Ministry of Education, Science and Innovation

SEE IIST
South East European International Institute for Sustainable Technologies

HITRI plus
Heavy Ion Therapy Research Integration

SCIENCE AND TECHNOLOGY PARK Montenegro

SAVE THE DATE

24–25 MARCH 2025

SCIENCE AND TECHNOLOGY PARK OF MONTENEGRO PODGORICA

HADRONTHERAPY WORKSHOP

FROM INNOVATION TO IMPLEMENTATION

PLEASE REGISTER AT THE FOLLOWING LINK BY FEBRUARY 9, 2025
HTTPS://INDI.TO/TLJ5J

WWW.HITRIPLUS.EU

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

HADRONTHERAPY WORKSHOP

March 25, 2025

HITRI plus
Heavy Ion Therapy Research Integration

Reirradiations with particles

Viviana Vitolo, CNAO

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

Outline

- ReRT: Definition and classification
- Advantages of Particle therapy in ReRT (Clinical Outcomes and toxicity) and mail clinical applications
- Ongoing clinical studies and future perspective
- CNAO experience

HITRI
Heavy Ion Therapy Research Integration

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

Definition and Classification of Reirradiation

European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus on re-irradiation: definition, reporting, and clinical decision making

N Andratschke **, Lancet Oncology 2022**

" New course of Radiotherapy
either in a previously irradiated volume
or where the cumulative dose raises concerns about toxicity."

Type 1: Geometric overlap of irradiated volumes.

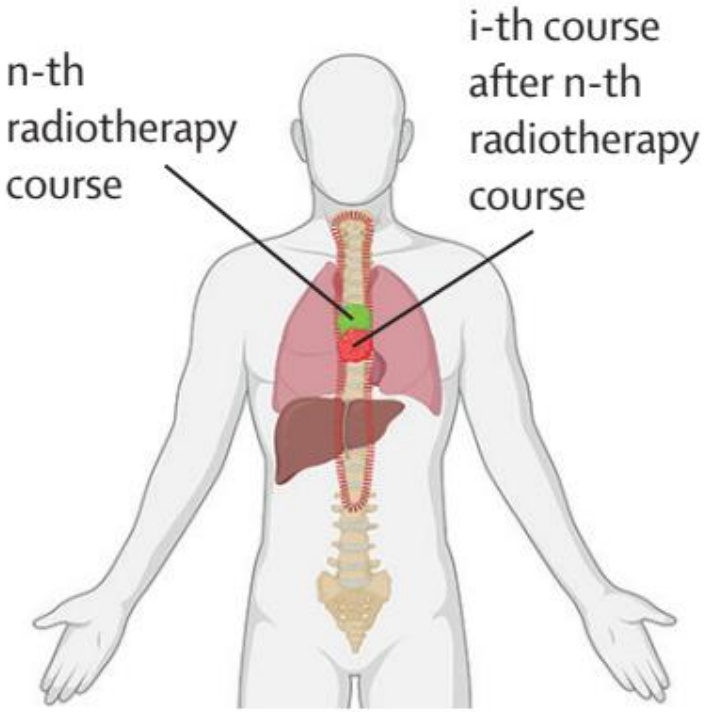
Type 2: Concerns about toxicity from cumulative doses, even without geometric overlap.

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

N Andratschke , Lancet Oncology 2022

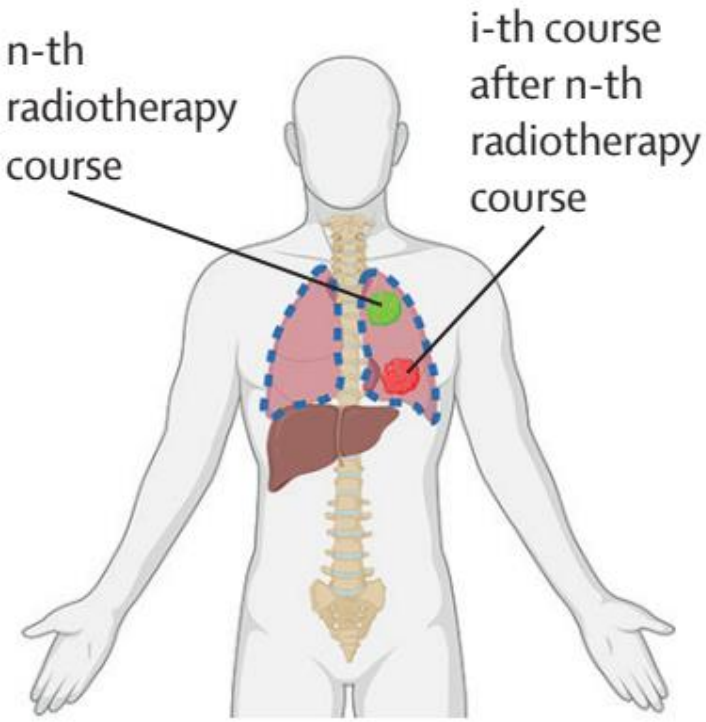
Re-irradiation

Type 1



- Overlap of irradiated volumes
- With or without concern for toxicity from cumulative doses

Type 2



- No overlap of irradiated volumes
- Concern for toxicity from cumulative doses

HITRI
Heavy Ion Therapy Research Integration

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

Reirradiation: key points

Indication: recurrent disease after a previous RT course, not suitable for surgery

- Keeping the dose to surrounding pre-irradiated tissue as low as possible
- To increase as max as possible the prescription dose since the chances of local control are dose-dependent

Particle therapy: Physical characteristics → superior risk-benefit-profile

HITRI
Heavy Ion Therapy Research Integration

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

Reirradiation: key points

Appropriate Patient selection: KPS, comorbidities, site , prognostic factors

Choice of dose prescription and fractionation: histology, volume of disease

Time interval from previous RT course

Tolerance of the OAR to a second course of RT

Assessment of Risk of potential adverse radiation related effects

HITRI
Heavy Ion Therapy Research Integration

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

Practical need for Radiation Oncologist

Evaluation and re construction of the Previously Delivered Dose

- RT dose, RT plan, RT structures, CT planning images (DICOM)
- In case of lack of DICOM files reconstruction by portals and available docs
- How to manage cases with no availability of previous RT Doc ….

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

Particle reRT: Literature series

HITRI
Heavy Ion Therapy Research Integration

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

Head and Neck Tumors: reRT

Particle re-irradiation

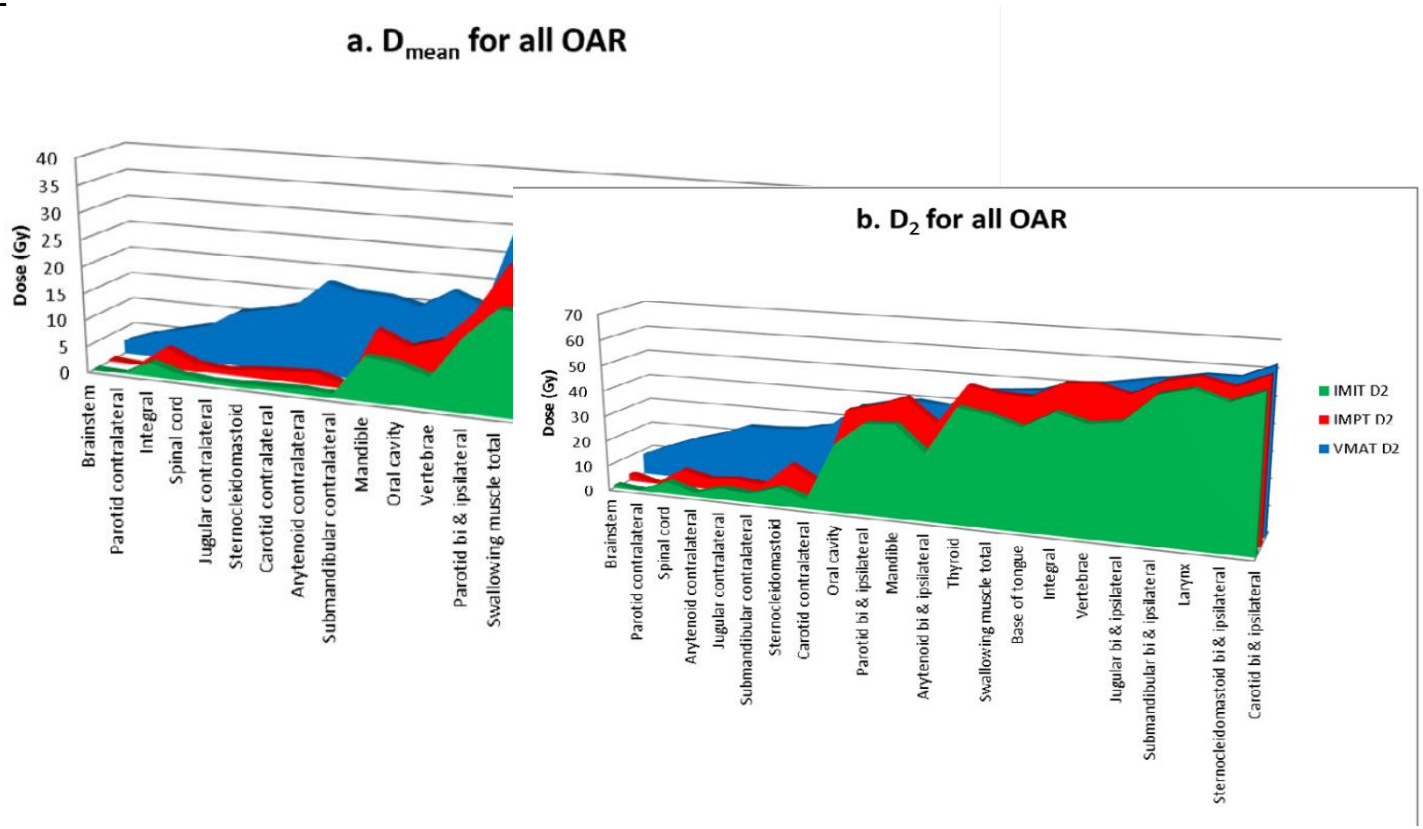
clinicaltrial.gov ID: NCT 02242916

Benefit of particle therapy in re-irradiation of head and neck patients. Results of a multicentric *in silico* ROCOCO trial

Eekers DBP, Radiother Oncol. 2016

25 patients , SCC, retrospectively replanned ;
Comparison : VMAT vs PT vs CIRT

PT (IMPT and IM CIRT) improve sparing of OAR compared to photon therapy (VMAT)



HITRI
Heavy Ion Therapy Research Integration

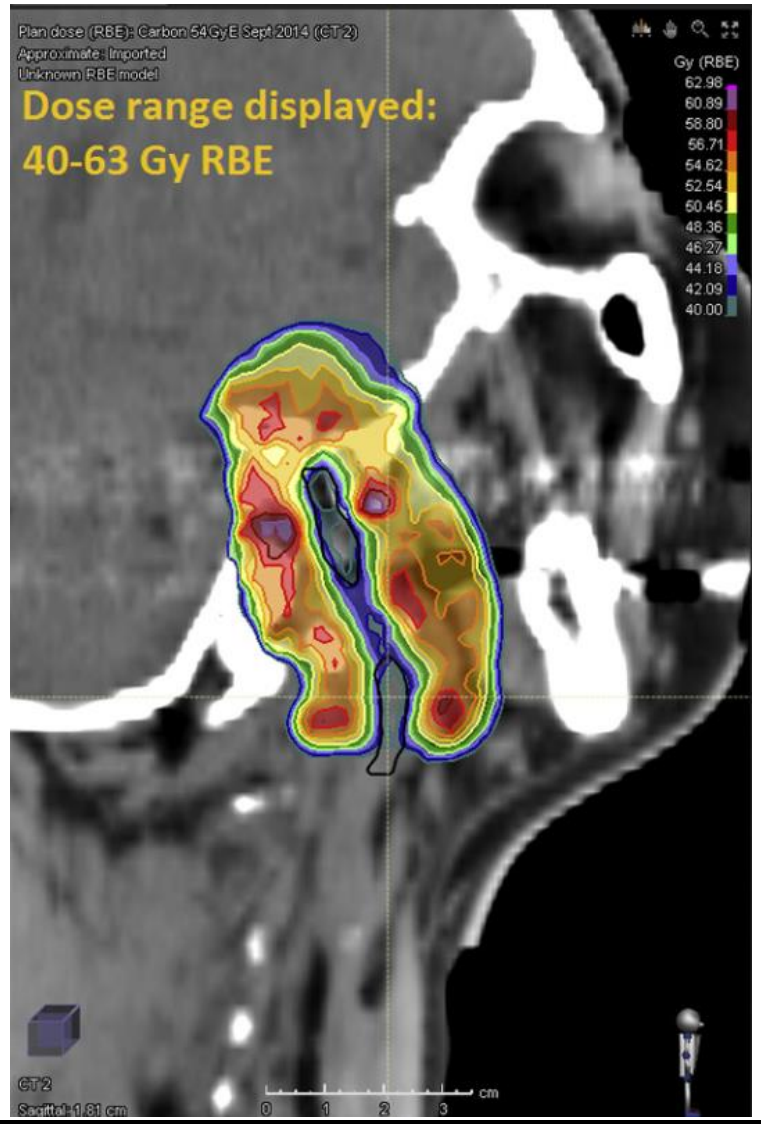
Literature series particle reRT: HN PT

Author	study/ n° pts	Tumor type	Prev RT dose (Gy) photons	Median PT dose (GyE)	Median FU (m)	Outcome	Late Toxicity > G3
McDonald, 2016	53	SCC 52%	64 (43-74)	70 (36-74)	15	2y OS 32% 2y LC 80%	G3 15.1% (8) B/ST necrosis G4 5.7 % (3) blindness **G5 3.8 %** (2) brainstem tox
Romesser, 2016	92	SCC 56%	61.4 (54-69.9)	60.6 (50-66)	13.3	1y OS 65% LP 34.4 m	G3 skin tox (8.6%), G3 dysphagia (7.1%) G3 gastrostomy tube 9.1% **G 5 hemorrhage 2% (2)**
Phan, 2016	60	-	60 Gy (30-70)	66 (50-70)	13.6	1y LRFS 80.8% 1y PFS 60.1% 1y OS 81.3%	20% G 3 late toxicity 10% feeding tubes **G 5 toxicity 3% (2)**

Literature series particle reRT: HN CIRT

Author	study/ n° pts	Tumor type	Prev RT dose (Gy)	PT dose (GyE)	Median FU (m)	Outcome	Late Toxicity > G3
Held, 2019	229	54% ACC 26% SCC	X or X and CIRT 67.4 (36.5–84)	CIRT 51 (36-66)	28.5	1y LC 60% mPFS: 24.2 m mOS: 26.1 m 1 y OS: 72%	Late toxicity ≥ G3 **14.5%**
Hu, 2018	75	NPC	IMRT 96%: 70 Gy (66–75.75)	CIRT 57.6 (50-66)	15.4	1y PFS: 82.2% 1y OS: 98.1%	9.3% mucosal necrosis **1.3%** temporal lobe necrosis
Jensen, 2015	52	ACC	66	CIRT(93%), X + CIRT 7% 51 3Gy/fr	14 (1–39)	1 y LC 70.3% 1y DPFS 72%	**CNS G3** **3.8%** (2) G3 bone necrosis 2 % (1) G4 carotid bo 3.8%(2)
Vischioni, 2020	51	ACC (75%) Other 25%	/	CIRT 60 (45-68.8)	19 (2-57)	1y PFS 71% 1y OS 90%	Trismus G3 7% (4) Visual tox G3 5% (3)
Dale, 2017	96 (79 CIRT)	ACC 29% SCC 28% Sarcoma 11% Others 32 %	60 (8-79.2)	CIRT (82%) 60 PT (18%) 54	13.4 (1-49)	1y OS 81.5 %	Carotid Blow out 2.7% (2)

Carotid Blow out Risk



Lowering the risk of carotid toxicity by selectively sparing the dose to the Carotid Artery

Dale J, Adv in Rad Onc, 2017

Literature series Particle reRT: BRAIN TUMORS

Author	study/ n° pts	Tumor type	Previous dose Gy	PT dose Gy (RBE)	Median FU (m)	Outcome	Late Toxicity
El Shafie, 2018	42	**Meningioma** WHO I: 10 WHO II: 25 WHO II: 6 Unknown: 1	IMRT (*n* = 16): 52.9 Gy(12–62.4) 3DCRT(*n* = 16): 54 Gy (50-55,8) SRS (*n* = 7): 12,1 (12–17) FSRT (*n* = 1): 58,8	Protons *n* = 8 Carbon ion *n* = 34 51 (15–60) Gy	49.7 m	1y PFS 71% 2 y PFS 56.5% 1y OS: 89.6% 2y OS 71.4%	CNS necrosis: No G 4 -G5 **3 pts (7%): G3**
Eaton, 2015	14	**Ependymoma**	Protons 85% photons 15% 55.8 (52.5–59.4)	Protons: 50.4 Gy (RBE)(35–55.8)	37.8 m	3y PFS 28.1% 3y OS 78.6%	CNS necrosis: **0% G3** 3 pts: (21.4%) G2
Eberle 2020	Retro 30	**Glioma**	60 (37.5–61.2) n= 29 37.5 (2.5 Gy/fr)	CIRT 45 (3 Gy/fr)	11 m (1-23)	6 m LC 45% 12 m LC 30%	No G 4 -G5 **8 pts (26%): G3** Fatigue (2) dysphasia (1) Seizure (2) emiparesis (1) CNS necrosis (2)

Literature series particle reRT: sarcomas of the skull base & HN

Author	study/ n° pts	Tumor type	Previous dose Gy	PT dose Gy (RBE)	Median FU (m)	Outcome	Late Toxicity ≥ G3
Uhl, 2014	**25**	Chordoma 20 Chondro 25	Particles 56%: 60 (42-72) Photons 44%: 66 (38–72.5)	Carbon ions: 51 [45–60) BED (α/β = 2) 63.8 (56.2-75]	14 m	2y LPFS 79.3%	**G3 bone necrosis 4% (1)**
Yang, 2019	**12**	Head and neck sarcoma	68 Gy (13–78)	Carbon ions: 60 Gy (RBE)	15.7	1-y OS: 67%	G4 bleeding 8% (1) G5 bleeding 8% (1)

HITRI
Heavy Ion Therapy Research Integration

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

Ongoing Clinical Studies

Original Article

Ongoing prospective studies on reirradiation: A systematic review of a clinical trials database

Willmann J, Radiotherapy and Oncology **2025**

99 prospective studies

Site:	
CNS	40%
Head and Neck	23%
Pelvis	17%

Radiotherapy techniques:	
Stereotactic radiotherapy	17 %
Hypofractionated External Beam Radiotherapy	8 %
Particle therapy (proton or carbon ion therapy)	**17 %**

41% Studies: RERT **+ systemic therapies**

HITRI
Heavy Ion Therapy Research Integration

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

Ongoing Clinical Studies

Willmann J, Radiotherapy and Oncology **2025**

NCT number	Site	Modality	Dose escalation mode
NCT03073278	Pelvis: Prostate	SBRT	Three dose levels: 6 x 6 Gy; 6 x 6.33 Gy; 6 x 6.66 Gy
NCT04536805	Pelvis: Prostate	SBRT	Three dose levels in the first phase: 5 x 5 Gy; 5 x 6 Gy; 6 x 6 Gy. Combined with metformin
NCT03253744	Pelvis: Prostate	SBRT	Four dose levels: to the tumor 5 x 8 Gy; 5 x 8.5 Gy; with and without 5 x 6 Gy to the whole prostate
NCT03438552	Pelvis: Prostate	SBRT	Three dose levels: 5 x 5 Gy; 5 x 6 Gy; 6 x 6 Gy
NCT04827732	Pelvis: Rectum	Protons	Three dose levels
NCT04455438	Thorax: NSCLC	SBRT	Three dose levels: 5 x 6 Gy; 5 x 8 Gy; 5 x 10 Gy. Time-To-Event Bayesian Optimal Interval (TITE-BOIN)
NCT06344130	CNS: Glioblastoma	EBRT, hypofractionated	Three dose levels, 3 + 3 design
NCT05284643	CNS: Glioblastoma	Protons	Two dose levels: 10 x 3.5 Gy; 10 x 4 Gy
NCT01464177	CNS: Glioblastoma	SRT	Randomization between to doses: 5 x 5 Gy; 5 x 7 Gy
NCT05737212	CNS: Glioma	Neutrons (Boron Neutron Capture Therapy)	Three dose levels, 3 + 3 design
NCT04533620	–	Head/neck: NPC	II	Carbon-ion reirradiation standard *vs.* individualized prescription based on normal tissue complication model
NCT04143984	–	Head/neck: NPC	II	Camrelizumab + Carbon-ion reirradiation *vs.* Carbon-ion reirradiation alone
NCT03546582	KEYSTROKE	Head/neck: mixed	II	Pembrolizumab + SBRT reirradiation *vs.* SBRT reirradiation
NCT03164460	–	Head/neck: mixed	II	SBRT reirradiation *vs.* IMRT/IMPT reirradiation
NCT04215510	–	Head/neck: NPC	III	IMRT reirradiation *vs.* endonasal endoscopic surgery
NCT04453813	–	Head/neck: NPC	III	Toripalimab + reirradiation + concurrent chemotherapy *vs.* reirradiation + concurrent chemotherapy
NCT03879109	GRECCAR15	Pelvis: Rectum	III	Neoadjuvant chemotherapy + reirradiation *vs.* neoadjuvant chemotherapy alone
NCT05904119	LEGATO	CNS: Glioblastoma	III	Lomustine + reirradiation *vs.* lomustine alone

lorizon 2020
› 101008548

Modern RT techniques make Reirradiation feasible, there is the Need of further investigation possibly by randomized control trials

Ongoing studies most frequently focus on CNS, head and neck, and pelvic site

A particular need is for other site not yet well investigated
Lung, breast, and gynecological cancers

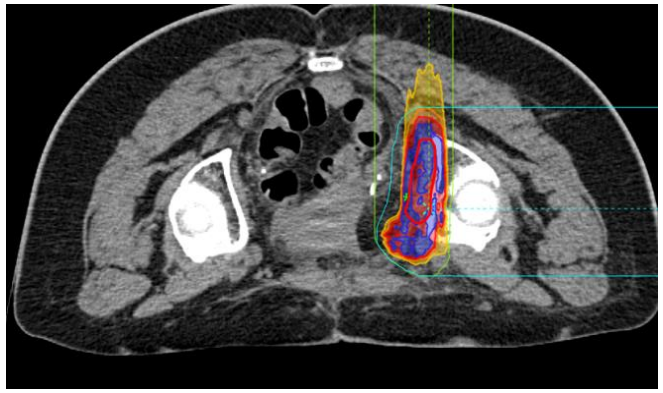
HITRI
Heavy Ion Therapy Research Integration

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

Reirradiation of Gynecological tumors at CNAO

Patient/Tumor hallmaks

Number of patients/lesions	27 / 28
Age (median, range)	64.5 years (39-60)
Previous RT dose (median, range)	52.5 Gy (45-59,4)
Primary tumor	
-Cervical carcinoma	*29,60%*
-Endometrial carcinomas	*25,90%*
-Ovarian Cancers	*22%*
-Sarcomas & Melanomas	*22,50%*
CTV at Re-RT time (median, range)	107 cc (15-1381)



Re-RT treatment

- ✓ PT (n=12 lesions) →43.5 Gy[RBE] (range:39-60 GyRBE)
- ✓ CIRT (n=16 lesions) →48 Gy[RBE] (range:39-68 GyRBE)
- ✓ No concomitant systemic therapies during re-RT

HITRI
Heavy Ion Therapy Research Integration

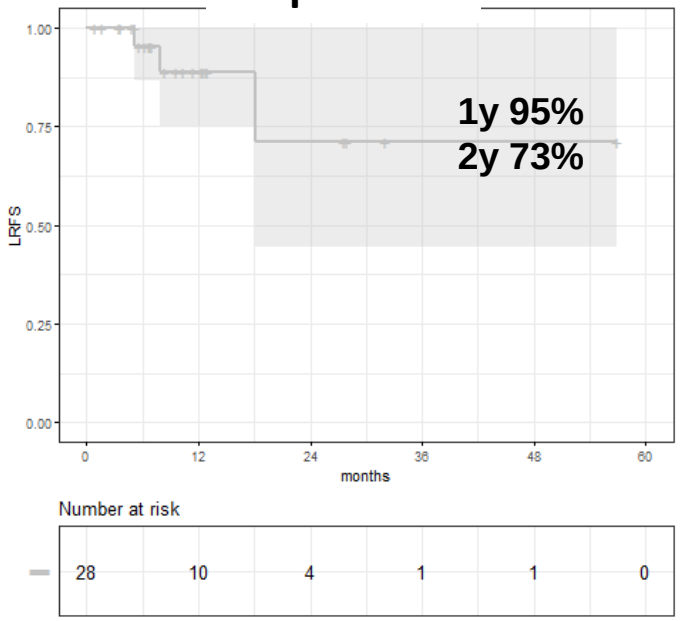
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Re-RT in gynecological tumors at CNAO

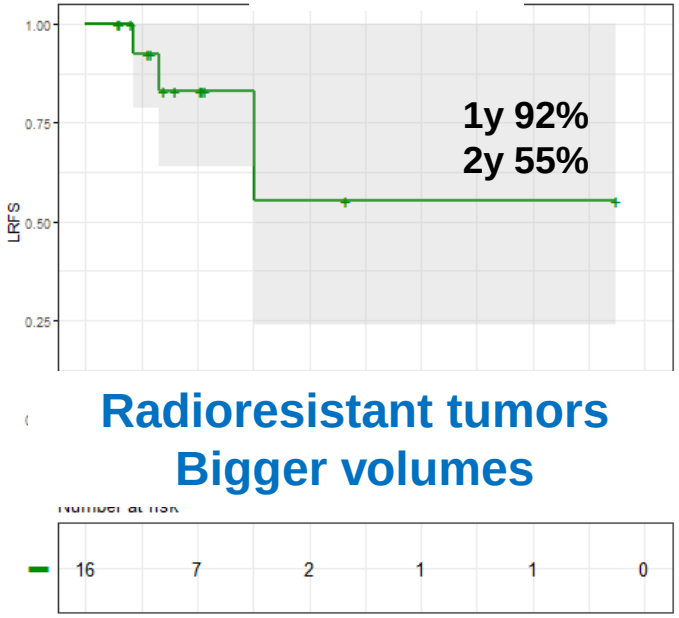
LRFS

✓ **Critelli, Pezzulla et al Gyn Oncol. 2023**	→ **1y= 74%;**	2y=49%	**G3-G4: 26%**
✓ **Pollock et al Adv Radiat Oncol. 2023**	→ 1y= 83,5%		G3: 10%
✓ **Shiba et al Anticancer Research 2017**	→ 1y= 94%		G3-G4 0%

All patients

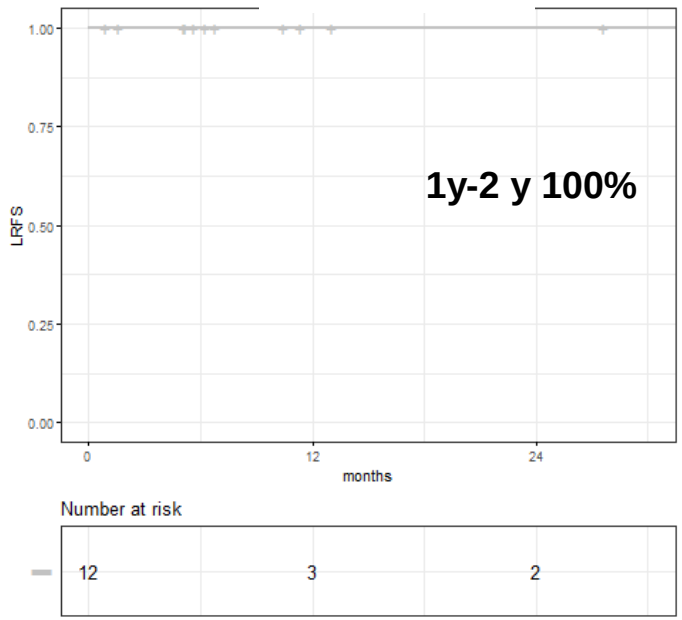


CIRT



Radioresistant tumors
Bigger volumes

Proton



3 cases of marginal recurrences after CIRT,
1 case of Late peripheral neuropathy G2

HITRI
Heavy Ion Therapy Research Integration

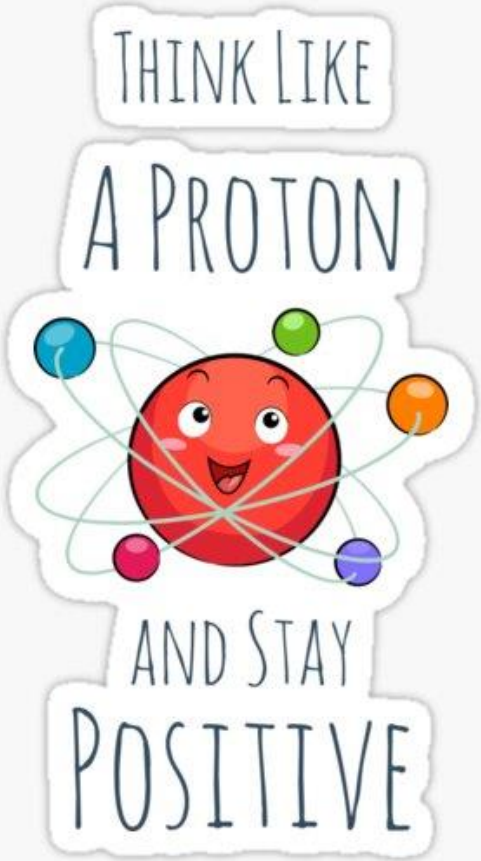
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Conclusions & take home messages

- ✓ Treatment of recurrent disease is challenging
- ✓ Reirradiation with particles is a **valid therapeutic approach** and may offer a chance of treatment with curative intent and acceptable toxicity
- ✓ Literature data are promising but still based **on retrospective** mono-institutional series
- ✓ Further prospective studies are necessary to generate **evidence** and to **enlarge clinical indications**

HITRI
Heavy Ion Therapy Research Integration

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



Thanks for your attention!

HITRI
Heavy Ion Therapy Research Integration

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