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Clinical Investigation

Initial Results of a Multicenter Phase 2 Trial of Stereotactic Ablative Radiation Therapy for Oligometastatic Cancer

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Summary

Here we report the initial outcomes of an international multicenter phase 2 prospective trial assessing the role of stereotactic ablative radiation therapy (SABR) for oligometastatic cancer. Our results demonstrate SABR to be a safe and effective treatment modality that demonstrates excellent overall survival and local control. Additionally, we report very low rates of acute and late grade 3 toxicity and show SABR to have no significant

Purpose: Oligometastatic disease has emerged as a potentially curable state in the spectrum of cancer progression. Aggressive local therapy such as stereotactic ablative radiation therapy (SABR) may improve oncologic outcomes. Herein, we report the initial oncologic outcomes and patient-reported quality of life (PR-QoL) from a phase 2 multicenter trial for patients with oliogmetastatic disease.

Methods and Materials: Patients with oligometastatic disease (1-5 metastases) were prospectively recruited between 2011 and 2017. SABR dose and fractionation was dependent on the lesion size and location. Patient follow-up occurred within 6 weeks of completion of SABR and at 3-month intervals. Patients received a Functional Assessment of Cancer Therapy-General questionnaire at baseline and at each follow-up to assess for PR-QoL. Median follow-up was calculated by reverse Kaplan-Meier method. Overall survival (OS), local progression-free survival, and distant progression-free survival were calculated using the Kaplan-Meier method.

Results: We enrolled 147 patients with oligometastatic cancer with a median age of 66.4 years (interquartile range, 59.9-74.6). The most common primary tumors included lung (21.8%, non-small cell: n = 29, small cell: n = 3), colorectal adenocarcinoma (21.1%), and head and neck (10.9%, squamous cell carcinoma: n = 11). In

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adverse effect on patient-reported quality of life.

a median follow-up of 41.3 months (interquartile range: 14.6-59.0), the median OS was 42.3 months (95% confidence interval: 27.4-∞) with 5-year OS of 43%. Five-year local progression-free survival and distant progression-free survival were 74% and 17%, respectively. Acute grade 2+ and 3+ toxicity were 7.5% and 2.0%, respectively, and late grade 2+ and 3+ toxicity were both 1.4%. There was no significant change in quality of life at completion and 6 weeks, 3 months, and 9 months after treatment. At 6 and 12 months, patients were found to have statistically significant improvement in PR-QoL.

Conclusions: This multicenter prospective phase 2 study demonstrates that SABR for recurrent oligometastatic cancer is a feasible and tolerable treatment option with minimal acute and late grade 3 toxicity. Additionally, PR-QoL was not adversely affected.

Introduction

Metastatic cancer has a notoriously poor prognosis, with 5-year survival ranging from 4% to 38% based on tumor location and histology.[1] Numerous reports have identified a subset of patients with a limited volume of metastatic disease, termed oligometastatic, who may respond well to aggressive local therapy.[2-4] Because oligometastatic disease has not yet experienced widespread tumor cell dissociation, the sites of tumor burden are limited.[5] Aggressive treatment to oligometastatic disease sites could, therefore, decrease tumor burden and provide long-term disease control. Surgical series have demonstrated survival benefits to this approach in numerous cancer types.[6-9] Stereotactic ablative radiation therapy (SABR) consists of high-dose radiation delivered in a highly precise manner.[10] SABR allows for excellent local control and limited radiation to surrounding normal tissue. SABR is well tolerated and thus can be performed in patients who are not fit for surgery. Herein we report patient outcomes, toxicity, and quality of life of patients with oligometastatic cancer prospectively treated with SABR.

Methods and Materials

Patient selection

This was a multicenter prospective phase 2 study evaluating the safety and feasibility of SABR for patients with oligometastatic cancer. Patients included in this analysis were aged ≥18 years and had biopsy-proven oligometastatic or recurrent cancer. Oligometastatic disease was defined as 5 or fewer total sites of metastases in 3 or fewer organs on fluorodeoxyglucose positron emission tomography/computed tomography (CT) scan within 8 weeks of enrollment. Additional eligibility criteria included Zubrod Performance Status of 0 to 1 and adequate laboratory parameters (absolute neutrophil count ≥1800 cells/mm^3, platelets ≥100,000 cells/mm^3, and hemoglobin ≥8.0 g/dL) within 4 weeks before registration. Patients with lymphoma, leukemia, multiple myeloma, and central nervous primaries were ineligible for enrollment. Furthermore, any patient with another primary cancer diagnosed or treated within the last 3 years (other than cutaneous skin cancer), diffuse metastatic spread confined to 1 organ (ie, leptomeningeal spread in central nervous system or peritoneal carcinomatosis), metastatic disease sites not treatable via SABR, pregnancy, or severe active medical comorbidities (unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months, transmural myocardial infarction within the last 6 months, acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration, hepatic insufficiency resulting in clinical jaundice and/or coagulation defects) were excluded. There were no exclusion criteria based on treatment of primary tumor. Additionally, patients could be enrolled either at initial diagnosis of oligometastatic disease or after prior treatment to metastatic sites. Patients with synchronous oligometastases at diagnosis of their primary tumor were excluded because they were the focus of a separate clinical trial. At registration, demographic information, management of primary tumor, and prior treatments for oligometastases were documented. The protocol was approved by the university investigation review board, and all study participants signed informed consent. This trial was prospectively registered with ClinicalTrials.gov (NCT01345552).

Treatment plan

All metastatic disease sites were treated with SABR as described by the American College of Radiology and American Society for Therapeutic Radiology and Oncology.[11] SABR was performed on either CyberKnife robotic radiosurgery (Accuray Inc, Sunnyvale, CA) or nonrobotic linear accelerator–based platforms (Trilogy, TrueBeam) (Varian Medical Systems, Palo Alto, CA). All treatments were completed within 3 weeks of each other. The gross target volume (GTV) was defined by CT scan, fluorodeoxyglucose positron emission tomography scan, and clinical information. The planning treatment volume was defined as the GTV with a margin appropriate for the location and surrounding normal tissue constraints, as per

site-appropriate protocols. Margins were adjusted based on adjacent normal organs with planning treatment volume edited out of normal organs. Dose and fractionation for each site was based on location, size, and dose constraints of organs at risk, following recommendations of national protocols (Table E1; available online at https://dx.doi.org/10.1016/j.ijrobp.2018.08.027).[12,13] A minimum of 48 hours was required between stereotactic radiosurgery/SABR treatments for each treatment site.

Patient assessment and follow-up

Patients were seen in follow-up by study physicians 6 weeks after completion of stereotactic radiosurgery/SABR, then at 3-month intervals for 3 years, and at 6-month intervals thereafter. Toxicity was evaluated at each follow-up visit using the Common Terminology Criteria for Adverse Events version 4.0. Follow-up imaging with CT was performed every 3 months for the first 2 years and then every 6 months until 5 years after completion of therapy. Measurement of response was determined by the Response Evaluation Criteria in Solid Tumors as complete response, partial response, stable disease, or progressive disease at each follow-up visit. Response was determined and recorded based on last follow-up. The primary endpoint was feasibility of SABR in patients with oligometastatic disease. Prospectively determined secondary outcomes included 5-year overall survival (OS), 5-year local-progression-free survival (LPFS), quality of life outcomes, and toxicity. Although not prospectively determined, distant-progression-free survival (DPFS) was also analyzed. OS was defined as the time from completion of SABR to death due to any cause. LPFS was defined as the time from completion of SABR to first documentation of local failure at treated oligometastatic site. DPFS was defined as the time from completion of SABR to documentation of new distant metastases. Quality of life was assessed at baseline, completion of SABR, and at each follow-up using the 27-item Function Assessment of Cancer Therapy-General (FACT-G). The FACT-G questionnaire included 4 categories: physical, social/family, emotional, and functional wellbeing. The total FACT-G scores were calculated at each time point.

Statistical analysis

The sample size was set to have approximately 15 patients per primary cancer type with an expected 10% drop-out rate. Median follow-up was calculated by reverse Kaplan-Meier method.[14] Three survival endpoints—OS, LPFS, and DPFS—were analyzed with the Kaplan-Meier method. The association of these survival endpoints with risk factors was studied with univariate Cox proportional hazards models. To build multivariable Cox models for the survival endpoints, stepwise variable selection was performed. All variables from univariate models that had a P value of $< .1$ were included as potential predictors. Variables were removed from the multivariable model if the P value was $> .05$. All P values reported are 2-sided. For quality of life analysis, the total FACT-G score was compared between baseline and each time point using the Wilcoxon signed rank test. Statistical analysis was performed using IBM SPSS Statistics version 22.

Results

Patient and treatment characteristics

From 2011 to 2017, 147 patients were enrolled. The median age at enrollment was 66.4 years (interquartile range, 59.9-74.6) with 51.0% being female. The most common primary tumors included lung (21.8%; non-small cell lung cancer: n = 29; small cell lung cancer: n = 3), colorectal adenocarcinoma (21.1%), head and neck (10.9%, squamous cell carcinoma: n = 11), breast carcinoma (8.8%), and prostate adenocarcinoma (7.5%). The primary lung tumor was treated with a combination of surgery (73.5%), chemotherapy (63.9%), or radiation (50.3%). The primary tumor was treated with either single modality (32.7%) or multimodal (67.3%) therapy. Before SABR, separate metastatic sites were treated with surgery (25.9%), chemotherapy (34.7%), and radiation (15.0%) for disease recurrence/distant metastases at non-SABR-treated sites. Patients had 1 (70.7%), 2 (19.0%), 3 (6.8%), 4 (0.7%), or 5 (2.7%) metastases treated with SABR for a total of 218 treated lesions. The lung was the most common site, representing 52.3% (n = 114) of the metastases, followed by 16.5% (n = 36) in lymph nodes, 14.7% (n = 32) in bone, and 6.9% (n = 15) in liver. Patients were treated on Truebeam (52.3%), Trilogy (24.3%) (Varian Medical Systems, Palo Alto, CA), Cyberkinfe (3.2%) (Accuray Inc., Sunnyvale, CA), or Synergy (0.5%). Patient and treatment characteristics are summarized in Tables 1 and 2. After SABR, patients received chemotherapy (46.9%), targeted therapies (12.2%), immunotherapy (12.2%), surgery (7.5%), and/or additional radiation (28.6%) as either adjuvant therapy or for disease progression (Table E2; available online at https://dx.doi.org/10.1016/j.ijrobp.2018.08.027).

Survival

Within a median follow-up of 41.3 months (interquartile range, 14.6-59.0), the median OS was 42.3 months (95% CI, 27.4-∞) with 1- and 5-year OS of 84% and 43%, respectively (Fig. 1). A detailed list of variables analyzed with univariate analysis can be found in Table E3 (available online at https://dx.doi.org/10.1016/j.ijrobp.2018.08.027). On multivariate analysis Karnofsky Performance Status $\leq$80 ($P < .001$; hazard ratio [HR], 3.53; 95% confidence interval [CI], 1.95-6.41]) was found to be associated with significantly worse OS. Multivariate analysis also identified metastasectomy before SABR ($P = .037$; HR 0.44; 95%

Table 1 Patient characteristics at diagnosis

	N = 147
Median age at diagnosis (interquartile range), y	62.5 (54.7-70.1)
Sex	
Male	72 (49.0%)
Female	75 (51.0%)
Race	
Caucasian	99 (66.9%)
African American	4 (2.7%)
Asian	1 (0.7%)
Unknown	43 (29.2%)
Location of primary	
Lung	32 (21.8%)
Colorectal	31 (21.1%)
Head and neck	16 (10.9%)
Breast	13 (8.8%)
Prostate	11 (7.5%)
Kidney	8 (5.4%)
Esophagus	7 (4.8%)
Uterus	5 (3.4%)
Ovaries	5 (3.4%)
Bladder	5 (3.4%)
Other	14 (9.5%)
Histology	
Adenocarcinoma	64 (43.5%)
Squamous cell carcinoma	21 (14.3%)
Invasive ductal carcinoma	8 (5.4%)
Clear cell carcinoma	5 (3.4%)
Renal cell carcinoma	5 (3.4%)
Melanoma	4 (2.7%)
Small cell carcinoma	3 (2.0%)
Urothelial carcinoma	3 (2.0%)
Carcinosarcoma	3 (2.0%)
Other	31 (21.1%)
Initial surgery	
Yes	108 (73.5%)
No	39 (26.5%)
Initial chemotherapy	
Yes	94 (63.9%)
No	53 (36.1%)
Initial radiation	
Yes	74 (50.3%)
No	73 (49.7%)

CI, 0.21-0.95) associated with improved OS. OS was also found to be significantly different among the 5 most common primary malignancies ($P = .002$). Median OS was 54.4 months (95% CI, incalculable) for colorectal, 26.8 months (95% CI, 8.1-45.4) for lung, 17.6 months (95% CI, 12.6-47.0) for head and neck, not reached for breast, and not reached for prostate (Fig. 2).

Local and distant progression–free survival

The estimated median LPFS was not reached, but 1- and 5-year LPFS rates of 91% and 75%, respectively, were

Table 2 Patient characteristics at enrollment

	N = 147 Metastasis = 218
Median age at enrollment (IQR), y	66.4 (59.9-74.6)
Karnofsky Performance Status	
100	50 (34.0%)
90	49 (33.3%)
80	18 (12.2%)
70	4 (2.7%)
60	1 (0.7%)
Unknown	25 (17.0%)
Prior surgery for DM/recurrence	
Yes	38 (25.9%)
No	109 (74.1%)
Prior chemotherapy for DM/recurrence	
Yes	51 (34.7%)
No	96 (65.3%)
Prior radiation for DM/recurrence	
Yes	22 (15.0%)
No	125 (85.0%)
Prior immunotherapy for DM/recurrence	
Yes	1 (0.7%)
No	146 (99.3%)
Number of lesions treated with SABR/SRS	
1	104 (70.7%)
2	28 (19.0%)
3	10 (6.8%)
4	1 (0.7%)
5	4 (2.7%)
Lesion location	
Lung	114 (52.3%)
Lymph node	36 (16.5)
Bone	32 (14.7%)
Liver	15 (6.9%)
Adrenal	8 (3.7%)
Hilar mass	5 (2.3%)
Pelvic mass	3 (1.4%)
Head and neck	2 (0.9%)
Brain	2 (0.9%)
Muscle	1 (0.5%)
Median sum of lesions longest diameter (IQR), cm	2.3 (1.48-3.7)
Median sum of GTV (IQR), cm^3	5.87 (2.2-17.6)
Treatment characteristics	
Median dose (IQR), Gy	48 (41-54)
Median fractions (IQR)	4 (3-5)
Median dose/fx (IQR)	12 (9-18)
Median GTV (IQR), cm^3	3.3 (1.5-10.6)
Median PTV (IQR), cm^3	15.9 (8.2-30.8)
Median isodose (IQR)	87% (82%-90%)
Treatment platform	
Truebeam	114 (52.3%)
Trilogy	53 (24.3%)
Cyberknife	7 (3.2%)
Syngery	1 (0.5%)
Unknown	43 (19.7%)

Abbreviations: DM = distant metastasis; GTV = gross tumor volume; IQR = interquartile range; SABR = stereotactic ablative radiation therapy; SRS = stereotactic radiosurgery.

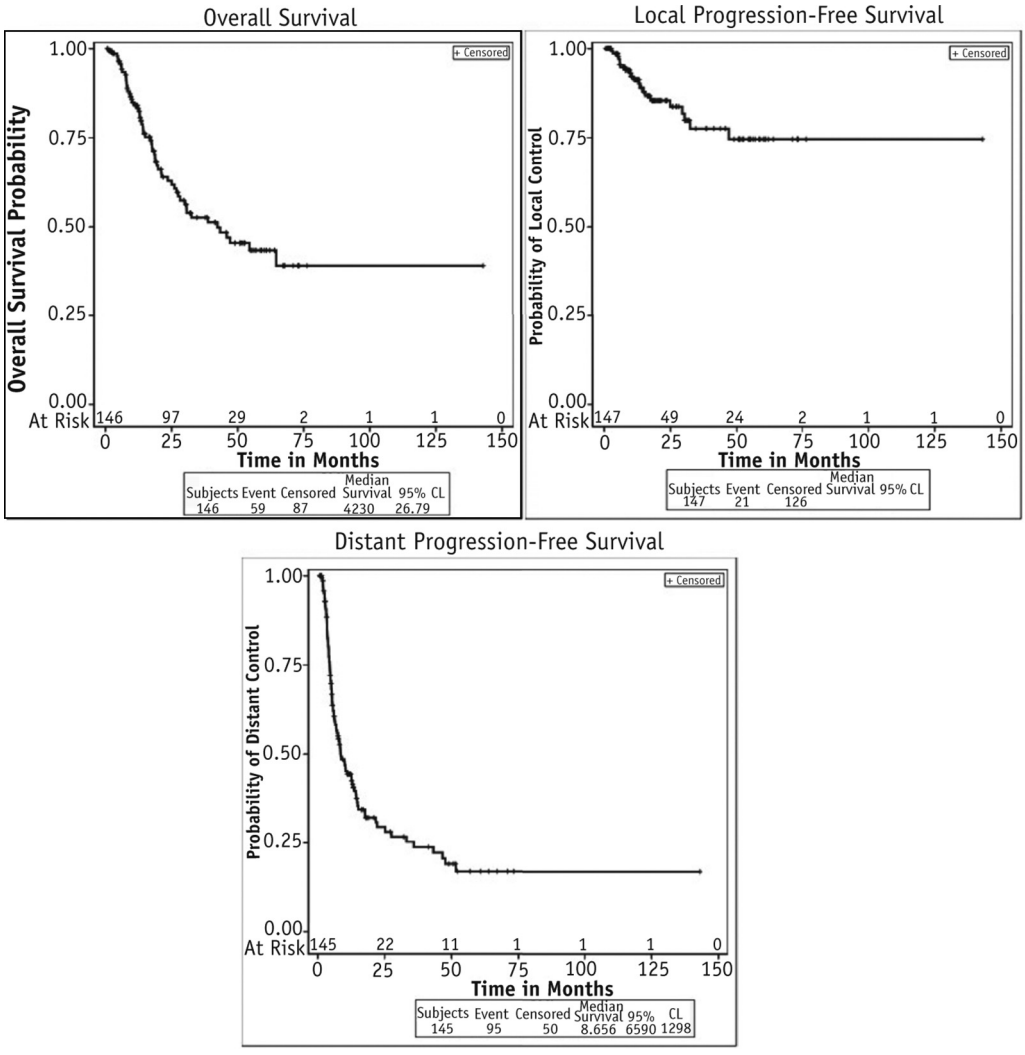

Fig. 1. Kaplan-Meier curves of OS, LPFS, and DPFS. *Abbreviations:* DPFS = distant-progression-free survival; LPFS = local-progression-free survival; OS = overall survival.

demonstrated (Fig. 1). Response to treatment included 25.9% (n = 38) complete response, 25.9% (n = 38) partial response, 32% (n = 32) stable disease, and 14.3% (n = 21) progressive disease; response could not be determined in 12.2% of patients (Table E2; available online at https://dx.doi.org/10.1016/j.ijrobp.2018.08.027). A detailed list of variables analyzed with univariate analysis can be found in Table E4 (available online at https://dx.doi.

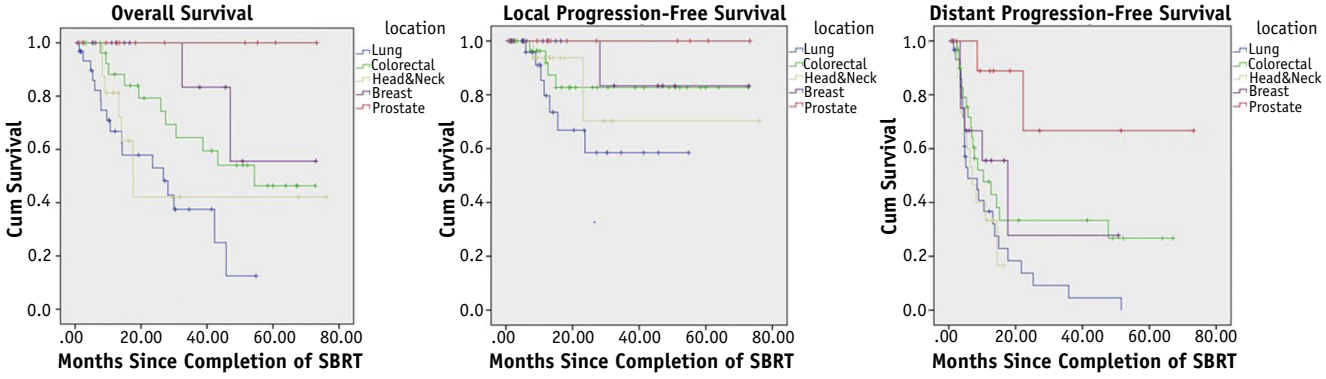

Fig. 2. Kaplan-Meier curves of OS, LPFS, and DPFS based on primary tumor location. *Abbreviations:* DPFS = distant-progression-free survival; LPFS = local-progression-free survival; OS = overall survival.

Table 3 Multivariate analysis of OS, LPFS, DPFS

Factor	Hazard ratio (95% confidence interval)	*P* value
OS		
KPS ≤80	3.53 (1.95-6.41)	<.001
Surgery for DM before SABR	0.44 (0.21-0.95)	.037
LPFS		
≥3 vs <3 metastases	6.66 (2.52-17.56)	.0001
Surgery for primary	0.39 (0.16-0.96)	.040
DPFS*		

Abbreviations: DM = distant metastasis; DPFS = distant-metastasis-free survival; KPS = Karnofsky Performance Status; LPFS = local-progression-free survival; OS = overall survival; SABR = stereotactic ablative radiation therapy.
* No multivariable model was found.

org/10.1016/j.ijrobp.2018.08.027). Multivariate analysis identified ≥3 metastases ($P < .001$; HR, 6.66; 95% CI, 2.52-17.56) as associated with inferior LPFS, and surgery for the primary tumor ($P = .040$; HR. 0.39; 95% CI, 0.16-0.96) as associated with improved LPFS (Table 3, Fig. 3). LPFS was not found to be significantly among the 5 most common primary malignancies ($P = .167$) (Fig. 2). The median DPFS was 8.7 months (95% CI, 6.6-13.1) with a 1- and 5-year DPFS rate of 44% and 17%, respectively (Fig. 1). DPFS was significantly associated with the primary malignancy ($P = .008$). Median DPFS was 5.7 months (95% CI, 0.0-11.4) for lung, 7.0 months (95% CI, 3.5-10.5) for head and neck, 10.4 months (95% CI, 3.2-17.6) for colorectal, 17.7 months (95% CI, 6.3-29.1) for breast, and not reached for prostate (Fig. 2).

Quality of life and toxicity

For the entire cohort, acute grade 2+ and grade 3+ toxicity rates were 7.5% and 2.0%, respectively, and the late grade 2+ and grade 3+ toxicity rates were both 1.4%. Acute grade 3 toxicity included dyspnea (n = 1), dermatitis (n = 1), and anemia (n = 1). Late toxicity included grade 3 ureter obstruction (n = 1) and grade 4 small bowel obstruction (n = 1). There was no significant change in quality of life at completion or 6 weeks, 3 months, and 9 months after treatment. At 6 ($Z = -2.42$, $P = .02$) and 12 months ($Z = -2.14$, $P = .03$) patients were found to have statistically significant improvement in quality of life.

Discussion

This prospective phase 2 trial investigated the safety and efficacy of SABR for oligometastatic cancer. The oligometastatic state is hypothesized as an interim stage of systemic disease, with a higher potential for durable disease control after aggressive local treatments.[2,4] SABR has generated significant interest in providing localized treatment of oligometastatic lesions. Herein we show SABR to be a safe treatment modality with excellent local control and OS for patients with oligometastatic disease.

Milano et al previously reported a prospective study of 121 patients with 5 or fewer oligometastases from any primary site. For the entire cohort, 2-year OS and freedom from distant metastases was 50% and 35%, respectively. After SABR 0.8% of patients experienced grade 3+ toxicity.[15] This trial found the GTV sum to be significantly associated with both OS and local control on univariate analysis for non-breast cancer, which was not identified in the present study. Wong et al also evaluated long-term survival after SABR for 61 patients with 5 or fewer oligometastases. This prospective study treated 113 metastases and reported 2- and 5- year OS and treated metastases control of 57%, 32%, 51% and 44%, respectively. After SABR, 3.3% of patients experienced acute grade 3+ toxicity.[16] Our results compare favorably with 5-year OS, LPFS, and distant-progression-free survival of 43%, 75%, and 17%. Additionally, we report similarly low rates of grade 3+ toxicity. It is, however, difficult to fully appreciate any differences among these 3 prospective studies because the cohorts contained different ratios of primary tumor sites and number of oligometastases. These

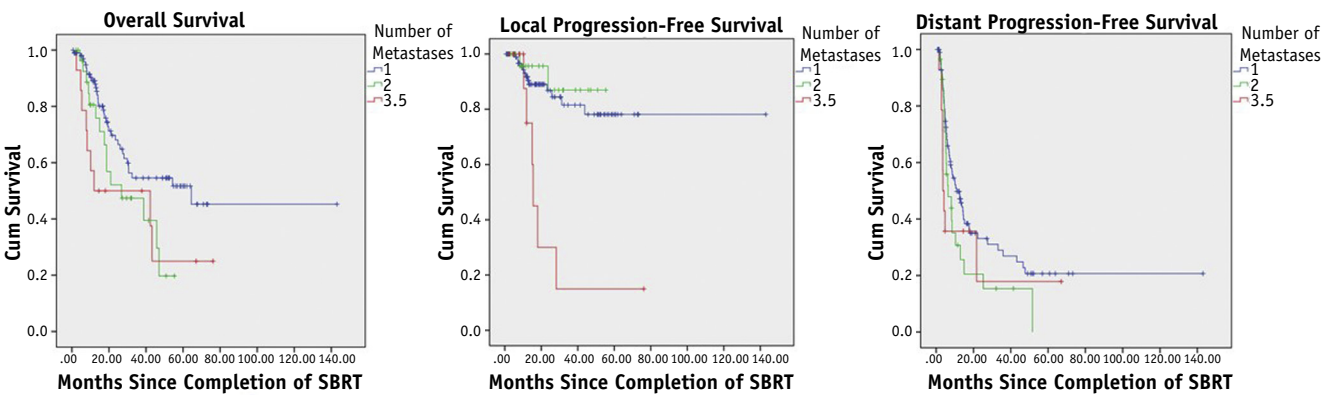

Fig. 3. Kaplan-Meier curves of OS, LPFS, and DPFS based on number of metastases. *Abbreviations:* DPFS = distant-progression-free survival; LPFS = local-progression-free survival; OS = overall survival.

factors could both have a significant effect on primary outcomes.

We identified the primary tumor site as significantly associated with both OS and distant-progression-free survival for the 5 most common malignancies within our cohort. Prior reports assessing aggressive local therapy have identified prostate and breast cancer as experiencing the best outcomes, with 5-year OS of 88% and 49%, respectively.[17,18] This is followed by colorectal and lung cancer, with median survival ranging from 32 to 43 months and 13 to 24 months, respectively.[19-24] Our results demonstrate similar outcomes, with 5-year OS of 100% and 56% for prostate and breast cancer and median OS of 54.4 months and 26.8 months for colorectal and lung, respectively. Our median OS for head and neck cancer exhibited the worst median survival of 17.6 months, likely because of early deaths. The 5-year OS for head and neck cancer was 42%. Previous reports have demonstrated that 5-year OS exceeds 20% with pulmonary/liver metastasectomy; however, no studies have reported on outcomes of SABR for oligometastatic head and neck cancer.[25]

Although our study demonstrates SABR is a feasible and effective treatment strategy for oligometastatic disease, it has numerous limitations. Our patient population was extremely heterogenous, including a variety of primary tumors, primary treatments, treatments for metastases before SABR, and number and location of metastases. Additionally, some patients were enrolled and treated upon initial diagnosis of oligometastatic disease, and others had extensive treatment for oligometastatic disease before enrollment. Finally, our study was nonrandomized. Because of these shortcomings, future randomized phase 3 trials should be developed to support our results.

Conclusions

This multicenter prospective phase 2 study demonstrates the feasibility and safety of SABR for oligometastatic cancer. This treatment regimen was well tolerated with limited grade 3+ acute and late toxicity and no significant adverse effect on quality of life. Our results demonstrate excellent long-term survival and local control of metastatic sites. Future randomized controlled trials will be needed to definitively determine the role of aggressive local therapy for oligometastatic disease.

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