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CLINICAL INVESTIGATION

Efficacy and Safety of Stereotactic Body Radiation Therapy in Oligometastatic Uterine Cancer (MITO-RT2/RAD): A Large, Real-World Study in Collaboration With Italian Association of Radiation Oncology, Multicenter Italian Trials in Ovarian Cancer, and Mario Negri Gynecologic Oncology Group Groups

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Purpose: This retrospective, multicenter study analyzes the efficacy and safety of stereotactic body radiation therapy in a large cohort of patients with oligometastatic/persistent/recurrent uterine cancer.

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Methods and Materials: Clinical and radiation therapy data from several radiation therapy centers treating patients by stereotactic body radiation therapy between March 2006 and October 2021 were collected. Objective response rate was defined as complete and partial response, and clinical benefit included objective response rate plus stable disease. Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer and Common Terminology Criteria for Adverse Events scales were used to grade toxicities. Primary endpoints were the rate of complete response to stereotactic body radiation therapy, and the 2-year actuarial local control rate "per-lesion" basis. Secondary endpoints were progression-free survival and overall survival, as well as toxicity.

Results: In the study, 157 patients with oligometastatic/persistent/recurrent uterine cancer bearing 272 lesions treated by stereotactic body radiation therapy at 14 centers were analyzed. Lymph node metastases (137, 50.4%) were prevalent, followed by parenchyma lesions (135, 49.6%). Median total dose was 35 Gy (10-75.2), in 5 fractions (range, 1-10). Complete and partial responses were 174 (64.0%), and 54 (19.9%), respectively. Stable disease was registered in 29 (10.6%), and 15 (5.5%) lesions progressed. Type of lesion (lymph node), volume (≤13.7 cc) and total dose (BED_{10} >59.5 Gy) were significantly associated with a higher probability of achieving complete response. Patients achieving complete response (CR) "per-lesion" basis experienced a 2-year actuarial local control rate of 92.4% versus 33.5% in lesions not achieving complete response (NCR; $P < .001$). Moreover, the 2-year actuarial progression-free survival rate in patients with CR was 45.4%, and patients with NCR had a 2-year rate of 17.6% ($P < .001$). Finally, patients who had a CR had a 2-year overall survival rate of 82.7%, compared with 56.5% for NCR patients ($P < .001$). Severe acute toxicity was around 2%, including one toxic death due to gastric perforation, and severe late toxicity around 4%.

Conclusions: The efficacy of stereotactic body radiation therapy in this setting was confirmed. The low toxicity profile and the high local control rate in complete responder patients encourage the wider use of this approach.

Introduction

Uterine corpus cancer is the most common invasive gynecologic cancer among United States women.[1] The overall relapse rate has remained unchanged in recent decades. Recurrences occur in approximately 20% of endometrioid (ie, type I histology) and 50% of nonendometrioid cases (ie, type II histology).[2] The approaches should be considered according to site (ie, locoregional, abdominal, and extra-abdominal recurrence), previous treatments, comorbidities, and burden of disease, even if the benefit of metastases-directed therapies across histologies remains uncertain.[3] One of the options of metastases-directed therapies used for curative-intent treatment strategies is represented by Stereotactic Body Radiation therapy (SBRT), a high conformal and modulated radiation therapy technique, characterized by increased dose distribution conformity, reduced normal tissue toxicity, and potential dose escalation. SBRT delivers high radiation doses to small volumes in few fractions and represents an active and definitive treatment that can be integrated into a multidisciplinary strategy including surgery, conventional chemotherapy, and the target-based drugs in the setting of oligometastatic/persistent/recurrent (MPR) disease.[4,5] In fact, SBRT has been shown to be an effective strategy in other settings such as lung[6,7] and prostate cancer,[8-11] either because of the reported improvement of several outcomes (progression-free survival,[6-8] overall survival,[9] and prolongation of androgen deprivation treatment-free survival as well castrate resistant prostate cancer-free survival[10,11]) or because of the potential to delay further systemic therapy, which is frequently less effective, especially in the oligoprogressive setting. Besides that, SBRT has been shown to be active in chemoresistant disease, and potentially able to mount immune response through the release of tumor neoantigens after cell killing, the latter allowing the synergism of SBRT with immunotherapeutic approaches.[12,13]

There are few studies that specifically address the role of SBRT in patients with oligo-MPR uterine cancer[14-17]; furthermore, the small sample size of some series and adoption of multiple SBRT schedules prevented the definition of the optimal total dose, dose per fraction, and referral dose point, as for other gynecologic tumors.[5,18,19] Finally, how patients should be best selected and treated using this modality has not been fully clarified.

This multicenter, retrospective study has the aim of defining the efficacy and safety of SBRT in a significant real-world data set of patients with uterine cancer with oligo-MPR. To find potential indicators of prognostic outcome, clinical or SBRT parameters have been examined.

Methods and Materials

Study design and endpoints

This is a multicenter, retrospective study (MITO-RT2/RAD) aimed at assessing the efficacy and safety of SBRT in patients with oligo-MPR uterine cancer treated in several Italian Radiation therapy Institutions. Patients with oligo-MPR were defined as patients with ≤5 new or enlarging synchronous metastases in an otherwise well-controlled disease status and, therefore, candidates for curative-intent treatment; with the inherent limits of a retrospective nature of our study, only this kind of patients entered the study. The study was initiated and carried out within the Multicenter Italian Trials in Ovarian Cancer (MITO) group, in collaboration with the

gynecologic group of the Italian Association of Radiation Oncology (AIRO Gyn) and the Mario Negri Gynecologic Oncology Group (MAnGO). The study was approved by the Institutional Review Board of promoting Institution (N° 62967/2020 ASREM Ethical Committee), and patients at each center should have signed an informed consent form before their clinical data being used for educational or research purposes. The primary endpoint of the MITO-RT2/RAD study was the clinical complete response rate of disease to SBRT. The 2-year actuarial local control rate, defined on a "per-lesion" basis as the disease progression within the SBRT field of irradiation, the rate and severity of acute and late toxicities as well as the 2-year actuarial late toxicity-free survival represented the secondary endpoints. Additionally, actuarial progression-free survival and overall survival were investigated. The dose-fractionation regimen was at the discretion of the treating physician. Inclusion criteria were age >18 years, oligometastatic/persistent/recurrent patients with uterine cancer histologic documented, ≤5 synchronous metastases, any site of disease, relative contraindication to further systemic therapy because of serious comorbidities, unavailability of potentially active chemotherapy, previous severe chemotherapy toxicity, salvage surgery or other local therapies not suitable. Only patients with a controlled primary site at the time of SBRT, who had received external beam treatments with rigid or proper immobilization, accurate target localization, large dose per fraction, highly conformal treatment, and daily image guidance to ensure the safe delivery of ultrahigh doses of radiation to small targets, were included into the study.

Procedures

Principal Investigators (G.M. and G.F.) established a specific data set for standardized data collection. Some of the variables required were age, histotype, number and type of comorbidities, past surgeries and medical treatments, and previous in site radiation therapy (ie, retreatment of a volume previously irradiated). Technical SBRT details and data concerning response, acute and late toxicities, outcome measures, and follow-up were also gathered.

The efficacy of treatment was determined by means of radiologic imaging. We used contrast-enhanced computed tomography (CT) or positron emission tomography (PET)-based radiologic imaging to evaluate disease response according to the RECIST (Response Evaluation Criteria in Solid Tumors) criteria (version 1.1).[20] Complete response (CR) was defined as the disappearance of the lesions at CT scan; a reduction greater than 30% was considered partial response; any growing lesion not clearly ascribable to fibrosis was reported as a progression of the disease. The objective response rate was defined as the sum of complete response and partial response, and the clinical benefit consisted of objective response rate and stable disease.

The occurrence of tumor response was converted into a binary outcome (complete response versus any other eventuality). Actuarial local control (LC) was termed on a "per-lesion" basis as the time gap between the date of SBRT and the date of in-site SBRT field relapse/progression of lesions or the date of the last clinical evaluation. Actuarial progression-free survival (PFS) was termed on a "per patient" basis as the time gap between the date of SBRT and the date of out-of-field progression or the date of the last clinical evaluation; overall survival (OS) was termed as the time gap between the date of SBRT and the date of death of disease or the date of the last clinical evaluation. According to center policy, the toxicity evaluation was performed by Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer and Common Terminology Criteria for Adverse Events scales.[21,22]

Analysis of data and statistical methods

All data were collected at the Radiation Therapy Unit of Gemelli Molise Hospital, Università Cattolica del S. Cuore, Campobasso, Italy, and entered into an electronic database. The data processing was performed by D.P., G.M., and G.F. Patient characteristics were reported as medians and ranges for continuous variables and percentages for categorical variables. The cutoff for analyses was considered the median values. The Pearson χ^2 test was used to test the differences between subgroups, choosing a P value $< .05$ for statistical significance definition. Binary logistic regression was used to carry out the univariate and multivariate analysis of factors predicting clinical complete response on "a per-lesion" basis. The result of the logistic regression model was expressed as odds ratios with 95% confidence intervals. Only variables with a $P < .2$ at univariate analysis were selected for the multivariate analysis. To analyze actuarial outcomes was used the Kaplan-Meier method; differences among subgroups were evaluated by log-rank tests and the univariate and multivariate Cox regression analysis. Also in this case, only variables with a $P < .2$ at univariate analysis were selected for the multivariate analysis. Statistical analysis was carried out by SPSS statistical software (IBM Corp, released 2011; IBM SPSS Statistics for Windows, version 20.0. Armonk, NY).

Results

Fourteen radiation oncology Centers from all throughout Italy gave consent to this retrospective study; after evaluation of inclusion/exclusion criteria, data from 157 patients with uterine cancer, carrying out 272 lesions treated by SBRT between March 2006 and February 2022, were retrieved and included in the analysis. After receiving satisfactory responses to relevant queries, the data were deemed suitable for analysis. Table 1 details data relative to the patients' features. The median age of the patients was 69.7 years (range, 36.0-90.5), and the large majority (96.2%) had an Eastern Cooperative Oncology Group performance status of 0 to 1. Comorbidities were reported in 108 patients (69.3%), with hypertension,

Table 1 Patient characteristics

	N. (%)
All	157
Age, y	
Median (range)	69.7 (36.0-90.5)
Eastern Cooperative Oncology Group Performance status	
0	111 (70.7)
1	40 (25.5)
2	6 (3.8)
Comorbidities per patient	
0	42 (26.9)
1	45 (28.8)
2	34 (21.8)
3	16 (10.3)
4	7 (4.6)
≥5	6 (3.8)
n.a.	6 (3.8)
Histotype	
Endometroid	116 (73.9)
Carcinosarcoma	14 (8.9)
Serous	13 (8.3)
Other	14 (8.9)
No. patients undergoing surgery before SBRT	
No	7 (4.5)
Yes	150 (95.5)
No. patients undergoing chemotherapy before SBRT	
No	42 (26.8)
Yes	110 (70.1)
n.a.	5 (3.1)
No. of lines of previous chemotherapies	
Median (range)	1 (1-6)
No. patients undergoing hormonal therapy before SBRT	
No	132 (84.1)
Yes	24 (15.3)
n.a.	1 (0.6)
No. of lines of previous hormonal therapy	
Median (range)	1 (1-2)
No. patients undergoing previous radiation therapy	
No	41 (26.1)
Yes	116 (73.9)
No. patients undergoing previous in site* radiation therapy	
No	91 (78.4)
Yes	25 (21.6)
No. of patients bearing	
1 lesion	97 (61.8)
2 lesions	34 (21.7)
3 lesions	14 (8.9)
4 lesions	1 (0.6)
5 lesions	8 (5.1)
>5 lesions	3 (1.9)

Abbreviations: n.a. = not available; SBRT = stereotactic body radiation therapy.
* Calculated on the number of patients undergoing previous radiation therapy (N = 116).

heart disease, diabetes, and thyroid diseases being the most common. Endometrioid carcinoma (73.9%), carcinosarcoma (8.9%), and serous carcinoma (8.3%) were the most frequent tumor histotypes. Regarding the prior treatment(s) to SBRT, the majority of patients underwent radical surgery (n = 150); previous chemotherapy was administered in 110 patients (median number of lines, 1; range, 1-6), whereas previous hormonal therapy was administered in 24 patients (median number of lines, 1; range, 1-2). One hundred sixteen patients (73.9%) have previously received radiation therapy, with 25 (21.6%) receiving in-site radiation therapy. Ninety-seven patients (61.8%) had just one metastatic lesion, whereas 60 patients (38.2%) had more than one synchronous or metachronous lesion.

SBRT treatment on "per-lesion" basis

The features of the lesions (N = 272) and their treatment are listed in Table 2: lymph node metastases accounted for 50.4% of this series, followed by parenchyma lesions (49.6%); thorax (38.3%), abdomen (27.9%), and pelvis (24.2%) were the most common anatomic districts.

Lesions had a median gross tumor volume of 4.0 cc (range, 0.05-181.10), and a median planning target volume of 13.7 cc (range, 2.0-196.5).

Dose-fractionation schedules were at the discretion of the treating physician, therefore because of the large variability of regimens, the biologically effective dose (BED) was estimated using 10 as the α/β ratio (Supplementary Table E1). Overall, the median total dose was 35 Gy (range, 10-75.2), given in 5 fractions (range, 1-10), and the median $BED_{\alpha/\beta 10}$ was 59.5 Gy (range, 20.0-156.1).

Two hundred and forty-two metastases (89.0%) were treated by SBRT (multiple fractions), and 30 lesions (11.0%)

Table 2 Features of lesions and details of treatment

	No. (%)
	272
Type of lesion(s)	
Lymph node	137 (50.4)
Parenchyma	135 (49.6)
Anatomic district	
Brain	16 (5.9)
Neck	2 (0.8)
Thorax	104 (38.3)
Abdomen	76 (27.9)
Pelvis	66 (24.2)
Bone	8 (2.9)
GTV	
Median, range (cc)	4.0 (0.05-181.10)
PTV	
Median, range (cc)	13.7 (2.0-196.5)
Equipments	
Linear accelerator (LINAC)	223 (82.0)
CyberKnife	44 (16.2)
Tomotherapy	5 (1.8)
Techniques	
VMAT	165 (60.7)
IMRT	93 (34.2)
3D-CRT	14 (5.1)
Type of treatment	
SBRT, stereotactic radiation therapy (more fractions)	242 (89.0)
SRS, stereotactic radiosurgery (single fraction)	30 (11.0)
Total dose, Gy	
Median (range)	35 (10-75.2)
No. of fractions	
Median (range)	5 (1-10)
$BED_{\alpha/\beta 10}$	
Median (range)	59.5 (20.0-156.1)
Referral dose	
Specific isodose	120 (44.1)
Isocenter	88 (32.4)
Target mean	64 (23.5)

Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy; BED = biologic effective dose; GTV = gross tumor volume; IMRT = intensity modulated radiation therapy; PTV = planning target volume; SBRT = stereotactic body radiation therapy; SRS = single fraction radiation therapy; VMAT = volumetric arc radiation therapy.

were managed by single fraction radiation therapy (SRS). The multiple fractions radiation therapy median total dose was 35 Gy (range, 25-61.5) with a median $BED_{\alpha/\beta 10}$ of 59.5 Gy (range, 37.5-156.1). The most frequent SBRT schedules were 30 Gy (16.1%), 35 Gy (15.7%), or 40 Gy (12.8%) in 5 fractions. The SRS median total dose was 24 Gy (range, 10-32) with a median $BED_{\alpha/\beta 10}$ of 81.6 Gy (range, 20.0-134.4). The most frequently used schedule for SRS was 24 Gy in 1 fraction (36.7%). More details are reported in Supplementary Table E1. The abscopal effect was not registered.

Efficacy

The median time for evaluating the best response was 4 months (range, 1-15.9 months); complete response (CR), partial response (PR), stable disease (SD), and progressive disease were observed in 174 (64.0%), 54 (19.9%), 29 (10.6%), and 15 lesions (5.5%), respectively. The objective response rate (CR + PR) was 83.9%, and the clinical benefit (CR + PR + SD) was 94.5%. We performed a statistical comparison across the groups to test the idea that lymph node and parenchyma lesions could differ from one another and be treated differently. A statistically significant difference in terms of volumes of lesions, total dose, BED, histotype, and previous in-site radiation therapy were registered (Table 3). Indeed, parenchyma lesions, despite being numerically comparable, were significantly smaller in volume, were treated with higher doses, were more frequently from non endometrioid histotypes, and had been irradiated less previously than the lymph node lesions. In the univariate analysis of variables predicting complete response per-lesion, endometrioid histology, lymph nodes, small volume lesions (≤13.7 cc), and target receiving a BED_{10} >59.5 Gy were significantly associated with a higher probability of achieving CR. Type of lesion (lymph node), volume (≤13.7 cc), and total dose (BED_{10} >59.5 Gy) were confirmed at the multivariate analysis (Table 4). Finally, because of the prevalence of the endometrioid histology in our series, we performed a further subgroup analysis focusing on this group of lesions: at the univariate analysis of variables predicting complete response per-lesion, only lymph nodes (odds ratio [OR], 0.514; 95% confidence interval [CI], 0.273-0.966; P = .039) and small volume lesions (≤13.7 cc; OR, 0.368; 95% CI, 0.191-0.755; P = .003) were significantly associated with a higher probability of achieving CR and both the variables were confirmed at the multivariate analysis (OR for lymph nodes, 0.468; 95% CI, .239-0.914; P = .026; OR for small volume lesions, 0.328; 95% CI, 0.167-0.645; P = .001).

Clinical outcomes

Median follow-up was 14.5 months (range, 3-143) as of May 2022; in terms of local control, 60 of 272 irradiated lesions (22%) have progressed over time and the 2-year actuarial

Table 3 Distribution of SBRT features according to lymph node and parenchyma lesions

	Lymph node lesions median (range)	Parenchymal lesions median (range)	*P* value*
All lesions	137	135	
GTV, cm^3	4.9 (0.05-50.3)	2.3 (0.07-181)	.001
PTV, cm^3	17.0 (0.2-144.6)	10.9 (0.4-196.5)	.004
Total dose, Gy	35.0 (10.0-50.0)	40.0 (10.0-72.5)	<.001
No. fractions	5 (1-5)	5 (1-10)	.503
Dose/fraction, Gy	5.0 (5-24)	8.0 (5.0-32)	.203
$BED_{\alpha/\beta 10}$, Gy	59.5 (20-100.8)	72.0 (20.0-156.1)	<.001
Histotype			
Endometrioid	105 (76.6)	77 (57.0)	<.001†
Other	32 (23.4)	58 (43.0)	
Previous in site radiation therapy			
No	109 (79.6)	121 (89.6)	.022†
Yes	28 (20.4)	14 (10.4)	

Abbreviations: BED = biologic effective dose; GTV = gross tumor volume; PTV = planning target volume; SBRT = stereotactic body radiation therapy.
* Calculated by the Mann-Whitney test.
† Calculated by the χ^2 test.

local control rate was 75% (Fig. 1a). The 2-year actuarial local control rate was comparable between nodal and parenchyma lesions (74.0 vs 76.8, log-rank $P = .736$; data not shown).

We registered progression of disease in 95 patients (60.5%), and death of disease in 52 patients (33.1%). The 2-year actuarial progression-free survival rate on a "per-patient" basis, was 35.4%, and, the 2-year actuarial overall survival rate was 73.3%, as shown in Fig. 1c and e.

Figure 1b summarizes the effect of achievement of complete response on the local control; patients achieving complete response on a "per-lesion basis" experienced a 2-year actuarial local control of 92.4 versus 33.5% in lesions not achieving complete response ($P < .001$).

We looked for disease characteristics that might be linked to a higher likelihood of achieving local control "per-lesion." Absence of prior radiation therapy and a disease volume ≤13.7 cc were significantly associated with better LC in multivariate analysis (Table 5). As far as progression-free survival is concerned, the 2-year actuarial rate in patients with CR was 45.4%, while patients undergoing partial response, or stable or progressive disease had a 2-year rate of 17.6% ($P < .001$; Fig. 1d).

Finally, patients who had a complete response had a 2-year overall survival rate of 82.7%, compared with 56.5% for those who did not reach a complete response ($P < .001$; Fig. 1f).

In terms of endometrioid lesions, the 2-year LC rate for endometrioid (75.2%) and non endometrioid (76.7%) lesions was comparable (P: 0.383), and patients with endometrioid lesions achieving complete response experienced a 2-year actuarial local control of 91.8% versus 25.0% in lesions not achieving complete response ($P = .001$; Supplementary Fig. 1a and b). For patients with endometrioid lesions, a disease volume ≤13.7 cc was significantly associated with better LC in the univariate analysis (HR, 0.210; 95% CI, 0.093-0.478; $P < .001$) and confirmed in the multivariate one (HR, 0.219; 95% CI, 0.096-0.503; $P < .001$), and age ≤69.7 years was confirmed only at the multivariate analysis (HR, 2.141; 95% CI, 1.090-4.206; P: 0.027). In terms of progression-free survival, the 2-year actuarial rate in patients with endometrioid lesions was 41.1%, and patients with other histologies had a 2-year rate of 18.8% ($P = .001$). Moreover, patients with endometrioid lesions achieving complete response experienced a 2-year actuarial progression-free survival of 53.9% versus 23.7% in lesions not achieving complete response ($P <.001$; Supplementary Fig. 1c and d). Finally, patients with endometrioid lesions had a 2-year overall survival rate of 76.2%, comparable to the 65.2% for those with other histologies ($P = .052$), and patients with endometrioid lesions achieving complete response experienced a 2-year actuarial overall survival of 85.2% versus 58.0% in lesions not achieving complete response ($P = .001$; Supplementary Fig. 1e and f).

Safety

Twenty-eight patients (17.8%) had acute toxicity, with a total of 58 side effects, 47 of which were grade 1 and 7 grade 2, 2 grade 3 (flare up pain), one grade 4 (flare up pain) and one grade 5 (toxic death due to gastric perforation). Pain flare-up was the most prevalent symptom (in 17 cases), followed by lower gastrointestinal toxicity (9 cases), and asthenia (6 cases). As far as late toxicity is concerned, only 18 patients (11.4%) experienced late toxicity, with 5 pulmonary toxicity (4 grade 1 and 1 grade 2), 4 lower gastrointestinal (1 grade 2 and 3 grade 3), 2 grade 3 upper gastrointestinal, 3 grade 1 skin, 2 neurotoxicity (1 grade 1 and 1 grade 3), 1

Table 4 Univariate and multivariate logistic regression analysis of variables predicting complete response to SBRT on "per-lesion" basis

			Univariate			Multivariate		
Variable	All lesions	CR No.	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Age, y								
>69.9	124	82	1					
≤69.9	148	92	1.188	0.722-1.957	.497			
Previous RT								
Yes	201	126	1					
No	70	48	1.299	0.727-2.319	.397			
Previous RT in field								
Yes	42	29	1					
No	230	145	0.765	0.377-1.551	.457			
Histology								
Other	90	49	1			1		
Endometrioid	181	125	0.535	0.318-0.901	.019	0.625	0.355-1.101	.104
Type of lesion								
Parenchyma	135	75	1			1		
Lymph node	137	99	0.480	0.290-0.795	.004	0.352	0.195-0.634	<.001
PTV								
>13.7 cc	134	73	1			1		
≤13.7 cc	134	98	0.440	0.264-0.733	.002	0.418	0.242-0.723	.002
BED								
≤59.5 Gy	146	84	1			1		
>59.5 Gy	126	90	0.542	0.326-0.900	.018	0.411	0.231-0.728	.002

Abbreviations: BED = biologic effective dose; CI = confidence interval; CR = complete response; PTV = planning target volume; RT = radiation therapy; SBRT = stereotactic body radiation therapy

grade 1 pain and 1 grade 4 hematological toxicity. Toxicity profile of the study is detailed in Table 6.

Discussion

Summary of main results

To our knowledge, this is the largest multicenter series on the efficacy and safety of SBRT in oligo-MPR uterine cancer, comprising data of 272 lesions from 157 patients. As per primary endpoint of MITO-RT2/RAD study, we found a 64% CR rate in irradiated lesions, the highest evidence among the few SBRT cohorts containing uterine cancer and providing clinical response data, with reported CR rates ranging from 17% to 60%.[14-16] Lymph node disease, low tumor volume and total dose were found to be independent predictors of a high likelihood of CR, likewise the findings of a previous study on SBRT in oligometastatic ovarian cancer.[18]

The importance of obtaining a complete disappearance of the irradiated lesion as a key factor in outcomes is one of this trial's most significant findings, which justifies the necessity of making every attempt to obtain SBRT complete response. The achievement of CR acted as a major driver for 2-year local control, which reached 92.4% in patients with CR versus 33.5% in lesions not achieving CR ($P < .001$). The excellent LC in complete responder patients is expected to postpone progression to a polymetastatic condition and prolong chemotherapy free interval, as reported by a recent study by Nicosia et al[23] in the SBRT liver oligometastases setting and by Lazzari et al[24] and Shen et al[25] for SBRT-treated oligometastatic ovarian cancer (median time without systemic therapy: 7.4 months [24 and 14 months],[25] respectively). On the contrary, the analysis of clinical and dosimetric characteristics of not complete responder patients might guide the clinicians to tailor more aggressive therapy and treatment intensification to improve the prognosis.

Indeed, the rate of progression outside of the target lesions remains high and this series is biased by the lack of information on systemic treatments after stereotactic

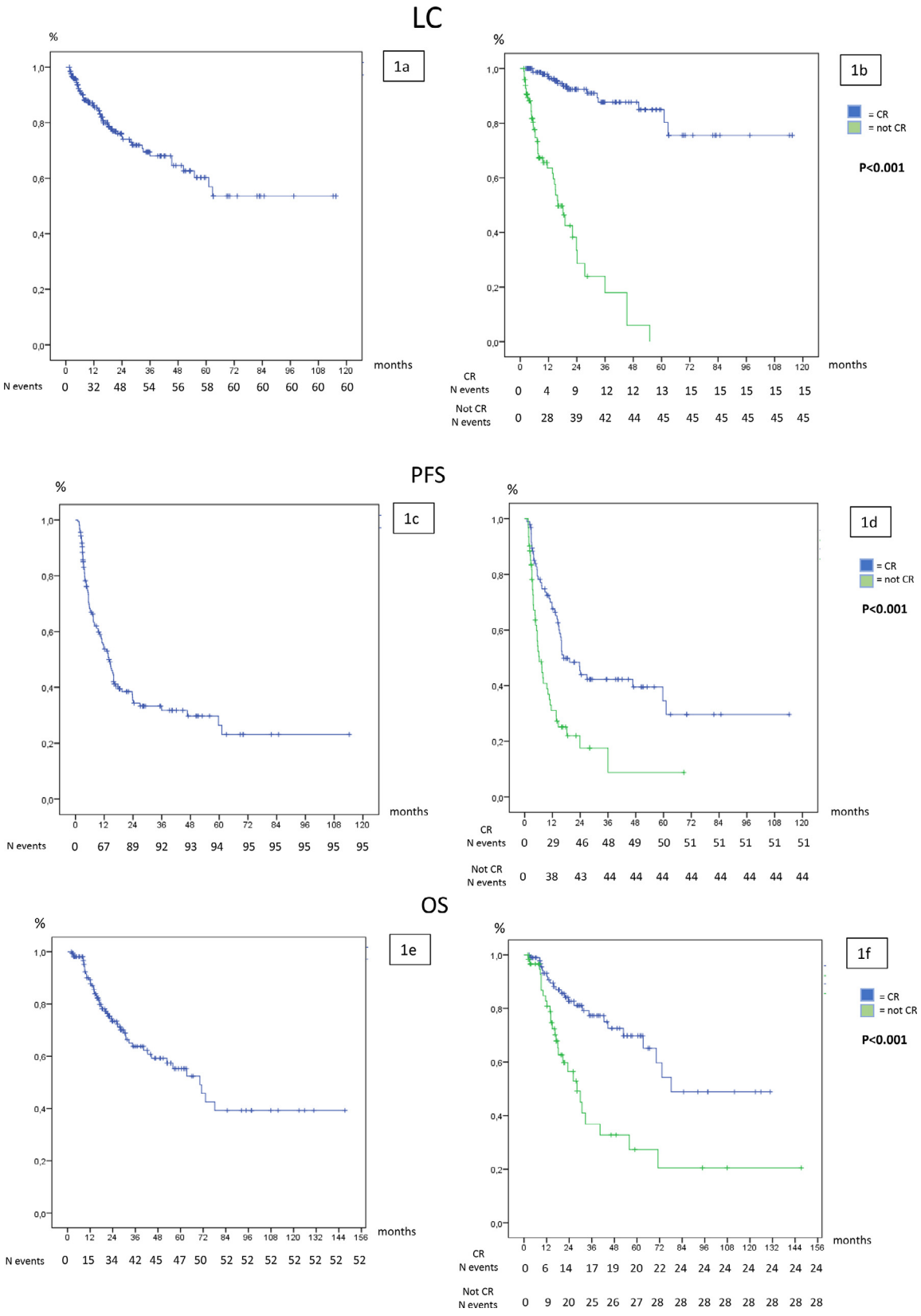

Fig. 1. Actuarial local control in the overall lesion series (a) and according to best response (complete versus other response). (b) Actuarial progression-free survival (PFS; progression outside stereotactic body radiation therapy field-free survival) in the overall patient series (c) and according to best response (d). Actuarial overall survival (OS) in the overall patient series (e) and according to best response (f). Blue lines = complete response (CR) to SBRT; green lines = other response (not CR).

Table 5 Univariate and multivariate Cox regression analysis of variables predicting LC on "per-lesion" basis

		Univariate			Multivariate		
Variable	**N.**	**Hazard ratio**	**95% CI**	***P* value**	**Hazard ratio**	**95% CI**	***P* value**
Age, y							
>69.9	124	1					
≤69.0	148	1.065	.637-1.683	.809			
Previous RT							
Yes	201	1			1		
No	70	0.425	.209-0.867	.019	0.474	0.228-0.987	.046
Previous RT in field							
Yes	42	1			1		
No	230	0.645	.348-1.194	.162	1.337	0.669-2.668	.411
Histology							
Other	89	1					
Endometrioid	182	0.731	.428-1.248	.251			
Type of lesion							
Parenchyma	135	1					
Lymph node	137	1.092	.655-1.819	.736			
PTV							
>13.7 cc	134	1			1		
≤13.7 cc	134	0.248	.132-0.469	<.001	3.812	1.983-7.327	<.001
BED							
≤59.5 Gy	146	1			1		
>59.5 Gy	126	0.689	.410-1.156	.158	0.762	0.436-1.332	.340

Abbreviations: CI = confidence interval; BED = biologic effective dose; LC = local control; PTV = planning target volume; RT = radiation therapy.

radiation therapy. Nevertheless, patients with CR performed much better than the other patients in terms of 2-year PFS and OS; to the best of our knowledge, this finding is published for the first time in a large primary site uterine cancer series, after previously being reported in the prostate, colorectal, breast, and lung settings.[6-11]

A low-grade toxicity profile was also observed, which contributed to the study's extremely positive cost-effectiveness ratio, especially given the median age and the multiple prior treatments; thus, this data add to the body of evidence supporting the method's safety in unfavorable settings. No abscopal effects were reported in our series, but the majority of patients had previously received radiation to the lymph node stations, thereby a potential impairment of the immune response, furthermore the average total doses were modest.

Results in the context of published literature

According to a recent review of the literature on the role of SBRT for oligometastatic uterine cancer, only a small series of 27 patients have focused exclusively on uterine cancer[17] and there are little published evidence or consistent recommendations for dose/fractionation schedules. Patients in our series got a median SBRT dose of 59.5 Gy BED10 in 5 fractions, in line with the range of 43.2 to 72 Gy reported in mixed series,[14-16] but it must be acknowledged that a plethora of doses and fractionations were registered (Supplementary Table E1). Despite this, and in agreement with Mesko et al,[15] the median dose in our series correlated with the outcomes. Furthermore, several authors reported adverse outcomes linked to larger target sizes.[14,15,17-19,26,27] In our data set, we found that bearing a parenchyma lesion was detrimental in addition to verifying that a lesion volume greater than 13.7 cc was linked to a worse local control. Indeed, despite being numerically comparable with lymph node lesions, the parenchyma ones were significantly smaller in volume, were treated with higher doses, were more frequently from non endometrioid histotypes, and had been irradiated less previously than the lymph node lesions.

Whether all these factors can explain the observation that SBRT is more effective against lymph node disease than parenchyma lesions in this series is not completely clear.[18,19,24,28] A thorough assessment of lymph node lesion responsiveness in comparison to parenchyma disease and in accordance with the intrinsic biomolecular characteristics is

Table 6 Acute and late toxicity

Acute toxicities	n (%)	Late toxicities	n (%)
All	58	All	18
Asthenia	6	Asthenia	-
G1	6		-
Pain flare-up	17	Pain	1
G1	12		1
G2	2		-
G3	2		-
G4	1		-
Upper GI disorders	9	Upper GI disorders	2
G1	7		-
G2	1		-
G3	-		2
G5	1		-
Lower GI disorders	9	Lower GI disorders	4
G1	7		-
G2	2		1
G3	-		3
GU disorders	3	GU disorders	-
G1	3		-
Pulmonary toxicity	5	Pulmonary toxicity	5
G1	4		4
G2	1		1
Skin toxicity	3	Skin toxicity	3
G1	3		3
Neurotoxicity	3	Neurotoxicity	2
G1	3		1
G3	-		1
Hematologic disorders	1	Hematologic disorders	1
G2	1		-
G4	-		1
Other	2	Other	-
G1	2		-

Abbreviations: G = grade of toxicity; GI = gastrointestinal; GU = genitourinary.

required and expected in the context of tailored medicine, considering the significant role that molecular characterization plays in endometrial cancer today. In terms of local control rate, SBRT provided a 2-year actuarial rate of 75% in our series, which is comparable to Reddy's one (75.9%)[17] and other mixed series reporting 82% to 100% rates.[14-16]

Despite the encouraging local control, the rate of progression-free survival remains poor (35.4%), consistent with the few mixed series.[14-16] According to the evidence suggesting the potential role of SBRT in enhancing tumor immunogenicity and promoting systemic activity, a therapeutic strategy combining SBRT and immunotherapy should be pursued to improve results[29,30] (see also www.clinicaltrials.gov).

Concerning toxicity, the few specific reviews available on the topic[5,17,31,32] concur that the toxicity is tolerable, highlighting wide variability in the more severe toxicities reporting, which are compatible with the sites, dosages, and volumes of the treated lesions. In our series we registered around 2% severe acute toxicity, including 1 toxic death due to gastric perforation and around 4% severe late toxicity.

Strengths and weaknesses

We have to acknowledge that the retrospective physician-reported toxicity assessment could have been biased, minimizing the toxicity. SBRT, on the other hand, is widely acknowledged to be characterized by lower normal tissue toxicity.[6-11,18,19]

Moreover, the range of SBRT regimens in terms of total dose or BED_{10} provided evidence that the dose issue was quite variable in our study. In fact, in real-world situations, the dose must be adjusted based on several factors, including the location and extent of the disease, the proximity of healthy tissues, the patient's morbidities, the radiation oncologist's skill, and the technical capabilities of the facility. To align the techniques and provide more consistent and reliable results, prospective trials for a better characterization of SBRT regimens should be advantageous. The best response evaluation time span was broad, spanning from 1 to 15.9 months; indeed, the patients may have gotten further treatment during this time, which could have an effect on the results. However, the retrospective and multicenter nature of the study, as well as the unselected sample, must be taken into consideration while analyzing these findings. Finally, one could argue that the evaluation of response is critical and different imaging modalities having different diagnostic sensitivity could influence the results, biasing the results. Indeed, in retrospective series on SBRT in primary uterine cancer, the authors frequently used CT and PET/CT in response assessment alternately.[14-17,33] In the present study, we used PET-CT based radiologic imaging (as per the 2021 report by Kataria e al[14]) and only RECIST criteria were used to assess response. This adjustment ensures that the data are more reproducible.

Implications for practice and future research

The significance of SBRT must be recognized considering our findings, even in a group that was unfairly chosen, which prompts us to think about giving SBRT a more consistent place in the clinical history of disease. Identifying suitable patients is a critical first step in developing optimal SBRT programs for uterine cancer. The location and the size of the tumor, the patient's medical history and comorbidities, and the patient's overall health status are critical

information in determining whether a patient is a suitable candidate for SBRT and whether the potential benefits of SBRT outweigh the potential risks. Once fit patients are identified, determining the optimal individual radiation dose can further optimize the treatment approach.

Moreover, before the development of a disseminated disease, the local control of isolated recurrences may result in better patient outcomes and delay further systemic/surgical therapies.[6,11,23-25] Future studies should aim to demonstrate an increase in time to resumption of a subsequent line of chemotherapy/biologic therapy and potentially overall survival in gynecologic series. Additionally, SBRT's possible function in boosting tumor immunogenicity and fostering systemic activity may support the efficacy of immunotherapy.

Conclusions

Despite the heterogeneity of the patient population, treatment modalities, and follow-up procedures, SBRT treatment provided excellent rates of objective response rate with minimal toxicity and showed the potential to achieve long-term survival outcomes. Determining the optimal strategies for patient selection, dose, and treatment delivery are areas of ongoing study.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics. *CA Cancer J Clin* 2019;69:7-34 2019.
2. Bokhman JV. Two pathogenetic types of endometrial carcinoma. *Gynecol Oncol* 1983;15:10-17.
3. Restaino S, Dinoi G, La Fera E, et al. Recurrent endometrial cancer: Which is the best treatment? Systematic review of the literature. *Cancers (Basel)* 2022;14:4176.
4. Lievens Y, Guckenberger M, Gomez D, et al. Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document. *Radiother Oncol* 2020;148:157-166.
5. Shenker R, Stephens SJ, Davidson B, Chino J. Role of stereotactic body radiotherapy in gynecologic radiation oncology. *Int J Gynecol Cancer* 2022;32:372-379.
6. Gomez DR, Blumenschein Jr GR, 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.
7. 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.
8. Phillips R, Shi WY, Deek M, et al. Outcomes of observation versus stereotactic ablative radiation for oligometastatic prostate cancer: The ORIOLE phase 2 randomized clinical trial. *JAMA Oncol* 2020;6:650-659.
9. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: Long-term results of the SABR-COMET phase II randomized trial. *J Clin Oncol* 2020;38:2830-2838.
10. 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.
11. Ost P, Reynders D, Decaestecker K, et al. Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence (STOMP): Five-year results of a randomized phase II trial. *J Clin Oncol* 2020;38:10.
12. Rodríguez-Ruiz ME, Vanpouille-Box C, Melero I, et al. Immunological mechanisms responsible for radiation-induced abscopal effect. *Trends Immunol* 2018;39:644-655.
13. Formenti SC, Rudqvist NP, Golden E, et al. Radiotherapy induces responses of lung cancer to CTLA-4 blockade. *Nat Med* 2018;24:1845-1851.
14. Kataria T, Naga P, Banerjee S, et al. CyberKnife stereotactic ablative radiotherapy for recurrent or oligometastatic gynecological cancers. *South Asian J Cancer* 2021;10:107-111.
15. Mesko S, Sandler K, Cohen J, et al. Clinical outcomes for stereotactic ablative radiotherapy in oligometastatic and oligoprogressive gynecological malignancies. *Int J Gynecol Cancer* 2017;27:403-408.
16. Kunos CA, Brindle J, Waggoner S, et al. Phase II clinical trial of robotic stereotactic body radiosurgery for metastatic gynecologic malignancies. *Front Oncol* 2012;2:181.
17. Reddy AV, Mills MN, Reshko LB, Martin Richardson K, Kersh CR. Stereotactic body radiation therapy in oligometastatic uterine cancer: Clinical outcomes and toxicity. *Cancer Invest* 2020;38:522-530.
18. Macchia G, Lazzari R, Colombo N, et al. A large, multicenter, retrospective study on efficacy and safety of stereotactic body radiotherapy (SBRT) in oligometastatic ovarian cancer (MITO RT1 Study): A collaboration of MITO, AIRO GYN, and MaNGO groups. *Oncologist* 2020;25:e311-e320.
19. Macchia G, Nardangeli A, Laliscia C, et al. Stereotactic body radiotherapy in oligometastatic cervical cancer (MITO-RT2/RAD study): A collaboration of MITO, AIRO GYN, and MaNGO groups. *Int J Gynecol Cancer* 2022;32:732-739.
20. 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.
21. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995;31:1341-1346.
22. National Cancer Institute Common Terminology Criteria for Adverse Events v.4.03 (CTCAE v.4.03).
23. Nicosia L, Cuccia F, Mazzola R, et al. Stereotactic body radiotherapy (SBRT) can delay polymetastatic conversion in patients affected by liver oligometastases. *J Cancer Res Clin Oncol* 2020;146:2351-2358.
24. Lazzari R, Ronchi S, Gandini S, et al. Stereotactic body radiation therapy for oligometastatic ovarian cancer: A step toward a drug holiday. *Int J Radiat Oncol Biol Phys* 2018;101:650-660.
25. Shen J, Tao Y, He L, Guan H, Zhen H, Liu Z, Zhang F. Clinical application of radiotherapy in patients with oligometastatic ovarian cancer: A sharp tool to prolong the interval of systemic treatment. *Discov Oncol* 2022;13:82.
26. Park HJ, Chang AR, Seo Y, et al. Stereotactic body radiotherapy for recurrent or oligometastatic uterine cervix cancer: A cooperative study of the Korean Radiation Oncology Group (KROG 14-11). *Anticancer Res* 2015;35:5103-5110.
27. Choi CW, Cho CK, Yoo SY, et al. Image-guided stereotactic body radiation therapy in patients with isolated para-aortic lymph node metastases from uterine cervical and corpus cancer. *Int J Radiat Oncol Biol Phys* 2009;74:147-153.
28. Ponti E, Lancia A, Ost P, et al. Exploring all avenues for radiotherapy in oligorecurrent prostate cancer disease limited to lymph nodes: A systematic review of the role of stereotactic body radiotherapy. *Eur Urol Focus* 2017;3:538-544.
29. Lee L, Matulonis U. Immunotherapy and radiation combinatorial trials in gynecologic cancer: A potential synergy? *Gynecol Oncol* 2019;154:236-245.

30. Reynders K, Illidge T, Siva S, et al. The abscopal effect of local radiotherapy: Using immunotherapy to make a rare event clinically relevant. *Cancer Treat Rev* 2015;41:503-510.
31. Mendez LC, Leung E, Cheung P, et al. The role of stereotactic ablative body radiotherapy in gynaecological cancers: A systematic review. *Clin Oncol* 2017;29:378-384.
32. Yegya-Raman N, Cao CD, Hathout L, et al. Stereotactic body radiation therapy for oligometastatic gynecologic malignancies: A systematic review. *Gynecol Oncol* 2020;159:573-580.
33. Laliscia C, Fabrini MG, Delishaj D, et al. Clinical outcomes of stereotactic body radiotherapy in oligometastatic gynecological cancer. *Int J Gynecol Cancer* 2017;27:396-402.