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Clinical Investigation

Stereotactic Ablative Radiation Therapy to All Lesions in Patients With Oligometastatic Cancers: A Phase 1 Dose-Escalation Trial

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Purpose: Increasing evidence suggests that patients with a limited number of metastases benefit from SABR to all lesions. However, the optimal dose and fractionation remain unknown. This is particularly true for bone and lymph node metastases. Therefore, a prospective, single-center, dose-escalation trial was initiated.

Methods: Dose-Escalation trial of STereotactic ablative body RadiOtherapY for non-spine bone and lymph node metastases (DESTROY) was an open-label phase 1 trial evaluating SABR to nonspine bone and lymph node lesions in patients with up to 3 metastases. Patients with European Cooperative Oncology Group performance status $\leq$1, an estimated life expectancy of at least 6 months, and histologically confirmed nonhematological malignancy were eligible. Three SABR fractionation regimens, ie, 5 fractions of 7.0 Gy versus 3 fractions of 10.0 Gy versus a single fraction of 20.0 Gy, were applied in 3 consecutive patient cohorts. The rate of $\geq$grade 3 toxicity, scored according to the Common Toxicity Criteria for Adverse Events v. 4.03, up to 6 months after SABR, was the primary endpoint. The trial was registered on clinicaltrials.gov (NCT03486431).

Results: Between July 2017 and December 2018, 90 patients were enrolled. In total 101 metastases were treated. No $\geq$grade 3 toxicity was observed in any of the enrolled patients (95% CI 0.0%-12.3% for the first cohort with 28 analyzable patients; 95% CI 0.0%-11.6% for the second and third cohort with 30 analyzable patients each). Treatment-related grade 2 toxicities occurred in 4 out of 30 versus 2 out of 30 versus 2 out of 30 patients for the 5, 3 and 1 fraction schedule, respectively. Actuarial local control rate at 12 months was 94.5%.

Conclusion: All 3 treatment schedules were feasible and effective with remarkably low toxicity rates and high local control rates. From a patient and resource point of view, the single-fraction schedule is undoubtedly most convenient. © 2020 The

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The trial protocol did not include a data sharing plan, and therefore data from the trial will not be shared publicly as sharing was not included in the ethical approvals.

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Introduction

The oligometastatic paradigm, introduced in 1995, proposed that some patients with a limited number of metastases are in an intermediate state between localized disease and extensive systemic spread.[1] It was consequently suggested that through ablation of these oligometastases, further disease progression could be delayed or perhaps even avoided. Recently, a consistent nomenclature for oligometastatic disease (OMD) states was defined.[2] Surgery and SABR are the most commonly used metastasis-directed therapies (MDTs). SABR is defined as highly conformal radiation therapy (RT) with extremely narrow safety margins and steep dose fall-off around the target volume in a limited number of fractions (typically 5 or less) and with high doses per fraction. Although no universally accepted SABR definition and procedure exists, the American Association of Physicists in Medicine (AAPM) Task Group 101 report is the most frequently referenced, providing methodology and constraints for 5, 3, or 1 fraction(s).[3]

Recently, randomized evidence from the tumor-agnostic phase 2 Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastases (SABR-COMET) trial in patients with metachronous oligorecurrent (1-5 metastases and a controlled primary) OMD suggested that combining SABR with the systemic standard of care (SOC) treatment improves progression-free as well as overall survival.[4] This hypothesis is being further investigated in several prospective trials. However, the optimal dose and fractionation of SABR remain unknown. For instance, in the SABR-COMET trial, a wide variety of schedules, ranging from 1 to 8 fractions, was allowed.[4] This uncertainty is especially evident for bone and lymph node metastases, which account for a large proportion of all oligometastatic lesions. Also, toxicity in the SABR-COMET trial was somewhat higher than expected, with 3 (4.5%) toxic deaths in the investigational arm.[4] Therefore, research should continue to focus on finding optimal SABR fractionation schedules and on minimizing toxicity.[4]

A prospective dose-escalation trial of SABR for bone and lymph node metastases was initiated in our center. As compatible with a phase 1 design in RT, we consecutively reduced the number of fractions and increased the dose per fraction. Although this might not result in biological dose escalation for all tumor types, it probably does for breast and prostate cancers, which have a similar sensitivity to fractionation compared with most healthy tissues.[5] In any case, hypofractionation theoretically exposes organs at risk (OARs) to increased toxicity. Consequently, toxicity (grade 3 or higher) was considered the most relevant primary endpoint. This trial constitutes the first prospective evaluation of the 3 most commonly used stereotactic regimens for bone and lymph node metastases.

Patients and Methods

Study design and participants

The Dose-Escalation trial of STereotactic ablative body RadiOtherapY for non-spine bone and lymph node metastases (DESTROY) was an investigator-initiated, single-center, open-label phase 1 trial evaluating SABR for bone and lymph node lesions in patients with OMD. All patients with OMD (defined as 3 metastases or fewer) referred to our center for ablative treatment were screened for eligibility. Patients were required to be aged 18 years or older, with Eastern Cooperative Oncology Group performance status $\leq$1, an estimated life expectancy of at least 6 months, and a histologically confirmed nonhematological malignancy. Importantly, patients should have at least 1 metastasis in nonspinal bone and/or lymph node. All "target" bone and lymph node lesions had to be identifiable on computed tomography (CT) scan and measure less than 5 cm in largest diameter. Patients with previous RT to the targeted area were excluded unless reirradiation to the required dose level could be delivered while respecting the cumulative dose constraints for the relevant OARs, taking into account the previous dose distribution. SABR could be combined with SOC systemic treatment as decided by the treating physician. Simultaneous presence of brain, liver, vertebral, and/or lung lesions was allowed, provided they could be treated radically according to institutional protocol. For those patients whose primary tumor was not controlled, radical treatment of either the primary tumor or the local recurrence was mandatory.

Regulatory approval, including ethical approval, was obtained. The trial was registered on clinicaltrials.gov (NCT03486431). All patients provided written informed consent. The clinical protocol has been previously published.[6] This report follows the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Interventions

Three SABR fractionation regimens, that is, 5 fractions of 7.0 Gy versus 3 fractions of 10.0 Gy versus a single fraction of 20.0 Gy, were applied to treat the target lesions in 3 consecutive cohorts. Equivalent doses in 2 Gy fractions, calculated using the linear quadratic model with $\alpha/\beta = 3$ Gy to account for late effects, were 70 Gy versus 78 Gy versus 92 Gy for the 5 fractions, 3 fractions, and single fraction schedule, respectively.[7] OAR constraints from the AAPM Task Group 101 were respected.[3] Details of the SABR treatments are provided in detail in the study protocol.[6] Briefly, gross tumor volume (GTV) consisted of all visible tumor on planning CT. All available diagnostic imaging (including magnetic resonance imaging [MRI] or positron

emission tomography [PET]) was used to delineate the GTV. No additional margin was added for microscopic disease spread. Planning target volume (PTV) was created by expanding the GTV by 3 mm (in case of bony lesions) or 5 mm (in case of nodal lesions) to account for organ motion and setup errors. Dose was prescribed to the periphery of the PTV, ie, 80% of the dose needed to cover ≥90% of the PTV. As per usual in SABR, dose constraints for OARs were consistently prioritized over PTV coverage. Treatments were planned using RayStation (RaySearch, Stockholm, Sweden) and delivered on a TrueBeam STX (Varian, Palo Alto, CA).

Follow-up was every 3 months for 1 year with registration of toxicity and quality of life. Patient follow-up was performed according to SOC. At 6 months, mandatory imaging was performed to assess local control (LC). As a minimum, imaging included a CT of the irradiated lesions, but MRI or PET/CT imaging was recommended, especially if available at baseline. Afterward, imaging was only performed on biochemical or clinical suspicion of progression.

Outcomes

Toxicity was graded using Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v.4.03). Dose-limiting toxicity (DLT), defined as any ≥grade 3 within 6 months after SABR, was scored as the primary endpoint. Secondary endpoints were all acute (up to 3 months after treatment) and late (from 3 months after treatment on) toxicities, quality of life, LC at 6 months after SABR, local failure (LF) during subsequent follow-up, and progression-free survival (PFS) defined as the time from inclusion to disease progression at any site or death. LC of lymph nodes was evaluated by the Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v.1.1).[8] For bony lesions, the MD Anderson Cancer Center criteria were used.[9] If PET imaging was available, lesions were also evaluated by the Positron Emission tomography Response Criteria In Solid Tumors (PERCIST 1.0).[10] LF was scored as an event if an irradiated lesion showed an increase in size of ≥20% according to RECIST v.1.1 or 30% uptake in tracer according to PERCIST. For quality of life, the European Organization for Research and Treatment of Cancer core questionnaire QLQ-C30 was used.[11,12]

Statistical methods

The primary endpoint was the rate of DLT. The 3 fractionation regimens were consecutively tested. A regimen was considered acceptable if the rate of treatment-related grade 3 toxicity did not exceed 5%, and a regimen with a grade 3 toxicity rate of >15% was deemed unsafe. In the design of the trial, early stopping rules for terminating the study in case of excessive treatment-related toxicity were incorporated. Among the first 25 analyzable patients, if ≥4 treatment-related adverse events grade ≥3 were reported, that arm would be terminated and deemed unsafe. If ≤1 event was reported, that arm would also be terminated and deemed safe. If 1 to 3 events were reported, 35 additional patients would be included at the same dose level. A regimen would be considered unsafe if a total of ≥7 events of 60 analyzable patients was observed. This design yields a 1-sided type I error of 0.05 and an actual power of 80%. Fisher exact test was used to compare differences in categorical data between treatment groups. For continuous data, Kruskal-Wallis and 1-way ANOVA tests were used. Time-to-event outcomes (PFS) were estimated using the Kaplan-Meier method with differences compared with the stratified log-rank test. The association of PFS with risk factors was studied with univariate Cox proportional hazards models. To build a multivariable Cox model for PFS, stepwise variable selection was performed. All variables from univariate models that had a P value of $< .05$ were included as potential predictors. No imputation for missing values was needed. The Clopper-Pearson method was used to calculate the 95% confidence interval (CI) of binomial rates. All statistical analyses were performed in R (version 3.5.3; R Development Core Team 2009, Vienna, Austria). RayAnalytics (RaySearch, Stockholm, Sweden) was used to evaluate target coverage and median target dose as plan quality parameters.

Results

Patient population

Between July 2017 and December 2018, 94 OMD patients were referred to our center and assessed for eligibility (Fig. 1). Three patients were excluded in the screening period: 1 lesion exceeded 5 cm in largest diameter, 1 patient had more than 3 metastases, and 1 patient had a metastatic lymph node in a previously irradiated region where SABR was not feasible. One patient with mediastinal node involvement could not be treated according to protocol as the relevant OAR dose constraints could not be met. In total, 90 patients received the trial intervention to a total of 101 lymph node and nonspine bone metastases. For 8 patients, radical treatment of the primary tumor or local relapse was implemented simultaneously. Twelve patients received concurrent SABR for metastases other than nonspine bone or lymph nodes, which were treated according to our institutional protocol.

Median follow-up was 17.2 months (interquartile range [IQR] 15.0-20.0). Baseline characteristics for all treated patients are presented in Table 1. Although nonrandomized, treatment groups were well-balanced for patient and tumor characteristics. Using the recent consensus recommendation for characterization and classification of OMD, 49% (44 of 90) of the patients met the definition of metachronous OMD.[2] Synchronous OMD (19% of patients; 17 of 90) and repeat oligorecurrence (11% of patients; 10 of 90) were the second and third most frequent scenarios, respectively.

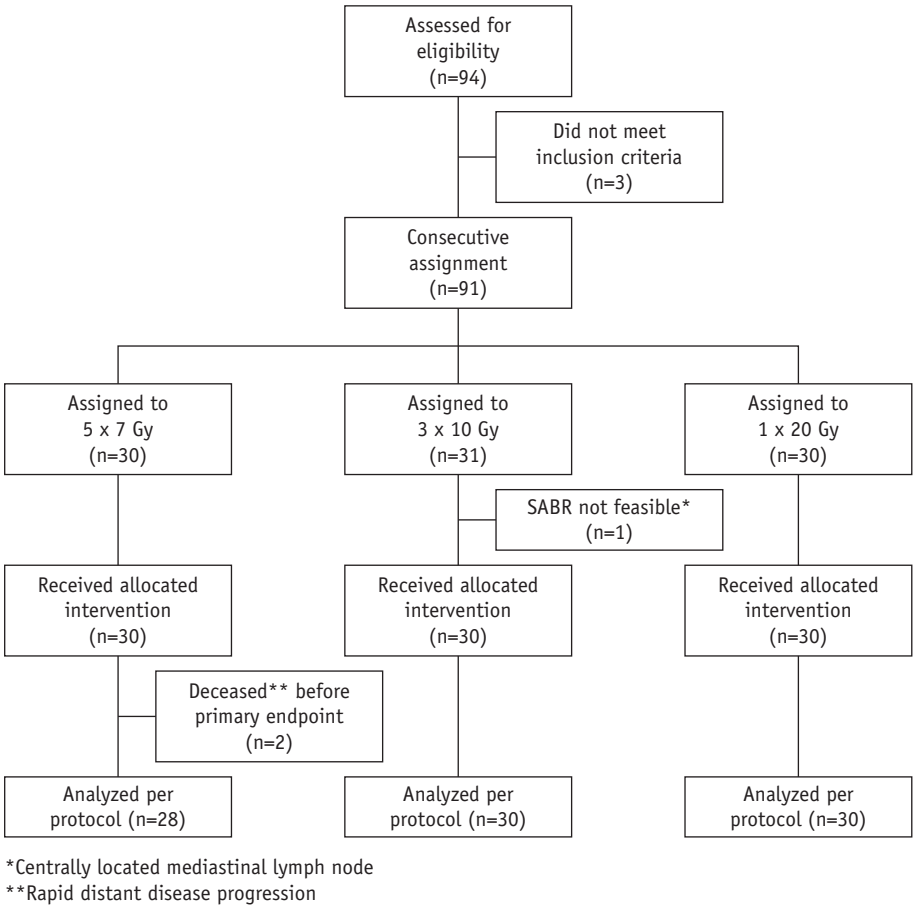

Fig. 1. Consolidated Standards of Reporting Trials diagram.

Primary endpoint: toxicity

No dose-limiting toxicity (ie, ≥grade 3 within 6 months after treatment) was observed in any of the treatment arms (95% CI 0.0%-12.3% for the first cohort with 28 analyzable patients; 95% CI 0.0%-11.6% for both the second and third cohorts, with 30 analyzable patients each). Two patients died before 6 months' follow-up due to distant disease progression; none of them had ≥grade 2 treatment-related toxicity. Also, no ≥grade 3 toxicity was observed during the entire follow-up period.

Reported grade 2 toxicity rates were not different between the 3 treatment schedules (4 of 30 vs 2 of 30 vs 2 of 30 for the 5, 3 and 1 fraction schedule, respectively, $P = .49$; Table 2). Acute SABR-related grade 2 toxicity consisted of 3% (3/90) gastrointestinal toxicity (loose stools) and 3% (3/90) pain flare. Acute toxicity resolved in all patients within 3 months. Late grade 2 toxicity was seen in 2 patients. One rib fracture was seen 12 months after administration of 1 × 20.0 Gy in a patient presenting with mild chest discomfort localized to the treated area and not requiring narcotic pain medication. One patient presented with loose stools (increase of 6 stools per day over baseline) 6 months after receiving 3 × 10.0 Gy to a pelvic lymph node recurrence in a region where previous chemoradiotherapy was administered for a colorectal carcinoma. Deterioration of this patient's condition, with increasing diarrhea and loss of weight, led to the diagnosis of thyrotoxicosis caused by Graves disease. Because her complaints resolved with adequate treatment of the Graves disease, this toxicity was considered unrelated.

Secondary endpoints

Local control at 6 months

Eighty-three patients with 94 target lesions were assessable for LC at 6 months after SABR. Among the 7 patients who were not assessable for LC, 2 died before 6 months' follow-up without evidence of local progression at follow-up imaging obtained at 3 months. Five patients refused to undergo imaging to assess local response of the target lesion(s) for various reasons, but none of them showed any signs or symptoms indicative of local progression.

At evaluation 6 months after treatment, in the 5, 3, and single fraction group, 66% (19 of 29), 63% (20 of 32), and 52% (17 of 33) of the target lesions showed a complete response; 14% (4 of 29), 22% (7 of 32), and 30% (10 of 33)

Table 1 Baseline patient-, tumor-, and treatment-related characteristics

Characteristic	5 × 7.0 Gy (n = 30)		3 × 10.0 Gy (n = 30)		1 × 20.0 Gy (n = 30)		*P* value
Age (y)							.5
Median (IQR)	69	(62-77)	70	(62-73)	70	(65-77)	
Sex							.5
Men	24	80%	23	77%	20	67%	
Women	6	20%	7	23%	10	33%	
Site of original primary tumor							.6
Prostate	18	60%	18	60%	16	53%	
Breast	2	7%	5	17%	6	20%	
Other*	10	33%	7	23%	8	27%	
Time from diagnosis of primary tumor to inclusion (y)							.4
Median (IQR)	5.4	(1.6-11.1)	2.8	(0.4-4.5)	3.5	(0.0-4.3)	
OMD classification							.1
Synchronous OMD	3	10%	6	20%	8	27%	
Metachronous oligorecurrence	13	43%	19	63%	12	40%	
Metachronous oligoprogression	6	20%	0	0%	2	7%	
Repeat oligorecurrence	4	13%	4	13%	2	7%	
Repeat oligopersistence	0	0%	0	0%	1	3%	
Repeat oligoprogression	1	3%	1	3%	1	3%	
Induced oligopersistance	1	3%	0	0%	1	3%	
Induced oligoprogression	2	7%	0	0%	3	10%	
No. of prior lines of systemic therapy							.2
None	12	40%	20	67%	12	40%	
1	8	27%	6	20%	10	33%	
2 or more	10	33%	4	13%	8	27%	
No. of nonspine bone and lymph node metastases per patient							.4
1	28	93%	27	90%	24	80%	
2	2	7%	3	10%	6	20%	
Peri-SABR systemic treatment†							.3
None	16	53%	17	57%	12	40%	
Hormonal therapy	12	40%	12	40%	15	50%	
Chemotherapy	0	0%	0	0%	1	3%	
Immune therapy	2	7%	0	0%	0	0%	
Targeted therapy	0	0%	1	3%	2	7%	
Type and location of metastasis (n = 101 lesions)							.2
Bone	14/32	44%	19/34	56%	23/35	66%	
Femur/hip	2/32	6%	3/34	9%	4/35	11%	
Humerus/shoulder	0/32	0%	3/34	9%	2/35	6%	
Pelvis	5/32	16%	6/34	18%	10/35	29%	
Rib/sternum	7/32	22%	7/34	21%	7/35	20%	
Lymph node	18/32	56%	15/34	44%	12/35	34%	
Abdomen	5/32	16%	6/34	18%	6/35	17%	
Axilla	1/32	3%	0/34	0%	1/35	3%	
Pelvis	10/32	31%	9/34	26%	4/35	11%	
Thorax‡	2/32	6%	0/34	0%	1/35	3%	

(*continued on next page*)

Table 1 (*continued*)

Characteristic	5 × 7.0 Gy (n = 30)		3 × 10.0 Gy (n = 30)		1 × 20.0 Gy (n = 30)		*P* value
Response assessment							.4
CT	4/32	13%	1/34	3%	6/35	17%	
PET-CT	24/32	75%	30/34	88%	23/35	66%	
CT + bone scintigraphy	3/32	9%	2/34	6%	4/35	11%	
Refused by patient	1/32	3%	1/34	3%	2/35	6%	
GTV volume (cm^3)							
Median (IQR)	5.90	(1.71-22.9)	4.54	(1.76-6.48)	8.27	(4.16-11.50)	.5

Abbreviations: CT = computed tomography; GTV = gross tumor volume; IQR = interquartile range; OMD = oligometastatic disease; PET-CT = positron-emission tomography-CT.

* Other comprises bladder (n = 1), colorectum (n = 3), endometrium (n = 1), gallbladder (n = 1), kidney (n = 4), lung (n = 8), ovarium (n = 2), skin (n = 1), stomach (n = 1), and ureter (n = 3).

† Peri-SABR systemic treatment was defined as treatment administered in the timeframe of 4 weeks before and after SABR. Hormonal therapy: androgen deprivation therapy, androgen receptor signaling inhibitor, selective estrogen receptor modulator. Chemotherapy: paclitaxel. Immune therapy: anti-PD1 inhibitors. Targeted therapy: HER2-targeted therapies, CDK4/6 inhibitor.

‡ Included thoracic lymph nodes could be located in the thoracic wall as well as in the mediastinum.

showed partial response; and 21% (6 of 29), 16% (5 of 32), and 15% (5 of 33) showed stable disease, respectively. One rib metastasis from a non-small cell lung cancer, treated with 1 × 20.0 Gy, was progressive 6 months after treatment. There was no significant difference in LC at 6 months between the treatment schedules (Fig. 2, $P = .63$).

Local failure

Actuarial LC rate at 12 months was 94.5%. At last follow-up, LF was observed in 4 of 101 (4%) of target lesions, 2 from non-small cell lung cancer, 1 from transitional cell cancer of the ureter, and 1 from colorectal cancer. The median time to LF was 8.5 months (range, 6.0-12.3). Of the 4 patients with local disease progression, 2 had a nodal lesion located in the pelvis. The other LFs occurred in rib metastases (n = 2). One pelvic node was treated with 3 fractions, 1 rib metastasis received a single fraction, and the remaining 2 lesions received 5 fractions. Planning parameters are presented in Supplementary Table E1. In 2 of the aforementioned cases, partial underdosage of the target was accepted owing to OAR dose constraints: for a large presacral pelvic lymph node treated in 3 fractions, the dose-restricting OAR was the sacral plexus (even necessitating partial underdosage of the lymph node itself); in the second case, concerning a single fraction treatment for a rib metastasis, the proximity of the spinal cord prevented full PTV coverage, although the GTV appeared well covered in this instance. In the 2 other cases, the target volumes were apparently well covered. All 4 LF could be safely reirradiated for symptom control.

Progression-free survival

Median PFS for all patients was 15.4 months (95% CI 9.8-17.8) (see Fig. 3). Primary tumor, OMD classification, addition or continuation of SOC systemic therapy, site of metastasis, and fractionation schedule were evaluated. On univariate analysis, breast cancer histology (hazard ratio [HR], 0.3, 95% CI 0.1-0.8, $P = .005$) and systemic therapy (HR, 0.5, 95% CI 0.3-0.9, $P = .03$) were significant favorable predictors for PFS (Table 3). However, none of these predictors remained statistically significant on multivariable analysis.

Quality of life

All patients completed the baseline questionnaires. Thereafter, 87 (97%), 79 (88%), and 76 (84%) patients completed the questionnaires at the end of the treatment, and at 3 and

Table 2 Treatment-related grade 2 adverse events

	Grade 2 adverse event	5 × 7.0 Gy	3 × 10.0 Gy	1 × 20.0 Gy	*P* value
Acute	Pain flare	2/30 (7%)	1/30 (3%)	0/30 (0%)	
	Gastrointestinal	2/30 (7%)	0/30 (0%)	1/30 (3%)	
	ALL	4/30 (13%)	1/30 (3%)	1/30 (3%)	.36
Late	Gastrointestinal	0/30 (0%)	1/30 (3%)	0/30 (0%)	
	Fracture	0/30 (0%)	0/30 (0%)	1/30 (3%)	
	ALL	0/30 (0%)	1/30 (3%)	1/30 (3%)	1.00
Acute + late	ALL	4/30 (13%)	2/30 (7%)	2/30 (7%)	.49

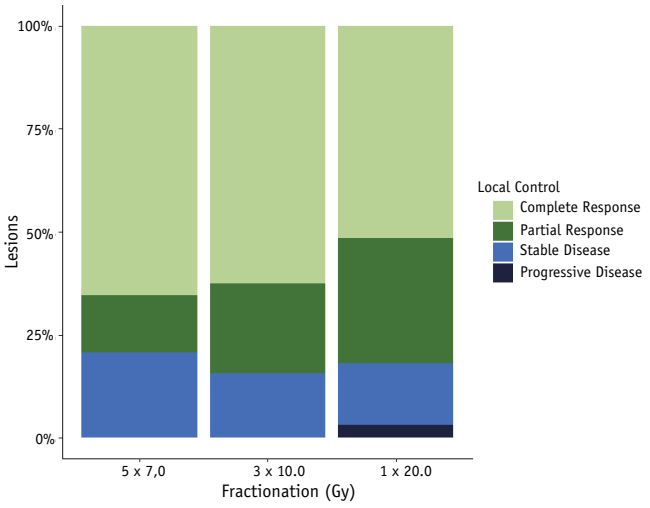

Fig. 2. Local control at 6 months after SABR.

6 months after treatment, respectively. Figure 4 depicts the global health score and the summary score for all schedules at the 4 time points. No clinically relevant or statistically significant differences among the 3 treatment schedules were observed, nor was there any clinically relevant deterioration compared with baseline.

Dosimetry

To evaluate the feasibility of delivering the prescribed dose schedule, dosimetric analysis was performed. It is important to emphasize that the prescribed doses were not minimum PTV doses. Indeed, a dose inhomogeneity in the PTV overlapping with a PRV was allowed, to comply with the dose constraints for OARs. Actually delivered doses are presented in Supplementary Table E2 according to the International Commission of Radiation Units 91 guidelines.[13] For the first, second, and third dose prescription, partial underdosage of the PTV caused by OAR dose constraints was accepted in 9 of 32 (28%), 5 of 34 (15%), and 10 of 35 (29%) cases, respectively (Supplementary Table E3). Comparison of PTV coverage (PTV R100%) and median PTV dose (PTV D50%) among the 3 schedules showed that PTV coverage and PTV D50% were lower for the 5 fraction schedule (median PTV coverage of 0.90, 0.94, and 0.95 for the 5 fractions, 3 fractions, and single fraction schedule, respectively; $P = .03$; median PTV D50% of 1.08, 1.16, and 1.13 for the 5, 3, and 1 fraction schedule, respectively; $P < .001$; Supplementary Fig. E1).

Discussion

In this phase 1 trial, the 3 most common SABR fractionation schedules, that is, 5, 3, and single fraction(s), were for the first time prospectively evaluated. Given the increasing use but still limited evidence of SABR in OMD and the possible frailty in this sometimes heavily pretreated population, the incidence of ≥grade 3 treatment-related toxicity was chosen as the primary endpoint. Furthermore, LC is typically excellent with SABR, independent of the schedule. For several metastatic sites, such as brain, lung, and spine, a preferred SABR schedule has been defined.[14-16] Because no optimal schedule exists for nonspine bone and lymph node metastases, although these are frequent sites of oligometastatic spread and are especially prevalent in breast and prostate cancer, these types of lesions formed the primary focus of our study.

Regarding the primary endpoint, no grade 3 or higher toxicity was reported in any of the 3 fractionation schedules during follow-up of nearly 1.5 years. Even grade 2 toxicities were rare, with only 6.7 % of all patients reporting any grade 2 side effects, and, if present, these were typically mild and temporary. Only 1 patient experienced late grade 2 toxicity attributable to SABR, which was also mild and controllable with minor intervention. Although the focus of this trial was grade ≥3 toxicity, there was no significant difference between the 3 fractionation schedules regarding grade 2. Moreover, the quality of life data confirm that all 3 SABR regimens were very well tolerated.

These results are very reassuring and suggest that even extremely hypofractionated SABR can be safely administered. In this regard, it is important to emphasize that our trial cohort was virtually unselected as it consisted of an almost "real-life" population of OMD patients referred to our center from several community-based hospitals. All but 3 of these patients could be included in the trial, and only 1 patient did not receive the intended treatment due to technical constraints resulting from the mediastinal location of the metastasis. Of the 94 screened patients, 2 patients had an (ultra-)central thoracic lesion (so-called "no-fly zone" for SABR).[17] One patient had an infracarinal node (maximal diameter of 4.1 cm, directly adjacent to the esophagus) and was assigned to the 5 fraction cohort. This treatment could be safely delivered while respecting the 5 fraction dose constraints for mediastinal organs. The second patient presenting with an infracarinal node (maximal diameter of 2.2 cm, directly adjacent to the esophagus) was included in the 3-fraction arm. Ultimately, the AAPM dose constraints could not be attained in this patient, even with significant underdosage of the target. Therefore, this patient was excluded from the trial (see Fig. 1). These anecdotal observations appear consistent with emerging evidence, suggesting that SABR treatment is feasible in this area for most patients, maybe excluding the highest fraction size.[18] Most patients (63%) had at least received 1 line of prior systemic treatment. The broad applicability of our results is further suggested by the wide range of OMD types in our patients. In that respect, this trial is different from SABR-COMET, in which only patients with metachronous oligorecurrent OMD were included. Therefore, our population was generally more pretreated and possibly frailer. Still, we did not observe any major toxicity. This might be because

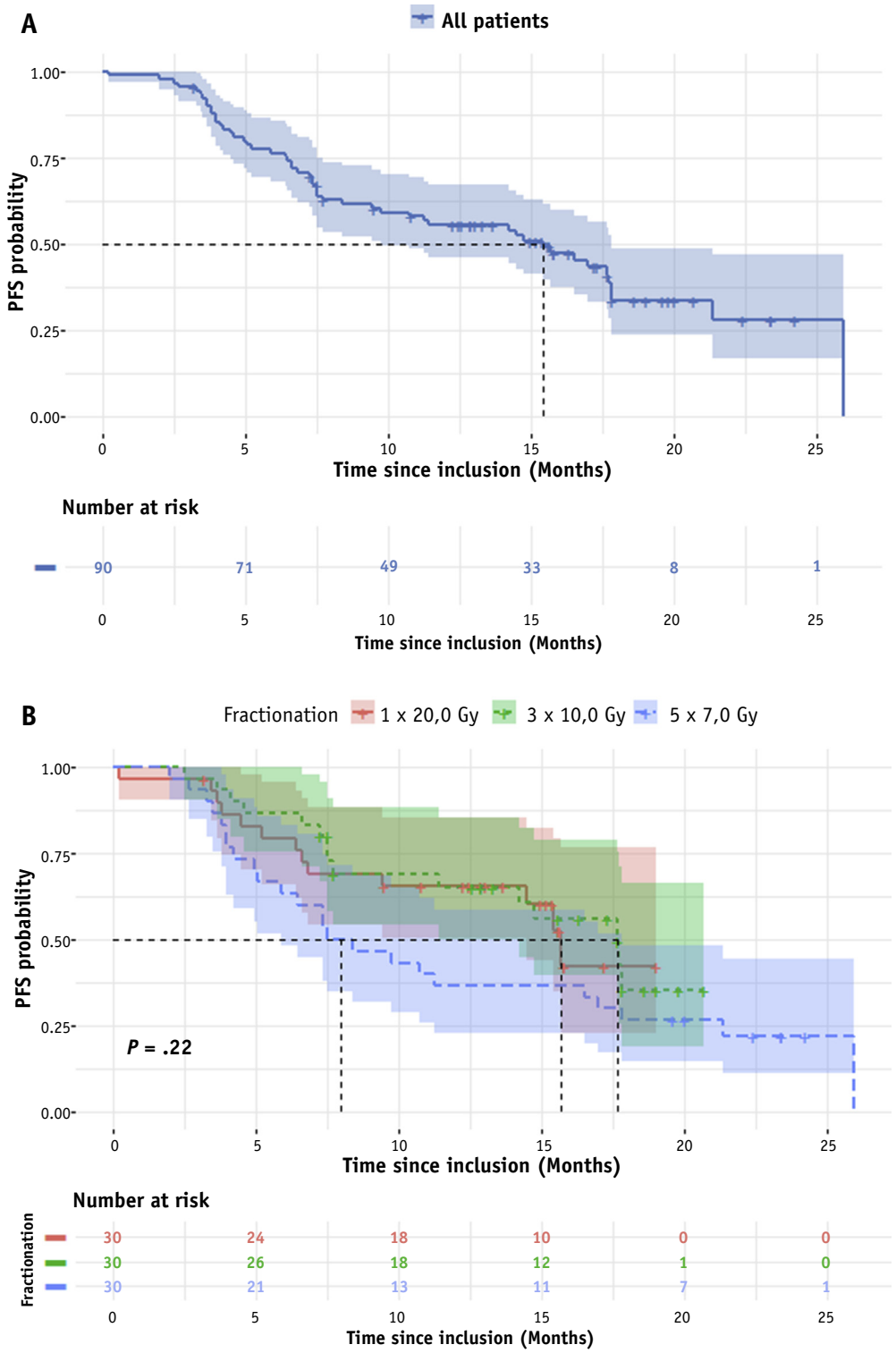

Fig. 3. Progression-free survival (defined as the time from inclusion to disease progression at any site or death).

fewer lesions located close to critical organs were irradiated. In SABR-COMET, 2 of the 3 toxic deaths were seen after SABR to lung lesions. In our trial, no clinically or radiologically relevant radiation pneumonitis was detected in the 24 patients with thoracic located targets. Also, several pelvic and abdominal lymph nodes in close vicinity to the intestines were irradiated, without any severe complication such as bleeding, ulceration, or perforation. Another point of major concern was the fracture risk after SABR to bone metastases, especially in weight-bearing

Table 3 Uni- and multivariable Cox regression results of factors affecting progression-free survival

Variable	Median PFS (mo)	Univariate		Multivariate	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value
Primary tumor					
Breast	Not reached	0.3 (0.1-0.8)	.005	0.4 (0.1-1.2)	.10
Other	14.2	Reference			
OMD classification					
Synchronous OMD	Not reached	0.6 (0.3-1.4)	NS		
Other	14.7	Reference			
SOC systemic therapy					
Yes	17.0	0.5 (0.3-0.9)	.03	0.7 (0.4-1.1)	.14
No	7.5	Reference			
Site of metastases					
Nodal recurrence only	14.5	1.0 (0.5-1.7)	NS		
Other recurrence	15.7	Reference			
Fractionation schedule					
5 × 7.0 Gy	8.0	Reference	NS		
3 × 10.0 Gy	17.7	0.6 (0.31-1.1)			
1 × 20.0 Gy	15.7	0.6 (0.31-1.3)			

Abbreviations: CI = confidence interval; HR = hazard ratio; NS = not specified; OMD = oligometastatic disease; PFS = progression-free survival; SOC = standard of care.

structures such as femoral heads. Erler et al reported a fracture risk of 8.5% for nonspine bone lesions treated with SABR.[19] In the current trial, no fractures were seen in 9 hip/femur metastases, and only 1 mildly symptomatic rib fracture occurred among the 22 that were treated.

In conclusion, these data support the use of a single fraction of 20.0 Gy for nonspine bone and lymph node metastases, as single fraction schedules are more resource efficient and convenient for the patient.[20] Also, as the world adjusts to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, fewer hospital visits are preferred. Currently, our center is evaluating SABR in the setting of antalgic treatment for bone metastases.[21] In that trial, patients are simulated and treated in 1 day, suggesting that it is feasible to give these high-precision treatments to all patients.

Regarding LC at 6 months and long-term LF rates, the excellent results with SABR were confirmed, irrespective

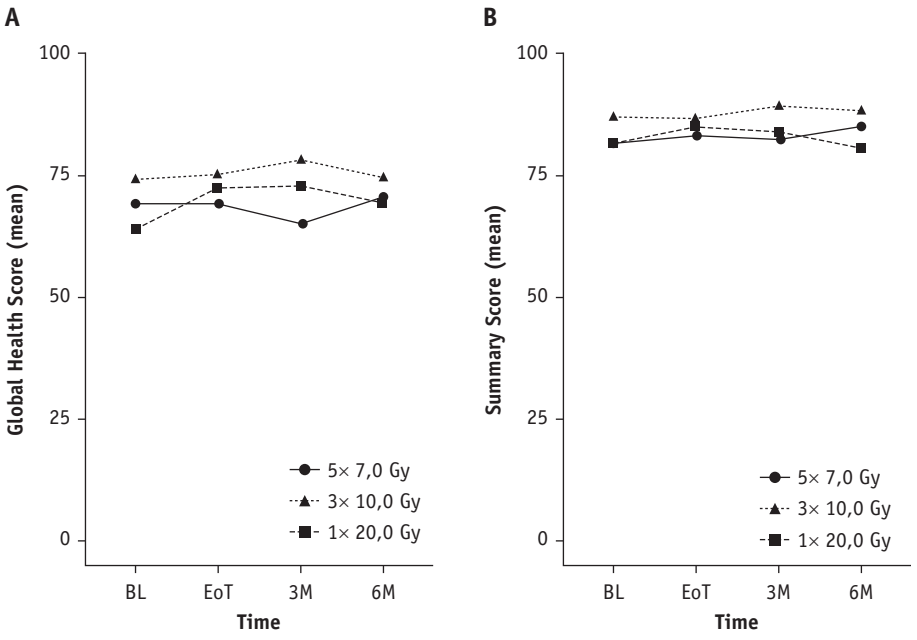

Fig. 4. Quality of life score: global health score (A) and summary score (B). BL = baseline; EoT = end of treatment; M = months; QoL = quality of life.

of the schedule used. The LC rate of almost 95% was very reassuring and in line with most other SABR data. Still, 4 LFs were observed, albeit all 4 amenable for symptomatic reirradiation. Further investigation of an optimal dose and fractionation regimen with respect to long-term LC is currently being undertaken by the Memorial Sloan Kettering Cancer Center.[22]

Progression-free survival in our trial is in line with what is recorded in most phase 2 trials for OMD including SABR-COMET, Surveillance or metastasis-directed Therapy for OligoMetastatic Prostate cancer recurrence (STOMP), and Observation versus Stereotactic Ablative Radiation for Oligometastatic Prostae Cancer (ORIOLE).[4,23,24] Obviously, the heterogenous histologies, lack of randomization or stratification, and allowing SOC systemic therapies make interpretation of this secondary endpoint difficult. Several trials are currently further exploring the role of SABR as MDT in OMD, such as SABR-COMET-3, SABR-COMET-10, and the OligoCare and OligoRare registry projects.[25-27]

This trial has several limitations. First, the design was not randomized. Still, patients were included in a very short timeframe (18 months) without changes in referral patterns and/or treatment techniques. The 3 groups were extremely well-balanced for patient-, tumor-, and treatment-related characteristics among the 3 cohorts. Second, some sort of learning curve in treatment planning and/or delivery is not impossible. Indeed, dosimetric target coverage was lowest in the patients who received 5 fractions (and were treated first). Therefore, it seems prudent to adopt a single fraction of 20.0 Gy for nonspine bone and lymph node lesions only in centers with SABR experience. Third, it was a single-center trial, possibly hampering the general applicability of these results. However, it should be noted that patients were referred from several regional hospitals, and that very common planning and dose constraints were used as well as a standard linear accelerator.

Conclusion

These data support the use of a single fraction of 20.0 Gy, as well as the other approaches in 3 or 5 fractions, for SABR to nonspine bone and lymph node metastases. Because single fraction schedules already have been shown to be more resource efficient as well as convenient for the patient, this is the first choice. Also, as the world adjusts to the SARS-CoV-2 pandemic, fewer hospital visits are preferred.

References

1. Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol* 1995;13:8-10.
2. Guckenberger M, Lievens Y, Bouma AB, et al. Characterisation and classification of oligometastatic disease: A European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. *Lancet Oncol* 2020;21:e18-e28.
3. Benedict SH, Yenice KM, Followill D, et al. Stereotactic body radiation therapy: The report of AAPM Task Group 101. *Med Phys* 2010;37:4078-4101.
4. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): A randomised, phase 2, open-label trial. *Lancet* 2019;393:2051-2058.
5. Ray KJ, Sibson NR, Kiltie AE. Treatment of breast and prostate cancer by hypofractionated radiotherapy: Potential risks and benefits. *Clin Oncol (R Coll Radiol)* 2015;27:420-426.
6. Mercie C, Dirix P, Meijnders P, et al. A phase I dose-escalation trial of stereotactic ablative body radiotherapy for non-spine bone and lymph node metastases (DESTROY-trial). *Radiat Oncol* 2018;13:152.
7. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. *Br J Radiol* 1989;62:679-694.
8. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228-247.
9. Costelloe CM, Chuang HH, Madewell JE, et al. Cancer response criteria and bone metastases: RECIST 1.1, MDA and PERCIST. *J Cancer* 2010;1:80-92.
10. Wahl RL, Jacene H, Kasamon Y, et al. From RECIST to PERCIST: Evolving considerations for PET response criteria in solid tumors. *J Nucl Med* 2009;50(Suppl 1):122S-150S.
11. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85:365-376.
12. Giesinger JM, Kieffer JM, Fayers PM, et al. Replication and validation of higher order models demonstrated that a summary score for the EORTC QLQ-C30 is robust. *J Clin Epidemiol* 2016;69:79-88.
13. Seuntjens J, Lartigau E, Cora S. ICRU report 91. Prescribing, recording, and reporting of stereotactic treatments with small photon beams. *J ICRU* 2014;14:101-109.
14. Lehrer EJ, Peterson JL, Zaorsky NG, et al. Single versus multifraction stereotactic radiosurgery for large brain metastases: An international meta-analysis of 24 trials. *Int J Radiat Oncol Biol Phys* 2019;103:618-630.
15. Siva S, Slotman BJ. Stereotactic ablative body radiotherapy for lung metastases: Where is the evidence and what are we doing with it? *Semin Radiat Oncol* 2017;27:229-239.
16. Glicksman RM, Tjong MC, Neves-Junior WFP, et al. Stereotactic ablative radiotherapy for the management of spinal metastases: A review. *JAMA Oncol* 2020;6:567-577.
17. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol* 2006;24:4833-4839.
18. Shahi J, Poon I, Ung YC, et al. Stereotactic body radiation therapy for mediastinal and hilar lymph node metastases [e-pub ahead of print]. *Int J Radiat Oncol Biol Phys*. https://doi.org/10.1016/j.ijrobp.2020.10.004. Accessed December 21, 2020.
19. Erler D, Brotherston D, Sahgal A, et al. Local control and fracture risk following stereotactic body radiation therapy for non-spine bone metastases. *Radiother Oncol* 2018;127:304-309.
20. Gandhidasan S, Ball D, Kron T, et al. Single fraction stereotactic ablative body radiotherapy for oligometastasis: Outcomes from 132 consecutive patients. *Clin Oncol (R Coll Radiol)* 2018;30:178-184.
21. Mercier C, Dirix P, Ost P, et al. A phase III randomized-controlled, single-blind trial to improve quality of life with stereotactic body radiotherapy for patients with painful bone metastases (ROBOMET). *BMC Cancer* 2019;19:876.
22. US National Library of Medicine. Randomized study comparing two dosing schedules for hypofractionated image-guided radiation therapy.

Available at: https://clinicaltrials.gov/ct2/show/NCT01223248. Accessed December 20, 2020.

23. Ost P, Reynders D, Decaestecker K, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: A prospective, randomized, multicenter phase II trial. *J Clin Oncol* 2018; 36:446-453.
24. Phillips R, Shi WY, Deek M, et al. Outcomes of observation vs stereotactic ablative radiation for oligometastatic prostate cancer: The ORIOLE phase 2 randomized clinical trial. *JAMA Oncol* 2020;6:650-659.
25. Olson R, Mathews L, Liu M, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of 1-3 oligometastatic tumors (SABR-COMET-3): Study protocol for a randomized phase III trial. *BMC Cancer* 2020;20:380.
26. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of 4-10 oligometastatic tumors (SABR-COMET-10): Study protocol for a randomized phase III trial. *BMC Cancer* 2019;19:816.
27. Ost P. SP -0642: OLIGOCARE, the EORTC ESTRO initiative for oligometastasis: A pragmatic platform. *Radiother Oncol* 2018;127:S340-S341.