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Radiation Oncology

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

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Stereotactic body radiotherapy • Stereotactic radiosurgery • Ovarian cancer • Oligometastasis • Oligorecurrences • Personalized medicine

Abstract

Background. Recent studies have reported improvement of outcomes (progression-free survival, overall survival, and prolongation of androgen deprivation treatment-free survival) with stereotactic body radiotherapy (SBRT) in non-small cell lung cancer and prostate cancer. The aim of this retrospective, multicenter study (MITO RT-01) was to define activity and safety of SBRT in a very large, real-world data set of patients with metastatic, persistent, and recurrent ovarian cancer (MPR-OC).

Materials and Methods. The endpoints of the study were the rate of complete response (CR) to SBRT and the 24-month actuarial local control (LC) rate on "per-lesion" basis. The secondary endpoints were acute and late toxicities and the 24-month actuarial late toxicity-free survival. Objective response rate (ORR) included CR and partial response (PR). Clinical benefit (CB) included ORR and stable disease (SD). Toxicity was evaluated by the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer

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(EORTC) and Common Terminology Criteria for Adverse Events (CTCAE) scales, according to center policy. Logistic and Cox regression were used for the uni- and multivariate analysis of factors predicting clinical CR and actuarial outcomes.

Results. CR, PR, and SD were observed in 291 (65.2%), 106 (23.8%), and 33 (7.4%) lesions, giving a rate of CB of 96.4%. Patient aged ≤60 years, planning target volume (PTV) ≤18 cm^3, lymph node disease, and biologically effective dose $\alpha/\beta 10 > 70$ Gy were associated with higher chance of CR in the multivariate analysis. With a median follow-up of 22 months (range, 3–120), the 24-month actuarial LC rate was 81.9%. Achievement of CR and total dose >25 Gy were associated with better LC rate in the multivariate analysis. Mild toxicity was experienced in 54 (20.7%) patients; of 63 side effects, 48 were grade 1, and 15 were grade 2. The 24-month late toxicity-free survival rate was 95.1%.

Conclusions. This study confirms the activity and safety of SBRT in patients with MPR-OC and identifies clinical and treatment parameters able to predict CR and LC rate.

The Oncologist 2019;24:1–10

Implications for Practice: This study aimed to define activity and safety of stereotactic body radiotherapy (SBRT) in a very large, real life data set of patients with metastatic, persistent, recurrent ovarian cancer (MPR-OC). Patient age <60 years, PTV <18 cm^3, lymph node disease, and biologically effective dose $\alpha/\beta 10$ >70 Gy were associated with higher chance of complete response (CR). Achievement of CR and total dose >25 Gy were associated with better local control (LC) rate. Mild toxicity was experienced in 20.7% of patients. In conclusion, this study confirms the activity and safety of SBRT in MPR-OC patients and identifies clinical and treatment parameters able to predict CR and LC rate.

Introduction

Despite the advances in cytoreductive efforts and the incorporation of bevacizumab to front-line chemotherapy (CT) in advanced ovarian cancer (OC), recurrence is a common event, with >70% of women experiencing relapse within 2 years from diagnosis [1]. The traditional management of patients with recurrent ovarian cancer is represented by systemic CT chosen on the basis of platinum sensitivity [2], even though additional parameters have been acknowledged to contribute to the decision-making process (e.g., histotype, status of BRCA genes or homologous recombination deficiency, pattern of relapse). Moreover, the introduction of Poly(ADP-Ribose)-Polymerase inhibitors in second-line and, very recently, in first-line treatment for patients with BRCA mutated OC would modify the management of disease relapse [3–5].

In this rapidly changing scenario, the role of radiotherapy (RT), considered up to some years ago as relegated to the palliative setting, has been revalued. Indeed, we have seen over time a gradual but progressive shift toward the concept of RT as an active and definitive treatment that can be integrated into a multidisciplinary strategy including surgery, conventional CT, and the novel options derived from target-based medicine [6–8].

In the context of high conformal and modulated techniques characterized by increased dose distribution conformity, reduced normal tissue toxicity, and potential dose escalation, stereotactic body radiotherapy (SBRT), also known as stereotactic ablative radiotherapy (SABR), represents the cutting edge of modern RT [9–14]. SBRT delivers high radiation doses to small volumes in few fractions (usually 3–5 fractions) and can be employed for curative-intent treatment strategies in low-burden primary or metastatic cancer (oligometastatic state) [15]. SBRT is one of the options of so-called metastases-directed therapy (MDT) used in numerous solid tumors; it provides a high local control (LC) and is usually well tolerated in the majority of patients, even though the randomized phase II SABR-COMET trial reported 4.5% deaths due to toxicity in spite of strict dose constraints and a requirement for peer review of RT treatment plans [15]. In the re-irradiation setting, toxicity risks seem to be acceptable, although appreciable risks of severe (19%–28%), and potentially fatal (1%–10%), toxicity have been reported, thus highlighting a careful assessment of the toxicity-benefit ratio [16, 17].

In addition, SBRT could be integrated within the conventional CT regimens, even though the documentation of grade ≥3 toxicity rate (around 9%) and one toxic death (3%) suggests a cautious analysis of risk factors including a dose-volume histogram analysis [18]. Moreover, SBRT has been demonstrated a useful strategy for a potential delay of further systemic therapy, frequently less effective, especially in the oligoprogression situation, as reported in other settings such as lung and prostate cancer [19, 20].

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 [7, 21].

On the basis of this background and the increased confidence with this technique, SBRT has been adopted more and more frequently [10–12]; in fact, very recently, three prospective randomized studies have reported improvement of several outcomes (progression-free survival, overall survival, and prolongation of androgen deprivation treatment-free survival) with SBRT in non-small cell lung cancer and prostate [22–24].

In addition, SBRT has been attempted even in unexpected settings, such as OC, which has been considered for years as not susceptible to benefit of a local treatment because of common documentation of diffuse abdominal disease [25–28]. There are only a few studies focusing on the role of SBRT in patients with metastatic, persistent, recurrent (MPR)-OC [26–28]; in addition, the relatively small size of some series and adoption of several SBRT schedules did not allow definition of the optimal total dose, dose per fraction, and referral dose point, as for other solid tumors [29–31].

Indeed, the identification of clinical and/or treatment variables able to accurately predict the chance of complete response to SBRT and the achievement of a long-term LC is

Table 1. Patient characteristics

Characteristics	*n* (%)
All	261
Median age (range), yr	60 (28–85)
Eastern Cooperative Oncology Group performance status	
0	190 (72.7)
1	29 (11.1)
2	38 (14.5)
3	4 (1.5)
Comorbidities per patient	
None	154 (59.0)
1	78 (29.9)
2	30 (11.5)
3	6 (2.3)
4	2 (0.8)
5	1 (0.4)
Comorbidities[a]	
Hypertension	54 (31.9)
Diabetes mellitus	24 (14.2)
Thyroid disease	20 (11.8)
Autoimmune diseases[b]	20 (11.8)
Any previous malignancies	17 (10.0)
Liver disease	10 (5.9)
Heart disease	6 (3.5)
Peripheral vascular disease	5 (2.9)
Osteopathy	4 (2.4)
Chronic pulmonary disease	3 (1.8)
Lymphoproliferative disease	2 (1.2)
Cerebrovascular disease	2 (1.2)
Dyslipidemia	1 (0.6)
Moderate or severe renal disease	1 (0.6)
Histotype	
High grade serous cell	186 (71.3)
Endometrioid	36 (13.8)
Clear cell	11 (4.2)
Undifferentiated	6 (2.3)
Mixed mullerian; carcinosarcoma	6 (2.3)
Other	16 (6.1)
Patients undergoing surgery before SBRT[c]	
No	3 (1.2)
Yes	253 (98.8)
n.a.	5
Previous surgery, median (range)	1 (0–7)
Patients undergoing chemotherapy before SBRT[c]	
No	0
Yes	256 (100)
n.a.	5
Median no. of lines of previous chemotherapy (range)	2 (1–11)
Patients undergoing previous in site radiotherapy[c]	
No	247 (96.5)
Yes	9 (3.4)
n.a.	5

[a]Calculated on the number of comorbidities (*n* = 169).
[b]Pemphigus, Crohn's disease, secondary sarcoidosis, rheumatoid arthritis, ophthalmopathy, connective tissue disease, polyneuropathy.
[c]Calculated on cases with available data.
Abbreviations: n.a., not applicable; SBRT, stereotactic body radiotherapy.

urgently needed to optimize the efficacy-toxicity ratio and provide indications for building specific guidelines.

The aim of this retrospective, multicenter study was to define activity and safety of SBRT in very large, real-world data set of patients with MPR-OC. Clinical and/or SBRT parameters have been analyzed to identify potential predictors of clinical outcome.

Subjects, Materials, and Methods

Study Design and Endpoints

This is a multicenter, retrospective study (MITO RT-01) aimed at assessing the efficacy and safety of patients with SBRT in MPR-OC treated in Italian Radiotherapy Institutions. The study was initiated and carried out within the Multicenter Italian Trials in Ovarian cancer (MITO) group, in collaboration with the Gynecological group of Italian Association of Radiation Oncology (AIRO Gyn) and the Mario Negri Gynecologic Oncology Group (MAnGO)

Patients already signed the informed consent for treatment and use of their clinical data for research or educational purposes. The coprimary endpoints of the study were the rate of clinical complete response of disease to SBRT and as the 24-month actuarial LC (progression of disease inside SBRT field) rate on "per-lesion" basis. The secondary endpoints were rate and severity of acute and late toxicities as well as the 24-month actuarial late toxicity-free survival.

Inclusion criteria were age >18 years, oligo-recurrent, persistent, progressive patients with histological documentation of OC at primary diagnosis, up to five synchronous lesions, any site of disease, salvage surgery or other local therapies not feasible, relative contraindication to further systemic therapy because of serious comorbidities, previous severe toxicity, unavailability of potentially active CT, and patient refusal.

Patients with an uncertain diagnosis of ovarian carcinoma or with more than five synchronous lesions were excluded.

Oligo-recurrent, progressive patients were defined as patients with five or less new or enlarging metastases in an otherwise well-controlled disease status. Oligo-persistent disease was defined as five or less persistent lesions after systemic therapy.

Procedures

A specific data set for standardized data collection was developed by the Principal Investigators (G.M. and G.F.). Participating

centers were required to fill data sets including age, number and type of comorbidities, histotype, number of previous surgeries, previous medical treatments, and previous in site radiotherapy. Technical and dosimetric details of SBRT and data about response of disease, acute and late toxicities, follow-up, and outcome measures were also collected. The data of some patients included in the previous study of Lazzari et al. [28] were updated and incorporated to the current series.

Best radiologic response to SBRT was evaluated by computed tomography scan or positron emission tomography scan and classified according to the RECIST (version 1.1) or PERCIST criteria.

Objective response rate (ORR) included complete response (CR) and partial response (PR). Clinical benefit (CB) included ORR and stable disease (SD).

Actuarial LC was defined as the time interval between the date of SBRT and the date of inside SBRT field relapse and/or progression of disease or the last follow-up visit.

Actuarial progression-free survival (PFS) was defined on "per-patient" basis as the time interval between the date of SBRT and the date of out of field progression or the last follow-up visit; OS was defined as the time interval between the date of SBRT and the date of death of disease or the last follow-up visit.

Toxicity was evaluated by RTOG/EORTC and CTCAE scales, according to center policy.

Analysis of Data and Statistical Methods

Data were retrieved from the historical database of Radiation Oncologists who joined the study; data were centrally collected at the Radiotherapy Unit of Fondazione "Giovanni Paolo II," Università Cattolica del S. Cuore, Campobasso, Italy, and entered into an electronic database. The data processing was carried out by G.M. and G.F., and advanced statistical modeling was carried out by G.C.

Patient characteristics were represented as frequencies and percentages for categorical variables and as medians and ranges for continuous variables.

The differences between subgroups were tested using the Pearson χ^2 test. Statistical significance was defined as p value < .05. Univariate and multivariate analysis of factors predicting clinical CR on a per-lesion basis was carried out by logistic regression. The results of the logistic regression model are expressed as odds ratios with 95% confidence intervals.

The Kaplan-Meier method was used to analyze actuarial outcomes; differences between subgroups were evaluated by log-rank tests and the univariate and multivariate Cox regression analysis. Statistical analysis was performed using Stata 15.1 statistical software (StataCorp LLC; College Station, TX).

Results

Fifteen radiation oncology institutions and departments participated to the study; after evaluation of inclusion and exclusion criteria, 261 patients with MPR-OC, carrying a total of 449 lesions treated by SBRT between May 2005 and November 2018, were selected for the enrollment. Data were considered suitable for the analysis after obtaining adequate response to specific queries.

Table 2. Features of lesions and details of SBRT (n = 449)

	***n* (%)**
Type of lesion(s)	
Lymph node	292 (65.0)
Parenchyma	157 (35.0)
Anatomical district	
Abdomen	248 (55.2)
Pelvis	85 (18.5)
Thorax	6 (14.7)
Brain	37 (8.2)
Neck	13 (5.2)
Patients bearing	
1 lesion	146 (55.9)[a]
2 lesions	70 (26.8)
3 lesions	28 (10.7)
4 lesions	9 (3.4)
5 lesions	6 (2.3)
6–7 lesions	2 (0.8)[b]
Equipment	
Linear accelerator (LINAC)	401 (89.3)
CyberKnife	34 (7.6)
Tomotherapy	11 (2.4)
Gamma Knife	3 (0.7)
Median GTV (range), cm^3	4.5 (0.04–68.4)
Median PTV (range), cm^3	17.9 (0.04–136.4)
Median total dose (range), Gy	25 (5–75)
Median no. of fractions (range)	4 (1–13)
Median dose/fraction, (range), Gy	8 (3–30)
Median $BED_{\alpha/\beta 10}$ (range)	50.7 (7.5–262.5)
Type of treatment	
SBRT, stereotactic radiotherapy (more fractions)	396 (88.2)
SRS, stereotactic radiosurgery (single fraction)	53 (11.8)
Referral dose	
Specific isodose	235 (52.3)
Isocenter	159 (35.4)
Target mean	55 (12.3)

[a]Calculated on the number of patients (n = 261).
[b]Metachronous lesions.
Abbreviations: BED, biological effective dose; GTV, gross tumor volume; PTV, planning target volume; SRS, single fraction radiotherapy; SBRT, stereotactic body radiotherapy.

As shown in Table 1, median age was 60 years (range, 28–85), and the vast majority of patients (83.8%) presented Eastern Cooperative Oncology Group performance status 0–1. One hundred and seventeen patients (41.0%) had comorbidities, mainly represented by hypertension, diabetes mellitus, thyroid disorders, and autoimmune disease. The most frequent tumor histotype was high-grade serous (71.3%), followed by endometrioid (13.8%) and clear cell disease (4.2%). As far as the previous treatment(s) before SBRT are concerned, the vast majority of patients underwent at least one cytoreductive surgery (n = 253); previous

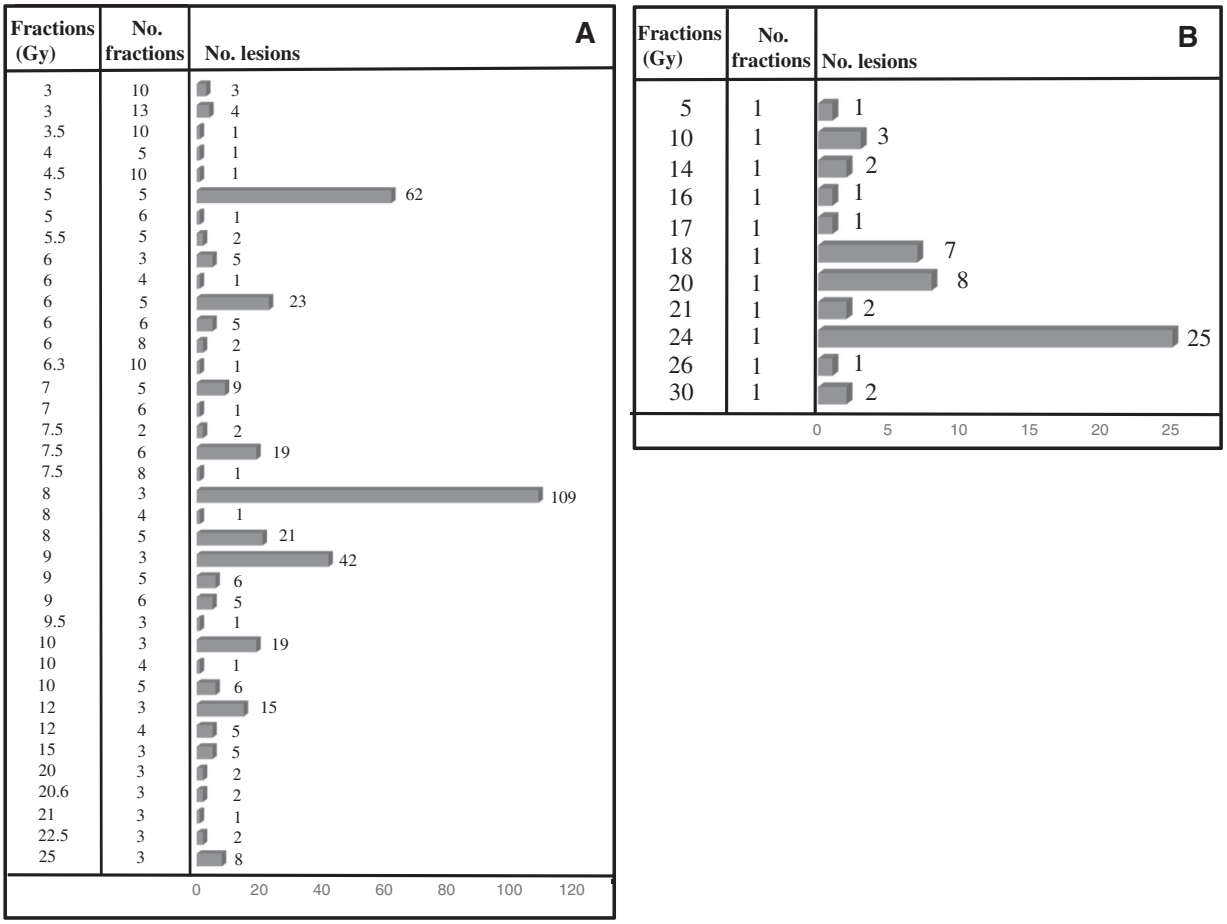

Figure 1. Summary of different radiotherapy schedules according to stereotactic body radiotherapy **(A)** and single fraction radiotherapy **(B)**.

CT was administered in 256 patients (median number of lines, 2; range, 1–11), whereas only 9 patients (3.4%) had been treated by previous in site RT.

SBRT Treatment on Per-Lesion Basis

Table 2 shows characteristics of lesions (n = 449) and detailed treatment: lymph node lesions accounted for 65.0% of this series, followed by parenchymal ones (35.0%), and the most frequent anatomical district was the abdomen (55.2%), followed by pelvis (18.5%) and thorax (14.7%).

One hundred and forty-six patients presented only one lesion (55.9%) and received a single SBRT course, whereas concurrent or sequential SBRT treatments were carried out in 115 patients bearing more than one lesion.

SBRT was delivered using different machines, the linear accelerator (LINAC) being the most frequently used (89.3%); volumetric arc radiotherapy was the most frequently reported technique (individual data not shown).

The median gross tumor volume was 4.5 cm^3 (range, 0.04–68.4), whereas the median planning target volume (PTV) was 17.9 cm^3 (range, 0.04–136.4).

Overall, the median total dose prescription was 25 Gy (range, 5–75), given in four fractions (range, 1–13), with a median dose per fraction of 8 Gy (range, 3–30). because of the variety of schedules in terms of dose and fractionation schemes for each treatment site (Fig. 1), the biologically effective dose (BED) was calculated using the following equation, considering 10 as the α/β ratio per OC:

$$\text{Total dose} \times \left(1 + \frac{\text{dose per fraction}}{(\alpha/\beta_{10})}\right)$$

The median $BED_{\alpha/\beta 10}$ was 50.7 Gy (range, 7.5–262.5) in the whole series.

Three-hundred and ninety-six lesions (88.2%) were treated by SBRT (multiple fractions), and 53 (11.8%) lesions were treated by single fraction radiotherapy (SRS). Treatment fractionations depended on the tumor location and indication; overall, the number of lesions treated with more than five fractions accounted for only 10.2%.

The median dose delivered by SBRT was 27 Gy (range, 18–75), with a median $BED_{\alpha/\beta 10}$ of 48 Gy (range, 28–262.5; individual data not shown). The most frequent schedules for SBRT were 8 Gy × 3 fractions, 5 Gy × 5 fractions, and 9 Gy × 3 fractions (Fig. 1A).

The median dose delivered by SRS was 24 Gy (range, 5–30); in terms of $BED_{\alpha/\beta 10}$, the median $BED_{\alpha/\beta 10}$ was 81.6 Gy (range, 7.5–120; individual data not shown). The most frequently adopted schedule for SRS was 24 Gy × 1 fraction, as reported in Figure 1B.

Lymph node lesions (n = 292) presented a median volume of 15.7 cm^3 (range, 1.2–155.0; individual data not

Table 3. Univariate and multivariate logistic regression of variables predicting complete response to SBRT on "per-lesion" basis

			Univariate		Multivariate	
Variable	***n***	**Complete response, *n* (%)**	**Odds ratio (95% CI)**	***p value*[a]**	**Odds ratio (95% CI)**	***p value*[a]**
All lesions	446[b]	291 (65.2)				
Age, yr				**.048**		**.027**
>60	213	129 (60.6)	1		1	
≤60	233	162 (69.5)	1.486 (1.004–2.198)		1.616 (1.056–2.472)	
Histotype				.538		
Serous	320	206 (64.4)	1			
Others	126	85 (67.5)	1.147 (0.741–1.777)			
Type of lesions				**<.001**		**<.001**
Parenchyma	155	76 (49.0)	1		1	
Lymph nodes	291	215 (73.9)	2.940 (1.953–4.428)		2.937 (1.888–4.569)	
Total dose, Gy				.928		
≤25	226	147 (65.0)	1			
>25	220	144 (65.4)	1.018 (0.689–1.504)			
No. of fractions				.868		
≤4	271	176 (64.9)	1			
>4	175	115 (65.7)	1.034 (0.694–1.543)			
Dose/fraction, Gy				.286		
≤8	172	107 (62.2)	1			
>8	274	184 (67.1)	1.242 (0.834–1.849)			
$BED_{\alpha/\beta 10}$, Gy				.531		**.006**
≤70	314	202 (64.3)	1		1	
>70	132	89 (67.4)	1.147 (0.746–1.766)		1.979 (1.214–3.227)	
PTV, cm^3				**.006**		**.005**
>18	187	106 (56.7)	1		1	
≤18	232[c]	162 (69.8)	1.768 (1.182–2.646)		1.857 (1.207–2.857)	

Boldface = statistically significant results.
[a]Calculated with logistic regression.
[b]Data relative to complete response unavailable for three lesions.
[c]27 missing.
Abbreviations: BED, biological effective dose; PTV, planning target volume.

Table 4. Prediction of rate of complete response to SBRT on "per-lesion" basis according to the variables included in the model

	Complete response to SBRT, % (95% confidence interval)			
	Age ≤60 yr		**Age >60 yr**	
Variables	**PTV ≤18 cm^3**	**PTV >18 cm^3**	**PTV ≤18 cm^3**	**PTV >18 cm^3**
Lymph node lesions				
$BED_{\alpha/\beta\ 10}$ ≤70 Gy	78.7 (72.0–85.5)	66.6 (56.8–76.4)	69.6 (61.3–77.9)	55.2 (44.3–66.2)
$BED_{\alpha/\beta\ 10}$ >70 Gy	88.0 (81.5–94.5)	79.8 (70.7–88.9)	81.9 (73.7–90.1)	71.0 (60.6–81.3)
Parenchyma lesions				
$BED_{\alpha/\beta\ 10}$ ≤70 Gy	55.8 (44.5–67.0)	40.4 (28.7–52.2)	43.8 (31.6–56.1)	29.6 (18.4–40.8)
$BED_{\alpha/\beta\ 10}$ >70 Gy	71.4 (59.9–82.9)	57.3 (45.1–69.6)	60.7 (47.9–73.5)	45.4 (33.4–57.4)

Abbreviations: BED, biological effective dose; PTV, planning target volume; SBRT, stereotactic body radiotherapy.

shown), and received a median total dose of 25 Gy (range, 5–63); median number of fractions was three (range, 1–13). Conversely, parenchyma lesions (n = 157) had a median volume of 19.4 cm^3 (range, 0.03–135.8) and received the median total dose of 27 Gy (range, 10–75); median number of fractions was 3 (range, 1–6; individual data not shown). Total dose was prescribed to a specific isodose (52.3%), to isocenter (35.4%), or to the target mean (12.3%).

Efficacy

CR, PR, SD, and progressive disease (PD) were observed in 291 (65.2%), 106 (23.8%), 33 (7.4%), and 16 lesions (3.6%),

Table 5. Univariate and multivariate Cox regression analysis of variables predicting local control (LC) on "per lesion" basis

		Univariate		Multivariate	
Variable	***n***	**Hazard ratio (95% CI)**	***p* value**	**Hazard ratio (95% CI)**	***p* value**
Total	446[a]				
Age, yr			**.048**		.156
≤60	233	1		1	
>60	213	0.578 (0.336–0.994)		0.666 (0.381–1.167)	
Histotype			.491		
Serous	320	1			
Others	126	0.814 (0.455–1.459)			
Type of lesions			.651		
Lymph nodes	291	1			
Others	155	0.88 (0.507–1.528)			
Total dose, Gy			**.001**		**.011**
≤25	226	1		1	
>25	220	0.374 (0.213–0.655)		0.424 (0.219–0.820)	
Fractions			.554		
≤4	271	1			
>4	175	0.855 (0.509–1.435)			
Dose/fraction, Gy			.059		
≤8	274	1			
>8	172	0.554 (0.300–1.024)			
$BED_{\alpha/\beta\ 10}$, Gy			**.023**		.843
≤70	314	1		1	
>70	132	0.456 (0.231–0.899)		0.923 (0.420–2.030)	
PTV, cm^3			.606		
≤18	232	1			
>18	187[b]	0.869 (0.510–1.480)			
Clinical response			**<.001**		**<.001**
Not complete	155	1		1	
Complete	291	0.234 (0.139–0.393)		0.228 (0.135–0.384)	

Boldface = statistically significant results.
[a]Data relative to local control unavailable for three lesions.
[b]27 missing.
Abbreviations: BED, biological effective dose; CI, confidence interval; PTV, planning target volume.

respectively. ORR was 89%, whereas the overall CB was 96.4%.

As shown in Table 3, univariate analysis of variables predicting CR per lesion showed that patient age ≤ 60 years, PTV ≤18 cm^3, and lymph node disease were significantly associated with a higher probability of achieving CR. Even though the variable $BED_{\alpha/\beta10}$ did not show any association with CR, it was considered suitable for being introduced in the multivariate model on the basis of its role as measure of treatment: therefore, before running the multivariate analysis, we first verified the distribution of lymph node and parenchyma lesions according to $BED_{\alpha/\beta10}$ and demonstrated that lymph node lesions were less frequently treated with $BED_{\alpha/\beta10}$ > 70 Gy compared with parenchyma lesions (22.2% vs. 42.6%, respectively; *p* value < .001; individual data not shown). In this context, we hypothesized that this latter finding could represent a confounding factor potentially masking the role of $BED_{\alpha/\beta10}$ in terms of achievement of CR. For this reason, we decided to include also the variable $BED_{\alpha/\beta10}$ in the multivariate analysis together with the three above-cited parameters (Table 3). All of them were shown to play a statistically significant independent role in predicting clinical CR.

An easier tool providing the predicted rate of CR on per-lesion basis according to different combinations of the variables included in the final multivariate model was enclosed in Table 4; for instance, lymph node lesions with PTV ≤18 cm^3, treated with $BED_{\alpha/\beta10}$ > 70 Gy in patients aged ≤60 years, would have the highest chance of CR (88.0%; CI, 81.5–94.5). In contrast, parenchymal lesions with PTV >18 cm^3 treated with $BED_{\alpha/\beta10}$ ≤ 70 Gy in patients older than 60 would expect the lowest percentage of CR (29.6%; 95% CI, 18.4–40.8).

Clinical Outcome

As of February 2019, median follow-up was 22 months (range, 3–120): 64 patients (24.6%) were alive with no evidence of disease; 111 patients (42.6%) were alive with disease in the SBRT site (*n* = 5), outside of field (*n* = 67), or both (*n* = 39); and 86 patients (32.8%) had died of disease.

Table 6. Acute and late toxicity

Acute toxicities	*n* (%)	Late toxicities	*n* (%)
All	63	All	19
Asthenia		Asthenia	
G1	9 (14.2)	G1	
G2		G2	
Pain		Pain	
G1	6 (9.5)	G1	2 (10.5)
G2	5 (7.9)	G2	
Upper GI disorders		Upper GI disorders	
G1	19 (30.1)	G1	2 (10.5)
G2	5 (7.9)	G2	
Lower GI disorders		Lower GI disorders	
G1	9 (14.3)	G1	8 (42.1)
G2	3 (4.7)	G2	
GU disorders		GU disorders	
G1	1 (1.5)	G1	1 (5.2)
G2	1 (1.5)	G2	
Pulmonary toxicity		Pulmonary toxicity	
G1	1 (1.5)	G1	1 (5.2)
G2	1 (1.5)	G2	2 (10.5)
Skin toxicity (erythema), G1	2 (3.1)	Skin toxicity (fibrosis), G1	2 (10.5)
Neurotoxicity (dizziness), G1	1 (1.5)	Neurotoxicity (diplopia), G1	1 (5.2)

Abbreviations: GI, gastrointestinal; GU, genitourinary.

We documented PD in 61 of 446 irradiated lesions (13.7%): the 24- and 36-month actuarial LC rates were 81.9%, and 79.9%, respectively (supplemental online Fig. 1A).

Univariate analysis of variables predicting LC rate per lesion showed that older age, total dose >25 Gy, achievement of CR, and $BED_{\alpha/\beta10} \geq 70$Gy were significantly associated with a higher probability of LC rate (Table 5). In the multivariate analysis, the achievement of CR and administration of total dose >25 Gy resulted significantly associated with better LC rate (Table 5).

As far as the outside field actuarial recurrence rate on per-patient basis is concerned, the 24- and 36-month actuarial PFS rates were 15.4% and 12.7%, respectively (supplemental online Fig. 1B). The 24- and 36-month actuarial OS rates were 73.6%, and 56.3%, respectively (supplemental online Fig. 1C).

Safety

Of 261 patients, 54 patients (20.7%) experienced mild acute toxicity, totaling 63 side effects, of which 48 were grade 1 and 15 were grade 2 (Table 6).

In contrast, only 16 patients (6.1%) presented late toxicity, accounting for 19 side effects; only 2 of them were grade 2 (pulmonary disorders). The 24- and 36-month late toxicity-free survival rates were 95.1%, and 92.1%, respectively (individual data not shown).

Discussion

To the best of our knowledge, this is the largest series focusing on efficacy and safety of SBRT in MPR-OC, having collected data on 449 lesions from 261 patients treated in 15 radiation oncology institutions.

As far as the primary endpoint is concerned, we documented a rate of 65.2% CR of irradiated lesions; despite the limits inherent to the heterogeneity over time of frequency and type of imaging for assessment of clinical response, our finding well matches with data of some OC SBRT series [26, 27]. The 100% rate of CR reported by Trippa et al. [26] is likely to be ascribed to the small sample size and/or the inclusion of only lymph node disease, which is recognized as presenting a higher response to SBRT compared with parenchymal lesions [28, 32]. A comprehensive summary of the literature focused on SBRT in ovarian cancer is reported in supplemental online Table 2.

In addition, we also reported PR and SD in 23.8% and 7.4% of lesions, respectively, thus achieving a CB in 96.4% of lesions, which is in agreement with other experiences [26–28]. Among clinical and treatment parameters, only age ≤ 60, PTV ≤18 cm^3, lymph node disease, and $BED_{\alpha/\beta10} > 70$ Gy emerged as independent predictors of high chances of CR.

The independent favorable role of younger age and lower tumor volume (PTV) in predicting CR has been already reported by other studies [33, 34]. Conversely, lymph node lesions showed a higher responsiveness compared with parenchymal disease, and this behavior was confirmed in all settings originated from the combinations of variables identified by the multivariate analysis; similar findings have been mentioned in the literature, but these are few [27, 28], and a comprehensive evaluation of this issue is lacking. In the context of the personalized medicine, further insights on intrinsic biomolecular features of lymph node and parenchymal lesions would be of interest considering that in our series this variable has emerged as the most powerful independent predictor of CR.

As far as the LC rate is concerned, in our series SBRT provided a high and durable rate (24-month rate: 81.9%). Among variables associated with longer LC, achievement of CR acts as a major driver followed by total dose >25 Gy; relative to the latter finding, it has to be acknowledged that total dose, which contributes predominantly to $BED_{\alpha/\beta10}$ value, could be used in place of it. Indeed, also in other solid tumors a $BED_{\alpha/\beta10} > 70$ Gy was reported to be associated to a higher rate of response [34, 35].

The dose issue, in terms of total dose or $BED_{\alpha/\beta10}$, represents the only modifiable variable that can makes the difference; obviously, in the real practice (as testified by the variety of schedules summarized in Fig. 1), this assumption needs to adjust to heterogeneity of type, site, and size of disease, patients' features, radiation oncologists' experience or attitude, and availability of equipment. It has to be acknowledged that the excellent results of the present series were obtained with rather low doses (e.g., 5 Gy × 5 fractionation is also used outside SBRT setting); this finding could be related

to a more cautious approach to SBRT schedules at the early phase of its development.

Therefore, efforts aimed at formulating and sharing proposals for optimized dose and fractionation SBRT schedules could be helpful in order to align the approaches and provide more homogeneous and robust results.

Despite the excellent LC, which is likely to improve palliation of symptoms and quality of life and may prolong chemotherapy free interval, the rate of progression outside of the target lesions remains high, ranging between 60 and 80% [27, 28] (current series). In this context, the data sustaining the potential role of SBRT in increasing tumor immunogenicity and promoting systemic activity suggest potential synergism between SBRT and immunotherapy [36] (see also www.clinicaltrials.gov).

Conclusions

The efficacy of SBRT is accompanied by a quite favorable toxicity profile in our series, thus configuring an acceptable cost-effectiveness ratio; in particular, only 20.6% of patients experienced low grade acute toxicity, and the 24-month late toxicity-free survival was 95.1%. Considering that half of patients were > 60 years, and 46% received two or more previous lines of CT and at least one major surgery, this issue is a further confirmation of safety of this technique also in unfit setting. However, we have to acknowledge that the retrospective physician-reported toxicity scoring could have been biased, especially in the presence of a long-term follow-up, as reported in our study. Moreover, the risk of underestimating the rate of late toxicity for adverse events occurring far from the irradiated site(s) has to be recognized. For example, in the randomized phase II SABR-COMET trial, a fatal subdural hemorrhage was reported following surgery required to repair a SABR-related perforated gastric ulcer [15]. In this scenario, the criteria defining abdominal-pelvic lesions not eligible for SBRT is clinically relevant; in principle, all MPR-OC lesions are eligible, but the doses and fractionation can largely vary on the basis of lesion size, proximity to organs at risk (especially small bowel and large vessels), previous irradiation, bowel fixity, and performance status. In conclusion, our large, real world study confirms the activity and safety of SBRT in patients with MPR-OC and identifies clinical and treatment parameters able to predict CR and LC rate. Optimal SBRT schedules should be defined taking into account the need to guarantee the best personalized radiation dose.

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Disclosures

The authors indicated no financial relationships.

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