Stereotactic body radiotherapy (SBRT) in the management of oligometastatic gynecological cancer

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Obiettivo dello studio

- Efficacia della SBRT nei tumori ginecologici oligometastatici
- Fattori predittivi di controllo locale (LC), sopravvivenza libera da progressione di malattia (PFS) e sopravvivenza globale (OS)

Materiali e Metodi

❖Criteri di inclusione

- ➢Età maggiore di 18 anni
- ➢Eastern Cooperative Oncology Group [ECOG] performance status [PS] ≤ 2
- ➢Aspettativa di vita ≥ 6 mesi
- ➢Malattia Oligometastatica (n° totale di metastasi ≤ 5)
- ➢Diametro maggiore della lesione < 6 cm
- ➢Assenza di pregresso trattamento nel volume irradiato
- ➢Normale funzionalità midollare ossea

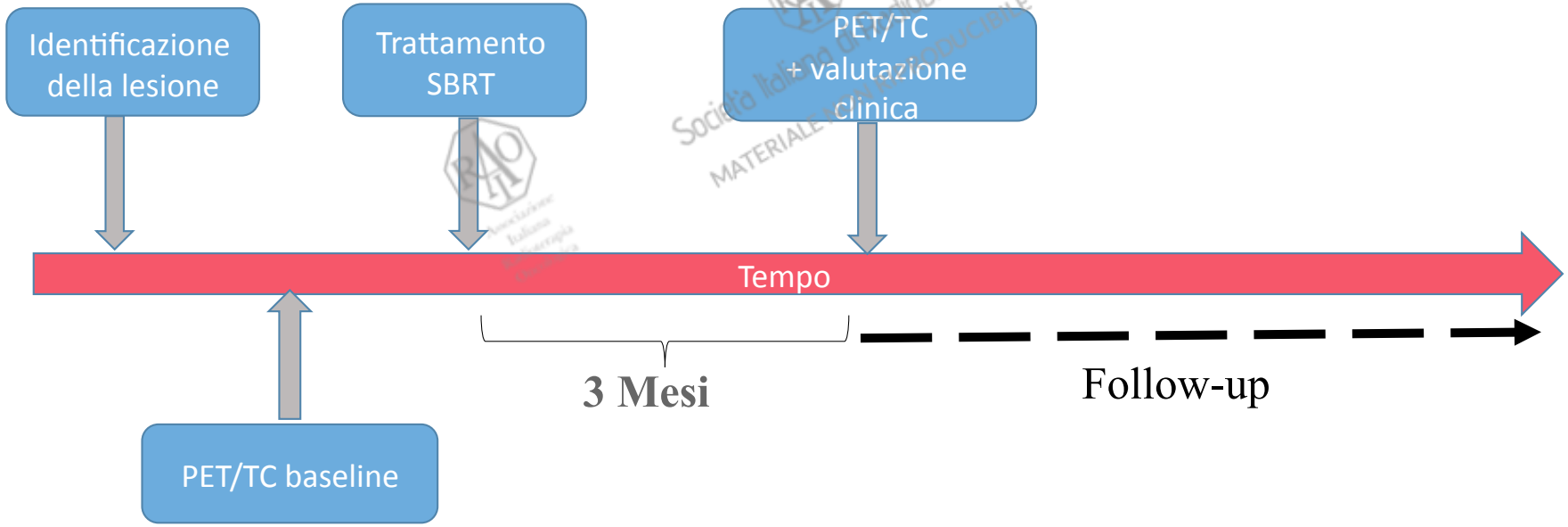
Materiali e Metodi

❖ Trattamento

- True Beam Linac
- Eclipse Planning System (Versione 10.0)
- Tecnica V-MAT
- 6 MeV Flattening Filter Free (FFF)
- Frazionamento : 24Gy/1ff; 27Gy/3ff (9 Gy/ff)

Materiali e Metodi

❖ Valutazione della risposta e follow-up



Materiali e Metodi

Measurement of Clinical and Subclinical Tumour Response Using [18F]-fluorodeoxyglucose and Positron Emission Tomography: Review and 1999 EORTC Recommendations

H. Young,[1] R. Baum,[2] U. Cremerius,[3] K. Herholz,[4] O. Hoekstra,[5] A.A. Lammertsma,[5] J. Pruim[6] and P. Price[1] on behalf of the European Organization for Research and Treatment of Cancer (EORTC) PET Study Group

1. *Progressive metabolic disease (PMD)* to be classified as *an increase in [18F]-FDG tumour SUV of greater than 25% within* the tumour region defined on the baseline scan, visible increase in the extent of [18F]-FDG tumour uptake (20% in the longest dimension) or the appearance of new [18F]-FDG uptake in metastatic lesions.
2. *Stable metabolic disease* (SMD) would be classified as *an increase in tumour [18F]-FDG SUV of less than 25% or a decrease of less than 15%* and no visible increase in extent of [18F]-FDG tumour uptake (20% in the longest dimension).
3. *Partial metabolic response (PMR)* would be classified as a *reduction of a minimum of 15±25% in tumour* [18F]-FDG SUV after one cycle of chemotherapy, and greater than 25% after more than one treatment cycle.
An empirical 25% was found to be a useful cut-off point, but there is a need for a reproducibility analysis to determine the appropriate cut-offs for statistical significance. A reduction in the extent of the tumour [18F]-FDG uptake is not a requirement for partial metabolic response.
4. *Complete metabolic response* (CMR) would be *complete resolution of [18F]-FDG uptake within the tumour volume* so that it was indistinguishable from surrounding normal tissue.

Caratteristiche dei pazienti

Patients **Characteristics**	**Nr**
Number of patients	**45**
Age (years) median (range)	**66 (27-90)**
Primary tumor	
Ovarian	**21**
Endometrium	**15**
Cervix	**9**
RT primary tumor	
No	**27**
Yes	**18**
Chemotherapy	
Yes	**41**
No	**4**
Interval between treatment and recurrences (median, range).	**15 (3-68)**

Treatment Characteristics	**Nr**
Number of treated lesions	**70**
Treatment site	
Lymph nodes	**43**
Lung	**12**
Liver	**8**
Soft tissue	**7**
PET(suv) pre SBRT treatment	
PET(suv) < 8	**20**
PET(suv) ≥ 8	**25**
PTVcc	
< 15	**22**
≥ 15	**23**
Dose Gy/fractions	
One fraction (24 Gy)	**20**
Three fractions (27 Gy)	**50**

Risultati

RISPOSTE	LESIONI	%
CR	45	64.3
PR	14	20.0
SD	5	7.1
PD	6	8.6

Fattori predittivi per il controllo locale, sopravvivenza libera di malattia e sopravvivenza totale

Complete Response

Explicative variable	Univariate analysis HR	CI 95%	p
Age	1.51	0.18-12.55	0.70
(0) ≥ 70			
(1) < 70			
PTV cc	0.88	0.19-3.96	0.87
(0) < 15			
(1) ≥ 15			
RT schedule	0.59	0.13-2.70	0.49
(0) One			
(1) Three			
Site of lesions	1.26	0.15-10.54	0.82
(0) Other			
(1) Liver			
PET pre-SUV	5.20	0.52-51.84	0.16
(0) <8			
(1) ≥ 8			
Primary tumor	2.63	0.80-8.64	0.11
(0) Endometrium			
(1) Cervix			
(2) Ovary			
Ovary primary tumor	6.39	0.76-53.13	*0.08*
(0) No			
(1) Yes			
RT primary tumor	0.29	0.03-2.44	0.25
(0) No			
(1) Yes			

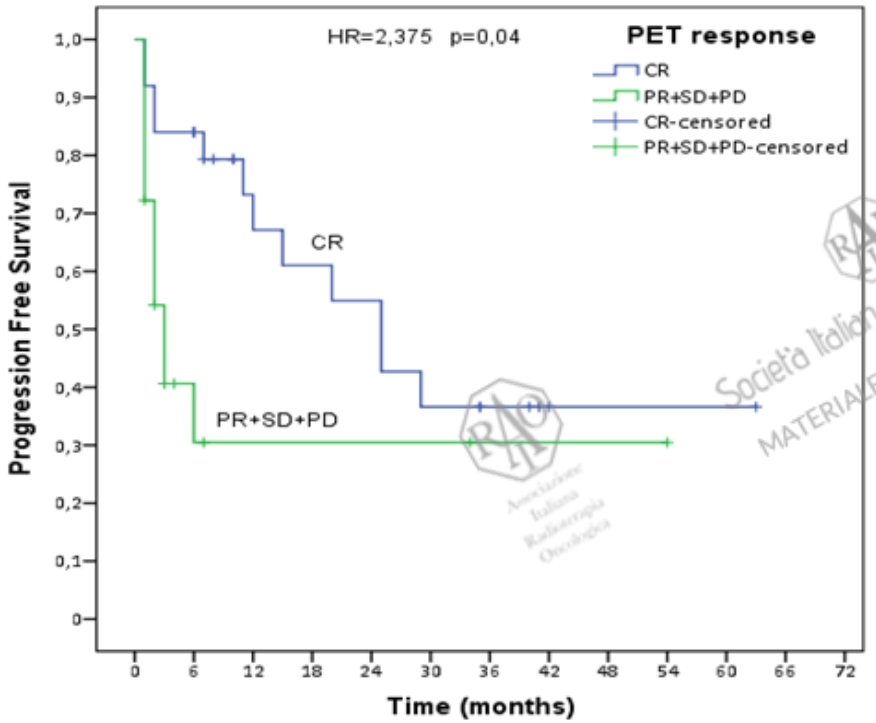
Progression Free Survival

Explicative variable	Univariate analysis HR	CI 95%	P
Age	2.13	0.72-6.25	0.16
(0) ≥ 70			
(1) < 70			
PTV cc	1.10	0.49-2.46	0.81
(0) <15			
(1) ≥ 15			
RT schedule	1.16	0.48-2.83	0.73
(0) One			
(1) Three			
Site of lesions	2.29	0.91-6.15	*0.08*
(0) Other			
(1) Liver			
PET pre-SUV	0.49	0.17-1.40	0.18
(0) <8			
(1) ≥ 8			
PET response	2.37	1.01-5.56	**0.04**
(0) CR			
(1) PR+SD+PD			
Primary tumor	1.45	0.89-2.36	0.13
(0) Endometrium			
(1) Cervix			
(2) Ovary			
Ovary primary tumor	1.94	0.85-4.31	0.11
(0) No			
(1) Yes			
RT primary tumor	0.93	0.40-2.15	0.87
(0) No			
(1) Yes			

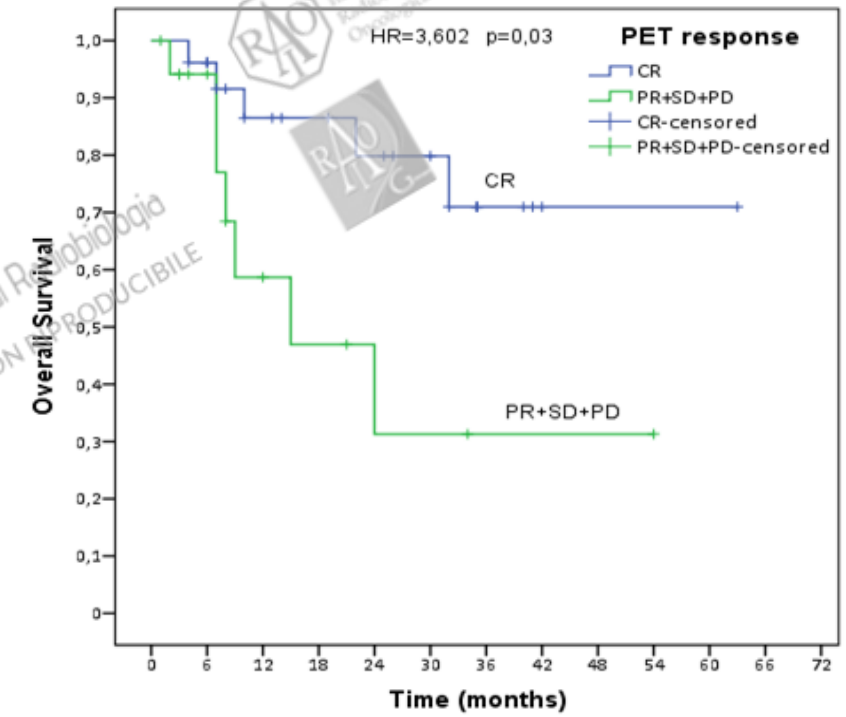
Overall Survival

Explicative variable	Univariate analysis HR	CI 95%	P
Age	1.85	0.41-8.39	0.42
(0) ≥ 70			
(1) < 70			
PTV cc	2.88	0.88-9.41	*0.08*
(0) <15			
(1) ≥ 15			
RT schedule	1.59	0.48-5.21	0.44
(0) One			
(1) Three			
Site of lesions	1.71	0.34-8.11	0.49
(0) Other			
(1) Liver			
PET pre-SUV	2.12	0.52-8.53	0.28
(0) <8			
(1) ≥ 8			
PET response	3.60	1.12-11.54	**0.03**
(0) CR			
(1) PR+SD+PD			
Primary tumor	1.19	0.63-2.26	0.57
(0) Endometrium			
(1) Cervix			
(2) Ovary			
Ovary primary tumor	1.18	0.39-3.55	0.75
(0) No			
(1) Yes			
RT primary tumor	1.68	0.56-5.01	0.35
(0) No			
(1) Yes			

Risultati

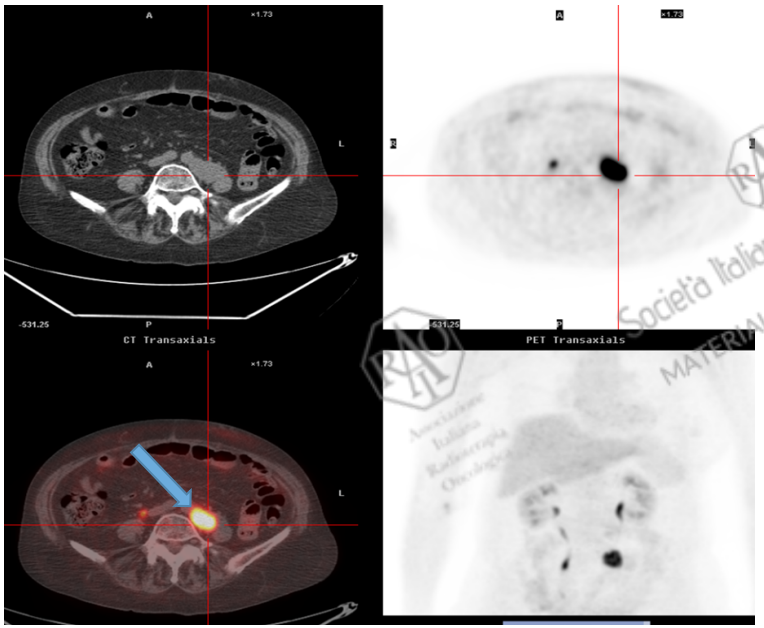


PFS 32% a 5 anni
Mediana PFS 15 mesi

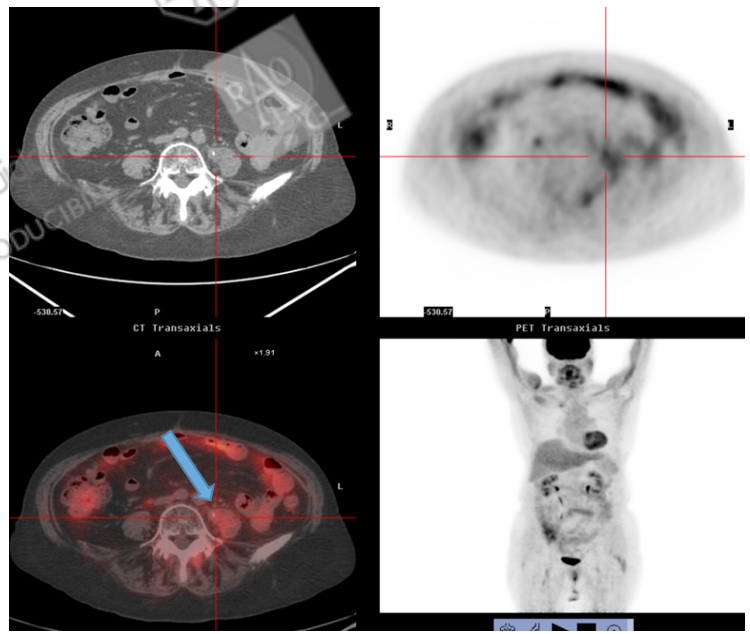


OS 56 % a 5 anni

Risultati

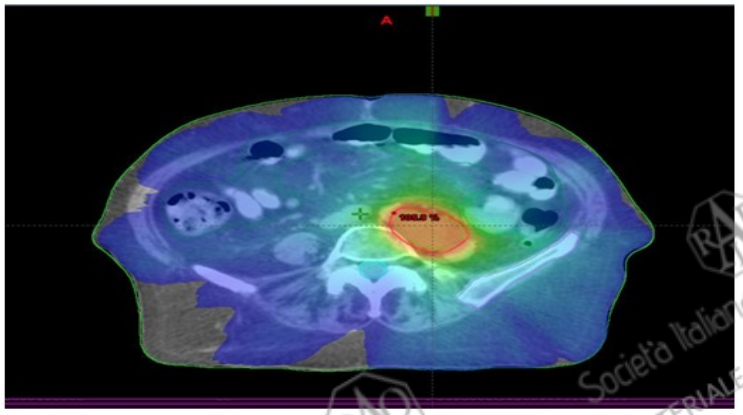


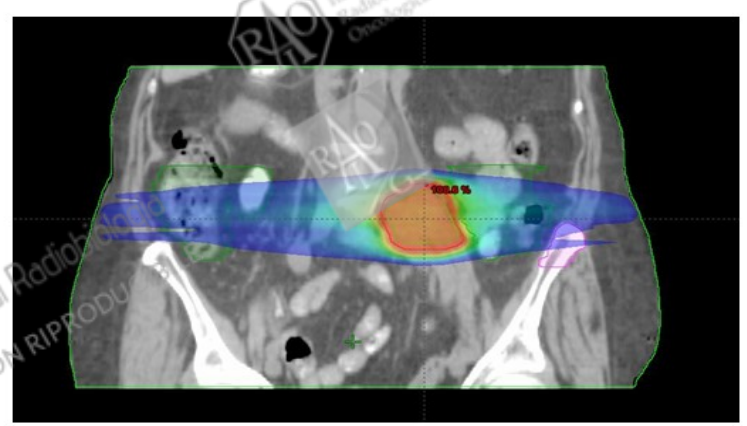
PET/TC prima del trattamento

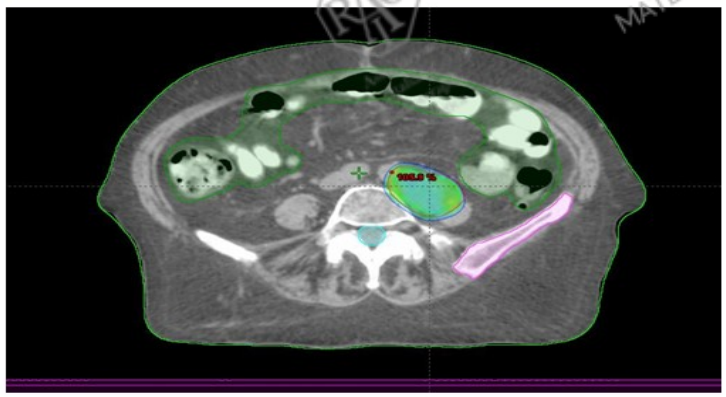


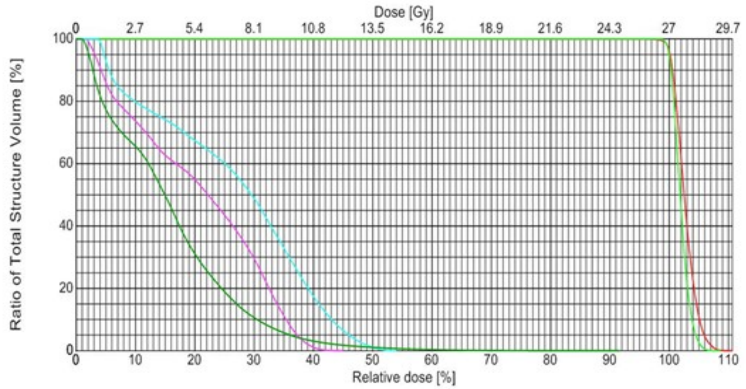
PET/TC 3 mesi dopo il trattamento

Risultati








Dose [Gy]
0
2.7
5.4
8.1
10.8
13.5
16.2
18.9
21.6
24.3
27
29.7
Ratio of Total Structure Volume [%]
100
80
60
40
20
0
0
10
20
30
40
50
60
70
80
90
100
110
Relative dose [%]

Tossicità

- Tossicità* G1/G2 in 13 pazienti (28.9 %).
  - Dolore in 9 pazienti (20 %)
  - Gastrointestinale in 5 pazienti (11.1 %)
  - Fatigue in 1 paziente (2.2%)
  - Dispnea 1 paziente (2.2 %)

* 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 ;31:1341-1346

Table 1 Summary of case series of stereotactic radiosurgery

Ref.	*n*	Cancer types	Disease setting	Dose	Response/ control rate	Survival	Grade 3/4 toxicities	Patterns of failure
Molla *et al*[5]	16	Cervical (7) Uterine (9)	Primary (stage 1-3) and recurrence	EBRT 45 GyT SRS 14-20 Gy/2-5 fractions +/- para-aortic boost (2 pts)	15 pts NED at 12.6 mo (1 recurrence)	Not reported	Rectal bleeding (1)	Not reported
Deodato *et al*[13]	11	Ovarian (4) Cervical (4) Uterine (3)	Recurrence	SRS 20-30 Gy/4-6 fractions	83.3% overall response rate 63% recurrence at 19 mo	Not reported	None	Systemic/distant progression (n = 4) Local progression (n = 1) Local and systemic progression (n = 1)
Guckenburger *et al*[7]	19	Cervical (12) Uterine (7)	Recurrence	EBRT 50 Gy SRS 15 Gy/3 fractions +/- vaginal BT (3 pts)	3 yr local control rate 81%	Median OS 25 mo, PFS 16 mo	Intestino-vaginal fistula (2) Small bowel ileus (1)	Systemic progression (n = 7) Local tumor progression (n = 1) Comorbid illness (n = 1) Unknown (n = 1)
Choi *et al*[10]	30	Cervical (28) Uterine (2)	Recurrence	EBRT 27-45 Gy SRS 13-45 Gy/1-3 fractions	4 yr local control rate 67.4%	Median PFS 32 mo	Various (5)	Locoregional failure (13.8%) Distant mets (10.3%) Local and distant failure (6.9%)
Dewas *et al*[9]	16	Cervical (4) Uterine (1) Rectal (4) Anal (6) Bladder (1)	Recurrence	EBRT 36-66 Gy (3 pts) SRS 36 Gy/6 fractions	1 yr local control rate 51.4%	Median OS 11.5 mo (DFS 8.3 mo)	None	Not reported
Haas *et al*[6]	6	Cervical (6)	Primary (stage 3B-4)	EBRT 45 Gy SRS 19.5-20 Gy/ 3-5 fractions +/- 50.4-61.2 Gy IMRT boost (5 pts)	100% local control at 14 mo	100% at 14 mo	None	Not reported
Hsieh *et al*[2]	9	Cervical (9)	Primary (stage 3B-4A)	EBRT 50.4 Gy SRS 15-27 Gy/ 5-9 fractions	3 yr local control rate 77.8%	Median OS 13 mo	Diarrhea (1) Thrombocytopenia (1) Rectal bleeding (3) Rectovaginal fistula (1)	Distant metastases (44%)
Hsieh *et al*[2]	31	Uterine (31)	Primary (stage 1B-3C)	IMRT or SRS *via* HT 45-50.4 Gy/25-28 fractions ICBT 4.5-5 Gy × 2-6 fractions	Not reported	Median OS 21 mo	None	Distant metastases
Kubicek *et al*[19]	11	Cervical 7) Uterine (2) Vaginal (2)	Primary (stage 2-3C) and recurrence	EBRT or IMRT 45-50.4 Gy SRS 5-27.5 Gy/1-5 fractions	Not reported	73% overall survival at follow-up	Rectal bleeding (1)	Not reported
Kunos *et al*[20]	3	Vulvar (3)	Recurrence	SRS 24 Gy/3 fractions	Not reported	1-3 mo PFS	None	Out of field recurrence
Kunos *et al*[15]	5	Endometrial (1) Ovarian (3) Cervical (1)	Recurrence	SRS 5-8 Gy × 3-5 fractions	Not reported	Not reported	Fatigue (1)	Distant metastases
Kunos *et al*[1] Phase II trial	50	Cervix (9) Endometrial (14) Ovarian (25) Vulvar (2)	Recurrence	SRS 24 Gy/3 fractions	6 mo clinical benefit 68%	Median OS 20.2 mo	Hyperbilirubinemia (1) Enterovaginal fistula (1)	Out of field recurrence (62%)

Long B et al . Stereotactic radiosurgery in gynecologic malignancies *World J Radiol* 2014 June 28; 6(6): 366-373

IMAGE-GUIDED STEREOTACTIC BODY RADIATION THERAPY IN PATIENTS WITH ISOLATED PARA-AORTIC LYMPH NODE METASTASES FROM UTERINE CERVICAL AND CORPUS CANCER

ChulWon Choi, M.D.,* Chul Koo Cho, M.D.,* Seong Yul Yoo, M.D.,* Mi Sook Kim, M.D.,* Kwang Mo Yang, M.D.,* Hyung Jun Yoo, M.D.,* Young Seok Seo, M.D.,* Jin Kyu Kang, M.D.,* Dong Han Lee, Ph.D.,† Kyung Hee Lee, M.D.,‡ Eui Don Lee, M.D.,‡ Sang Young Rhu, M.D.,‡ Suck Chul Choi, M.D.,‡ Moon Hong Kim, M.D.,‡ and Beob Jong Kim, M.D.‡

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- 30 pts with isolated para-aortic mts from cervical or endometrial carcinoma were treated with SBRT (33-45 Gy in 3 daily fractions).

RESULTS (29 pts evaluable)

- **CR** **65.5%**
- **PR** **31.0%**
- **4y-local control rate** **67.4%**
- **4y-OS rate** **50.1%**

frontiers in ONCOLOGY

CLINICAL TRIAL ARTICLE
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Phase II clinical trial of robotic stereotactic body radiosurgery for metastatic gynecologic malignancies

Charles A. Kunos[1], James Brindle[1], Steven Waggoner[2], Kristine Zanotti[2], Kimberly Resnick[2], Nancy Fusco[2], Ramon Adams[2] and Robert Debernardo[2]*

[1] *Department of Radiation Oncology, University Hospitals Case Medical Center and Case Western Reserve University, School of Medicine, Cleveland, OH, USA*
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50 patients with recurrent gynecologic cancer: 29 received SBRT as first-line therapy for metastatic disease (24 Gy in 3 daily fractions).

RESULTS

- **Response rate** **96%**
- 6-month clinical benefit 68%
- **Median PFS** **7.8 months**
- **Median OS** **20.2 months**
- **No SBRT CR targeted disease progressed**

Conclusioni

- SBRT è un trattamento efficace e ben tollerato nelle pazienti affette da tumori ginecologici oligometastatici
- Nessuna lesione con CR è progredita nella sede trattata
- Nessuna tossicità acuta G3/G4 e nessuna tossicità tardiva sono state riportate
- Ulteriori studi prospettici con maggior numero di pazienti sono necessari per ottimizzare le schedule di dose e frazionamento e per selezionare la tipologia di pazienti che possano beneficiare del trattamento SBRT.

Grazie per l’attenzione....