Stereotactic body radiotherapy in oligometastatic cervical cancer (MITO-RT2/RAD study): a collaboration of MITO, AIRO GYN, and MaNGO groups

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HIGHLIGHTS

- A clinical complete response to stereotactic body radiotherapy results in more favorable clinical outcomes.
- Stereotactic body radiotherapy showed mild acute and late toxicity profile.
- Stereotactic body radiotherapy provides a potentially curative approach to oligometastatic/persistent/recurrent cervical cancer patients.

ABSTRACT

Objective This retrospective, multicenter study analyzes the efficacy and safety of stereotactic body radiotherapy in a large cohort of patients with oligometastatic/persistent/recurrent cervical cancer.

Methods A standardized data collection from several radiotherapy centers that treated patients by stereotactic body radiotherapy between March 2006 and February 2021 was set up. Clinical and stereotactic body radiotherapy parameters were collected. Objective response rate was defined as a composite of complete and partial response, while clinical benefit included objective response rate plus stable disease. Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer and Common Terminology Criteria for Adverse Events scales were used to grade toxicities. The primary endpoints were the rate of complete response to stereotactic body radiotherapy, and the 2 year actuarial local control rate on a 'per lesion' basis. The secondary end points were progression-free survival and overall survival, as well as toxicity.

Results A total of 83 patients with oligometastatic/persistent/recurrent cervical cancer bearing 125 lesions treated by stereotactic body radiotherapy at 15 different centers were selected for analysis. Of the sites of metastatic disease, lymph node metastases were most common (55.2%), followed by parenchyma lesions (44.8%). Median total dose was 35 Gy (range 10–60), in five fractions (range 1–10), with a median dose/fraction of 7 Gy (range 4–26). Complete, partial, and stable response were found in 73 (58.4%), 29 (23.2%), and 16 (12.8%) lesions, respectively, reaching 94.4% of the clinical benefit rate. Forty-six (55.4%) patients had a complete response. Patients achieving complete response on a 'per lesion' basis experienced a 2 year actuarial local control rate of 89.0% versus 22.1% in lesions not achieving complete response ($p<0.001$). The 2 year actuarial progression-free survival rate was 42.5% in patients with complete response versus 7.8% in patients with partial response or stable or progressive disease ($p=0.001$). The 2 year actuarial overall survival rate was 68.9% in patients with complete response versus 44.3% in patients with partial response or stable or progressive disease ($p=0.015$). Fifteen patients (18.1%) had mild acute toxicity, totaling 29 side events. Late toxicity was documented in four patients (4.8%) totaling seven adverse events.

Conclusion Our analysis confirmed the efficacy of stereotactic body radiotherapy in oligometastatic/persistent/recurrent cervical cancer patients. The low toxicity profile encourages the wider use of stereotactic body radiotherapy in this setting.

INTRODUCTION

Cervical cancer is the fourth most common malignancy in women, with more than 500 000 new diagnoses per year, and a mortality rate of around 50%, worldwide.[1] Patients diagnosed with early stage have a 5 year progression-free survival in the range of 90–95%[2]; however, locally advanced cervical cancer patients, which account for 30–40% of new diagnoses, experience a 5 year progression-free survival between 60% and 75% after chemoradiation.[3] In patients with oligometastatic or recurrent/persistent disease, several therapeutic scenarios should be carefully considered on the basis of previous initial treatment(s), site(s) of disease spread, and efficacy of therapeutic approaches.[4] In this context, approximately 30% of patients with a local persistent/recurrent disease who undergo pelvic exenteration

could achieve pelvic control.[5] In case of diffuse, distant disease(s), platinum-based regimens with or without bevacizumab are considered the standard, despite a modest rate of response and poor survival.[6] Recently, attention has been focused on immunotherapy, such as immune checkpoint inhibitors mainly based on the programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) inhibitors[7]; however, systemic treatments (both cytotoxic or target-based chemotherapy) are characterized by adverse events and worsening quality of life.[7]

In oligometastatic/persistent/recurrent disease,[8] adoption of stereotactic body radiotherapy, one of the high modulated and conformal radiotherapy techniques, allows for treatment of small volumes with high doses of radiotherapy in few fractions, and may be recommended for curative-intent treatment strategies.[9 10] Stereotactic body radiotherapy has low acute and late toxicity, making it suitable for individuals who have already had radiotherapy.[11 12] Moreover, stereotactic body radiotherapy may be safely administered even during conventional systemic chemotherapy regimens since the short schedules can be easily inserted between cycles.[13] In addition, stereotactic body radiotherapy has also been proven to be effective in chemoresistant disease, and it may mount an immune response by releasing tumor neoantigens following cell death, thus allowing synergism with immunotherapeutic approaches.[14] Few studies on limited series have been published focusing on stereotactic body radiotherapy in oligometastatic/persistent/recurrent cervical cancer patients.[15–20] The purpose of this retrospective, multicenter study was to evaluate the efficacy and safety of stereotactic body radiotherapy in a wide, real-life dataset of such patients.

METHODS

Study Design and End-Points

The study was approved by the Institutional Review Board (N° 62967/2020 ASREM Ethical Committee) and patients at each center must have signed an informed consent prior to clinical data being used for educational or research purposes. The purpose of this retrospective study (MITO-RT2/RAD), involving 15 Italian radiation oncology institutions, was to assess the efficacy and safety of stereotactic body radiotherapy in oligometastatic/persistent/recurrent cervical cancer patients. The study was promoted and performed by 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). Only patients with a controlled primary site at the time of stereotactic body radiotherapy, who had received external beam with rigid or proper immobilization, accurate target localization, large dose per fraction, highly conformal treatment, and daily image guidance to ensure safe delivery of ultra-high doses of radiation to small targets, were allowed to participate in the study. The dose-fractionation regimen was at the discretion of the treating physician. The co-primary endpoints of the MITO-RT2/RAD study were the clinical complete response rate of disease to stereotactic body radiotherapy, and the 2 year actuarial local control rate. It was defined on 'per lesion' basis as the disease progression within the stereotactic body radiotherapy field of irradiation.

Rate and severity of acute and late toxicities, as well as the 2 year actuarial late toxicity-free survival, represented the secondary endpoints; additionally, actuarial progression-free survival and overall survival were investigated.

Inclusion/Exclusion Criteria

Patients with histologically documented oligo-recurrent/persistent/progressive cervical cancer, who were unfit for surgery or systemic therapy, were suitable for inclusion in the study. All histological subtypes were eligible. Oligometastatic/recurrent/progressive patients were defined as patients with ≤5 new or enlarging metastases in an otherwise well-controlled disease status and, therefore, candidates for curative-intent treatment. Participants had to be >18 years of age and have measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria or Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) criteria[21 22]

Procedures

Principal investigators (GM and GF) established a specific dataset for standardized data collection. Age, histotype, number and type of comorbidities, past surgeries and medical treatments, and previous 'in site' radiotherapy were the required variables. Technical stereotactic body radiotherapy details and data concerning response, acute and late toxicities, outcome measures, and follow-up were also gathered. The radiologic response to stereotactic body radiotherapy was evaluated using a computed CT scan or a PET/CT scan, which was then categorized using the Response Evaluation Criteria in Solid Tumors (version 1.1) or Positron Emission Tomography Response Criteria in Solid Tumors criteria.[21 22] Objective response rate was defined as the sum of complete response and partial response, while the clinical benefit consisted of objective response rate and stable disease.

Actuarial local control was termed as the time gap between the date of stereotactic body radiotherapy and the date of 'in site' stereotactic body radiotherapy field relapse/progression of lesions or the date of the last clinical evaluation. Actuarial progression-free survival was termed on a 'per patient' basis as the time gap between the date of stereotactic body radiotherapy and the date of out of field progression or the date of the last clinical evaluation; overall survival was termed as the time gap between the date of stereotactic body radiotherapy and the date of death of disease or the date of the last clinical evaluation. According to center policy, the toxicity evaluation was performed by the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer and Common Terminology Criteria for Adverse Events scales.[23 24]

Analysis of Data and Statistical Methods

All data were collected at the Radiotherapy Unit of Gemelli Molise Hospital, Università Cattolica del S. Cuore, Campobasso, Italy, and entered into an electronic database. The data processing was performed by GF and GM. Patient characteristics were reported as medians and ranges for continuous variables and percentages for categorical variables. The Pearson χ^2 test was used to test the differences between subgroups, choosing a p value <0.05 for statistical significance definition. Logistic regression was used to carry out the univariate and multivariate analysis of factors predicting clinical

complete response on a 'per lesion' basis. The result of the logistic regression model was expressed as odds ratios with 95% confidence intervals. To analyze actuarial outcomes the Kaplan-Meier method was used; differences among subgroups were evaluated by log-rank tests, and univariate and multivariate Cox regression analysis. Statistical analysis was carried out by Statistical Package for the Social Sciences, version 27.0 software (SPSS, Inc, Chicago, IL).

RESULTS

Eighty-three cervical cancer patients, with a total of 125 lesions treated by stereotactic body radiotherapy between March 2006 and February 2021 at 15 radiation oncology institutions, were included. The median age was 58 years (range 30–92), and the majority (94.0%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 (Table 1). Comorbidities were found in 41 patients (49.4%), with hypertension, diabetes, and thyroid problems being the most common. Squamous carcinoma was the most common histotype (63.8%), followed by adenocarcinoma (24.1%). In terms of treatment(s) prior to stereotactic body radiotherapy, the majority of patients (67.5%) had at least one major surgery; previous chemotherapy was administered to 61 patients (73.5%) (median number of lines 2, range 1–5), while bevacizumab was administered only to 12 patients (14.4%). Previous radiotherapy was administered to 69 patients (83.1%), of which 28 (33.7%) underwent previous 'in site' radiotherapy.

Stereotactic Body Radiotherapy Treatment on 'Per-Lesion' Basis

The features of the lesions (n=125) and their treatment are listed in Table 2: lymph node metastases accounted for 55.2%, followed by parenchyma lesions (44.8%), pelvis (36.8%), thorax (27.2%), and abdomen (24.8%). Only 10 lesions (8.0%) were pelvic central recurrences, while 32 (25.6%) were pelvic lymph node recurrences. Fifty-eight patients (69.9%) had only one lesion, while 25 patients (30.1%) had >1 concurrent or sequential lesions. Lesions had a median gross tumor volume of 4.3 cm^3 (range 0.20–105.10), and a median planning target volume of 15.7 cm^3 (range 1.8–278.5). As summarized in Table 2, stereotactic body radiotherapy was administered with different sets of equipment, with linear accelerator most frequently used (85.6%). The most commonly mentioned technique was volumetric arc therapy (83.2%).

Overall, median total dose prescription was 35 Gy (range 10–60), given in five fractions (range 1–10), with a median dose for each fraction of 7 Gy (range 4–26). The biologically effective dose (BED) was estimated using 10 as the α/β ratio due to the variability of schedules in terms of dose and fractionation strategies for each treatment site. Overall, the median $BED_{\alpha/\beta 10}$ was 59.5 Gy (range 15.0–151.2). One hundred and fifteen metastases (92.0%) were treated by stereotactic body radiotherapy (multiple fractions), and 10 lesions were managed by single fraction radiotherapy. Fractionation schedules were prescribed according to tumor location and indication; overall, the number of lesions treated with >5 fractions accounted for 13.6% (17/125) (Figure 1). The stereotactic body radiotherapy median dose was 35 Gy (range 10–60) with a median $BED_{\alpha/\beta 10}$ of 59.5 Gy (range 15–151.20); the most represented stereotactic body radiotherapy schedules were 30 Gy or 40 Gy in

Table 1 Patient characteristics

	N (%)
All	83
Age, years	
Median (range)	58 (30–92)
Eastern Cooperative Oncology Group performance status	
0	56 (67.5)
1	22 (26.5)
2	4 (4.8)
3	1 (1.2)
Comorbidities per patient	
0	42 (50.6)
1	21 (25.3)
2	9 (10.8)
3	5 (6.0)
4	3 (3.6)
>5	3 (3.6)
Histotype	
Squamous	53 (63.8)
Adenocarcinoma	20 (24.1)
Adenosquamous	5 (6.0)
Other	5 (6.0)
Number of patients undergoing surgery before SBRT	
No	27 (32.5)
Yes	56 (67.5)
Number of patients undergoing chemotherapy before SBRT	
No	21 (25.3)
Yes	61 (73.5)
n.a.	1 (1.2)
Number of lines of previous chemotherapies	
Median (range)	2 (1–5)
Number of patients undergoing bevacizumab treatment	
No	69 (83.1)
Yes	12 (14.4)
n.a.	*2 (2.4)*
Number of patients undergoing previous radiotherapy	
No	13 (15.7)
Yes	69 (83.1)
n.a.	1 (1.2)
Number of patients undergoing previous 'in site' radiotherapy	
No	55 (66.3)
Yes	28 (33.7)

Continued

Table 1 Continued

	N (%)
Number of of patients bearing*	
1 lesion	58 (69.9)
2 lesions	13 (15.7)
3 lesions	9 (10.8)
4 lesions	1 (1.2)
5 lesions	2 (2.4)

*Calculated on the number of patients (n=83).
n.a., not available; SBRT, stereotactic body radiotherapy.

five fractions (Figure 1). The single fraction radiotherapy median dose was 18 Gy (range 10–26) with a median $BED_{\alpha/\beta10}$ of 50.4 Gy (range 20.0–93.6). The most frequently used schedule for single fraction radiotherapy was 18 Gy in one fraction (Figure 1). Abscopal effect was not registered.

Efficacy

The median time for evaluating the best response was 3 months (range 1.5–9 months); complete response, partial response, stable disease, and progressive disease were observed in 73 (58.4%), 29 (23.2%), 16 (12.8%), and seven lesions (5.6%), respectively. Objective response rate was 81.6%, while the overall clinical benefit was 94.4%.

We aimed to identify disease features potentially associated with a higher chance of reaching complete response 'per lesion' by binary logistic regression (data not shown); however, none of them were statistically significantly different. In this context, we checked the distribution of lymph node and parenchyma lesions according to $BED_{\alpha/\beta10}$ and found that lymph node lesions were handled with median $BED_{\alpha/\beta10}$ of 48 Gy (range 15.0–105.6) versus 59.5 Gy (range 15.0–151.2) in parenchymal lesions (p=0.042) (Table 3). As a result, we postulated that the latter finding could be a confounding factor, perhaps concealing the impact of $BED_{\alpha/\beta10}$ in complete response attainment, as reported in a previous experience with stereotactic body radiotherapy in ovarian cancer patients[25]; however, after inclusion of the $BED_{\alpha/\beta10}$ in the univariate and multivariate analysis, we did not find any variables with a statistically significant independent role in predicting clinical complete response (Online supplemental table 1).

Clinical Outcome

Median follow-up was 14.5 months (range 3–129) as of May 2021; in terms of local control, 27 of 125 irradiated lesions (21.6%) had progressed and the 2 year actuarial local control rate was 61.8%. There was progression of disease in 52 patients (62.6%), and death from disease in 34 patients (40.9%). The 2 year actuarial progression-free survival rate on 'per patient' basis was 28.9%, and the 2 year actuarial overall survival rate was 59.0%, as shown in Online supplemental figure 1.

Figure 2 summarizes the impact of complete response on local control, progression-free survival, and overall survival. Patients achieving complete response on 'per lesion' basis experienced a 2 year actuarial local control of 89.0% versus 22.1% in lesions not achieving complete response (p<0.001).

Table 2 Features of lesions and details of treatment

	N (%)
	125
Type of lesion(s)	
Lymph node	69 (55.2)
Parenchyma	56 (44.8)
Anatomical region	
Neck	7 (5.6)
Thorax	34 (27.2)
Abdomen	31 (24.8)
Pelvis	46 (36.8)
Bone	7 (5.6)
GTV	
Median, range (cm^3)	4.3 (0.2–105.1)
PTV	
Median, range (cm^3)	15.7 (1.8–278.5)
Equipment	
Linear accelerator (LINAC)	107 (85.6)
CyberKnife	10 (8.0)
Tomotherapy	1 (0.8)
GammaKnife	7 (5.6)
Techniques	
VMAT	104 (83.2)
IMRT	20 (16.0)
3D-CRT	1 (0.8)
Type of treatment	
SBRT, stereotactic radiotherapy (more fractions)	115 (92.0)
SRS, stereotactic radiosurgery (single fraction)	10 (8.0)
Total dose, Gy	
Median (range)	35 (10–60)
Number of fractions	
Median (range)	5 (1–10)
Dose/fraction, Gy	
Median (range)	7 (4.0–26.0)
$BED_{\alpha/\beta10}$	
Median (range)	59.5 (15.0–151.2)
Referral dose	
Specific isodose	48 (38.4)
Isocenter	31 (24.8)
Target mean	46 (36.8)

BED, biologically effective dose; 3D-CRT, three-dimensional conformal radiation therapy; GTV, gross tumor volume; IMRT, intensity modulated radiotherapy; PTV, planning target volume; VMAT, volumetric modulated arc therapy.

As far as progression-free survival is concerned, the 2 year actuarial rate was 42.5%, while patients undergoing partial response or stable or progressive disease had a 2 year rate of 7.8% (p=0.001). Patients achieving complete response experienced a 2 year overall

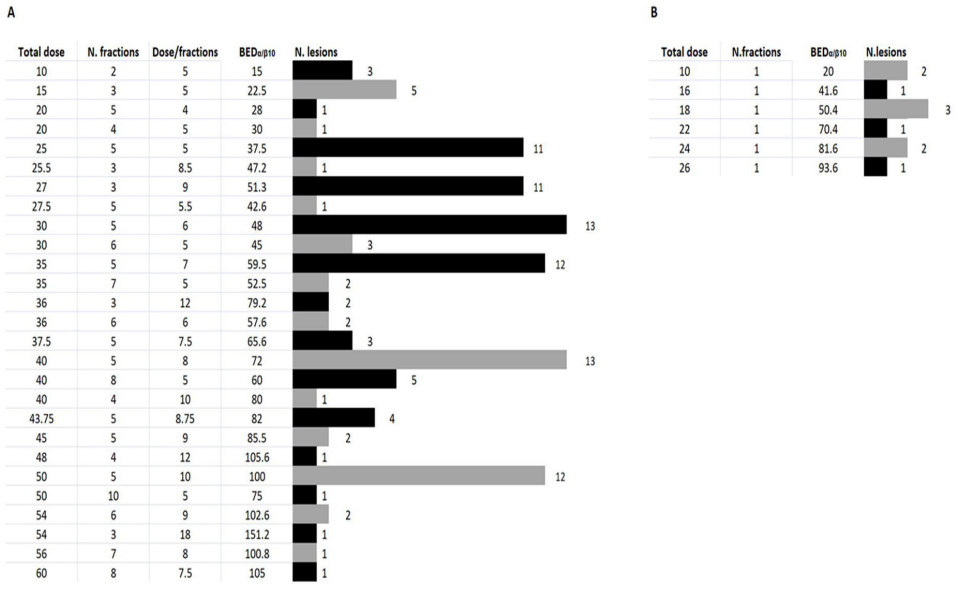

Figure 1 Summary of various radiation schedules based on (A) stereotactic body radiotherapy, and (B) stereotactic radiosurgery. BED, biologically effective dose.

survival rate of 68.9% versus only 44.3% in patients not achieving complete response (p=0.015).

Safety

Fifteen patients (18.1%) of 83 had mild acute toxicity, with a total of 29 events, 20 of which were grade 1 and nine were grade 2; upper gastrointestinal toxicity was the most common (nine patients, 10.8%), followed by asthenia (three patients, 3.6%), and lower gastrointestinal (three patients, 3.6%). As it pertained to late toxicity, only four patients (4.8%) had seven adverse events. One patient had grade 2 pain and grade 2 skin (erythema), the second experienced grade 1 lower gastrointestinal and grade 1 skin (erythema), the third had grade 1 asthenia and grade 1 pain, and the fourth patient had grade 3 pain.

DISCUSSION

Summary of Main Results

We observed a 58.4% complete response in irradiated lesions, which is consistent with previously published literature on cervical cancer stereotactic body radiotherapy cohorts providing clinical response data.[15–18] Furthermore, we found partial response and stable disease in 23.2% and 12.8% of lesions, respectively,

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

	Lymph node lesions Median (range)	Parenchymal lesions Median (range)	P value*
All lesions	69	56	
GTV, cm^3	3.7 (0.3–49.4)	7.0 (0.2–223.3)	0.141
PTV, cm^3	14.7 (1.8–135.4)	24.7 (3.6–135.4)	**0.005**
Total dose, Gy	30.0 (10.0–50.0)	35.0 (10.0–60.0)	0.098
Number of fractions	5 (1–9)	5 (1–10)	0.377
Dose/fraction, Gy	6 (3.0–25.0)	7.7 (3.0–26.0)	**0.010**
$BED_{\alpha/\beta10}$, Gy	48.0 (15.0–105.6)	59.5 (15.0–151.2)	**0.042**
Histotype			
Squamous	47 (68.1)	30 (53.6)	0.096†
Other	22 (31.9)	26 (46.4)	
Previous 'in site' radiotherapy			
No	43 (62.3)	41 (73.2)	0.197†
Yes	26 (37.6)	15 (26.8)	

*Calculated by the Mann-Whitney test,
†Calculated by the χ^2 test.
BED, biologically effective dose; GTV, gross tumor volume; PTV, planning target volume; SBRT, stereotactic body radiotherapy.

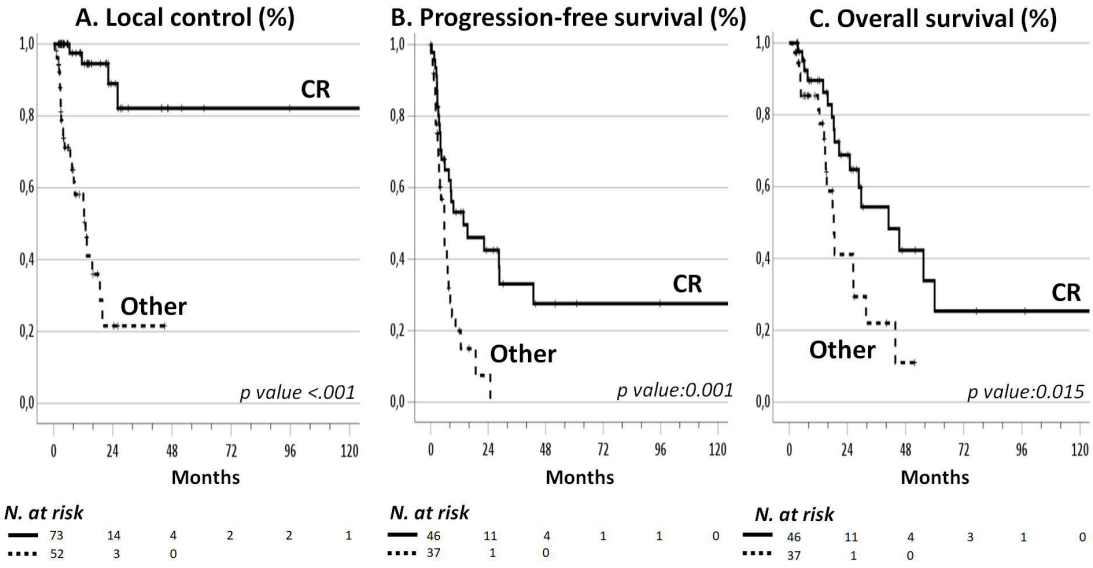

Figure 2 (A) Actuarial local control in the entire series of lesions according to clinical response (complete response vs partial/stable/progression). (B) Actuarial progression-free survival (progression outside SBRT field-free survival) in the entire series of patients according to clinical response. (C) Actuarial overall survival in the entire series of patients according to clinical response. Solid lines, complete response to SBRT; dashed lines, partial/stable/progression (other). CR, complete response; SBRT, stereotactic body radiotherapy.

resulting in a 94.4% clinical benefit. In regard to local control rate, stereotactic body radiotherapy provided a 2 year actuarial rate of 61.8%. The 2 year local control reached 89.0% in patients with complete response versus 22.1% in lesions not achieving complete response. Likewise, even the 2 year progression-free survival and overall survival were higher in patients with complete response compared with those without complete responders. Additionally, a low-grade toxicity profile was observed: only 18.1% of patients experienced low-grade acute toxicity, and only 4.8% experienced late toxicity. Given that one-third of patients had previously received 'in site' radiotherapy, 73.5% had received nearly two lines of chemotherapy, and more than two-thirds had undergone at least one major surgery, this finding provides further evidence of the safety of stereotactic body radiotherapy in unfavorable settings. In our series, no abscopal effect was registered, but we have to acknowledge that none of our patients had received immunotherapy treatment(s), most patients had previously been irradiated on lymph node stations virtually precluding the immune response, and the total doses were low.

Results in the Context of Published Literature

Choi et al, in a retrospective study on 30 patients with isolated paraaortic lymph node metastases from uterine cervical and corpus cancer who had received stereotactic body radiotherapy using the CyberKnife machine,[15] reported a 65.5% complete response rate; this value is higher than ours and is likely due to the small sample size and/or the inclusion of only lymph node disease, which responds better to stereotactic body radiotherapy than parenchymal lesions.[25–27] To date, a comprehensive evaluation of lymph node lesion responsiveness compared with parenchymal disease is still lacking; therefore, further information on the intrinsic biomolecular characteristics of lymph node and parenchymal lesions would be useful.

In contrast to our experience with stereotactic body radiotherapy in 446 oligometastatic/persistent/recurrent ovarian cancer lesions,[25] where we found that younger age, lower tumor volume, lymph node disease, and higher BED/10 resulted as independent predictors of a high likelihood of complete response, we found no variables with a statistically significant independent role in predicting clinical complete response in the current study. This finding is likely attributable to the lower number of patients. Despite the local control, which is expected to enhance symptom relief and quality of life, as well as the potential postponement of chemotherapy, the rate of progression outside of the target lesions remains high, ranging from 37–52%.[15–18] In this context, the evidence supporting the potential role of stereotactic body radiotherapy in enhancing tumor immunogenicity and promoting systemic activity suggests that stereotactic body radiotherapy and immunotherapy could synergize together.[28]

Strengths and Weaknesses

In our study, the delivered doses were variable, as evidenced by the wide range of stereotactic body radiotherapy regimens in terms of total dose or BED10; this finding is common in real-world practice, where the dose must be adjusted based on several factors such as the location and size of the disease, nearby healthy tissues, patient morbidities, radiation oncologist expertise, and technical equipment. We acknowledge that in the present series approximately one-third of patients were managed by low doses, probably due to the large percentages of previous irradiation. Moreover, previous chemotherapy lines and, above all, adoption of bevacizumab has to be taken into account given the increased rates of fistulae formation after bevacizumab therapy (5–9%).[29–31] As a logical result, efforts targeted at designing prospective trials for a better definition of stereotactic body radiotherapy regimens could be beneficial in order to align the approaches, and produce more consistent and reliable results.[25 32 33]

Our series had a median interval from diagnosis to stereotactic body radiotherapy of 24 months, ranging from a few months after primary treatment to more than 10 years. On the basis of the inclusion criteria (patients who are unfit for other treatments), one could argue that the patients in this study were more unfavorable than those who are currently included in stereotactic radiotherapy studies; however, stereotactic radiotherapy is increasingly being offered as a curative treatment as an alternative to other eradicating treatments, such as in the treatment of early stage prostate or lung cancer. To date, we currently use stereotactic body radiotherapy to treat isolated recurrences with the goal of cure, rather than as a last resort if systemic therapy is contraindicated and/or major comorbidities are present. However, patients in this study had been enrolled since 2006, and the benefits of stereotactic body radiotherapy were not well known. In the first decade of the 2000s, only a few centers in the world had treated oligometastatic gynecological patients with this technique, and international guidelines did not include this local approach, thus suggesting systemic therapy.

Implications for Practice and Future Research

This analysis suggests that stereotactic radiotherapy is a valuable treatment option for patients with a low burden of metastatic/recurrent/persistent cervical cancer. A link between clinical complete response to treatment and local control, progression-free survival, and overall survival rates has been identified. However, the variability in dosages and the unfavorable selection of patients failed to show a possible effect on overall survival or disease-free survival. Future research is needed to see if patients would benefit from combining this radiation technique with other treatments. Overall, these results should be regarded as hypothesis generating and could be evaluated further in appropriately designed and powered prospective studies aimed at defining the optimum individualized radiation dose and the best settings where it can be applied.

Conclusions

Our study showed the impact of complete response to stereotactic body radiotherapy on local control, progression-free survival, and overall survival. Patients achieving complete response experienced a 2 year actuarial local control of 89.0% versus 22.1% in lesions not achieving complete response. Acute and late toxicities were low, proving the safety of this treatment even in heavily pretreated patients. A prospective trial, like the one we currently have for ovarian cancer,[33] could better clarify these aspects.

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REFERENCES

1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020;70:7–30.
2 Ramirez PT, Frumovitz M, Pareja R, *et al*. Minimally invasive versus abdominal radical hysterectomy for cervical cancer. *N Engl J Med* 2018;379:1895–904.
3 Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC). Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis. *Cochrane Database Syst Rev* 2010;1.
4 National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Cervical Cancer.

Version 1.*2020* - January 14, 2020. Available: https://www.nccn.org/professionals/physician.gls/pdf/cervical.pdf
5 Chiantera V, Rossi M, De Iaco P, *et al*. Survival after curative pelvic exenteration for primary or recurrent cervical cancer: a retrospective multicentric study of 167 patients. *Int J Gynecol Cancer* 2014;24:916–22.
6 Tewari KS, Sill MW, Penson RT, *et al*. Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). *Lancet* 2017;390:1654–63.
7 Colombo N, Dubot C, Lorusso D, *et al*. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. *N Engl J Med* 2021;385:1856–67.
8 Lievens Y, Guckenberger M, Gomez D, *et al*. Defining oligometastatic disease from a radiation oncology perspective: an ESTRO-ASTRO consensus document. *Radiother Oncol* 2020;148:157–66.
9 Guckenberger M, Lievens Y, Bouma AB, *et al*. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. *Lancet Oncol* 2020;21:e18–28.
10 Chao ST, Dad LK, Dawson LA, *et al*. ACR-ASTRO practice parameter for the performance of stereotactic body radiation therapy. *Am J Clin Oncol* 2020;43:545–52.
11 Palma DA, Olson R, Harrow S, *et al*. Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastatic cancers: long-term results of the SABR-COMET phase II randomized trial. *J Clin Oncol* 2020;38:2830–8.
12 Deodato F, Macchia G, Cilla S, *et al*. Dose escalation in extracranial stereotactic ablative radiotherapy (DESTROY-1): a multiarm phase I trial. *Br J Radiol* 2019;92:20180422.
13 Gurka MK, Kim C, He AR, *et al*. Stereotactic body radiation therapy (SBRT) combined with chemotherapy for unresected pancreatic adenocarcinoma. *Am J Clin Oncol* 2017;40:152–7.
14 Rodríguez-Ruiz ME, Vanpouille-Box C, Melero I, *et al*. Immunological mechanisms responsible for radiation-induced abscopal effect. *Trends Immunol* 2018;39:644–55.
15 Choi CW, Cho CK, Yoo SY, *et al*. Image-guided stereotactic body radiation therapy in patients with isolated para-aortic lymph node metastases from uterine cervical and corpus cancer. *Int J Radiat Oncol Biol Phys* 2009;74:147–53.
16 Seo Y, Kim M-S, Yoo H-J, *et al*. Salvage stereotactic body radiotherapy for locally recurrent uterine cervix cancer at the pelvic sidewall: feasibility and complication. *Asia Pac J Clin Oncol* 2016;12:e280–8.
17 Hou X, Wang W, Zhang F, *et al*. Stereotactic body radiation therapy for oligometastatic pulmonary tumors from cervical cancer. *Asia Pac J Clin Oncol* 2019;15:e175–80.
18 Park HJ, Chang AR, Seo Y, *et al*. Stereotactic body radiotherapy for recurrent or oligometastatic uterine cervix cancer: a cooperative study of the Korean Radiation Oncology Group (KROG 14-11). *Anticancer Res* 2015;35:5103–10.
19 Macchia G, Deodato F, Cilla S, *et al*. Volumetric modulated arc therapy for treatment of solid tumors: current insights. *Onco Targets Ther* 2017;10:3755–72.
20 Yegya-Raman N, Cao CD, Hathout L, *et al*. Stereotactic body radiation therapy for oligometastatic gynecologic malignancies: a systematic review. *Gynecol Oncol* 2020;159:573–80.
21 Eisenhauer EA, Therasse P, Bogaerts J, *et al*. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–47.
22 Wahl RL, Jacene H, Kasamon Y, *et al*. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. *J Nucl Med* 2009;50 Suppl 1:122S–50.
23 Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995;31:1341–6.
24 National Cancer Institute common terminology criteria for adverse events v.4.03 (CTCAE v.4.03).
25 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.
26 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.
27 Ponti E, Lancia A, Ost P, *et al*. Exploring all avenues for radiotherapy in oligorecurrent prostate cancer disease limited to lymph nodes: a systematic review of the role of stereotactic body radiotherapy. *Eur Urol Focus* 2017;3:538–44.
28 Lee L, Matulonis U. Immunotherapy and radiation combinatorial trials in gynecologic cancer: a potential synergy? *Gynecol Oncol* 2019;154:236–45.
29 Kim N, Choi SH, Chang JS, *et al*. Use of bevacizumab before or after radiotherapy increases the risk of fistula formation in patients with cervical cancer. *Int J Gynecol Cancer* 2021;31:59–65.
30 Kim YB, Cho JH, Keum KC, *et al*. Concurrent chemoradiotherapy followed by adjuvant chemotherapy in uterine cervical cancer patients with high-risk factors. *Gynecol Oncol* 2007;104:58–63.
31 Yoon HI, Cha J, Keum KC, *et al*. Treatment outcomes of extended-field radiation therapy and the effect of concurrent chemotherapy on uterine cervical cancer with para-aortic lymph node metastasis. *Radiat Oncol* 2015;10.
32 Chopra S, Mangaj A, Sharma A, *et al*. Management of oligo-metastatic and oligo-recurrent cervical cancer: a pattern of care survey within the EMBRACE research network. *Radiother Oncol* 2021;155:151–9.
33 Macchia G, Jereczek-Fossa BA, Lazzari R, *et al*. Efficacy and safety of stereotactic body radiotherapy (SBRT) in oligometastatic/persistent/recurrent ovarian cancer: a prospective, multicenter phase II study (MITO-RT3/RAD). *Int J Gynecol Cancer* 2021:ijgc-2021-002709.