



STANDARD TREATMENTS AND NEW DIRECTIONS IN GYNAECOLOGICAL CANCERS

MILANO June 26th-29th, 2025

Responsabili Scientifici:
NICOLETTA COLOMBO, FRANCESCO RASPAGLIESI



Oncological Hadrontherapy for Complicated Challenges

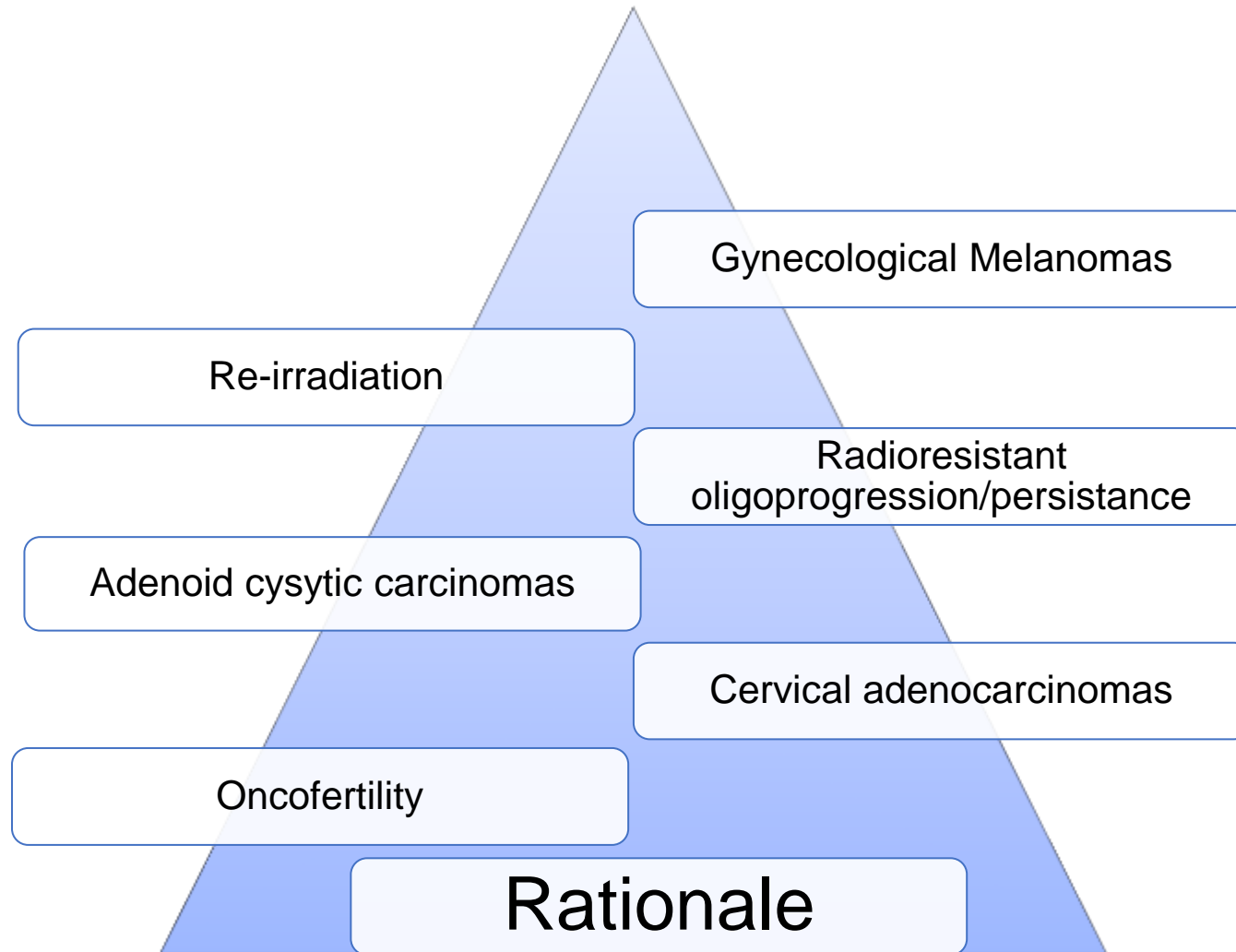
Amelia Barcellini

*National Center for Oncological Hadrontherapy
University of Pavia*

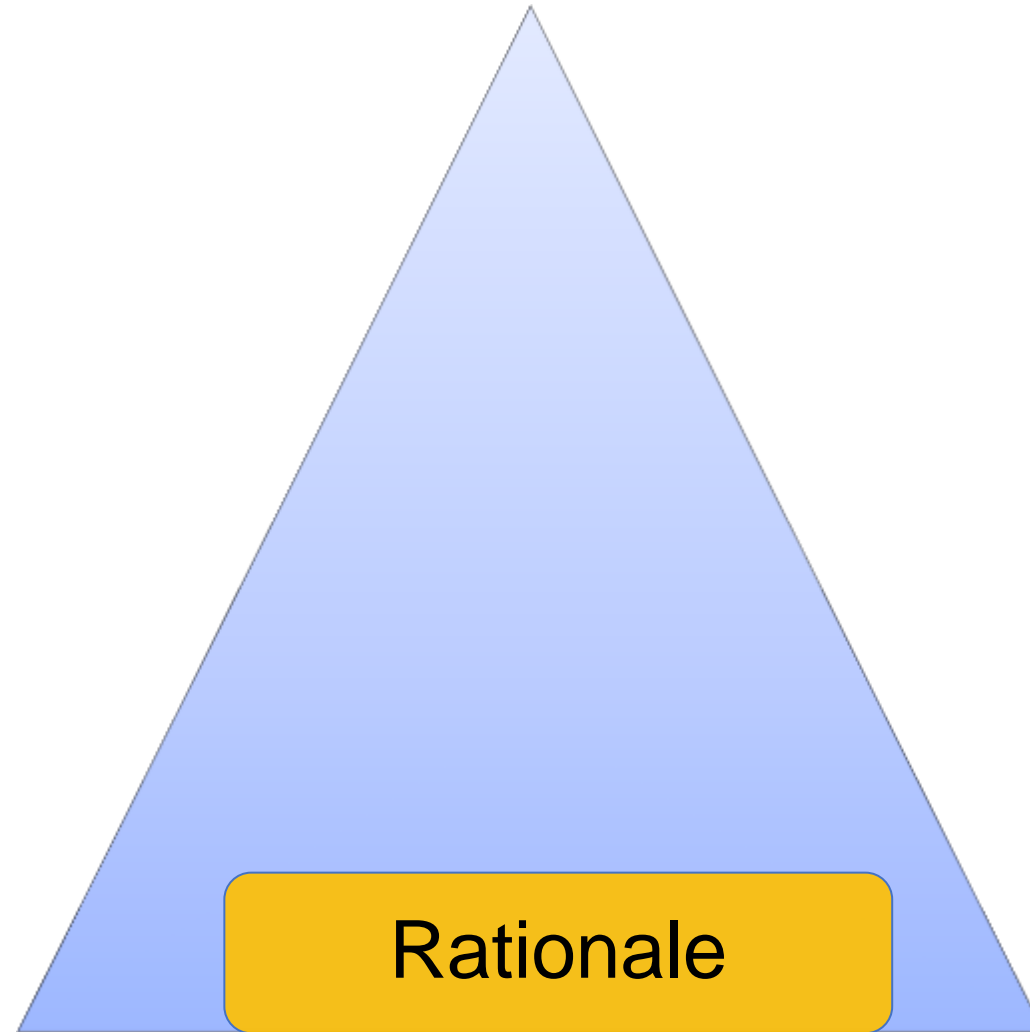
Disclosure

None

Agenda

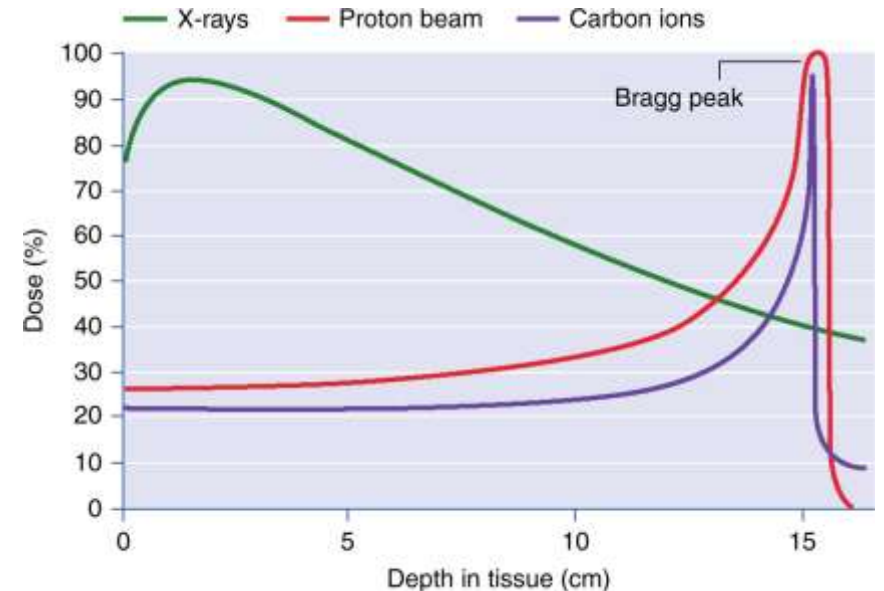
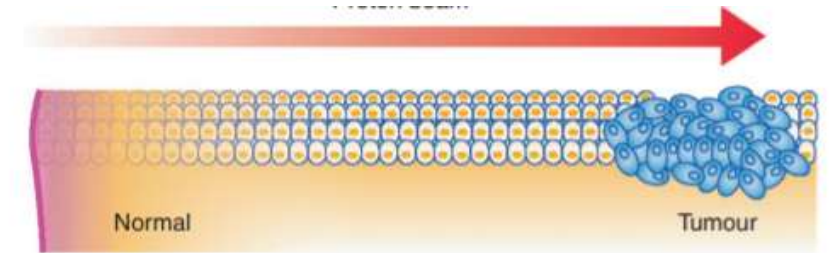


Agenda



Rationale

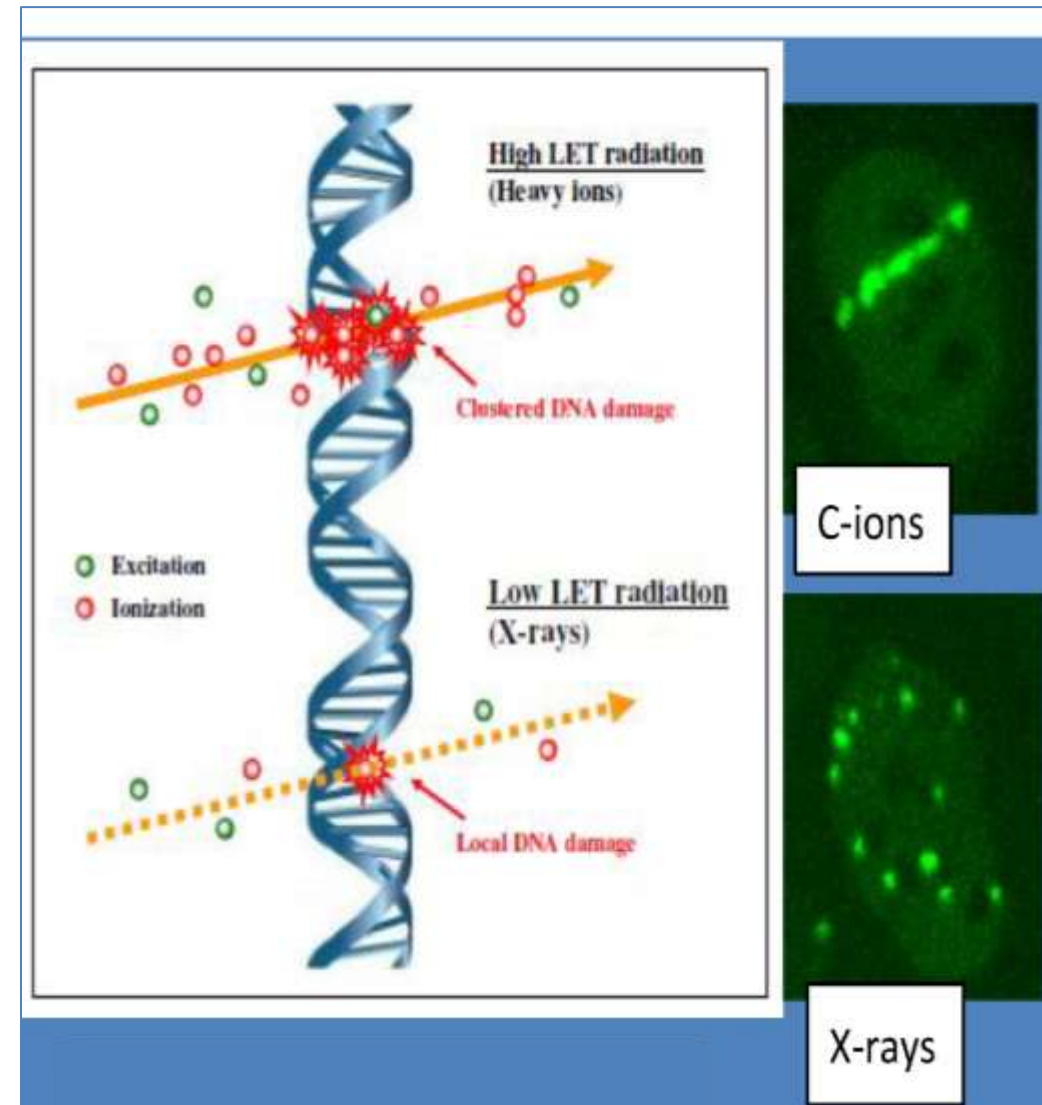
- Compared to traditional RT, particle beam RT has dosimetric and radiobiological advantages
- **Dosimetric hallmarks:**
 - ✓ **favourable depth–dose curve:**
 - X-ray energy decreases exponentially with dose
 - Hadrons deposit most of their initial energy close to the end of the range (Bragg peak) within the tumour target



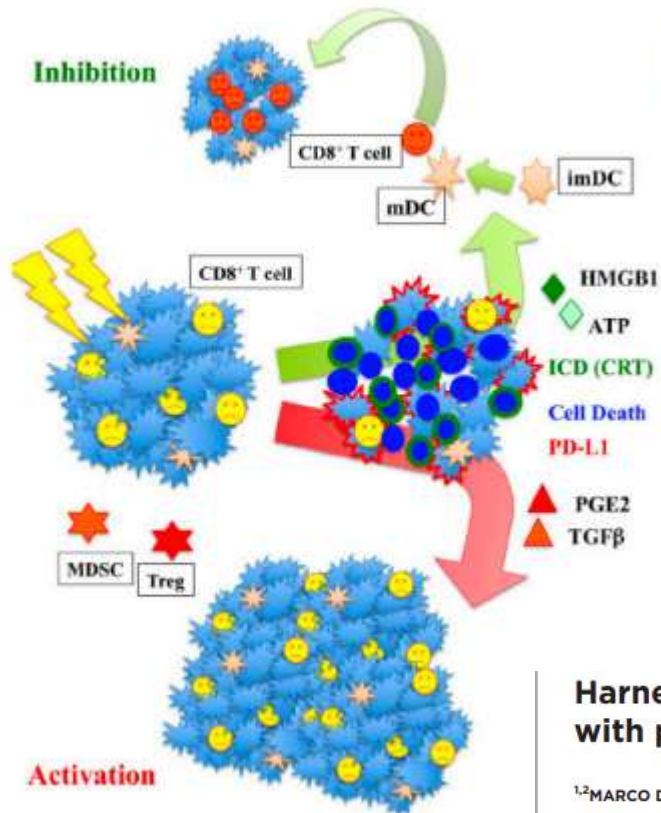
Rationale

- Radiobiological advantages

- ✓ charged particles have a **higher LET**, which ensures a **higher relative biological effectiveness** than conventional RT
- ✓ they can mainly induce more serious damage (i.e. **oxidative stress, more DNA double-strand breaks**)
- ✓ DSBs are the most lethal, as an accumulation of misrepaired or unrepaired DSBs can lead to a **massive loss of genetic information and cell death**
- ✓ Reduced dependence of fractionation and cell-cycle stage
- ✓ **Reduced** oxygen enhancement ratio (**OER**) in the tumour



Rationale



Harnessing radiation to improve immunotherapy: better with particles?

^{1,2}MARCO DURANTE, PhD and ³SILVIA FORMENTI, MD

Teaching Case

Pembrolizumab After Carbon Ion Radiation Therapy for Alveolar Soft Part Sarcoma Shows a Remarkable Abscopal Effect: A Case Report

Masahiko Okamoto, MD, PhD,^{a,b,*} Hiro Sato, MD, PhD,^{a,b}
Xianshu Gao, MD, PhD,^c and Tatsuya Ohno, MD, PhD^{a,b}



Optimal radiation dose to induce an abscopal effect by combining carbon-ion radiotherapy and anti-CTLA4 antibody

Liqiu Ma^{a,b,c,*}, Yang Li^b, Yoshimitsu Sakamoto^a, Lin Xie^a, Saaya Suzuki^a, Yukari Yoshida^b,
Li Sui^a, Gang Guo^a, Jialing Wen^a, Wangcai Ren^a, Kazuhiro Kakimi^b, Kensuke Osada^a,
Akihisa Takahashi^b, Takashi Shimokawa^{a,b}

Biology Contribution

Reduction of Lung Metastases in a Mouse Osteosarcoma Model Treated With Carbon Ions and Immune Checkpoint Inhibitors

Alexander Helm, PhD,^{a,*} Walter Tinganelli, PhD,^a
Palma Simonello, PhD,^{a,1} Fuki Kurosawa, BSc,¹ Claudia Fournier, PhD,^a
Takashi Shimokawa, PhD,¹ and Marco Durante, PhD^{a,1}



Bystander effect and abscopal effect in recurrent thymic carcinoma treated with carbon-ion radiation therapy: A case report

Yan-Shan Zhang, Yi-He Zhang, Xiao-Jun Li, Ting-Chao Hu, Wei-Zuo Chen, Xin Pan, Hong-Yu Chai, Yan-Cheng Ye

Advances in Radiation Oncology (2017) 2, 333-338

Teaching Case

Abscopal effect in recurrent colorectal cancer treated with carbon-ion radiation therapy: 2 case reports

Daniel K. Ebner BS^{a,b}, Tadashi Kamada MD, PhD^a,
Shigeru Yamada MD, PhD^{a,*}

Rationale

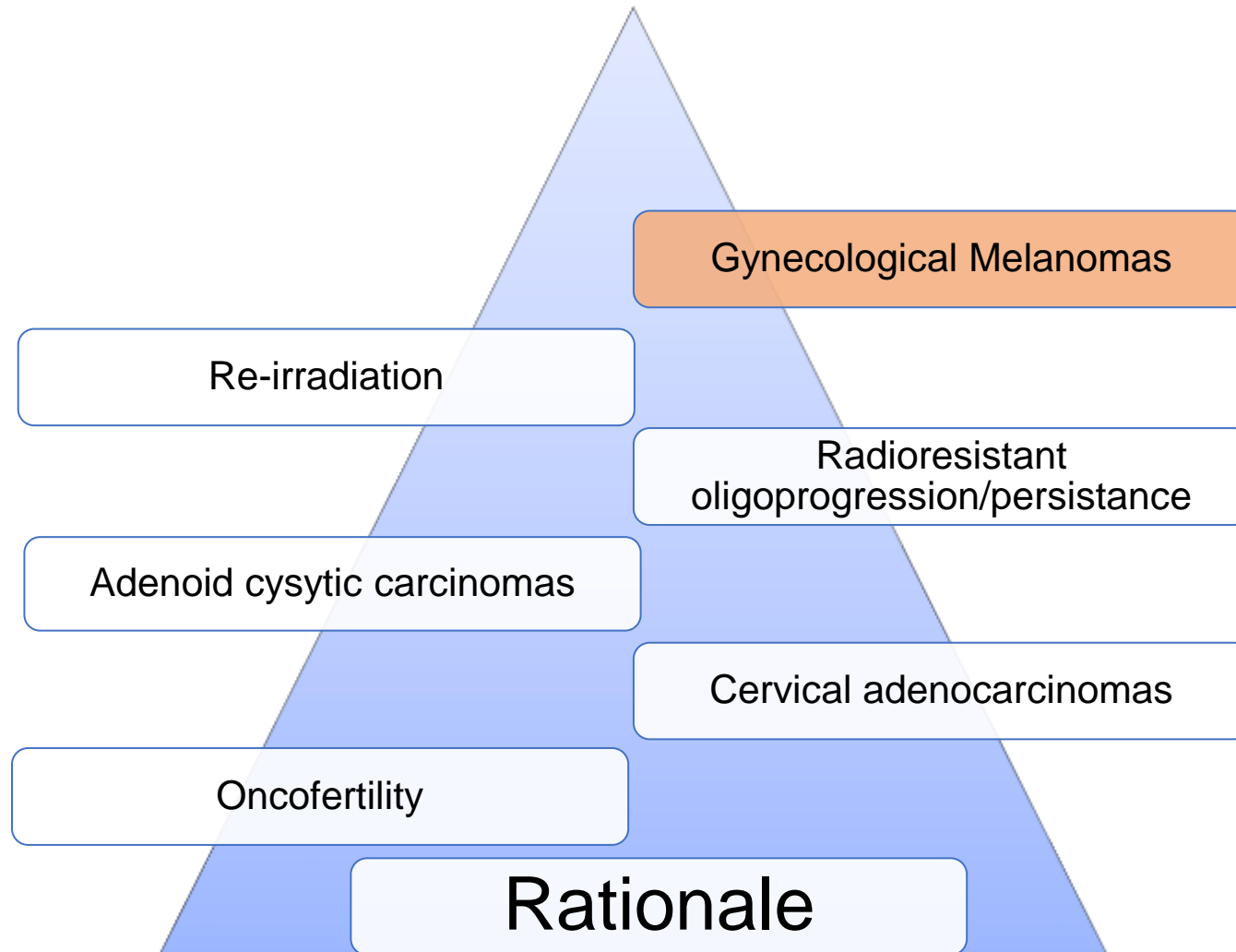
- **Normal tissue** sparing, **higher dose to tumor**
- Effectiveness to **hypoxic** and **radioresistent** tumors
- Ability to **reverse tumor immune desertification** and resistance



suitable for

- tumors close to radiation-sensitive organs (bowel, spinal cord, brain...)
- local recurrences after photon beam radiotherapy
- slow-growing tumors
- oxygen-poor tumors
- “cold” tumors

Agenda



Gynecological Melanomas

- **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%



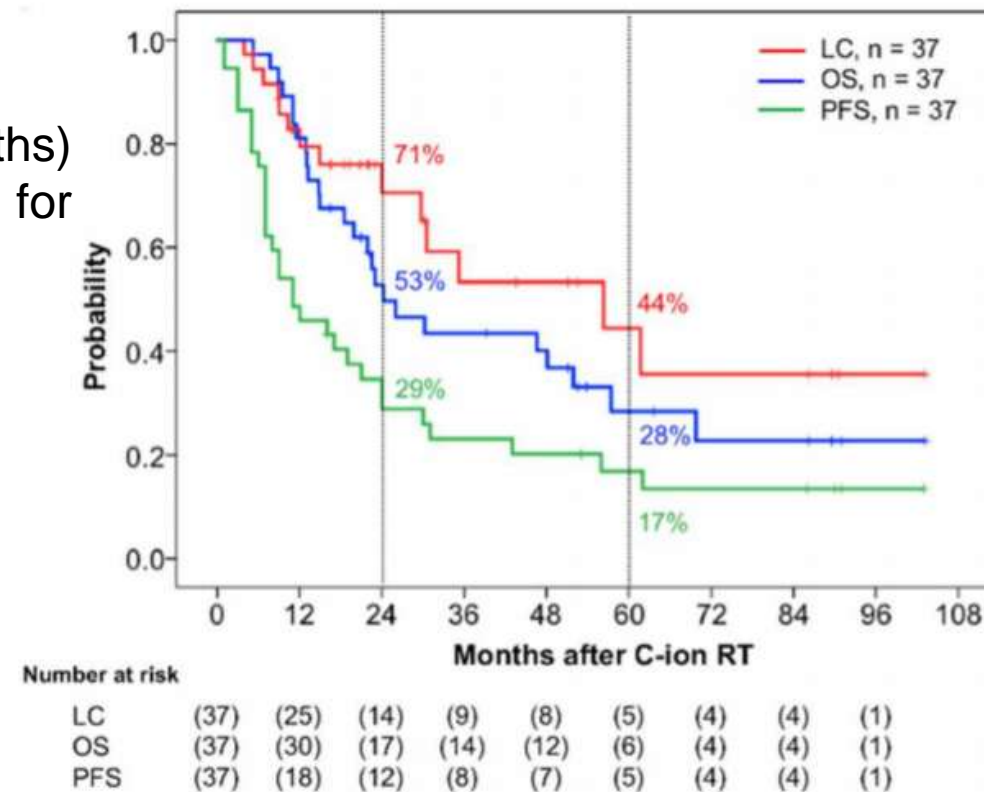
- Management based on data concerning gyn cancers & cutaneous melanoma
- **Surgery** is the treatment of choice (early stages) → surgical challenges (proximity of bladder, anus rectum)
- **CIRT** is a promising alternative

Gynecological Melanomas

- Retrospective analysis of **37 patients**
- Median follow-up periods: **23 months** (range: 5–103 months) for all patients and 53 months (range: 16–103 months) for survivors
- **2-y LC 71%**

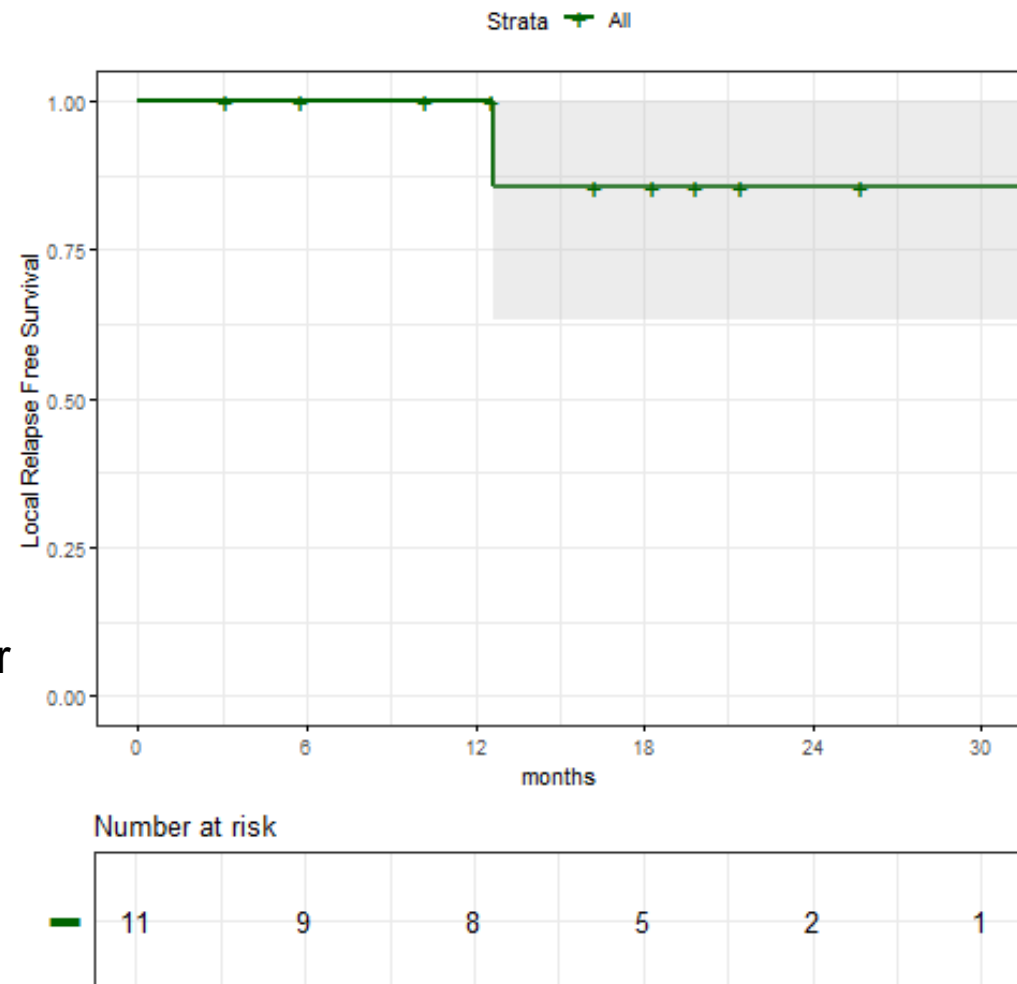
Acute Toxicity	CTCAE v.4 Scoring				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4–5
Dermatitis/mucositis	2	18	14	3	0
Genitourinary toxicity	28	9	0	0	0
Lower gastrointestinal toxicity	17	14	6	0	0

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

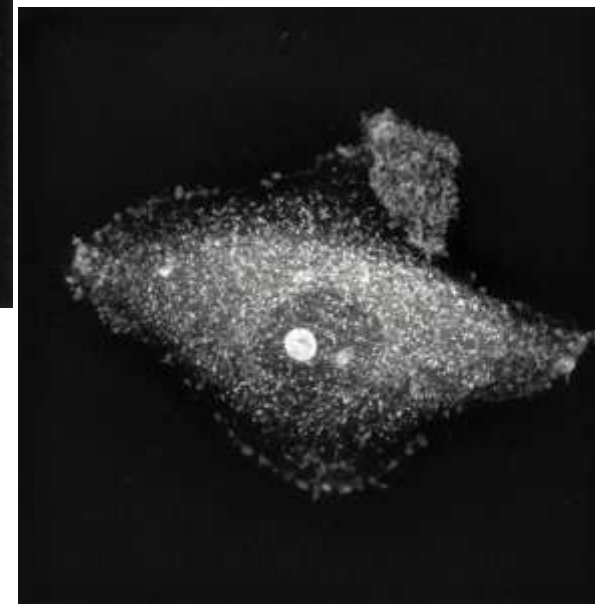
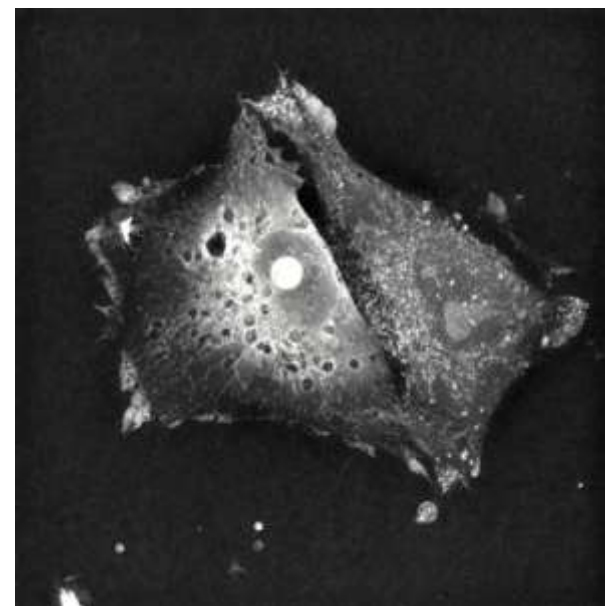
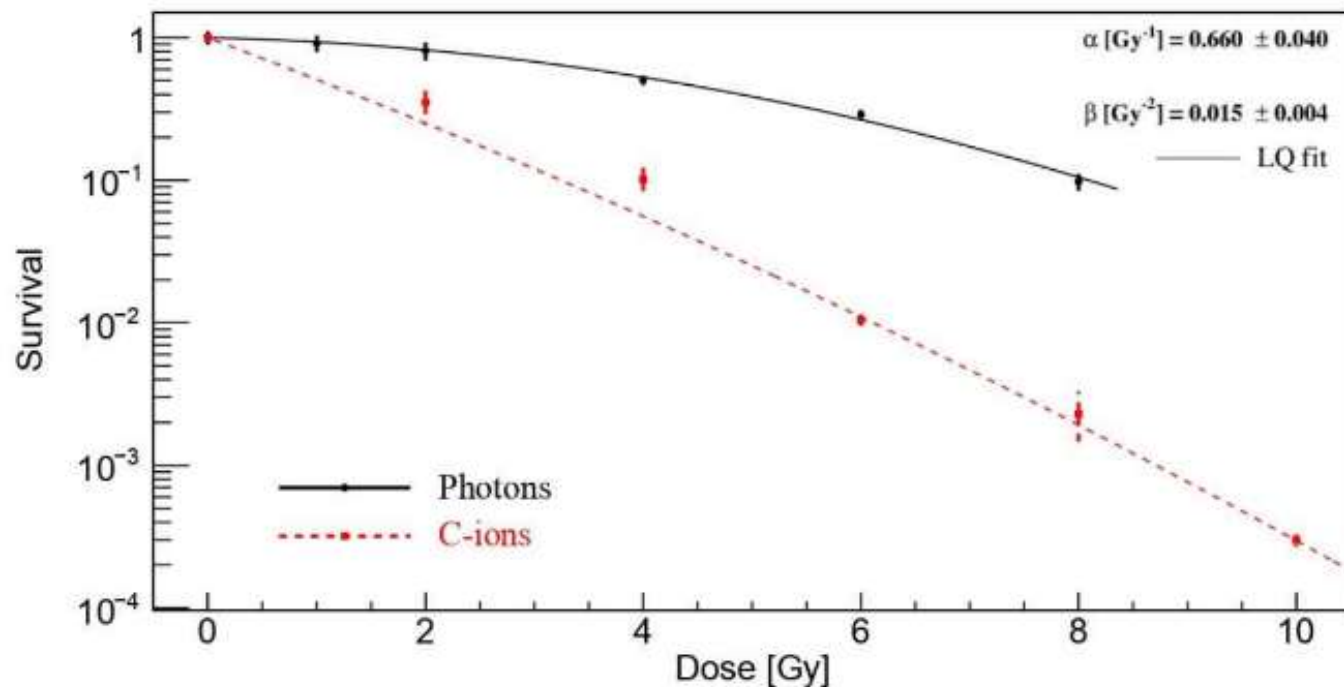


Gynecological Melanomas

- Retrospective analysis of 11 patients
- Total dose 68.8 GyRBE
- Median follow-up 18 months (IQR: 8.7, 20.3)
- ORR :82%
- CB of 100 %
- **1-y and 2-y LC were 100% and 86%**
- Patients with an age >60 years seemed to experience a better LC ($p = 0.014$)



Gynecological Melanomas



Gynecological Melanomas



Contents lists available at [ScienceDirect](https://www.sciencedirect.com/journal/ijpt)

International Journal of Particle Therapy

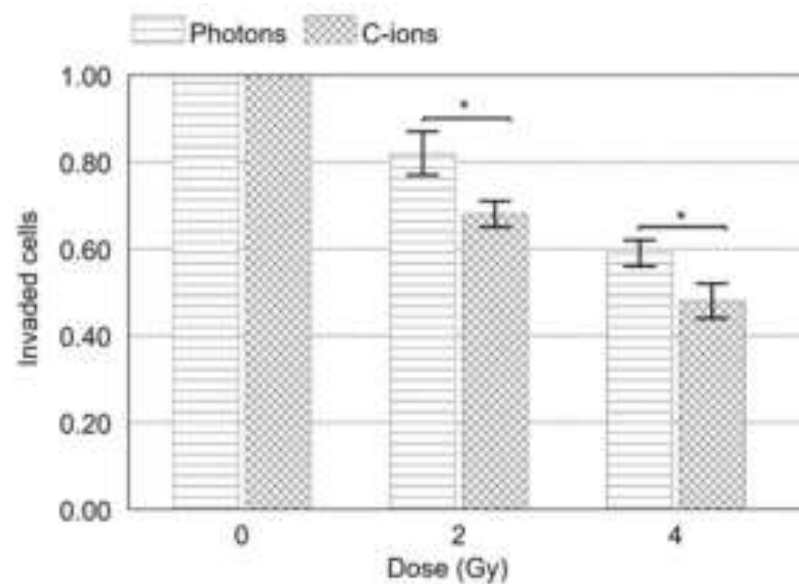
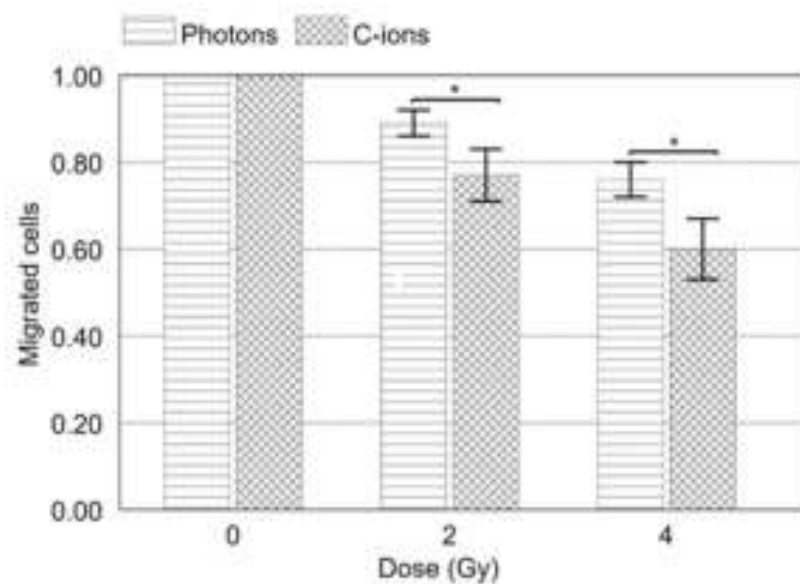
journal homepage: www.sciencedirect.com/journal/ijpt



Vaginal Mucosal Melanoma Cell Activation in Response to Photon or Carbon Ion Irradiation



Alexandra Charalampopoulou (MsC)^{1,2,*}, Amelia Barcellini (MD)^{3,4}, Margarita Bistika (MsC)⁵, Giovanni Battista Ivaldi (MD)⁶, Sara Lillo (MD)³, Giuseppe Magro (PhD)⁷, Ester Orlandi (MD)^{3,8}, Marco Giuseppe Pullia (PhD)⁹, Sara Ronchi (MD)³, Paola Tabarelli De Fatis (MSc)¹⁰, Angelica Facchetti (PhD)¹



Gynecological Melanomas



Study Design	Monocentric, prospective phase II study
Patients	Unresectable
Treatment	68.8 GyRBE in 16 fractions, 4 fractions per week
Endpoints	<p>The primary endpoint of the study is to estimate 2-year PFS in patients diagnosed with mucosal melanoma of the lower genital tract, treated with carbon ion radiation therapy.</p> <p>Secondary endpoints:</p> <ul style="list-style-type: none">•Overall survival (OS)•Toxicity according to Common Terminology Criteria for Adverse Events (CTCAE version 5.0)•Objective response rate (ORR) according to RECIST•Evaluation of the association between the clinical-radiological response at 6 weeks and the late response (> 6 months)•Quality of life.

RECRUITING

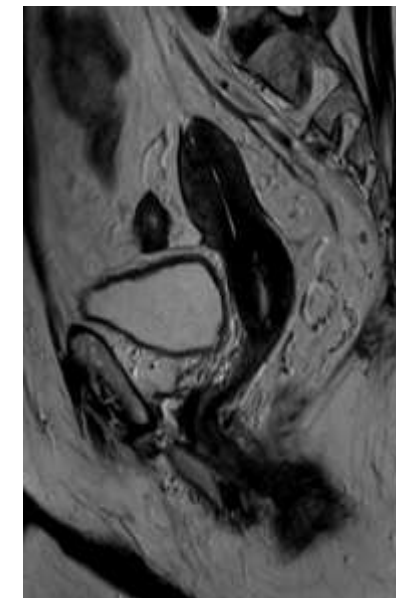
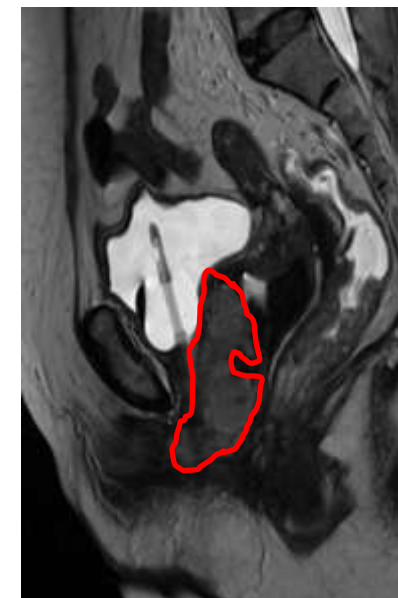
Carbon Ion Radiation Therapy in the Treatment of Mucous Melanomas of the Female Lower Genital Tract (CYCLE)

ClinicalTrials.gov ID: NCT05478876

Sponsor: CNAD National Center of Oncological Hadrontherapy

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

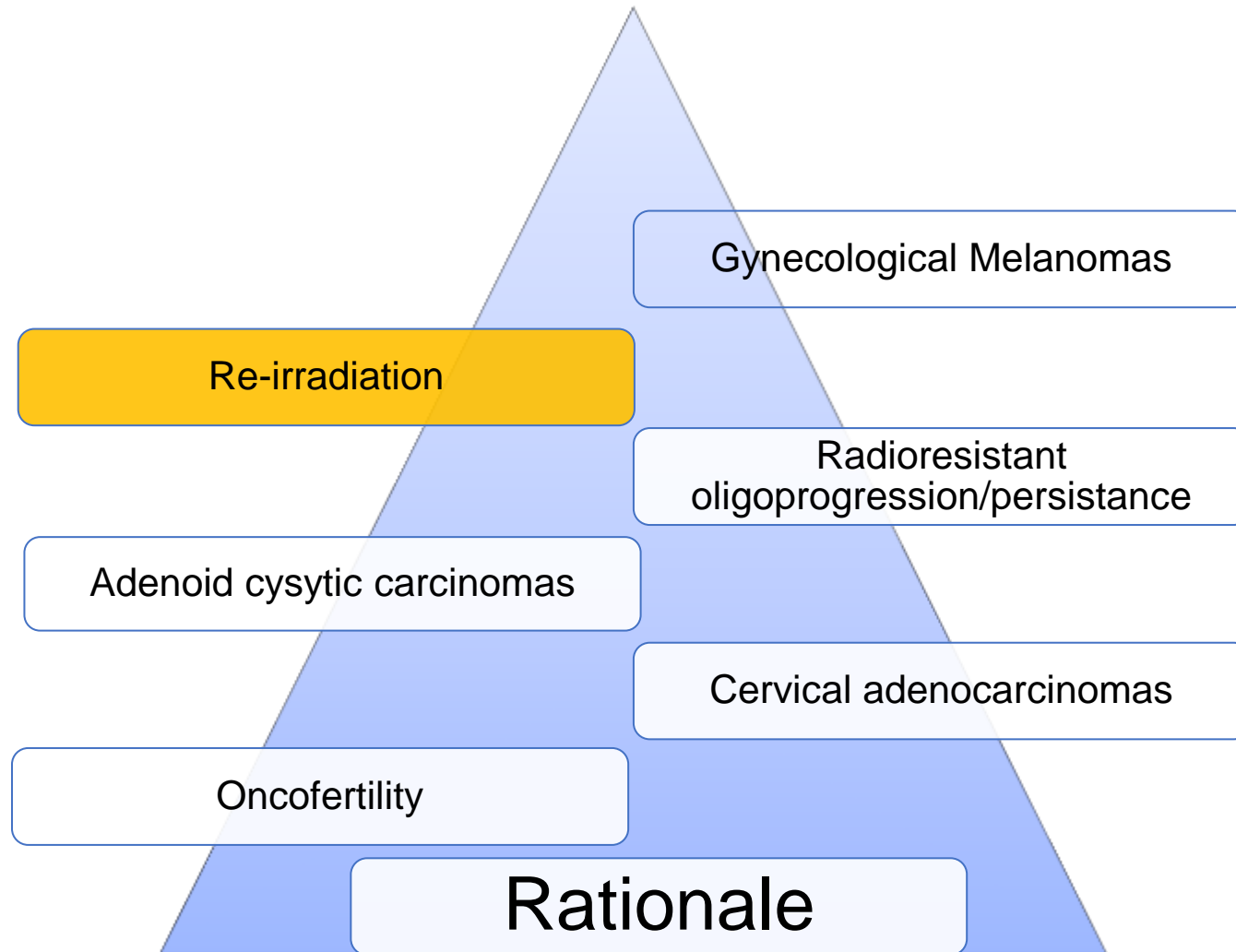
Last Update Posted: 2022-07-28



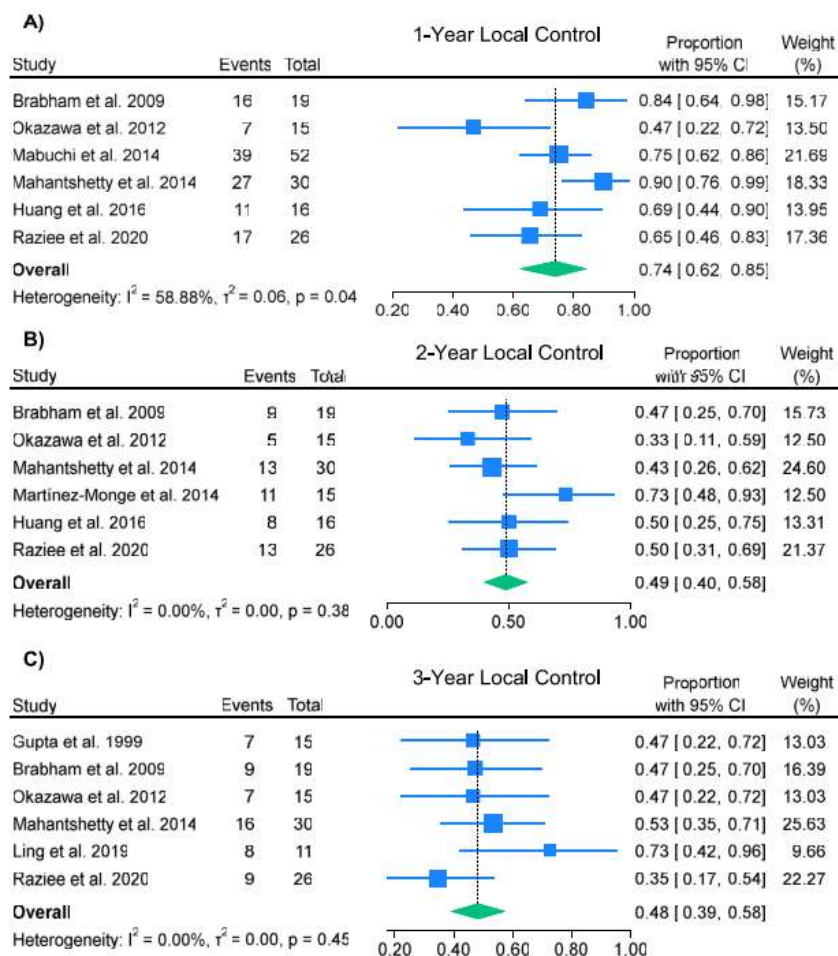
Preliminary data

- **LC= 100%**
- **Late Toxicity:** no G \geq 3

Agenda



Re-irradiation



- 522 patients

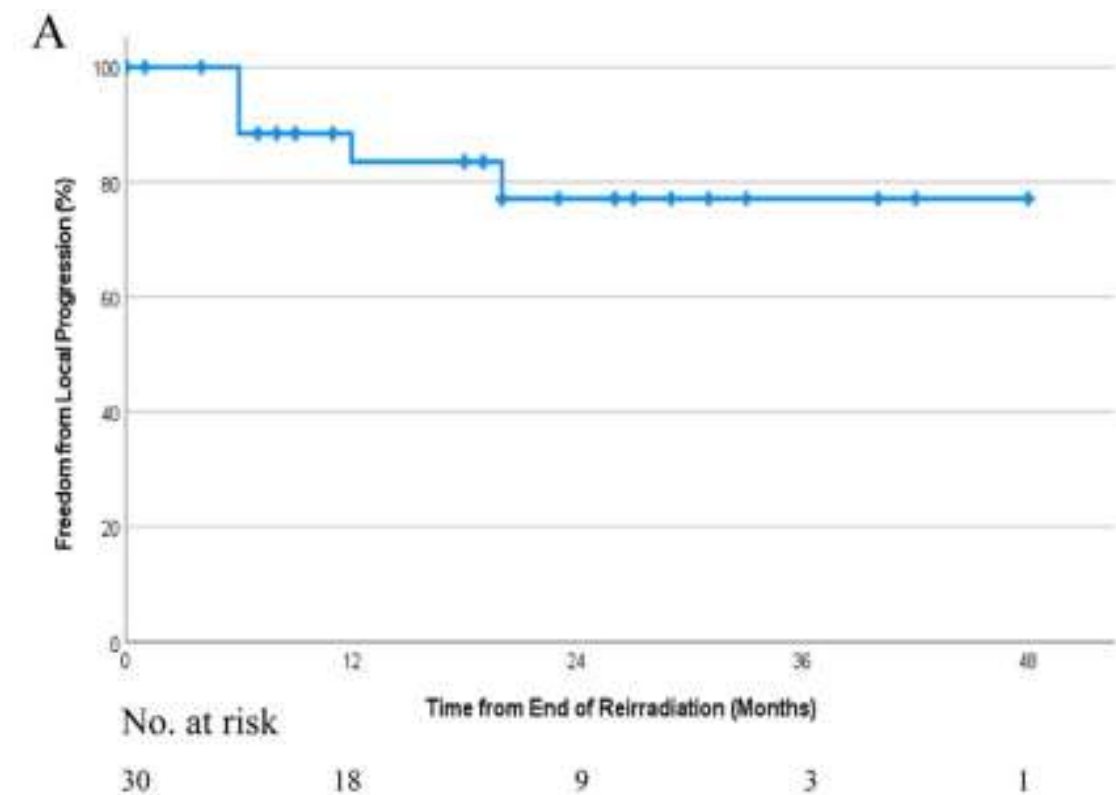
Local Control:

- ✓ 1y= 74% (95% CI, 62- 75)
- ✓ 2y=49% (95% CI, 40- 58)
- ✓ 3y=48% (95% CI, 39 -58)

G3-G4 Toxicity Rate:

- ✓ BT: 26%
- ✓ SBRT + Chemo: 20%
- ✓ SBRT alone: <10%

Re-irradiation



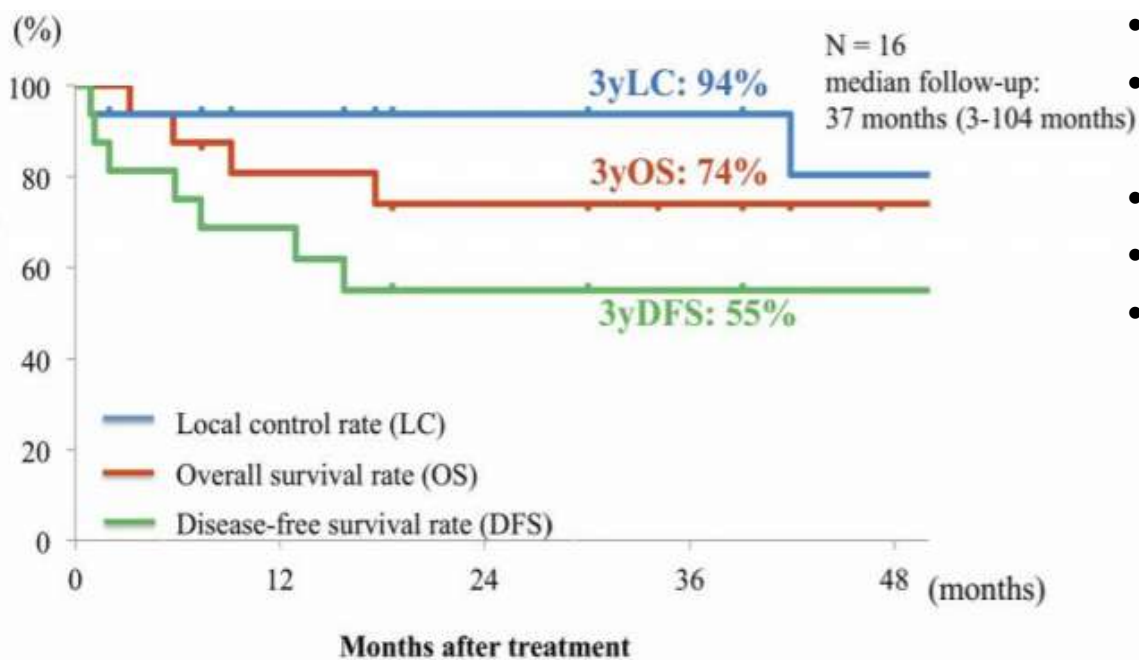
- Retrospective series of **29 cases treated with PBT** → 49.2 GyE (range, 30-61.6 GyE; IQR, 11 GyE)
- Unresectable recurrence at the edge of the previously irradiated field
- With a median follow-up of 23 months, **1-year local control was 83.5%**

Table 4 Acute and late toxicities graded by Common Terminology Criteria for Adverse Events, version 5.0

	Acute toxicities		Late toxicities	
	Grade 2, no. (%)	Grade 3, no. (%)	Grade 2, no. (%)	Grade 3, no. (%)
Genitourinary	1 (3)	0	2 (7)	0
Gastrointestinal	2 (7)	1 (3)	3 (10)	1 (3)
Hematologic	2 (7)	2 (7)	0	0
Skin	5 (17)	1 (3)	0	2 (7)

There were no acute or late grade 4 or 5 toxicities. Acute toxicity: during treatment or within 3 months; late toxicity: after 3 months.

Re-irradiation



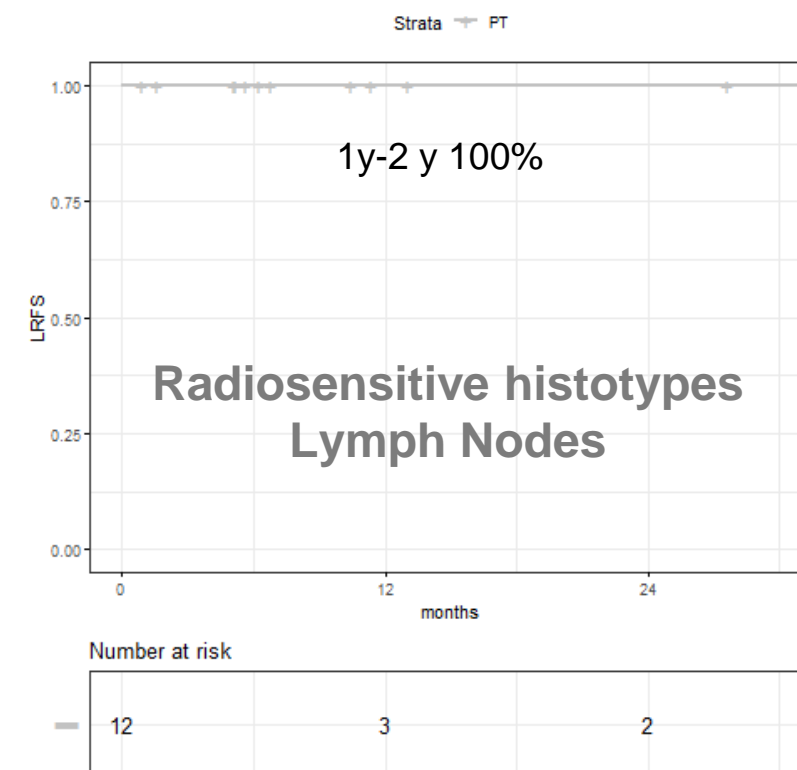
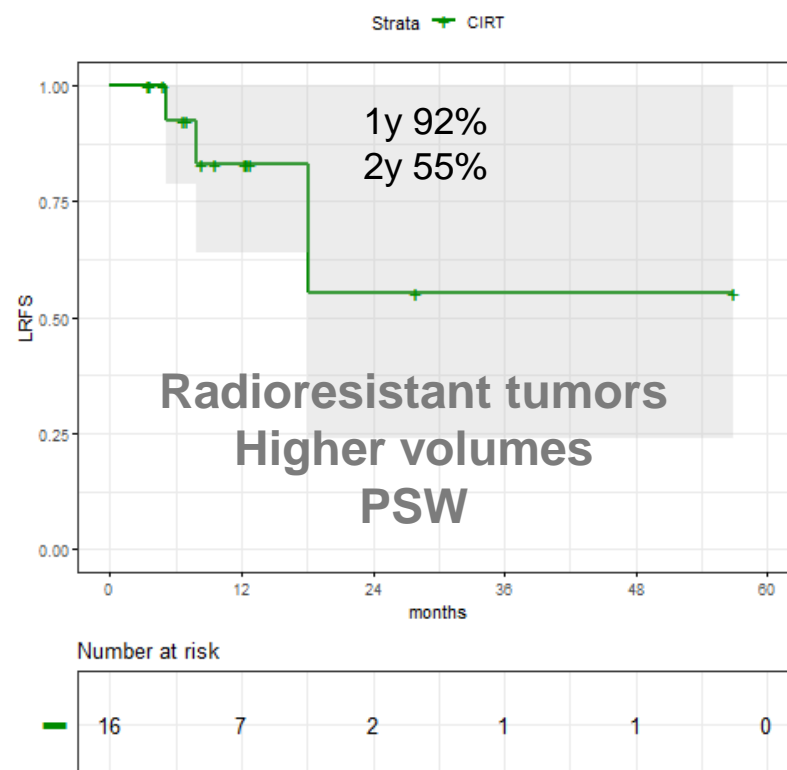
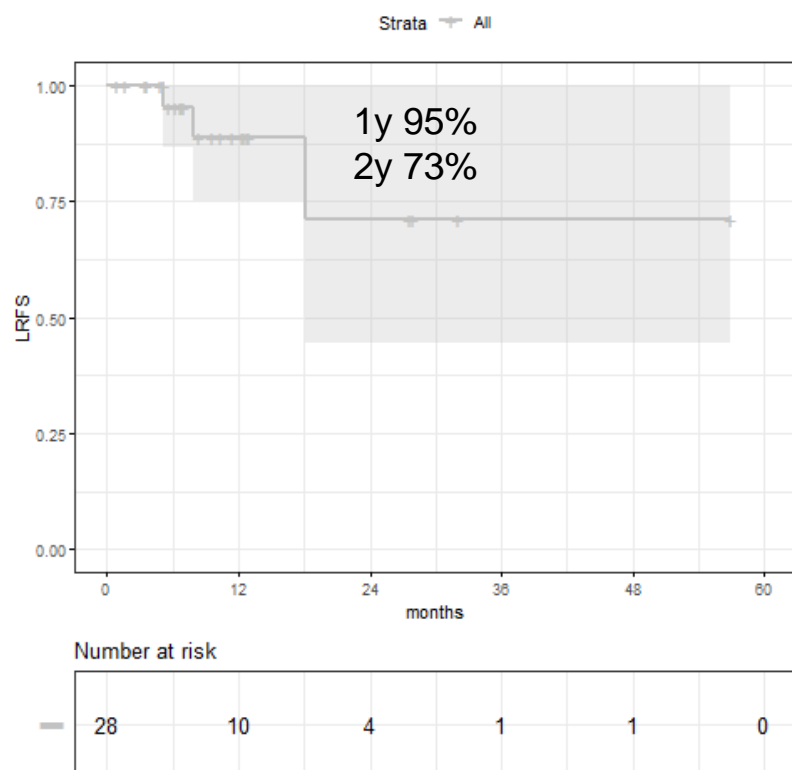
- Retrospective series of **16 cases**
- **Unresectable** recurrence at the edge of the previously irradiated field
- Median age 57 years (range=35-79 years)
- Median **tumor size was 27 mm** (range=14-80 mm)
- Total dose range: **48-57.6 GyE**

Organs involved	G0	G1	G2	G3	G4
Gastrointestinal tract	14	2	0	0	0
Urinary tract	15	1	0	0	0
Leg edema	15	0	1	0	0
Lower extremity nerve	14	2	0	0	0

RTOG/EORTC, Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer.

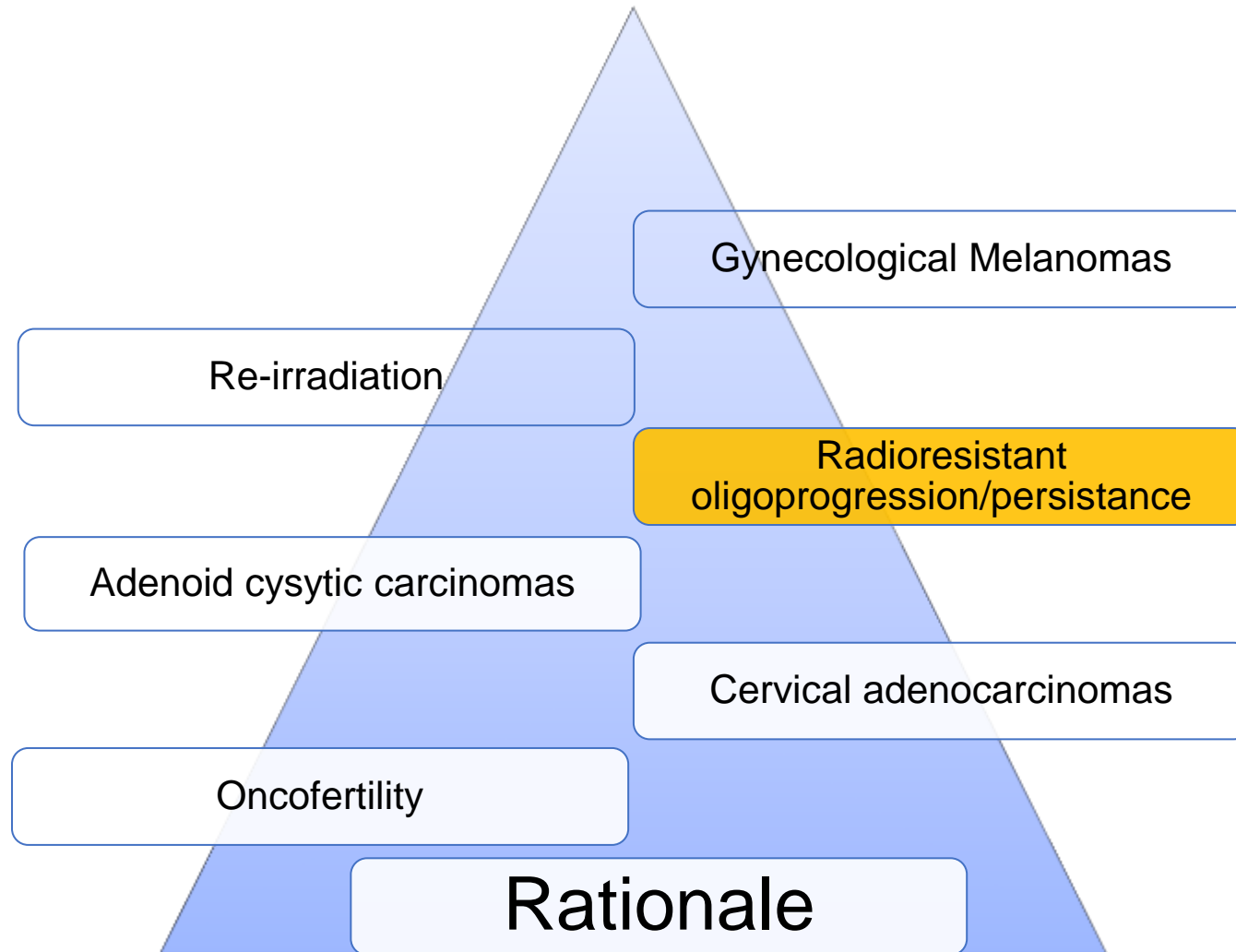
Re-irradiation

- ✓ Critelli, Pezzulla et al Gyn Oncol. 2023 → 1y= 74%; 2y=49%
- ✓ Pollock et al Adv Radiat Oncol. 2023 → 1y= 83,5%
- ✓ Shiba et al Anticancer Research 2017 → 1y= 94%



No G> 3 AEs

Agenda



Oligoprogressive / Oligorecurrent



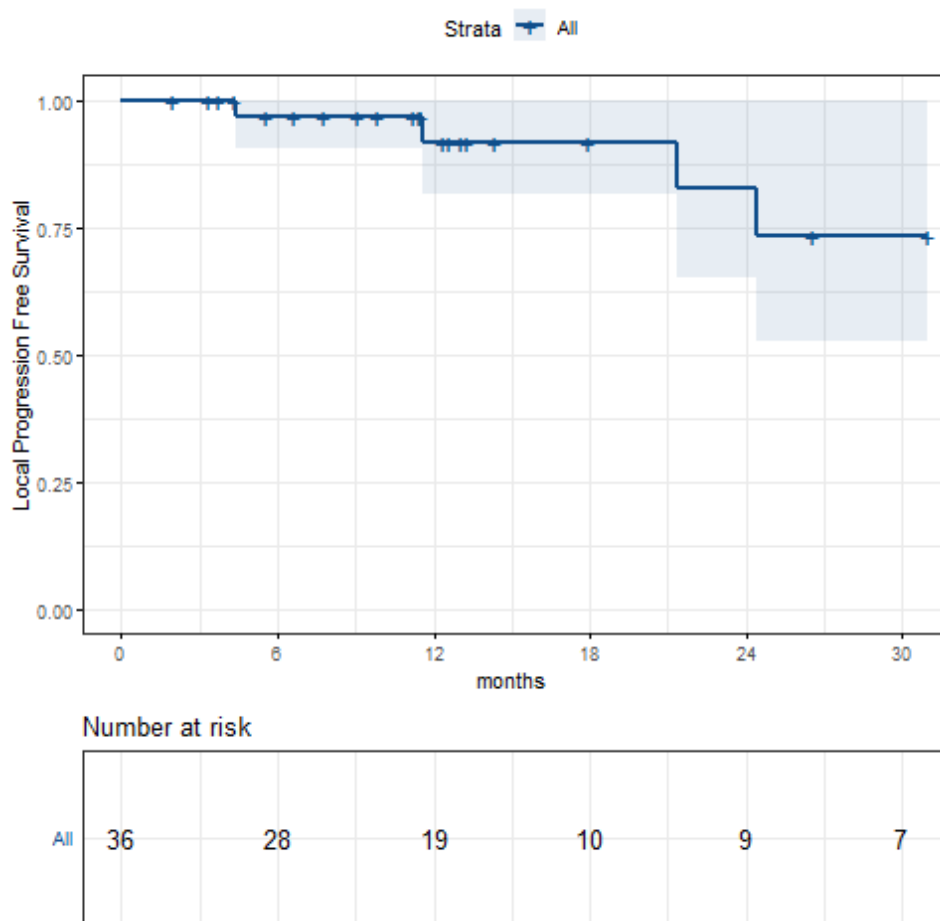
Original Research Article

The first real-world study on the role of carbon ion radiotherapy for oligo-metastatic, persistent, or recurrent (MPR) ovarian/fallopian tube cancer

Amelia Barcellini^{a,b,1,*}, Kazutoshi Murata^{c,1}, Giulia Fontana^d, Alessandro Vai^e, Chiara Cassani^{f,g}, Fabio Landoni^h, Laura Deborah Locati^{a,1}, Francesco Raspagliesi^j, Simona Secondino^k, Mattia Pecorilla^l, Shigeru Yamada^c, Noriyuki Okonogi^{c,m,2}, Ester Orlandi^{f,b,2}

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

Oligoprogressive / Oligorecurrent



After a median follow-up of **13 months** (6-193 months)

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

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

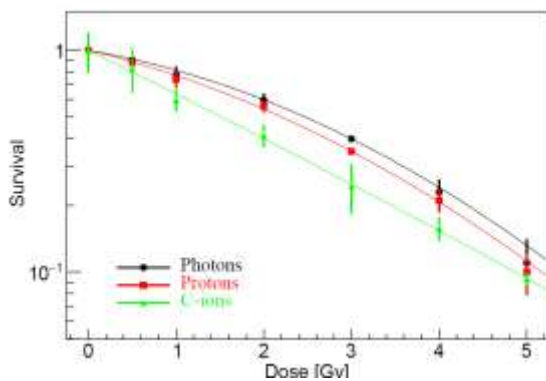
- 17 lesions (**47%**, 95% CI: 31%-64%) achieved CR within 1 year
- **OR rate was 97%** (95% CI: 92%-100%).

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

Oligoprogressive / Oligorecurrent

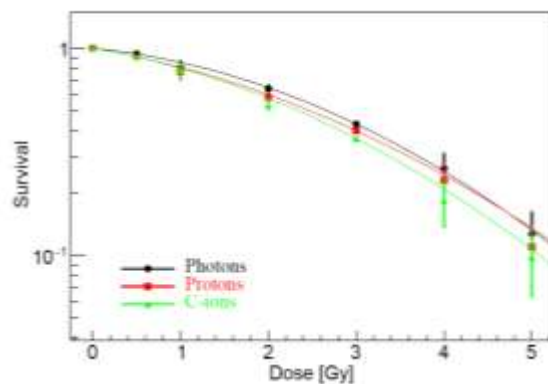
- Clonogenic Survival

OVSAHO



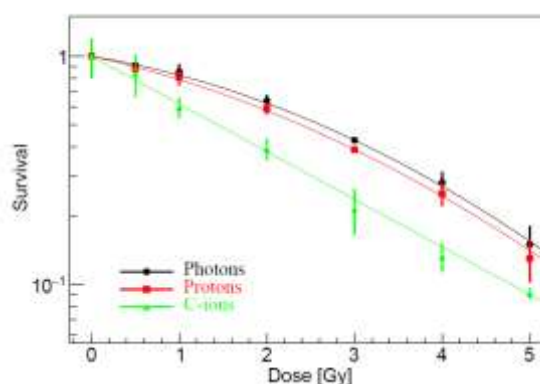
BRCA2 mutated

OVCAR8



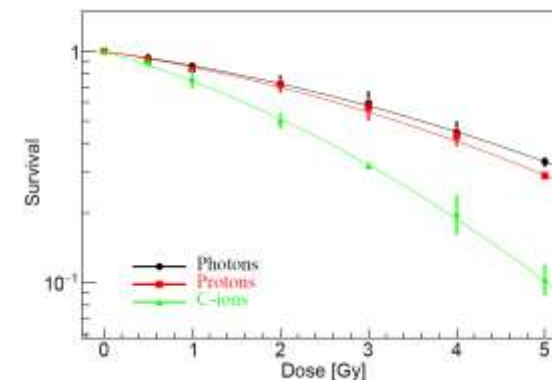
Methylation BRCA1

COV362



BRCA1 mutated

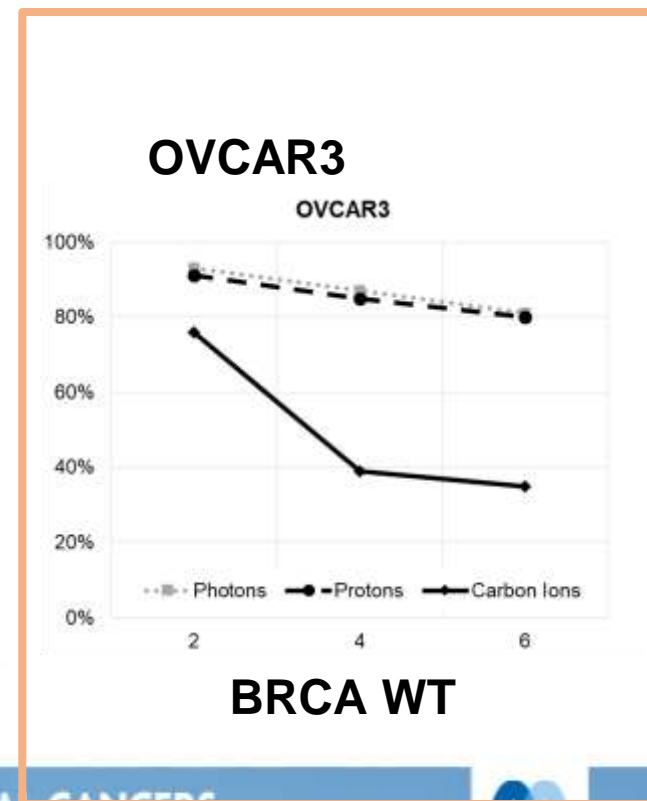
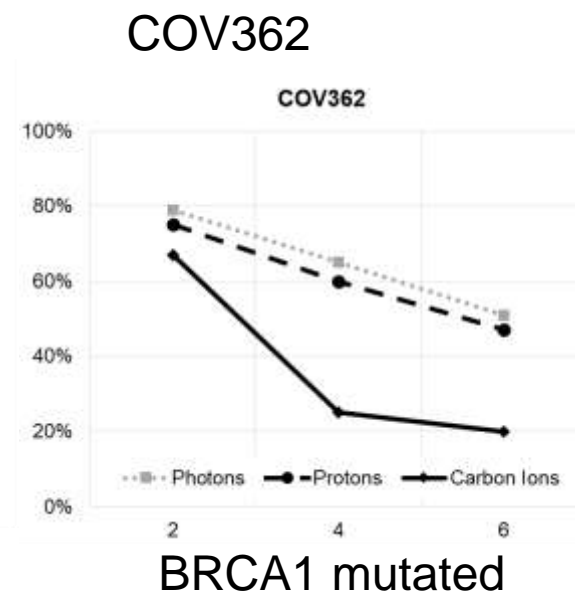
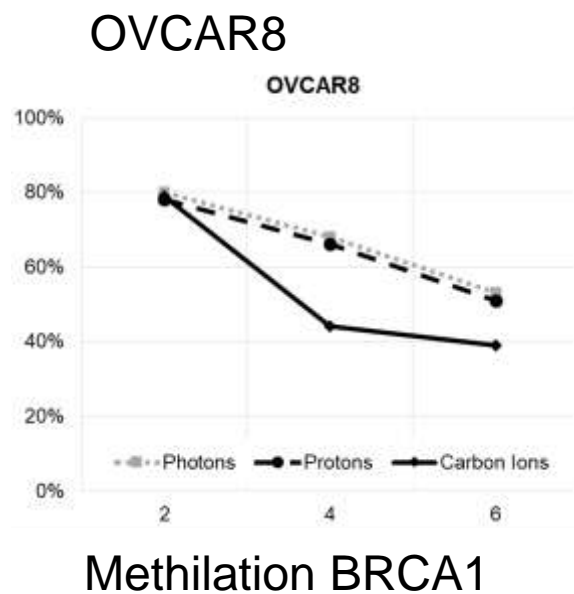
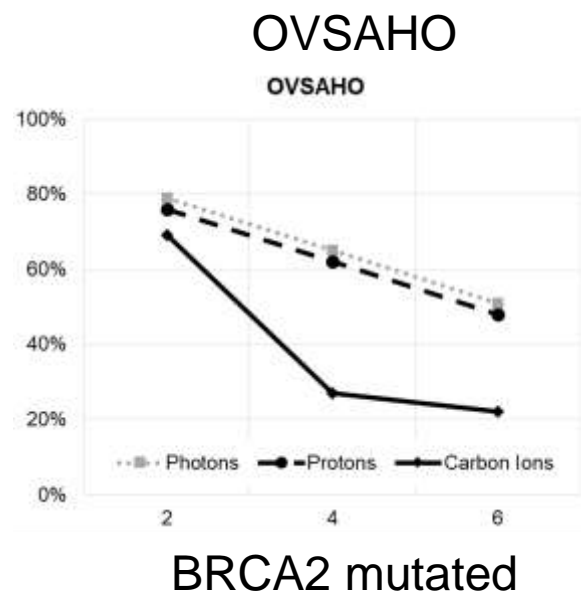
OVCAR3



BRCA WT

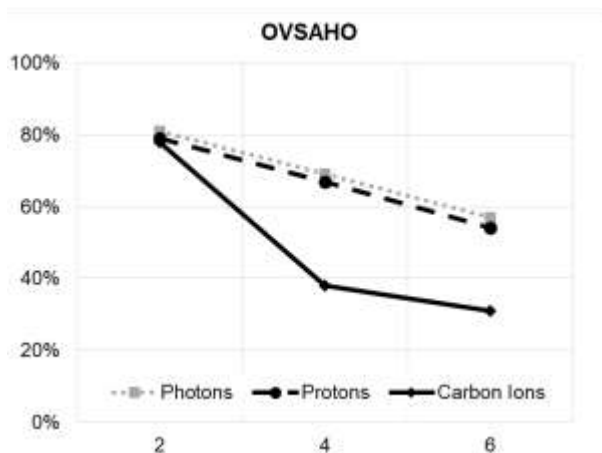
Oligoprogresive / Oligorecurrent

Metastatic processes 1) invasion assay

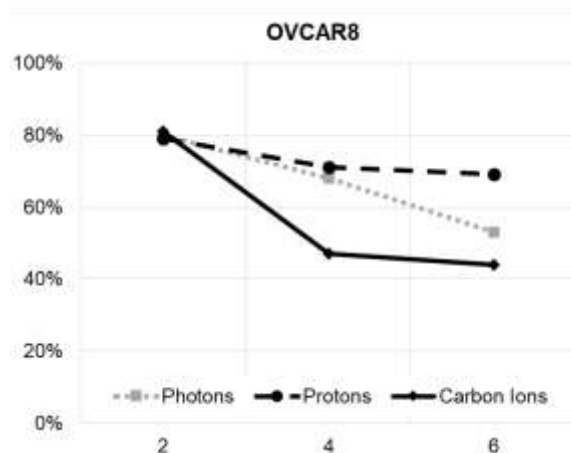


Oligoprogresive / Oligorecurrent

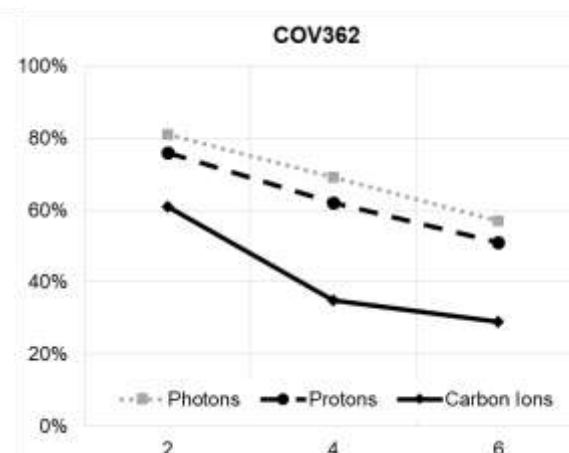
Metastatic processes 1) migration assay



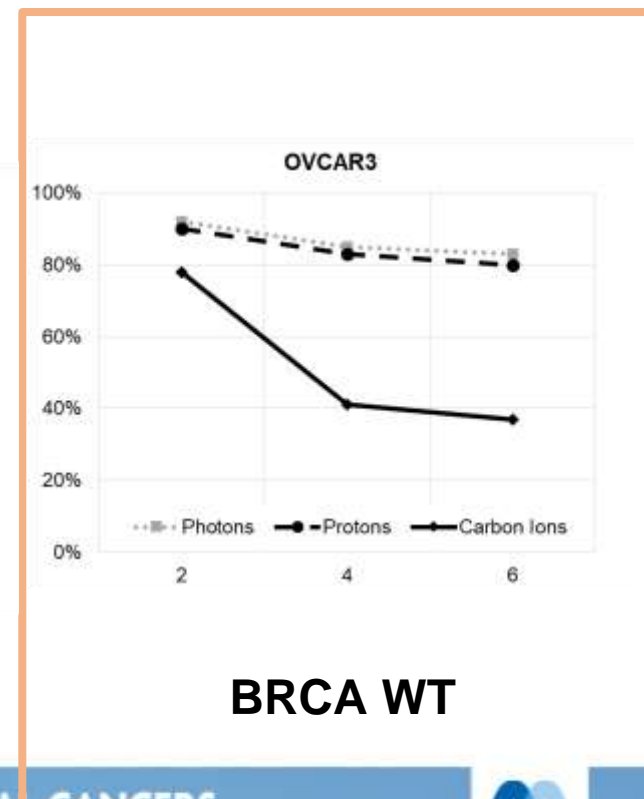
BRCA2 mutated



Methilation BRCA1



BRCA1 mutated



BRCA WT

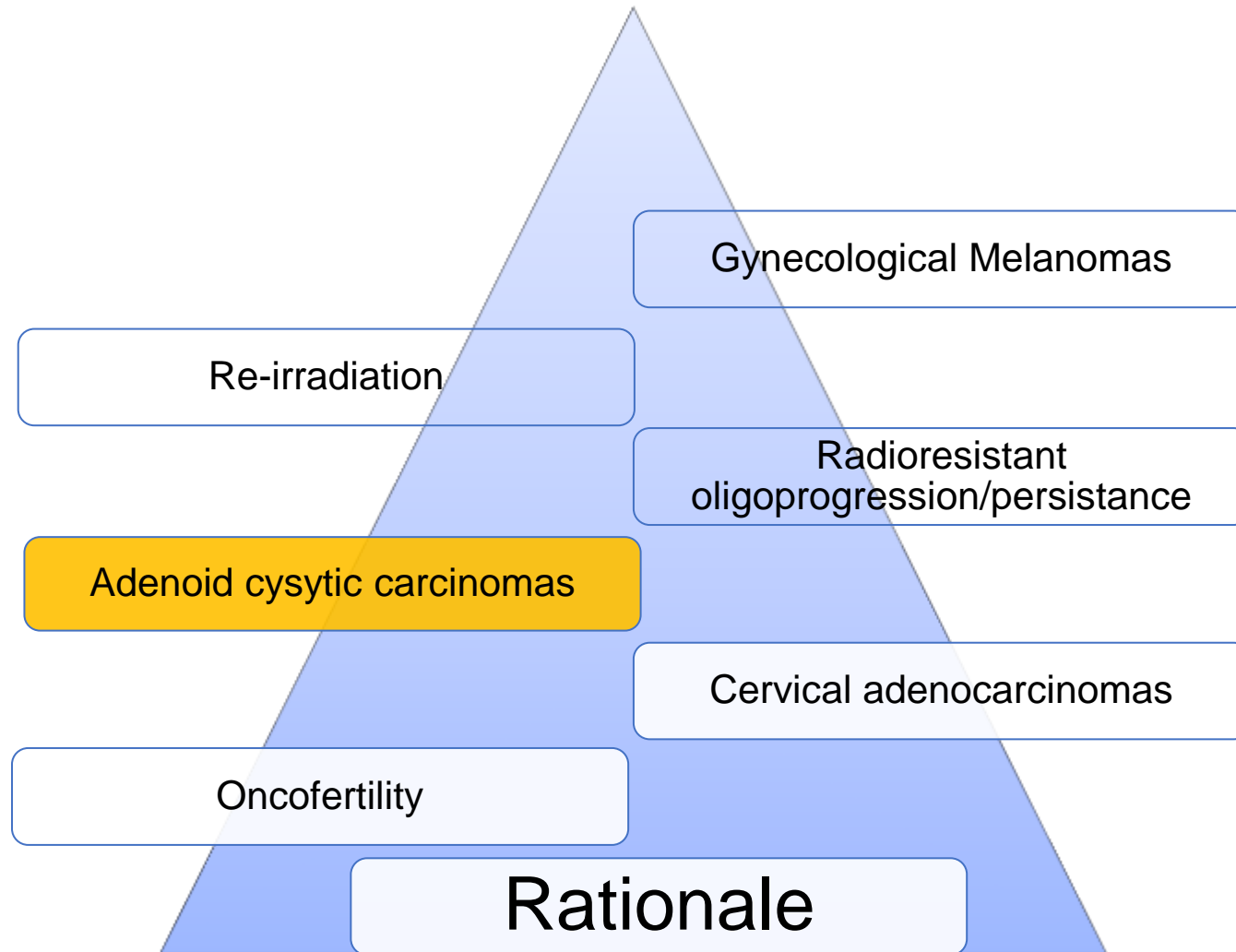
Oligoprogressive / Oligorecurrent

Study Design	Monocentric, prospective phase II study
Patients	Oligo-recurrent, persistent, progressive gynaecological tumours with the exclusion of squamous/adenosquamous histologies
Treatment	48-52.8 GyRBE in 12 fractions, 4 fractions per week (LEM or MKM)
Endpoints	<p>First endpoints</p> <ul style="list-style-type: none">• achievement of complete response (CR) PER LESION BASIS! <p>Secondary endpoints:</p> <ul style="list-style-type: none">• Objective response rate• 12 and 24 months- actuarial LC, PFS and OS• Toxicity (CTCAE version 5.0)• Symptoms control and QoL

Inclusion Criteria

- Patients ≥ 18 years of age and Karnofsky Index ≥ 70
- Histological or radiological diagnosis of oligo-recurrent, persistent, progressive gynaecological tumours **with the exclusion of squamous/adenosquamous histologies**
- oligo recurrent, oligometastatic and oligopersistent gynaecological in an otherwise well-controlled disease status **(Up to five synchronous lesions, any site of disease)**
- Exclusion of salvage surgery or other local therapies in a **multidisciplinary tumour board**
- Patients **previously treated with photon beam RT or hadrontherapy can be enrolled.**
- Possibility to perform surgery to space the intestinal loops, **in case of close distance between the intestinal tract and tumour.**
- **If needed**, spacer in biocompatible material (i.e. silicon, goretex) or anatomical material (i.e. omentum, muscle patch), non-absorbable.
- DICOM images of the previous treatment plan availability **in case of re-irradiation**
- Written informed consent
- Patients ability to understand the characteristics and consequences of the clinical trial

Agenda



Gynecological ACCs

ACC adverse characteristics	Molecular determinants	Biological rationale of CIRT
Tumor antigenicity	Low TMB	↗ tumor immunogenicity
Immunosurveillance escape	↗ PD-L2 and HLA-G expression ↘ ICAM-1 expression	↗ ICAM1
Immunotolerant microenvironment	↘ CD1a and CD83 infiltrate ↘ MDSC and M2 macrophage infiltrate T-cell exclusion phenotype	↗ DC ↘ M2 and MDSC ↗ proinflammatory cytokines ↗ CD8, ± NK
Hypoxia	↗ HIF1a expression VEGFA-mediated vascular mimicry	low OER ↘ tumorigenesis and angiogenesis
Stemness	↗ HSP27 expression ↗ Brachyury expression VEGF A, Nodal, Lefty, Oct-4, Pac6, Rex1, Nanog	Anti-tumor response on radioresistant tumor cell lines
Autophagy	ATG3, 4A, 5, PIK3R4, MAP1LC3B	
Perineural invasion	BNDF/TrkB; CCLR/CCR5; NGF/TrkA	↘ migration, invasion, adhesion ↘ cell mobility ↘ integrin expression
Tumoral heterogeneity	Biphasic tumor: ductal and myoepithelial components Molecular heterogeneity within/between primary tumors and metastatic disease	Anti-tumor response ± independent on tumoral heterogeneity

The rationale to use CIRT for ACC management is based on immunological, molecular, and pathological considerations, despite the fact that no in vitro or preclinical study have specifically evaluated CIRT irradiation on ACC cell lines; CD, cluster of differentiation; DC, dendritic cell; HIF1a, hypoxia-inducible factor 1a; ICAM-1, intercellular adhesion molecule 1; MDSC, myeloid-derived suppressor cell; NK, natural killer cell; OER, oxygen enhancement ratio; TMB, tumor mutational burden; VEGF, vascular-endothelial growth factor.

Gynecological ACCs

Oncology

Oncology
DOI: 10.1159/000506485

Adenoid Cystic Carcinoma of Bartholin's Gland: What Is the Best Approach?

Amelia Barcellini^a Angiolo Gadducci^b Concetta Laliscia^c Sara Imparato^a
Viviana Vitolo^a Lorenzo Preda^{a, d} Francesca Valvo^a

Cancer Management and Research

Open Access Full Text Article

Dovepress

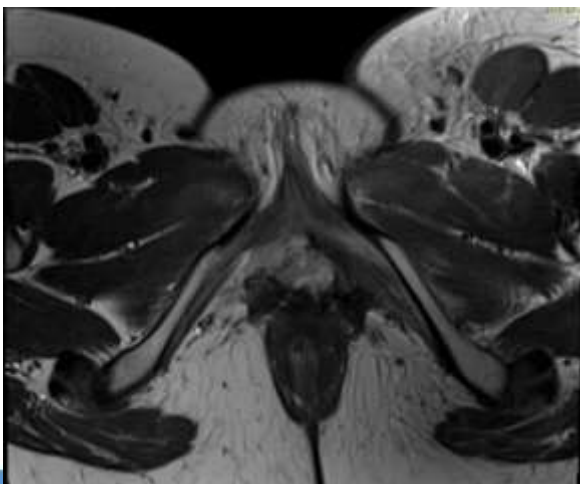
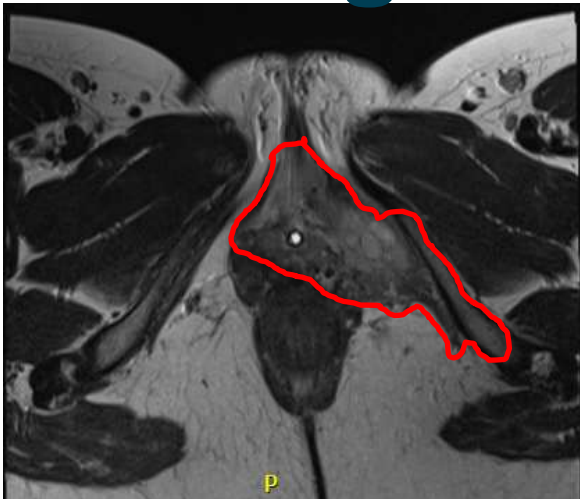
open access to scientific and technical research

CASE SERIES

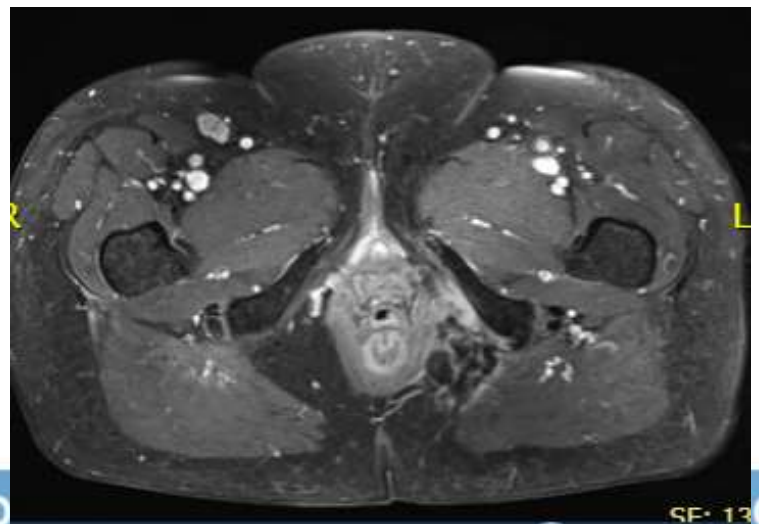
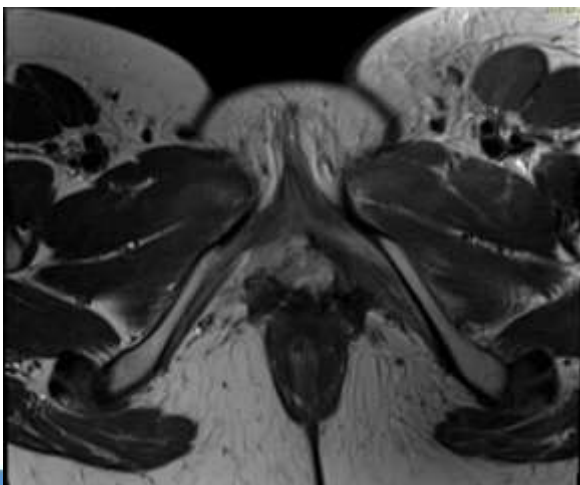
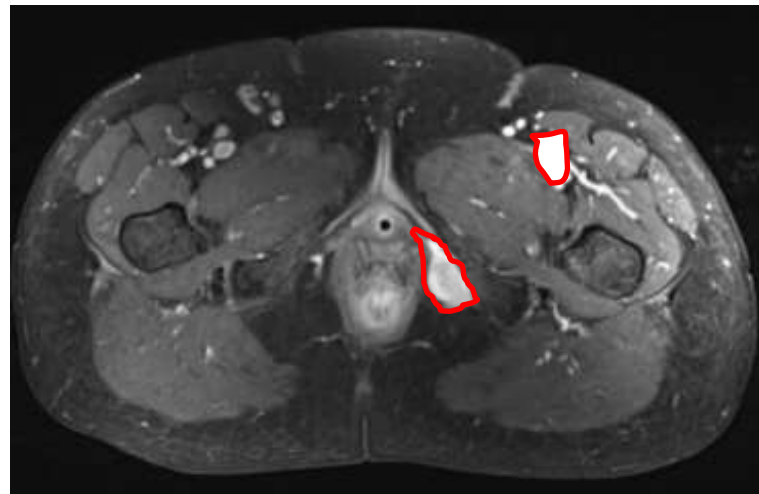
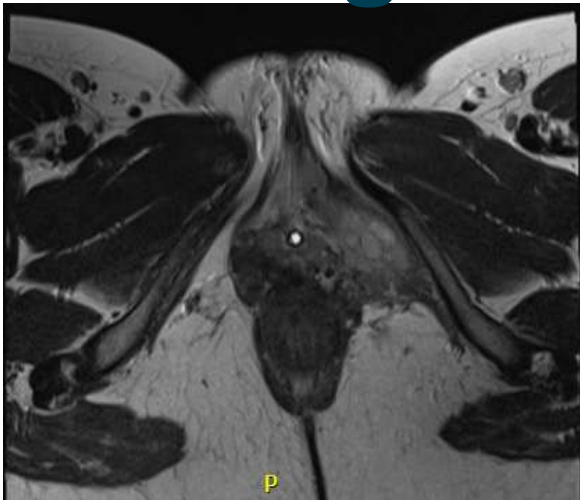
Bimodality treatment of patients with pelvic adenoid cystic carcinoma with photon intensity-modulated radiotherapy plus carbon ion boost: a case series



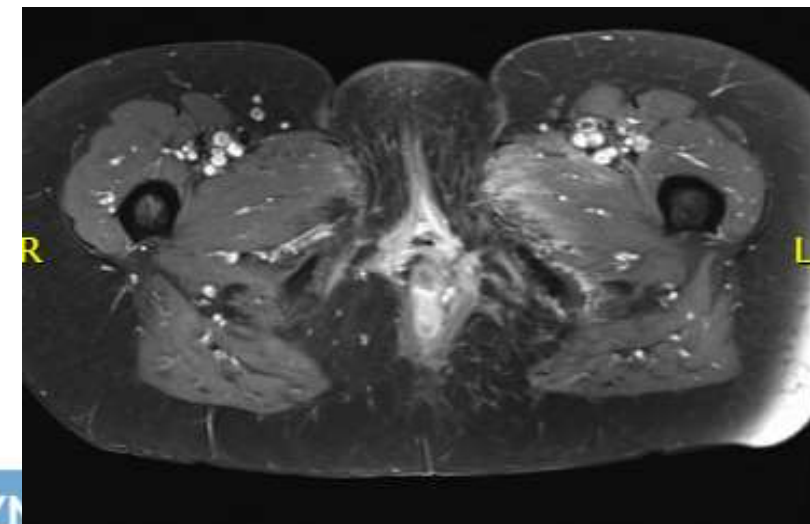
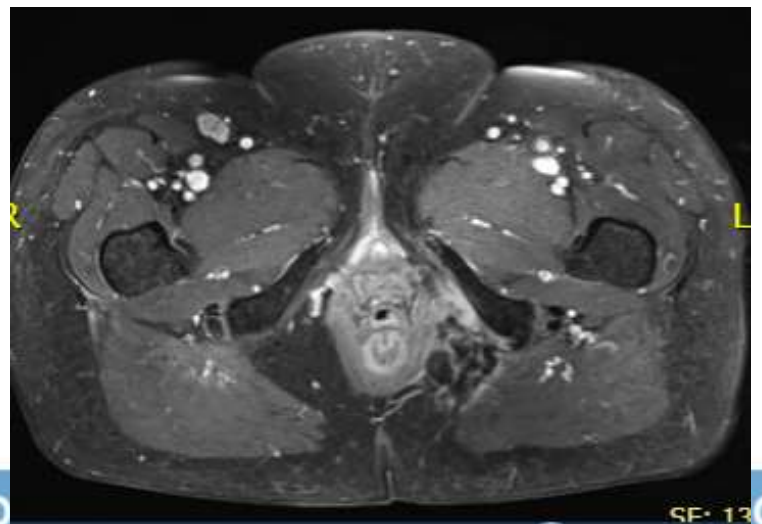
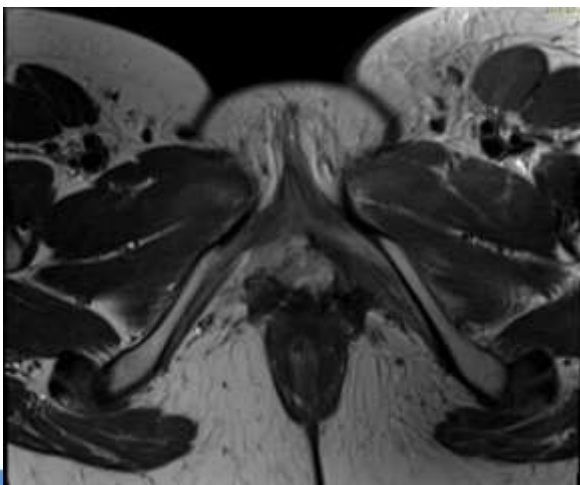
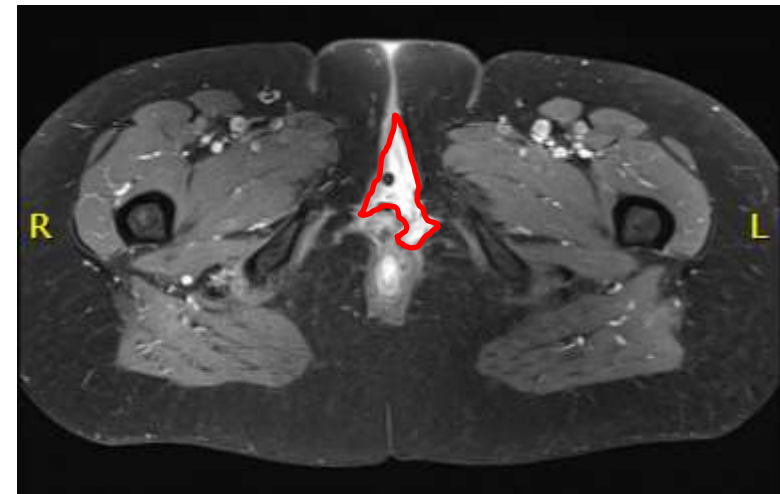
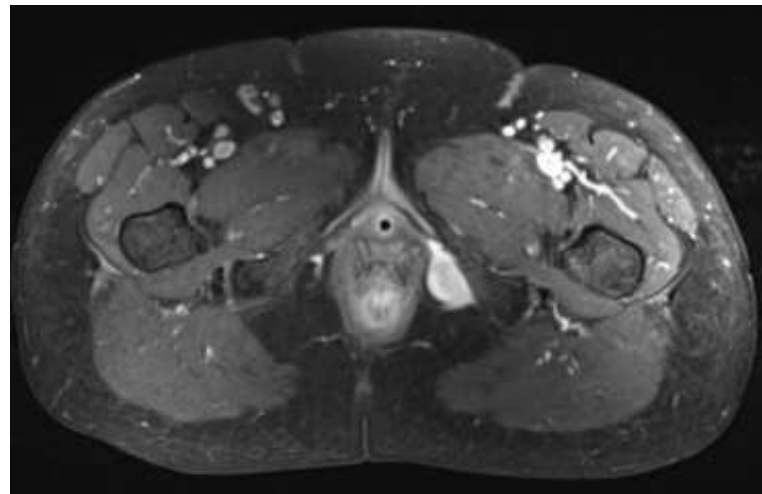
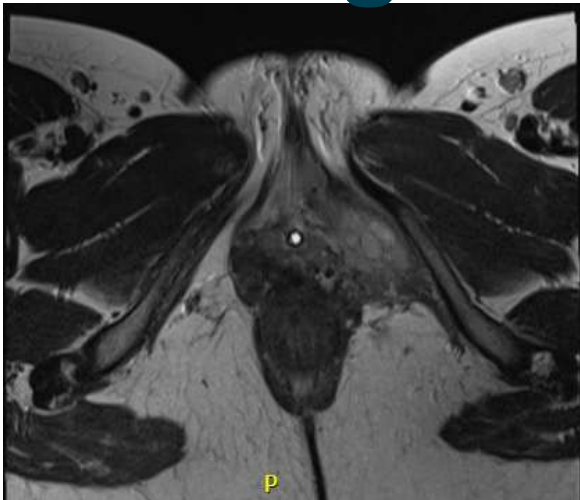
Gynecological ACCs



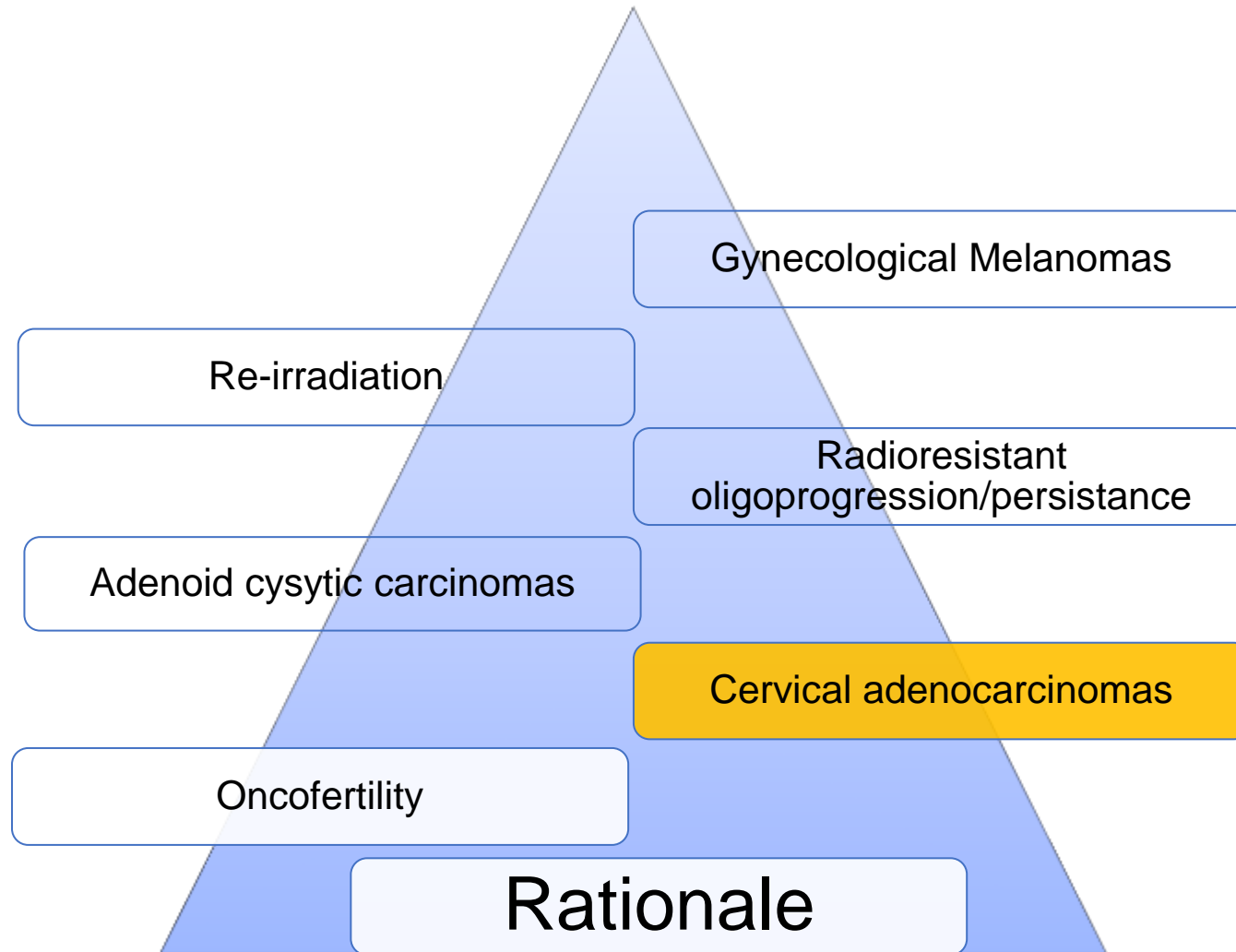
Gynecological ACCs



Gynecological ACCs



Agenda



Cervical Adenocarcinomas

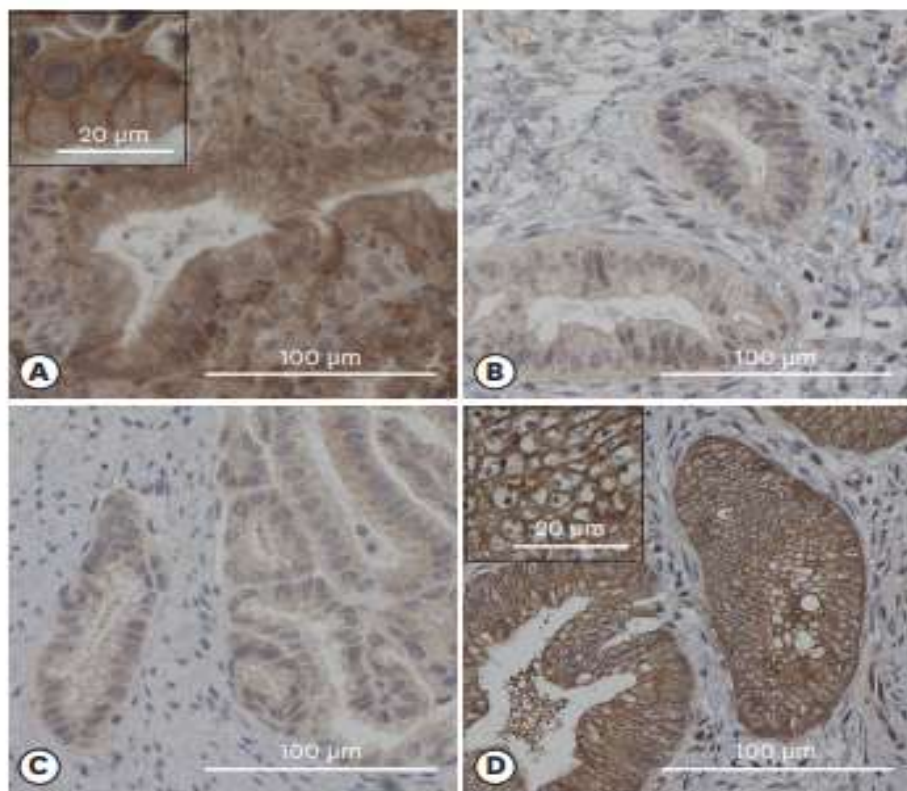
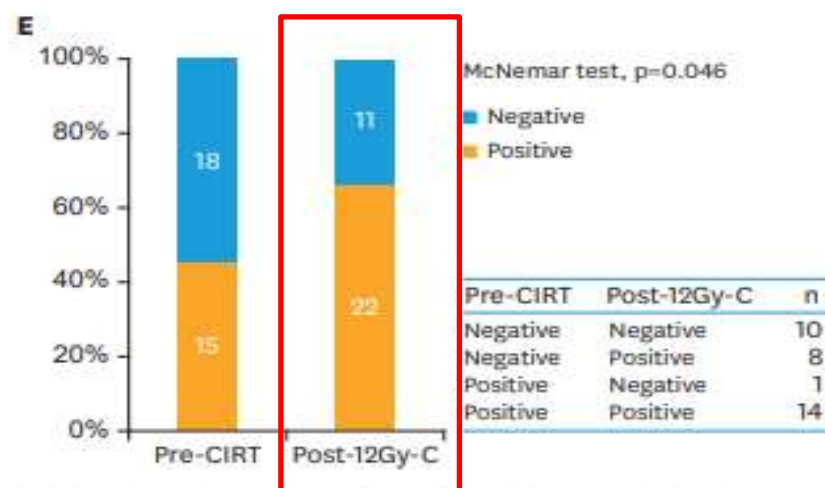
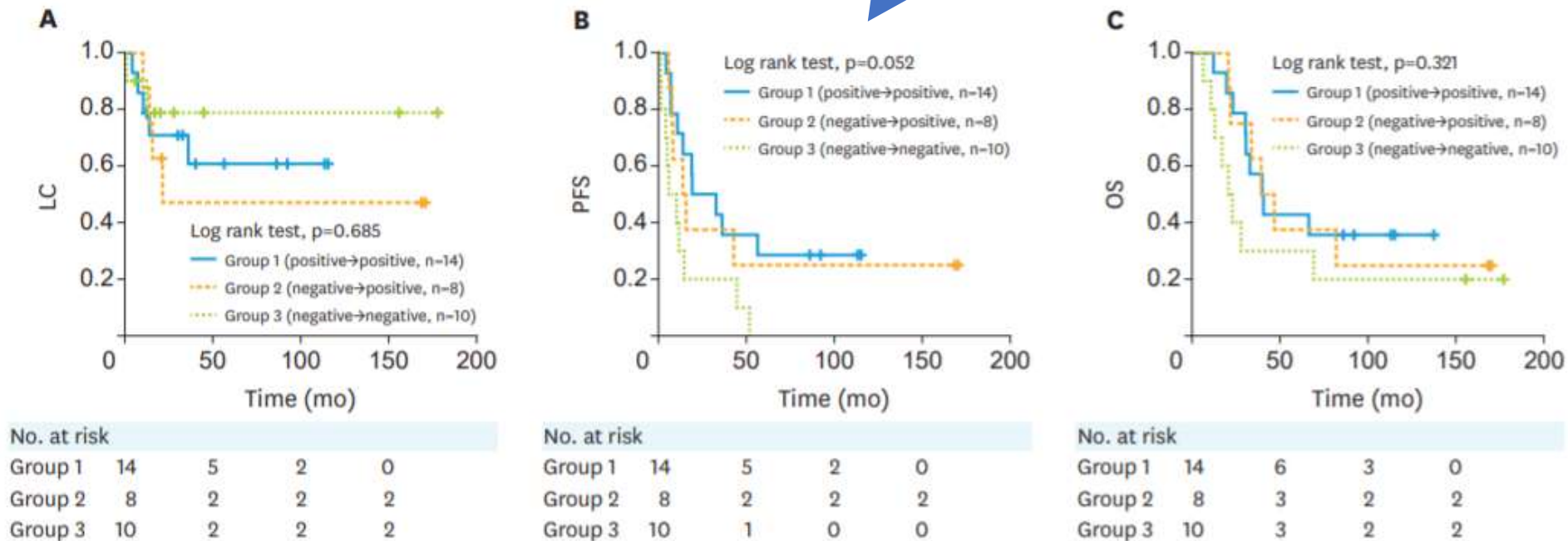


Fig. 2. PD-L1 staining and changes in PD-L1 status pre-CIRT and post-12Gy-C. (A) PD-L1 staining with a membranous pattern. (B) Negative PD-L1. (C, D) PD-L1 staining of specimens from the same patient before CIRT (C) and after 12 Gy of CIRT (D). The inset at a higher magnification. (E) Change in PD-L1 status pre-CIRT and post-12Gy-C.
CIRT, carbon-ion radiotherapy; PD-L1, programmed cell death-ligand 1.

The specimens were collected at **least 4 weeks before CIRT** and **after 12 GyE (4 fractions)** 1 week after starting CIRT



Cervical Adenocarcinomas



Patients with **positive post-12Gy-C PD-L1** expression had a **longer PFS** than those with negative PD-L1 expression

LC and OS between the 2 groups showed no significant difference



CLINICAL INVESTIGATION

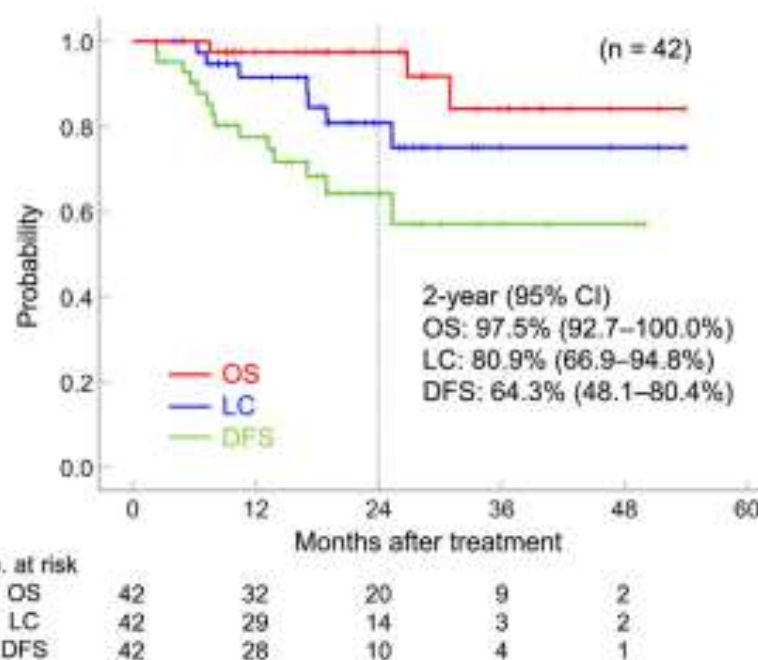
**Carbon-Ion Radiation Therapy for
Adenocarcinoma of the Uterine Cervix: Clinical
Outcomes of a Multicenter Prospective
Registry-Based Study in Japan (2016-2020)**

Kazutoshi Murata, MD, PhD,^a Noriyuki Okonogi, MD, PhD,^{a,†} Ken Ando, MD, PhD,[†] Keisuke Tsuchida, MD, PhD,[†]
Kaori Fukunishi, MD,[†] Daisuke Irie, MD, PhD,[†] Yoshiaki Ohyama, MD, PhD,[†] Masaru Wakatsuki, MD, PhD,[†]
Munetaka Takekuma, MD, PhD,[†] Shingo Kato, MD, PhD,^{†,‡} and Tatsuya Ohno, MD, PhD[†]

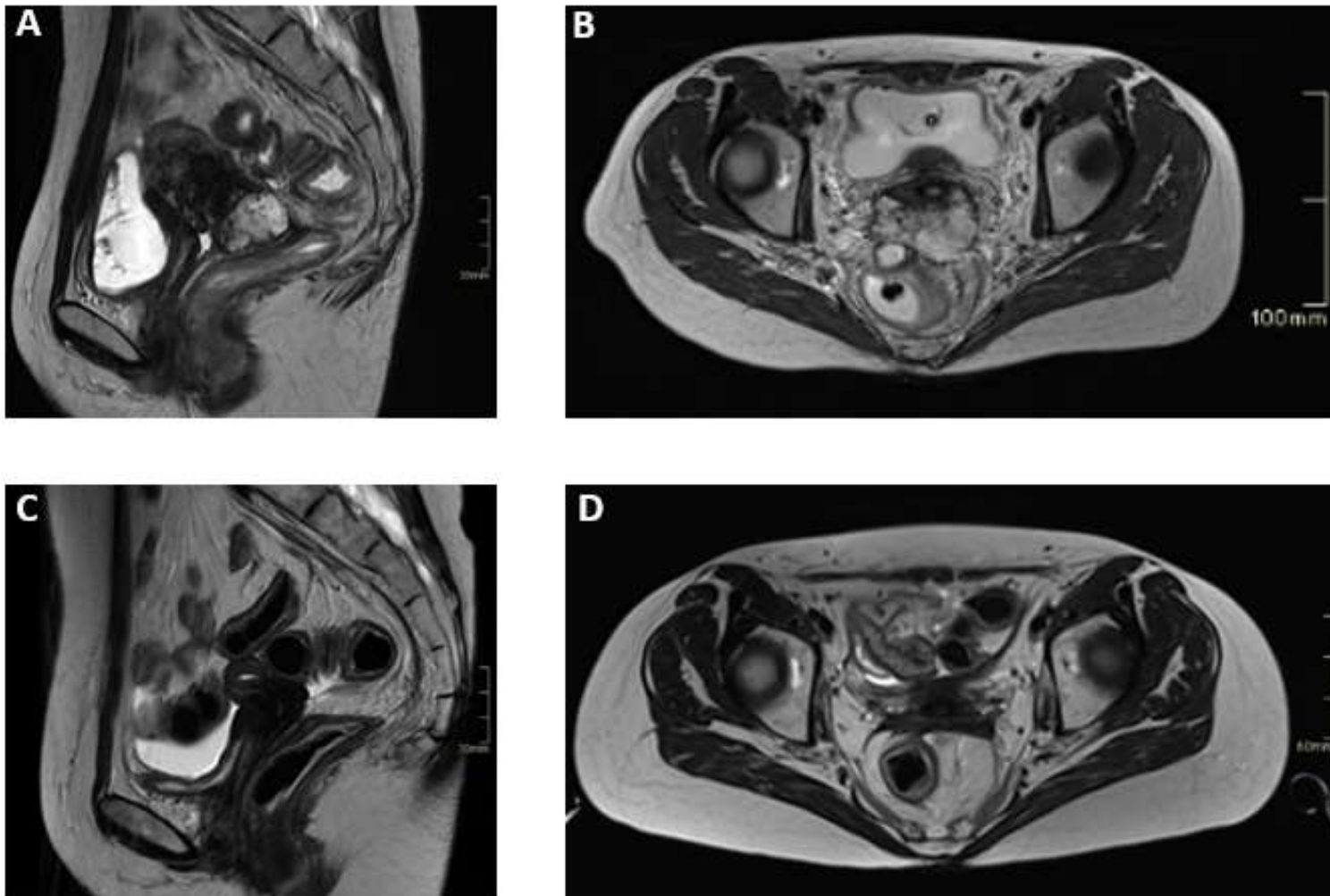
Table 4 Comparison of outcomes of radiation therapy for adenocarcinoma of the cervix or adenosquamous carcinoma of the uterine cervix

Author (y) ^{ref}	No. of patients	Median follow-up (mo)	Study design	Stage distribution stage I-II/III-IV	Treatment	2-y OS (%)	5-y OS (%)	Late toxicity ≥ grade 3 (%)
Rose et al ⁵ (2014)	182	N/A	Retrospective, multi-institutional	75%/25%	CCRT	58	45	N/A
Chen et al ⁶ (2014)	35	59	Retrospective, multi-institutional	74%/26%	CCRT	73	41	22
Huang et al ¹⁴ (2011)	148	90	Retrospective, single-institutional	79%/21%	CCRT	68	47	6
Niibe et al ¹⁵ (2010)	61	N/A	Retrospective, multi-institutional	0%/100%*	CCRT	41	20	13 (including grade 2)
Yin et al ²² (2018)	30	40	Retrospective, single-institutional	67%/33%	CCRT	63	46	3
Miyasaka et al ²³ (2020)	71	37	Retrospective, multi-institutional	51%/49%	CCRT, IGBT	70	50	N/A
Wakatsuki et al ¹³ (2014)	58	38	Prospective, single-institutional	34%/66%	CIRT alone	66	38	2
Okonogi et al ¹⁶ (2018)	31	30	Prospective, single-institutional	65%/35%	Chemo-CIRT	88	N/A	6
Okonogi et al ¹⁹ (2021)	55	68	Retrospective, multi-institutional	67%/33%	Chemo-CIRT	89	71	8
This study	42	24	Prospective, multi-institutional	62%/38%	Chemo-CIRT	98	N/A	7

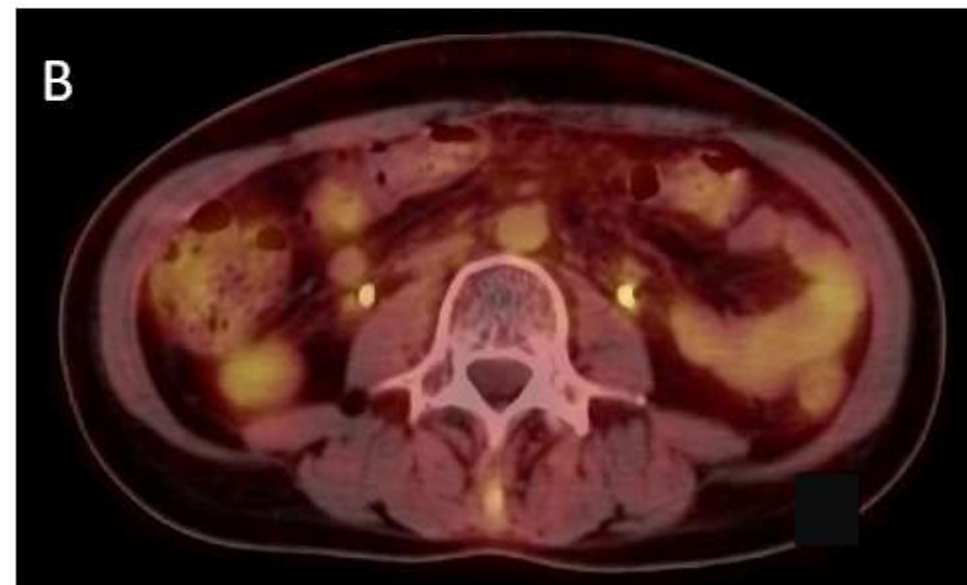
Abbreviations: CCRT = concurrent chemoradiation therapy; CIRT = carbon-ion radiation therapy; IGBT = image-guided brachytherapy; N/A = not available; No. = number; OS = overall survival.
* All cases in stage IIIB.



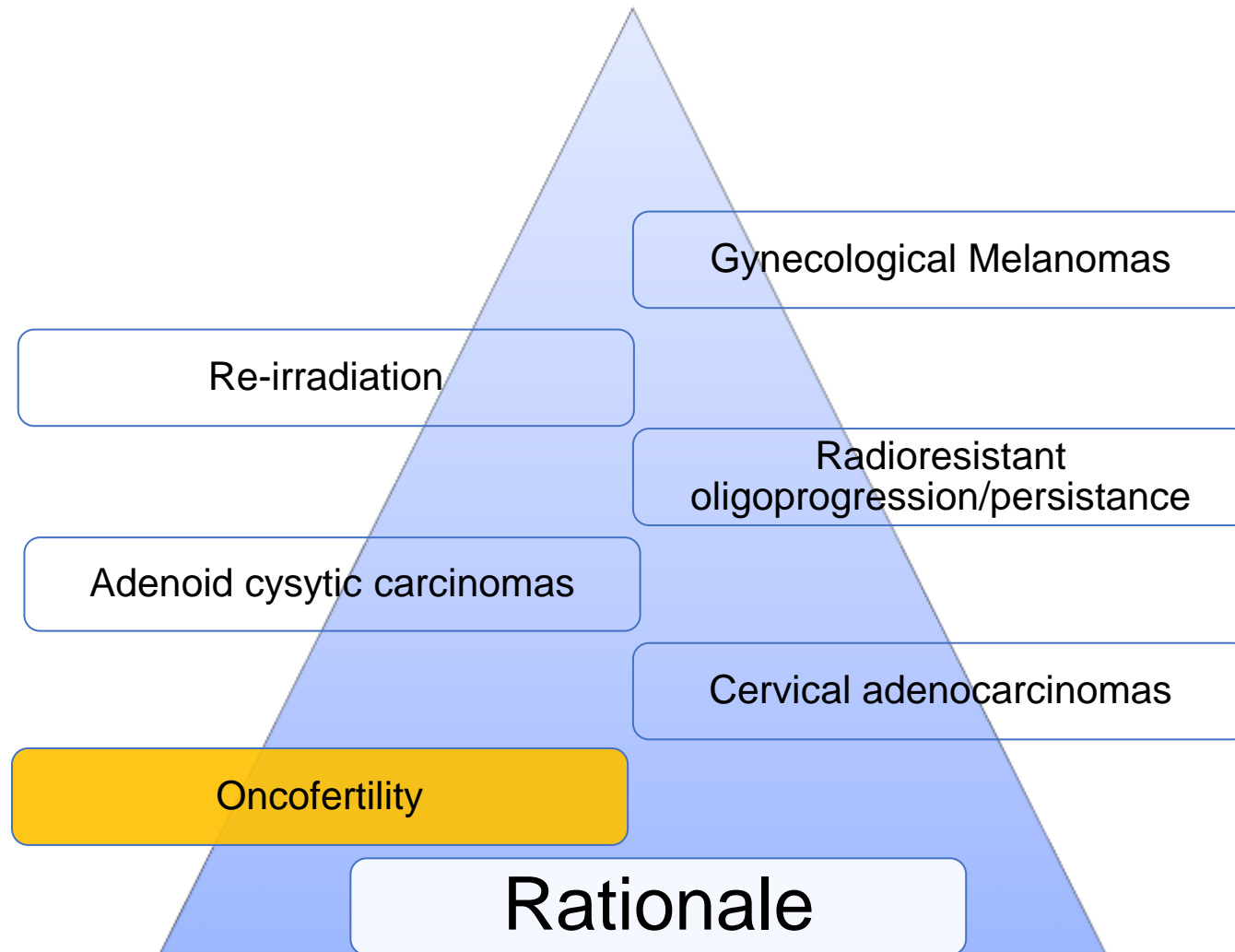
Cervical Adenocarcinomas



Cervical Adenocarcinomas



Agenda



Oncofertility

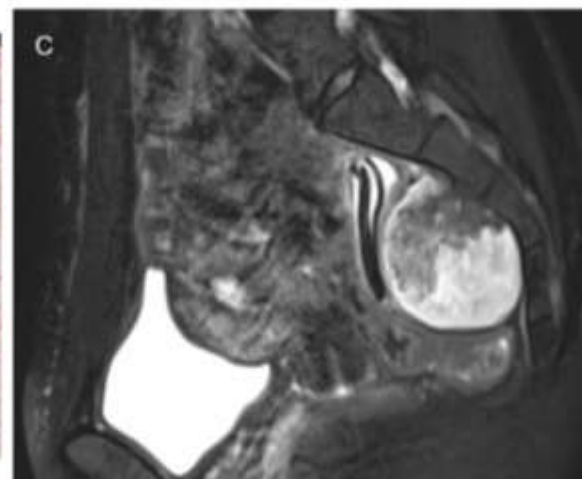
Original Research Article

TJ Tumori
Journal

Is motherhood still possible after pelvic carbon ion radiotherapy? A promising combined fertility-preservation approach

Amelia Barcellini^{1,2*}, Chiara Cassani^{3,4*}, Ester Orlandi^{1,3},
Rossella E. Nappi^{3,5}, Federica Broglia⁶, Maria Paola Delmonte⁶,
Silvia Molinelli⁷, Alessandro Vai⁸, Viviana Vitolo¹,
Alessandro Gronchi⁸, Giocchino D'Ambrosio⁹,
Lorenzo Cobiانchi^{3,10,11} and Maria Rosaria Fiore¹⁸

Tumori Journal
1-7
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Rock'n'roll baby

Conclusions

- Hadrontherapy appears to be a safe, effective and feasible treatment method, which has shown **advantages over photon therapy**
- **Preclinical studies** are crucial
- RCTs (maybe for ROC?) are unrealistic → the development of **clinical registries** might help to elucidate current uncertainties
- National and International **multidisciplinary cooperation** is of utmost importance to make a step forward



Thank you for your kind attention!



“True progress is when the advantages of new technology are available for all”

XXII ASSEMBLEA MaNGO | STANDARD TREATMENTS AND NEW DIRECTIONS IN GYNAECOLOGICAL CANCERS
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H. Ford