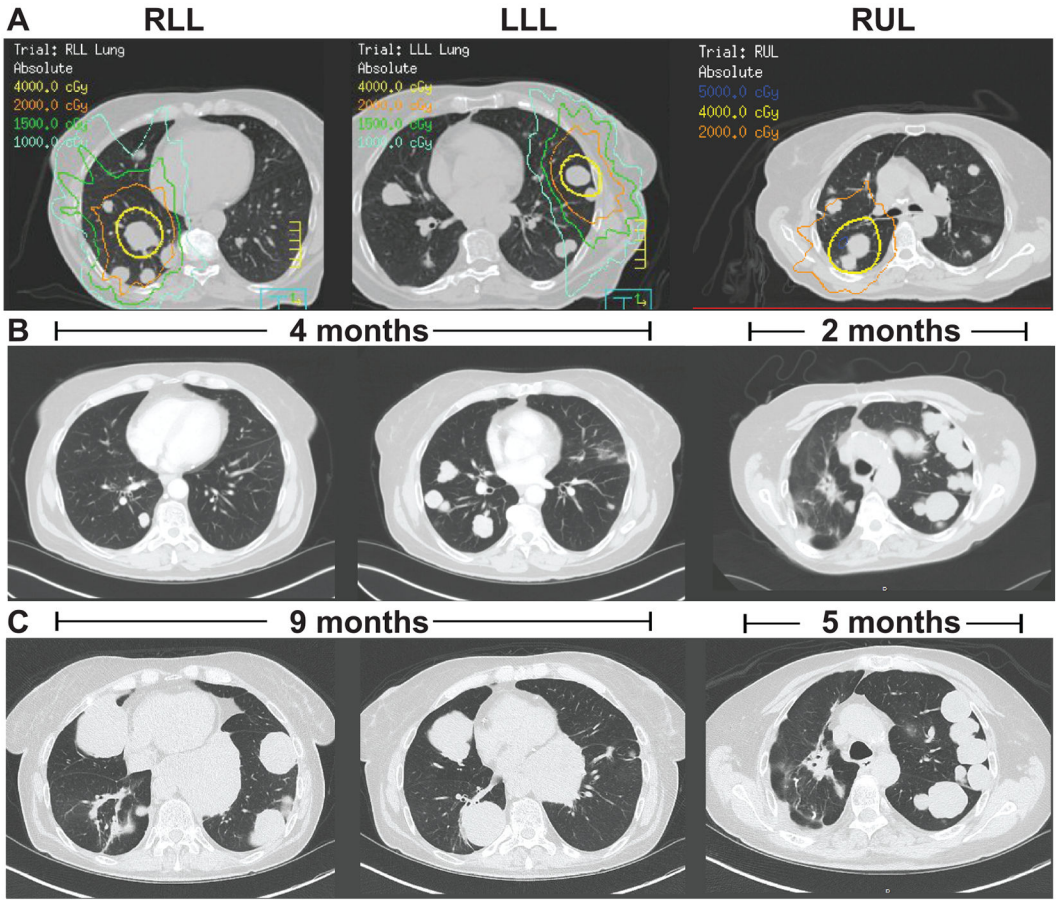

FIG. 2.

Patient 2 with SBRT to RLL (left-side column), LLL (middle column) and separately, a RUL lesion (right-side column) with regression of nearby lesions receiving ≥20 Gy at 2–9 months post-SBRT.

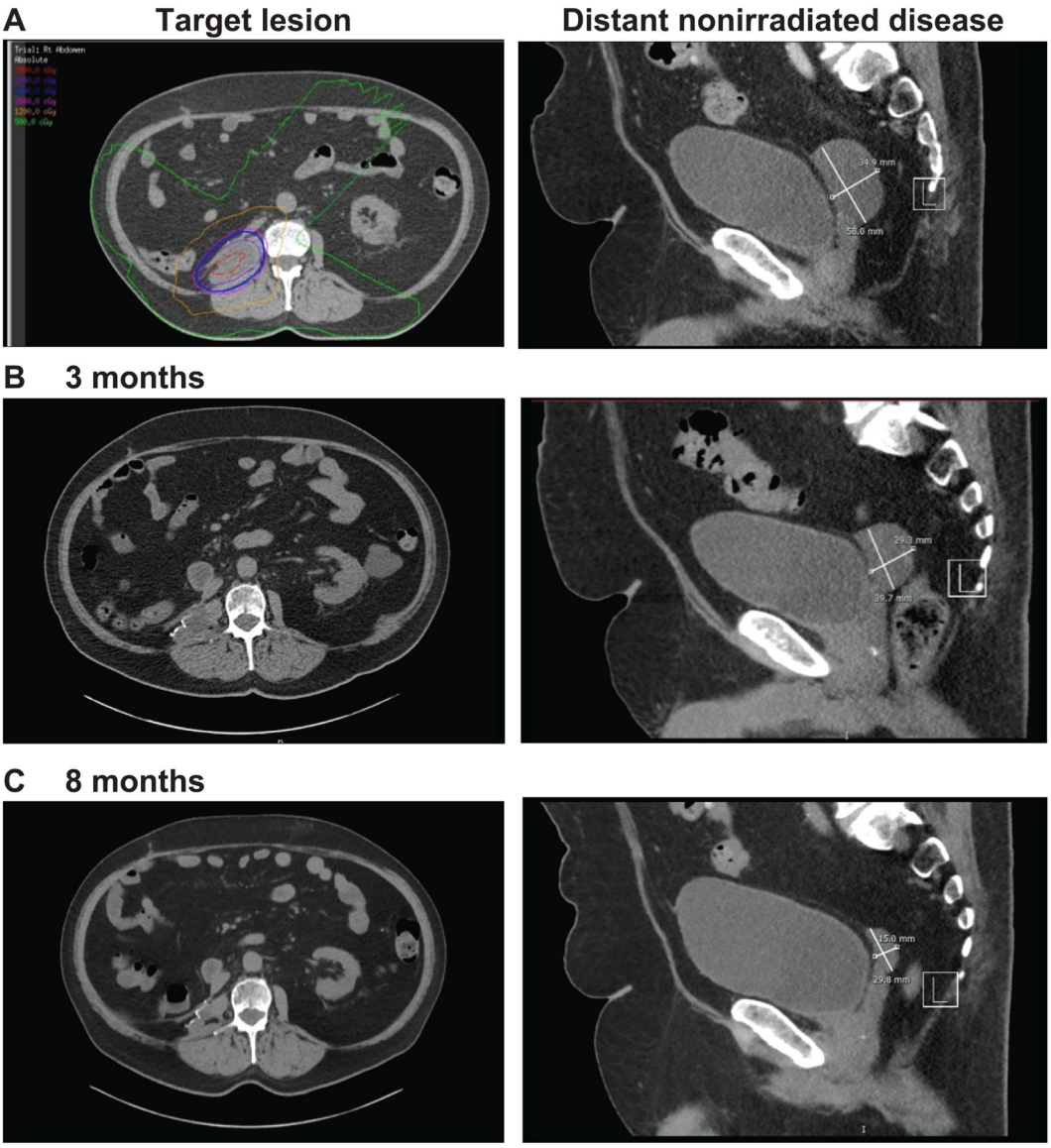

FIG. 3.

Patient 4 with local recurrence in post-nephrectomy bed (left-side column) and solitary distant metastatic lesion posterior to the bladder (right-side column) at (panel A) simulation, (panel B) 3 months and (panel C) 8 months post-SBRT.

TABLE 1

Patient Demographics

Patient ID no.	Age	Location of primary	Histology	FNCLCC grade	AJCC stage	%PD-L1 tumor cells	%PD-L1 immune cells	Resection of primary	Conventional radiation	Cycles of pembrolizumab	No. of courses of SBRT	Lesions treated with SBRT	SBRT total dose and fractionation	BED (α/β = 10)	No. of cycles pembrolizumab prior to, during and after SBRT
1	50	Right ventricle	Intimal sarcoma (high-grade pleomorphic)	3	T2aN0M1	5–10%	<5%	Subtotal resection	55.4 Gy in 29 fractions post-op	20	1	Left lung/ bronchus	21 Gy in 3 fractions	36	9 cycles prior, 11 cycles after SBRT
2	61	Left anterior thigh	Undifferentiated pleomorphic sarcoma	2	T2bN0M0	>75%	<5%	Gross total resection	50 Gy in 25 fractions pre-op	21	2	RLL and LLL RUL	40 Gy in 5 fractions 40 Gy in 5 fractions	72 72	6 cycles prior to first SBRT, 7 cycles in-between 1st and 2nd, and 8 cycles after 2nd SBRT
3	35	Left posterior thigh	Undifferentiated pleomorphic sarcoma	2	T2bN0M0	<1%	<5%	Gross total resection	50 Gy in 25 fractions pre-op	13	2	Left inguinal/ pelvic lymph nodes RUL, inferior LUL, and superior LUL pulmonary lesions	21 Gy in 3 fractions 54 Gy in 3 fractions	36 151.2	5 prior to 1st SBRT, 1 during 1st SBRT, 2 in-between 1st and 2nd SBRT, 1 during 2nd SBRT, and 4 after 2nd SBRT
4	77	Right retroperitoneum /kidney	Undifferentiated pleomorphic sarcoma	3	T4N0M0	<1%	<10%	Gross total resection	N/A	26	1	Post-nephrectomy bed	24 Gy in 3 fractions	88	2 prior to and 24 after SBRT
5	62	Left pelvis	Chondroblastic osteosarcoma	3	T2N0M1	<1%	5–10%	Positive margin	N/A	2	1	RML lung lesions	30 Gy in 3 fractions	60	1 prior to and 1 during SBRT

BED = biologically effective dose; FNCLCC = Fédération Nationale des Centres de Lutte Contre Le Cancer; PD-L1 = programmed death-1 ligand; SBRT = stereotactic body radiotherapy; RML = right middle lobe.

TABLE 2

Adverse Events by CTCAE Criteria

	During SBRT		Acute (<3 months)		Chronic (>3 months)	
Grade	**1–2**	**3**	**1–2**	**3**	**1–2**	**3**
Fevers	0	0	1	0	0	0
Chills	0	0	0	0	0	0
Fatigue	3	0	5	0	1	0
Skin rash	0	0	1	0	0	0
Diarrhea	1	0	2	0	0	0
Colitis	0	0	0	0	1	0
Hypothyroidism	0	0	0	0	0	0
Hypoadrenalism	0	0	0	0	0	0
Hypopituitarism	0	0	0	0	0	0
Pneumonitis	0	0	1	0	2	0
Pulmonary fibrosis	0	0	0	0	0	0
Nausea	1	0	4	0	1	0
Vomiting	0	0	0	0	1	0
Weight loss	0	0	0	0	0	0
Anemia	0	0	2	1	2	0
Lymphopenia	1	1	5	1[a]	0	2
Thrombocytopenia	0	0	0	1	0	0

[a]There was one acute grade 4 lymphopenia and no grade 5 toxicities. See individual patient narratives for clinical context.

TABLE 3

Patient Outcomes

	Outcome
Local control of metastatic lesion treated with SBRT (RECIST criteria)	Complete response (50%)
	Partial response (10%)
	Stable disease (30%)
	Progressive disease (10%)
Systemic disease control by RECIST criteria (incidence)	Complete response (0)
	Non-complete response or progressive disease (1)
	Progressive disease (4)
Distant progression-free survival after SBRT (months)	4 months, 0–18 months (median, range)[a]
Radiographic follow-up after SBRT (months)	14.9 months, 1.5–20.5 months (median, range)[a]
Overall survival from date of SBRT (months)	16 months, 2–18 months (median, range)[a]
Overall survival from date of diagnosis (months)	22 months, 13–33 months (median, range)[a]
During SBRT toxicities by CTCAE criteria (incidence)	Grade 1–2
	Fatigue (3)
	Diarrhea (1)
	Nausea (1)
	Lymphopenia (1)
	Grade 3
	Lymphopenia (1)
	Grade 4 and 5
	None
Toxicities by CTCAE criteria, <3 months after SBRT (incidence)	Grade 1–2
	Fatigue (4)
	Diarrhea (2)
	Pneumonitis (1)
	Skin rash (1)
	Nausea (1)
	Fever (1)
	Lymphopenia (2)

Outcome		
	Grade 3	
		Lymphopenia (2)
	Grade 4 and 5	
		None
Toxicities by CTCAE criteria, >3 months after SBRT (incidence)	Grade 1–2	
		Fatigue (2)
		Anemia (2)
		Nausea (1)
		Pneumonitis (1)
		Colitis (1)
	Grade 3	
		Lymphopenia (1)
	Grade 4	
		Lymphopenia (1)
	Grade 5	
		None

[a] One patient remains alive at time of analysis.