HITBR plus
Heavy Ion Therapy Research Integration

Gynae and Rare Indications: Gynaecological Melanoma and Oligomet Ovarian Cancer

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CNAO National Center for Oncological Hadrontherapy

CNAO
Centro Nazionale di Adroterapia Oncologica

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Disclosure

- None

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Agenda

- **Gynecological Melanomas**
  - ✓ Epidemiology
  - ✓ Current Evidence: role of hadrontherapy in gynecological melanomas

- **Oligometastatic/ oligorecurrent/ oligorefractory ovarian cancers**
  - Literature data: epidemiology and current management
  - What role for CIRT?

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Gynecological Mucosal Malignant Melanomas

Epidemiology

- ✓ National Cancer Data Base Report → report on 84.836 cases (1985-1994)
  - 91.2% cutaneous, 5.2% ocular, **1.3% mucosal ,**2.2% unknown origin

Chang A.E. et al, Cancer, 1998
McLaughlin C.C et al,Cancer. 2005
Mallone S et al, Eur J Cancer. 2012

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- ✓ Incidence rate for mucosal melanomas is similar around the world estimated at **2.2 cases per million per year in USA and 2.6 cases per million per year in Europe**

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- ✓ Incidence rate for mucosal melanomas is similar around the world estimated at **2.2 cases per million per year in USA and 2.6 cases per million per year in Europe**
- ✓ Significant **regional variation** in incidence across Europe: the highest rate (2.7 cases per million per year) in Northern Europe and the lowest (0.88 cases per million per year) in Eastern Europe (*differences in reporting rare malignancy?)*

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Epidemiology

- ✓ Compared to cutaneous melanoma (annual ↗ in incidence), **annual incidence stable over several decades**

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- ✓ Incidence ↗ with age, > in ♀ (for higher rate of gynecological melanomas)

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- ✓ Incidence ↗ with age, > in ♀ (for higher rate of gynecological melanomas)
- ✓ Absolute incidence **higher in Caucasian populations** (2:1)

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Gynecological Mucosal Malignant Melanomas

Epidemiology

- ✓ **Vulva:** 2.4-10% of all vulvar cancers
  3-7% of all melanomas in women
  Incidence: 0.48-1.4/1000.000 women
  5-year OS: 37–50%

- ✓ **Vagina:** <3% of all vaginal cancers
  0-4-0-8% of all melanomas in women
  Approximately 500 cases reported in the literature
  5-year OS : 13–32%

- ✓ **Cervix:** extremely rare
  approximately **80 cases reported in the literature**
  5-year OS: approximately 10%

Gadducci A et al., Gynecol Oncol. 2018

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Gynecological Mucosal Malignant Melanomas

Current Evidence: role of hadrontherapy

- ✓ based on data concerning **gyn cancers & cutaneous melanoma**

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Review Article

Melanoma of the lower genital tract: Prognostic factors and treatment modalities

Angiolo Gadducci [a,*], Silvestro Carinelli [b], Maria Elena Guerrieri [a], Giovanni Damiano Aletti [c]

[a] Department of Clinical and Experimental Medicine, Division of Gynecology and Obstetrics, University of Pisa, Pisa, Italy
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- ✓ **Surgery** is the treatment of choice (early stages) → **surgical challenges** (proximity of bladder, anus rectum)

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- ✓ RT can be used in the adjuvant setting **(R+ or/and N+)**

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- ✓ **Adjuvant treatment is unproven**
- ✓ RT can be used in the adjuvant setting **(R+ or/and N+)**
- ✓ **CIRT is a promising alternative**

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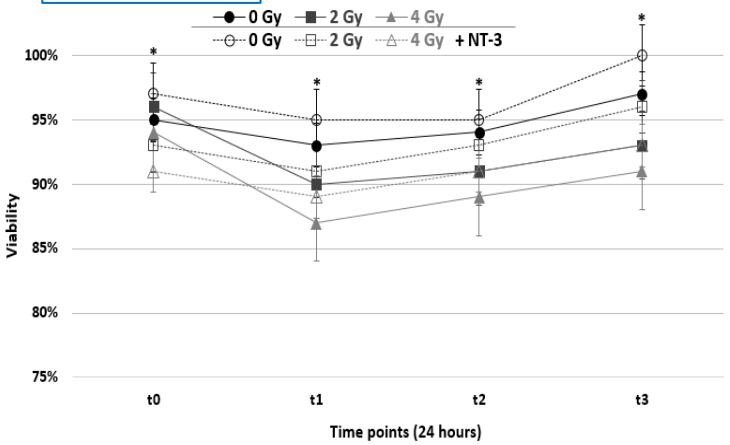
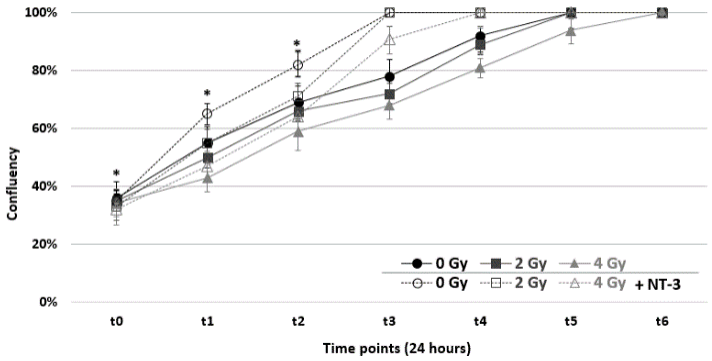
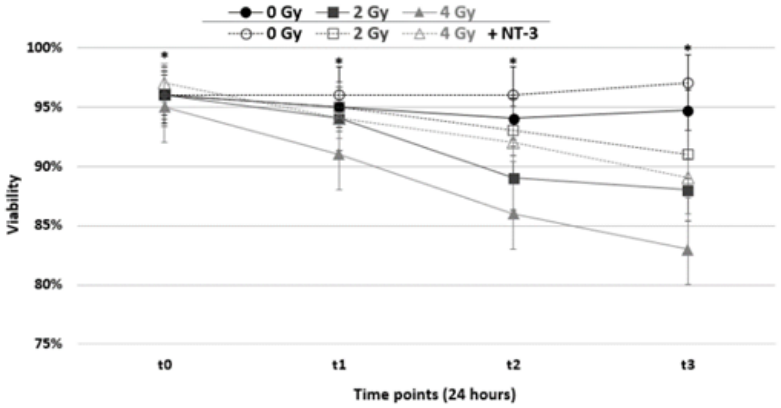
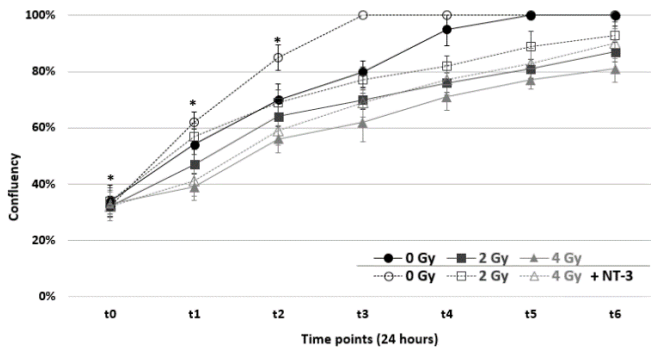
Photons

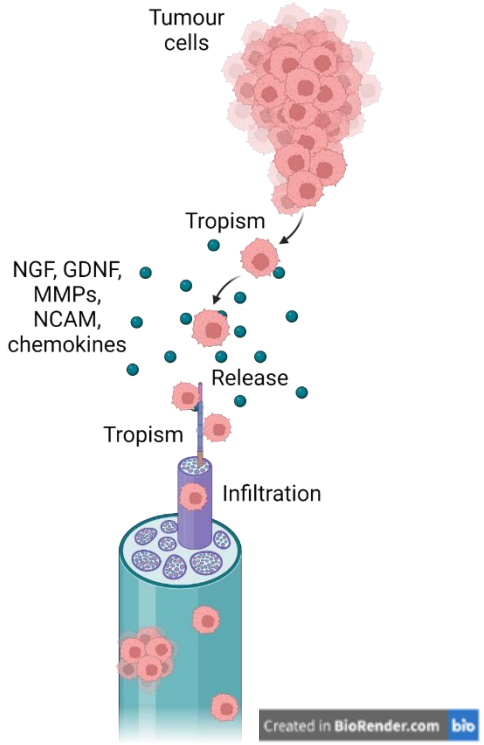




C-ions







Charalampopoulou A. et al., 2023

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Gynecological Mucosal Malignant Melanomas

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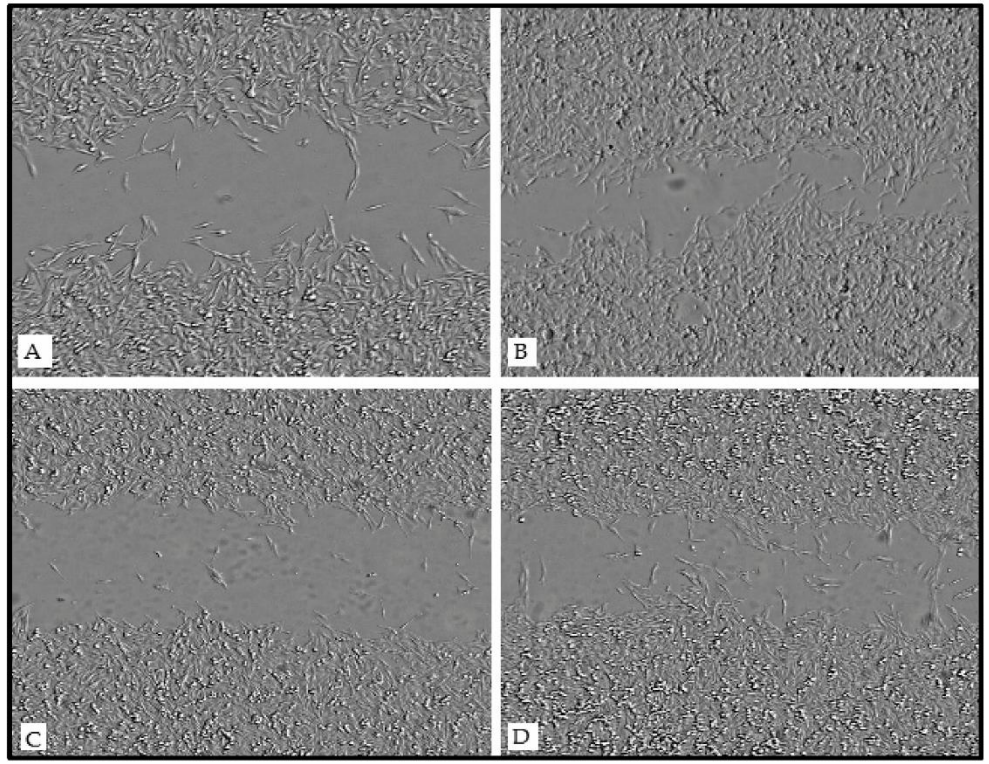

- Scratch migration assay after the exposure of HMV-II cells to C-ions without and with the addition of NT-3
- CIRT cause a more significant decrease in cell migration in vaginal mucosal melanoma cells since cell-free area percentages remain higher in all conditions

Charalampopoulou *A. et al., 2023*

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Current Evidence: role of hadrontherapy

Characteristics	Number of Patients	%
Age (median), years	51–88 (71)	
Tumor site		
Vagina	22	60
Vulva	12	32
Cervix uterus	3	8
Prior treatment		
Surgery	9	24
Chemotherapy	3	8
None	25	68
T stage (including recurrent T stage)		
T1	8	22
T2	21	56
T3	8	22
Tumor size in maximal diameter		
≤30 mm	29	78
>30 mm	8	22
Lymph node metastasis		
Positive	5	14
Negative	32	86
The reason for inoperableness		
Medically inoprerable	27	73
Patient's refusal	10	27
Total dose of C-ion RT		
57.6 Gy (RBE) in 16 fractions	35	95
64.0 Gy (RBE) in 16 fractions	2	5
Adjuvant therapy		
DAV/DAV Feron	9	24
Nivolumab	1	3
None	27	73

- Retrospective analysis of 37 patients

Murata et al Cancers (Basel). 2019

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- Median follow-up periods: 23 months (range: 5–103 months) for all patients and 53 months (range: 16–103 months) for survivors

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Surgery	9
Chemotherapy	3
None	25

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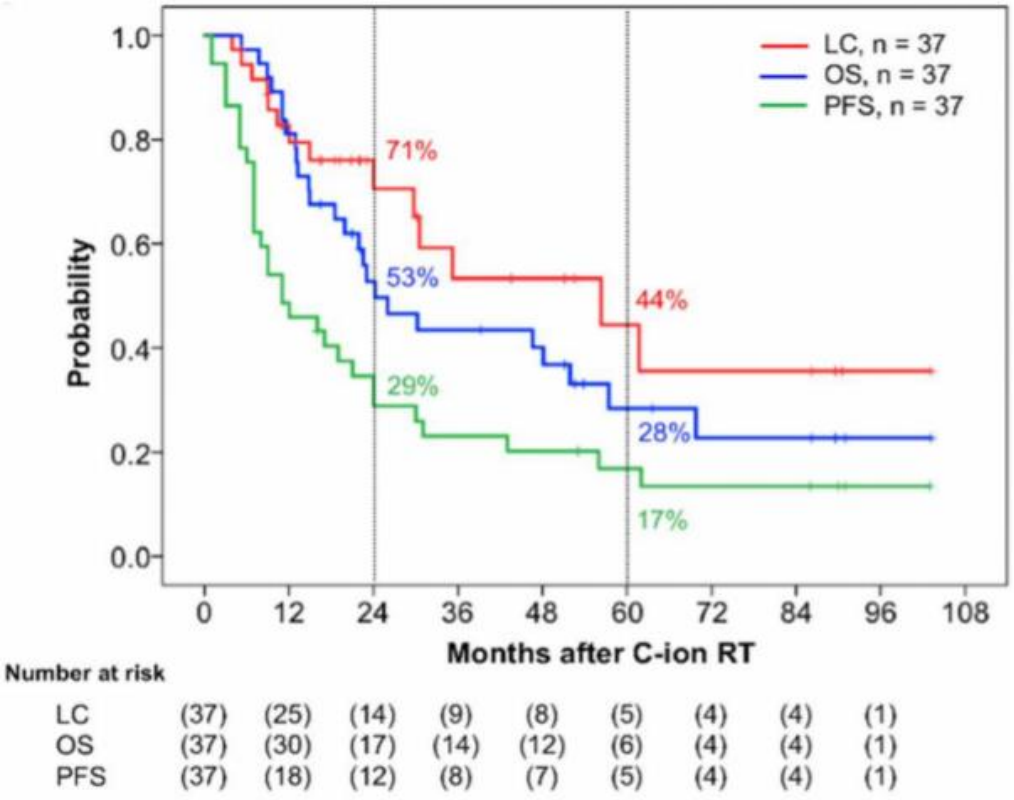

- Within 6 months **: 19 CR, 14 PR and 4 SD**

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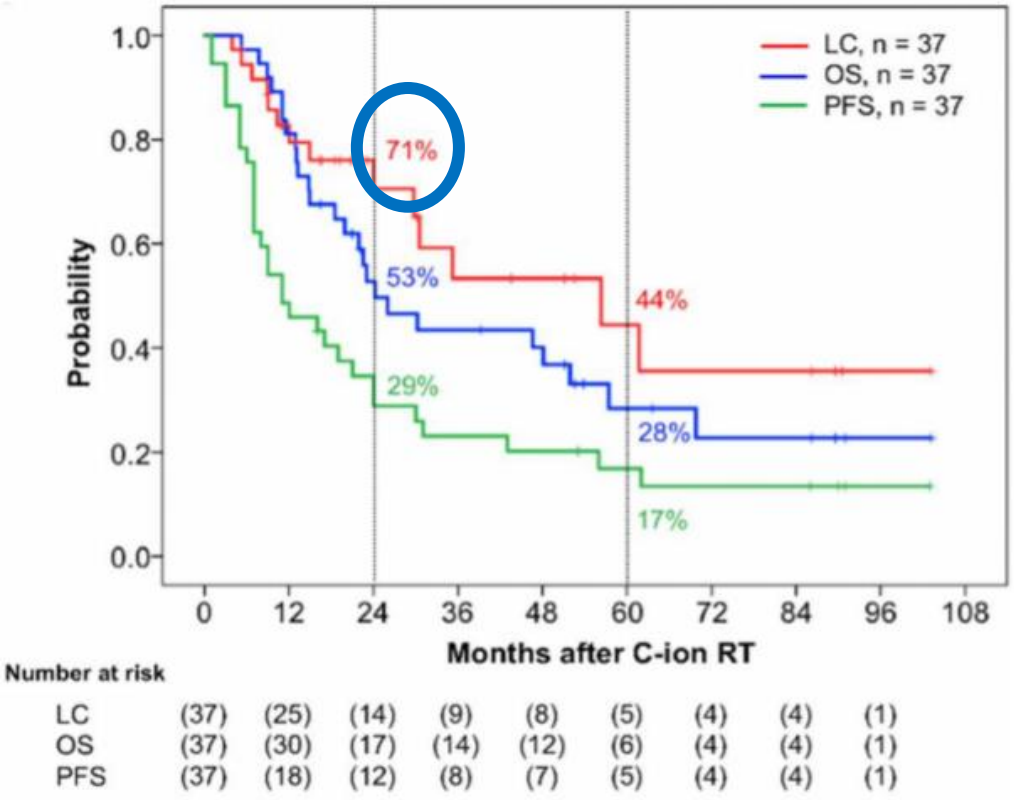

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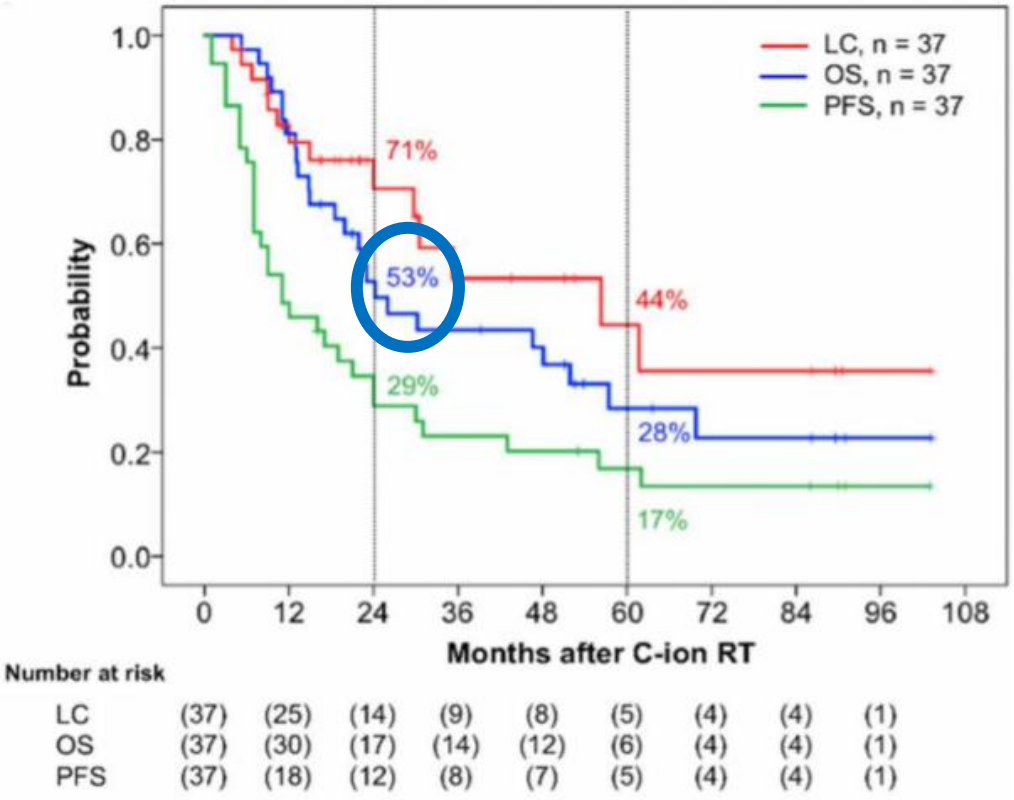

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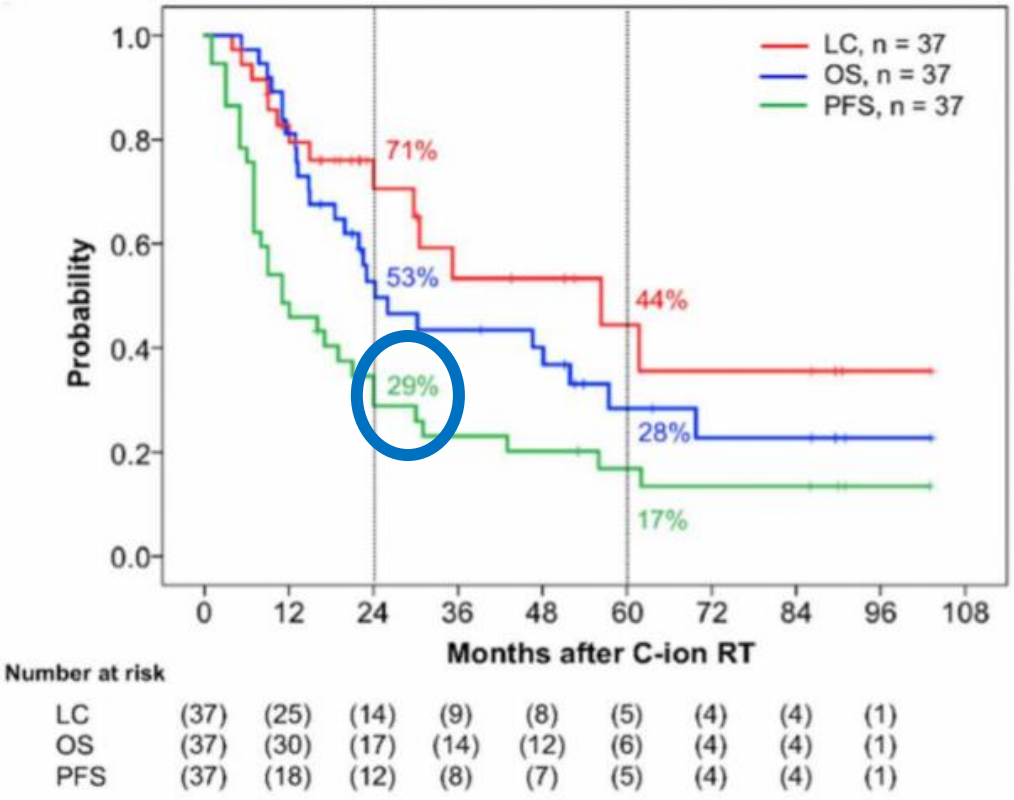

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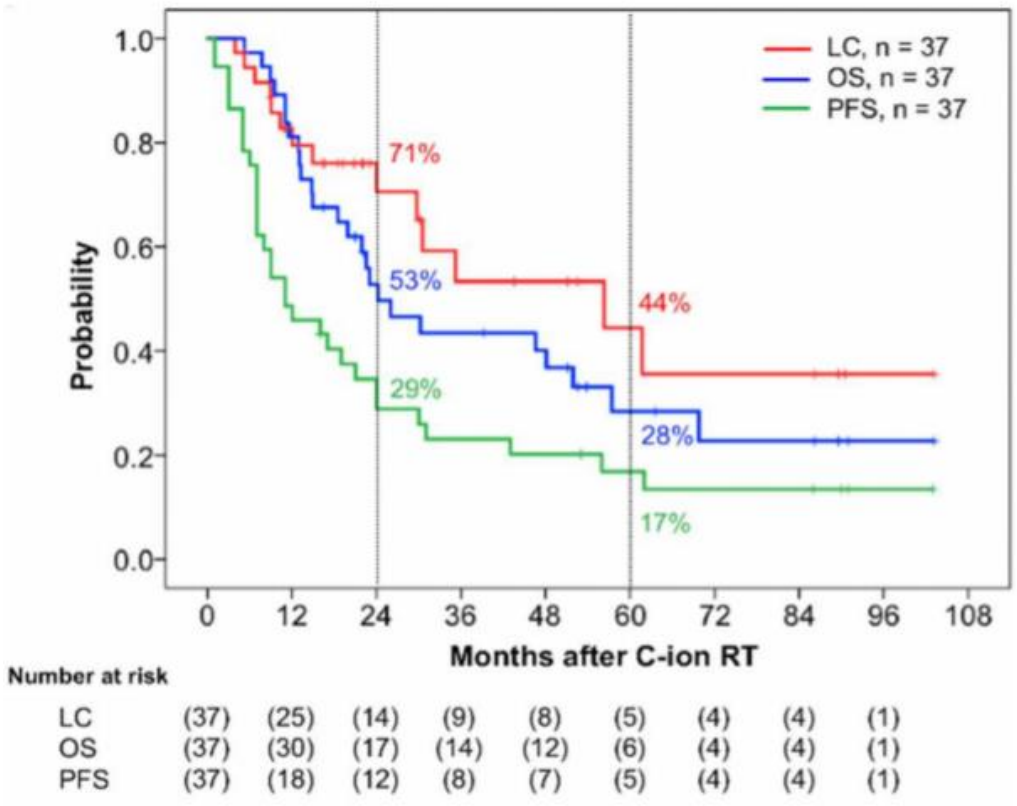

Acute Toxicity	CTCAE v.4 Scoring				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4–5
Dermatitis/mucositis	2	18	14	3	0
Genitourinary toxicity	28	9	0	0	0
Lower gastrointestinal toxicity	17	14	6	0	0
Late toxicity	**RTOG/EORTC Scoring**				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4–5
Dermatitis/mucositis	28	9	0	0	0
Genitourinary toxicity	30	3	4	0	0
Lower gastrointestinal toxicity	29	5	3	0	0

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Factor	No. of Patients	LC		PFS		OS		DM	
		2-Year (%)	*p*-Value	2-Year (%)	*p*-Value	2-Year (%)	*p*-Value	2-Year (%)	*p*-Value
Age (years)			0.213		0.617		0.983		0.041
<71	17	49.7		17.6		57.0		52.9	
≥71	20	89.2		39.4		43.3		40.1	
Prior treatment			0.468		0.547		0.564		0.242
No	12	69.4		30.5		53.5		37.6	
Yes	25	72.2		25.0		50.0		58.3	
T stage (including recurrence)			0.974		0.953		0.877		0.903
T1–2	29	65.4		26.6		53.7		48.0	
T3	8	87.5		37.5		37.5		37.5	
Tumor diameter			0.337		0.418		0.304		0.320
≤30 mm	29	73.9		33.4		57.2		46.3	
>30 mm	8	60.0		12.5		37.5		37.5	
LN metastasis			0.320		0.248		0.069		0.206
Positive	5	60.0		0.0		40.0		80.0	
Negative	32	73.0		40.4		54.9		39.1	
Adjuvant chemotherapy			0.535		0.142		0.382		0.796
No	27	65.8		20.4		53.8		43.4	
Yes	10	80.0		50.0		50.0		50.0	
Tumor response within 6 months after commencing C-ion RT			0.535		0.923		0.818		0.826
CR	19	77.7		23.7		61.5		43.2	
Non-CR	18	61.6		33.3		43.2		45.8	
Primary site			N.S.		N.S.		N.S.		N.S.
Vagina	22	73.4		26.5		55.2		53.0	
Vulva	12	76.4		33.3		58.3		33.3	
Cervix uterus	3	33.3		33.3		33.3		33.3	

- None of the factors examined significantly influenced LC, PFS, and OS in univariate analysis

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Prior treatment			0.468		0.547		0.564		0.242
No	12	69.4		30.5		53.5		37.6	
Yes	25	72.2		25.0		50.0		58.3	
T stage (including recurrence)			0.974		0.953		0.877		0.903
T1–2	29	65.4		26.6		53.7		48.0	
T3	8	87.5		37.5		37.5		37.5	
Tumor diameter			0.337		0.418		0.304		0.220
≤30 mm	29	73.9		33.4		57.2		46.3	
>30 mm	8	60.0		12.5		37.5		37.5	
LN metastasis									
Positive									
Negative									
Adjuvant chemotherapy									
No									
Yes									
Tumor response within 6 months after commencing C-ion									
CR									
Non-CR									
Primary site									
Vagina	22	75.4		26.5		53.2		33.0	
Vulva	12	76.4		33.3		58.3		33.3	
Cervix uterus	3	33.3		33.3		33.3		33.3	

Age (Year)	2-y DM(%)	p-Value
<71	52.9	0.041
>71	40.1	

- None of the factors examined significantly influenced LC, PFS, and OS in univariate analysis
- Age was associated with the rate of distant metastasis

Murata et al Cancers (Basel). 2019

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Gynecological Mucosal Malignant Melanomas

Current Evidence: CNAO's preliminary experience

- Retrospective analysis of 15 patients
- Median follow-up period: 35 months (range: 5–98 months) for all patients
- Higher mottled data!!! → prospective trial!

Unpublished data

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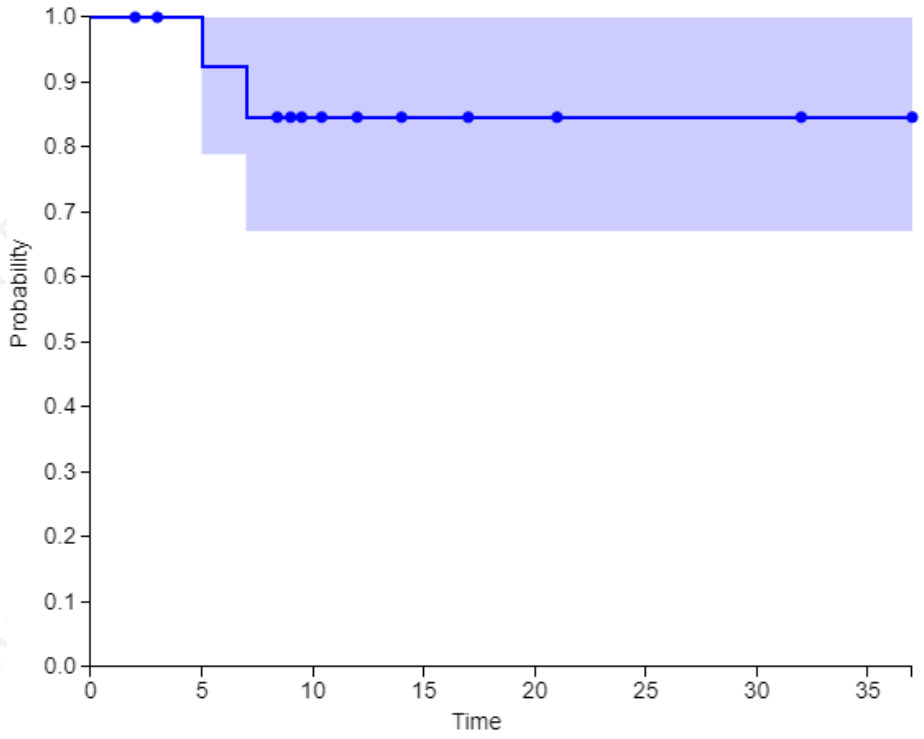
Gynecological Mucosal Malignant Melanomas

Current Evidence: CNAO's preliminary experience



- Retrospective analysis of 15 patients
- Median follow-up period: 35 months (range: 5–98 months) for all patients
- Higher mottled data!!! → prospective trial!

- **1-y LC and 2-y LC 82%**

Unpublished data

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Gynecological Mucosal Malignant Melanomas

Current Evidence: role of hadrontherapy

NIH National Library of Medicine

ClinicalTrials.gov

RECRUITING

Carbon Ion Radiation Therapy in the Treatment of Mucous Melanomas of the Female Lower Genital Tract (CYCLE)

ClinicalTrials.gov ID NCT05478876

Sponsor CNAO National Center of Oncological Hadrontherapy

Information provided by CNAO National Center of Oncological Hadrontherapy (Responsible Party)

Last Update Posted 2022-07-28

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Gynecological Mucosal Malignant Melanomas

Current Evidence: role of hadrontherapy

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Short Communication

Toxicity of carbon ion radiotherapy and immune checkpoint inhibitors in advanced melanoma

Stefano Cavalieri [a], Sara Ronchi [b,*], Amelia Barcellini [b], Maria Bonora [b], Barbara Vischioni [b], Viviana Vitolo [b], Riccardo Villa [b], Michele Del Vecchio [c], Lisa Licitra [a,d], Ester Orlandi [b]

- Thirty-three patients
- 15% (N=5) vaginal melanomas

Age	Primary	Site of CIRT	max acute AE	max late AE	ICI	ICI vs CIRT timing
59	Vaginal	primary T-N	1	1	anti-PD1	ICI after CIRT
52	Vaginal	primary (first course)	3	2	anti-CTLA4	sandwich
		liver recurrence (second course)	3		anti-PD1	sandwich
75	Vaginal	recurrence after surgery T-N	1	1	anti-CTLA4 followed by anti-PD1	ICI before CIRT
78	Vaginal	primary T	1	1	anti-PD1	sandwich

Cavalieri et al Radiother Oncol. 2021

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- With sequential CIRT and ICIs G3+ AEs are observed in 21% of patients.
- Late Aes are experienced in 79% of patients treated with sequential CIRT and ICIs.
- The frequency of **G3+ local AEs** is similar to what is observed with CIRT alone.
- The frequency of **G3+ AEs** is similar to what is observed with ICI without CIRT.

Cavalieri et al Radiother Oncol. 2021

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Gynecological Mucosal Malignant Melanomas

Current Evidence: role of hadrontherapy

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Agenda

- **Gynecological Melanomas**
  - ✓ Epidemiology
  - ✓ Current Evidence: role of hadrontherapy in gynecological melanomas

- **Oligometastatic/ oligorecurrent/ oligorefractory ovarian cancers**
  - Literature data: epidemiology and current management
  - What role for CIRT?

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Oligometastatic/oligorecurrent/oligorefractory ovarian cancer

Epidemiology

- 7th most frequent cancer diagnosed worldwide
- 5th cause of death in woman due to cancer after lung, breast, colorectal, and pancreas
- 1st cause of death due to gynecological cancer
- 80% diagnosed in advanced stage: a ‘chronic’ disease with multiple relapses

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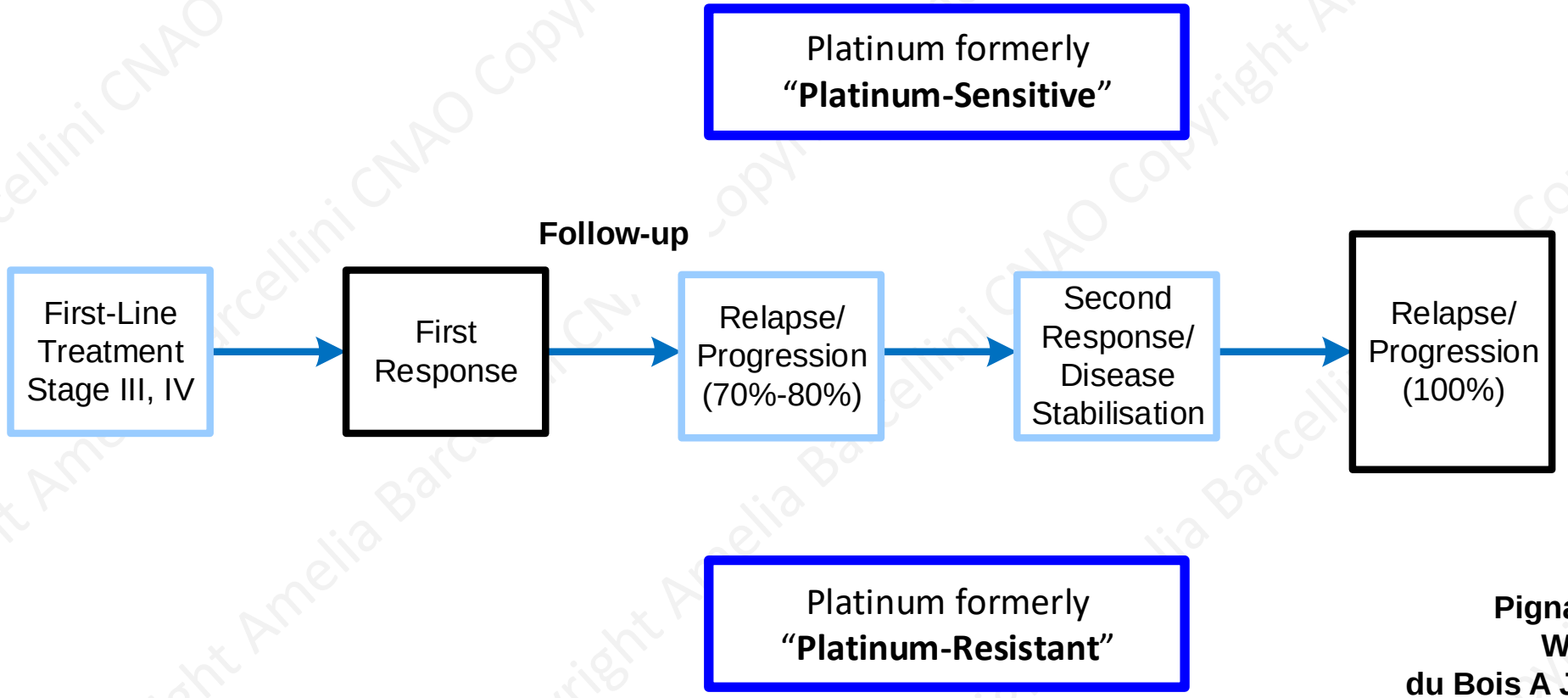
Oligometastatic/oligorecurrent/oligorefractory ovarian cancer

Management



Pignata S, Ann Oncology 2017
Wilson MK Ann Oncol 2017
du Bois A J. Zentralbl Gynakol. 2004

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Oligometastatic/oligorecurrent/oligorefractory ovarian cancer

Management

- The traditional is represented by systemic CT chosen on the basis of platinum sensitivity, histotype, status of BRCA genes or homologous recombination deficiency, pattern of relapse
- The introduction of PARP-inhibitors in first and second-line for BRCA mutated OC would modify the management of disease relapse
- RT shifts from a palliative aim toward the concept of RT as an active and definitive treatment that can be integrated into a multidisciplinary approach

Pignata S, Ann Oncology 2017
Wilson MK Ann Oncol 2017
du Bois A J. Zentralbl Gynakol. 2004

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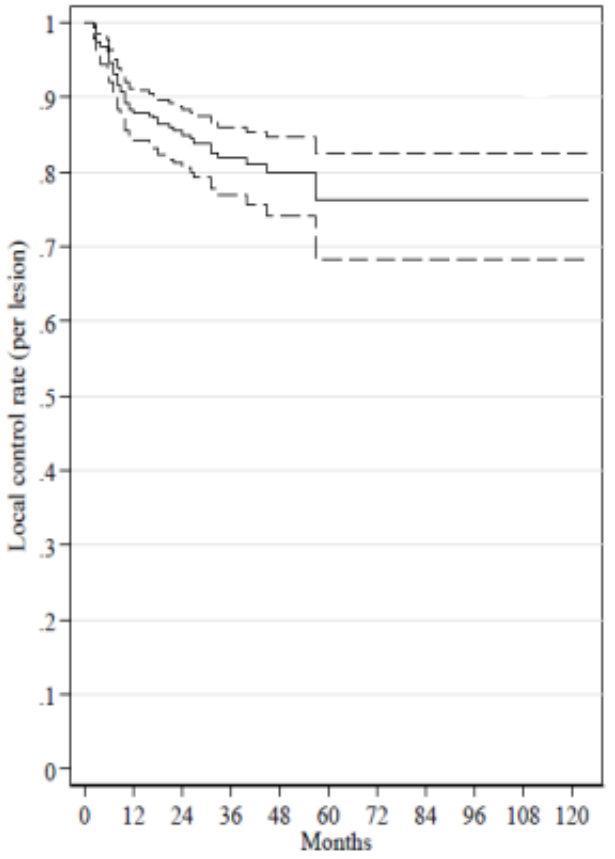
Oligometastatic/oligorecurrent/oligorefractory ovarian cancer

Role of Radiotherapy: MITO R1 study

- 261 patients carrying a total of 449 lesions
- the 24- and 36-month actuarial LC rates were 81.9% and 79.9%
- **ORR**: 89% with 13.7% of PD



Macchia G et al . Oncologist. 2020

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Oligometastatic/oligorecurrent/oligorefractory ovarian cancer

What role for CIRT?

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Clinical benefits of carbon ion radiotherapy for recurrent/refractory ovarian/salpinx cancer

A. Barcellini[1,2], N. Okonogi[3], G. Fontana[1], A. Vai[4], S. Molinelli[4], C. Cassani[5,6], S. Secondino[7], K. Murata[3], S. Yamada[3], E. Orlandi[1]

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Oligometastatic/oligorecurrent/oligorefractory ovarian cancer

What role for CIRT?

- **Background:** CIRT for recurrent/refractory ovarian/salpinx cancer (RR-OSC) commenced in 2006 at QST and in 2019 at CNAO
- **Aim:** to analyze the real-world data set of the (RR-OSC) treated with carbon ion radiotherapy (CIRT) at QST (Japan) and CNAO (Italy).

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Oligometastatic/oligorecurrent/oligorefractory ovarian cancer

What role for CIRT?

- **Material and Methods:**
  - ❖ Observational, retrospective study on "per-lesion" basis

First endpoints:
- ✓ objective response (OR) = sum of complete response (CR) and partial response (PR).
- ✓ 1 and 2-year local control (LC)

Secondary endpoints:
- ✓ Toxicity scored using RTOG/EORTC and CTCAE scales according to Center policy

  - ❖ Logistic and Cox regression were used for the uni- and multivariable analysis of factors predicting clinical OR rate and actuarial outcomes.

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Oligometastatic/oligorecurrent/oligorefractory ovarian cancer

What role for CIRT?

- 26 women (58% Asian and 42% Caucasian), for a total of 36 lesions, underwent CIRT for RR-OSC
- Median age at CIRT was 59.5 years (range:44-81)
- 21 patients were radiotherapy naïve, while 5 patients received CIRT for re-irradiation
- Median total dose of 52.8 GyE (range:39-64 GyE)

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Oligometastatic/oligorecurrent/oligorefractory ovarian cancer

What role for CIRT?

Characteristics	N	%
Histotype		
• High grade serous cell	11	42.3%
• Mucinous	3	11.5%
• Endometrioid	2	7.7%
• Clear Cells	1	3.8%
• Mixed mullerian	5	19.2%
• Undifferentiated	1	3.8%
• Other	3	11.5%

Characteristics	N (%)
Type of lesion(s)	
• Lymph node	15 (41.7%)
• Parenchyma	21 (58.3%)
✓ Abdominal	14
✓ Pelvic	5
✓ Brain	2

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Oligometastatic/oligorecurrent/oligorefractory ovarian cancer

What role for CIRT?

- 15 lesions (**41%**) achieved **CR within 12 months**
- **OR rate was 97%**

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Macchia G et al . Oncologist. 2020
OR rate: 89%

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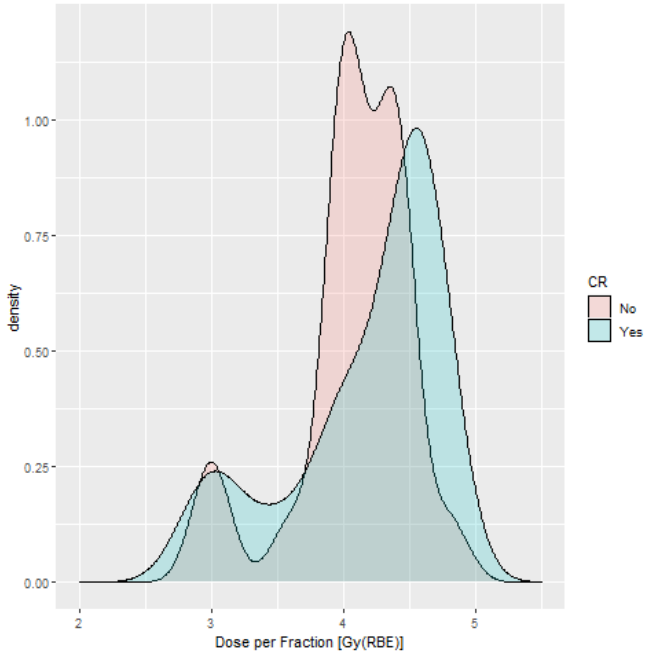

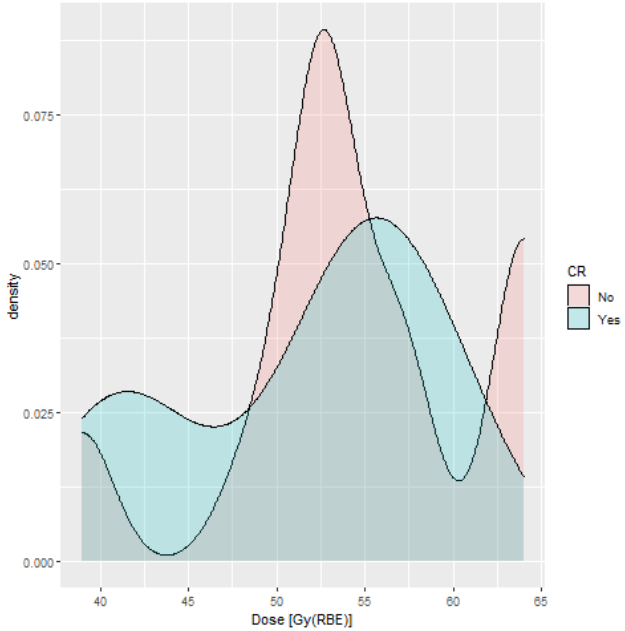

Dose per fraction> 4.2 Gy[RBE]
(*OR: 7,27% CI: 1,72-37,54, p=0.01)*

Total dose > 52,8 Gy[RBE]
(*OR: 6,88% CI: 1,67-33,93, p=0.01)*

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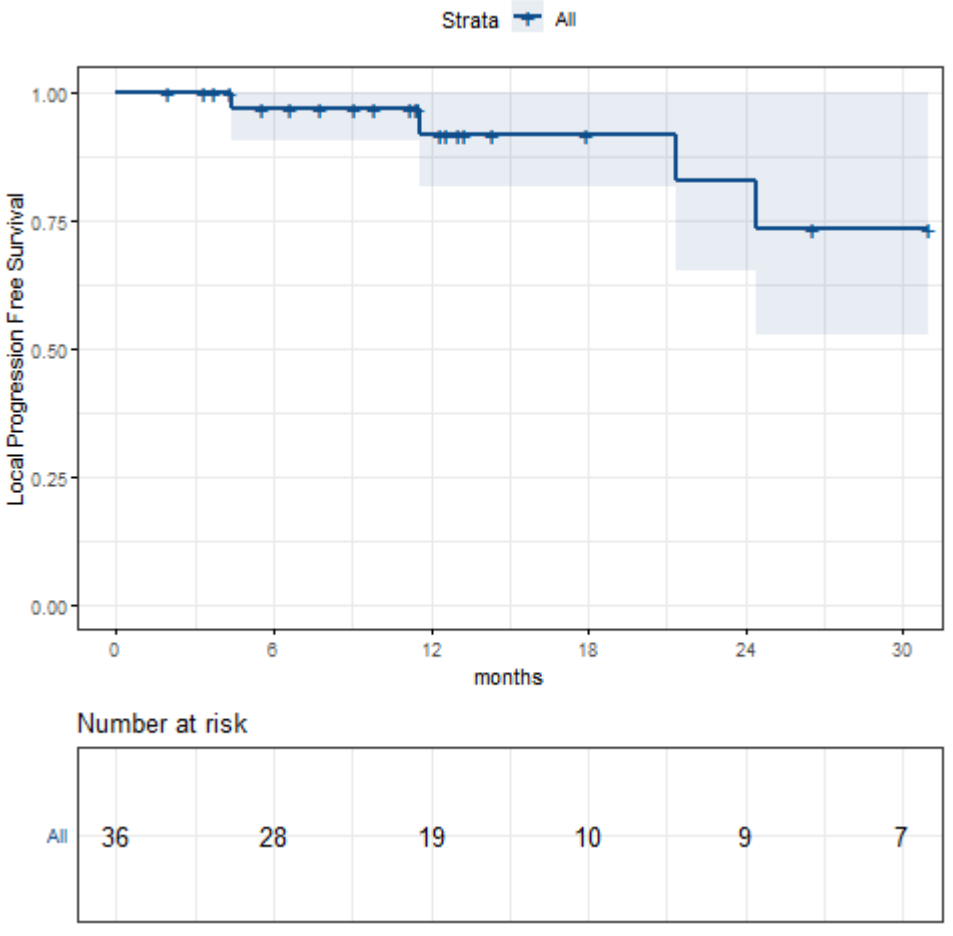

- After a median follow-up of **12.45 months (3-193 months)** :

1- year LC:**92%** (95% CI: 82%- 100%)
2- year LC:**83%** (95% CI: 65%-100%)

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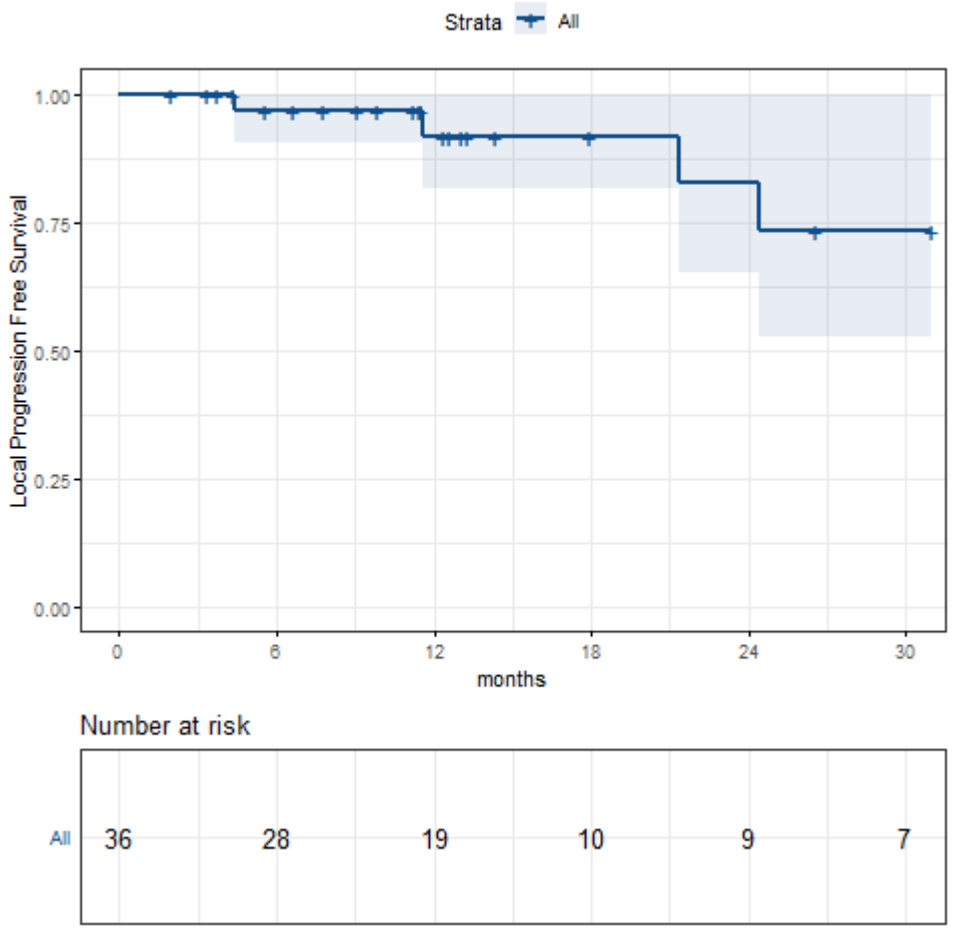
Oligometastatic/oligorecurrent/oligorefractory ovarian cancer

What role for CIRT?



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2- year LC:**83%** (95% CI: 65%-100%)

Macchia G et al . Oncologist. 2020
2-y LC 81.9%

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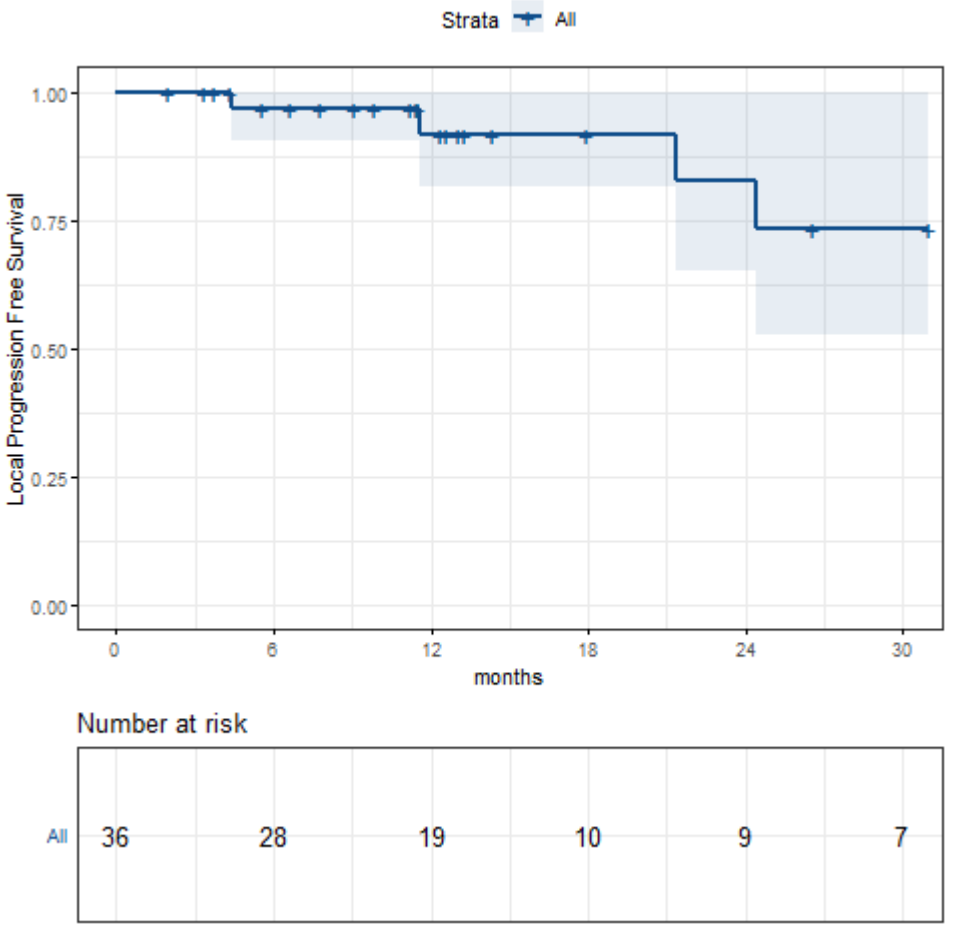
What role for CIRT?



- After a median follow-up of **12.45 months (3-193 months)** :

1- year LC:**92%** (95% CI: 82%- 100%)
2- year LC:**83%** (95% CI: 65%-100%)

Prognostic factors (adjusted for RBM):

- ✓ Age (p=0.69)
- ✓ Dose per fraction (p=0.30)
- ✓ Total dose (p=0.63)
- ✓ Tumor site (p=0.93)

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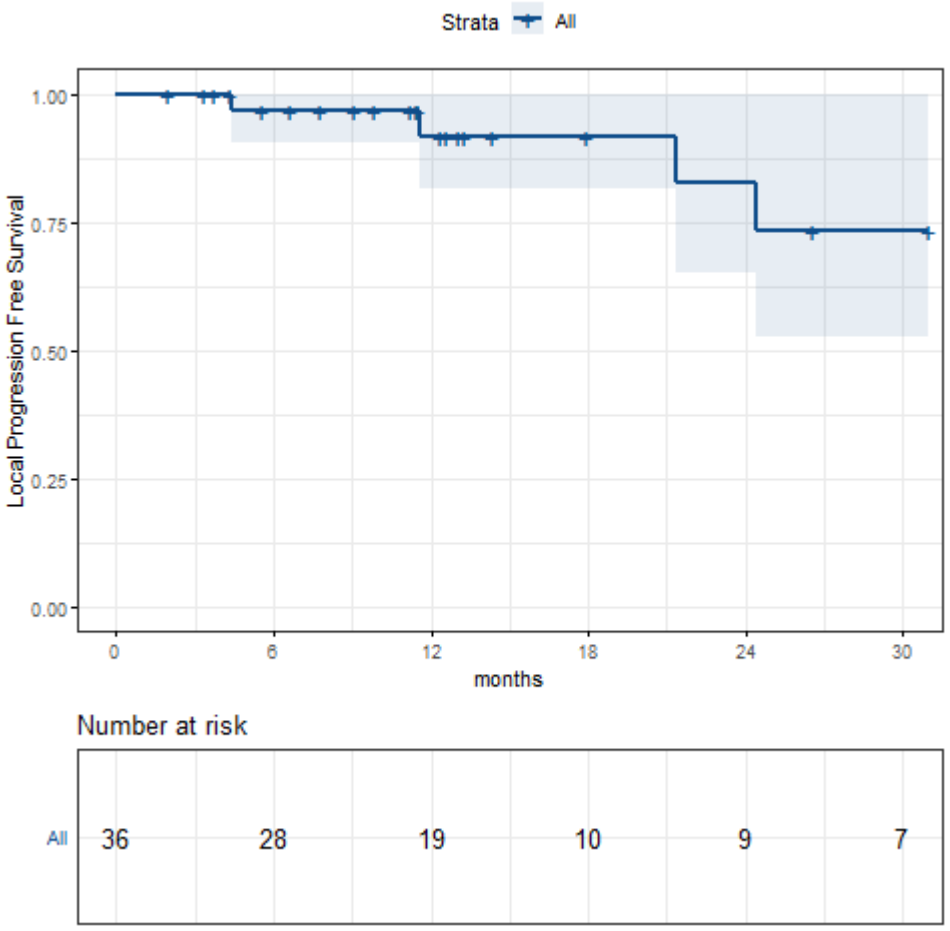
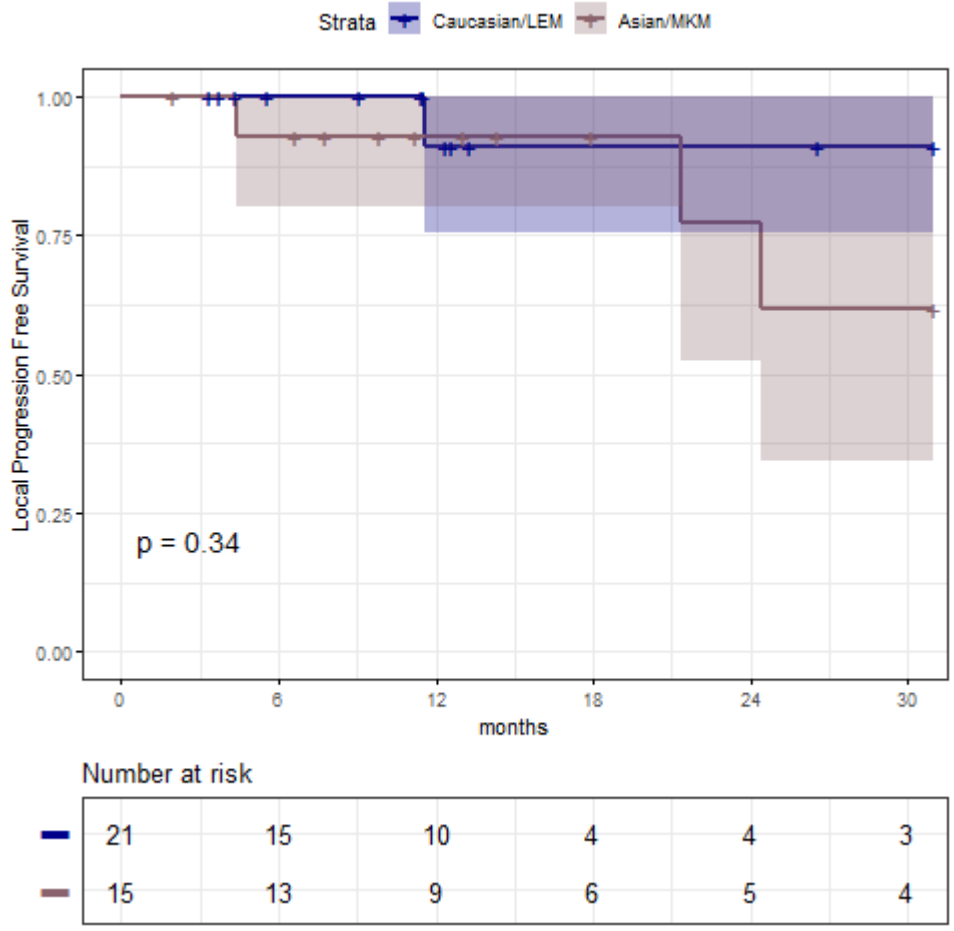
Oligometastatic/oligorecurrent/oligorefractory ovarian cancer

What role for CIRT?





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Oligometastatic/oligorecurrent/oligorefractory ovarian cancer

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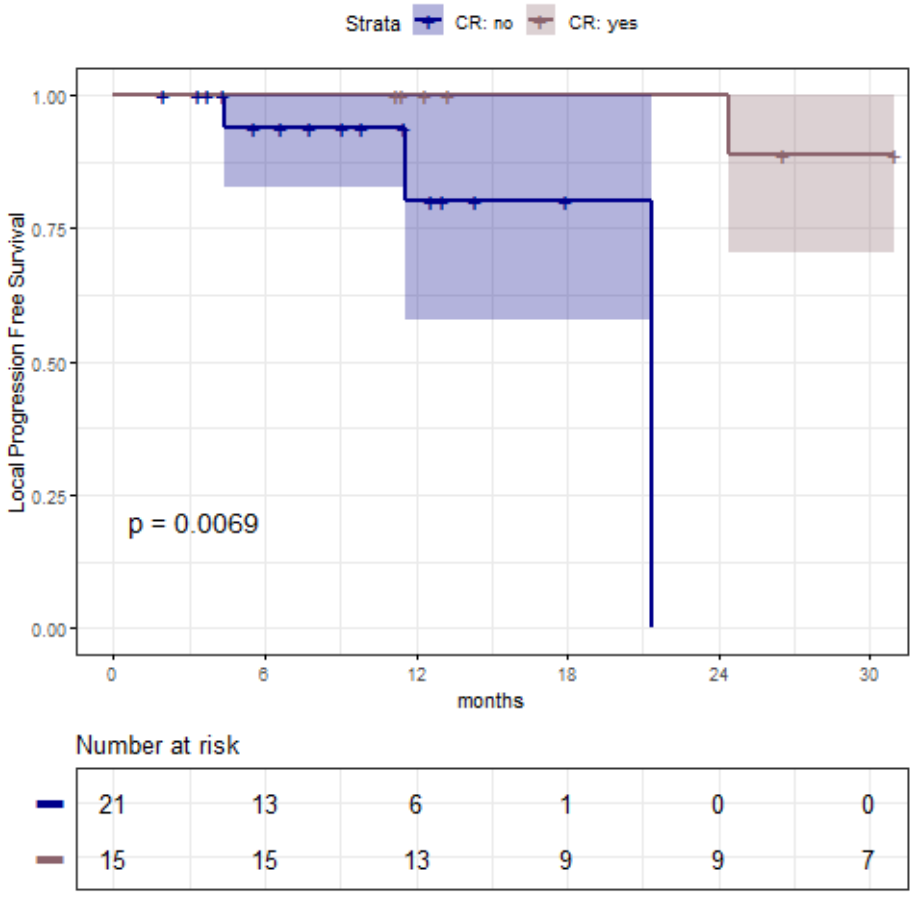

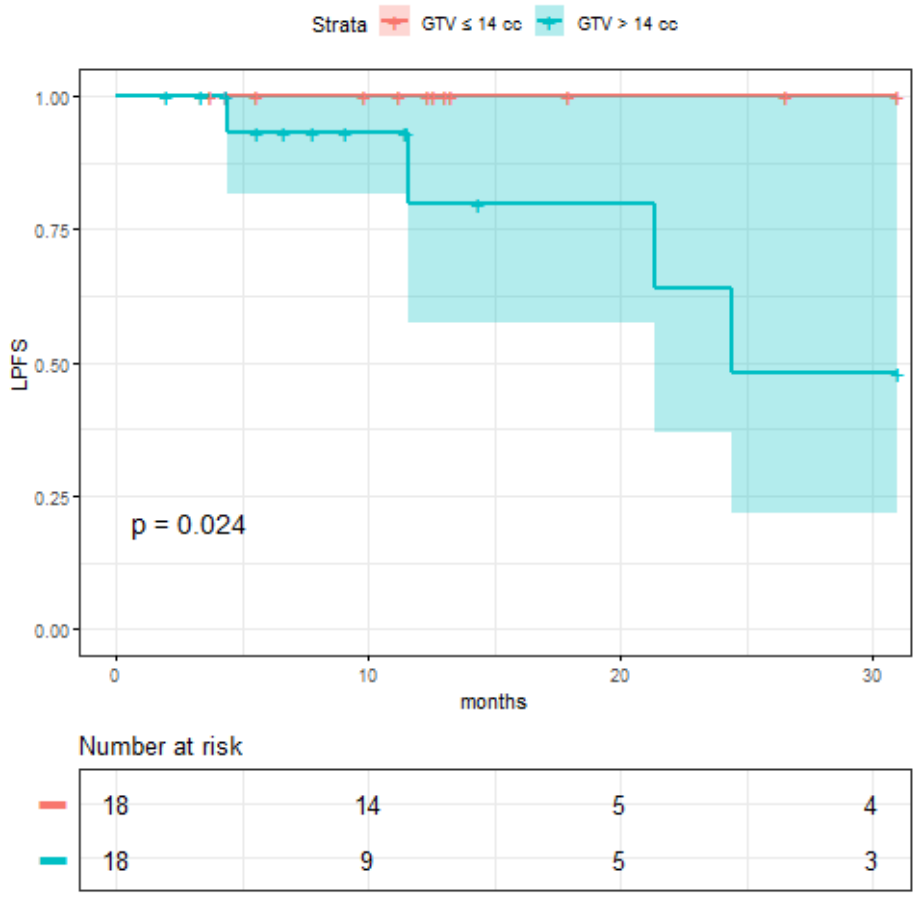

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ler grant agreement No 101008548

Oligometastatic/oligorecurrent/oligorefractory ovarian cancer

What role for CIRT?

- Only one case of G3 EORTC/RTOG enterocolitis in the acute and late phases was observed.
- No G≥3 toxicities were recorded in re-irradiated patients.
- 4 patients received PARP-i and 6 anti-VEGF (before and/or after CIRT), which seemed not to exacerbate the risk of severe toxicities

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Oligometastatic/olig y ovarian cancer

What role for CIF

- Only one case of G3 EC ate phases was observed.
- No G≥3 toxicities were r
- 4 patients received PAR IRT), which seemed not to exacerbate the risk of severe toxiciti

Acute toxicities	*n* (%)	Late toxicities	*n* (%)
All	63	All	19
Asthenia		Asthenia	
G1	9 (14.2)	G1	
G2		G2	
Pain		Pain	
G1	6 (9.5)	G1	2 (10.5)
G2	5 (7.9)	G2	
Upper GI disorders		Upper GI disorders	
G1	19 (30.1)	G1	2 (10.5)
G2	5 (7.9)	G2	
Lower GI disorders		Lower GI disorders	
G1	9 (14.3)	G1	8 (42.1)
G2	3 (4.7)	G2	
GU disorders		GU disorders	
G1	1 (1.5)	G1	1 (5.2)
G2	1 (1.5)	G2	
Pulmonary toxicity		Pulmonary toxicity	
G1	1 (1.5)	G1	1 (5.2)
G2	1 (1.5)	G2	2 (10.5)
Skin toxicity (erythema), G1	2 (3.1)	Skin toxicity (fibrosis), G1	2 (10.5)
Neurotoxicity (dizziness), G1	1 (1.5)	Neurotoxicity (diplopia), G1	1 (5.2)

Abbreviations: GI, gastrointestinal; GU, genitourinary.

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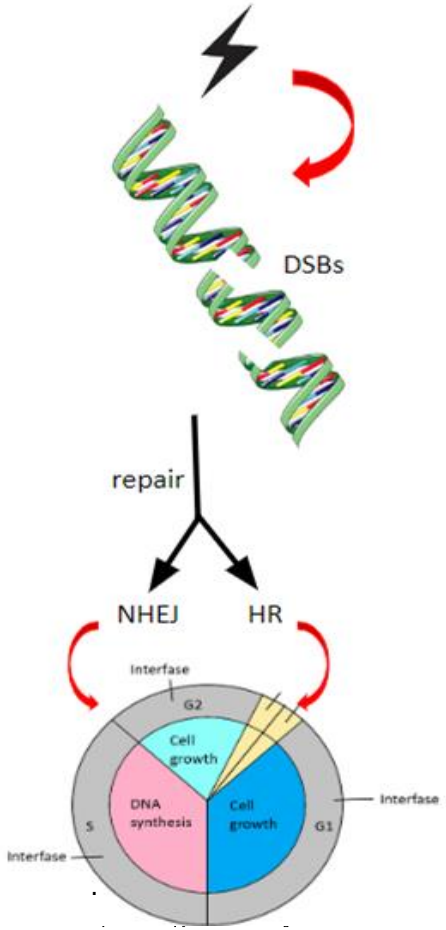
Oligometastatic/oligorecurrent/oligorefractory ovarian cancer

What role for CIRT?



- Repair Pathway Choice

✓ The two main DNA DSB repair pathways are non-homologous end joining (**NHEJ**) and homologous recombination (**HR**), the latter only active in S and G2-phases of the cell cycle

✓ An **increased usage of HR** has been observed after exposure to CIRT

Tinganelli W Cancers (Basel). 2020
Barcellini A, Charalampopoulou A Life (Basel), 2022

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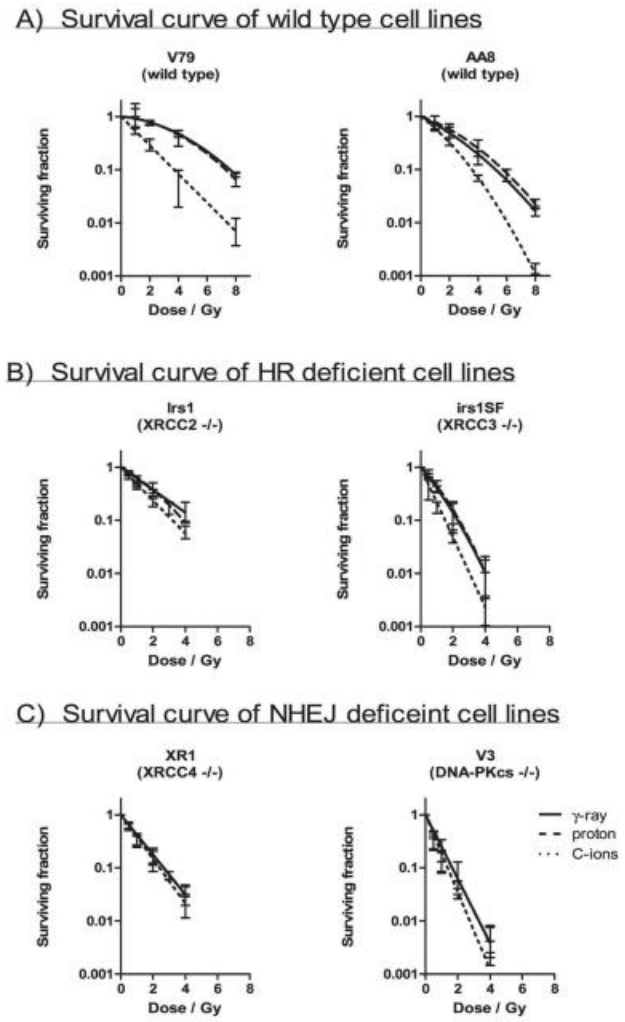

- ✓ The **wild-type cells were most resistant**, followed by the HR-deficient irs1, NHEJ-deficient XR1, HR-deficient irs1SF and NHEJ-deficient V3 cells to all radiation types examined
- ✓ The cells responded to **γ rays and proton beams in a nearly identical manner**
- ✓ **The wild-type and HR-deficient cell lines were more strongly sensitized to C ions** than the NHEJ-deficient cell lines

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Gerelchuluun A. Radiat Res. 2015

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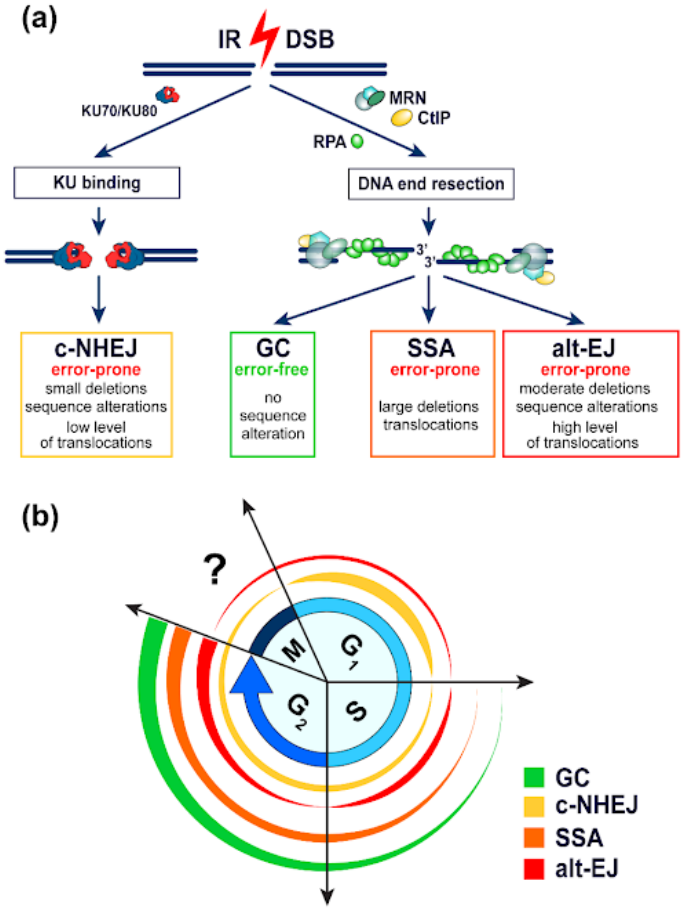
Oligometastatic/oligorecurrent/oligorefractory ovarian cancer

Which role for CIRT?



- Repair Pathway Choice

✓ DSB due to **high LET** triggers **alternative, error-prone DNA damage repair pathways**

✓ **alternative NHEJ:** DNA break resection followed by microhomology-mediated recombination (intrinsically error-prone, formation of translocations)

✓ **Resection in G1** increase with LET (↑↑ **for 100 keV/µm**)

Iliakis G Cancers (Basel). 2019
Tinganelli W Cancers (Basel). 2020

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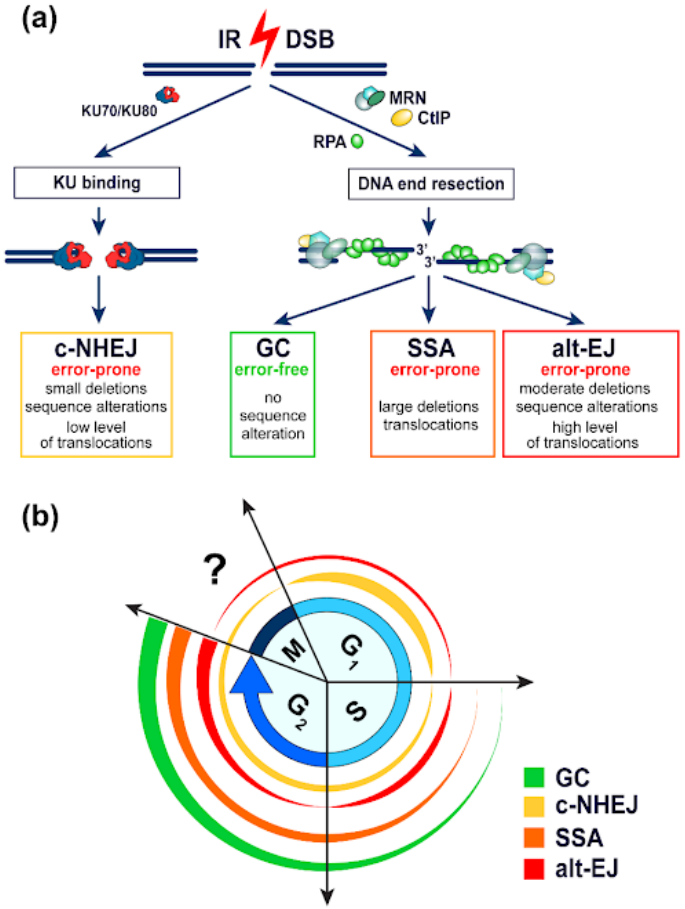

- Repair Pathway Choice

✓ **A large fraction of DSB due to CIRT is processed by NHEJ**

✓ An **increased usage of HR** has been observed after exposure to CIRT

✓ **Dose-dependent** with more breaks repairing by NHEJ at high dose when HR becomes saturated

Fontana AO, Radiother Oncol 2015
Grosse N et al Int J Radiat Oncol Biol Phys 2014
Barcellini A, Charalampopoulou A Life (Basel), 2022

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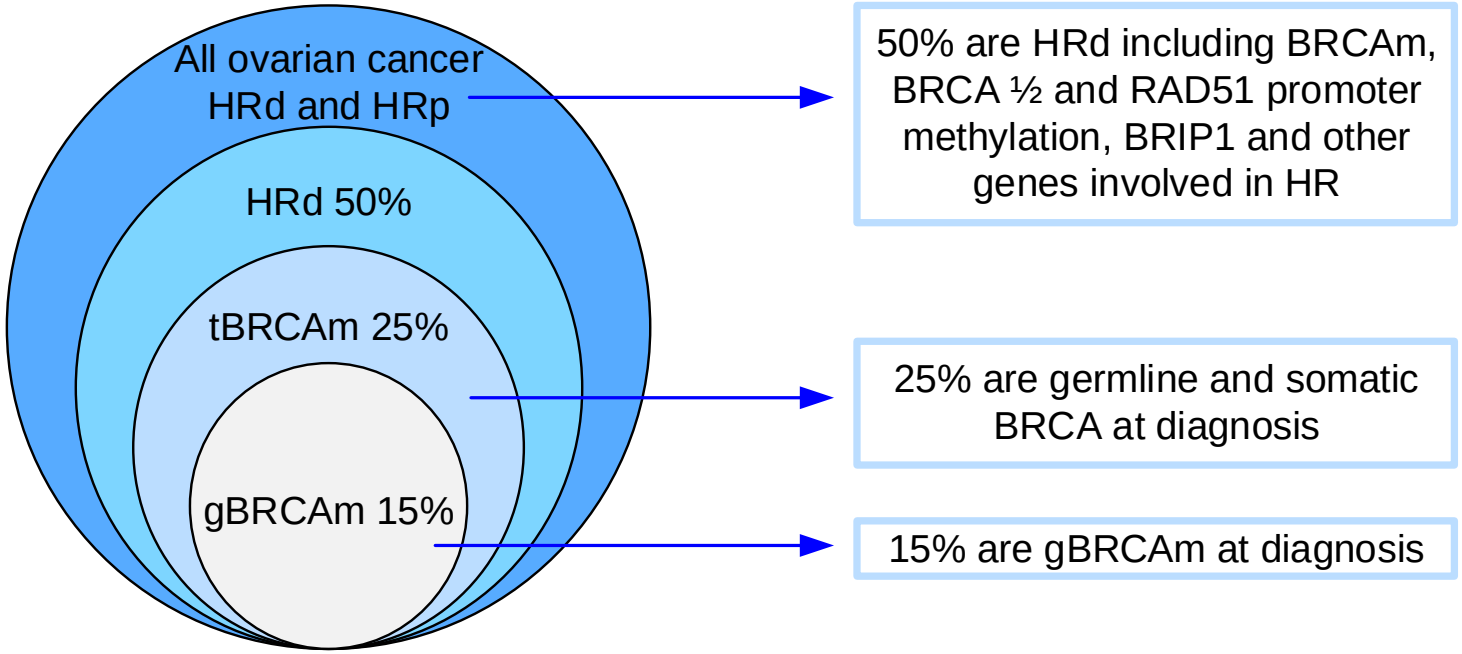

The Cancer Genome Atlas Research Network, Nature 2011
Konstantinopoulos PA, et al. Cancer Discov 2015

HITRI Heavy Ion Therapy Research Integration
CNAO The National Center for Oncological Hadrontherapy
Creation of Harmonious Diversity QST National Institutes for Quantum Science and Technology
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Oligometastatic/oligorecurrent/oligorefractory ovarian cancer

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Conclusions

1. Hadrontherapy appears to be a safe, effective and feasible treatment method, which has shown **advantages over photon therapy**

2. To test the **combo approach**

3. **Preclinical studies** are crucial

4. RCTs (maybe for ROC?) are unrealistic →the development **of clinical registries** might help to elucidate current uncertainties

5. National and International **multidisciplinary cooperation** is of utmost importance to make a step forward

HITRI
Heavy Ion Therapy Research Integration

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HITBR plus
Heavy Ion Therapy Research Integration

Gynae and Rare Indications: Gynaecological Melanoma and Oligomet Ovarian Cancer

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CNAO National Center for Oncological Hadrontherapy

CNAO
Centro Nazionale di Adroterapia Oncologica

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