Phenotype-oriented ablation of oligometastatic cancer with single-dose radiation therapy

Greco, C.; Pares, O.; Pimentel, N.; Louro, V.; Morales, J.; Nunes, B.; ... ; Fuks, Z.

International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation

Phenotype-Oriented Ablation of Oligometastatic Cancer with Single Dose Radiation Therapy

Carlo Greco, MD,* Oriol Pares, MD,* Nuno Pimentel, MD,* Vasco Louro, MD,* Javier Morales, MD,* Beatriz Nunes, MD,* Joana Castanheira, MD,* Carla Oliveira, MD,* Angelo Silva, MD,* Sofia Vaz, MD,* Durval Costa, MD,* Michael Zelefsky, MD,† Richard Kolesnick, MD,† and Zvi Fuks, MD*,†

**The Champalimaud Centre for the Unknown, Lisbon, Portugal; and †Memorial Sloan Kettering Cancer Center, New York, New York*

Received Sep 14, 2018. Accepted for publication Feb 12, 2019.

Summary

Inherent biologic drivers of the oligometastatic (OM) state determine conversion to polymetastatic (PM) dissemination over the impact of effective OM ablation by ultra-high dose radiation therapy. Baseline volumetric and metabolic OM metrics derived from positron emission tomography/computed tomography (PET/CT) scanning before radioablation predict long-term PM conversion after ablation, categorizing diverse OM phenotypes by susceptibility to PM conversion. The PET/

Purpose: The current oligometastatic (OM) model postulates that the disease evolves dynamically with sequential emergence of OM (SOM) lesions requiring successive rounds of SOM ablation to afford tumor cure. The present phase 2 study explores the ablative efficacy of 24 Gy single-dose radiation therapy (SDRT), its feasibility in diverse OM settings, and the impact of radioablation on polymetastatic (PM) dissemination.

Methods and Materials: One hundred seventy-five consecutive patients with 566 OM or SOM lesions underwent periodic positron emission tomography/computed tomography (PET/CT) imaging to stage the disease before treatment, determine tumor response, and monitor timing of PM conversion after SDRT. When 24 Gy SDRT was restricted by dose or volume constraints of serial normal organs, radioablation was diverted to a nontoxic 3×9 Gy SBRT schedule.

Results: SOM/SOMA occurred in 42% of the patients, and 24 Gy SDRT was feasible in 76% of the lesions. Despite 92% actuarial 5-year OM ablation by 24 Gy SDRT, respective PM-free survival (PMFS) was 26%, indicating PM conversion dominates over effective OM radioablation in many patients. Multivariate analysis of OM metrics derived from staging PET/CT scanning before first treatment predicted PMFS outcome after SDRT. Bivariate analysis of dichotomized high versus low baseline metric combinations of CT-derived tumor load (cutoff at 14.8 cm^3) and PET-derived metabolic

Reprint requests to: Carlo Greco, MD, Department of Radiation Oncology, Champalimaud Centre for the Unknown, Avenida Brasilia s/n, 1400-038 Lisbon, Portugal. Tel: +351 210 480 048; E-mail: carlo.greco@fundacaochampalimaud.pt

Patents unrelated to this work for Richard Kolesnick and Zvi Fuks (US7195775B1, US7850984B2, US10052387B2, US8562993B2, US9592238B2, US20150216971A1, US20170335014A1, US20170333413A1, and US20180015183A1). Richard Kolesnick and Zvi Fuks are co-founders of Ceramedix Holding L.L.C.

Disclosures: R. Kolesnick and Z. Fuks are inventors on a patent application not directly related to this study.

Supplementary material for this article can be found at https://doi.org/10.1016/j.ijrobp.2019.02.033.

Int J Radiation Oncol Biol Phys, Vol. 104, No. 3, pp. 593–603, 2019
0360-3016/$ - see front matter
https://doi.org/10.1016/j.ijrobp.2019.02.033

CT platform provides guidelines for phenotype-driven OM therapy and promotes discovery of tractable PM conversion drivers as targets for new experimental treatments.

SUV_{max} (cutoff at 6.5) yielded a 3-tiered PMFS categorization of 89%, 58% and 17% actuarial 5-year PMFS in categories 1, 2, and 3, respectively ($P < .001$), defining OM disease as a syndrome of diverse clinical and prognostic phenotypes.

Conclusion: Long-term risk of PM dissemination, predicted by preablation PET/CT staging, provides guidelines for phenotype-oriented OM therapy. In categories 1 and 2, radioablation should be a primary therapeutic element when pursuing tumor cure, whereas in the PM-prone category 3, radioablation should be a component of multimodal trials addressing primarily the risk of PM dissemination. PET/CT baseline staging also provides a platform for discovery of pharmacologically accessible PM drivers as targets for new phenotype-oriented treatment protocols.

Introduction

The biologic basis of oligometastatic (OM) disease remains a conundrum in cancer medicine. In 1995, Hellman and Weichselbaum[1,2] proposed the hypothesis that OM constitutes a temporary state of what might be termed *metastatogenic equilibrium*, providing a transient opportunity for tumor cure with localized ablative therapy if delivered before a polymetastatic (PM) escape occurs. The concept was derived from empirical surgical ablation of limited OM disease (1-5 lesions) from the lung or liver, yielding approximately 20% sustained disease-free survival at 10 to 20 years.[3,4] Although this model has driven the management of human OM disease, the underlying biologic mechanisms regulating metastatogenic equilibrium and PM escape have remained obscure.[5-8]

The introduction of image-guided, high-precision radiation therapy provides an alternative to surgery in metastasis-directed ablation. Whereas early phase 1/2 studies demonstrated the feasibility and safety of OM ablation by hypofractionated stereotactic body radiation therapy (SBRT),[9,10] the most effective outcomes have been achieved with ultra-high-dose (3 × 18-20 Gy) stereotactic ablative radiation therapy (SABR)[11-14] or with ≥24 Gy single-dose radiation therapy (SDRT),[15-18] yielding >90% actuarial local control of lesions at risk at 1 to 3 years. The impact of OM radioablation on clinical outcome has recently been confirmed in prospective randomized phase 2 studies. Two trials engaging OM non-small cell lung cancer (NSCLC) without progression after first-line systemic therapy demonstrated consolidative radiation therapy improved local progression-free survival over standard maintenance therapy,[19,20] whereas the SABR-COMET randomized trial[21] reported that in addition to progression-free survival, SABR also improved overall survival (OS) over standard of care therapy, regardless of OM tumor type or organs involved.

The phase 2 study reported here was designed to assess the efficacy and potential limitations of 24 Gy SDRT as a primary radioablation tool in the spectrum of a large cohort of consecutive patients with OM. Ultra-high dose SDRT has attracted increasing attention because of its unique mechanism of action, which is inherently different from that of fractionated radiation therapy,[22] rendering high rates of OM tumor ablation regardless of tumor type.[15-18,23,24] Early phase 1/2 studies reported a steep dose-dependent increase of OM ablation within the range of 18-24 Gy SDRT, plateauing at 24 Gy with approximately 90% actuarial local control at 1 to 3 years.[15,16,25] There is, however, a known limitation to 24 Gy SDRT, associated with anatomic proximity of OM lesions to serial normal organs.[14,26] Serial structures display organ-specific sensitivity to a single exposure within the range of 14 to 18 Gy to a so-called point volume (≤0.035 cm^3),[26] and violation of the dose-volume constraint can result in severe toxicity. When treatment planning deemed 24 Gy SDRT unfeasible because of a serial organ dose-volume constraint, the radioablation protocol was diverted to 3×9 Gy hypofractionated SBRT, known to be generally safe, albeit less effective in tumor ablation.[27] Importantly, the same serial organ dose-volume restrictions apply to 3 × 18-20 Gy SABR.[14]

Recent advances in the field provided evidence that human OM disease is a dynamic biologic entity, often producing sequential bouts of *bona fide* OM lesions (sequential oligometastases [SOMs]), requiring successive SOM ablations (SOMA) if tumor cure is pursued.[28,29] In the current phase 2 study, periodic PET/CT scans were used to explore the natural history of this phenomenon, defining the frequency and dynamics of SOM and the impact of SOMA on long-term clinical outcome. A cutoff of ≤6 metastatic lesions was adopted to dichotomize the OM from the PM state, as defined previously.[9,10] Furthermore, recent studies suggested that in-field local relapses (LRs) of irradiated OM lesions are potential targets for rescue with a repeated radioablation.[28] Hence, the primary endpoint of the study was to assess the feasibility and efficacy of 24 Gy SDRT in ablating initial OM, SOMs, or LR lesions whenever detected, provided the apparent clinical setting at each radioablative event fulfilled independently the protocol definition of an OM state (≤5 lesions), regardless of cumulative number of previously ablated lesions.

A secondary endpoint of the study was to identify the timing and incidence of clinical evidence of OM to PM transition in different OM clinical settings. A fundamental principle of the OM paradigm assumes that depletion of the OM compartment is sufficient to cure OM cancer, provided ablation is achieved before PM escape occurs. There may, however, be instances in which PM dissemination occurs

subclinically before effective ablation is achieved. Thus, periodic PET/CT scans were performed after radioablation to document LR-free survival (LRFS), polymetastasis-free survival (PMFS), and the first instance of ≥6 concomitant metastatic lesions as a clinical indicator of PM conversion. Figure E1 (available online at https://doi.org/10.1016/j.ijrobp.2019.02.033) displays a diagram demonstrating patient flow through the study and status at the last follow-up.

The study outcomes show that whereas 24 Gy SDRT renders an actuarial ≥92% ablation at 5 years, the respective PMFS was only 26%, indicating PM conversion inherently dominates effective radioablation in a large portion of patients with OM. Furthermore, baseline PET/CT volumetric and metabolic metrics acquired before the first radioablative event disclosed OM phenotypes with distinct tendencies for eventual PM conversion. A detailed analysis of local response, PMFS, and PM spread provides new insights into the natural history of the OM syndrome and defines the baseline PET/CT platform as a guide in selecting phenotype-oriented therapy.

Methods and Materials

Patient accrual criteria

Between November 2011 and March 2017, 175 consecutive eligible patients with ≤5 OM lesions were recruited to this institutional review board-approved phase 2 study (clinicaltrials.gov NCT03543696). Accrual eligibility included age ≥18 years, Karnofsky performance status ≥80, a controlled primary tumor, and ≤5 OM lesions independent of lesion location. Patients with brain tumors were excluded from the study. Systemic therapy was permitted at the discretion of the treating physician. Patients were staged at protocol admission with [^{18}F]-fluorodeoxyglucose–PET/CT scans, whereas prostate OM disease was staged with the PET tracer [^{68}Ga]prostate-specific membrane antigen. Detectable lesions were characterized in terms of volume, location, and PET metabolic parameters (SUV_{max} and metabolic tumor volume).

SDRT/SBRT techniques and doses

Simulation and treatment planning were performed as described previously,[30] based on PET/CT, co-registered with MRI whenever indicated, to outline the gross tumor volume (GTV) and to contour the clinical target volume (CTV). An isotropic margin of 3 mm was added to the CTV to generate the treatment planning volume (PTV). Four-dimensional CT scanning of mobile lesions in the lung was used to design an internal target volume (ITV) to compensate for respiratory target motion according to the Radiation Therapy Oncology Group 0236 guidelines. Treatment planning was performed with Eclipse software (Varian Medical Systems, Palo Alto, CA) using volumetric modulated arc therapy.[30] The same treatment planning guidelines were used for 24 Gy SDRT and 3×9 Gy SBRT. The EDGE/TrueBeam STx platforms (Varian Medical Systems) were used for treatment delivery. Both units are equipped with an ExactCouch system for 6-degrees-of-freedom patient setup.

Endpoints

Definitions of tumor response or failure were based on the PERCIST (PET Response Criteria in Solid Tumors) guidelines,[31] using PET/CT scans, initially at 3 months and subsequently at 6-month intervals. The duration of LRFS was calculated for each lesion independently from the date of radioablation, whereas the durations of PMFS and OS were calculated for each patient from the date of the first radioablative event. Acute and late toxicities were scored based on the National Institutes of Health Common Terminology Criteria for Adverse Events Guidelines, version 4.0.

Statistical analysis

Actuarial analysis was calculated using the Kaplan-Meier algorithm. Univariate analysis to explore the association of relevant prognostic variables with actuarial LRFS, PMFS, or OS was performed using the Cox proportional hazards regression method. A stepwise multivariate model was then set to estimate the association of covariates that had a significance alpha level = 0.10 in the univariate study, using the Cox proportional hazard algorithm. Hazard ratio, 95% confidence intervals, and χ^2 were obtained, and the level of statistical significance was set at $P < .05$. Whereas several of the covariates exhibiting statistical significance were registered as a continuum of quantitative values (eg, initial tumor load, metabolic SUV_{max}), univariate and multivariate analyses were also conducted with continuous-scale variables converted into binary-partitioned bins, using the method of Contal and O'Quigley.[32] This method provides an objective dichotomization via maximizing the hazard ratio of partitioning values based on log-rank statistics. Statistical computations were performed using R software Version 3.4.4 or GraphPad Prism 7.0 software (Prism, Reston, VA).

Results

Patients and lesions treated by radioablation

The study accrued 175 consecutive patients (Fig. E1; available online at https://doi.org/10.1016/j.ijrobp.2019.02.033) with initial 354 OM lesions. SOMA was used in 73 (42%) patients (Table 1; Fig. E1, available online at https://doi.org/10.1016/j.ijrobp.2019.02.033), contributing additional 191 lesions treated at 4-17 months intervals. Although in-field LRs were detected in 44 patients (25%), only 17 patients with 21 lesions were eligible for

Table 1 Patient characteristics

Characteristics	N = 175	%
Sex		
Male	95	54
Female	80	46
Age, y		
Median (range)	64.6 (36-90)	
Mean ± SD	65.1 ± 10.2	
Primary cancer		
Non-small cell lung cancer	31	18
Breast	30	17
Prostate	37	21
Colorectal	25	14
Pancreas	8	5
Bladder, urothelial	7	4
Sarcoma	6	3
Renal cell	6	3
Ovarian	4	2
Other	21	13
No. of OM lesions at first ablation		
1	74	42
2	54	31
3	25	14
4	14	8
5	8	5
Target organs involved initially		
1	126	72
2	42	24
3	7	4
Time (mo) to first ablation		
Median (range)	43.9 (1-327)	
Adjuvant Systemic therapy		
No	73	42
Yes	102	58
Regimen at first OM ablation		
SDRT 24 Gy	127	73
3 × 9 Gy	46	26
Both	2	1
Tumor burden at first OM ablation (sum of gross tumor volume, cm^3)		
Median (range)	15.3 (0.2-461.5)	
Mean ± SD	38.4 ± 62.2	
Highest SUV_{max} at first OM ablation		
Median (range)	9.6 (1.5-57.7)	
Mean ± SD	12.5 ± 10.8	
Sequential OM ablation		
No. of patients	73	42
1 event	43	24
2 events	19	11
≥3 events	10	6

Abbreviations: OM = oligometastatic; SDRT = single-dose radiation therapy.

radioablative LR rescue; in 20 patients LR occurred concomitant with PM conversion, and in 7 patients local rescue was not feasible because of restrictive comorbidities. When considering the final throughput of lesions in the ablation regimens, 108 patients (61%) with 322 lesions received 24 Gy SDRT alone, 31 (18%) patients with 59 lesions received 3×9 Gy hypofractionation alone, and 36 (21%) patients received a combination of 3×9 Gy hypofractionation (74 lesions) and 24 Gy SDRT (111 lesions). Fifty-five patients (35%) experienced grade 1 toxicity not requiring symptomatic therapy. There were no grade ≥2 toxicities. Follow-up for the entire study cohort ranged between 3.0 and 66.0 months (median, 28.2 months).

OM ablative potential of 24 Gy SDRT

Table 2 shows that of 566 lesions, 432 (76%) were treated with 24 Gy SDRT. An additional 134 (24%) lesions that did not fulfill serial organ dose−volume constraints for a 24 Gy exposure were treated with 3×9 Gy SBRT. OM lesion characteristics for each subgroup are listed in Table 2. Predictably, there was a prevalence of SDRT-treated lesions in organs with nonserial architecture (eg, lung and bone), as opposed to lesions treated with 3×9 Gy involving lymph nodes, frequently located adjacent to critical serial structures. Lesions treated with 3×9 Gy displayed a higher mean GTV (22.4 ± 47.2 cm^3; median, 7.9 cm^3) than lesions receiving 24 Gy SDRT (13.6 ± 29.8 cm^3; median. 4.9 cm^3; $P = .03$).

Figure 1A shows the actuarial OM LRFS at 5 years after 24 Gy SDRT was 92%, compared with 55% and 38% actuarial LRFS for lesions treated with 3×9 Gy SBRT at 3 and 4 years, respectively ($P < .0001$). LRFS of 24 Gy treated lesions was not affected by tumor size (Fig. 1B; overall volume range, 1-417 cm^3), tumor type (Fig. 1C), OM target organ (Fig. 1D), or application of adjuvant systemic therapy ($P = .70$; not shown). Although Figure 1C shows a borderline significant reduction of LRFS in NSCLC and colorectal OM lesions ($P = .05$), this could represent a dominating effect of 20% of these lesions (29 of 146) involving the mobile subdiaphragmatic liver and adrenals. The 3-year NSCLC and colorectal LRFS after 24 Gy SDRT in the adrenal and liver was 50%, compared with 88% 5-year LRFS for the same OM histologies in all other target organs ($P = .002$; not shown). A similar impact of target organ mobility on LRFS was not observed in the peripheral lung (actuarial 4-5 year LRFS of 93%; Fig. 1D), where an improved ability to precisely contour OM lesions and the use of the 4-dimensional CT-based ITV[33] successfully compensated for lesion respiratory motion. All evaluable locally relapsed and re-treated OM lesions have remained locally controlled at 7 to 38 months (median, 18.5 months), regardless of whether 3×9 Gy hypofractionation (n = 14) or SDRT (n = 8) was used.

Conversion from OM to PM

Serial follow-up PET/CT revealed clinical PM conversion begins in all subgroups shortly after completion of the first radioablative event (Fig. 2A-C), and it continues at a constant rate over 3 years. Figure 2A shows that despite a

Table 2 Lesion characteristics

Lesions	n (%)	SDRT 24 Gy (%)	3 × 9 Gy (%)	*P* value
Total	566	432 (76%)	134 (24%)	
Histology				.40
Breast	72 (13%)	54 (13%)	18 (13%)	
Colorectal	84 (15%)	63 (15%)	21 (15%)	
NSCLC	114 (20%)	83 (19%)	31 (23%)	
Prostate	139 (24%)	118 (27%)	21 (16%)	
Other histology	157 (28%)	114 (26%)	43 (32%)	
Lesion site				<.001
LN	192 (34%)	116 (26%)	76 (57%)	
Bone	185 (33%)	150 (35%)	35 (26%)	
Lung	103 (18%)	93 (22%)	10 (7%)	
Liver	39 (7%)	35 (8%)	4 (3%)	
Soft tissues	47 (8%)	38 (9%)	9 (7%)	
Systemic therapy				.91
No	93 (16%)	75 (17%)	18 (13%)	
Yes	473 (84%)	357 (83%)	116 (87%)	
GTV volume (cm^3)				.03
Median (range)	5.2 (0.1-417)	4.9 (0.1-283)	7.9 (0.3- 417)	
Mean ± SD	15.7 ± 34.9	13.6 ± 29.8	22.4 ± 47.2	
SUV_{max}				.2
Median (range)	7.0 (1.5-76.4)	6.9 (1.5-76.4)	7.4 (1.8-37.3)	
Mean ± SD	9.4 ± 8.7	9.1 ± 8.4	10.5 ± 9.2	

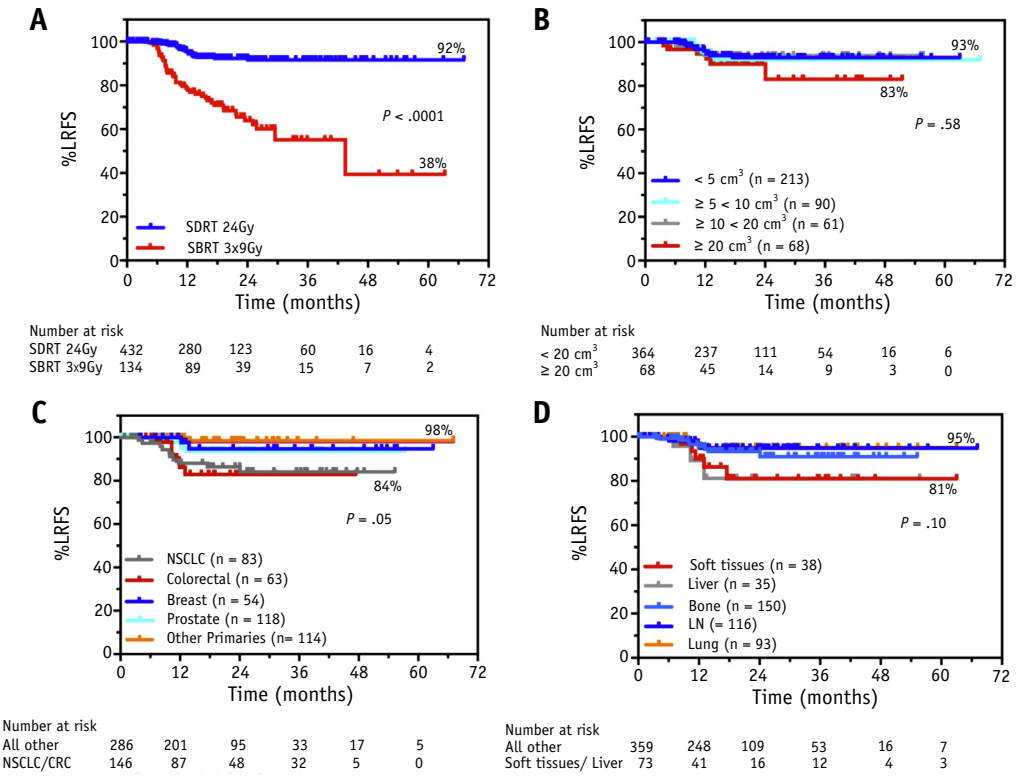

Fig. 1. Actuarial local relapse-free survival (LRFS) of oligometastatic tumors from the time of radioablative therapy of individual lesions. (A) LRFS after 24Gy single-dose radiation therapy (SDRT) or 3 × 9-Gy hypofractionated stereotactic body radiation (SBRT). LRFS after 24Gy SDRT by (B) tumor size, (C) tumor type, or (D) OM target organ. *Abbreviations:* CRC = colorectal cancer; NSCLC = non-small-cell lung cancer.

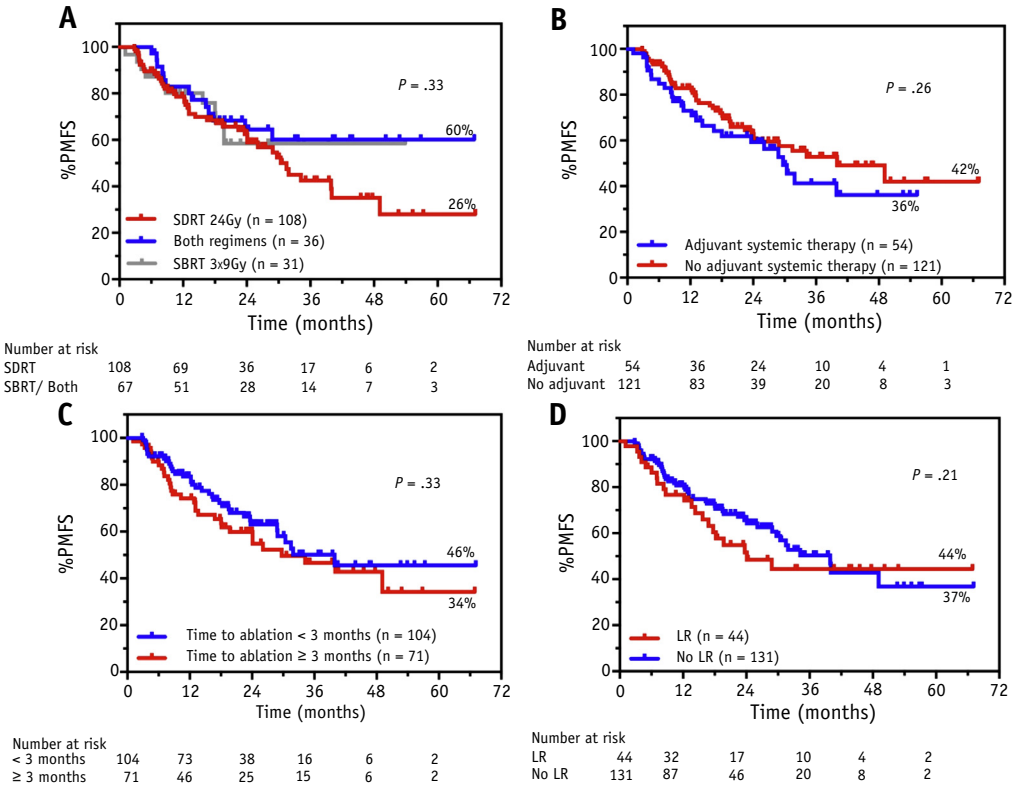

Fig. 2. Polymetastases-free survival (PMFS) in patients with oligometastases derived by serial follow-up PET/CT evaluations. Actuarial PMFS calculated from the time of the first radioablative therapy. PMFS is analyzed by (A) the radioablative regimen used, (B) treatment with adjuvant systemic chemotherapy or hormonal therapy, (C) time elapsing from first clinical diagnosis of oligometastases to the first attempt of radioablation, and (D) appearance of an in-field local relapse (LR). *Abbreviations:* SBRT = stereotactic body radiation therapy; SDRT = single-dose radiation therapy.

superior efficacy of 24 Gy SDRT in OM ablation (Fig. 1A), PMFS did not differ significantly in patients treated with 24 Gy SDRT versus 3×9 Gy SBRT (Fig. 2A; $P = .33$), nor did adjuvant systemic therapy (Fig. 2B; $P = .26$) or the time elapsing from clinical OM diagnosis to the first radioablation in early (<3 months) versus delayed (≥3 months; median, 11 months; range, 3-88 months) affect PMFS (Fig. 2C; $P = .33$). Similarly, PMFS was not affected by LRs (Fig. 2D, $P = .21$), OM histologic type (Table 3), single versus multiple lesions ($P = .40$; not shown), or single versus multiple OM target organs ($P = .55$; not shown).

Nonetheless, univariate analysis revealed that the initial OM tumor load (sum of GTVs of all OM lesions) derived from the baseline staging PET/CT before the first radioablative event, its respective metabolic ^{18}F-FDG- or [^{68}Ga]-SUV_{max}, and the application of SOMA each significantly affected PMFS (Table 3). Of note, the initial tumor load and the metabolic SUV_{max} are normally registered as a continuum of quantitative values, and the Cox proportional hazards regression analysis does not disclose which value range best predicts PM dissemination. To convert the continuous scale into binary-partitioned subgroups, we derived the most significant cutoff values for initial tumor load and SUV_{max} dichotomization, using the statistical partitioning method of Contal and O'Quigley.[32] This analysis yielded dichotomization cutoff values of 14.8 cm^3 for baseline staging tumor load (Fig. 3A) and a respective 6.5 for SUV_{max} (Fig. 3B) as the best predictors of PMFS.

Figure 3C shows that a bivariate analysis of a combination of <14.8 cm^3 initial tumor load and <6.5 SUV_{max} defines a favorable PMFS prognosis (category 1), exhibiting a 5-year actuarial PMFS of 89% (Fig. 3C), whereas the combination of <14.8 cm^3 OM initial tumor load and ≥6.5 SUV_{max} predicted intermediate prognosis (category 2) yielding 58% actuarial 5-year PMFS ($P = .02$ versus category 1). Figure 3C also shows that an initial tumor load value ≥14.8 cm^3 regardless of the SUV_{max} defined a poor prognostic category 3, showing a rapid deterioration of PMFS over the first 36 months after ablation, and rendering an actuarial 17% PMFS at 5 years ($P < .001$ as compared with category 2). Deterioration of PMFS in category 3 was not affected by the time elapsing between the initial clinical OM diagnosis and first radioablation, with nearly superimposed actuarial PMFS curves for early (<3 months) versus delayed (≥3 months) first ablation (not shown), rendering 20% and 14% PMFS at 5 years, respectively ($P = .22$).

Table 3 Univariate and multivariate analysis of PMFS and OS

Predictive factor	PMFS UV analysis			OS UV analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Sex	0.65	0.56-1.44	.65	0.39	0.22-0.70	.006
Age	1.00	0.98-1.03	.94	1.03	1.00-1.06	.06
First treatment SDRT	1.00	0.57-1.76	.99	0.77	0.41-1.48	.44
SOMA	0.38	0.23-0.63	< .001	0.70	0.39-1.26	.08
No. of OM (1 vs ≥ 2)	0.73	0.45-1.18	.42	1.00	0.56-1.79	.79
Time to first OM ablation (<3 mo)	0.81	0.48-1.36	.46	0.99	0.98-1.01	.29
OM primary site						
Breast	1.51	0.82-2.81	.19	0.23	0.06-0.97	.04
Prostate	0.45	0.17-1.20	.11	2.10	0.38-11.58	.39
NSCLC	0.53	0.23-1.24	.14	3.54	0.76-16.41	.10
Colorectal	4.38	0.80-24.4	.09	0.82	0.31-2.15	.68
Other	2.05	0.57-7.40	.27	0.72	0.36-1.35	.36
Initial tumor load (continuous variable)	1.00	1.00-1.00	.002	1.00	1.00-1.01	.001
SUV_{max} (continuous variable)	1.02	1.00-1.04	.03	1.04	0.99-1.05	.12
Initial tumor load (dichotomization by best cutoff)*	0.39	0.24-0.60	<.001	0.27	0.13-0.56	.004
SUV_{max} (dichotomization by best cutoff)†	0.59	0.35-0.99	.04	0.45	0.23-0.90	.02
	Predictive factors on MV analysis			Predictive factors on MV analysis		
Initial tumor load*	0.55	0.32-0.94	.02	0.35	0.19-0.67	.001
SUV_{max}†	0.58	0.34-0.99	.04			
Male sex				2.38	1.14-5.00	.02

Abbreviations: CI = confidence interval; HR = hazard ratio; MV = multivariate; NSCLC = non-small-cell lung cancer; OM = oligometastatic; OS = overall survival; PMFS = polymetastasis-free survival; SDRT = single-dose radiation therapy; SOMA = sequential oligometastases ablation; UV = univariate.

* Sum of gross tumor volumes; cutoff point at <14.8 cm^3.

† SUV_{max} cutoff point at <6.5.

The univariate analysis (Table 3) also revealed that SOMA delays PM dissemination (Fig. 4A; $P < .0001$). This phenomenon might reflect an impact of SOM disease on PM conversion. To further explore this notion, we performed trivariate analyses of SOMA effects in the context of the 3-tiered PET/CT-derived PMFS categories. In category 1, 12 of 24 patients (50%) required SOMA, which did not affect the inherent minimal rate of PM conversion (Fig. 4B; $P = .94$). In category 2, 29 of 60 patients (48%) underwent SOMA, revealing a tendency, albeit not statistically significant, of delayed PM conversion associated with SOMA (Fig. 4C; $P = .06$). In the poor prognostic category 3, 32 of 91 patients (35%) underwent SOMA, associated with a significant delay in PM conversion (Fig. 4C; $P = .02$), although by 48 months the SOMA/no-SOMA curves appeared to converge, indicating that SOMs can delay but not prevent clinical PM conversion.

Overall survival after OM ablation

Univariate and multivariate analyses revealed that OS significantly correlated with pretreatment baseline PET/CT-derived tumor load and SUV_{max} (Table 3). Categorizing patient survival by dichotomized metric combinations of these pretreatment parameters, as performed earlier for PMFS, yielded actuarial 5-year OS rates of 100%, 56%, and 36%, respectively (Fig. 5A), closely correlating with 3-tiered PMFS categories (Fig. 3C). The actuarial 5-year OS was not affected by the use of adjuvant systemic therapy after the first radioablative event ($P = .40$; Fig. 5B). Notably, the actuarial 5-year OS directly correlated in all tumor types with the actuarial PMFS (45% and 49%, respectively; Fig. 5C), except for in breast cancer, in which a relatively small group of breast OM patients (n = 30) displayed an actuarial 5-year PMFS of 21% versus an OS of 79% ($P < .01$; Fig. 5C). This unique pattern of breast cancer response is consistent with previous data reporting that breast OM patients treated with radioablation fare better than patients with other OM tumor types,[10] and with recent reports demonstrating that metastatic breast cancer is exceptionally sensitive to systemic therapies, promoting prolonged survival in the disseminated metastatic phase of the disease.[34]

Discussion

The present study confirms the attributes of 24 Gy SDRT as a robust and cost-effective radioablative tool, given that it renders ≥92% of sustained ablation of OM lesions in a wide range of OM settings. However, it also reveals a

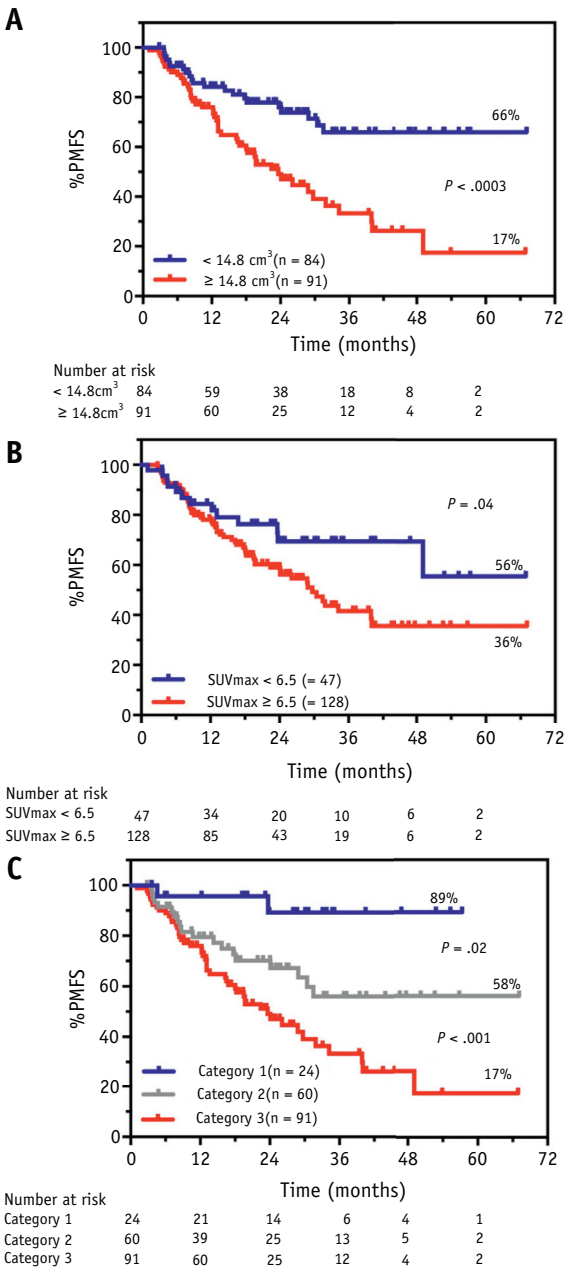

Fig. 3. Analysis of factors affecting polymetastases-free survival (PMFS). (A, B) Univariate analysis of volumetric and metabolic variables derived from baseline PET/CT evaluation performed before first treatment. (A) The effect of the initial tumor load calculated as the sum of CT-derived gross tumor volumes (GTVs) of all detected OM lesions dichotomized at a cutoff value 14.8 cm^3. (B) The respective metabolic PET SUV_{max} dichotomized at a cutoff value of 6.5. (C) Bivariate analysis of combined baseline tumor load and SUV_{max} on PMFS. Category 1 comprises patients with baseline oligometastases (OM) tumor load of <14.8 cm^3 and $SUV_{max} < 6.5$; category 2 with <14.8 cm^3 OM tumor load and $SUV_{max} \geq 6.5$; and category 3 with OM tumor load value of ≥ 14.8 cm^3 regardless of SUV_{max}.

relatively high incidence of serial normal organ interference with 24 Gy, requiring diversion to nontoxic ablative hypofractionated radiation therapy. The 3×9 Gy SBRT regimen used here was associated with a high rate of in-field LRs. Although LR rescue with repeated radioablation appeared to be effective in a limited number of patients, rescue was deemed unfeasible or of no therapeutic value in >60% of LR cases, highlighting a need for an alternative toxicity-free ablative approach to the 3×9 Gy regimen.

Given that ablative ultra-high-dose (3 × 18-20 Gy) SABR is restricted by the same serial organ constraints as SDRT,[14,35] lower doses per fraction of ablative SBRT (eg, 4×12 Gy[36,37] or ×8-10 Gy[14,38-40]) are the preferred alternatives to 3×9 Gy. SBRT schedules using ≤12 Gy/fraction are below the thresholds of serial organ point dose constraints[26] but could still result in toxicity.[41,42] Normal tissue complication probabilities of ≤12 Gy/fraction SBRT are determined by dose-volume correlations of the exposed organ at risk with increasing grades of toxicity.[43,44] Hence, when 24 Gy SDRT is restricted by serial organ tolerance and an alternative SBRT regimen is needed, emerging algorithms, such as the Dose-Volume Histogram Risk Maps protocol,[44] can be used at treatment planning to select an ablative SBRT schedule that predicts an acceptable risk of organ-at-risk toxicity.

An alternative approach can be derived from the recent understanding of the SDRT biology[22] that mechanistically links a transient microvascular acid sphingomyelinase (ASMase)-mediated ischemia or reperfusion to DNA double-strand break repair in parenchymal tumor cells, disabling tumor cell homology-directed double-strand break repair to render synthetic tumor cell lethality.[22] Pharmacologic enhancement of the ASMase response selectively radiosensitizes SDRT lethality,[45-47] rendering a 25% reduction of the nominal SDRT dose required to achieve an iso-cure effect normally observed at 20 Gy, with no added normal tissue toxicity.[47] Translation of this approach to clinical use could enable de-escalation of ablative SDRT tumor dosing to below the threshold of serial organ toxicity.[46,47] Hence, the use of advanced treatment planning algorithms, and the potential of pharmacologic modulation of the SDRT response, provides approaches to resolve the current intractable restriction of serial organ dose-volume constraints on ablative SDRT in OM cancer.

The development of a baseline PET/CT-based, 3-tiered PMFS categorization at initial OM diagnosis transforms the field because it provides an objective, noninvasive staging system based on functional tumor metrics, rather than the traditional arbitrary use of numerical counts of 3 or 5 lesions to define a dynamic biological entity. The 3-tiered categorization defines human OM disease as a syndrome of diverse clinical and prognostic phenotypes. We posit that the phenotypes share a common biologic core of transient metastatogenic equilibrium, with each driven by phenotype-specific pathways that regulate the balance

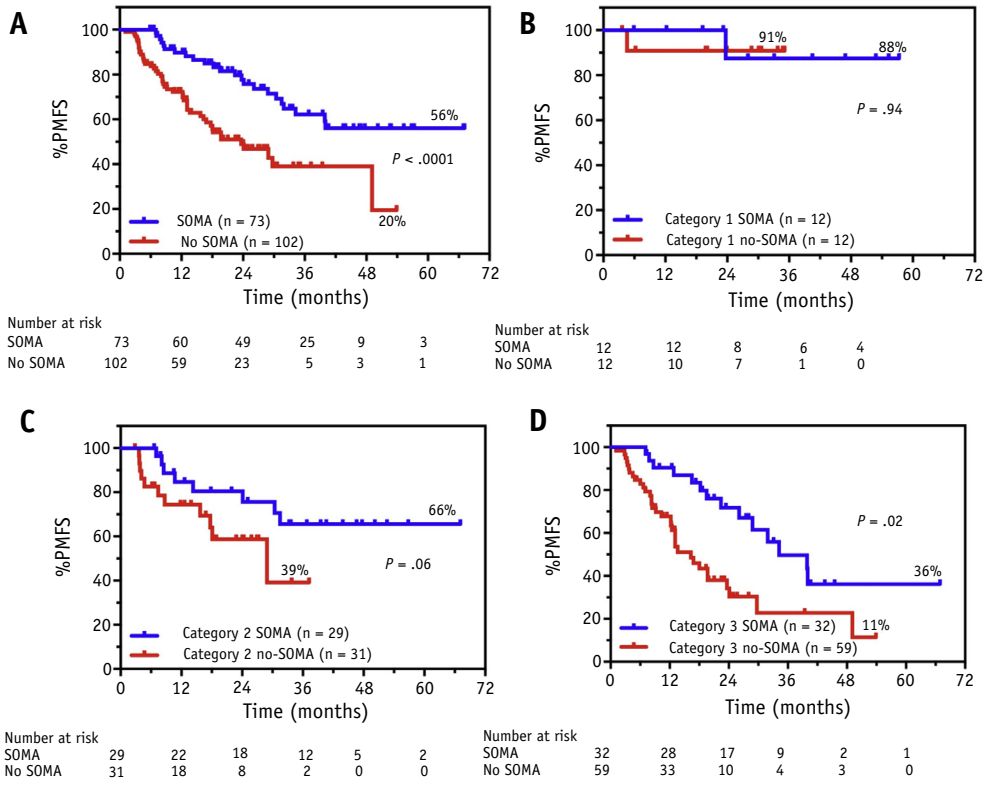

Fig. 4. Effect of sequential oligometastases ablation (SOMA) on polymetastases-free survival (PMFS) (A) in the total cohort of study patients, (B) in category 1, (C) in category 2, and (D) in category 3 patients.

between metastatogenic equilibrium and PM escape. A basic element of this paradigm is the apparent dichotomization between the PMFS favorable category 1, amenable to OM ablative cure, and category 3, which mostly converts to PM dissemination despite effective OM ablation. Thus, our reported 89% 5-year disease-free status in category 1 represents the classical OM phenotype originally predicted by Hellman and Weichselbaum[1,2] to be curable if ablated before a PM escape occurs. In this regard, previous studies reported that OM patients with no evidence of disease at 5 years after surgery exhibit a low risk (5%-11%) of subsequent relapse or PM dissemination.[48-50] Category 2 appears to represent a transitional phase from category 1 to category 3, wherein regulatory pathways that promote PM escape appear to be gradually activated. Although a significant proportion of patients in this category cross a point of no return in PM conversion, we suggest that until these patients can be identified upfront, there is an indication for consented OM radioablation in all category 2 patients; approximately 60% hold a chance of attaining cure of an otherwise life-threatening tumor progression. In category 3, the great majority of patients appear to be beyond rescue by ablation alone, and the current indiscriminate use of surgical or radiation OM ablation in this category is unwarranted. We suggest that comprehensive OM radioablation, if used in category 3, should be used as a component of prospective multimodality clinical trials designed primarily to address the risk of PM dissemination. Importantly, we foresee a potential for the PET/CT staging system in serving as a platform for discovery of biomarkers that define new phenotypic subgroups, potentially promoting innovation in phenotype-driven OM therapy.

There are no animal models of bona fide OM disease, and progress in the field largely depends on interpretation of clinical observations. Recent transcriptional profiling of archived human primary and metastatic lesions disclosed noncoding microRNA (miRNA)/mRNA networks are ectopically overexpressed in OM lesions (termed *oligomiRs*), discriminating OM from PM lesions across different tumor types.[51] A subgroup of oligomiRs encoded in a polycistronic miRNA gene locus on human chromosome 14q32 were characterized as tumor suppressors,[52] repressing experimental MDA-MB-231 metastatic colonization of the lung,[52] and arresting growth of HCT116 tumors in hepatic xenograft lesions.[53] Whether suppressor miRNA signatures are associated with our observation that SOM/SOMA delay PM conversion in category 3 disease (Fig. 4D) is a testable hypothesis. Furthermore, future research will be required to assess whether the 3-tiered PMFS categorization reflects phenotype-specific acquisition or loss of suppressor miRNA signatures.

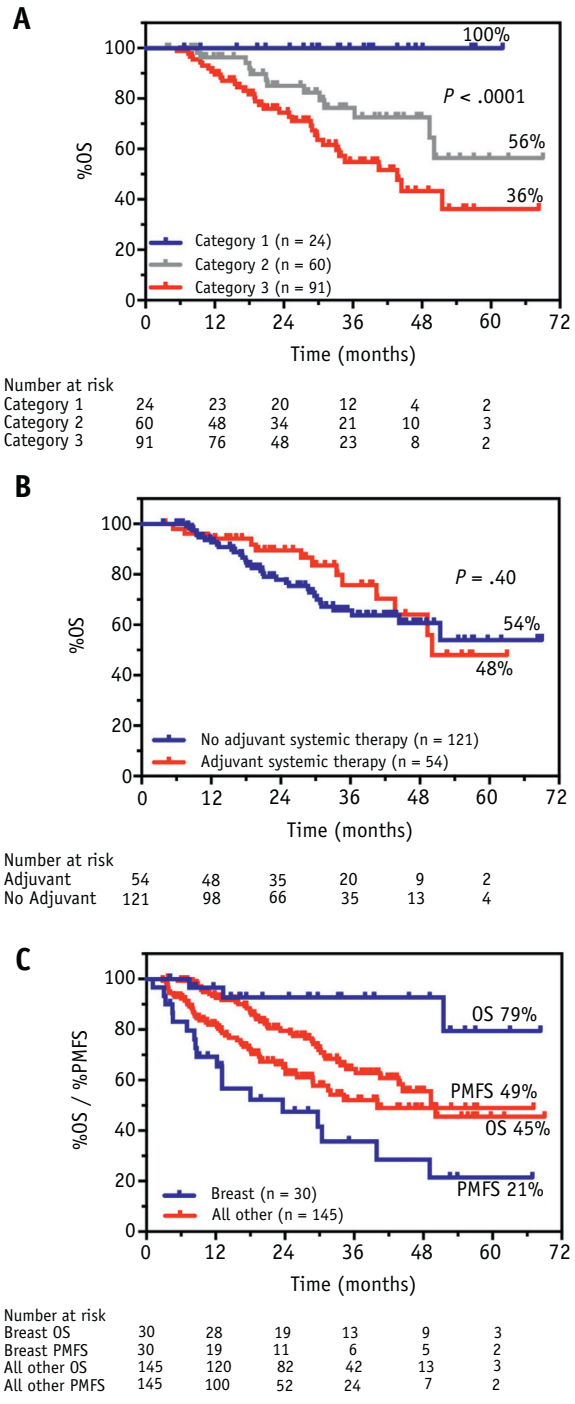

Fig. 5. Actuarial overall survival (OS) of patients treated with oligometastases (OM) radioablation by categories. (A) OS by the 3-tiered categorization of OM phenotypes as defined in Figure 3C. (B) Effect of adjuvant systemic therapy used after initial radioablative therapy on OS. (C) Comparison of PMFS and OS in patients with breast cancer compared with all other patients combined.

Conclusions

Coordinate exploration of OM biology in the context of the 3-tiered PMFS categorization holds promise in research of specific drivers of OM biology, with a potential for novel therapeutic approaches. Notwithstanding future developments, the current 3-tiered staging system has immediate practical implications for phenotype-oriented clinical trials in the treatment of OM disease.

References

1. Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol* 1995;13:8-10.
2. Weichselbaum RR, Hellman S. Oligometastases revisited. *Nat Rev Clin Oncol* 2011;8:378-382.
3. Fortner JG, Fong Y. Twenty-five-year follow-up for liver resection: The personal series of Dr. Joseph G. Fortner. *Ann Surg* 2009;250:908-913.
4. Pastorino U, Buyse M, Friedel G, et al. Long-term results of lung metastasectomy: Prognostic analyses based on 5206 cases. *J Thorac Cardiovasc Surg* 1997;113:37-49.
5. Palma DA, Salama JK, Lo SS, et al. The oligometastatic state - separating truth from wishful thinking. *Nat Rev Clin Oncol* 2014;11:549-557.
6. Reyes DK, Pienta KJ. The biology and treatment of oligometastatic cancer. *Oncotarget* 2015;6:8491-8524.
7. Correa RJ, Salama JK, Milano MT, Palma DA. Stereotactic body radiotherapy for oligometastasis: Opportunities for biology to guide clinical management. *Cancer J* 2016;22:247-256.
8. Weichselbaum RR. The 46th David A. Karnofsky Memorial Award Lecture: Oligometastasis—From conception to treatment. *J Clin Oncol* 2018;JCO1800847.
9. Salama JK, Chmura SJ, Mehta N, et al. An initial report of a radiation dose-escalation trial in patients with one to five sites of metastatic disease. *Clin Cancer Res* 2008;14:5255-5259.
10. Milano MT, Katz AW, Muhs AG, et al. A prospective pilot study of curative-intent stereotactic body radiation therapy in patients with 5 or fewer oligometastatic lesions. *Cancer* 2008;112:650-658.
11. McCammon R, Schefter TE, Gaspar LE, Zaemisch R, Gravdahl D, Kavanagh B. Observation of a dose-control relationship for lung and liver tumors after stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys* 2009;73:112-118.
12. Rusthoven KE, Kavanagh BD, Burri SH, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for lung metastases. *J Clin Oncol* 2009;27:1579-1584.
13. Rusthoven KE, Kavanagh BD, Cardenes H, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for liver metastases. *J Clin Oncol* 2009;27:1572-1578.
14. Folkert MR, Timmerman RD. Stereotactic ablative body radiosurgery (SABR) or Stereotactic body radiation therapy (SBRT). *Adv Drug Deliv Rev* 2017;109:3-14.
15. Yamada Y, Bilsky MH, Lovelock DM, et al. High-dose, single-fraction image-guided intensity-modulated radiotherapy for metastatic spinal lesions. *Int J Radiat Oncol Biol Phys* 2008;71:484-490.
16. Greco C, Zelefsky MJ, Lovelock M, et al. Predictors of local control after single-dose stereotactic image-guided intensity-modulated radiotherapy for extracranial metastases. *Int J Radiat Oncol Biol Phys* 2011;79:1151-1157.
17. Meyer JJ, Foster RD, Lev-Cohain N, et al. A phase I dose-escalation trial of single-fraction stereotactic radiation therapy for liver metastases. *Ann Surg Oncol* 2016;23:218-224.
18. 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.
19. Gomez DR, Blumenschein GR Jr., Lee JJ, et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: A multicentre, randomised, controlled, phase 2 study. *Lancet Oncol* 2016;17:1672-1682.

20. Iyengar P, Wardak Z, Gerber DE, et al. Consolidative radiotherapy for limited metastatic non-small-cell lung cancer: A phase 2 randomized clinical trial. *JAMA Oncol* 2018;4:e173501.
21. Palma DA, Olson RA, Harrow S, et al. Stereotactic Ablative Radiation Therapy for the Comprehensive Treatment of Oligometastatic Tumors (SABRCOMET): Results of a randomized trial. *Int J Radiat Oncol Biol Phys* 2018;102(Supplement):S3.
22. Bodo S, Campagne C, Thin TH, et al. Single-dose radiotherapy disables tumor cell homologous recombination via ischemia/reperfusion injury. *J Clin Invest* 2019;129:786-801.
23. Zelefsky MJ, Greco C, Motzer R, et al. Tumor control outcomes after hypofractionated and single-dose stereotactic image-guided intensity-modulated radiotherapy for extracranial metastases from renal cell carcinoma. *Int J Radiat Oncol Biol Phys* 2012;82:1744-1748.
24. Goodman KA, Wiegner EA, Maturen KE, et al. Dose-escalation study of single-fraction stereotactic body radiotherapy for liver malignancies. *Int J Radiat Oncol Biol Phys* 2010;78:486-493.
25. Yamada Y, Katsoulakis E, Laufer I, et al. The impact of histology and delivered dose on local control of spinal metastases treated with stereotactic radiosurgery. *Neurosurg Focus* 2017;42:E6.
26. 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.
27. Milano MT, Katz AW, Zhang H, Okunieff P. Oligometastases treated with stereotactic body radiotherapy: Long-term follow-up of prospective study. *Int J Radiat Oncol Biol Phys* 2012;83:878-886.
28. Milano MT, Philip A, Okunieff P. Analysis of patients with oligometastases undergoing two or more curative-intent stereotactic radiotherapy courses. *Int J Radiat Oncol Biol Phys* 2009;73:832-837.
29. Adam R, Pascal G, Azoulay D, Tanaka K, Castaing D, Bismuth H. Liver resection for colorectal metastases: The third hepatectomy. *Ann Surg* 2003;238:871-883; [discussion: 83-84].
30. Stroom J, Vieira S, Mateus D, et al. On the robustness of VMAT-SABR treatment plans against isocentre positioning uncertainties. *Radiat Oncol* 2014;9:196.
31. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving considerations for PET response criteria in solid tumors. *J Nucl Med* 2009;50(suppl 1):122S-150S.
32. Contal C, O'Quigley J. An application of changepoint methods in studying the effect of age on survival in breast cancer. *Comput Stat Data Analysis* 1999;30:253-270.
33. Shaverdian N, Tenn S, Veruttipong D, et al. The significance of PTV dose coverage on cancer control outcomes in early stage non-small cell lung cancer patients treated with highly ablative stereotactic body radiation therapy. *Br J Radiol* 2016;89:20150963.
34. Nishikawa G, Luo J, Prasad V. A comprehensive review of exceptional responders to anticancer drugs in the biomedical literature. *Eur J Cancer* 2018;101:143-151.
35. 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.
36. Nagata Y, Wulf J, Lax I, et al. Stereotactic radiotherapy of primary lung cancer and other targets: Results of consultant meeting of the International Atomic Energy Agency. *Int J Radiat Oncol Biol Phys* 2011;79:660-669.
37. Videtic GM, Paulus R, Singh AK, et al. Long-term follow-up on NRG Oncology RTOG 0915 (NCCTG N0927): A randomized phase 2 study comparing 2 stereotactic body radiation therapy schedules for medically inoperable patients with stage I peripheral non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2019; 103:1077-1084.
38. Modh A, Rimner A, Williams E, et al. Local control and toxicity in a large cohort of central lung tumors treated with stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys* 2014;90:1168-1176.
39. Hannan R, Tumati V, Xie XJ, et al. Stereotactic body radiation therapy for low and intermediate risk prostate cancer-Results from a multi-institutional clinical trial. *Eur J Cancer* 2016;59:142-151.
40. Wang CJ, Christie A, Lin MH, et al. Safety and efficacy of stereotactic ablative radiation therapy for renal cell carcinoma extracranial metastases. *Int J Radiat Oncol Biol Phys* 2017;98:91-100.
41. LaCouture TA, Xue J, Subedi G, et al. Small bowel dose tolerance for stereotactic body radiation therapy. *Semin Radiat Oncol* 2016;26:157-164.
42. Pollom EL, Chin AL, Diehn M, Loo BW, Chang DT. Normal tissue constraints for abdominal and thoracic stereotactic body radiotherapy. *Semin Radiat Oncol* 2017;27:197-208.
43. Kupchak C, Battista J, Van Dyk J. Experience-driven dose-volume histogram maps of NTCP risk as an aid for radiation treatment plan selection and optimization. *Med Phys* 2008;35:333-343.
44. Asbell SO, Grimm J, Xue J, Chew MS, LaCouture TA. Introduction and clinical overview of the DVH risk map. *Semin Radiat Oncol* 2016; 26:89-96.
45. Truman JP, Garcia-Barros M, Kaag M, et al. Endothelial membrane remodeling is obligate for anti-angiogenic radiosensitization during tumor radiosurgery. *PLoS One* 2010;5:e12310.
46. Rao SS, Thompson C, Cheng J, et al. Axitinib sensitization of high single dose radiotherapy. *Radiother Oncol* 2014;111:88-93.
47. Stancevic B, Varda-Bloom N, Cheng J, et al. Adenoviral transduction of human acid sphingomyelinase into neo-angiogenic endothelium radiosensitizes tumor cure. *PLoS One* 2013;8:e69025.
48. Tomlinson JS, Jarnagin WR, DeMatteo RP, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. *J Clin Oncol* 2007;25:4575-4580.
49. Pulitano C, Castillo F, Aldrighetti L, et al. What defines 'cure' after liver resection for colorectal metastases? Results after 10 years of follow-up. *HPB (Oxford)* 2010;12:244-249.
50. Roberts KJ, White A, Cockbain A, et al. Performance of prognostic scores in predicting long-term outcome following resection of colorectal liver metastases. *Br J Surg* 2014;101:856-966.
51. Lussier YA, Khodarev NN, Regan K, et al. Oligo- and polymetastatic progression in lung metastasis(es) patients is associated with specific microRNAs. *PLoS One* 2012;7:e50141.
52. Uppal A, Wightman SC, Mallon S, et al. 14q32-encoded microRNAs mediate an oligometastatic phenotype. *Oncotarget* 2015;6:3540-3552.
53. Oshima G, Guo N, He C, et al. In vivo delivery and therapeutic effects of a microRNA on colorectal liver metastases. *Mol Ther* 2017;25: 1588-1595.