Associazione Italiana Radioterapia e Oncologia clinica

Società Italiana di Radiobiologia

STEREOTACTIC BODY RADIOTHERAPY IN OVARIAN CANCER PATIENTS PROGRESSING WITHIN PARP-INHIBITOR MAINTENANCE REGIMEN: ADVERSE EVENTS AND ACTIVITY FROM THE RETROSPECTIVE "EPIMETHEO" STUDY

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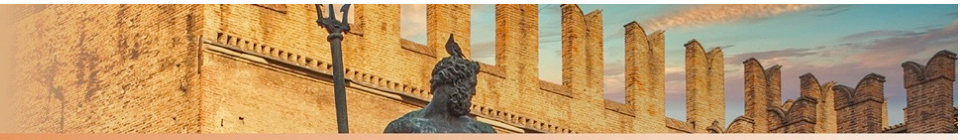


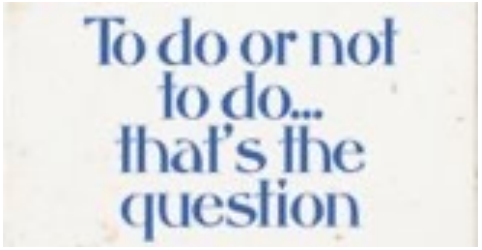
DICHIARAZIONE

Relatore: GABRIELLA MACCHIA

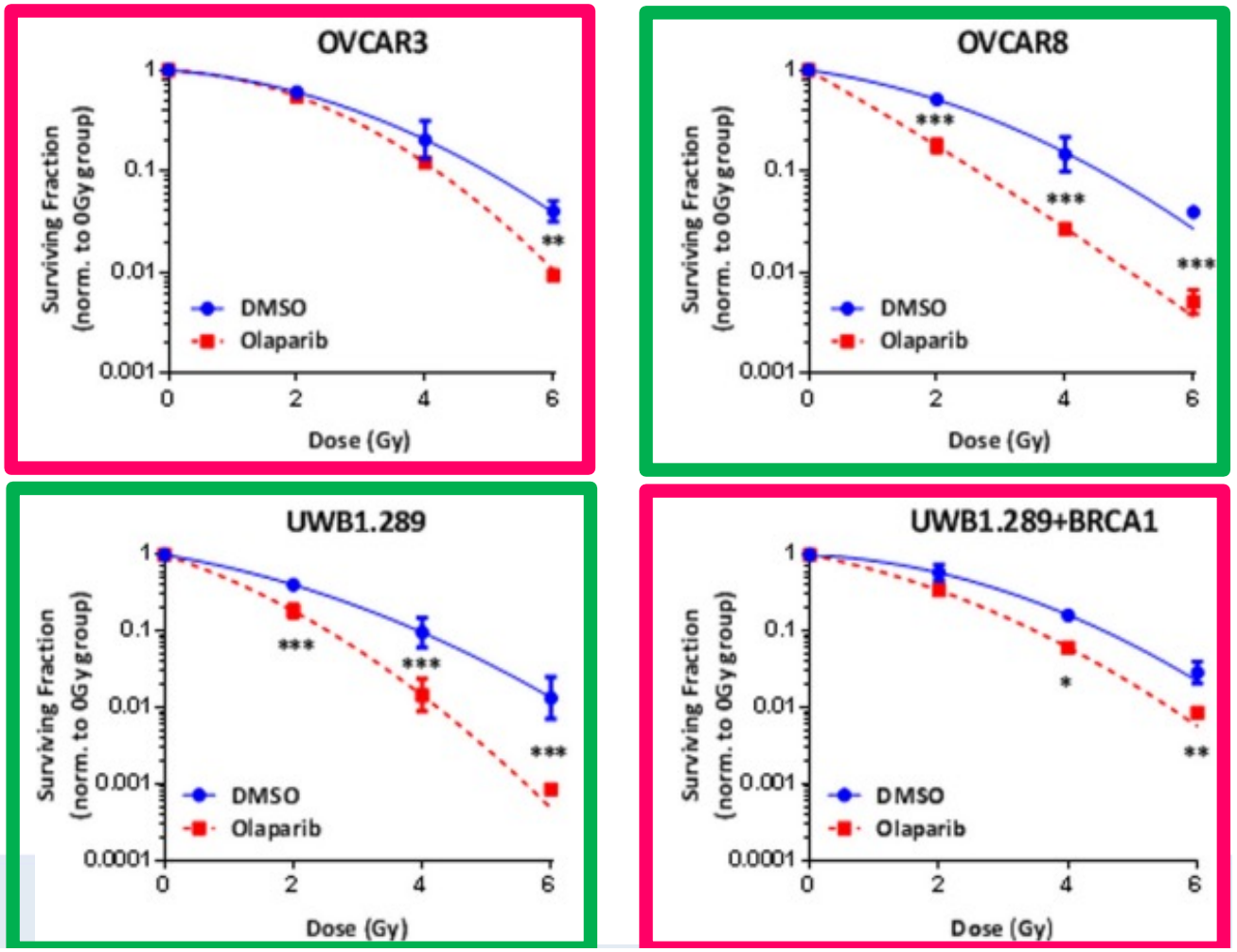
Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(Consultant/MSD (Italia) s.r.l, a subsidiary of Merck & Co)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(Relatore/AstraZeneca S.p.A.)**
- 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

PARP-Inhibitors & Radiotherapy



Clonogenic Survival Assay



- ✓ ***OVCAR8***
- ✓ ***UWB1.289***

BRCA inactive/mutated

- ✓ ***OVCAR3***
- ✓ ***UWB1.289+BRCA1***

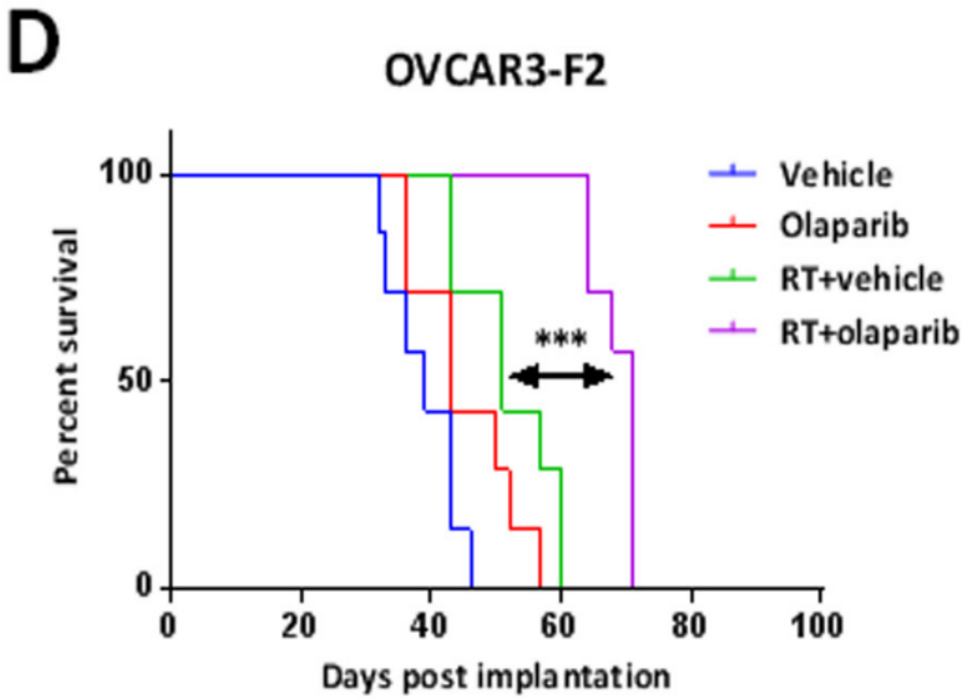
BRCA WT

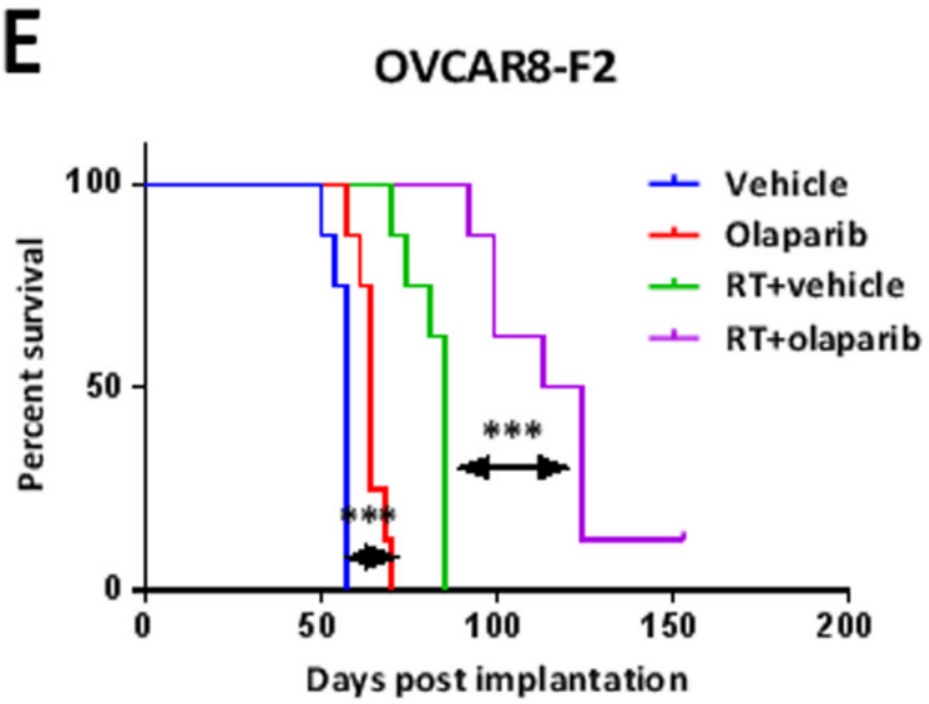
- ✓ *Cells seeded in plates (DMSO vs OLA 1μM) for 4 h*
- ✓ *Irradiated by increasing RT dose (0-6 Gy)*

- ✓ ***Cells with BRCA inactive/mutated***
  → higher radiosensitization

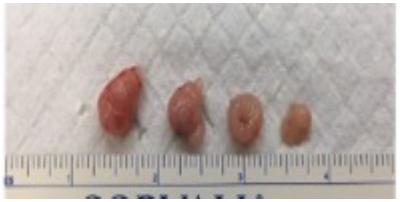
- ✓ ***Cells with BRCA WT***
  → lesser radiosensitization

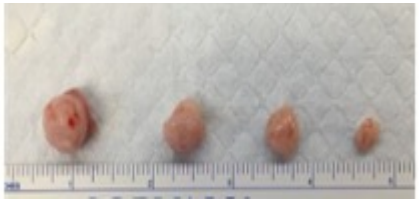
Bi Y., Gynecol Oncol 2018

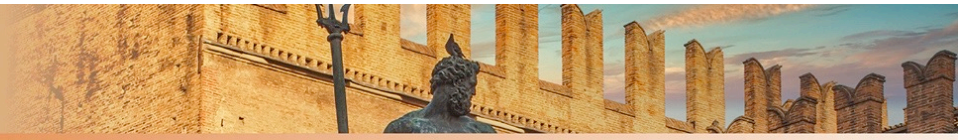




(D, E) Kaplan-Meier survival analysis of mice
in OVCAR3 and OVCAR8
***P 0.001







PARP Inhibitors & Radiotherapy

Study			Population		Intervention			
Author	Type of Study	Number of Patients (pts)	Age Median [Range]	Localization	Radiotherapy (Total Dose/Fraction) with or without Chemotherapy	Aim of Radiotherapy	Parp-INHIBITORS	Follow Up
Mehta (2015) [14]	Single-arm dose-escalation phase I	81	58 (31–84)	Brain metastases	30 Gy/10 fr or	Definitive	Veliparib	NA
Chabot (2017) [15]	Three-arm phase II controlled trial; placebo (102 pts) vs. Veliparib 50 mg (103 pts) vs. Veliparib 200 mg (102 pts).	307						
Czito (2017) [16]	Single-arm dose-escalation phase I	32						
Reiss (2017) [17]	Single-arm dose-escalation phase I	32	58 (55–65)	Peritoneal carcinomatosis (ovarian and fallopian cancer)	21.6 Gy/36 fr (BID)	Radical	Veliparib	45 months
Jagsi (2018) [18]	Single-arm dose-escalation phase I	30	50.5 (41–40)	Breast (inflammatory or locoregionally recurrent)	50 Gy + 10 Gy (boost)/25 fr	Adjuvant	Veliparib	3 years
Karam (2018) [19]	Single-arm dose-escalation phase I	16	61 (46–75)	Head and Neck (locally advanced)	69.3 Gy/33 fr + Cetuximab	Radical	Olaparib	26 months
Tuli (2019) [20]	Single-arm dose-escalation phase I	30	68 (60–77)	Pancreas (locally advanced)	36 Gy/15 fr + gemcitabine 400 mg/m^2	Radical	Veliparib	NA

Study			Population		Intervention			
Author	Type of Study	Number of Patients (pts)	Age Median [Range]	Localization	Radiotherapy (Total Dose/Fraction) with or without Chemotherapy	Aim of Radiotherapy	Parp-INHIBITORS	Follow Up
	Phase I/II trial: single-arm dose-escalation			Diffuse intrinsic	54 Gy/30 fr + Temozolomide	Radical	Veliparib	6.3 months (stopped early for futility)
					at the arm	Radical	Olaparib	14 months
Argiris (2021) [23]	by a two-arm controlled phase II trial placebo (13 pts) vs. Veliparib (18 pts)	21 (phase I) and 31 (phase II)	(47–78.9) (arm Veliparib), 65 (56.6–75.6) (arm placebo)	Lung (stage III NSCLC)	45 mg/m^2/carboplatin AUC2 (weekly concomitant and in consolidation)	Radical	Veliparib (concomitant and consolidation)	Phase I: 40.6 months; phase II: 26.9 months
Sim (2021) [24]	Two-arm controlled phase II trial; standard arm(41 pts) vs. Veliparib 200 mg (84 pts)	125	60 (22–78) (Veliparib arm) vs. 62 (24–73) (Standard Arm)	Glioblastoma (unmethylated MGMT promoter)	60 Gy/30 fr + Temozolomide (75 mg/m^2 OD concomitant and 150–200 mg/m^2 d1–5/28 d)	Radical	Veliparib	27.2 months
Loap (2020 and 2021) [12,13]	Single-arm dose-escalation phase I	24	46 (25–74)	Breast (triple negative)	50 Gy/25 fr; 50.4 Gy/28 fr ± SIB tumor boost (63 Gy)	Adjuvant	Olaparib	12 months

Clinical trials in humans are very few...

Almost none with SBRT fractionation

Barcellini A et al, Cancers 2021

How stereotactic radiotherapy might be useful during the use of PARPi?

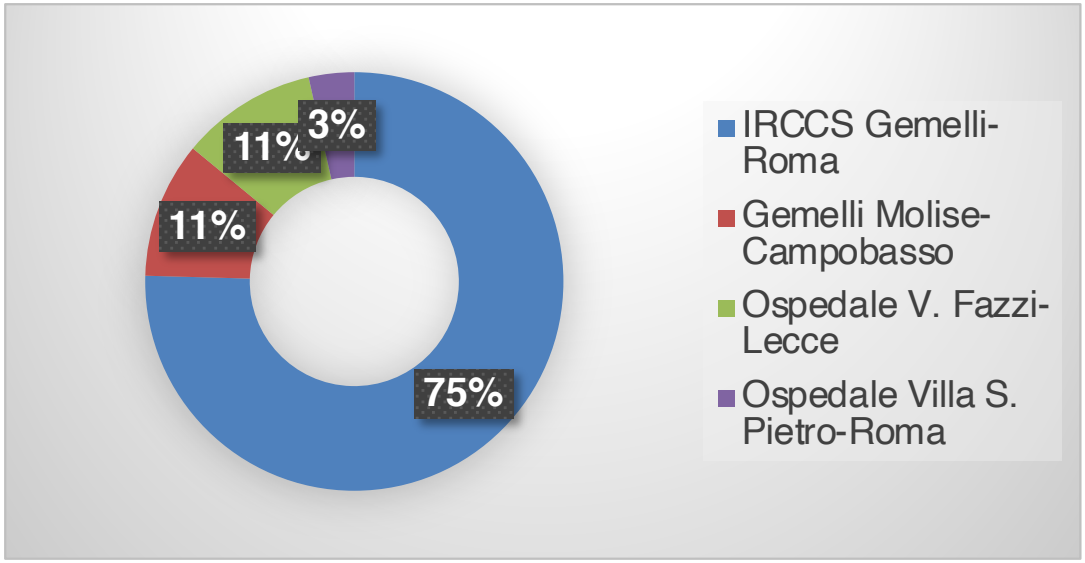
- High dose/short time
- Minimally invasive
- High local control
- Minimal toxicities
- Retreatment
- Safely administered during CT
- Active in chemoresistant disease
- Immune response activator

Quality of life improvement

Delay of chemotherapy

Epimetheo *(DIPUSVSP-15-11-2234)*

Observational, retrospective, multicenter study



Aim: to define **the activity and safety** of the SBRT in a **real-world data set** of oligometastatic OC patients **during PARPi maintenance**.

From May 2019 to July 2022,

SBRT was used to treat **57 OC** patients with **115 lesions (70 lymph nodes and 45 parenchymal lesions) under PARPi maintenance**.

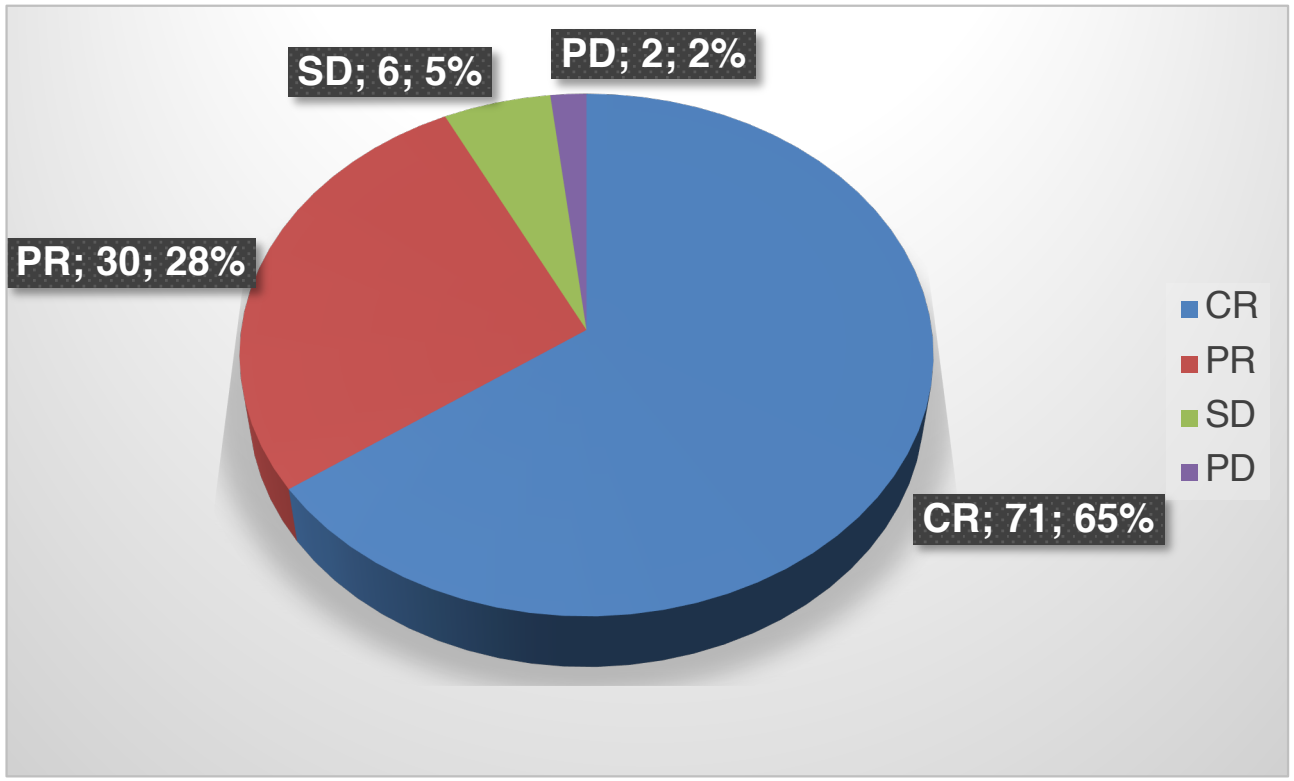
	N. (%)	
All	57	
Age, years at diagnosis		
Median (range)	52 (34-79)	
Histotype		
Serous	52 (91.2)	
Endometrioid	3 (5.3)	
Carcinosarcoma	2 (3.5)	
BRCA gene status		
Wild type	26 (45.6)	
Mutated BRCA1	18 (31.6)	
Mutated BRCA2	8 (14.0)	
VUS	5 (8.8)	
N. patients undergoing surgeries before SBRT[a]	**Major surgery**	**All surgeries**
Yes	57 (100)	57 (100)
N. patients undergoing chemotherapy before SBRT[a]		
Yes	57 (100)	
N. of chemotherapy lines, *Median (range)*	2 (1-5)	
Maintenance regimens		
Bevacizumab		
No	30 (52.6)	
Yes	27 (49.1)	
PARP inhibitors		
Olaparib	26 (45.6)	
Niraparib	26 (45.6)	
Rucaparib	5 (8.8)	

Type of lesion(s)	
Lymph node	70 (60.9)
Parenchyma/bone	45 (39.1)
Anatomical districts	
Abdomen	65 (56.5)
Thorax	28 (24.3)
Brain	11 (9.6)
Pelvis	9 (7.8)
Neck	2 (1.7)
GTV	
Median, range (cm^3)	2.05 (0.01-29.80)
PTV	
Median, range (cm^3)	7.50 (0.34-53.64)
Total dose/fraction, Gy	
Median (range)	40.0/8 (25.5-55.0)
$BED_{\alpha/\beta 10}$	
Median (range)	72.0 (31.25-100.0)

Response evaluation

109 lesions assessable

Median time to the best response of 5 months (1-14 months)



AIRO2022

Toxicity

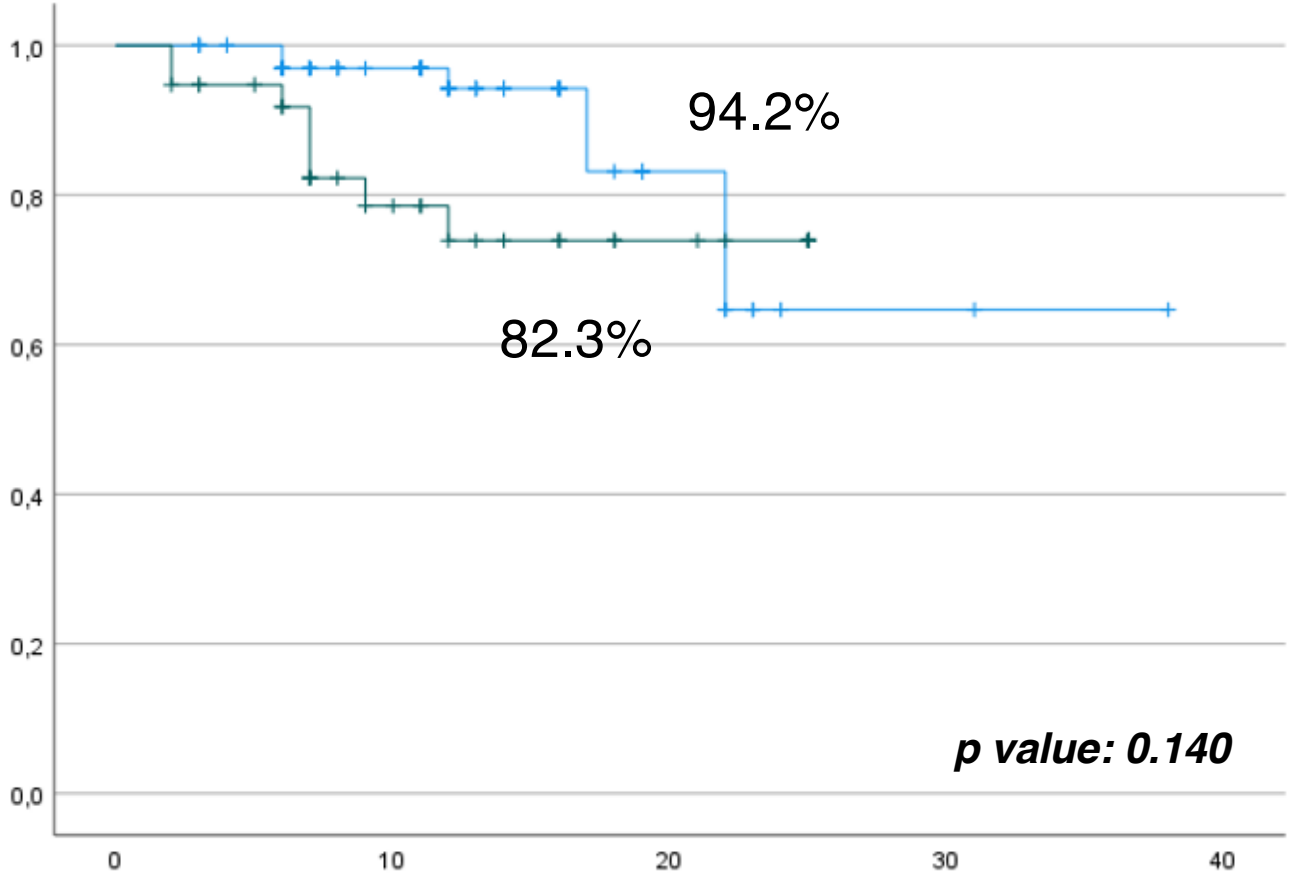
Pts 24 (42.1%)

AE 42 (34 Grade 1; 4 Grade 2; 4 Grade 3)

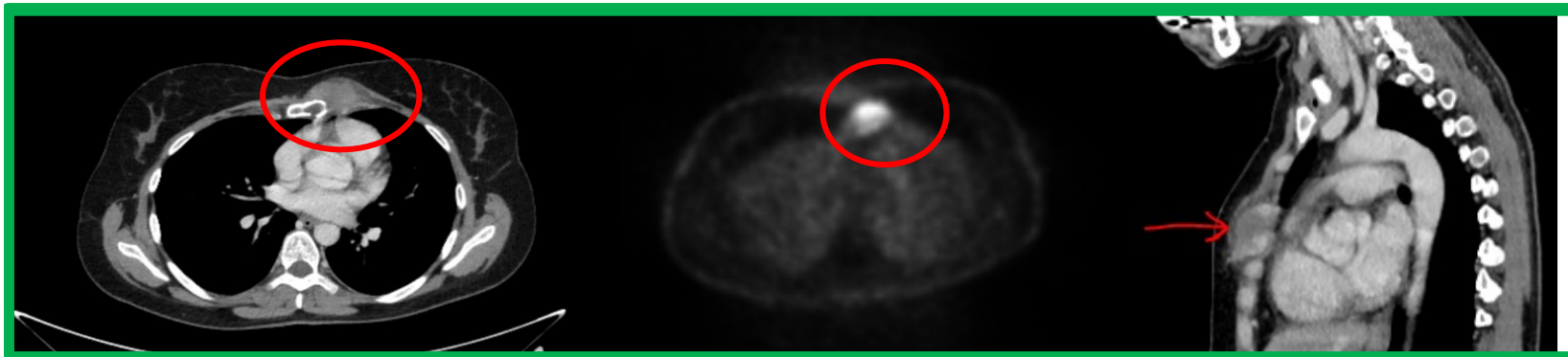
		ACUTE TOXICITY									LATE TOXICITY		
N.	ID	Asthenia	Lower GI	Upper GI	Pain	Skin toxicity	GU disorders	Lung toxicity	Other		Asthenia	Pain	Skin toxicity
1	*AR*												G1
2	*BE*	G2	G2				G1						
3	*BO*		G1										
4	*BR*				G1								
5	*CA*	G1			G1	G1							
6	*CE*								*Arthralgia* G1				
7	*CER*			G1									
8	*DA*	G1			G1						G1	G1	
9	*DF*	G1											
10	*DC*	G1											
11	*DZ*	G1	G1	G1	G1			G1					
12	*EV*	G1									G1		
13	*GE*			G1									
14	*GU*				G1							G1	
15	*IE*			G1									
16	*LA*										G1		
17	*LO*			**G3**	**G3**								
18	*MM*								Thrombocytemia G2				
19	*NI*	G1											
20	*NR*								Anaemia **G3**				
21	*LO*				G1	G2*							**G3***
22	*PA*	G1	G1										
23	*SO*						G1						
24	*ZA*	G1		G1									

GI=Gastrointestinal; GU=Genito-Urinary *previous in-field radiotherapy

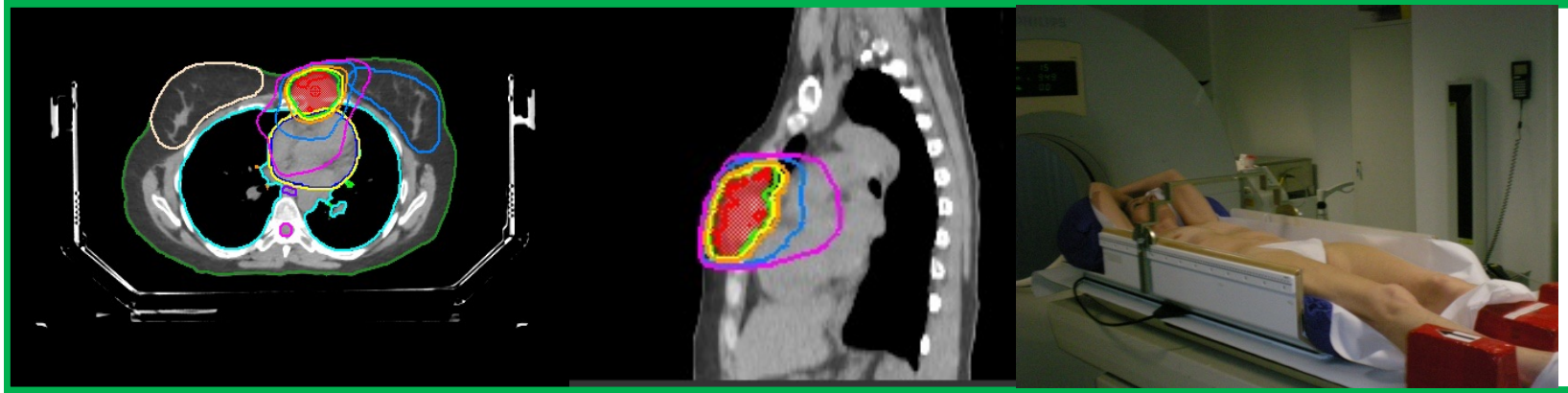
1-year actuarial local control rate in patients achieving CR vs no CR on a 'per lesion' basis



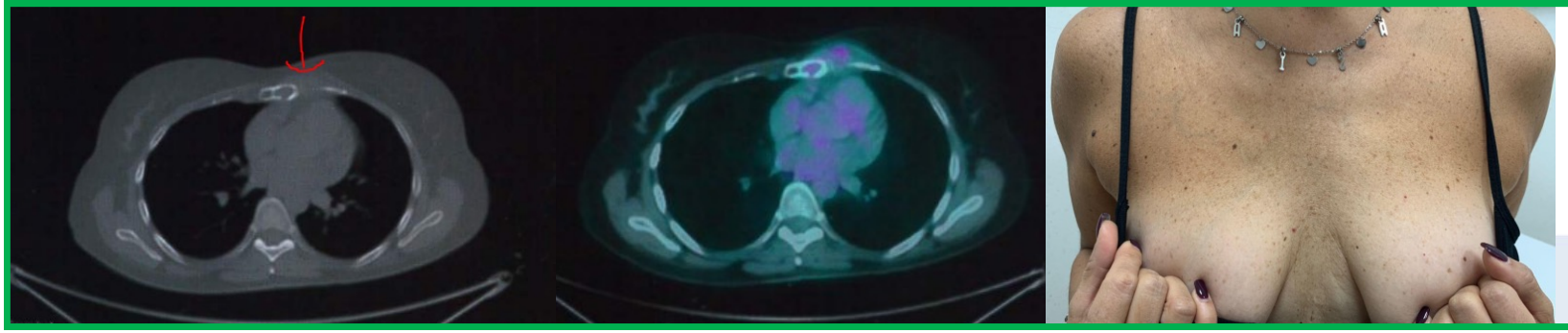
Dg 2015 (40 aa)→S→CT→1 rec LIS (feb 2018)→ S → CT→2 rec parasternal (ott 2021)→CT→PARPi (feb 2022)



CT and PET-CT
Feb 2022



SBRT 40 Gy/8 Gy fr
Mar 2022



PET-CT Nov 2022

BOLOGNA, 25-27 NOVEMBRE
PALAZZO DEI CONGRESSI

Conclusions

This study confirms the activity and safety of SBRT in patients in association with PARPi in this clinical setting

The toxicity rate in this series is consistent with that described in the literature on the stereotactic technique

The addition of the PARP inhibitor did not worsen the toxicity

Maura Campitelli, Simona Lucci, Donatella Russo

Gabriella Ferrandina