

Teaching Case

Stereotactic Body Radiation Therapy to a Splenic Metastasis in Oligoprogressive Non-small Cell Lung Cancer



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Introduction

Lung cancer is one of the leading causes of cancer-related death worldwide, accounting for an estimated 1.6 million deaths each year.¹ Non-small cell lung cancer (NSCLC) represents 85% of lung cancer diagnoses.² Approximately 40% of patients with NSCLC initially present with metastatic disease³ and nearly half of patients with locally advanced disease develop distant metastases despite aggressive treatment with chemoradiation.⁴ NSCLC most commonly metastasizes to the brain, bone, lung, adrenal gland, and liver. Splenic involvement occurs in only 1%-6% of lung cancer^{5,6} and is usually part of an extensive metastatic process.^{6,7} Although stereotactic body radiation therapy (SBRT) is frequently used to treat a limited number of metastases (up to 5) in oligometastatic NSCLC, the role of aggressive metastasis-directed treatment in diffuse metastatic disease is not well established.^{8,9} The case presented here describes a

progressive splenic metastasis from NSCLC treated with SBRT to achieve a durable complete tumor response in the setting of widespread, but otherwise stable systemic disease while on immunotherapy with nivolumab.

Case presentation

An 80-year-old woman with a 40-pack-year smoking history but no major medical comorbidities presented with an enlarging left parotid mass. Preoperative workup for removal of the mass revealed a 32 × 38 mm left lower lobe lung nodule with lesions in the liver, bones, brain, and spleen, highly suggestive of a primary lung malignancy with diffuse metastases. Computed tomography (CT)-guided biopsy of a liver lesion demonstrated moderately to poorly differentiated adenocarcinoma of the lung. No alterations in *EGFR*, *ALK*, or *ROS1* genes were detected. Fine-needle aspiration of the left parotid mass confirmed metastatic involvement. Although her splenic lesion was not biopsied, a 30 mm round hypodense area in the spleen on CT imaging was radiographically consistent with a metastasis.

Given her metastatic disease and unknown PD-L1 status, she initially underwent 6 cycles of chemotherapy with carboplatin and pemetrexed and had a partial

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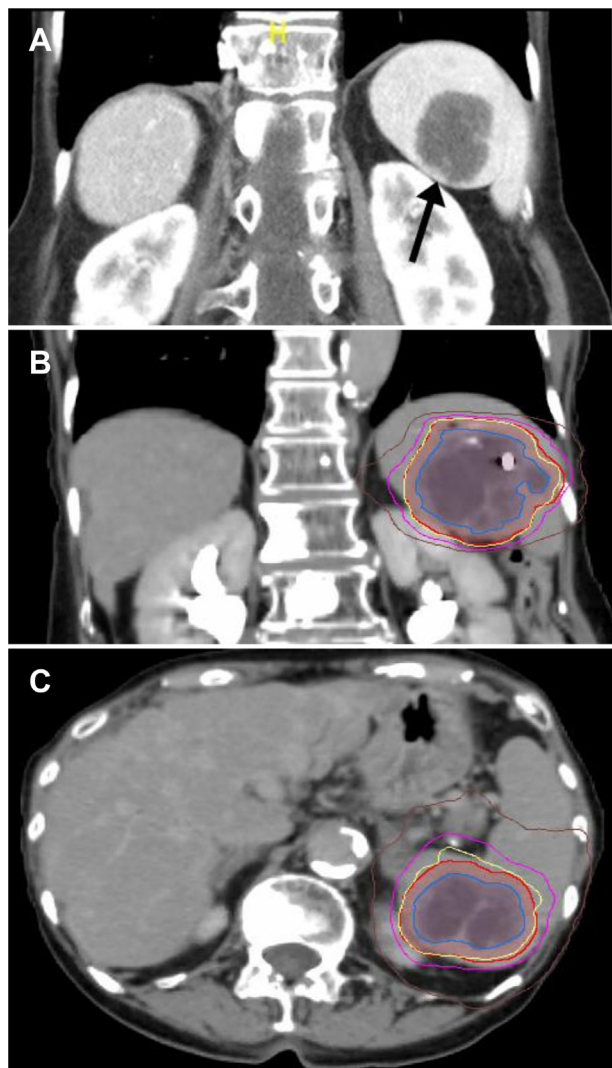


Figure 1 Splenic mass before stereotactic body radiation therapy (SBRT) and radiation plan. (A) Abdominal computed tomography showing a hypodense 36 mm × 26 mm lesion (arrow) in the spleen. SBRT plan to the splenic metastasis in (B) coronal and (C) axial view. Blue is internal target volume and red is planning target volume (PTV). The isodose lines representing the percentages of prescribed radiation therapy are indicated in the corresponding colors: yellow is 100%, purple is 80%, and brown is 50% isodose. PTV was planned to ensure 100% of the PTV received at least 95% of the prescription dose. Maximum dose heterogeneity was set at 107%.

response in the primary lung and hepatosplenic lesions. The brain metastasis was treated by stereotactic radiosurgery. After switching to maintenance pemetrexed, there was significant hepatosplenic progression and she was initiated on immunotherapy with nivolumab. During the first 9 months on nivolumab, there was a partial response in the hepatosplenic disease but progression in the brain and multiple bony sites, which were treated with stereotactic radiosurgery and external beam radiation

Table 1 Summary of radiation treatment plan for the splenic metastasis

	Metrics	Desired	Achieved
PTV	V100% Rx	≥95%	95.0%
	Min	>95% Rx	75.9% Rx
Colon	V25 Gy	<20 cm ³	0.0 cm ³
	D0.035 cm ³	<38 Gy	9.5 Gy
	Max	<38 Gy	12.7 Gy
Cord	V14.5 Gy	<1.2 cm ³	0.4 cm ³
	V23 Gy	<0.35 cm ³	0.0 cm ³
	D0.035 cm ³	<30 Gy	15.7 Gy
	Max	<30 Gy	16.3 Gy
Esophagus	V19.5 Gy	<5 cm ³	0.0 cm ³
	D0.035 cm ³	<35 Gy	16.5 Gy
	Max	<35 Gy	17.6 Gy
Kidneys, combined	Mean	<18 Gy	4.8 Gy
Lungs	V5 Gy	<30%	1.3%
	V20 Gy	<7%	0.0%
	Mean	<4.5 Gy	0.5 Gy
Ribs	V35 Gy	<1 cm ³	0.7 cm ³
	D0.035 cm ³	<43 Gy	43.0 Gy
	Max	<43 Gy	46.8 Gy*
Skin	D0.035 cm ³	<24 Gy	42.4 Gy*
	Max	<24 Gy	44.4 Gy*
Stomach	D0.035 cm ³	<32 Gy	30.4 Gy
	Max	<32 Gy	36.6 Gy*

Abbreviations: D0.035 mL = dose to 0.035 mL of organ of interest; PTV = planning target volume; Rx = prescription dose; V100% Rx = percent of target volume receiving 100% of the prescription dose; Vxx Gy = volume (cm³ or %) receiving xx Gy. * Necessary for target coverage.

therapy, respectively. For the next 8 months on nivolumab, she had stable disease in other sites but had isolated progression in the spleen (Fig 1A). Given her otherwise stable disease on nivolumab and desire to avoid cytotoxic chemotherapy, the decision was made to treat her splenic metastasis with SBRT while continuing nivolumab. In addition, although not necessarily expected in her case given the mixed response to nivolumab, consideration was given to the small chance of an abscopal effect which has been seen with SBRT and immunotherapy.¹⁰

A fiducial marker was placed in the splenic lesion for image-guided treatment. A wing board and VacQfix cushion were used to ensure proper positioning and immobilization. A high-resolution fine-cut contrast-enhanced 4-dimensional CT was taken. An abdominal magnetic resonance imaging was fused to the planning CT scan to aid in tumor volume delineation. The gross tumor volume was drawn. An internal target volume was created from the gross tumor volume to compensate for breathing motion. The planning target volume margin was 5 mm. A conformal photon radiation plan was designed using volumetric-modulated arc therapy. Orthogonal

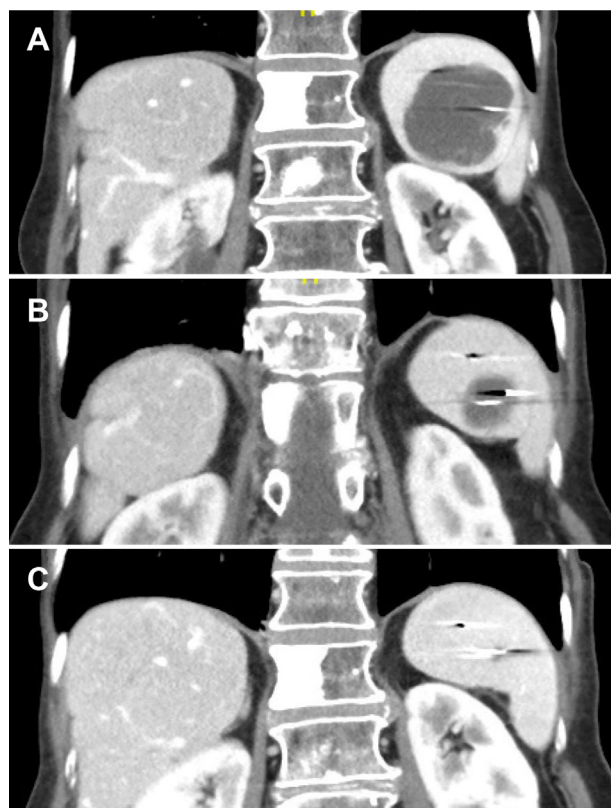


Figure 2 Abdominal computed tomography after stereotactic body radiation therapy (SBRT). (A) One-month post-SBRT showing necrotic enlargement of the mass to 49 × 43 mm. (B) Four months post-SBRT showing a significant reduction of the mass to 18 mm. (C) Ten-month post-SBRT showing barely perceptible splenic mass.

(anteroposterior and lateral x-rays) films and cone beam CT were taken daily to ensure proper positions.

A total of 50 Gy in 5 fractions was delivered to the splenic mass every other day using two 6 MV photon arcs. Details of the treatment plan are shown in Fig 1B-C and Table 1. The patient tolerated the SBRT well. There was initial pseudoprogression of the splenic mass at 1 month post-SBRT, but this was followed by partial and complete tumor response at 4 and 10 months respectively (Fig 2A-C). Twenty months after her SBRT, she remained without any recurrence or progression in the spleen or other body sites.

Complete blood counts of the patient before, during, and after SBRT are shown in Table 2 and Fig 3. Before treatment, she had moderate lymphopenia and mild thrombocytopenia likely secondary to her bony and splenic metastases. During her SBRT, she developed severe lymphopenia that lasted about 6 months post-SBRT before improving to mild lymphopenia by 14 months post-SBRT. Before her treatment, she had standard vaccinations, including pneumococcal vaccine, as part of her routine health maintenance, and she did not develop any infectious complications. Her platelet counts also slightly

Table 2 Complete blood count pre- and post-SBRT of the splenic metastasis

Time post-SBRT	Hgb (g/dL) /Hct (%)	WBC (K/UL)	Lymphocyte (% / K/UL)	Platelet (K/UL)
Pre-SBRT	12.7/39.5	7.3	7.7/0.56	139
During-SBRT*	12.5/39.0	5.6	3.8/0.21	115
11 d	13.3/41.1	7.4	4.6/0.34	110
25 d	12.9/40.0	5.7	5.3/0.30	118
39 d	12.5/39.2	6.6	6.5/0.43	136
2 mo	12.8/39.2	5.4	5.3/0.29	158
2.7 mo	12.0/37.5	7.2	6.2/0.45	179
4 mo	13.1/40.3	6.4	6.7/0.43	163
6 mo	12.0/37.8	6.5	8.4/0.55	209
9.4 mo	15.0/47.8	7.6	7.9/0.60	209
12 mo	13.8/44.2	7.6	9.7/0.74	228
14 mo	13.3/41.1	8.8	10.4/0.92	220

Abbreviations: Hct = hematocrit; Hgb = hemoglobin; SBRT = stereotactic body radiation therapy; WBC = white blood cell.

* After 4 SBRT sessions and delivery of total 40 Gy.

decreased during SBRT but improved to a normal count by 2 months post-SBRT.

Discussion

In this case presentation, SBRT was used to definitively treat the enlarging splenic metastasis despite disseminated disease given otherwise stable systemic disease on nivolumab, so that the patient could continue immunotherapy and avoid cytotoxic chemotherapy. SBRT was well tolerated and resulted in a complete tumor response, allowing the patient to remain on nivolumab without escalation of systemic therapy. This case suggests that SBRT may be used in oligoprogressive metastatic NSCLC with immunotherapy safely with durable local and systemic control.

Historically, the role of radiation therapy in metastatic NSCLC has been symptom palliation using lower-dose radiation.¹¹ However, with evidence supporting a survival benefit with the use of metastasis-directed ablative therapy in oligometastatic disease,^{12,13} SBRT is now commonly used for NSCLC with a limited number of metastases (up to 5). SBRT to the liver, lung, and adrenal glands in oligometastatic NSCLC has been associated with excellent and durable control of treated metastases, with 2-year tumor control rates ranging from 50% to 90%.^{9,14-19} For widespread metastatic disease, the use of aggressive metastasis-directed therapy is largely experimental and not well established. In an oligoprogressive setting where disease progression is limited to only a few sites while on systemic therapy, several studies including one single arm prospective trial

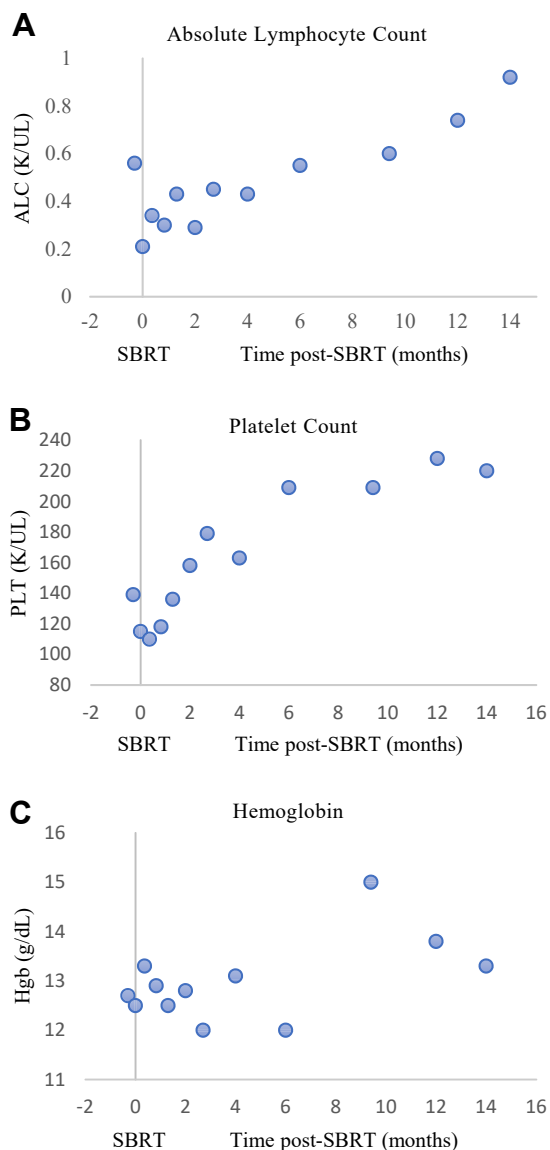


Figure 3 Complete blood count pre- and post-sterotactic body radiation therapy (SBRT) of the splenic metastasis.

suggest that ablative radiation of metastatic lesions increases progression-free survival.^{8,20-26} These studies mostly included oncogene-addicted NSCLC treated with targeted therapies.

The safety and efficacy of SBRT to oligoprogressive sites in NSCLC undergoing treatment with immune-checkpoint inhibitors are not well established. A recent phase I study demonstrated that pembrolizumab immunotherapy after multisite SBRT to solid tumor metastases is safe and well tolerated.²⁷ Reducing the tumor burden with SBRT to metastatic lesions may enhance systemic response to immunotherapy, as high tumor burden is associated with decreased efficacy of programmed cell death-1 immunotherapy.²⁸ Furthermore, concurrent SBRT and immunotherapy may be beneficial given the possibility of an abscopal effect, which has been reported in several case reports.²⁹⁻³²

The present case is also one of the first detailed reports of a splenic metastasis from NSCLC successfully treated with SBRT. Splenic metastasis is often treated definitively by splenectomy in the setting of an isolated metastasis or oligometastatic disease.^{6,33,34} To our knowledge, only 4 cases of SBRT to splenic metastases have been reported in the medical literature, with 2 cases describing a partial and complete response, respectively.³⁵⁻³⁷ In the present case, SBRT of the splenic mass resulted in pseudoprogression at 1-month post-SBRT, followed by partial and complete response within 4 and 10 months, respectively. We suggest that SBRT is more favorable over splenectomy given its minimal morbidity, non-invasiveness, and appropriateness for poor surgical candidates.

However, splenic irradiation presents a unique challenge as it can lead to immunosuppression from functional hyposplenism and lymphopenia, potentially reducing the body’s anti-tumor immune response and increasing the risk for infection. Higher mean spleen radiation dose has been associated with post-irradiation lymphopenia,³⁸⁻⁴⁰ and SBRT-induced severe lymphopenia with an absolute lymphocyte count of less than 0.5 K/UL in lung cancer patients has been correlated with worse overall survival.⁴¹ In addition, splenic irradiation with 40 Gy has been shown to cause splenic atrophy and functional hyposplenism, placing patients at risk for developing pneumococcal sepsis.^{42,43} Our patient experienced a 6-month period of severe lymphopenia post-SBRT. However, she had an excellent tumor response and the non-irradiated sites of disease remained stable. She also did not develop any infectious complications, perhaps as she had been previously vaccinated against pneumococcal bacteria. Nevertheless, given the association between lymphopenia and inferior survival, radiation-induced lymphopenia should be considered when choosing and delivering splenic SBRT. Splenic SBRT may not be appropriate for patients with severe lymphopenia. A potential approach to minimize SBRT-induced lymphopenia is partial treatment (irradiation of only a portion of the lesion), which has been shown to achieve similar treated metastasis control compared with complete treatment in a prospective trial.⁴⁴ Although the patient presented in this case was treated with SBRT, whether a lower dose conventional radiation could have achieved a similar tumor response and control with less severe lymphopenia is unknown. In addition to lymphopenia, thrombocytopenia is a potential side effect associated with splenic irradiation.⁴⁵ However, in our case of SBRT to the spleen, only slight worsening of baseline mild thrombocytopenia was observed.

In summary, our case suggests that SBRT is a safe and effective treatment modality for splenic metastasis from NSCLC. We also observe that SBRT can be used to achieve durable local and systemic control (20 months) in oligoprogressive NSCLC while on immunotherapy, avoiding systemic therapy escalation to

cytotoxic chemotherapy. However, splenic irradiation results in lymphopenia, and the benefit of metastasis control achieved with splenic SBRT should be balanced against such toxicity. Patients undergoing splenic irradiation should be recommended to receive vaccinations similar to those undergoing splenectomy to decrease the risk of infection in the period of treatment-related lymphopenia.

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