
XXXIII CONGRESSO NAZIONALE AIRO
AIRO2023
BOLOGNA,
27-29 OTTOBRE 2023
PALAZZO DEI CONGRESSI
Radioterapia Oncologica: l'evoluzione al servizio dei pazienti
Associazione Italiana
Radioterapia e Oncologia clinica

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COMBINAZIONE DI PARP INIBITORI E SBRT PER IL TRATTAMENTO DEL CARCINOMA OVARICO OLIGOMETASTATICO

Stefano Durante
Istituto Europeo di Oncologia - Milano

Istituto Giovanni Calabria
IRCCS Ospedale
Sacro Cuore Don Calabria

IEO
Istituto Europeo
di Oncologia

Civico Di Cristina Benfratelli
Azienda di Rilievo Nazionale ad Alta Specializzazione

Associazione Italiana
Radioterapia e Oncologia clinica

DICHIARAZIONE

Relatore: Stefano Durante

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**

Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**

Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**

Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**

Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**

Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**

Altro

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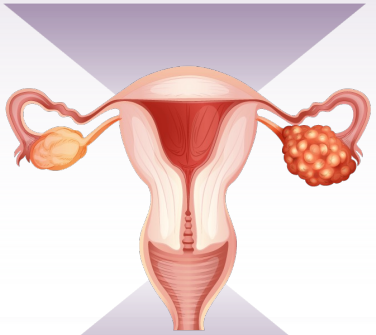
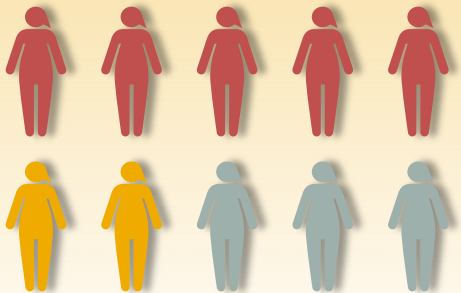
Radioterapia Oncologica:
l'evoluzione al servizio dei pazienti

Most patients with advanced ovarian cancer relapse following first-line multimodal therapy

Over **300,000**
women were **diagnosed** with ovarian cancer in 2020[1]



At least **60%** of newly diagnosed women will have **advanced disease**[2]



~70% **of women relapse**
within 3 years of first-line treatment[3]

5-year survival for newly diagnosed advanced ovarian cancer[2,4]

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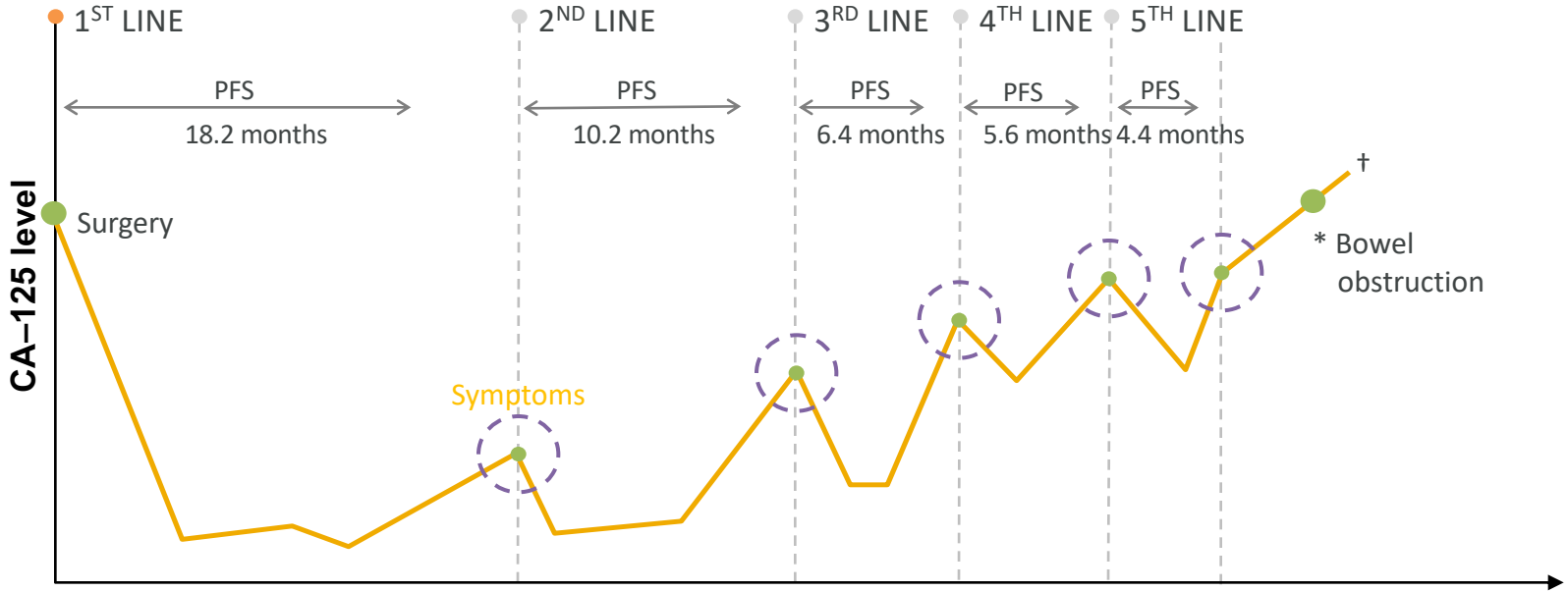
•1. Sung H, et al. *CA Cancer J Clin*. 2021;71(3):209–249; 2. du Bois A, et al. *Cancer* 2009;115:1234–1244; 3. LedermannJA, et al. *Ann Oncol* 2013;24(Suppl. 6):vi24–vi32; 4. Torre LA, et al. *CA Cancer J Clin* 2018;68:284–296; 5. Tewari KS, et al. *J Clin Oncol* 2019;37:2317–2328; 6. Bookman MA, et al. *J Clin Oncol* 2009;27:1419–1425; 7. Burger RA, et al. *N Engl J Med* 2011;365:2473–2483; 8. Perren TJ, et al. *N Engl J Med* 2011;365:2484–2496

Recurrent ovarian cancer

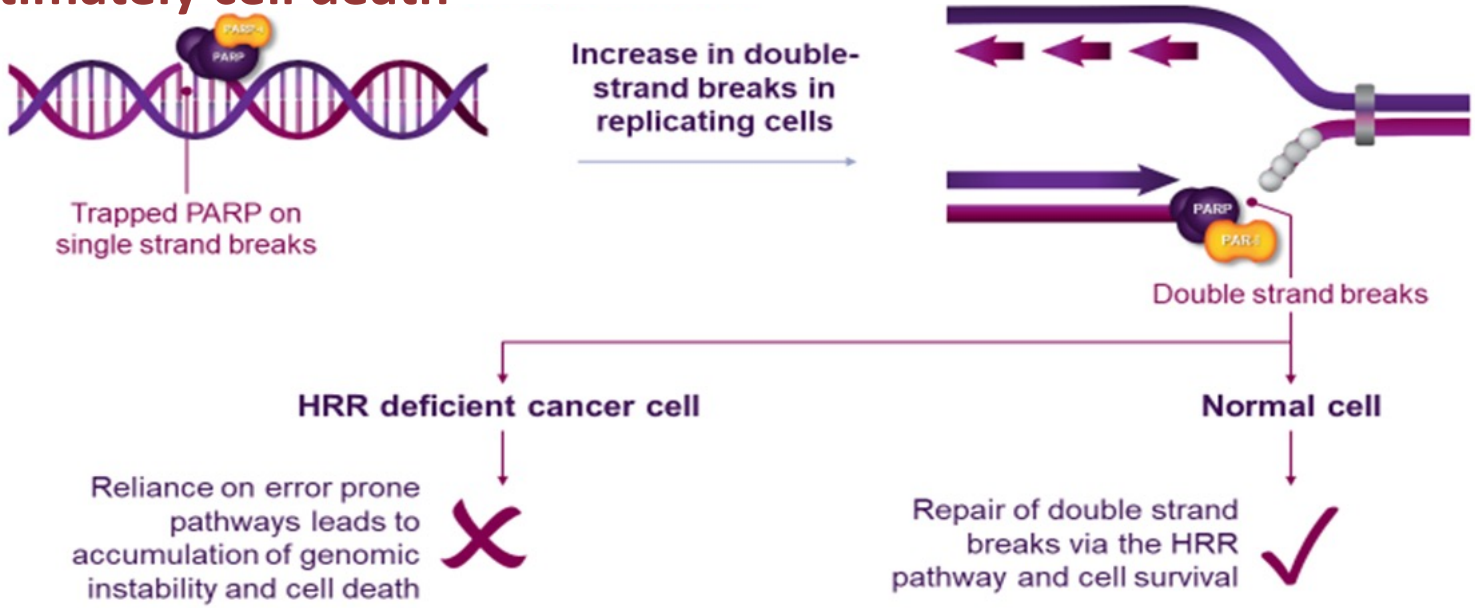
multiple lines of cytotoxic chemotherapy associated with cumulative toxicity and decreasing periods of remission[1-4]



† = Common indicator of fatality
CA-125 = cancer antigen 125; PFS = progression-free survival

1. Markman, M. et al. *The Oncologist*. 2000;5(1):26–35; 2. Hanker LC, et al. *Ann Oncol*. 2012;23(10):2605–2612; 3. Armstrong, D. K. *The Oncologist* 7, 20–28 (2002); 4.Fotopoulou, C. *Eur. J. Cancer Suppl.* 12, 73–76 (2014)

Deficiencies in HRR in cancer cells leads to the use of an error prone pathway and ultimately cell death



HRD=homologous recombination deficient; HRR=homologous recombination repair; PARP=poly (ADP-ribose) polymerase; SSB=single strand break

O'Connor MJ. *Mol Cell*. 2015;60:547–60

The Advent of Maintenance Therapy in Advanced Ovarian Cancer

2003

Chemotherapy

No further improvement in survival with chemotherapy alone since the introduction of platinum–taxane chemotherapy[1,2]

2011

Paradigm shift 1:
Bevacizumab

Bevacizumab improved PFS vs chemotherapy alone[3,4]

2018

Paradigm shift 2:
PARP inhibitors for *BRCA*-mutated ovarian cancer

Olaparib	SOLO-1[5] *NCT01844986*

2019

Paradigm shift 3:
PARP inhibitors beyond *BRCA* mutation

Olaparib + bevacizumab	PAOLA-1[6] *NCT02477644*
Niraparib	PRIMA[7] *NCT02655016*

Several studies with PARP inhibitors maintenance for newly-diagnosed advanced ovarian cancer[5–8]

PARP, poly(adenosine diphosphate) ribose polymerase; PFS, progression-free survival

1. McGuire WP, et al. *N Engl J Med* 1996;334:1–6; 2. du Bois A, et al. *J Natl Cancer Inst* 2003;95:1320–1329; 3. Burger RA, et al. *N Engl J Med* 2011;365:2473–2483; 4. Perren TJ, et al. *N Engl J Med* 2011;365:2484–2496; 5. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01844986 (Accessed August 2021); 6. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02477644 (Accessed August 2021); 7. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02655016 (Accessed August 2021); 8. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02470585 (Accessed August 2021)

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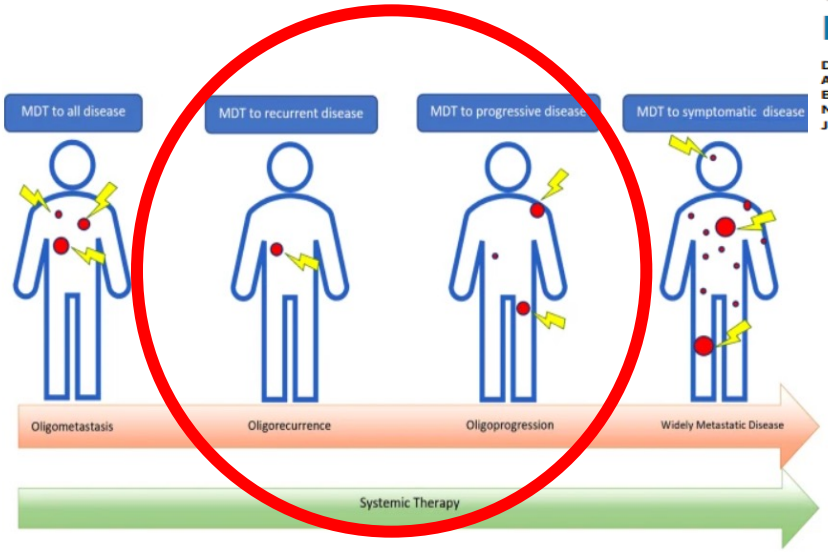
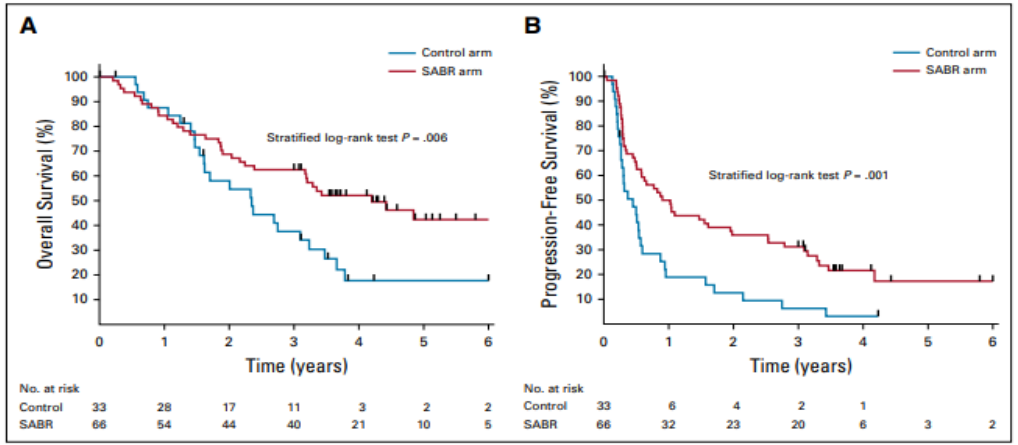
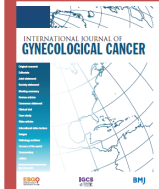
Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers: Long-Term Results of the SABR-COMET Phase II Randomized Trial

David A. Palma, MD, PhD[1]; Robert Olson, MD, MSc[2]; Stephen Harrow, MBChB, PhD[3]; Stewart Gaede, PhD[1]; Alexander V. Louie, MD, PhD[4]; Cornelis Haasbeek, MD, PhD[5]; Liam Mulroy, MD[6]; Michael Lock, MD[1]; George B. Rodrigues, MD, PhD[1]; Brian P. Yaremko, MD, PEng[1]; Devin Schellenberg, MD[7]; Belal Ahmad, MD[1]; Sashendra Senthi, MD, PhD[8]; Anand Swaminath, MD[9]; Neil Kopek, MD[10]; Mitchell Liu, MD[11]; Karen Moore, MSc[3]; Suzanne Currie, MSc[3]; Roel Schlijper, MD[2]; Glenn S. Bauman, MD[1]; Joanna Laba, MD[1]; X. Melody Qu, MD, MPH[1]; Andrew Warner, MSc[1]; and Suresh Senan, MBBS, PhD[5]







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

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

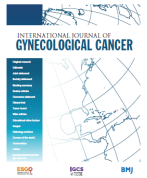
International Journal of Radiation Oncology*Biology*Physics
Volume 101, Issue 3, 1 July 2018, Pages 650-660

Clinical Investigation

Stereotactic Body Radiation Therapy for Oligometastatic Ovarian Cancer: A Step Toward a Drug Holiday

Roberta Lazzari MD *, Sara Ronchi MD †, Sara Gandini PhD ‡, Alessia Surgo MD *, Stefania Volpe MD *, Gaia Piperno MD *, Stefania Comi MSc ‖, Floriana Pansini MSc ‖, Cristiana Fodor MSc *, Roberto Orecchia MD ¶, Federica Tomao MD #, Gabriella Parma MD **, Nicoletta Colombo MD ** ††, Barbara Alicja Jereczek-Fossa MD, PhD *

Int J Gynecol Cancer 2022;



Management of oligometastatic ovarian cancer recurrence during PARP inhibitor maintenance

Eleonora Palluzzi [1], Claudia Marchetti [1,2], Serena Cappuccio [1,2], Giacomo Avesani [3], Gabriella Macchia [4], Maria Antonietta Gambacorta [2,3], Fabrizio Cocciolillo [5], Giovanni Scambia [1,2], Anna Fagotti [1,2]

The Oncologist 2020;

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Radiation Oncology

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

Gabriella Macchia [a,†], Roberta Lazzari [b,†], Nicoletta Colombo [c], Concetta Lalioia [d], Giovanni Capelli [e], Giuseppe Roberto D'Agostino [f], Francesco Deodato [a], Ernesto Maranzano [g], Edy Ippolito [h], Sara Ronchi [b], Fabiola Paiar [d], Marta Scorsetti [f,i], Savino Cilla [j], Rossana Ingargiola [b,k], Alessandra Huscher [l], Anna Maria Cerrotta [m], Andrei Fodor [n], Lisa Vicenzi [o], Donatella Russo [p], Simona Borghesi [q], Elisabetta Perrucci [r], Sandro Pignata [s], Cynthia Aristei [r], Alessio Giuseppe Morganti [t], Giovanni Scambia [u,v], Vincenzo Valentini [a,w], Barbara Alicja Jereczek-Fossa [b,k,††], Gabriella Ferrandina [u,v,††]

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PURPOSE

Evaluate, in oligorecurrent/oligoprogressive ovarian cancer, the continuation of PARPi after locally treated progression with SBRT.

ENDPOINTS

PRIMARY: PROLONGATION OF PARPI TREATMENT TIME

SECONDARY: SURVIVAL OUTCOME (OS, PFS,LC)

METHODS

Retrospective multicentre study: 3 radiation oncology departments;
Inclusion criteria:

- Age >18 years
- Patients with oligometastatic recurrent/progressive ovarian cancer in course of PARPi therapy
- At least one SBRT performed for oligoprogression in course of PARPi

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RESULTS

June 2012 - May 2023
(first SBRT+PARPi after 2016)

46 patients

89 treated lesions in 63 SBRT courses

Patients, tumor and treatment characteristics	N(%)
Age	
Median (IQ range)	58.5 (51.2 – 67.4)
ECOG Peformance Status	
0	40
1	6
Primary Histology	
Serous High grade	39 (84.8)
Clear cell carcinoma	3 (6.5)
Endometrioid	2 (4.3)
Mucinous cell carcinoma	2 (4.3)
FIGO stage at diagnosis	
I	0 (0)
II	4 (8.6)
III	39 (84.8)
IV	3(6.5)
Unknown	0
BRCA Status	
Negative	18 (39.1)
BRCA1 positive	19 (41.3)
BRCA2 positive	4 (8.7)
Unknown	5 (10.9)
Comorbidities	
Hypertension	11 (23.9)
Diabetes mellitus	2 (4.3)
Thyroid disease	2 (4.3)
Autoimmune diseases	4 (8.7)
Any previous malignancies	4 (8.7)
No comorbidities	28 (60.9)
Previous surgery, median (range)	1(1-5)
Previous Chemotherapy, median (range)	3 (1-7)
Time to RT, median (IQ range)	58.5 (51.2-67.4)
Number of treated lesions per treatment course	
1	80 (90.9)
2	5 (5.7)
>3	3 (3.4)
Number of SBRT treatment course per patient	
1	18 (39.1)
2	14 (30.4)
3	9 (19.6)
4	4 (8.7)
5	1 (2.2)

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RESULTS

June 2012 - May 2023

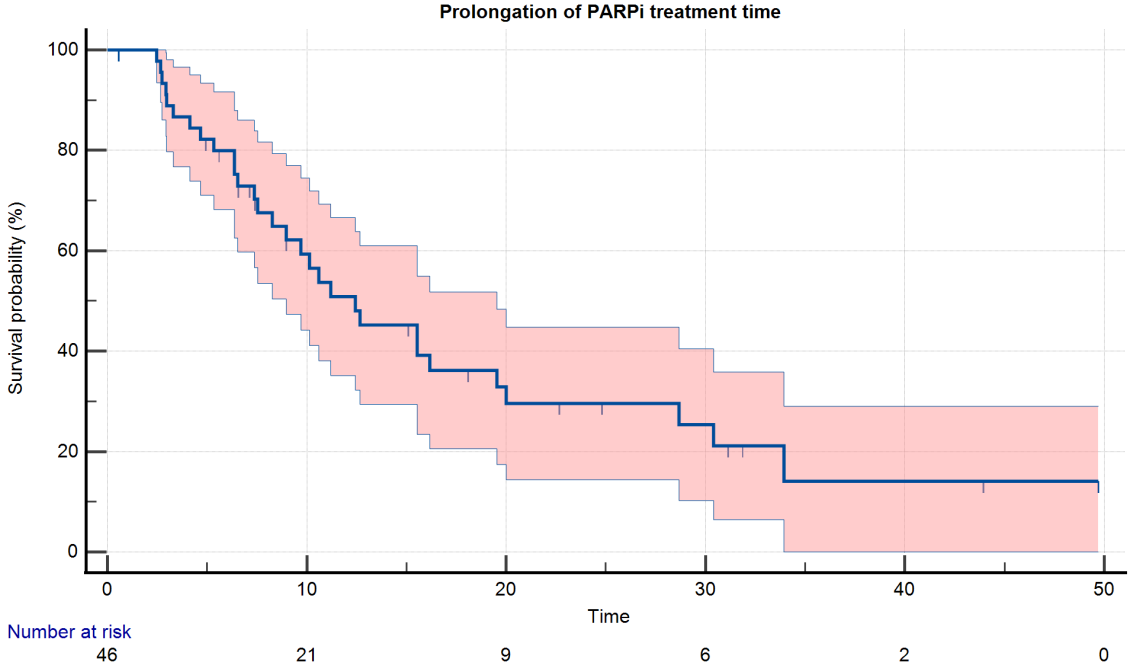
46 patients
(12 patients previously treated with SBRT without PARPi)

89 treated lesions in 63 SBRT courses

Characteristics	n(%)
SBRT treatment	
VERO system (Mitsubishi-Brainlab)	59 (66.3)
CyberKnife (Accuray)	3 (3.4)
Tomotherapy (Accuray)	25 (28.1)
Trilogy system (Varian)	1 (1.1)
Unity MR Linac (Elekta)	1 (1.1)
Lesion site	
Abdominal LN	40(44.9)
Pelvic LN	25 (28.1)
Thorax LN	11 (12.4)
Neck LN	3 (3.4)
Inguinal LN	1 (1.1)
Lung	6 (6.7)
Liver	2 (2.3)
Bone	1 (1.1)
Previous radiotherapy in the site of treated lesion	
Yes	10 (11.3)
No	79 (88.7)
Concomitant PARP Inhibitor	
Niraparib	53 (59.5)
Olaparib	32 (35.9)
Rucaparib	2 (2.3)
Missing	2 (2.3)
PARP inhibitor discontinuation time (days)	
Median, range	12 (4-14)
Interruption of PARPi during local treatment	
No	2 (2.3)
Yes	86 (97.7)
Number of fractions	
Median, range	5 (3-10)
Total dose per lesion	
24 Gy (8 Gy x 3 fr)	25 (28.1)
25 Gy (5 Gy x 5 fr)	17 (19.1)
30 Gy (10 Gy x 3 fr)	9 (10.1)
35 Gy (7 Gy x 5 fr)	12 (13.5)
Other regimens	26 (29.2)
BED in Gy (α/β=10 Gy)	
Median,Range	43.2 (19.5-112-5)
PTV volume (cm³)	
Mean	20.98
Median	13.36
Range	1.45-129.24

RESULTS – Prolongation of PARPi treatment time

- Median follow-up 25.9 months
- Median PARPi total treatment time (since first initiation) 24.7 months
- **Median PARPi prolongation treatment time after SBRT 12.4 months** (95% CI 8.3-19.5)
- Median PARPi discontinuation 12 days
- 69.6% of patients were referred to a new systemic therapy regimen, 30.4% maintained the ongoing PARPi regimen

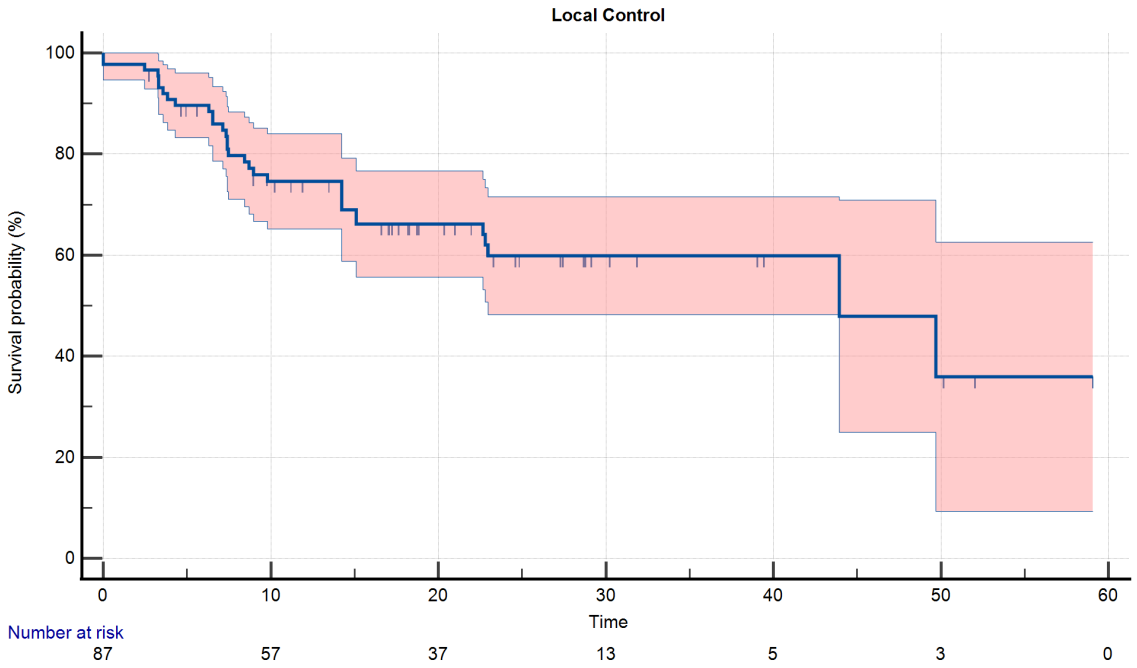


RESULTS - Prolongation of PARPi treatment time

	Univariable		Multivariable	
Variables	HR (95% CI)	**p-value**	HR (95% CI)	p-value
Pre-RT CA-125		**0,0308**		0,6050
≤ 35 U/ml	1.000		1.000	
> 35 U/ml	2,2817 (1,0794 to 4,8232)		1,3025 (0,4784 to 3,5461)	
No of target lesions		**0,0102**		0,0596
1-2	1.000		1.000	
>2	5,6045 (1,5053 to 20,8666)		5,0879 (0,9362 to 27,6499)	
Pre-SBRT Systemic treatment courses		**0,0204**		**0,0316**
≤5	1.000		1.000	
>5	2,9618 (1,1830 to 7,4153)		3,2142 (1,1085 to 9,3199)	

RESULTS – Local Control

- Median Local Control 43.9 months (95% CI 22.8-49.7)
- 1 Year LC 74.6%
  2 years LC 59.9%
- In field control 73/89 treated lesion at the last follow-up



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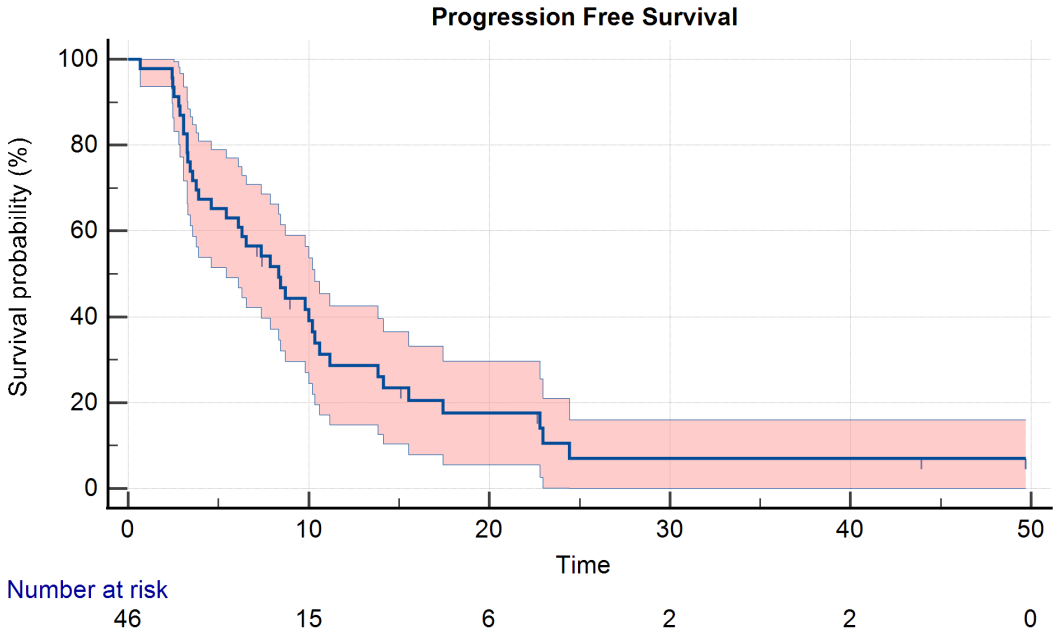
RESULTS – Local Control

	Univariable		Multivariable	
Variables	HR (95% CI)	p-value	HR (95% CI)	p-value
Re-irradiation		0,5950		
yes	1.000			
no	1,3307 (0,4641 to 3,8154)			
Dose		0,1112		
≤25 Gy	1.000			
>25 Gy	1,7635 (0,8774 to 3,5443)			
BED		0,1112		
≤43.2	1.000			
>43.2	1,7635 (0,8774 to 3,5443)			
Num Fraction		**0,0359**		
≤ 4	1.000			
>4	2,1798 (1,0526 to 4,5140)			
No of target lesions	1,8513	0,2249		
1-2	1.000			
>2	0,5505 (0,2099 to 1,4436)			
PTV		0,1343		
≤13.4cc	1.000			
>13.4 cc	1,7115 (0,8471 to 3,4582)			
Best radiological response		0,5033		
CR	1.000			
Other	1,2705 (0,6302 to 2,5614)			

RESULTS – Progression Free Survival

- Median PFS 8.3 months (95% CI 4.6-10.3)
- 1 Year PFS 28.7%
  2 years PFS 10.7%

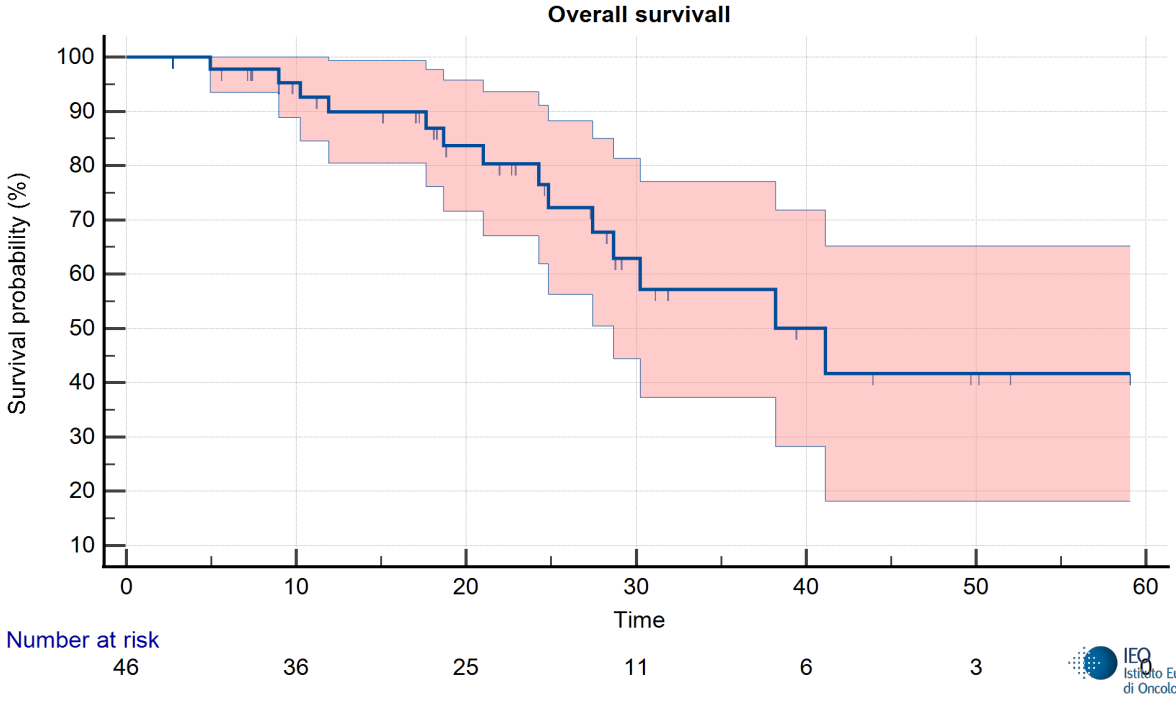


RESULTS – Progression Free Survival

	Univariable		Multivariable	
Variables	HR (95% CI)	p-value	HR (95% CI)	p-value
No of target lesions		**0,0009**		**0,0032**
1-2	1.000		1.000	
>2	6,9089 (2,2092 to 21,6062)		5,8910 (1,8117 to 19,1559)	
Pre-RT Systemic treatment courses		0,0684		
≤5	1.000			
>6	2,1105 (0,9452 to 4,7122)			
Pre-RT surgery		**0,0182**		**0,0454**
1	1.000		1.000	
>1	2,4262 (1,1625 to 5,0636)		2,1683 (1,0161 to 4,6271)	

RESULTS – Overall Survivall

- Median OS 41.1 months (95% CI 27.4 – 41.1)
- 2 Year OS 76.5%
  3 years OS 57.1%
- No difference between BRCA mutated patients and wild type



RESULTS – Overall Survivall

	Univariable		Multivariable	
Variables	HR (95% CI)	p-value	HR (95% CI)	p-value
BRCA		0,3599		
Mutaded	1.000			
Wild	0,7915 (0,2351 to 2,6645)			
Dose		0,0828		
≤25 Gy	1.000			
>25 Gy	3,7760 (0,8413 to 16,9474)			
Num Fraction		0,0695		
≤ 4	1.000			
>4	2,7790 (0,9217 to 8,3789)			
Pre-SBRT Systemic treatment courses		**0,0433**		0,1980
≤5	1.000		1.000	
>5	3,8579 (1,0414 to 14,2922)		2,7146 (0,5935 to 12,4169)	
Pre-RT surgery		0,0719		
1	1.000			
>1	2,7702 (0,9131 to 8,4043)			
Target lesion		**0,0082**		0,2069
Nodal	1.000		1.000	
Extra-nodal	5,6138 (1,5620 to 20,1753)		3,2020 (0,5254 to 19,5136)	
Stage		0,7071		
I,II	1.000			
III,IV	0,6765 (0,0881 to 5,1957)			
Pathology		0,3941		
Serous	1.000			
Other	0,5195 (0,1152 to 2,3430)			

RESULTS - Safety

- 91% of patients no acute or late toxicity observed
- 4 patients with G1 gastrointestinal acute events
- No G3-G4 acute or late events

CONCLUSION

- Results in line with the previous pubblied experiences
- SBRT useful therapeutic tool in the multidisciplinary management of oligometastatic ovarian carcinoma
- The combination of SBRT with PARP-i showed safety and tolerability in our series
- Limitations: retrospective study, small sample size, eterogenity of scheme and dose prescriptions

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