

# *Chordoma treatments at CNAO*

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MARIA ROSARIA FIORE



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## Chordoma characteristics

Rare tumor

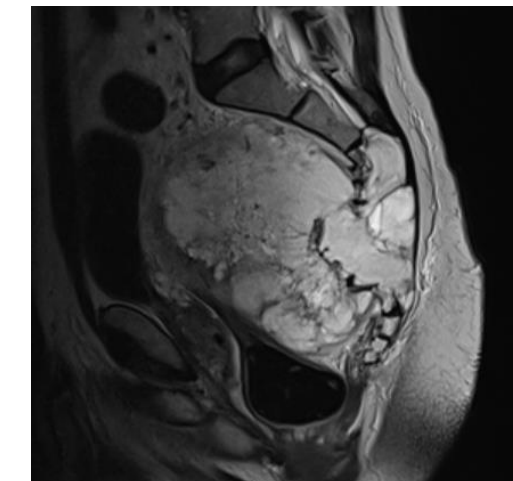
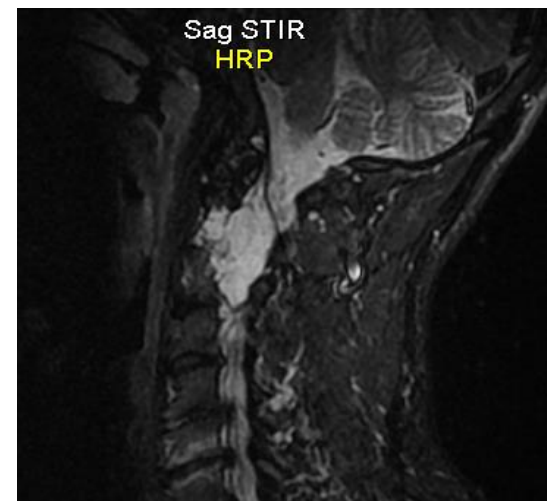
Radioresistant tumor

Locally aggressiveness

Slow growing

Site of origin: > 50% sacrum, followed by skull base, mobile spine.

**Peculiar aspect is the proximity to structures deputed to relevant functions**



# Chordoma

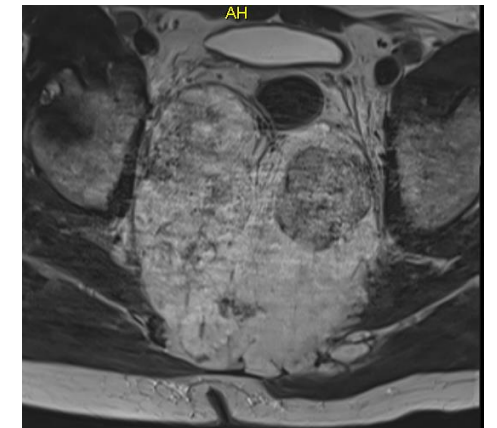
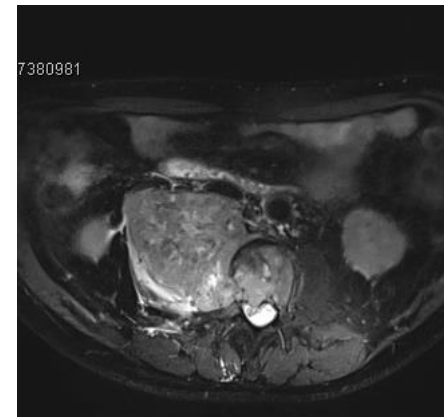
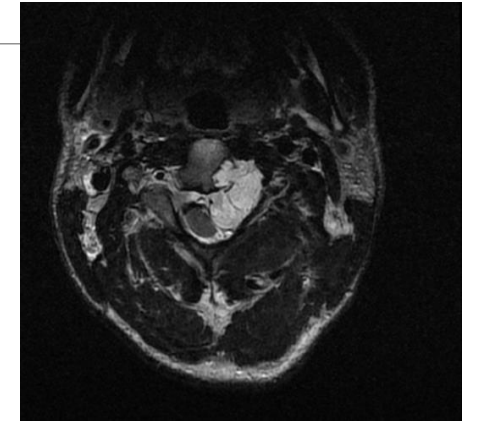
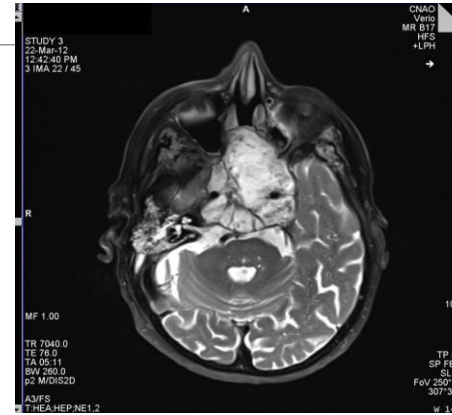
Therapeutic strategies are still challenging

Surgery remains the main therapy

- Complete resection R0 → skull base
- En bloc resection → mobile spine
- Wide margin resection → sacrum

Strongly improve local control

Complete resection is not always possible



# Chordoma

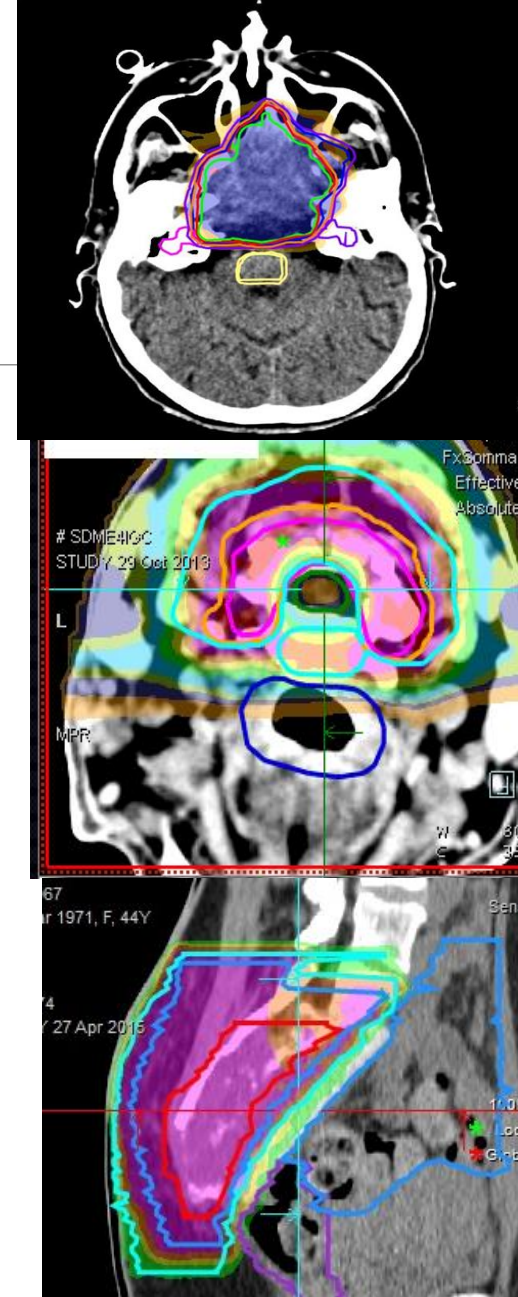
## Particle therapy

Well known as radioresistant tumors

High dose required for local control improvement

Dose-limiting structures (brainstem, optic pathway spinal cord, kidney, bowel....)

**For complex shaped and large tumor ,“Sculpting” of the dose distribution by protons and carbon ions are necessary**



# Guideline for sarcoma



SPECIAL ARTICLE

Bone sarcomas: ESMO—EURACAN—GENTURIS—ERN PaedCan Clinical Practice Guideline for diagnosis, treatment and follow-up<sup>☆</sup>

ANNALS OF  
ONCOLOGY  
driving innovation in oncology

2021



«*Heavy particle should be considered*»:

- Osteosarcoma: unresectable or adjuvant for high risk of LR
- **Chordoma: if R0 resection is not feasible**
- Chondrosarcoma: unresectable primary or recurrent after incomplete surgery

NCCN National Comprehensive Cancer Network®  
**NCCN Guidelines Version 2.2023**  
**Bone Cancer**

[NCCN Guidelines Index](#)  
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## PRINCIPLES OF RADIATION THERAPY

### General Principles

- Patients should be strongly encouraged to have RT at the same specialized center that is providing surgical and systemic interventions.
- Specialized techniques such as intensity-modulated RT (IMRT); particle beam RT with proton, carbon ions, or other heavy ions; or stereotactic radiosurgery (SRS) should be considered as indicated in order to allow high-dose therapy while maximizing normal tissue sparing.

Nowday the use of CIRT is recognised in international guide lines

ESMO 2021 european guidelines where «*Heavy particle should be considered*». For all of 3 histology mainly for unresectable tumors

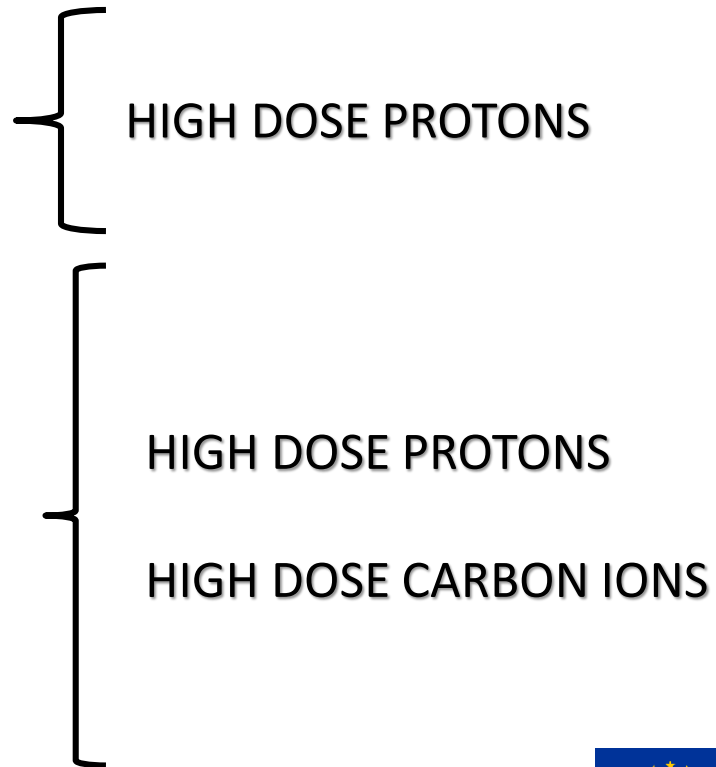
In NCCN american Guidelines as well we have reccomendation for using heavy particles

# Particle therapy for Chordoma @CNAO from 2012

## Protons and carbon ion beams available

### General approach in a curative setting

- SURGERY  
Microscopic residual
- SURGERY R2  
Macroscopic residual
- Advanced tumors  
(larger mass, critical structures involved) surgery not indicated



# Chordoma treatments by site

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# Skull base

- Surgery first: maximal safe resection or separation surgery from critical structures (brainstem/chiasm) based on shared strategy
- Adjuvant radiotherapy: **well defined indication even in case of R0**
- **High Dose Particle therapy >70Gy(RBE), has been historically employed to overcome dose-limiting structures**
- Data confirm that particle therapy achieve adequate target coverage in the skull base for prescription doses in excess of 70 Gy(RBE)

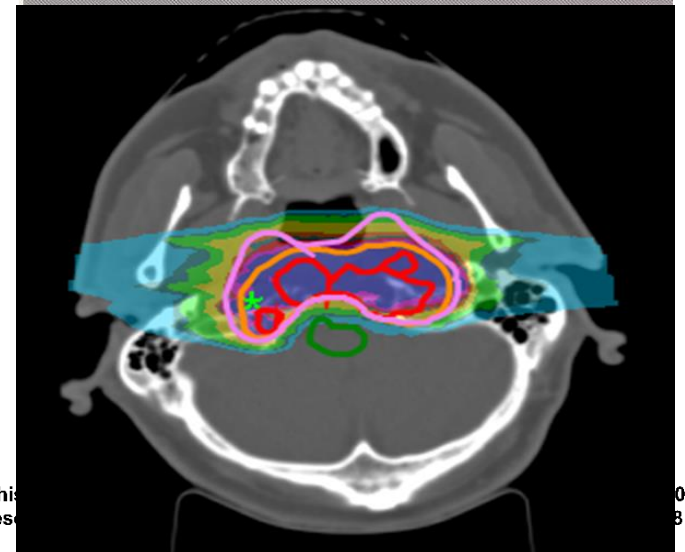
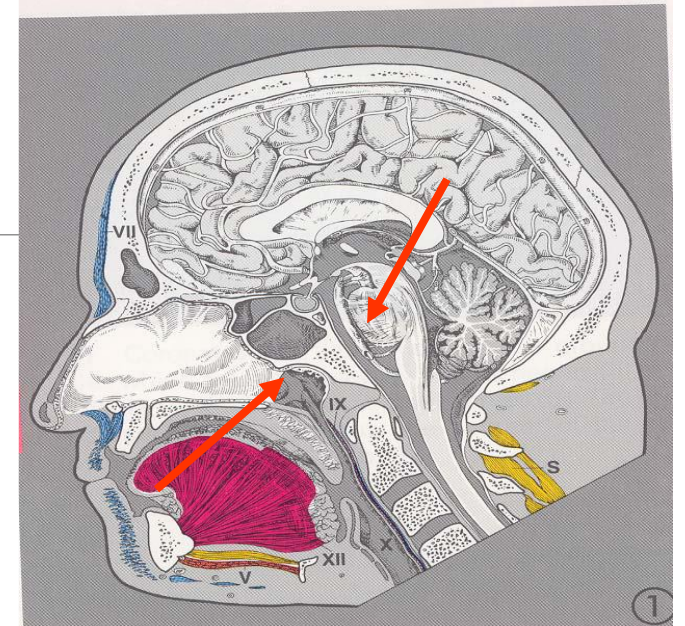




TABLE 1 Patients and treatment description of chordomas irradiated with proton or carbon ion (selected series).

Study	Particle	Patients (number)	Follow-up (months)	RT Dose (GyRBE)	LC (%)	OS (%)	Severe late toxicity
Hug, 1999 (16)	P	33	33 (median)	TD: 65–79 Dpf: 1.8–2	5-y: 59	5-y: 79	7%
Munzenrider, 1999 (17)	P + ph	169	41 (median)	TD: 66–83 Dpf: 1.8–1.9	5-y: 73 10-y: 54	5-y: 80 10-y: 54	Disaggregated data not reported or limited cohort followed-up for toxicity outcomes
Uhl, 2014 (18)	C	155	72 (median)	TD: 60 (median) Dpf: 3	5-y: 72	5-y: 85	0%
Weber, 2016 (19)	P	151	50 (mean)	TD: 72.5 (mean) Dpf: 1.8–2	7-y: 70.9	7-y: 72.9	8%
Fung, 2018 (20)	P + ph	106	61 (mean)	TD: 8.4–73.8 Dpf: 1.8	5-y: 75	5-y: 88	7%
Koto, 2019 (21)	C	34	108 (median)	TD: 60.8 (median) DpF: 3.8 (median)	5-y: 77	5-y: 93	11%
Iannalfi, 2020 (22)	P	135	49 (median) whole series	TD: 74 (median) Dpf: 1.8–2	5-y: 84	5-y: 83	12% (2% expected for tumor very close to optic nerve and/or pre-existing severe deficit). No G3 brain necrosis.
Iannalfi, 2020 (22)	C	65	49 (median) whole series	TD: 70.4 Dpf: 4.4	5-y: 71	5-y: 82	12% (2% expected for tumor very close to optic nerve and/or pre-existing severe deficit). No G3 brain necrosis.
Mattke, 2022 (23)	P	36	36 (median)	TD: 74 (median) Dpf: 1.8-2	5-y: 61	5-y: 92	13% (cumulative rates of brain injury) G3 toxicity reported, but disaggregated data for G3 not reported
Mattke, 2022 (23)	C	111	52 (median)	TD: 66	5-y: 65	5-y: 83	13% (cumulative rates of brain injury) G3 toxicity reported, but disaggregated data for G3 not reported

P, proton; C, carbon; RT, radiotherapy; TD, total dose; Dpf, dose per fraction; LC, local control; y, years; OS, overall survival.

# Proton and carbon ion radiotherapy in skull base chordomas: a prospective study based on a dual particle and a patient-customized treatment strategy

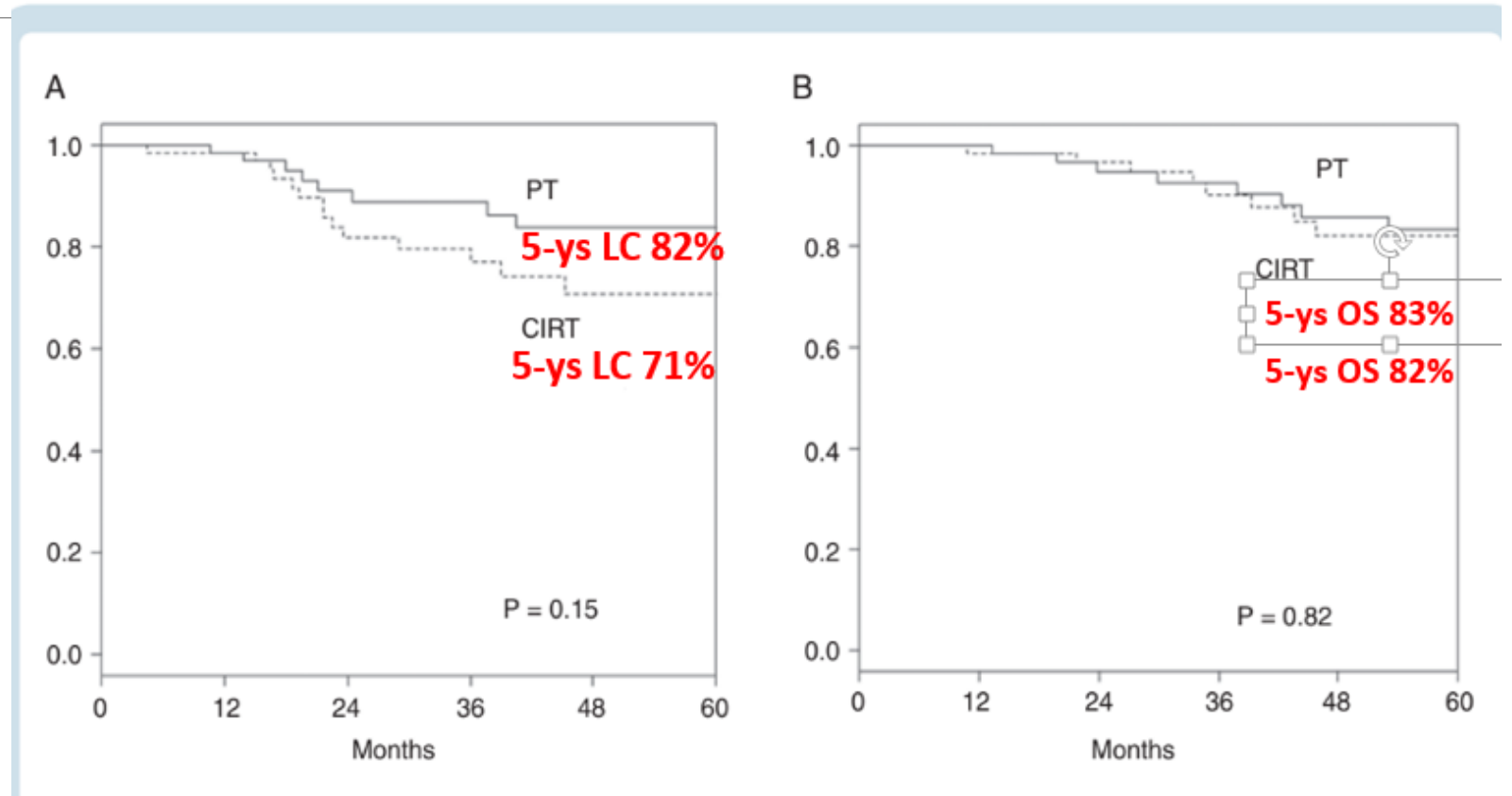
*Iannalfi A. et al, Neuro-Oncology, 2020*

135 patients, 2011/ 2018.

PT: 70 pts 74 Gy(RBE) in 37 fx

CIRT: 65 pts 70.4 Gy(RBE) in 16 fx

Median follow-up of 49 months



**Fig. 1** Kaplan–Meier curves of local control (LC) (A) and overall survival (OS) (B) for PT and CIRT.

# Proton and carbon ion radiotherapy in skull base chordomas: a prospective study based on a dual particle and a patient-customized treatment strategy

## Particle choice (Protons or Carbon ion) criteria:

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### Unfavorable profile: CARBON IONS

- Macroscopic disease larger GTV
- Histological characteristics: dedifferentiated subtypes, higher proliferative index
- Proximity to critical organs compression of brainstem, optic pathway

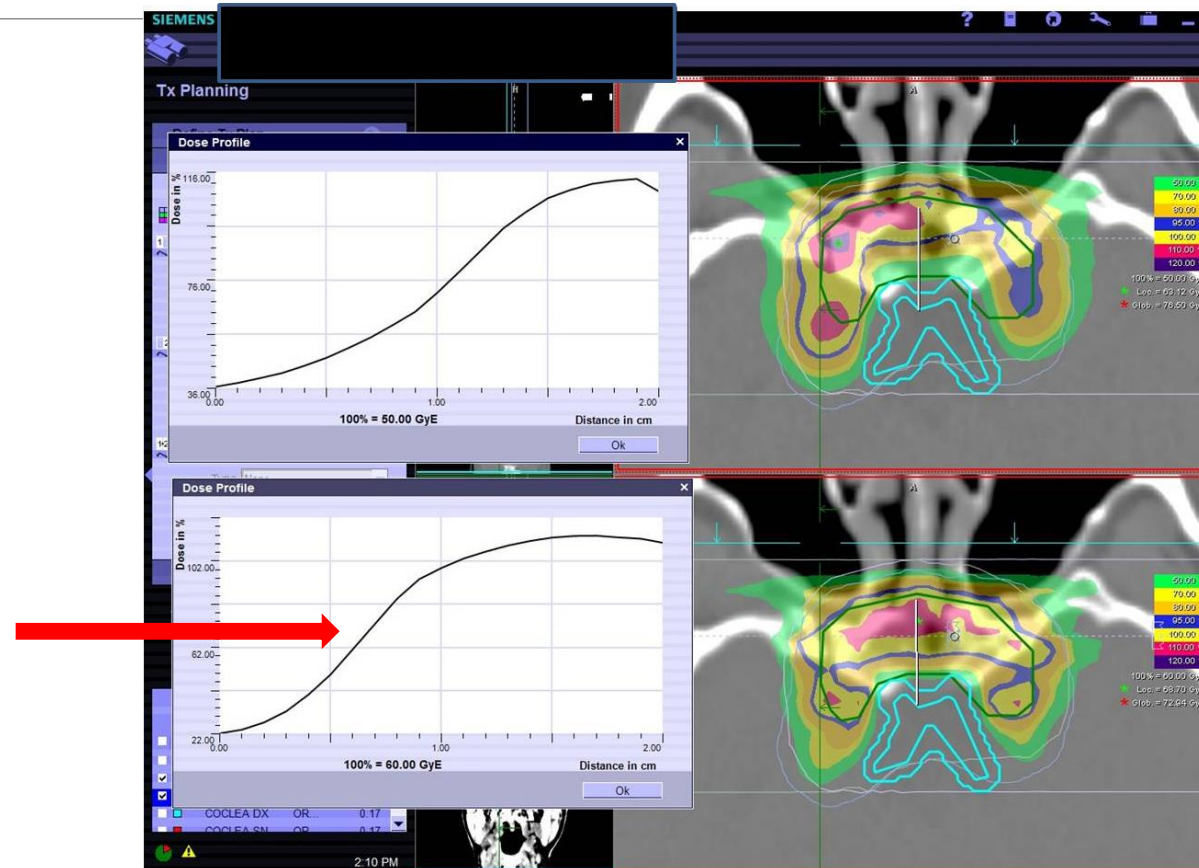
## Proton - Carbon ions plans: Steep dose gradient

### Proton plan

1 cm the dose falls down  
from 76% to 36%

### Carbon ions plan

1 cm the dose falls down  
From 102% to 22%



# Mobile Spine chordoma

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# Mobile Spine chordoma

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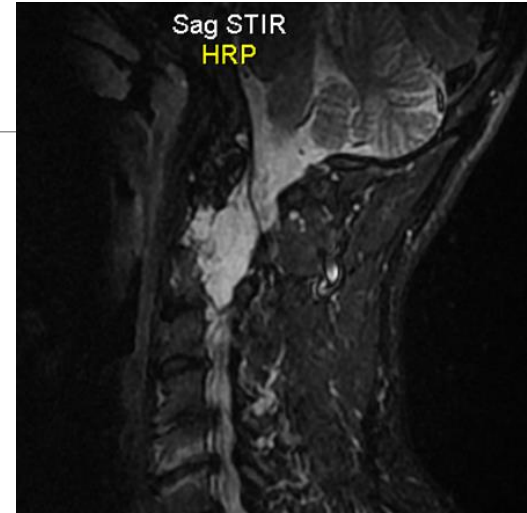
***En bloc resection:*** best results in terms of LC and DFS

The typical presentation often with intracanalicular invasion makes difficult the surgery

**Role of particle therapy well defined in adjuvant setting**

High dose > 60-66 Gy(RBE) after separation surgery

Gained a role to avoid disabling surgery



## Protons and carbon ion series for mobile spine chordoma

Authors	Nr pts	Modality RT	Median Dose	Local control	Survival rate
Schulz-Ertner D et al. 2003	16	CIRT / IMRT	68.4 GyRBE	~88% 3-year	~88% 3-y OS
Snider et al 2015	100	Proton/photon	74GyRBE	63% 5-year	88% 5-y
Rutz et al. 2007	26	Proton +/- photon	72.0 GyRBE	86% 3-year	84% 3-year OS rate
DeLaney TF et al 2014	23	Proton +/- photon	76.6 GyRBE	>96% 5-year	5-year actuarial OS 84%
Rotondo RL et al. 2015	95	Proton +/- photon	72.4 GyRBE	68% 5-year	82% 5-year OS rate
Indelicato D et al 2016	26	Proton +/- photon	70.2 GyRBE	88% 4-year	83% 4-year OS rate
<b>Matsumoto 2013</b>	<b>9</b>	<b>CIRT</b>	<b>70,4GyRBE</b>	<b>79% (5y)</b>	<b>52% (5y)</b>
<b>Shiba 2021</b>	<b>32</b>	<b>CIRT</b>	<b>70,4GyRBE</b>	<b>79,7% (3y)</b>	<b>69.8% (3y)</b>
<b>Aoki 2022</b>	<b>19</b>	<b>CIRT</b>	<b>60,8GyRBE</b>	<b>75.2 (5y)</b>	<b>68.4% (5y)</b>

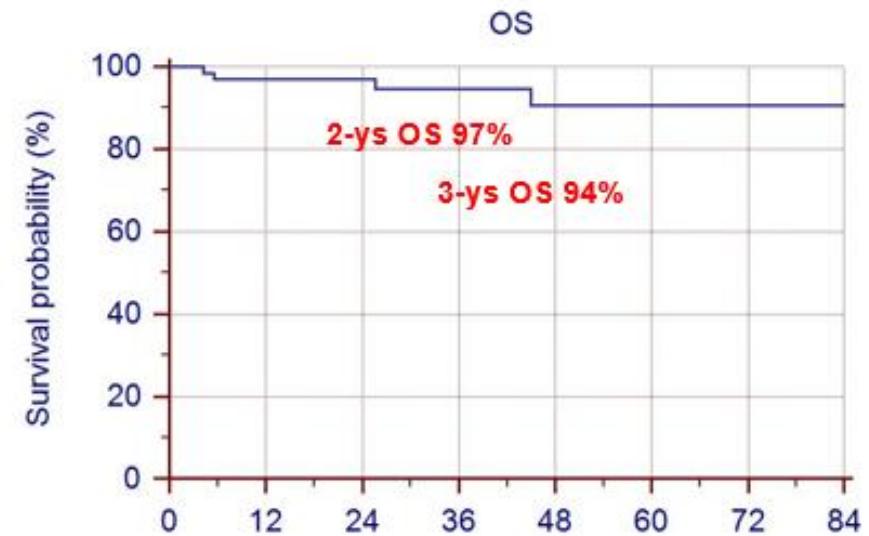
# Spine chordoma: preliminary outcome of CIRT @CNAO

*under evaluation*

64 patients:

- **54 pts (85%) CIRT after R2 surgery**
- **6 unresectable: definitive CIRT**
- Total dose range was 66-70.4 GyRBE
- Follow-up: median 36.7 months (12.77 - 107.63)

Median TTR 26.4 months (12.4- 84.2)



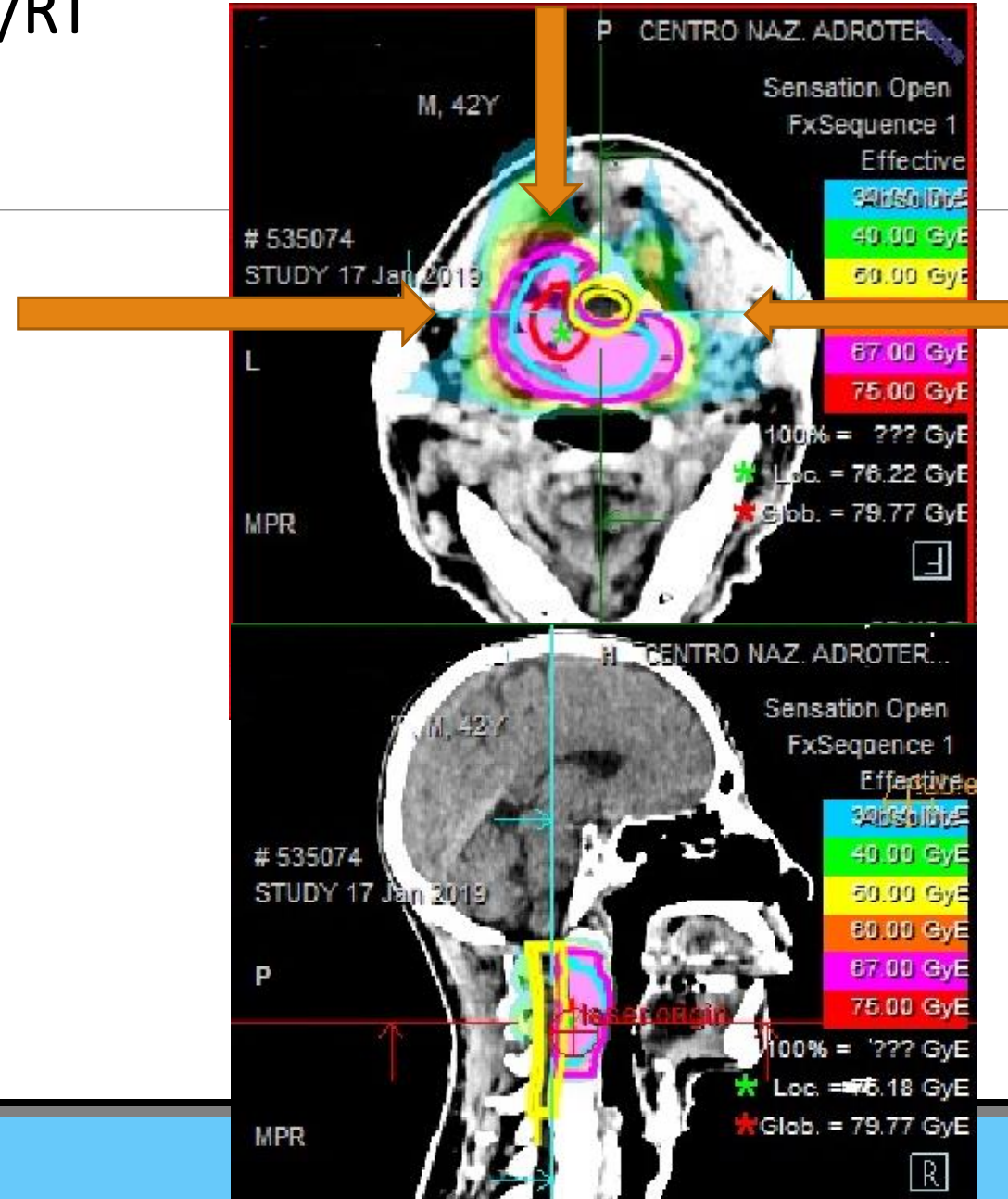
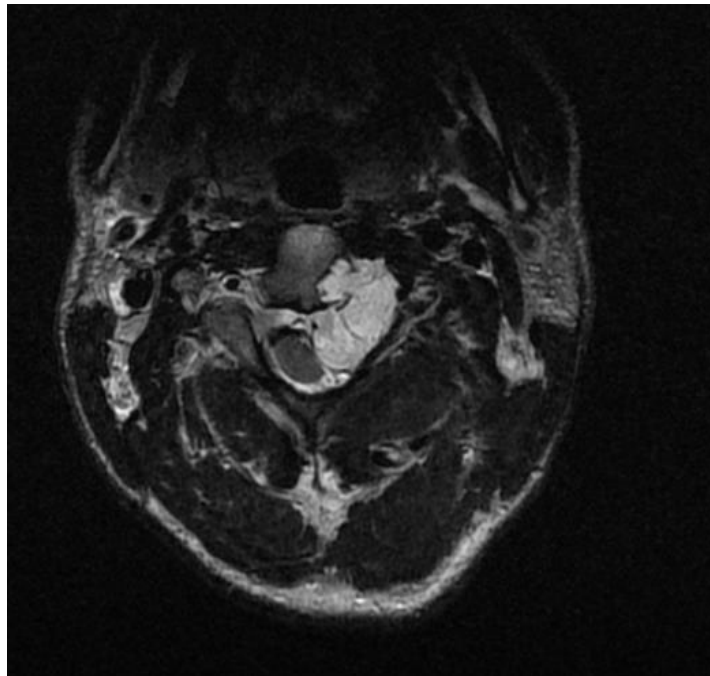


# Best result: separation surgery/RT

42 y, chordoma C2-C3

R2 Surgery → CIRT 03/2019

04/2024 FUP 5y: SD



# Skull base-mobile spine treatments common characteristics

## Surgery and adjuvant high dose particle radiotherapy recommended

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Cooperation and case discussion between radiation oncologist and surgeon since pre-operative phase, sharing and taking into account:

- Prognostic factors in surgery perspective
- Prognostic factors radiation oncologist perspective
- Possibility of reconstruction (skull base) or orthopedical stabilization (mobile spine)
- Where expected necessity of metal implants : sharing timing and geometry of device affecting RT planning

# Sacral chordoma

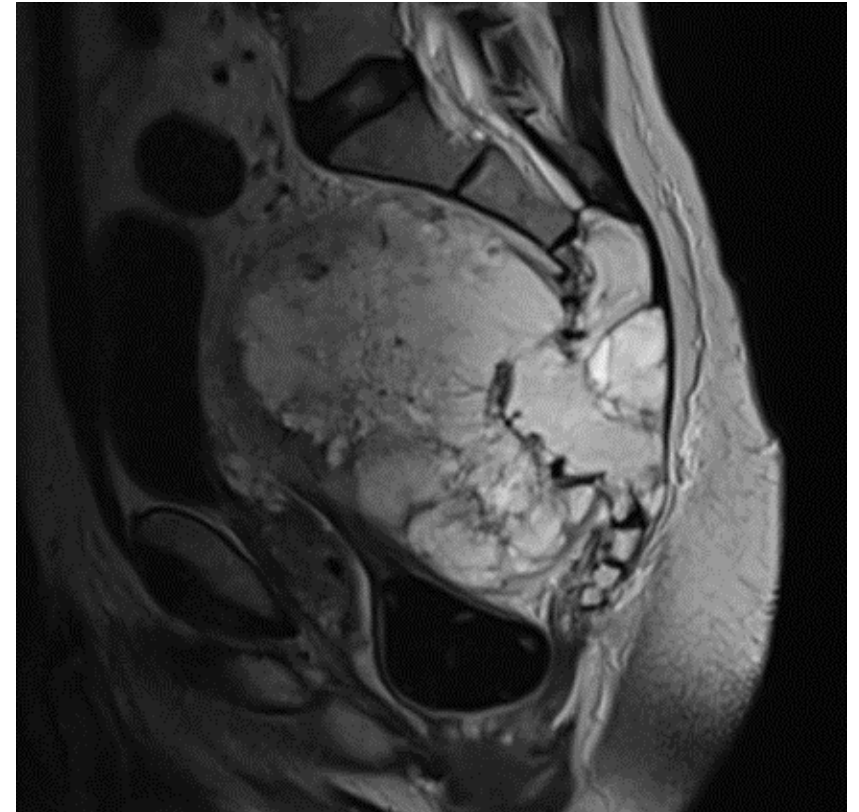
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# Sacral chordoma

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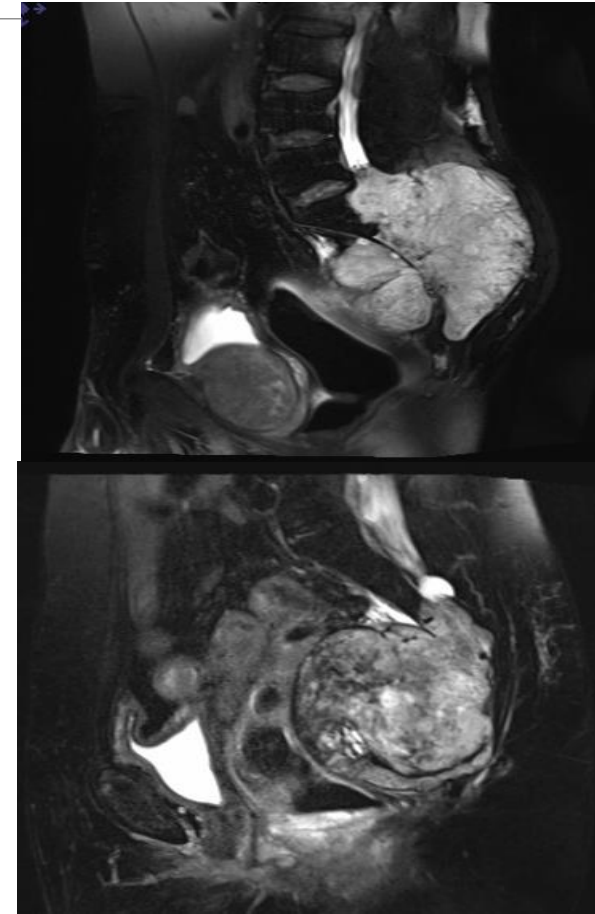
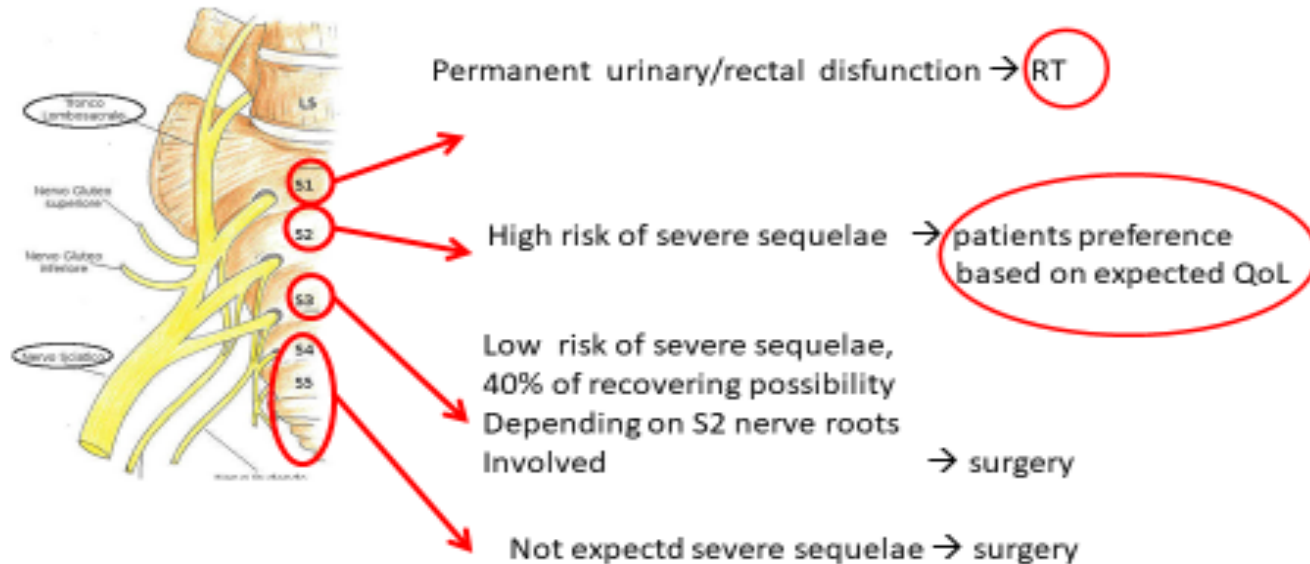
More than the other sites:

- ❑ Large mass at diagnosis
- ❑ Not suitable for wide margin resection
- ❑ The most recognised indication for heavy particles → CIRT in radical setting



# Sacral chordoma

Wide margin surgery it is not always possible  
S1-S2 extension RT as an alternative to be  
considered because of invalidating sequelae



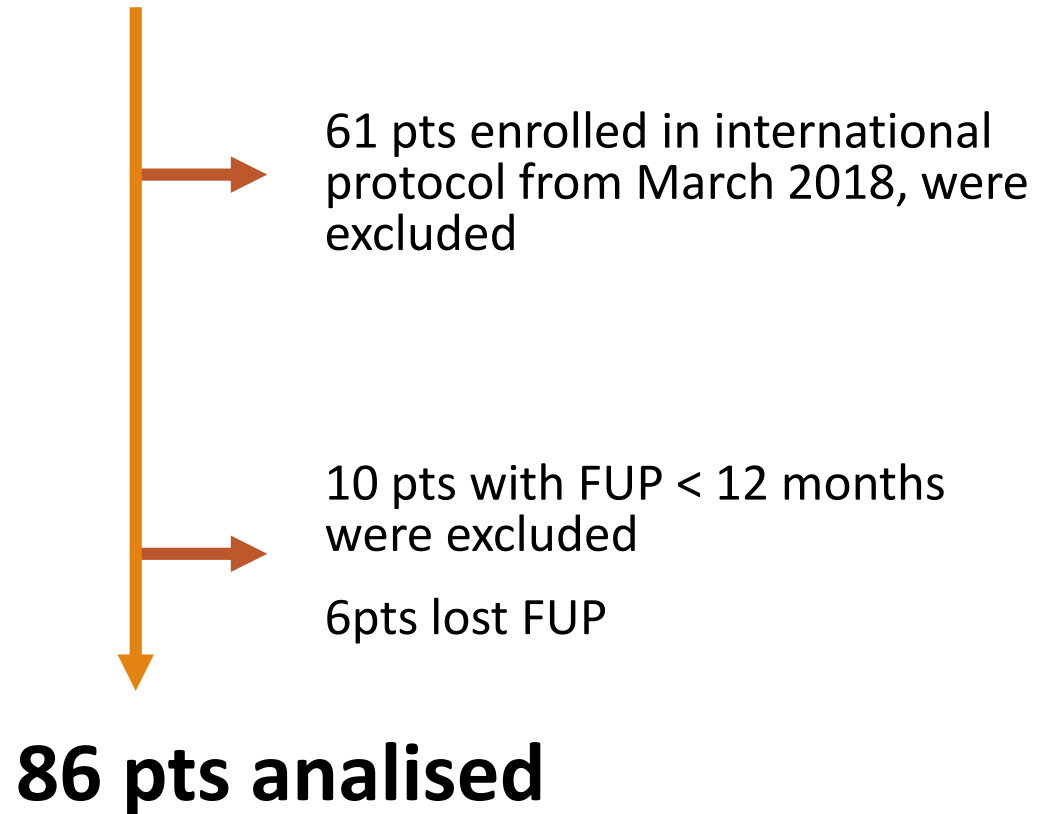
# Carbon ion series of definitive treatment for sacral chordoma

Series	Patients (n)	Median FUP (months)	LC (%)	OS (%)	Toxicity >G3 (n; events)
Imai 2016	<b>188</b>	62	<b>77% (5y)</b>	<b>81% (5y)</b>	9 ; skin disorders, peripheral nerve injuries
Demizu 2021 Multicentric study	<b>219</b>	56	<b>72% (5y)</b>	<b>84%(5y)</b>	13 ; skin disorders, myositis, etc.

# Sacral chordoma preliminary outcome @CNAO

From March 2013: **163 pts treated with definitive CIRT**

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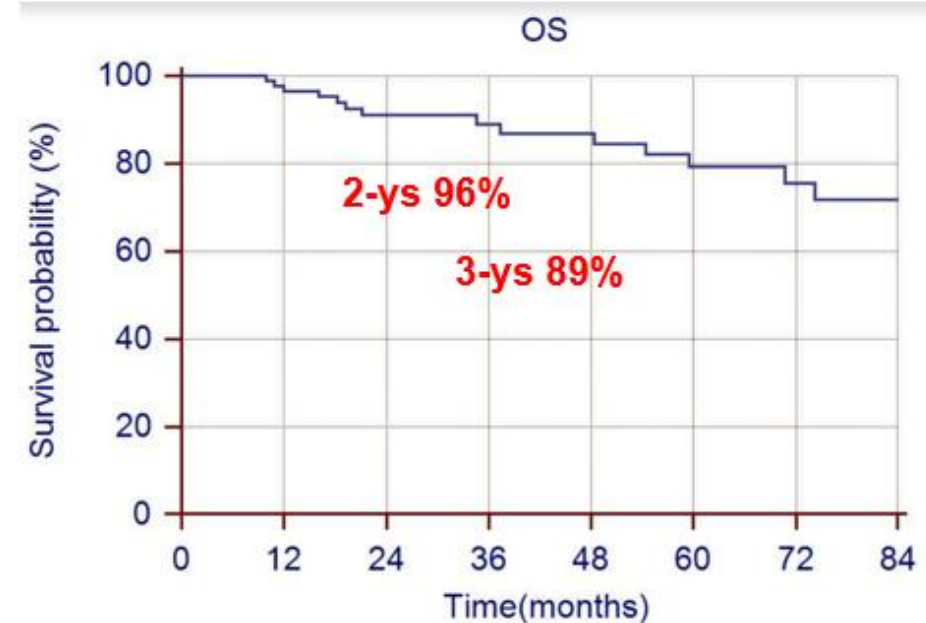
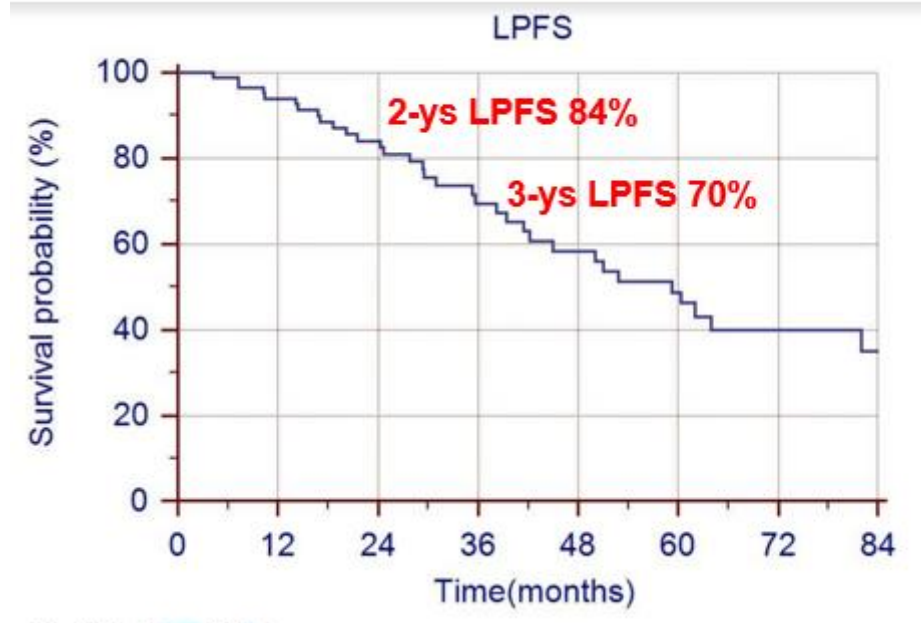
**Sacral Chordoma: a Randomized & Observational study on surgery versus definitive radiation therapy in primary localized disease (SACRO)**

# Sacral Chordoma

Total dose range, 60 - 78.2 GyRBE

Follow up median: 31.89 months (range, 12.2 - 126.12)

Mediam TTR: 24.63 months





# What we can do for better results

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- ❑ Expected learning curves
- ❑ Improvement over the years
- ❑ Increasing collaborations with referral centers
- ❑ Improvements of treatment planning system
- ❑ Better knowledge of LET and RBE distribution
- ❑ Radiobiological model

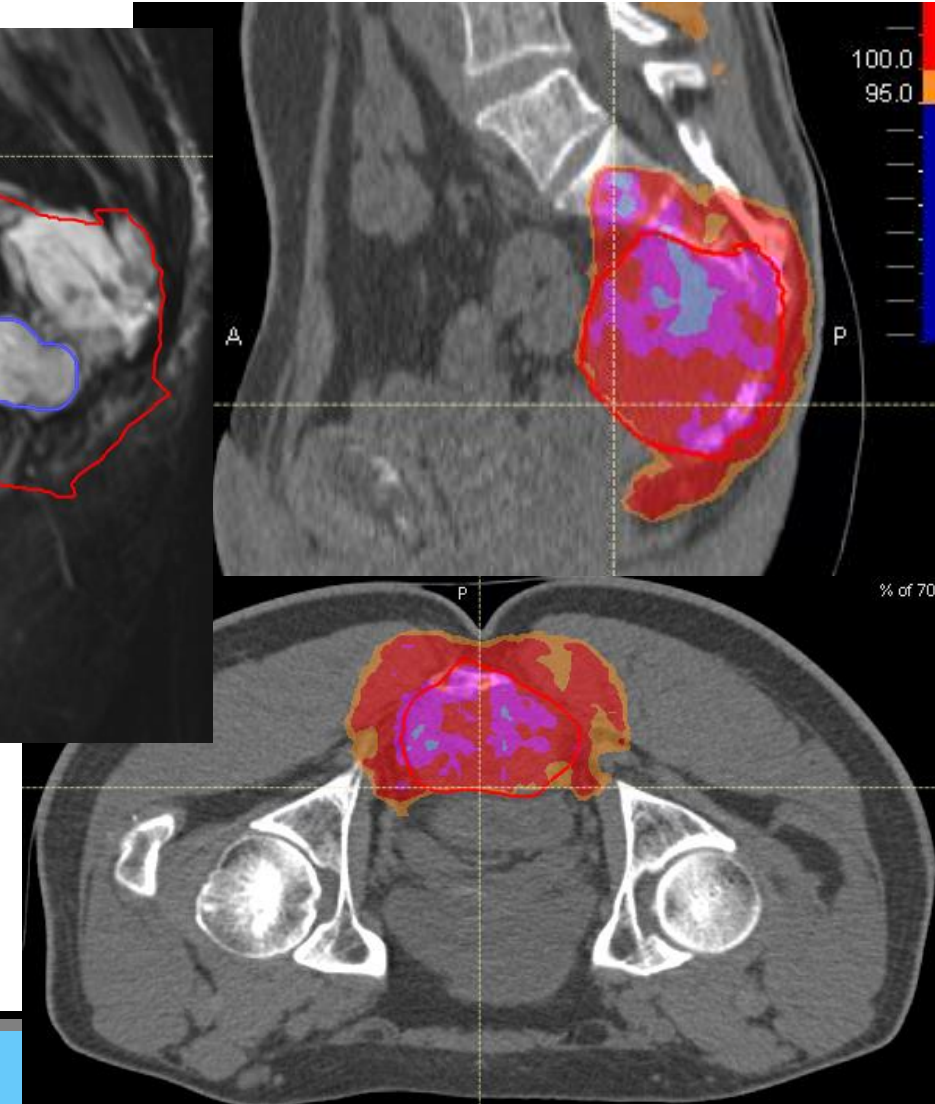
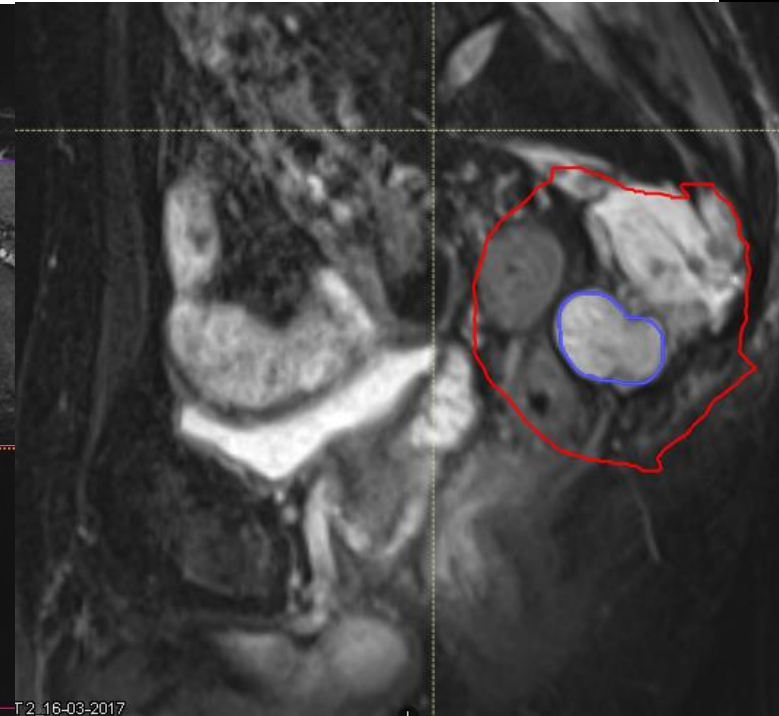
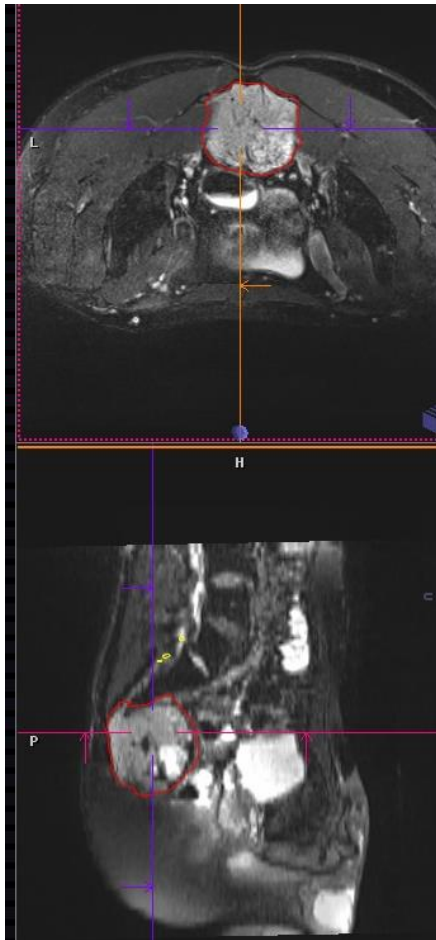
# Analisy of recurrences

## In Field relapse : pararectal site

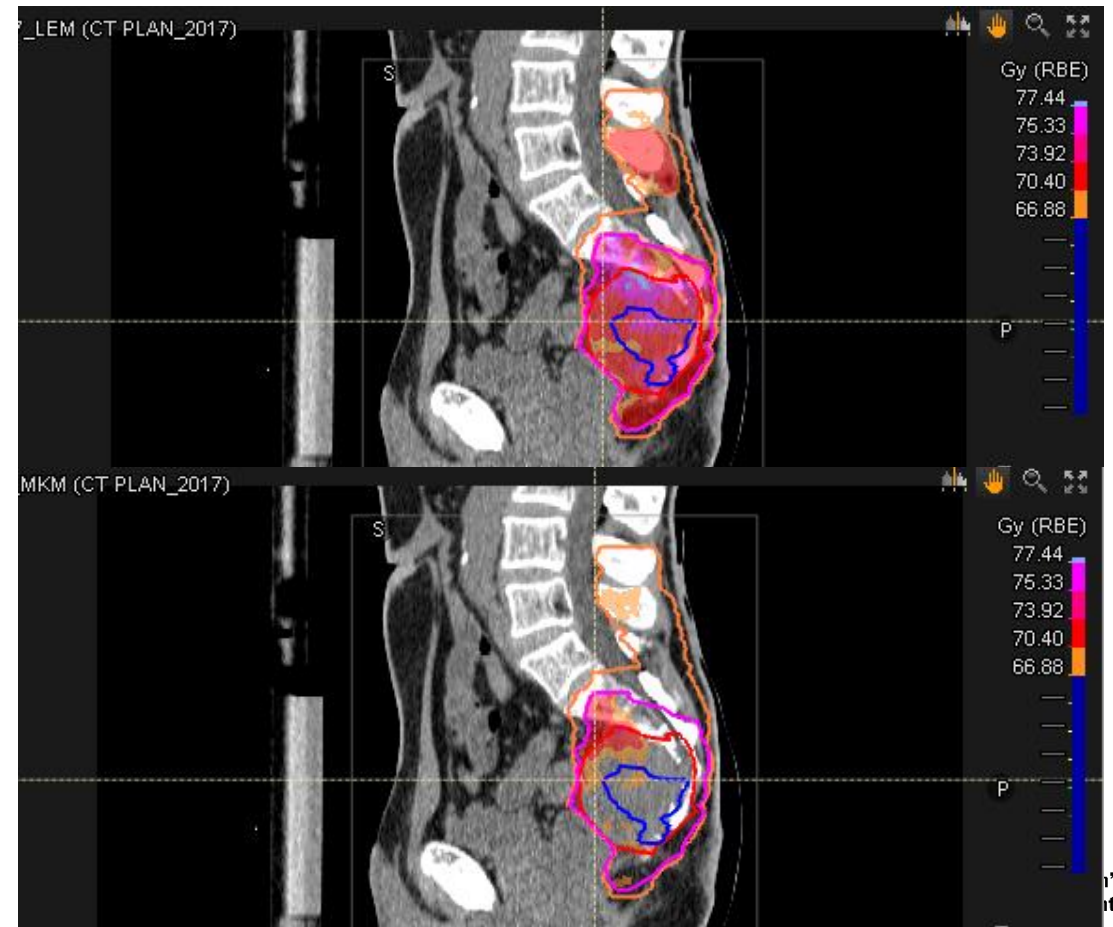
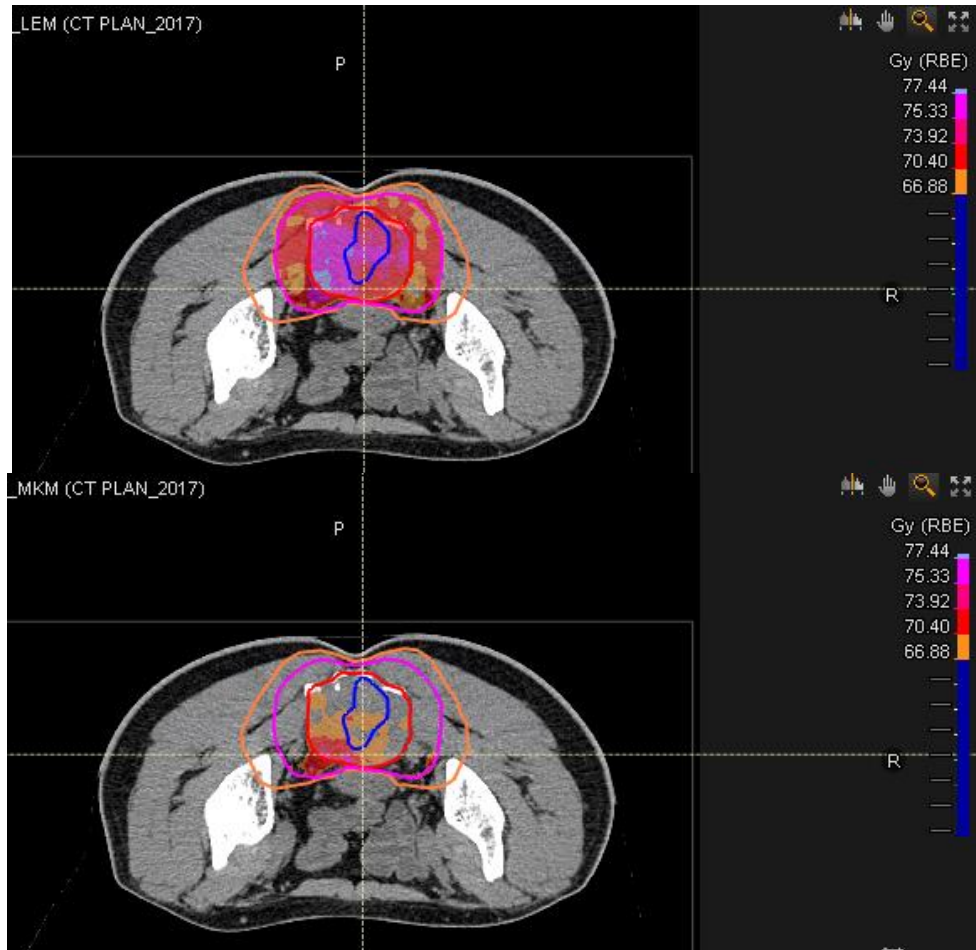
baseline 03.2017

FUP 29 m, 08.2019

FUP 5 years, 06.2022

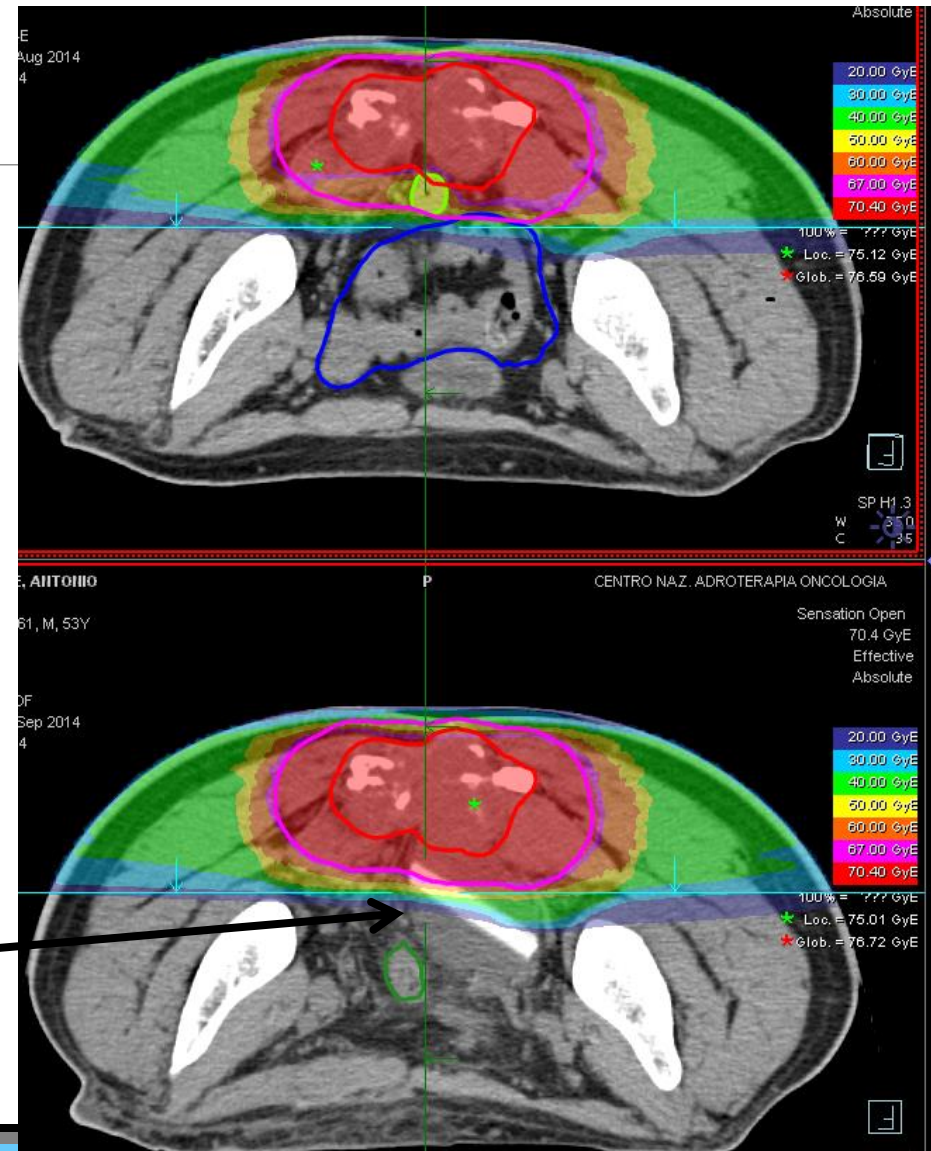
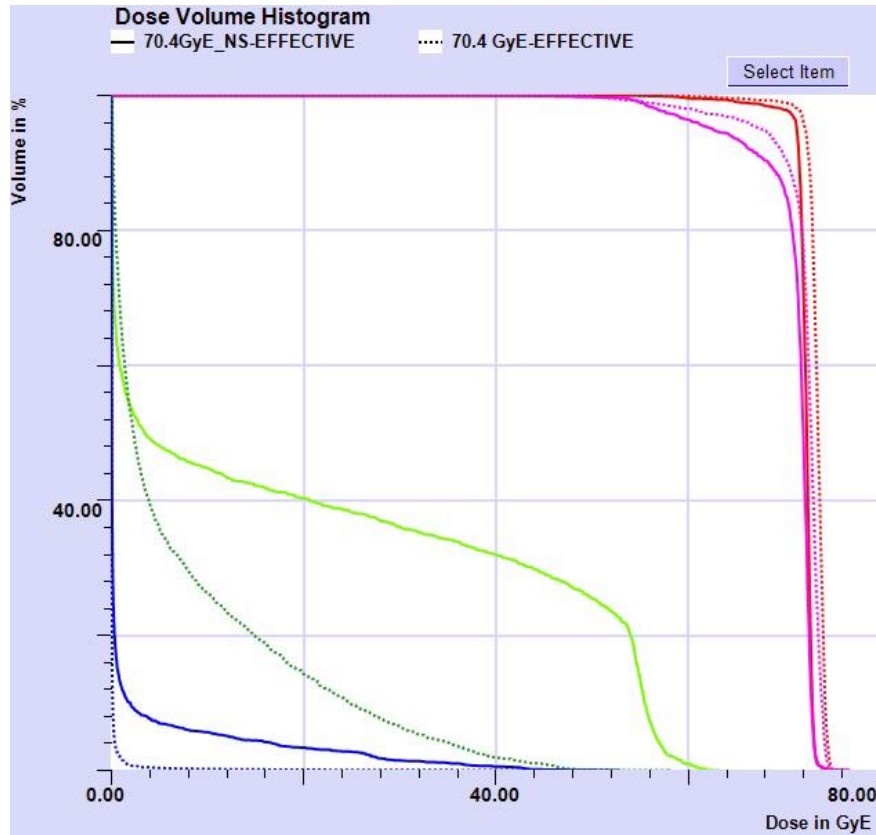


# Radiobiological model: LEM vs MKM *dosimetric comparison from 2019*



# Bowel displacement

## With spacer surgical implant is recommended

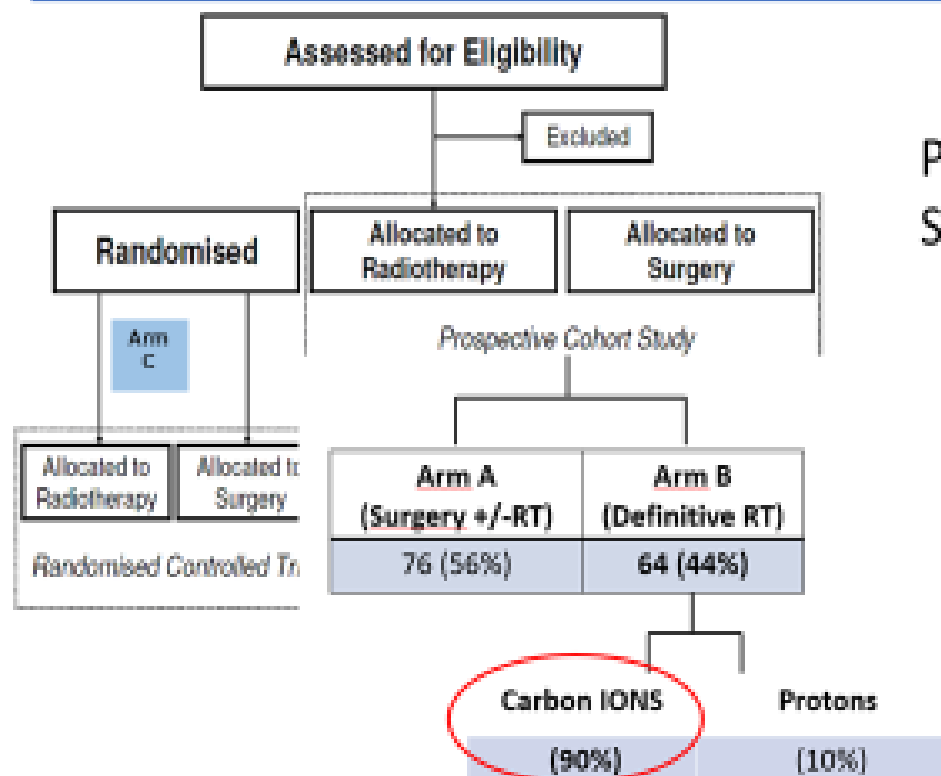


*Cobianchi et al*  
*World J Surg Oncol. 2016*

spacer

# SACRAL Chordoma: a Randomized & Observational study on surgery versus definitive radiation therapy in primary localized disease (SACRO)

## Study design

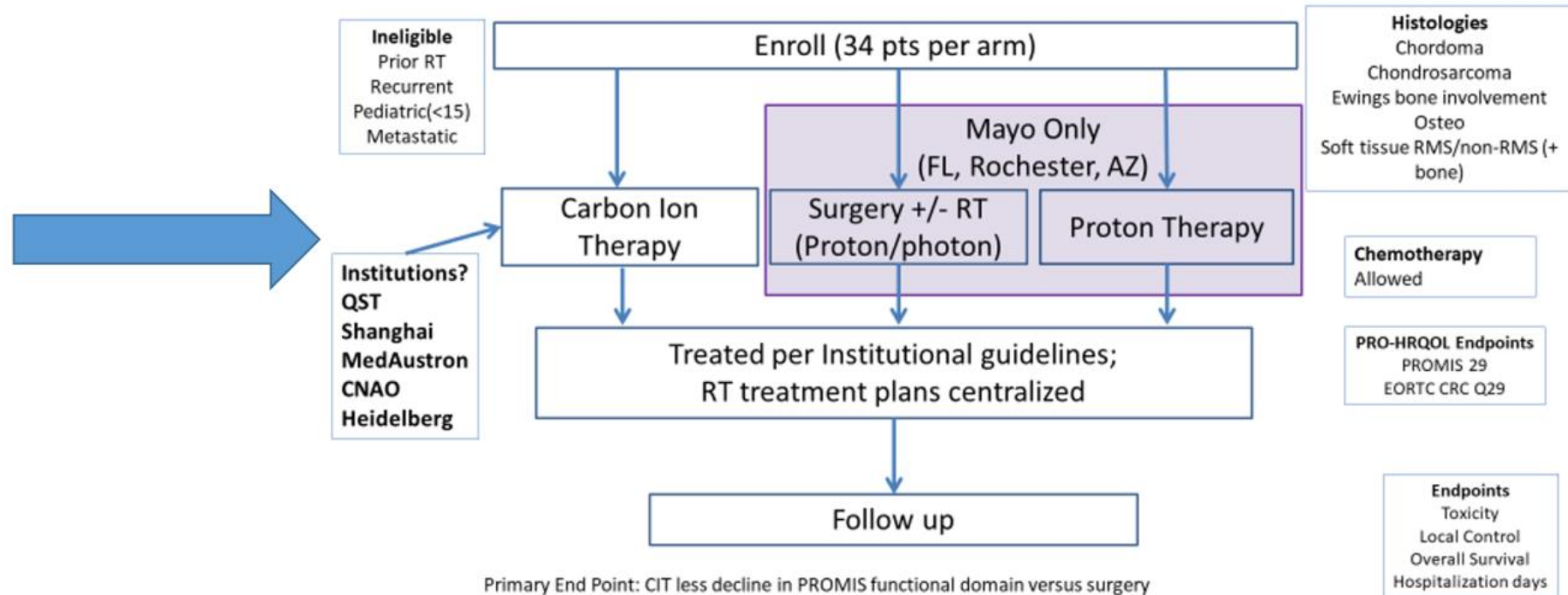


Primary endpoint: relapse-free survival.  
Secondary endpoints: OS, QoL

# PROSPER Study:

## A Comparative Effectiveness Trial of Carbon Ion Therapy, Surgery, and Proton Therapy for Pelvic Sarcomas involving the Bone

### Pragmatic prospective trial of CIT versus surgery or proton therapy for pelvic sarcomas



**Primary End Point: CIT less decline in PROMIS functional domain versus surgery**

**2<sup>nd</sup> End Point: Proton vs Carbon ion alone: 3 yr freedom from pelvic recurrence**

# CONCLUSIONS

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- ❑ Better treatment strategy for skull base and mobile spine: maximal safe resection or separation surgery from critical structures based on shared strategy followed by High Dose Particle Therapy
- ❑ Definitive high dose CIRT could be a favorable strategy with acceptable toxicity for sacral chordoma where surgery is expected to be disabling.
- ❑ Well dose coverage is important for LC improvement
- ❑ Work in progress the optimization radiobiological model

**Multidisciplinary discussion with specialized team is mandatory for sarcoma patients**

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*Working together makes difference*

*Thank you !*

