The Use of SBRT in the Management of Oligometastatic Gynecological Cancer: Report of Promising Results in Terms of Tolerability and Clinical Outcomes

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Abstract

Background

The use of stereotactic radiotherapy (SBRT) for oligometastases is supported by several literature studies, but in the setting of gynecological malignancies, this scenario remains quite unexplored. This study reports a preliminary assessment of clinical outcomes in a cohort of 40 patients with oligometastatic gynecological neoplasms.

Methods

Radiotherapy was delivered in 3-10 fractions with VMAT-IGRT technique. Toxicity was retrospectively collected according to CTCAE v4.0. Data were retrospectively collected and analyzed. Univariate and multivariate analysis were performed for assessing any potential predictive factor for clinical outcomes.

Results

A total of 63 oligometastases were treated from December 2014 to February 2021. Median age was 63 years (range, 30-89). Most frequent primary tumors were ovarian cancer in 42.5% and endometrium cancer in 42.5%. With a median follow-up of 27 months (range, 6-69), no local failures were observed, our progression-free survival rates were 43.6% and 23% at one and 2 years, respectively, while 1- and 2-years overall survival rates were both 70%. No acute or late $G \geq 2$ adverse events were observed.

Conclusions

In our experience, SBRT for oligometastatic gynecological malignancies resulted in promising results in terms of clinical outcomes, with excellent local control and no evidence of severe toxicity, highlighting the effectiveness of this therapeutic option. Prospective studies to further explore this approach in this setting are advocated.

Introduction

Gynecological malignancies are highly represented in general population. Endometrial is the most common among them [1], with continuously rising incidence rates, also due to the increasing prevalence of obesity [2]; cervical cancer is one of the leading causes of death among women, while ovarian cancer is the seventh most common cancer worldwide and it is frequently diagnosed in advanced stage. [3, 4]

In the last years, improvements in diagnostic imaging techniques, such as 18F-FDG-positron-emission tomography (PET)/computed tomography (CT) and magnetic resonance imaging (MRI), have led to a significant improvement in terms of tumor detection rate, increasing the number of patients characterized by a limited number of metastases.

This brings to a newly-defined subgroup of patients, so called oligometastatic, represented by an intermediate stage of disease between locally-advanced and widely-disseminated. In this scenario, local control may help improving systemic control and the SABR COMET study has clearly demonstrated that stereotactic body radiotherapy (SBRT) in addition to standard of care can improve overall survival in oligometastatic patients. [5]

Oligometastatic disease (usually considered between 3 and 5 lesions) can be divided into three main categories: oligorecurrence, oligoprogression, and oligopersistence. Nowadays the best therapeutic strategies for the different kinds of oligometastatic disease remain undefined. [6]

The traditional and current management of patients with metastatic or recurrent cervical, endometrial and ovarian cancer is represented by systemic therapy, with addition of PARP inhibitors and bevacizumab to platinum-based chemotherapy. [7–9]

Currently, SBRT in the setting of metastatic gynecological patients has been rarely investigated in the literature, mainly consisting of retrospective series. Macchia et al. [10] and Reschko et al. [11] described SBRT as a well-tolerated and efficient treatment in recurrent, persistent or oligometastatic gynecological cancers. Furthermore, also within a previously irradiated fields, SBRT for isolated pelvic or intra-abdominal recurrences of gynecologic malignancies is feasible with an acceptable toxicity rate. [12]

In the present study, we have retrospectively evaluated the outcomes of a cohort of 40 patients affected by gynecological malignancies who have received extracranial SBRT for oligometastatic cancer.

Methods

Written informed consent was obtained from all the patients. From December 2014 to February 2021, 40 patients with extracranial oligometastatic gynecological malignancies were treated at our Department, assuming as oligometastatic disease any presentation with up to five lesions amenable for a local treatment, with a maximum diameter ≤ 5 cm. Concurrent systemic therapy or previous pelvic radiotherapy were not exclusion criteria for the purpose of this study.

SBRT was proposed to all patients with a Karnofsky Performance Status ≥ 70 and a life expectancy of ≥ 6 months. Treatment management was assessed basing on a multidisciplinary assessment. Table 1 collects patients' characteristics.

Table 1
Patients' characteristics

Characteristic	Results
Age	63 years (30–89)
Primary Histology	Endometrium = 42.5% (n = 17); Cervix = 10%(n = 4); Ovary = 42.5% (n = 17); Vagina = 5%(n = 2);
RT site	Lymph nodes = 55.5%(n = 35); liver = 8%(n = 5); lung = 30%(n = 19); bone = 3%(n = 2); other = 3%(n = 2)
Concurrent CT	20% (n = 8)
Type of Oligometastases	Oligorecurrent = 55.5% (n = 35); oligoprogressive = 27%(n = 17); oligopersistent = 17.4% (n = 11)
Number of metastases treated	1 lesion = 65%(n = 26); 2 = 22.5%(n = 9); ≥ 3 = 12.5%(n = 5);
BED	72Gy ₁₀ (range, 48–180 Gy ₁₀).

Radiotherapy Procedures

A 1-2.5 mm slice thickness computed tomography (CT) was acquired for planning purposes. Immobilization for treatment simulation was performed either with an abdominal thermoplastic mask plus compression in the case of abdominal targets, or with 4-dimensional CT for thoracic targets. In the case of liver SBRT, contrast-enhanced CT-scans were acquired. In the case of pelvic targets, immobilization was performed in supine position by means of a knee-ankle device.

Regarding the target volume delineation process, the gross tumor volume (GTV) consisted of the radiologically evident disease; when available, contouring was performed with co-registered diagnostic imaging (PET or MRI). Clinical target volume (CTV) was considered equal to the GTV. The planning target volume (PTV) was created by adding an isotropic margin ranging from 5 to 7 mm, depending on tumor site and critical structures proximity. The dosimetric goal for treatment planning was to guarantee at least 95% of the prescribed dose to the 95% of the PTV. Dose constraints for organs at risk were derived from peer-reviewed literature. [13–16]

In all cases, SBRT was performed by means of image guided volumetric modulated arc therapy (IGRT-VMAT).

Clinical Outcomes Assessment

Follow-up visits were performed every 3 months after SBRT for the first year, and every 6 months starting from the second year. Treatment response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria v1.1 and PET Response Evaluation Criteria in Solid Tumors (PERCIST)

criteria v1.0 in the case of metabolic imaging. Toxicity was prospectively collected and assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Statistical Analysis

Descriptive statistics were collected for baseline patients' characteristics. Local control (LC), progression free survival (PFS) and overall survival (OS) were assessed using Kaplan-Meier method. Univariate and multivariate analyses were performed to assess any potential predictive factor for clinical outcomes. A $p < 0.05$ was assumed as statistically significant. All statistical analyses were carried out using Graphpad Prism v9.0.2 (Graphpad, San Diego, CA, USA)

Results

A total of 63 oligometastases treated in 40 oligometastatic gynecological patients were retrospectively analyzed for the purpose of this study. The median age of the cohort was 63 years (range, 30–89). The majority of the treated metastases were from ovarian cancer in 43% of cases ($n = 27$), endometrial cancer in 41% ($n = 26$), cervical cancer in 13% ($n = 8$), vaginal cancer in 3% ($n = 2$). SBRT to oligometastatic disease was delivered to lymph nodal metastases in 55.5% ($n = 35$); lung metastases in 30% ($n = 19$), liver metastases in 8% ($n = 5$), bone metastases in 3% ($n = 2$), paravaginal space in 3% ($n = 2$). 35 oligometastases out of 63 were oligo-recurrent lesions (55.5%), oligo-persistent in 17.4% ($n = 11$), oligo-progressive in the remaining 27% of cases ($n = 17$).

In nine patients, SBRT was delivered to 2 synchronous oligometastases, while five subjects received SBRT to more than 2 lesions. In the remaining cases ($n = 26$), SBRT was delivered to a single oligometastatic target.

Concurrent systemic therapy was administered in 8 patients (20%), consisting of PARP-inhibitors in 5 cases, anti-VEGF antibody in 2 cases and trastuzumab in one patient.

SBRT was delivered in 3–10 fractions for a median total dose of 42 Gy (range, 24–70), and a median biologically effective dose (BED) = 72Gy_{10} (range, 48–180 Gy_{10}).

Clinical outcomes

The median follow-up was 27 months (range, 6–69); for the entire cohort, median local control (LC) was 19 months, leading to 2-years LC rates of 100%. (Fig. 1)

One and two-years progression-free survival (PFS) rates for the entire population were respectively 43.6% and 23%. Neither univariate nor multivariate analysis found any significant correlation for this clinical outcome. (Tables 2–3)

Table 2
Univariate analysis

	PFS	OS
BED $\geq$ 90	0.55	0.08
RT site	0.13	0.11
Primary Histology	0.31	0.12
Age	0.49	0.21
DFI	0.39	0.13
Concurrent CT	0.08	0.82
N° of metastases treated	0.78	0.82
Type of oligometastases	0.08	0.62
SOMD	-	0.47
PFS	-	0.05

Table 3
Multivariate Analysis

	PFS	OS
BED $\geq$ 90	-	0.96
RT site	0.7	0.28
Primary Histology	-	0.92
Age	0.47	0.45
DFI	-	0.92
Concurrent CT	0.26	-
N° of metastases treated	-	-
Type of oligometastases	0.11	-
PFS	-	0.97

Sixteen patients developed a sequential oligometastatic disease, for which a further SBRT course was proposed, with a second progression-free survival (PFS2) of 13 months (range, 2–27), although this did not lead to a survival advantage, when compared to patients who developed immediate polymetastatic

spread ($p = 0.47$). In the remaining 24 patients, polymetastatic spread occurred in 47.5% of cases ($n = 19$), with five subjects with no evidence of disease until last follow-up.

Two and 3-years overall survival rates were both 70%, with only one patient who died by other causes. (Fig. 2)

At univariate analysis, progression-free survival was associated to worse OS rates ($p = 0.05$), although this was not confirmed on multivariate analysis. (Tables 2–3)

Toxicity

SBRT treatment was well tolerated and all patients completed the planned treatment without any interruption. No acute or late grade 2 or higher adverse events were observed.

Discussion

The role of SBRT in the management of oligometastatic cancer disease has been supported by several literature experiences, both as a potentially curative treatment option, and as a means to postpone the start of a new systemic therapy. [17, 18]

Nonetheless, in the specific setting of gynecological malignancies, it is hard to draw definitive conclusions, since this subpopulation is usually under-represented in these trials. [19]

This is probably due to the natural history of gynecological cancer, such as ovarian or cervical cancer, in which the addition of systemic therapy takes place early, given the high propensity to metastatic spread. A recent review by Zhang et al. highlights the substantial feasibility of SBRT for oligometastatic gynecological cancer especially for lymph-nodal metastases, even in the case of previous pelvic irradiation. On the contrary, a major risk of $G \geq 3$ adverse events is reported in the case of pelvic side wall or central pelvic recurrences treated with SBRT. [20]

In the present series, we have recorded the outcomes of 63 lesions in 40 patients treated with SBRT for extracranial oligometastases from gynecological malignancies. No local failures were observed in our series, highlighting the effectiveness of the SBRT treatment. Unlike previous experiences, we have not recorded a survival advantage in those patients who developed a sequential oligometastatic progression, further treated with a second course of SBRT. [21, 22]

This evidence may raise the issue of the real role of focal treatments in this setting, suggesting a different natural history of gynecological malignancies when compared to other scenarios, as also highlighted by the sub-optimal PFS rates of most of the published studies concerning gynecological oligometastases.

Nonetheless, in the last years, encouraging preliminary experiences report the outcomes of SBRT applied to this setting of patients. (Table 4 ^{10,11,23–27})

Table 4
Literature experiences of SBRT for gynecological malignancies

Author	Number of patients	Number of metastases	Follow-up (months)	Primary Histology	Toxicity	Clinical Outcomes
Iftode et al. ²³	26	44	28.5	OC = 100%	Late G2 = 11%	2yrLC = 92.9% 2yrPFS = 38% 2yrOS = 92.7%
Macchia et al. ¹⁰	261	449	22	OC = 100%	2 year late G2 toxicity-free survival = 95.1%	2yrLC = 95.1% 2yrPFS = 15.4% 2yrOS = 73.6%
Reshko et al. ¹¹	86	209	20	OC = 30/86 CC = 20/86 EC = 27/86 Other = 9/86	Acute G $\geq$ 2 = 4.3%	3yrLC = 68% 3yrPFS = 3yrOS = 39%
Reddy et al. ²⁴	27	61	16.9	EC = 100%	One case of late G2 pneumonitis	1yrLC = 80.3% 1yrPFS = 75.9% 1yrOS = 62%
Ning et al. ²⁵	38	41	35.2	CC = 100%	Acute G2 = 39%	2yrLC = 2yrPFS = 48% 2yrOS = 74%

Author	Number of patients	Number of metastases	Follow-up (months)	Primary Histology	Toxicity	Clinical Outcomes
Onal et al. ²⁶	29	35	15.3	CC = 21/29 OC = 8/29	Acute G2 = 17%	2yrLC = 95.1% 2yrPFS = 18% 2yrOS = 73.6%
Smile et al. ²⁷	34	43	12	OC = 12/34 EC = 11/34 CC = 7/34 Other = 4/34	3 acute G2 events	2yrLC = 92.5% 1yrPFS = 60.2% 2yrOS = 70.2%
Present experience	40	63	27	OC = 17/40 CC = 4/40 EC = 17/40 Other = 2/40	No acute or late G ≥ 2 events	2yrLC = 100% 2yrPFS = 23%; 2yrOS = 70%

Abbreviations: CC=cervical cancer; EC=endometrial cancer; OC=ovarian cancer; LC=local control; PFS=progression-free survival; OS=overall survival

Iftode et al. collected data concerning a series of 44 metastatic lesions arising from ovarian cancer who received SBRT, collecting satisfactory outcomes in terms of LC and PFS, with negligible toxicity. [23]

Ning et al. in a previous report focused their attention on cervical cancer oligometastases, collecting promising results, in agreement with the abovementioned studies. Of note, this study included both SBRT and conventional fractionation treatments, making harder to draw definitive conclusions. [25]

Reddy et al. documented excellent local control results in a series of 27 patients with oligometastatic uterine cancer, recording worse local control rates in the case of liver metastases. [24]

The favorable toxicity profile of our series supports this therapeutic approach, also when combined with conventional systemic therapies that for gynecological malignancies still represent the standard of care. This is also confirmed by one of the largest series available in the literature, in which in a multicenter

series published by Macchia et al., the authors collected a 2-years toxicity free survival rate of 95.1%. Interestingly, keeping in mind that this study refers to ovarian cancer oligometastases, a statistically significant correlation was found for higher LC rates, when a BED > 70 Gy radiotherapy schedule is applied. [10]

Similarly to our experience, a recent study by Smile et al. included different primary gynecological cancers also highlighting excellent results in terms of both toxicity and clinical outcomes. [27]

The present study has several limitations; first of all, we retrospectively collect data of a heterogeneous sample of patients including different primary histologies and both patients who received and received not systemic therapy. Nonetheless, we report one of the largest series with the longest follow-up currently available, and the results are promising and in agreement with other literature experiences supporting the role of SBRT, also in this relatively unexplored field of the oligometastatic disease.

Conclusions

This mono-institutional experience supports the use of SBRT in the management of the oligometastatic gynecological cancer, by collecting no relevant toxicity and promising results in terms of clinical outcomes. Prospective studies are needed to further evaluate this therapeutic option in this scenario.

Declarations

Authors' Contribution:

FC, CV and EP: manuscript drafting; LN, VF, MR, FR, CV, GA: data collection; FC, CV, FA: study design; FA, RM, NGL, RR: editing and revision; All author: final approval

Competing interests:

all authors declare no competing interests

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Figure

Figure 2 is not available with this version.

Figures

Figure 1

Kaplan-Meier curves for progression-free survival (PFS) and overall survival (OS)