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Scientific Article

Effect of Immunotherapy and Stereotactic Body Radiation Therapy Sequencing on Local Control and Survival in Patients With Spine Metastases

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Abstract

Purpose: Stereotactic body radiation therapy (SBRT) is commonly used to treat spinal metastases in combination with immunotherapy (IT). The optimal sequencing of these modalities is unclear. This study aimed to investigate whether sequencing of IT and SBRT was associated with differences in local control (LC), overall survival (OS), and toxicity when treating spine metastases.

Methods and Materials: All patients at our institution who received spine SBRT from 2010 to 2019 with systemic therapy data available were reviewed retrospectively. The primary endpoint was LC. Secondary endpoints were toxicity (fracture and radiation myelitis) and OS. Kaplan-Meier analysis was used to determine whether IT sequencing (before versus after SBRT) and use of IT were associated with LC or OS.

Results: A total of 191 lesions in 128 patients met inclusion criteria with 50 (26%) lesions in 33 (26%) patients who received IT. Fourteen (11%) patients with 24 (13%) lesions received the first IT dose before SBRT, whereas 19 (15%) patients with 26 (14%) lesions received the first dose after SBRT. LC did not differ between lesions treated with IT before SBRT versus after SBRT (1 year 73% versus 81%, log rank = 0.275, $P = .600$). Fracture risk was not associated with IT timing ($\chi^2 = 0.137$, $P = .934$) or receipt of IT ($\chi^2 = 0.508$, $P = .476$), and no radiation myelitis events occurred. Median OS was 31.8 versus 6.6 months for the IT after SBRT versus IT before SBRT cohorts, respectively (log rank = 13.193, $P < .001$). On Cox univariate analysis and multivariate analysis, receipt of IT before SBRT and Karnofsky performance status <80 were associated with worse OS. IT treatment versus none was not associated with any difference in LC (log rank = 1.063, $P = .303$) or OS (log rank = 1.736, $P = .188$).

Conclusions: Sequencing of IT and SBRT was not associated with any difference in LC or toxicity, but delivering IT after SBRT versus before SBRT was associated with improved OS.

Introduction

Management of spinal metastases is a rapidly evolving branch of oncology. Like brain metastases, a spinal metastasis can alter prognosis not only by indicating the presence of metastatic spread but also by causing

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life-changing local damage, resulting in pain and crippling neurologic deficits. Just as management paradigms of brain metastases have drastically changed over the previous decade to incorporate targeted ablative therapies and spare normal brain, management of spinal metastases has seen a shift from conventional palliative regimens toward stereotactic body radiation therapy (SBRT) as the result of its ability to enhance local control (LC) and pain response.[1-4] Recent landmark trials have investigated SBRT's potential as both a survival-prolonging entity in oligometastatic disease and as a superior form of spinal pain palliation relative to conventional palliative radiation regimens.[3-7] Owing to the high conformality of SBRT, the prescription dose can be delivered only to areas at high risk for disease spread, sparing the cord and allowing for greater doses of radiation to be delivered. This elevated dose per fraction has been suspected to promote disease control and has been hypothesized to modify the immune response to radiation therapy (RT).[8,9] The effect of SBRT on the immune response in the context of the immunotherapy (IT) revolution has generated interest in enhancing both local and systemic disease response by using SBRT and IT together in combinatorial approaches.

Both clinical and laboratory studies have indicated that RT and IT have synergistic effects.[8-12] Proposed mechanisms of immune enhancement by RT include increasing the release of inflammatory cytokines (examples include tumor necrosis factor α, interferon [IFN] gamma, IFN-α, and IFN-β), enhancing T-cell differentiation and dendritic cell maturation via radiation-induced antigen release, improving T-cell infiltration into tumors, and increasing T-cell recognition of malignant cells.[9,13-15] These mechanistic enhancements have translated into superior likelihood of cancer control at the cost of potentially increased toxicity risk with the addition of IT to RT.[16-21] Specifically, IT has been shown to enhance both LC and overall survival (OS) when added to stereotactic radiosurgery (SRS) for central nervous system metastases, with the most robust data for melanoma.[16-19] In contrast, RT has been shown to have the potential to result in an abscopal effect in a small percentage of patients, in which radiation results in immunosensitization to nonirradiated lesions and subsequent systemic disease response.[22,23] Despite the evidence of synergy between the 2 modalities, optimal clinical strategies for timing and sequencing IT and SBRT have not been well-defined. One frequent clinical decision requirement is to sequence SBRT before or after IT. Mechanistically, arguments exist for both options. For example, studies have shown that CD8 T cells upregulate programmed cell death ligand 1 expression on tumor cells after the delivery of fractionated RT, which suggests it may be advantageous to administer programmed cell death 1/programmed cell death ligand 1 –targeted therapies before RT.[24] In contrast, anti-OX40 therapy has better results when delivered 1 day after versus 7 days before RT.[25] The question of optimal RT and IT sequencing has been investigated in the setting of brain metastases with varying results[8,26-31] but has yet to be evaluated in the setting of spinal disease, where local progression can also severely affect quality of life.

Here, we discuss a retrospective study conducted on a cohort of patients with spinal metastases treated with SBRT. Specifically, we evaluate whether the sequence of SBRT and IT, as well as the receipt of IT at any time, affected fracture risk, local tumor control, and OS.

Methods and Materials

Patient selection and treatment

An institutional review board–approved retrospective review was carried out on all patients treated with SBRT for a spinal (C1-S5) metastasis and who had systemic therapy data available from 2010 to 2019. IT was defined as any targeted agent with a primary mechanism of action designed to enhance immunologic activity against malignancy. SBRT was defined as a treatment using ≤5 fractions and a dose of at least 6 Gy/fraction. The electronic medical record was used to obtain patient characteristics and dates of SBRT and IT administration.

Treatment was delivered using a TrueBeam (Varian Medical Systems, Palo Alto, CA) platform with either 1 or 3 fractions. Targets were visualized using computed tomography simulation in conjunction with high-resolution magnetic resonance imaging with T1- and T2-weighted sequences. The gross tumor volume, clinical tumor volume, and planning treatment volume were contoured in accordance with consensus guidelines.[4,32] Treatment plans were generated using Eclipse software (Varian Medical Systems). Maximum dose to the spinal cord was limited to 14 Gy for single-fraction treatments and 21.9 Gy for 3-fraction treatments in accordance with published guidelines.[32,33] Patients underwent a clinical evaluation and magnetic resonance imaging every 3 months for 1 year and then follow-up intervals increased to every 6 months.

Outcomes

The primary outcome of the study was LC, defined as the absence of a progressively enhancing lesion or pathology that demonstrated malignancy at the treated vertebral level(s). Secondary outcomes included OS, rates of SBRT-related fracture within the treatment volume, and radiation myelitis (RM), defined as clinical evidence of spinal cord damage at the irradiated level and an absence of other causes of spinal damage at that level, such as mechanical compression after fracture and locally recurrent disease.[34] SBRT-related fracture was defined as a new or worsened compression fracture within the treatment

volume. OS statistics were reported by patient, and LC was reported by lesion. All outcomes are reported with the date of the first SBRT fraction as day zero.

For comparison of the primary and secondary outcomes, patients who had received IT were divided into 2 groups: those who received the first dose of IT before the first dose of SBRT (IT first), and those who received the first dose of SBRT before the first dose of IT (SBRT first). Primary and secondary outcomes among those who received IT were compared with those who did not. Intervals were calculated both by patient and by lesion because some patients had more than 1 lesion. To account for potential selection bias associated with IT timing, metastatic burden was recorded at the time of SBRT. Patients were categorized into 3 groups of metastatic burden: spine metastases only, spine and extraspinal metastases present with an absence of brain metastases, and spine and brain metastases present. Metastatic burden was then converted to a binary variable wherein patients with only spinal metastases were compared with patients with any extraspinal metastatic burden (including both brain and nonbrain) for statistical analysis. Karnofsky performance status (KPS) (≥80 versus <80), histology (radiosensitive versus radioresistant), and number of vertebrae treated (1 versus >1) were converted to binary categorical variables. Radioresistant histologies were defined as thyroid carcinoma, sarcoma, colorectal carcinoma, non-small cell lung carcinoma, melanoma, and renal cell carcinoma.[1] All other histologies were considered radiosensitive.

Statistical analysis

Continuous variables were expressed using sample medians and categorical variables were expressed as percentages. The χ^2 method was used to compare categorical variables including toxicity. The Kaplan-Meier method was used to estimate LC and OS. Cox proportional hazards model was used to identify independent predictors of LC and OS, whereas binary logistic regression was used to assess predictors of toxicity. All analysis was done using SPSS (SPSS Statistics for Macintosh, version 24.0; IBM Corp, Armonk, NY) using a P value <.05 for statistical significance.

Results

Patient and disease characteristics

A total of 191 lesions in 128 patients were included for analysis. The median age was 62 years (range, 16-91). Median follow-up was 16.5 months (interquartile range [IQR], 5.7-34.1). Median KPS was 80 (range, 40-90). In total, 107 (56%) lesions were treated in a single fraction using either 16 Gy (n = 77, 45%) or 18 Gy (n = 13, 7.6%). The remainder (n = 84, 44%) were treated in 3 fractions using a median dose of 24 Gy (range, 18-27). The most common primary histologies were non-small cell lung cancer (n = 35, 18%), breast cancer (n = 35, 18%), renal cell carcinoma (n = 26, 14%), prostate cancer (n = 18, 9.4%), and melanoma (n = 13, 7%). Among 128 patients, extra−central nervous system metastases and brain metastases were present in 70 (55%) and 17 (13%) of patients, respectively. Of the 191 spinal lesions, 24 (13%) were treated with separation surgery before SBRT. Summaries of patient characteristics, for the population overall and for the cohort that received IT stratified by sequence with radiation, are included in Tables 1 and 2, respectively.

Thirty-three (26%) patients with 50 (26%) lesions received IT. Fourteen patients with 24 (13%) lesions received IT before SBRT, whereas 19 patients with 26 (14%) lesions received IT after SBRT. In the group of lesions that received IT first, the median time between IT and SBRT was 3.9 months (IQR, 1.6-9.7). In the group of lesions that received SBRT first, the median time between IT and the SBRT was 16.7 months (IQR, 8.1-29.1

Table 1 Patient characteristics for overall population

Patient characteristics (n = 128)	
Age, y, median (range)	62 (16-91)
Median follow-up, mo (range)	16.5 (1-118)
Systemic therapy (by lesion n = 191)	
Received immunotherapy	50 (26%)
Received systemic therapy	172 (90%)
Previous decompression surgery (by lesion n = 191)	
Yes	24 (13%)
No	167 (87%)
SBRT fractionation (by lesion n = 191)	
Single fraction (median dose, 16 Gy)	107 (56%)
Three fractions (median dose, 8 Gy)	84 (44%)
Histology (by lesion n = 191)	
NSCLC	35 (18%)
Breast	35 (18%)
Renal cell	26 (14%)
Prostate	18 (9%)
Melanoma	13 (7%)
Head and neck	12 (6%)
Sarcoma	9 (5%)
Myeloma	8 (4%)
Other	35 (18%)

Abbreviations: IT = immunotherapy; NSCLC = non-small cell lung cancer; SBRT = stereotactic body radiation therapy.

Table 2 Patient characteristics among cohort sequence of IT and SBRT

Patient characteristic (n = 128)	SBRT alone	IT first	SBRT first
Age, y, median (range)	63 (16-89)	63 (28-91)	68 (41-76)
Sex			
Male	42 (44%)	10 (71%)	9 (47%)
Female	53 (56%)	4 (29%)	10 (53%)
KPS			
60	9 (10%)	1 (7%)	0 (0%)
70	28 (30%)	5 (36%)	3 (16%)
80	42 (45%)	7 (50%)	13 (68%)
90	15 (16%)	1 (7%)	3 (16%)
Metastatic burden			
Spine only	30 (32%)	6 (43%)	5 (26%)
Non-CNS extraspinal	51 (54%)	8 (57%)	11 (58%)
Spine and brain	14 (15%)	0 (0%)	3 (16%)
Histology (by lesion n = 191)			
NSCLC	24 (17%)	4 (17%)	7 (27%)
Breast	33 (23%)	0 (0%)	2 (8%)
Renal cell	12 (9%)	7 (29%)	7 (27%)
Prostate	16 (11%)	0 (0%)	2 (8%)
Melanoma	8 (6%)	9 (38%)	4 (15%)
Head and neck	8 (6%)	1 (4%)	2 (8%)
Other	40 (28%)	3 (13%)	2 (8%)
Involved spinal segment (by lesion n = 191)			
Cervical	20 (14%)	1 (4%)	1 (4%)
Cervical and thoracic	2 (1%)	0 (0%)	0 (0%)
Thoracic	71 (50%)	10 (42%)	12 (46%)
Thoracic and lumbar	4 (3%)	0 (0%)	2 (8%)
Lumbar	36 (26%)	12 (50%)	10 (39%)
Lumbar and sacral	5 (4%)	1 (4%)	1 (1%)
Sacral	3 (2%)	0 (0%)	0 (0%)
Number of involved vertebrae (by lesion n = 191)			
1	82 (58%)	12 (60%)	11 (42%)
2	20 (14%)	5 (21%)	7 (27%)
3	24 (17%)	5 (21%)	7 (27%)
4	12 (9%)	2 (8%)	1 (4%)
5	2 (1%)	0 (0%)	0 (0%)
6	1 (1%)	0 (0%)	0 (0%)
Total fractions (by lesion n = 191)			
1	80 (57%)	14 (58%)	13 (50%)
3	61 (43%)	10 (42%)	13 (50%)

Abbreviations: CNS = central nervous system; IT = immunotherapy; KPS = Karnofsky performance status; NSCLC = non-small cell lung cancer; SBRT = stereotactic body radiation therapy.
"SBRT no IT" includes patients who received nonimmunotherapy systemic therapies and those who did not receive systemic therapy; "spine only" includes all metastatic disease in spinal column; "non-CNS extraspinal" includes spinal metastases and extraspinal metastases outside of the CNS; and "spine and brain" includes metastases present in brain and in spine.

Table 3 Details of immunotherapies used across treatment groups reported by lesion

Immunotherapy	IT first	SBRT first
Atezolizumab	0	4
Durvalumab	1	0
Ipilimumab	2	3
Nivolumab	15	8
Nivolumab/Ipilimumab	1	1
Pembrolizumab	5	5
Sipuleucel-T	0	2
REGN2810	0	2
REGN3767	0	1
Total	24	26

Abbreviations: IT = immunotherapy; SBRT = stereotactic body radiation therapy.

months). Non-IT systemic therapies were administered to 117 (91%) patients with 172 (90%) lesions. Among patients who received IT at any point, brain metastatic burden was numerically greater in the SBRT-first group versus the IT-first group (3 versus 0 patients with brain metastasis present). The rate of extraspinal metastatic disease at the time of SBRT was similar between the SBRT-first versus IT-first groups ($\chi^2 = 0.992$, $P = .319$). A summary of immunotherapeutic agents employed in this study is included in Table 3.

Local control

Median LC by lesion across the whole population was not reached. Among patients who received IT, LC did not significantly differ between lesions treated with IT before SBRT versus after SBRT. LC for the IT-first versus the SBRT-first groups at 1, 2, and 3 years was 73% versus 81%, 55% versus 81%, and 55% versus 60%, respectively. LC based on IT sequencing is depicted in Fig. 1. Overall rates of local recurrence are depicted in Table 4. LC at 1, 2, and 3 years based on treatment group, including the group that did not receive IT, is depicted in Table 5. There were no significant differences in LC based on IT/SBRT sequencing (log rank = 0.275, $P = .600$). No significant LC differences existed between patients who received IT and those who did not (log rank = 1.063, $P = .303$). On both univariate and multivariate Cox regression, sequencing of IT, age, sex, systemic therapy use, histology, metastatic burden, and previous surgery were not significant predictors of LC.

Overall survival

Median OS by patient across the whole population was 24.8 (IQR, 5.7 -34.1) months. Median survival did not

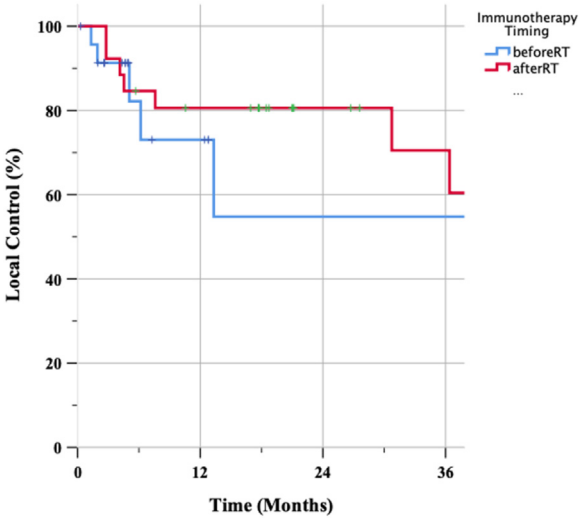

Figure 1 Kaplan-Meier analysis of local control in lesions receiving immunotherapy before stereotactic body radiation therapy (blue) and immunotherapy after stereotactic body radiation therapy (red). *Abbreviation:* RT = radiation therapy.

Table 4 Comparison of local recurrence and fracture at any time point between treatment groups

	SBRT no IT	IT first	SBRT first
Local recurrence (by lesion n = 191)			
Yes	24 (17%)	5 (21%)	7 (27%)
No	117 (83%)	19 (79%)	19 (73%)
Fracture (by lesion n = 191)			
Before RT	15 (12%)	3 (13%)	2 (8%)
After RT	15 (12%)	2 (8%)	4 (15%)
SBRT no IT	93 (76%)	18 (79%)	20 (77%)

Abbreviations: IT = immunotherapy; RT = radiation therapy; SBRT = stereotactic body radiation therapy.
"SBRT no IT" includes patients who received nonimmunotherapy systemic therapies and those who did not receive systemic therapy.

Table 5 Comparison of local control and overall survival at 1, 2, and 3 years between patients who received immunotherapy before SBRT versus those who received SBRT before immunotherapy

	Local control			Overall survival		
	1 y	2 y	3 y	1 y	2 y	3 y
SBRT no IT	82%	77%	77%	65%	50%	43%
IT first	73%	55%	55%	32%	32%	32%
SBRT first	81%	81%	60%	95%	61%	48%

Abbreviations: IT = immunotherapy; SBRT = stereotactic body radiation therapy.
"SBRT no IT" includes patients who received nonimmunotherapy systemic therapies and those who did not receive any systemic therapy.

Table 6 Univariate and multivariable Cox regression for overall survival

Variable	Univariate analysis				Multivariate analysis			
	HR	95% CI		*P* value	HR	95% CI		*P* value
		Lower	Upper			Lower	Upper	
Immunotherapy timing (ref: after SBRT)	4.445	1.882	10.501	**.001**	5.581	1.640	18.998	**.006**
Age	0.992	0.958	1.028	.671	0.998	0.961	1.036	.899
Sex (ref: female)	1.930	0.788	4.726	.150	1.086	0.384	3.071	.876
Radiosensitivity*(ref: radiosensitive)	1.326	0.490	3.589	.578	2.138	0.532	8.591	.284
Systemic therapy (ref: yes)	1.078	0.456	2.549	.864	1.112	0.359	3.446	.854
Local recurrence (ref: yes)	1.381	0.508	3.758	.527	1.079	0.331	3.517	.900
Total fractions (ref: 1 fraction)	1.000	0.439	2.279	.999	0.916	0.256	3.278	.892
KPS (ref: >80)	3.133	1.300	7.547	**.011**	3.878	1.111	13.540	**.034**
Metastatic burden (ref: spine only)	0.911	0.380	2.182	.834	0.733	0.260	2.063	.556

A *P* value <0.05 is considered significant (in bold). *Abbreviations*: CI = confidence interval; HR = hazard ratio; KPS = Karnofsky performance status; ref = category listed when binary categorical variable used; SBRT = stereotactic body radiation therapy.
*Radioresistant histologies were defined as thyroid carcinoma, sarcoma, colorectal carcinoma, non-small cell lung carcinoma, melanoma, and renal cell carcinoma.[1] All other histologies were considered radiosensitive.

significantly differ between patients treated with IT and those who did not receive it (27.8 versus 18.7 months, log rank = 1.736, $P = .188$). Among patients who received IT, OS was shorter when patients received IT before SBRT versus after SBRT, with a median OS of 6.6 months versus 31.8 months, respectively (log rank = 13.193, $P < .001$). OS for the IT-first versus the SBRT-first cohorts at 1, 2, and 3 years were 32% versus 95%, 32% versus 61%, and 32% versus 48%, respectively. Data for OS at 1, 2, and 3 years based on treatment group are depicted in Table 5. On Cox univariate regression, IT timing before SBRT (hazard ratio [HR], 4.445, $P < .001$) and KPS <80 (HR, 3.133, $P = .011$) were significant predictors of worsened survival. This finding remained significant on multivariate analysis, which indicated receiving IT before SBRT (HR, 5.581, $P = .006$) and having KPS <80 (HR, 3.878, $P = .034$) predicted worse OS while controlling for age, sex, systemic therapy use, radiosensitivity of histology, local recurrence, number of fractions, and metastatic burden, as shown in Table 6. OS based on IT sequencing is depicted in Fig. 2.

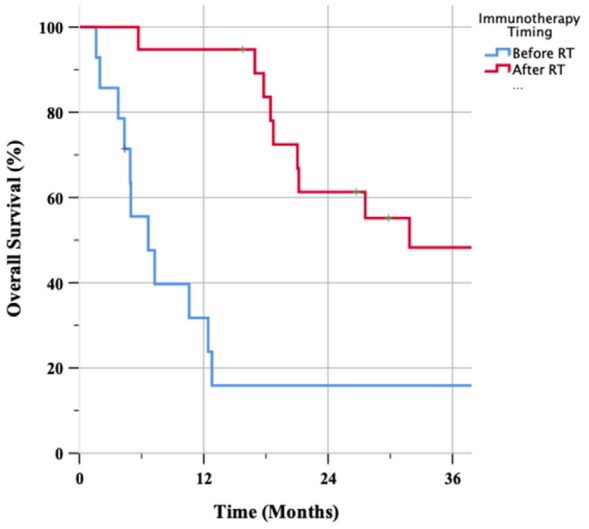

Figure 2 Kaplan-Meier analysis of overall survival in patients receiving immunotherapy before stereotactic body radiation therapy (blue) and immunotherapy after stereotactic body radiation therapy (red). *Abbreviation:* RT = radiation therapy.

Toxicity: fracture and RM

Vertebral fractures occurred in 21 of 191 (11%) lesions. No significant differences existed between fracture risk among lesions treated with SBRT in patients who received IT versus those who did not (6/50 = 12% versus 15/141 = 11%, $\chi^2 = 0.137$, $P = .934$). Fracture risk among those who received IT was not associated with sequence of IT and SBRT, with 2 of 24 (8%) versus 4 of 26 (15%) lesions developing fractures in the IT-first versus SBRT-first groups, respectively ($\chi^2 = 0.508$, $P = .476$). There were no incidences of grade ≥3 RM. Overall rates of fracture are reported in Table 4. Binary logistic regression with univariate and multivariate analyses did not find sequencing of IT, age, sex, radiosensitive histology, number of vertebrae irradiated, fractionation schema, KPS, surgery, sex, or age to be predictors of fracture.

Discussion

This represents the first study to our knowledge evaluating how sequencing of IT and SBRT affects LC and OS in patients with spine metastases. We found that rates of LC did not differ significantly based on the receipt of IT and its timing in relation to SBRT. Survival, however, was significantly lower in patients who received IT before SBRT compared with those who received IT after SBRT. No patients in our cohort suffered from RM, and fracture rate was similar regardless of IT receipt and sequencing.

Although our study is the first assessment of the association between SBRT/IT sequencing on LC rates in the spine, many studies have assessed the effect of IT sequencing on LC of metastatic disease in the brain, most commonly with melanoma primaries.[18,29-31,35] Kiess et al[30] analyzed 46 patients with 113 melanoma brain metastases and found that patients treated with SRS for melanoma brain metastases during or before ipilimumab had better OS and less regional recurrence than those treated with SRS after ipilimumab (1-year OS 65% versus 56% versus 40%, $P = .008$; 1-year regional recurrence 69% versus 64% versus 92%, $P = .003$). SRS delivered concurrently with ipilimumab also trended toward lower rates of local recurrence in comparison with SRS before or after ipilimumab (1-year local recurrence 0% versus 13% versus 11%, $P = .21$). Cohen-Inbar et al[35] analyzed 46 patients with 232 melanoma brain metastases and found that patients who received SRS before IT with ipilimumab had better LC than those who received SRS after or during IT (19.6 versus 3.0 months, $P = .005$). Schapira et al[26] assessed 37 patients with 85 lung cancer brain metastases and found that programmed cell death-1 pathway inhibitors improved LC when given either concurrently or before versus after SRS (1-year LC, 100% versus 72%, $P = .016$).

Although the primary endpoint of LC was not significantly different between treatment groups in this study, patients who received SBRT before their first dose of IT experienced better survival than those who received IT first. This finding is consistent with reports from other studies investigating sequencing of IT with RT in brain metastases. Cohen-Inbar et al[35] reported a trend toward improved OS for patients who received SRS before or during ipilimumab compared with those who received ipilimumab before SRS (13.8 versus 6.4 months, $P = .118$). Silk et al[8] reported improved OS among patients who received RT before ipilimumab versus after ipilimumab among patients with melanoma brain metastases (18.4 versus 8.1 months, P value not reported). Schoenfeld et al[36] reported a series of 16 patients who had received RT and ipilimumab for melanoma brain metastases, which showed that receipt of SRS before ipilimumab was associated with an OS of 26 months versus 6 months for those who received SRS after ipilimumab ($P < .001$). Shaverdian et al[37] conducted a secondary analysis of the 98 lung cancer patients who received pembrolizumab in the KEYNOTE-001 trial, showing that those who had received previous radiation to any part of their body had improved OS (HR, 0.58; $P = .026$) and progression-free survival (HR, 0.56; $P = .019$) compared with those who did not. Improvement in survival with previous RT was present even when comparing patients with only extracranial RT. In a meta-analysis including patients who received IT before, concurrently with, and after SRS by Badrigilan et al,[27] concurrent administration of IT with SRS was associated with better OS versus nonconcurrent administration (HR, 1.67; confidence interval, 1.35-2.06), with differences most pronounced when comparing patients who received concurrent treatment to those who received IT before SRS (HR, 2.55; confidence interval, 1.53-4.26).

Other reports did not detect a difference in OS based on SRS/IT sequencing in patients with brain metastases. Rauschenberg et al[18] evaluated 141 patients who received IT within 6 weeks of RT for melanoma brain metastases and found that there was no difference in OS between patients who received IT before SRS versus before and after SRS versus after SRS only. Skrepnik et al[31] analyzed 25 patients with 58 melanoma brain metastases based on IT timing and found that OS was not significantly different between groups, but time to progression in the central nervous system was improved when concurrent instead of sequential therapy was given ($P = .04$), with the most pronounced difference between the concurrent and the SRS before IT groups (30.2 versus 4.15 months). Knisely et al[28] reported no difference in survival among 27 patients who received ipilimumab before versus after SRS for melanoma brain metastases (19.8 versus 21.3 months, $P = .58$). In a National Cancer Database Analysis of unresectable pancreatic adenocarcinoma treated with RT and IT, Amin et al[19] found no OS differences between patients treated with concurrent treatment (defined as RT within 30 days of IT), RT before IT, or IT before RT.

Toxicities in this cohort, regardless of whether IT was given, fell within expected ranges seen in the literature for spine SBRT. RM risk is known to be very low when spine SBRT is executed according to international guidelines, with an expected rate of less than 0.5%. Thus, this study cohort's absence of any grade ≥ 3 RM events is not surprising.[7,32,38] The fracture incidence of 11% in our cohort is also within reported ranges of the literature. In a systematic review of 11 studies including 2911 stereotactically irradiated spinal segments, Faruqi et al[39] reported a vertebral compression fracture rate of 14%, with individual studies reporting fracture rates ranging from 5.7% to 39%. Cunha et al[40] evaluated 167 spinal segments treated with SBRT in 90 patients and also found a fracture risk of 11% at a median of 7.4 months.

Some limitations merit consideration. A relatively small proportion of the patients included in the study

received IT (n = 33), which resulted in a limited sample size and a correspondingly limited ability to match outcomes based on prognostic factors such as age, performance status, and histology. That said, this sample size is similar to that of many other single-institution studies assessing interaction between IT and SRS for brain metastases provided in the discussion, which reported outcomes using sample sizes of 16 to 46 patients.[8,26,31,35,36] The retrospective nature of the study and sample size also limited the ability to eliminate confounding factors such as time interval between RT and IT. A potential reason for improved OS in the SBRT-first cohort versus the IT-first cohort could be that patients who were already receiving IT before starting SRS/SBRT had more advanced or aggressive disease at the time of irradiation. To address this potential confounder, patients who received IT were assessed for extraspinal metastatic burden at the time of SBRT. No statistically significant differences in metastatic burden were present between the IT-first and SBRT-first cohorts, and IT timing remained a significant predictor of OS in the multivariate analysis including metastatic disease burden. In addition, this study included immunotherapies with multiple mechanisms, and the optimal sequence for SBRT and IT may vary depending on the mechanism or specific IT agent in question. Finally, this study occurred at a single institution, potentially limiting extrapolation to centers with different practice patterns.

Conclusion

Combined treatment with IT and stereotactic RT holds promise for the future of cancer care, and little investigation has been done into the optimal sequencing of these important therapeutic modalities for metastatic spinal disease. This study's results suggest there may be a potential survival advantage to delivering IT after spinal SBRT. Additional studies including large prospective trials are necessary to further refine our understanding of this complex topic and determine the optimal sequencing of spinal SBRT and IT treatment.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2023.101179.

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