Efficacy and safety of stereotactic body radiotherapy (SBRT) in oligometastatic/persistent/recurrent ovarian cancer: a prospective, multicenter phase II study (MITO-RT3/RAD)

Gabriella Macchia ,[1] Barbara Alicja Jereczek-Fossa,[2,3] Roberta Lazzari,[2] Annamaria Cerrotta,[4] Francesco Deodato,[1,5] Edy Ippolito,[6] Cynthia Aristei,[7] Maria Antonietta Gambacorta,[5,8] Giovanni Scambia,[9,10] Vincenzo Valentini,[5,8] Gabriella Ferrandina[9,10]

For numbered affiliations see end of article.

Correspondence to
Dr Gabriella Macchia, Radiotherapy Unit, Gemelli Molise, Campobasso, Molise, Italy; macchiagabriella@gmail.com

Accepted 4 June 2021

To cite: Macchia G, Jereczek-Fossa BA, Lazzari R, *et al. Int J Gynecol Cancer* Published Online First: [please include Day Month Year]. doi:10.1136/ijgc-2021-002709

ABSTRACT

Background Stereotactic body radiotherapy (SBRT) has shown promising results in the clinical setting of oligometastatic, persistent, or recurrent disease in several malignancies including ovarian cancer.

Primary Objective The MITO-RT3/RAD trial is a prospective, multicenter phase II study aimed at identifying potential predictors of response and clinical outcome after SBRT treatment.

Study Hypothesis Radiotherapy delivered by predefined SBRT treatment schedules and shared constraints could improve the rate of complete response.

Trial Design All patients accrued will be treated with a radiotherapy dose in the range of 30–50 Gy by 1, 3, or 5 SBRT daily fractions to all sites of active metastatic disease according to diagnostic imaging. Schedules of treatment and dose prescription have been established before considering target sites and healthy organ dose constraints. Follow-up and monitoring of side effects will be carried out every 3 months for the first year with imaging and clinical evalutation, and every 4 months within the second year; thereafter, surveillance will be carried out every 6 months. The best response on a per lesion basis will be evaluated by computed tomographic (CT) scan, positron emission tomography/CT, or magnetic resonance imaging in case of brain lesions, every 3 months.

Major Inclusion/Exclusion Criteria The study includes patients with oligometastatic, persistent, or recurrent ovarian cancer for which salvage surgery or other local therapies are not feasible due to any relative contra-indication to further systemic therapy because of serious co-morbidities, previous severe toxicity, unavailability of potentially active systemic therapy, or patient refusal.

Primary Endpoint The primary endpoint of the study is the clinical complete response rate to SBRT by imaging on a per lesion basis.

Sample Size Approximately 205 lesions will be treated (90 lymph nodes and 115 parenchyma lesions).

Estimated Dates for Completing Accrual and Presenting Results Fifty-two centers have expressed their intention to participate. Enrollment should be completed by March 2023 and analysis will be completed in September 2023.

Trial Registration NCT04593381.

INTRODUCTION

Stereotactic body radiotherapy (SBRT) is a high conformal and modulated radiotherapy that delivers high radiation doses to small tumor volumes in a few fractions (usually 3–5) while sparing surrounding organs at risk. SBRT can provide high rates of local control in low volume metastatic, persistent, or recurrent lesions with minimal acute and late toxicities.[1] Furthermore, SBRT is posssible even in patients who have already been managed with radiotherapy. In addition, SBRT has been shown to be active in chemoresistant disease and may stimulate immune responses through the release of tumor neoantigens after cell killing, thus allowing synergism with immunotherapeutic approaches.[2]

SBRT has been widely adopted in the clinical setting of oligometastatic, persistent, or recurrent disease (up to five lesions) in several malignancies including ovarian cancer[3–6] with promising results. In the SABR-COMET trial which included 99 patients with different cancers and up to five metastatic lesions, SBRT doubled progression-free survival (12 vs 6 months, p=0.001).[7] Moreover, the recently published retrospective multicenter Italian study (MITO-RT1) has confirmed the efficacy and safety of SBRT in oligometastatic, persistent, or recurrent ovarian cancer providing a model that can predict the chance of complete response of tumor lesions to SBRT as well as local control rate.[5]

The MITO-RT3/RAD trial is a prospective Italian multicenter phase II study aimed at evaluating the efficacy and safety of SBRT in patients with oligometastatic, persistent, or recurrent ovarian cancer treated at national community hospitals, academic institutions, and other settings. Clinical and imaging data as

well as SBRT technical parameters will be analyzed with the aim of identifying potential predictors of response to treatment and clinical outcomes. The suffix 'RAD' in the title of the study emphasizes the intent to analyze the radiomic features of the lesions in order to potentiate the power of the predictive models published in our retrospective study.[5 8 9] Furthermore, given the crucial role played by the mutational status of BRCA 1/2 genes in this disease,[10] the assessment of BRCA gene status will be mandatory.

METHODS

Trial Design

All accrued patients will be treated with SBRT to all sites of active metastatic disease as per diagnostic computed tomographic (CT) scan or positron emission tomographic (PET)/CT and/or magnetic resonance imaging (MRI). Radiotherapy set-up is left to the radiation oncologist's choice according to lesion site, internal guidelines, and center policy. Three-dimensional conformal radiotherapy is acceptable, four-dimensional conformal radiotherapy is strongly encouraged for tumors which are likely to be displaced due to respiratory motion such as lung, liver, and adrenal sites; treatment motion control devices are allowed. The CT slice thickness should be no greater than 3 mm. Use of intra-venous contrast and fiducial markers is allowed if judged necessary or useful. For all lesions, the clinical target volume is defined as the gross tumor volume—that is, the visible tumor on CT and/or PET/CT and/or MRI. The planning target volume is individually defined for each patient based on the internal margin and the set-up margin assessment. The internal margin volume definition will be personalized on the basis of respiratory excursions analysis (free breathing or abdominal compression/active breathing coordinator), while the set-up margin will be set at 3 mm. Protocol variations need to be discussed and authorized by the coordinator center.

All patients accrued will be treated with a radiotherapy dose in the range of 30–50 Gy by 1, 3, or 5 SBRT daily fractions to all sites of active metastatic disease according to diagnostic imaging. Pre-defined SBRT treatment schedules, dose prescription, and constraints have been established by the authors considering target sites and healthy organ dose constraints. Where a range of doses is provided, it is advised that the maximum dose that can be achieved while meeting the organs at risk planning constraints is prescribed. The organs at risk dose constraints adopted for this study will refer to the guidelines by UK consensus on normal tissue dose constraints for stereotactic radiotherapy.[11] Treatment could be carried out by LINAC accelerator, CyberKnife, GammaKnife, and Tomotherapy. The use of image-guided radiotherapy is recommended throughout all treatment fractions. Follow-up and monitoring of side effects will be carried out with imaging and clinical evaluation every 3 months for the first year, and every 4 months within the second year; thereafter, surveillance will be carried out every 6 months for 1 year more. The best response on a per lesion basis willbe evaluated by CT scan, PET/CT, or brain MRI in case of brain lesions, every 3 months. Fifty-two centers in Italy, mainly of the MITO, MANGO and AIRO network, have expressed their intention to participate.

The list of active recruiting study sites is available at https://clinicaltrials.gov/ct2/show/record/NCT04593381 as centers gain approval from their ethics committee. Multi-center recruitment will allow more precise assessment of the intervention, with the aim of demonstrating that implementing radiotherapy in this setting is both feasible and safe among the centers. Enrollment should be completed by March 2023 and analysis will be completed in September 2023.

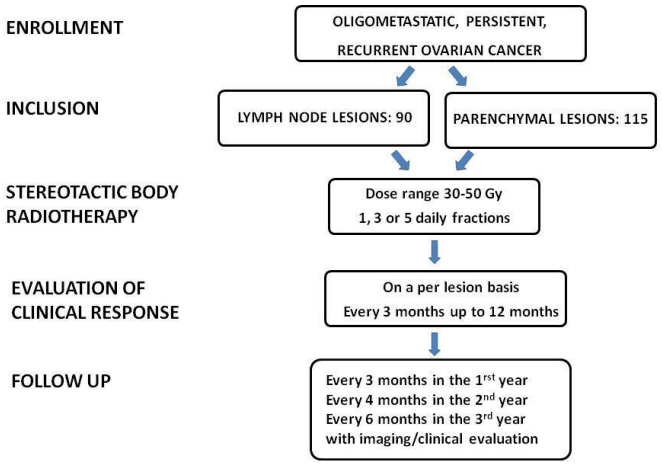

Figure 1 Study schema

The study schema is reported in Figure 1.

Participants

Participants entering the MITO-RT3/RAD trial must have oligometastatic, persistent, or recurrent ovarian cancer with a histologically-confirmed diagnosis. Oligo-recurrent/progressive patients are defined as patients with ≤5 new or enlarging metastases in an otherwise well-controlled disease status. Oligo-persistent disease is defined as ≤5 persistent lesions after systemic therapy. Major inclusion criteria are: expected life expectancy >6 months, <5 synchronous lesions, assessment of mutational status of BRCA1/2 genes, salvage surgery or other local therapies not feasible. Re-treatment of lesions already treated with conventional external beam radiotherapy is allowed (Table 1). Major exclusion criteria are mucinous, borderline, or non-epithelial ovarian tumors, co-morbidities and functional impairment considered clinically precluding the safe use of SBRT, previous toxicity. Eligible participants will provide informed consent to the principal investigator or to other physicians involved in this trial. Participating centers will be required to fill a dedicated electronic case report form including pathological and clinical data, as well as technical/dosimetric details about SBRT and data about the clinical response of the disease, acute and late toxicity, follow-up, outcome measures, and quality of life parameters. Study data will be stored and managed by the RedCap™ database system (www.redcap.org) with sensitive data tied to the patient's unique ID.

Outcomes

The primary endpoint of the study is the rate of clinical complete response to SBRT by imaging on a per lesion basis. The radiologic response will be evaluated by morphological (contrast-enhanced CT scan and/or MRI) or functional imaging modalities (18F-fluorodeoxyglucose-PET) and classified according to the RECIST (version 1.1) or PERCIST criteria. The objective response rate includes complete response and partial response. Clinical benefit includes the objective

Table 1 Summary of eligibility criteria

MITO-RT3/RAD	
Inclusion	**Exclusion**
1. Diagnosis of ovarian cancer	1. Mucinous ovarian cancer
2. Age >18 years	2. Borderline ovarian tumors
3. ECOG performance status 0–3	3. Non-epithelial ovarian cance
4. Expected life expectancy >6 months	4. Previous radiotherapy severe toxicity
5. 1–5 synchronous lesions	5. Co-morbidities and functional impairment considered clinically precluding the safe use of SBRT
6. Any site of disease	6. Pregnancy
7. Compulsory assessment of mutational status of BRCA1/2 genes (either germline or somatic)	7. Any psychological, sociological, or geographical issue potentially hampering compliance with the study
8. Salvage surgery or other local therapies not feasible	8. Lesion diameter >5 cm
9. Relative contra-indication to further systemic therapy because of serious co-morbidities	
10. Previous severe systemic therapy toxicity	
11. Unavailability of potentially active systemic therapy	
12. Patient refusal of systemic therapy	
13. Re-treatment of lesions already treated with conventional external beam radiotherapy is allowed*	

*Biological effective dose calculation should be used to achieve tolerance doses recommended.

response rate and stable disease. The response on a per lesion basis will be evaluated by CT scan, PET-CT, or MRI every 3 months (Figure 1). Assessment of best response will be carried out up to 12 months.

The secondary endpoints are the 2-year actuarial local control rate (progression of disease inside SBRT field) on a per lesion basis, progression-free survival (progression of disease out of SBRT field), overall survival, treatment-free interval (the interval from the SBRT and the start of a new systemic treatment or surgery), as well as the rate of toxicity and the 2-year actuarial late toxicity-free survival. Toxicity will be classified according to the CTCAE version 5.0 (www.ctcae-cloud.com). Timing for follow-up and monitoring of side effects are shown in Figure 1. Adverse events and other unintended effects of trial interventions will be registered on the RedCap™ database system Case Report Form and will be managed according to the center's internal guidelines. The cancer linear analog scale will be adopted for quality of life evaluation,[12] while assessment of pain will be evaluated by the visual analog scale score.

As an important translational endpoint, this study will also correlate radiomic single features or clusters with pathological and clinical parameters. Radiotherapy planning CT images acquired using different manufacturers and local imaging protocols will be evaluated for radiomic analysis. The images will be processed for indexing and storage by the Moddicom software developed by the Knowledge-Based Oncology Laboratory of A Gemelli, IRCCS, Rome, Italy.

Sample Size on a Per Lesion Basis

As far as lymph node ovarian cancer lesions are concerned, sample size is quantified based on the previous study reporting a rate of complete response to SBRT of around 70.0% on average.[5] Based on the optimal two-stage design by Simon,[13] we tested the null hypothesis that the true rate of complete response to treatment would improve from 70.0% to the clinically relevant alternative of 85.0%, using an α error of 0.05 (two-sided) and a β error of 0.1. Thus, the first step was planned to treat 25 lesions; if ≥18 lesions achieved a complete response, the study would enroll patients up to a total of 79 lesions. The regimen would be considered active if a complete response was obtained in ≥61 lesions. Considering a dropout rate around 10.0%, around 90 lesions will be treated. As far as parenchyma lesions are concerned, sample size was quantified based on the previous studies reporting a rate of complete response to SBRT of around 40.0%.[5] In this setting, we tested the null hypothesis that the true rate of complete response to treatment would improve from 40.0% to the clinically relevant alternative of 55.0%, using an α error of 0.05 (two-sided) and a β error of 0.1. Thus, the first step was planned to include 45 lesions; if ≥19 lesions achieved a complete response, the study would enroll patients up to a total 104 lesions. The regimen would be considered active if a complete response is obtained in ≥49 lesions. Considering a dropout rate of around 10%, approximately 115 lesions will be treated. Overall, in the whole study, approximately 205 lesions will be treated, of which around 90 are lymph node and 115 parenchyma lesions.

Statistical Methods

Patient characteristics will be reported as frequencies and percentages for categorical variables and medians and ranges for continuous variables. The differences between sub-groups will be tested using the Pearson $\chi 2$ test. Statistical significance will be defined as $p<0.05$. For the primary endpoint, univariate and multivariate analysis of factors predicting a complete clinical response on a per lesion basis will be carried out by logistic regression. The results of the logistic regression model will be expressed as ORs with 95% confidence intervals. Tests of interaction will be carried out, if required. For the secondary end points, the Kaplan–Meier method will be used to analyze actuarial outcomes; differences between sub-groups will be tested with the log-rank test and multivariate analysis using stepwise Cox regression. Statistical analysis will be performed using SPSS software version 19 (SPSS Inc).

DISCUSSION

The traditional management of patients with recurrent ovarian cancer is systemic chemotherapy chosen on the basis of platinum

sensitivity. The traditional management of patients with recurrent ovarian cancer is systemic chemotherapy chosen on the basis of platinum sensitivity. These lesions represent a challenge for clinical management involving an increasing number of patients due to the potential chronicity of illness associated with the use of bevacizumab and PARP- inhibitors.[14 15] In this scenario, the role of radiotherapy is shifting from palliative to curative setting, being SBRT an active and definitive treatment susceptible to be also integrated into a multidisciplinary strategy including surgery, conventional CT, and novel target-based drugs.

Even though there are few retrospective studies focused on the role of SBRT in oligometastatic, persistent, or recurrent ovarian cancer,[3–6] the relatively small size of these series as well as adoption of several different SBRT schedules across institutions does not allow definition of the optimal total dose, dose per fraction, and referral dose point, as they do for other solid tumors.[16] In particular, the SBRT schedules are not globally codified, thus leading to heterogeneous prescriptions in the clinical approaches; no clear guidelines for disease prescription doses between lymph node and parenchymal lesions are available.

Therefore, efforts aimed at defining optimized dose and fractionation SBRT schedules could be helpful in order to align approaches and could provide more homogeneous and robust results. In this context, the MITO-RT3/RAD study represents the first prospective study aimed at defining the activity and safety of SBRT in oligometastatic, persistent, or recurrent ovarian cancer with defined schedules of treatment and dose prescriptions according to target sites. Moreover, the study has planned a comprehensive analysis integrating clinical and histological parameters, SBRT details, radiomics features, and BRCA mutational status with the aim of identifying potential predictors of response to treatment and clinical outcome and developing a more robust predictive model. This study hopes to address an unmet need in optimizing the efficacy/toxicity ratio and to provide indications for developing specific guidelines.

Among the secondary endpoints, the treatment-free interval represents an important goal. SBRT is likely active in sensitive/resistant sub-clones within oligo-progressive lesions, and the benefit that may be gained by treating oligometastatic, persistent, or recurrent ovarian cancer lesions with SBRT is the postponement of further treatment which can have a favorable impact on quality of life. This may also change the natural history of disease progression by delaying widespread disease and improving overall outcome.

At this time, 52 radiotherapy centers/institutions have expressed their intention to participate. Their actual participation in the study is bound by the approval of local ethics committees. The promoting center ethics committee approval for the MITO-RT3/RAD trial was given on September 2020. The first patient was recruited in March 2021. Considering that in our previous retrospective study most patients (70–80%) presented with one or two single lesions, we will need to enroll approximately 140–160 patients; assuming five new patients/center per year, the target accrual of patients should be reached within 2 years.

CONCLUSION

The MITO-RT3/RAD trial will provide an insight into the efficacy of SBRT in oligometastatic, persistent, or recurrent ovarian cancer. Highlights of this study include personalization by prognostic score stratification, selection based on imaging-driven scores, ultra-conformed radiotherapy planning, and a lower number of radiotherapy sessions. The results will clarify whether this highly personalized approach would be practice-changing in the setting of oligometastatic ovarian cancer.

Author affiliations
[1]Radiotherapy Unit, Gemelli Molise Hospital, Campobasso, Italy
[2]Division of Radiotherapy, IEO European Institute of Oncology, IRCCS, Milano, Italy
[3]Department of Oncology and Hemato-oncology, University of Milan, Milano, Italy
[4]Radiotherapy Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy
[5]Istituto di Radiologia, Università Cattolica del Sacro Cuore Facoltà di Medicina e Chirurgia, Roma, Italy
[6]Department of Radiation Oncology, Campus Bio-Medico University, Roma, Italy
[7]Radiation Oncology Section, University of Perugia and Perugia General Hospital, Perugia, Italy
[8]Unità Operativa Complessa di Radioterapia, Dipartimento di Scienze Radiologiche, Radioterapiche ed Ematologiche, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Italy
[9]Gynecologic Oncology Unit, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Italy
[10]Istituto di Ginecologia e Ostetricia, Università Cattolica del Sacro Cuore Facoltà di Medicina e Chirurgia, Roma, Italy

Acknowledgements We thank Dr L Boldrini from the Radiotherapy Department in Rome for access to KBO labs and for the facilities made available to the multicenter protocol. We also thank Dr M Campitelli and Dr A Nardangeli for their contribution to the study and design of the Case Report Form (CRF), and Mr Mauro Manna for the preparation of the CRF on the RedCap™ database system.

Collaborators Luca Boldrini; Maura Campitelli; Alessia Nardangeli; Mauro Manna.

Contributors Conception and design: GM, GF. Revision of study design and protocol: GF, GM, BAJF, CA, AC, MAG. Study coordination: GM, GF, FD, MAG. Acquisition of data and patient recruitment: GF, GM, BAJF, RL, CA, AC, FD, EI, GS, MAG, VV. Radiotherapy quality check (of protocol): GM, BAJF, CA, FD, EI. Data management and statistical analysis: GF, GM. Revision, adaptation, and final approval of manuscript: All authors. Accountable for all aspects of the work: All authors.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study is approved by the Ethics Committee of the ASREM Molise (CE 07-14-2020) and is registered on ClinicalTrials.gov (NCT04593381). Each participating institution will submit the protocol to its ethics committee for approval before starting accrual. Eligible participants who have provided consent and meet the inclusion criteria will be anonymously registered on the case report form by assigning a numerical code.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available.

ORCID iD
Gabriella Macchia http://orcid.org/0000-0002-0529-201X

REFERENCES

1 Otake S, Goto T. Stereotactic radiotherapy for oligometastasis. *Cancers* 2019;11:133.
2 Rodríguez-Ruiz ME, Vanpouille-Box C, Melero I, *et al*. Immunological mechanisms responsible for radiation-induced abscopal effect. *Trends Immunol* 2018;39:644–55.
3 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.
4 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;101:650–60.

5 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:e311–20.
6 Kowalchuk RO, Waters MR, Richardson KM, *et al*. Stereotactic body radiation therapy in the treatment of ovarian cancer. *Radiat Oncol* 2020;15.
7 Palma DA, Olson R, Harrow S, *et al*. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet* 2019;393:2051–8.
8 Aerts HJWL, Velazquez ER, Leijenaar RTH, *et al*. Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. *Nat Commun* 2014;5:4006.
9 Boldrini L, Bibault J-E, Masciocchi C, *et al*. Deep learning: a review for the radiation oncologist. *Front Oncol* 2019;9:977.
10 Sun C, Li N, Ding D, *et al*. The role of BRCA status on the prognosis of patients with epithelial ovarian cancer: a systematic review of the literature with a meta-analysis. *PLoS One* 2014;9:e95285.
11 Hanna GG, Murray L, Patel R, *et al*. UK consensus on normal tissue dose constraints for stereotactic radiotherapy. *Clin Oncol* 2018;30:5–14.
12 Sutherland HJ, Walker P, Till JE. The development of a method for determining oncology patients' emotional distress using linear analogue scales. *Cancer Nurs* 1988;11:303–8.
13 Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 1989;10:1–10.
14 Zhou M, Yu P, Qu X, *et al*. Phase III trials of standard chemotherapy with or without bevacizumab for ovarian cancer: a meta-analysis. *PLoS One* 2013;8:e81858.
15 Lin Q, Liu W, Xu S, *et al*. PARP inhibitors as maintenance therapy in newly diagnosed advanced ovarian cancer: a meta-analysis. *BJOG* 2021;128:485–93.
16 Potters L, Steinberg M, Rose C, *et al*. American Society for Therapeutic Radiology and Oncology and American College of Radiology practice guideline for the performance of stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys* 2004;60:1026–32.