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Efficacy of stereotactic body radiotherapy and response prediction using artificial intelligence in oligometastatic gynaecologic cancer

Gabriella Macchia [a,*], Savino Cilla [b,1], Donato Pezzulla [a], Maura Campitelli [c], Concetta Laliscia [d], Roberta Lazzari [e], Lorena Draghini [f], Andrei Fodor [g], Giuseppe R. D'Agostino [h], Donatella Russo [i], Vittoria Balcet [j], Martina Ferioli [k], Lisa Vicenzi [l], Arcangela Raguso [m], Vanessa Di Cataldo [n], Elisabetta Perrucci [o], Simona Borghesi [p], Edy Ippolito [q], Piercarlo Gentile [r], Vitaliana De Sanctis [s], Francesca Titone [t], Clelia Teresa Delle Curti [u], Alessandra Huscher [v], Maria Antonietta Gambacorta [c,w], Gabriella Ferrandina [x], Alessio G. Morganti [k,y], Francesco Deodato [a,w]

[a] Radiation Oncology Unit, Responsible Research Hospital, Campobasso, Molise, Italy
[b] Medical Physics Unit, Responsible Research Hospital, Campobasso, Molise, Italy
[c] UOC di Radioterapia, Dipartimento di Scienze Radiologiche, Radioterapiche ed Ematologiche, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Italy
[d] Department of Translational Medicine, Division of Radiation Oncology, University of Pisa, Italy
[e] Department of Radiotherapy, IEO European Institute of Oncology IRCCS, Milan, Italy
[f] Radiation Oncology Center, S Maria Hospital, Terni, Italy
[g] Department of Radiation Oncology, IRCCS San Raffaele Scientific Institute, Milan, Italy
[h] Radiotherapy and Radiosurgery Department, Humanitas Clinical and Research Center-IRCCS, via Manzoni 56, 20089, Rozzano, Mi, Italy
[i] Radiotherapy Unit, Ospedale "Vito Fazzi", Lecce, Italy
[j] UOC Radioterapia, Nuovo Ospedale degli Infermi, Biella, Italy
[k] Radiation Oncology, Department of Medical and Surgical Sciences (DIMEC), University of Bologna, Bologna, 40138, Italy
[l] Radiation Oncology Unit, Azienda Ospedaliera Universitaria Ospedali Riuniti, Ancona, Italy
[m] UOC Radioterapia, Fondazione "Casa Sollievo della Sofferenza", IRCCS, S. Giovanni Rotondo, Foggia, Italy
[n] Radiation Oncology Unit, Oncology Department, University of Florence, Firenze, Italy
[o] Radiation Oncology Section, Perugia General Hospital, Perugia, Italy
[p] Radiation Oncology Unit of Arezzo-Valdarno, Azienda USL Toscana sud est, Arezzo, Toscana, Italy
[q] Department of Radiation Oncology, Campus Bio-Medico University, Roma, Italy
[r] Radiation Oncology Unit, UPMC Hillman Cancer Center San Pietro FBF, Roma, Italy
[s] Radiotherapy Oncology, Department of Medicine and Surgery and Translational Medicine, Sapienza University of Rome, S. Andrea Hospital, Roma, Italy
[t] Department of Radiation Oncology, University Hospital Udine, Italy
[u] Department of Gynecologic Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Via Venezian 1, 20133 Milan, Italy
[v] Fondazione Poliambulanza, U.O. di Radioterapia Oncologica "Guido Berlucchi", Brescia, Italy
[w] Istituto di Radiologia, Università Cattolica del Sacro Cuore Roma, Italy
[x] UOC Ginecologia Oncologica, Dipartimento Scienze della Salute della Donna e del Bambino, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Italy
[y] Radiation Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, 40138, Bologna, Italy

HIGHLIGHTS

- A large series of 846 oligometastatic gynecological cancers from 21 Institutions underwent Stereotactic Radiotherapy.
- Excellent objective response and local control rates were reported in the whole series.
- An Artificial Intelligence model (Machine learning analysis) was performed to find variables predicting complete response.
- High dose, small target volume, and type of lesion were able to predict complete response in uterine and ovarian cancers.

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ABSTRACT

Purpose. We present a large real-world multicentric dataset of ovarian, uterine and cervical oligometastatic lesions treated with SBRT exploring efficacy and clinical outcomes. In addition, an exploratory machine learning analysis was performed.

* Corresponding author.
E-mail address: gabriella.macchia@responsible.hospital (G. Macchia).
[1] Author responsible for statistical analysis: Savino Cilla, PhD, Medical Physics Unit, Responsible Research Hospital, Campobasso, Molise, Italy.

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Methods. A pooled analysis of gynecological oligometastases in terms of efficacy and clinical outcomes as well an exploratory machine learning model to predict the CR to SBRT were carried out. The CR rate following radiotherapy (RT) was the study main endpoint. The secondary endpoints included the 2-year actuarial LC, DMFS, PFS, and OS.

Results. 501 patients from 21 radiation oncology institutions with 846 gynecological metastases were analyzed, mainly ovarian (53.1%) and uterine metastases(32.1%).Multiple fraction radiotherapy was used in 762 metastases(90.1%).The most frequent schedule was 24 Gy in 3 fractions(13.4%). CR was observed in 538(63.7%) lesions. The Machine learning analysis showed a poor ability to find covariates strong enough to predict CR in the whole series. Analyzing them separately, in uterine cancer, if RT dose≥78.3Gy, the CR probability was 75.4%; if volume was <13.7 cc, the CR probability became 85.1%. In ovarian cancer, if the lesion was a lymph node, the CR probability was 71.4%; if volume was <17 cc, the CR probability rose to 78.4%. No covariate predicted the CR for cervical lesions. The overall 2-year actuarial LC was 79.2%, however it was 91.5% for CR and 52.5% for not CR lesions($p < 0.001$). The overall 2-year DMFS, PFS and OS rate were 27.3%, 24.8% and 71.0%, with significant differences between CR and not CR.

Conclusions. CR was substantially associated to patient outcomes in our series of gynecological cancer oligometastatic lesions. The ability to predict a CR through artificial intelligence could also drive treatment choices in the context of personalized oncology.

1. Introduction

Radiation therapy (RT) is routinely used as part of a multimodal treatment regimen for gynaecologic cancers. Stereotactic Body RadioTherapy (SBRT) is a high conformal and modulated RT technique, characterized by increased dose distribution conformity, reduced normal tissue toxicity, and dose escalation possibility. 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 approach including surgery, chemotherapy, immunotherapy and targeted therapies in the setting of oligometastatic/persistent/recurrent (MPR) disease [1,2]. In fact, SBRT has been shown to be an effective strategy in a range of solid malignancies such as lung [3,4], colorectal, breast, and prostate cancer [5–8], either because of the reported improvement of several outcomes (progression-free survival (PFS) [3–5], overall survival (OS) [6], and prolongation of androgen deprivation treatment-free survival as well as castration-resistant prostate cancer-free survival [7,8]) or because of the potential to delay further systemic therapy, which is frequently less effective, especially in the oligoprogressive setting. SBRT has being employed also in gynecological cancers [2,9–18] despite most published analyses are retrospective and therefore suffer from wide heterogeneity in patient selection, total delivered dose, fractionation, volumes and treatment techniques [2,10–12]. As per ovarian cancer setting, a prospective study (NCT04593381) aimed to reduce heterogeneity of these factors is ongoing with the aim to optimize the efficacy/toxicity ratio and to provide indications for developing specific guidelines [19]. However, the only evidences now available are those derived from large databases, which compensate for the lack of stronger evidence from prospective and randomized studies.

Furthermore, artificial intelligence (AI) is a promising technology to advance clinical practice, as many decisions rely on expert opinions in the absence of high-quality data-driven evidence [20,21]. Indeed, the use of AI has significantly aided large-database analysis, allowing researchers to develop predictive models that are becoming increasingly reliable and applicable in clinical practice for outcome prediction [20,21]. To the best of our knowledge, no accurate prediction models for clinical outcomes of gynaecologic oligometastatic cancer treated with SBRT exist, nor it is clear if attaining a complete response (CR) following SBRT influences oncologic outcomes. The aim of this paper was to perform a pooled analysis as well a detailed comparison of a large real-world multicentric dataset of ovarian, uterine and cervical oligometastatic lesions treated with SBRT in terms of efficacy and clinical outcomes. In addition, an exploratory machine learning analysis was performed to find variables able to predict the CR after SBRT.

2. Material and methods

2.1. Patients and study endpoints

Patients data were retrieved from the historical databases of Radiation Oncologists who joined the three multicenter, retrospective studies (MITO RT01 for Ovarian Cancer and MITO-RT02/RAD study for Cervical Cancer and Uterine Cancer) [10–12] approved by the Institutional Review Board of promoting Institution (N° 62,967/2020 ASREM Ethical Committee). Patients at each Institution had signed an informed consent form prior to their clinical data being used for educational or research purposes. Oligo-MPR gynecological cancer patients were defined as patients with ≤5 new or enlarging metastases in an otherwise well-controlled disease status and, therefore, candidates for ablative-intent treatment; with the inherent limits of the retrospective nature of our study, only this kind of patients entered the study. The dose fractionation protocol was at discretion of the treating physician. The clinical CR rate of disease following SBRT was the study main endpoint in the MITO-RT trials. The secondary end-point included the 2-year actuarial local control (LC) rate, defined on a "per-lesion" basis as any disease progression within the SBRT field of irradiation 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. Further secondary endpoints were actuarial Distant Metastases Free Survival (DMFS), Progression Free Survival (PFS), and Overall Survival (OS). Actuarial DMFS was termed on "per patient" basis as any out of field progression between the date of SBRT and the date of out of field progression or the date of the last clinical evaluation; actuarial PFS was termed on "per patient" basis as any local and/or out of field progression between the date of SBRT and the date of local and/or out of field progression or the date of the last clinical evaluation. Actuarial OS was termed on "per patient" basis as the time between the date of SBRT and the date of death of disease or the date of the last follow-up. Finally, an exploratory machine learning analysis was performed to find variables able to predict the treatment complete response.

Procedures.

Specific data set for standardized data collection from MITO studies were used as detailed in previous experiences [10–12]. Data on nodal and parenchymal lesions (defined as metastases affecting tissues other than lymph nodes) were collected. Computed Tomography (CT) scan or Positron Emission Tomography (PET)/CT scan were used to evaluate the best radiologic response after SBRT, which was then categorized using the Response Evaluation Criteria in Solid Tumors (version 1.1) [22], to dichotomize complete response, defined as "disappearance of all target lesions or any pathological lymph nodes (whether target or

non-target) with reduction in short axis to <10mm", versus others (Not-Complete-Responders, NCR). The objective response rate was defined as the sum of complete response and partial response (PR), while the clinical benefit consisted of objective response rate and stable disease (SD).

2.2. Variables selection and statistical analysis

This pooled analysis included all cohorts utilized in earlier investigations [10–12]. All data were collected and analyzed at the Radiotherapy Unit of Responsible Research Hospital, Campobasso, Italy, and entered into an electronic database. Patient characteristics were reported as medians and ranges for continuous variables and percentages for categorical variables. The differences among the three primary tumour groups (ovarian versus cervical versus uterine cancer) in terms of lesion burden (1 versus >1 lesion), age, lesion type (lymph node versus parenchymal lesions), planning target volume, total dose, dose per fraction, biologic effective dose (BED_{10}) and number of fractions (1 versus >1 fraction) were evaluated by the Kruskal-Wallis test. The Kaplan-Meier method was used to analyse actuarial outcomes; differences among subgroups (CR versus NCR) were evaluated by log-rank tests.

2.3. AI modelling

All datasets were combined and randomly divided into training and validation sets. The machine learning (ML) procedure was split into two parts: the selection of reliable prognostic variables and the model training and validation, using the subset of selected variables. The Least Absolute Shrinkage and Selection Operator (LASSO) method was used to pick variables. This approach gives a simple way to quantify the effect of various input variables on the "complete response" variable, indicating which should be eliminated from the model. In details, at the beginning we entered into the LASSO model the following variables: age (≤63 years versus >63 years), primary tumour (cervix versus ovary versus endometrium), disease burden (one lesions versus more than one lesion), type of lesion (nodal versus parenchymal ones), previous radiotherapy (yes versus not), Planning Target Volume (as a continuous variable), and BED (as a continuous variable). Subsequently, the remaining covariates as considered significant by the LASSO were used to create a Classification And Regression Tree analysis (CART) model for classifying complete respondent or not complete respondent lesions. The CART is a decision tree-based data mining tool that can identify data linkages, search for patterns automatically, and find hidden structures even in very large datasets. The CART model is often represented as a binary tree, with each root node representing a single input feature and a split point on that feature. The performance of the model was assessed using receiver operator characteristic curves (ROCs) and area under the curve (AUC). The XLSTAT statistics programs were used for statistical analysis, including machine learning training and testing (Addinsoft, New York, USA).

3. Results

3.1. Patients

This large real-world study included 21 radiation oncology institutes. For the analysis, 501 patients with oligo MPR-Ovarian (OC), uterine (UC), and cervical (CC) cancer who had received SBRT for a total of 846 lesions between May 2005 and October 2021 were selected. Median age was 63 years (range, 28–92 years) and nearly 90% presented Eastern Cooperative Oncology Group performance status 0–1 (Table 1). Most of them had one or more comorbidities; regarding the prior treatment(s), the majority of patients underwent radical surgery ($n = 459$), and previous chemotherapy was administered in 427 patients before SBRT. Sixty-two patients (12.4%) have previously received in-site radiotherapy. Three hundred and one patients (60.1%) had just one metastatic lesion, whereas 200 patients (39.9%) had more than one synchronous or metachronous lesion.

Table 1
Patient characteristics.

Primary Tumour		Ovary	Cervix	Uterus	All
Number of patients		261	83	157	501
Median age (years) (range)		60.0 (28–85)	58.0 (30–92)	69.7 (36–91)	63.0 (28–92)
ECOG	0	190	56	111	357
	1	29	22	40	91
	2	38	4	6	48
	3	4	1	0	5
Number of Comorbidities* for patients	0	154	42	42	238
	1	78	21	45	144
	2	30	9	34	73
	3	6	5	16	27
	4	2	3	7	12
	≥5	1	3	6	10
	na	0	0	6	6
Surgery before SBRT	no	3	27	7	37
	yes	253	56	150	459
	na	5	0	0	5
Chemotherapy before SBRT	no	0	21	42	63
	yes	256	61	110	427
	na	0	1	5	6
Previous in site RT	no	247	55	91	393
	yes	9	28	25	62
	na	5	0	0	5

* The number of one or more additional conditions co-occurring with the primary condition.

Table 2 shows characteristics of lesions ($n = 846$) and detailed treatment: lymph node lesions accounted for 58.8% of this series, followed by parenchymal ones (defined as lesions localized in other types of parenchyma, e.g. lung, bone, brain, etc.) (41.2%), and the most frequent anatomical district was the abdomen (41.9%), followed by pelvis (23.2%) and thorax (17.0%). The majority of lesions were ovarian (449, 53.1%) and uterine metastases (272, 32.1%) in origin, followed by 125 (14.8%) lesions from cervical cancer (Table 2). In detail, ovarian cancer had more abdominal metastases, whereas uterine cancer had more lesions in the thorax and cervical cancer in the pelvis.

The differences among the primary tumour groups (ovarian versus cervical versus uterine cancer) were found statistically significant for all covariates, as reported in Table 3.

3.2. SBRT treatment on "per-lesion" basis

Lesions had a median gross tumour volume of 4 cc (range: 0.04–181), and a median planning target volume of 16 cc (range: 0.4–278.5). Dose-fractionation schedules were largely heterogeneous among different centres, with biologically effective dose (BED_{10}) ranging from 7.5 to 262.5 Gy (Supplementary Tables 1 and 2).

Multiple fractions radiotherapy was used to treat 762 metastases (90.1%), while single fraction radiotherapy was used to treat 84 lesions (9.9%). We registered a total of 75 different used fractionations schedules, where the most used ones were 24 Gy in 3 fractions (13.4%), 25 Gy in 5 fractions (10.6%), 27 Gy in 3 fractions (8.9%) or 24 Gy in 1 fraction (4.4%). Detailed reports of the most frequent doses and fractions are provided in Supplementary Tables 1 and 2, while comprehensive reports have been already published [10–12].

3.3. Efficacy

Complete response (CR), partial response (PR), stable disease (SD), and progressive disease were observed in 538 (63.7%), 189 (22.3%), 80 (9.5%), and 38 lesions (4.5%), respectively. Overall, objective response rate (CR + PR) was 85.9%, while the clinical benefit (CR + PR + SD) was 91.8%.

Table 2
Features of lesions and details of Stereotactic Body Radiation Therapy (SBRT).

Primary Tumour		Ovary	Cervix	Uterus	All
N lesions		449	125	272	846
Lesions type	lymph node	292	69	137	498
	parenchyma	157	56	135	348
Anatomical district	brain	37	0	16	53
	neck	13	7	2	22
	thorax	6	34	104	144
	abdomen	248	31	76	355
	pelvis	85	46	66	197
	bone	0	7	8	15
Number of patients bearing	1 lesion	146	58	97	301
	2 lesions	70	13	34	117
	3 lesions	28	9	14	51
	4 lesions	9	1	1	11
	5 lesions	6	2	8	16
	>5 lesions	2	0	3	5
GTV (cc) (range)		4.5 (0.04–68.4)	4.3 (0.2–105.1)	4 (0.05–181.1)	4 (0.04–181)
PTV (cc) (range)		17.9 (0.4–136.4)	15.7 (1.8–278.5)	13.7 (2–196.5)	16 (0.4–278.5)
Equipment	LINAC	401	115	223	739
	CyberKnife	34	10	44	88
	Thomotherapy	11	1	5	17
	Gammaknife	3	0	0	3
Techniques	VMAT	434	104	165	703
	IMRT	5	20	93	118
	3DCRT	8	1	14	23
	N.A.	0	0	0	0
Reference dose	Specific	235	48	120	403
	Isocenter	159	31	88	278
	Target mean	55	46	64	165
Median Total dose (Gy) (range)		25.0 (5–75)	35.0 (10–60)	35.0 (10–75.2)	30.0 (5–75.2)
Median N of fractions (range)		4 (1−13)	5 (1−10)	5 (1–10)	5 (1–13)
Median BED (Gy) (range)		50.7(7.5–262.5)	59.5 (15–151.2)	59.5 (20.0–156.1)	51.0 (7.5–262.5)

GTV: Gross Tumour Volume; PTV: Planning Target Volume; LINAC: Linear Accelerator; VMAT: Volumetric Arc Radiotherapy; IMRT: Intensity Modulated Radiotherapy; 3DCRT: 3-dimensional conformal radiotherapy; N.A.: Not available; BED: Biologically Effective Dose.

Any lesions that did not have a complete response were referred to as not-complete-responders (NCR group) in order to separate them from the group of patients with complete responsive lesions (CR group). The analysis of the 3 major gynecological malignancies revealed that OC had a CR rate of 65.2%, whilst UC and CC had rates of 64.0% and 58.4%, respectively.

3.4. Clinical outcomes

The median follow-up was 55.9 months (range: 1–147 months) as of May 2022. The overall 2-year actuarial LC rate was 79.2%, however it was 91.5% for CR and 52.5% for NCR lesions ($p < 0.001$) (Fig. 1A). Looking at the three distinct malignancies, the 2-year actuarial LC delta (Δ) between patients who achieved CR versus those who did not was 66.9%, 58.9%, and 19.2% for CC, UC, and OC, respectively ($p < 0.001$). The overall 2-year actuarial DMFS rate was 27.3%, however it was 35.4% and 10.8% ($p < 0.001$) for CR and NCR patients, respectively (Fig. 1B). The 2-year actuarial DMFS Δ between CR and NCR was 34.7%, 27.8%, and 20.0%, for CC, UC, and OC, respectively ($p < 0.001$). The overall 2-year actuarial PFS rate was 24.8%, however it was 35.7% and 7.1% ($p < 0.001$) for CR and NCR patients, respectively (Fig. 1C). The 2-year actuarial PFS Δ between CR and NCR was 35.1%, 35.6%, and 21.6%, for CC, UC, and OC, respectively ($p < 0.001$).

Similarly, the overall 2-year actuarial OS rate was 71.0%, however it was 80.9% and 51.5% ($p < 0.001$) for CR and NCR patients, respectively (Fig. 1D). The 2-year actuarial OS Δ between CR and NCR was 24.6%, 26.2%, and 32.2% for CC, EC, and OC, respectively ($p < 0.001$).

Table 3
Differences among the primary tumour groups.

Primary Tumour	**Ovary**	**Cervix**	**Uterus**	**p value**[a]
All lesions	449	125	272	
Lesion burden				
1 lesion	146 (32.5%)	66 (52.8%)	97 (35.7%)	**<0.001**
>1 lesion	303 (67.5%)	59 (47.2%)	175 (64.3%)	
Median Age (IQR)	60 (51–68)	57 (52–70)	68.6 (60.6–75.55)	**<0.001**
Lesion Type				
Lymph node	292 (65.0%)	69 (55.2%)	137 (50.4%)	**<0.001**
Parenchyma	157 (35.0%)	56 (44.8%)	135 (49.6%)	
Median PTV, cc	17.9 (8–31)	15.7 (8.13–37.9)	13.7 (5.81–27)	**0.031**
Median Total dose, Gy (IQR)	25 (24–36)	35 (26–40)	35 (27–41)	**<0.001**
Median Dose/fraction, Gy (IQR)	4 (6.3–10)	5 (5–9)	5 (6–10)	**0.008**
Median BED10, Gy (IQR)	50.7(43.2–72)	59.5 (48–72)	59.5 (48–81.6)	**<0.001**
N of fractions				
>1 fraction	396 (88.2%)	115 (92.0%)	251 (92.3%)	**<0.001**
1 fraction	53 (21.8%)	10 (8.0%)	21 (7.7%)	

[a] Calculated by the Kruskall-Wallis test; BED: Biological Effective Dose; IQR: interquartile range 25th–75th.

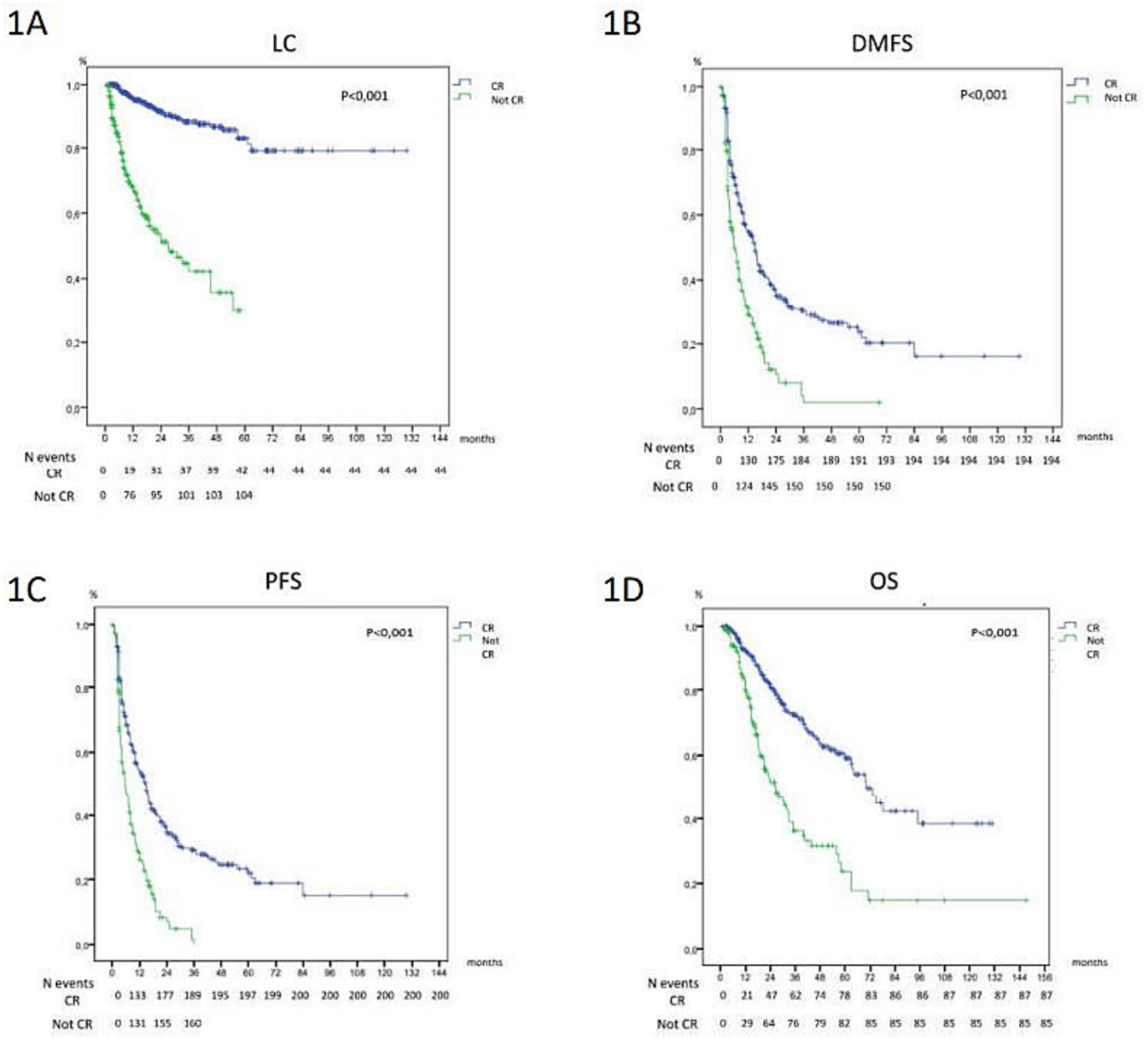

Fig. 1. Overall 2-year actuarial local control rate (1 A), Distant Metastases Free Survival (DMFS) (1B), Progression Free Survival (PFS) (1C), and Overall Survival (OS) (1D).

3.5. Variables selection and AI modelling

The LASSO method applied to all series showed a poor ability to find covariate strong enough to predict CR. Therefore, it was decided to analyse in a post-hoc way each of the three different malignancies separately. No covariate predicted the CR for cervical lesions. Three variables (BED_{10}, lesion volume, and type of lesion) have been identified as being predictive of CR for ovarian and uterine lesions (LASSO coefficients not zero), while the other variables have been excluded by the analysis. The chosen covariates served as input for the CART model for uterine and ovarian, but not for cervical cancer. The CART for the most informative variables is displayed in Fig. 2. The likelihood that a lesion falls within the CR or NCR category as well as the split covariate were provided for each node (N) (Fig. 2). Briefly, the CART model identified two predictive pathways to obtain the highest possible CR probability: for UC, lesions with BED ≥ 78.3Gy and PTV < 13.7 cc achieve a CR probability of 85.1%; for OC, lymph node lesions and PTV < 17.0 cc achieve a CR probability of 78.4%. In the validation test for UC, the CART model achieved an AUC of 0.744 (95% CI: 0.703–0.784) with an accuracy of 71.9%, sensitivity 81.4% and specificity 55.6%. For OC, the AUC was 0.702 (95% CI: 0.670–0.733) with an accuracy of 68.8%, sensitivity 87.1% and specificity 36.8%.

For the sake of clarity, we repost a detailed explanation of how to read and interpret the decision-making tree through an example. Given a new patient, the overall probability (Node 1) of CR before any criteria had been applied is 63.7%. First stratification follows primary tumour with 64.3 (Node 2) and 63.3% (Node 3) CR rate probability for UC and OC, respectively. As per UC, Nodes 4 and 5 reflect the effect of introducing the BED10 as the first decision criterion. The BED10 ≥ 78.3Gy relocates a large number of lesions to Node 5 with a probability for CR of 75.4%. Similarly, the BED10 < 78.3Gy reduces the probability for CR to 59.8% (Node 4). The lesions in node 5 will be subjected to the second criterion for further segregation, i.e., the target volume (PTV). At this second decision level, PTV values smaller than 13.7 cc relocate the lesions

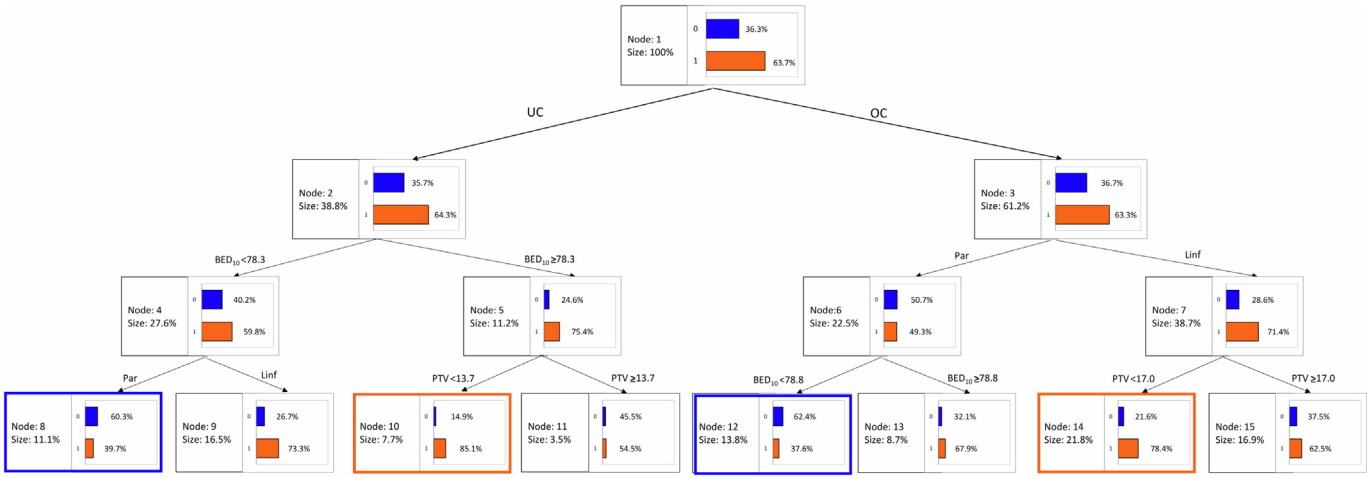

Fig. 2. Classification and Regression Tree analysis (CART) for the most informative variables.

in the Node 10 with a CR probability of 85.1%, while PTV values >13.7 cc decrease the probability of CR to 54.5% (Node 11). Looking at Fig. 2, the rule built by the algorithm can be expressed in natural language as "If BED10 ≥ 78.3Gy then the lesion will have a CR probability of 75.4%; moreover, if also the PTV<13.7cc the CR probability increases to 85.1%". On the other hand, if a uterine lesion is treated with a BED10 inferior to 78.3Gy and belong to parenchymal type, its CR probability fall down from the initial value of 64.3% to 39.7%. Concerning OC, Node 3 reflects the effect of introducing the lesion type as the first decision criterion. Lesions belonging to the lymph nodes type are relocated to Node 7 with a probability for CR of 71.4%. Similarly, the lesions belonging to parenchymal type will have a probability for CR of 49.3% (Node 6). The lesions in Node 7 will be subjected to the second criterion for further segregation, i.e., the PTV. At this second decision level, PTV values smaller than 17.0 cc relocate the lesions in the Node 15 with 78.4% probability, while a PTV value ≥17.0 cc decrease the probability of CR to 62.5%. Looking at Fig. 2, the rule built by the algorithm can be expressed in natural language as "If lesion belong to lymph nodes type then its CR probability increase from 63.3 to 71.4%; moreover, if also the PTV < 17.0cc the CR probability increases to 78.4%". Vice versa, if a ovarian lesion belong to parenchymal type and it is treated with a BED10 inferior to 78.8Gy, its CR probability fall down from the initial value of 63.3% to 37.6%.

4. Discussion

This large real-world multicentric dataset of ovarian and uterine MPR lesions was successfully pooled to analyse the efficacy of SBRT. To the best of our knowledge, this is the first instance in which 21 radiation therapy centres have combined their data on 846 lesions from 501 patients in an effort to identify CR predictors and to strengthen the role of SBRT in the gynecological setting, despite the lack of clear and uniform protocols. Additionally, this is the first time in which a large number of oligometastases in gynecological neoplasms has been studied through AI algorithms. The emphasis on SBRT efficacy is strongly linked to the finding that complete response is significantly related to patient prognosis, implying its relevance in the oligometastatic scenario [5,6,8,23] as a delayer of further systemic therapy as well as outcomes improver. Because SBRT treatments are one of the few metastasis-directed therapeutic choices, the "a priori" knowledge of the probability rate of partial/no treatment response allows for more aggressive therapy and treatment escalation to improve prognosis. As per primary endpoint, we documented an overall CR rate of 63.7% in this heavily treated population. We also included 12.4% of patients who had undergone previous in-site RT, representing a disadvantaged population. Despite the drawbacks inherent in the heterogeneity of imaging frequency and type for assessing clinical response over time, our findings are consistent with previous studies on gynecological series that demonstrated the ability of SBRT to achieve complete response in two-thirds of patients, particularly for ovarian and uterine cancer [10–15].

Furthermore, we reported a robust and consistent CART model for UC and OC, based on three clinical variables, that may guide oncologists through the increasing likelihood of CR (Fig. 2). The most predictive variables for ovarian cancer were the type of lesion (nodal), followed by small volume (<17.0 cc), whereas for uterine cancer they were the high dose (BED_{10} ≥ 78.3 Gy) and sequentially tumour size (<13.7 cc).

The observation that the OC lymph nodes would be more responsive had already been raised [10,15,24,25]. Lymph nodes may respond better to SBRT than parenchymal malignancies for a variety of reasons. To begin, because of their relatively fixed anatomical position and well-defined boundaries, lymph nodes are often easier to target with high accuracy. Parenchymal lesions, on the other hand, can be more difficult to target precisely, especially if they are irregularly shaped or located near critical structures like as blood vessels or nerves. Secondly, lymph nodes may be more susceptible to radiation-induced cell death than parenchymal lesions due to differences in their cellular composition. Lymph nodes are highly vascularized and composed of a variety of immune cells, including T cells, B cells, and dendritic cells, which are known to be highly radiosensitive. In contrast, parenchymal lesions are often composed of more radioresistant cells, such as fibroblasts, which may be less sensitive to the effects of radiation. Finally, lymph nodes may be more responsive to SBRT due to their role in the body's immune response. By delivering high doses of radiation to lymph nodes, SBRT may stimulate an immune response that can help to destroy cancer cells both locally and systemically.

The impact of a high radiation dose (i.e. high BED_{10}) in order to produce a complete response in UC lesions, on the other hand, is simpler to explain and has already been detailed in other settings, along with the implications in achieving better LC [10,26–28]. A radiation paradigm states that the higher the dose, the better the effect, moreover, the SBRT dose represents one of the few partly modifiable variables by radiation oncologists. In the real practice the choice of the dose has to be done according to cancer histology, lesion type, site, and size, nearby organs at risk, patients' previous treatments, radiation oncologists' expertise, and equipment. The complexity of this choice, as well the lack of clear and shared guidelines is testified by the variety of SBRT schedules summarized in Supplementary Tables 1 and 2, prompting to studies focused to harmonize the approaches to dose prescription. Indeed, considering the more recent literature, a few of the presented schedules could barely meet the bar for being considered ablative SBRT, rather than

hypofractionated treatments. However, we must also consider that some patients have been treated 20 years ago, at the beginning of SBRT implementation in the various radiotherapy centres, meaning that the first patients were probably treated more cautiously starting from low dose levels. Nevertheless, these treatments could be defined SBRT for the ablative intent they were proposed for and for the stereotactic modalities (spatial target localization, daily Image guide/fiducials/tracking/gating, etc.…) employed.

Finally, the role of the volume of the irradiated lesion, which has already been reported elsewhere [10–12,26,29], confirms that the likelihood of achieving a CR increases with decreasing volume for both the ovarian and the uterine lesions. As a result, if a metastatic lesion could be treated early and without delay, a lesser volume might probably be irradiated. On the contrary, for larger lesions, radiation oncologist may treat the patient after systemic therapy as consolidation treatment to achieve better results. Additionally, radiation oncologist might further minimize the margins (and hence the volume) of the lesion to be treated by utilizing the most advanced irradiation technologies e.g. breath-hold or surface guided radiotherapy. Last, the smaller the volume, the greater the total dose that can be safely delivered.

Apparently, for the setting of cervical cancer it was not possible to identify any variables that were sufficiently predictive to create a model, confirming data from Cox analysis reported by Macchia and colleagues [11]. The lack of some input factors, such as the HPV status or other genetic/epigenetic variables able to better determine the core biology of the disease might be the cause of this failure. This is regrettable because, as remarked in Fig. 1, the CR to SBRT is a powerful predictor of outcome. As a result, significant efforts must be expended in the cervical cancer setting to determine which variables predict the CR and are able to differentiate between responsive and non-responsive tumors to treatment.

In terms of LC rate, SBRT gave a high and long-lasting rate (2-year rate: 79.2%) in our series. As per results obtained in the previous published series [10–15], the achievement of CR acts as a major driver and influenced all the outcome variables. Therefore, all efforts must be made to obtain a CR at the time of the SBRT. On the contrary, the "a-priori" identification of NCR patients might guide the clinicians to tailor more aggressive therapy and treatment intensification in order to improve the prognosis. Indeed, obtaining the CR does not rule out the possibility that other biological/therapeutic factors, not considered in the previous studies, could have influenced these results. Despite the excellent LC in complete respondent patients, which may prolong chemotherapy free interval, the rate of progression outside of the target lesions remains high and this series is biased by the lack of information on systemic treatments following SBRT. Nevertheless, PFS and OS also showed a correlation with the CR rates, as in the prostate, colorectal, breast and lung settings [3–8]; future studies should aim to demonstrate an increase in time to resumption of a subsequent line of chemotherapy/biologic therapy and potentially OS.

In term of opportunities the encouraging results of this large gynecological series prompt the use of SBRT as valid alternative metastasis directed therapy, particularly given this procedure is widely known for being fast, painless, and cost effective. Moreover, this study propones for the first time an exploratory machine learning analysis which was able to identify some clinical and dosimetric covariates that can predict the CR after SBRT. The low number of clinical and dosimetric input variables should be viewed as a gain because such models will be less likely to overfit and easier to understand [30]. This AI predictive model, after a rigorous external validation, could allow the shift from large database to patient bedside and enable radiation oncologists to predict the response and, personalizing their intervention before carrying it out, to influence clinical outcomes. This quantitative method might be readily integrated into current decision-making processes, enhancing trust in the SBRT technology. Finally, the overview of attitude of the Italian Radiation Oncologist in the setting of the MPR of the gynecologic neoplasms, lays the theoretical and experiential foundations to start with prospective trials (e.g. NCT04593381 [19]) where pre-defined SBRT treatment schedules and shared constraints will be tested.

A few relevant limitations of the current analysis should be mentioned. A possible drawback is the retrospective nature of the study and the unavailability of some data, e.g. histological data, treatment intent, systemic chemotherapy (type, timing, etc.) or oligometastatic status according to ESTRO/EORTC definition[1]. Another limitation is the heterogeneous population, in particular the variability of the main intervention in terms of dose and fractionation, which is to some extent rectifiable by BED_{10} calculations, but has its own shortcomings as well, particularly with the questions raised about applicability of Linear Quadratic model in high doses per fraction. Finally, the machine learning model in this paper is based on a modest number of clinical and dosimetric parameters. As a result, other variables with potential influence on outcome prediction may be overlooked. Yet, in a large multicentric study, predictive models must be built using characteristics that are consistently accessible in all centres. Our model was developed utilizing readily available data, which did not necessitate costly and time-consuming data processing (as in radiomics or genomics), resulting in more basic and understandable model that was also accurate. This final element should be seen as a strength of the study.

In conclusion, the largest series of oligometastatic lesions from gynecological cancer is presented together with a practical tool for predicting the CR rate. Its relevance in the scenario of oligometastatic disease, despite the potential confundents, is shown by the observation that CR is substantially associated to patient outcomes, therefore every effort must be taken to eradicate oligo-disease. The ability to predict a CR through artificial intelligence could be useful to improve the likelihood that the SBRT will be effective. These promising results could be a starting point to drive treatment choices in the context of personalized oncology. Further prospective studies to define doses, fractionations and volumes are needed, as well studies on the combination of SBRT with radiotherapy sensitizer, targeted drugs and immunotherapy.

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Gabriella Macchia: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Savino Cilla:** Data curation, Formal analysis, Methodology, Software, Writing – original draft. **Donato Pezzulla:** Data curation, Formal analysis, Writing – original draft. **Maura Campitelli:** Writing – review & editing. **Concetta Laliscia:** Writing – review & editing. **Roberta Lazzari:** Writing – review & editing. **Lorena Draghini:** Writing – review & editing. **Andrei Fodor:** Writing – review & editing. **Giuseppe R. D'Agostino:** Writing – review & editing. **Donatella Russo:** Writing – review & editing. **Vittoria Balcet:** Writing – review & editing. **Martina Ferioli:** Writing – review & editing. **Lisa Vicenzi:** Writing – review & editing. **Arcangela Raguso:** Writing – review & editing. **Vanessa Di Cataldo:** Writing – review & editing. **Elisabetta Perrucci:** Writing – review & editing. **Simona Borghesi:** Writing – review & editing. **Edy Ippolito:** Writing – review & editing. **Piercarlo Gentile:** Writing – review & editing. **Vitaliana De Sanctis:** Writing – review & editing. **Francesca Titone:** Writing – review & editing. **Clelia Teresa Delle Curti:** Writing – review & editing. **Alessandra Huscher:** Writing – review & editing. **Maria Antonietta**

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Data availability

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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