HITRI plus
Heavy Ion Therapy Research Integration

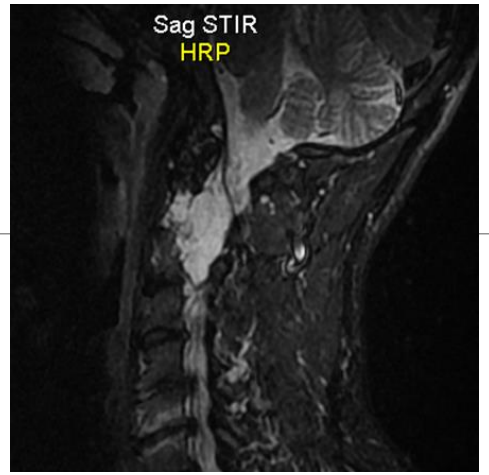
Chordomas and Chondrosarcomas: spine and sacrum

MARIA ROSARIA FIORE

FONDAZIONE CNAO, PAVIA

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

Spine chordoma and chondrosarcoma



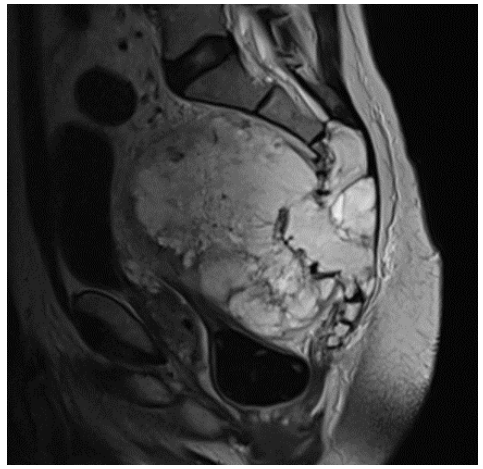
Most frequent sites is **sacrum** (50%), followed by mobile **spine** (about 20%)

Common characterisctics with skull base:

Locally aggressive growth pattern

High local recurrence rate

Peculiar aspect is the proximity to structures deputed to relevant functions …**spinal cord …bowel….kidney**



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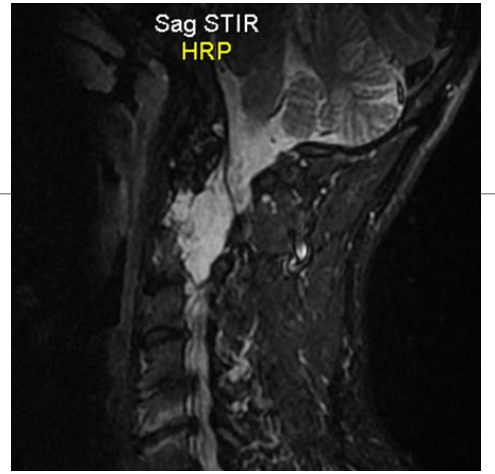
Spine chordoma and chondrosarcoma

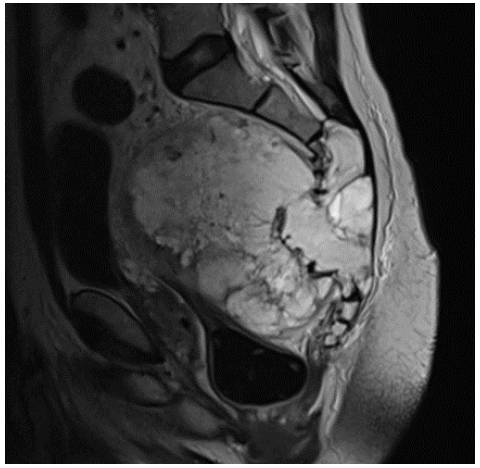
Surgery is the main therapy

En bloc resection improve both local recurrence and disease free survival in spine chordoma and chondrosarcoma.

The anatomical region and typical presentation with large mass makes difficult the surgery with wide margin

Radiotherapy gained a rule in a therapeutic strategy, when incomplete resection or an intralesional margin are expected





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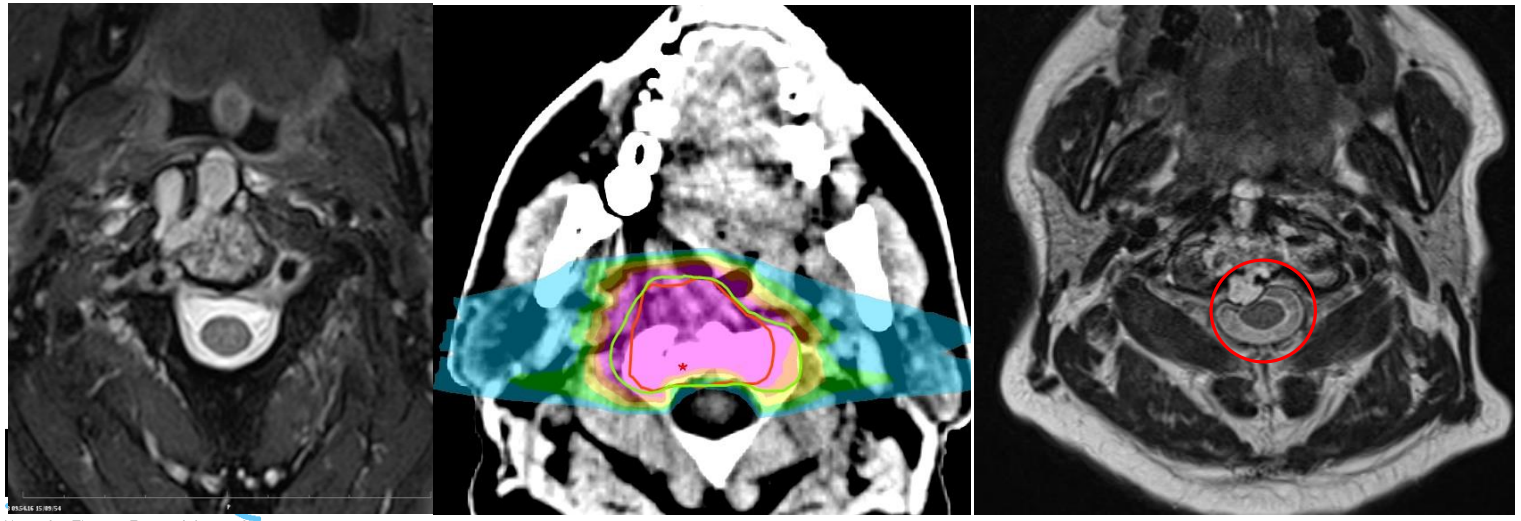
Spine chordoma and chondrosarcoma

Which kind of radiotherapy for tumor …..

Well konwn radioresistant tumors

High dose indicated

High dose required are limited by dose-limiting structures (spinal cord, bowel)



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Radiotherapy

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2023
Bone Cancer

NCCN Guidelines Index
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Discussion

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 protons, 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.

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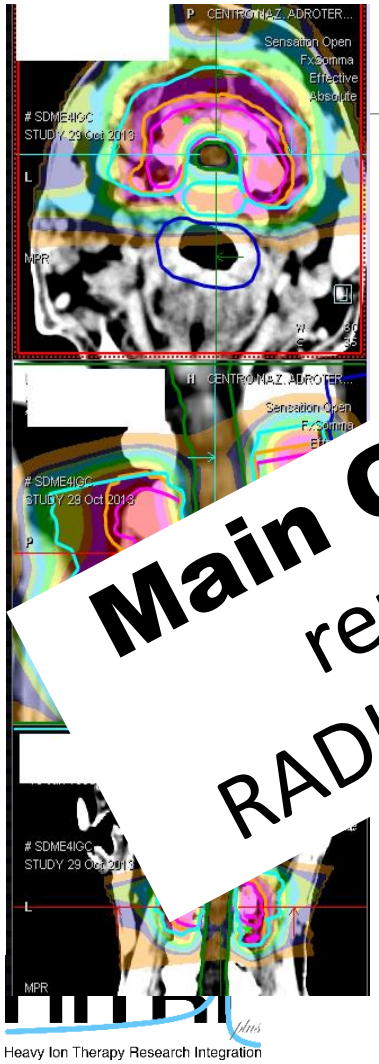
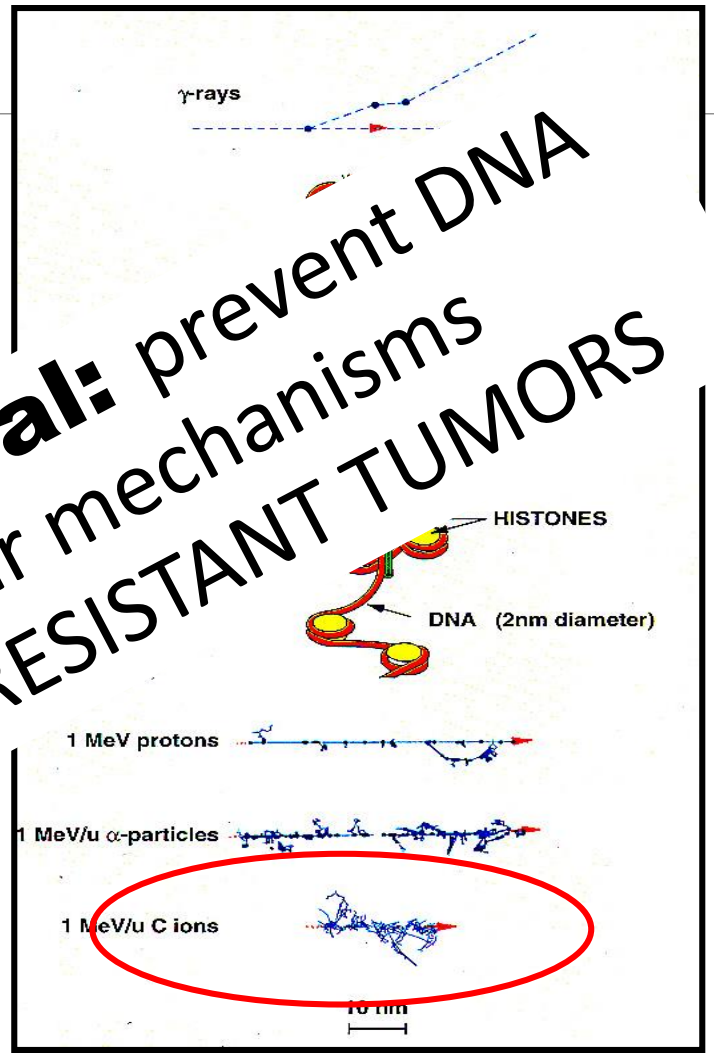
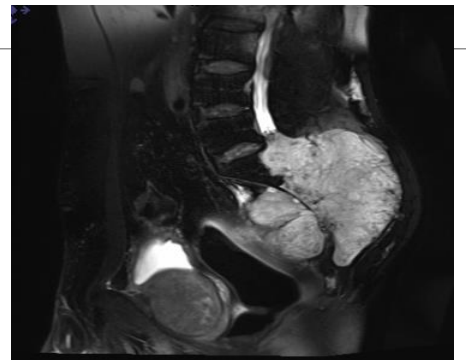
Carbon ions:
Dosimetric and radiobiological properties

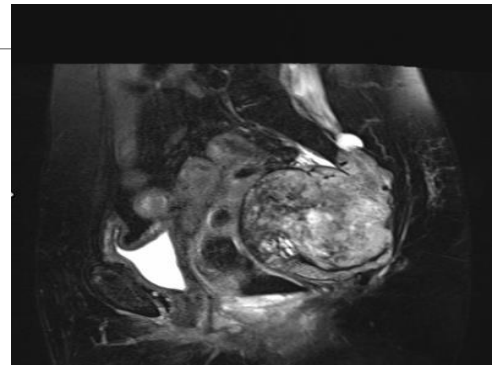


Heavy Ion Therapy Research Integration

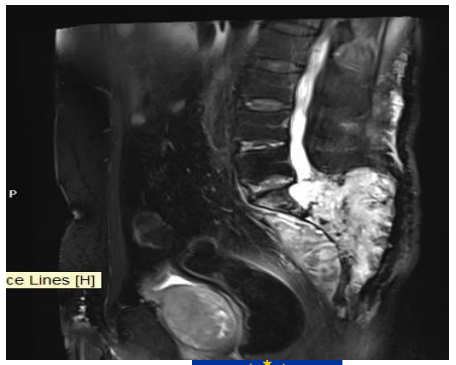


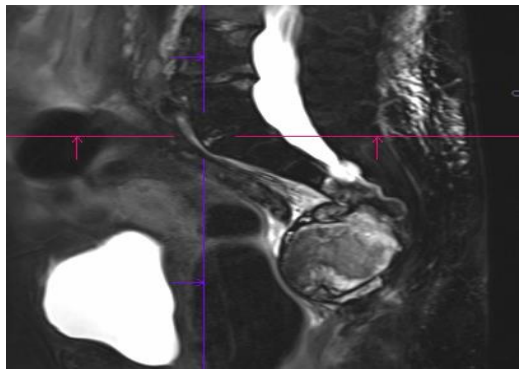
Main Goal: prevent DNA repair mechanisms RADIORESISTANT TUMORS





1y after CIRT





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Carbon Ion Radiotherapy (CIRT)

CIRT: first treatments in 1994 in Japan for

unresectable bone sarcoma

To date still limited number of reports on the clinical outcomes of C-ion RT for bone sarcoma:

Few center available for CIRT in clinical practice

Rarity of histologies

Lack of homogeneity of data

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Particle Therapy Co-Operative Group

An organisation for those interested in proton, light ion and heavy charged particle radiotherapy

You are here: Home » Facilities in Operation

Particle therapy facilities in clinical operation (last update: (Januar 2023)

Information about technical equipment.

COUNTRY	PARTICLE	BEAM DIRECTIONS	START
Japan, Chiba	C-ion	fixed beams, **1 gantry**	1994
Japan, Hyogo	C-ion	fixed beams	2002
Germany HIT, Heidelberg	C-ion	fixed beams, **1 gantry**	2009
Japan, Gumna	C-ion	fixed beams	2010
Italy, Pavia	C-ion	fixed beams	2012
Japan, Tosu	C-ion	fixed beams	2013
China, Shanghai	C-ion	fixed beams	2014
Germany, Marburg	C-ion	fixed beams	2015
Japan, Yokohama	C-ion	fixed beams	2015
Japan, Osaka	C-ion	fixed beams	2018
Austria, Wiener Neustadt	C-ion	fixed beams	2019
China, Gnasu	C-ion	fixed beams	2019
Japan, Yamagata	C-ion	fixed beams **1 gantry**	2021
Taiwan, Taipei	C-ion	fixed beams	2022

C-ion facilities in clinical operation 14

Versus

Proton facilities in clinical operation >100

Heavy Ion T

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Carbon ion series

	Patients (n)	Histology	Mean dose Gy(RBE)	LC rates	OS rates	Toxicity >G3 (n)
Matsumoto 2013	47: 35 unresect. 12 recurrence	OS (13), **CS (13)** **Chord (9)** Various(20)	64-70,4	79% (5y)	52% (5y)	6 pts: 5 skin ulceration 1 myelitis
Imai 2016	188 unresect	**Chordoma Sacrum**	67,2-70,4	77% (5y)	81% (5y)	15 pts: Sciatic neurophaty
Imai 2017	73 unresect.	**CS pelvis**	64-73,6	53% (5y)	34% (5y)	8 pts: 3 skin reaction 5 fractures
Shiba 2021	53: 39 Unresect 14 Surg R2	**Chord (32), CS (8),** OS (9), various	70,4	79,7% (3y)	69.8% (3y)	3 pts fractures
Aoki 2022	19 cervical unresect.	**chordoma**	60,8	75.2 (5y)	68.4% (5y)	6 pts: 5 fractures 1 myelitis

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Common aspects

High LC and OS, low toxicity

Limiting dose : spinal cord/bowel

Most of the marginal recurrences develop adjacent to the spinal cord or bowel due to the lower radiation doses to this area

Common significant prognostic factors:

Larger volume associated with lower LC

Higher total dose were significantly associated with better LC and OS.

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Chondrosarcoma pelvis

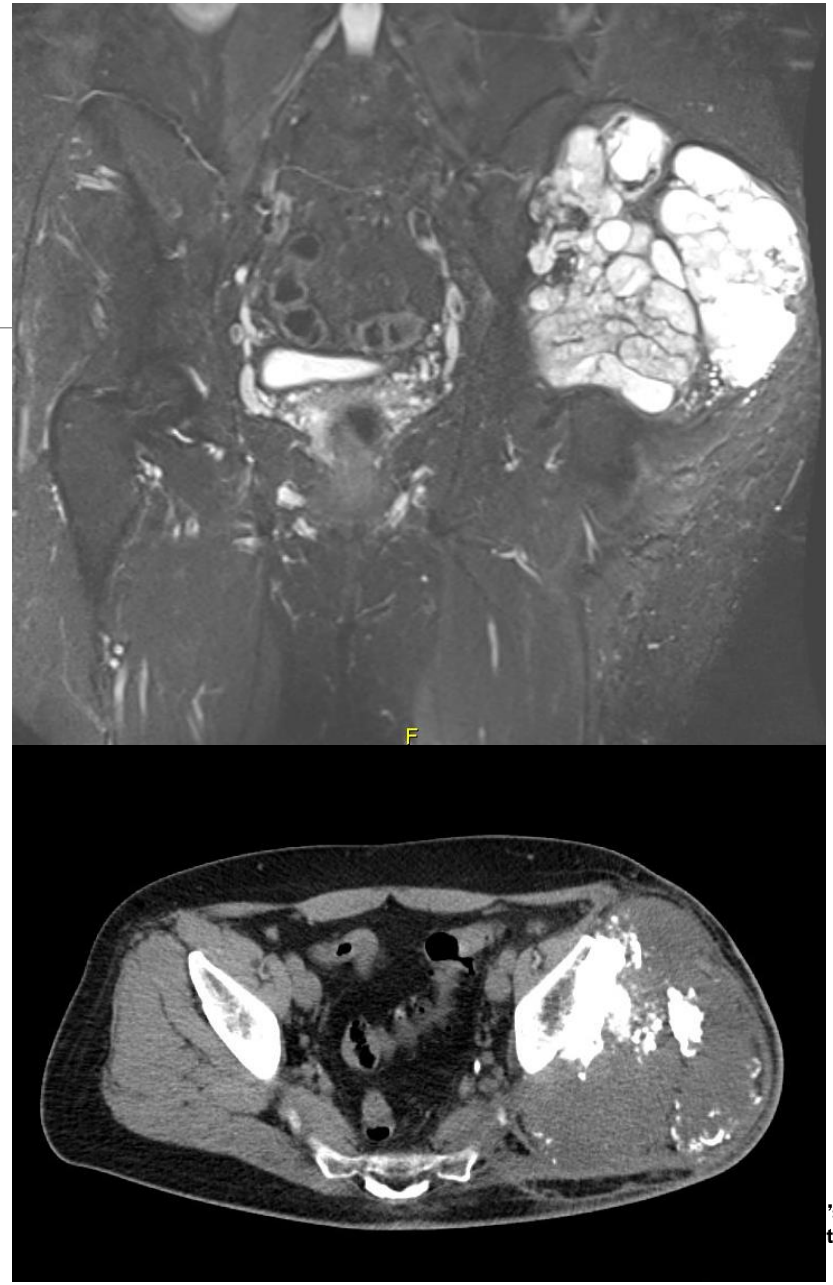
poor prognosis than others site

Delay in diagnosis

Advanced stage with a large tumor size

Difficulty in achieving adequate surgical margins

More aggressive sub-type (e.g.de-differentiated)



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Anticancer Research 2017

Clinical Efficacy of Carbon Ion Radiotherapy for Unresectable Chondrosarcomas

REIKO IMAI[1], TADASHI KAMADA[1], NOBUHITO ARAKI[2] and
THE WORKING GROUP FOR BONE and SOFT-TISSUE SARCOMAS

Table I. *Patient characteristics (73 patients with 75 lesions).*

Characteristic	Value
Median age (range), years	57 (17-77)
Male:female, no. of patients	42:31
Median tumor size (range), cm^3	471(25-2900)
Tumor type, no. of lesions	
Primary tumor with no prior surgery	55
Recurrent tumor after resection	17
Metastatic tumor	3
Irradiation site, no. of lesions	
Spine (cervix/thorax/lumber/sacrum)	26 (3/5/4/14)
Pelvis (iliac/pubic/ischium)	38 (36/1/1)
Paraspinal region	1*
Rib	6
Scapula	2
Sternum	1
Femur	1
Histology, no. of patients	
Conventional chondrosarcoma	69
Grade 1	14
Grade 2	5 1
Grade 3	4
Dedifferentiated	4
Total irradiated dose [Gy(RBE) in 16 fractions], no. of lesions	
64.0	4
70.4	69
73.6	2

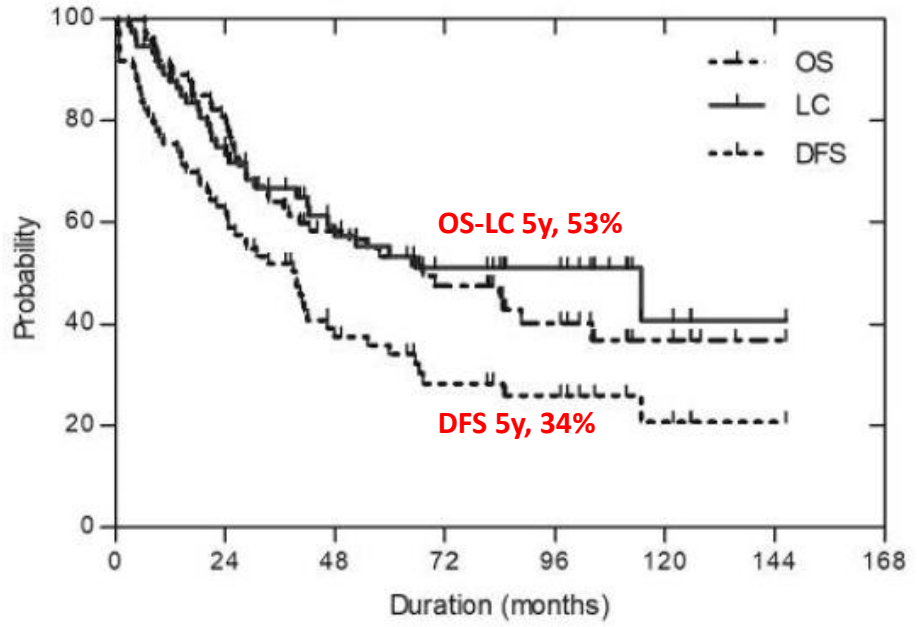

Figure 2. *Local control (LC), overall survival (OS), and disease-free survival (DFS) rates for the whole group of 73 patients with 75 chondrosarcomas. The 5-year rates were 53%, 53%, and 34%, respectively.*

Clinical Efficacy of Carbon Ion Radiotherapy for Unresectable Chondrosarcomas

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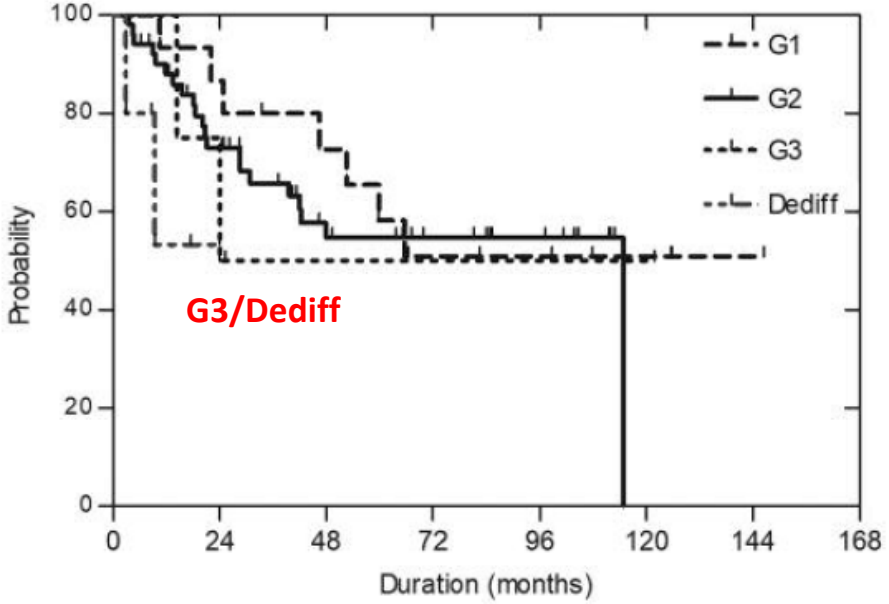

Figure 3. *Local control rates according to histology. Of 15 lesions of G1 chondrosarcoma, the 5-year local control (LC) rate was 58%. Of 51 lesions of G2 chondrosarcoma, the 5-year LC rate was 55%. Of four lesions of G3 chondrosarcoma, three had local recurrence before death, and of five lesions of de-differentiated chondrosarcoma two had local recurrence before death.*

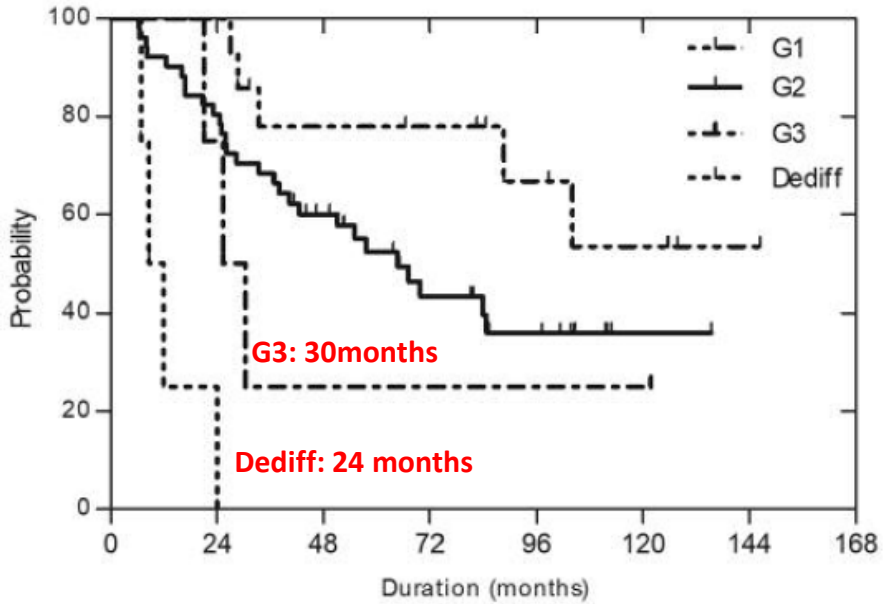

Figure 5. *Overall survival rates according to histology. Of 14 patients with G1 chondrosarcoma, the 5-year survival rate was 77.9%. Of 51 patients with G2 chondrosarcoma, the 5-year survival rate was 52.9%. Of four patients with G3 chondrosarcoma, three died within 30 months, and all four patients with dedifferentiated chondrosarcoma died within 24 months.*

Clinical Efficacy of Carbon Ion Radiotherapy for Unresectable Chondrosarcomas

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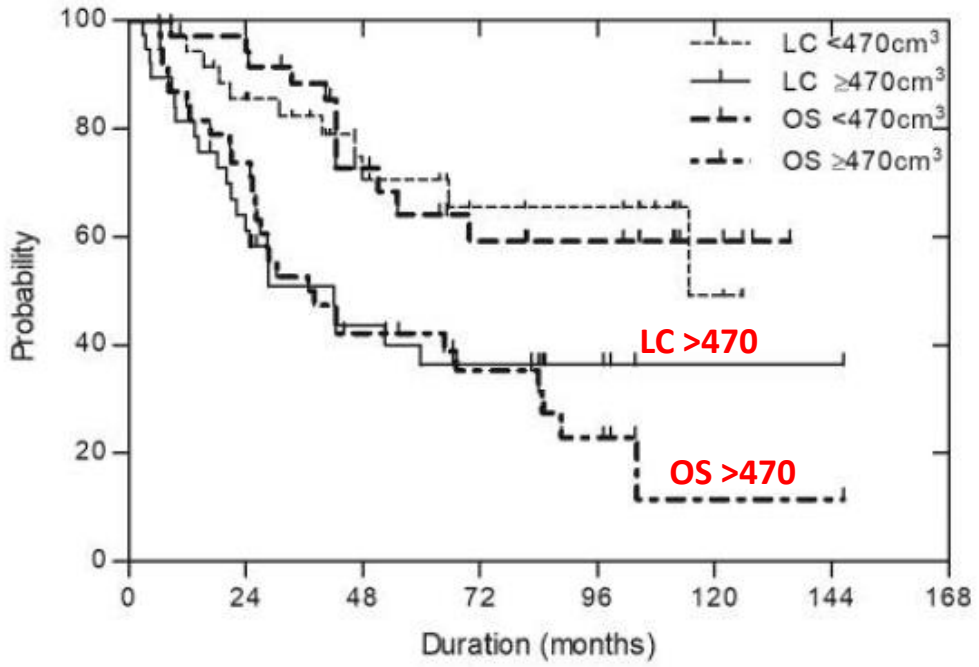


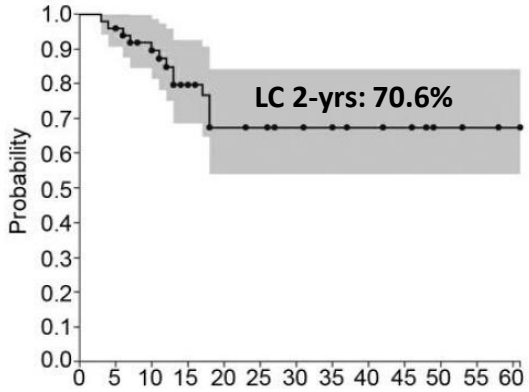
Figure 4. *Local control (LC) and overall survival (OS) rates according to tumor size. The 73 patients and 75 lesions were divided into two groups according to tumor size: above or below the median tumor volume of 470 cm^3. The large tumor group consisted of 38 lesions in 38 patients and the small tumor group of 37 lesions in 35 patients. There were significant differences in LC and OS rates (at p=0.009 and p=0.0008, respectively) between the two groups as determined by univariate analysis.*

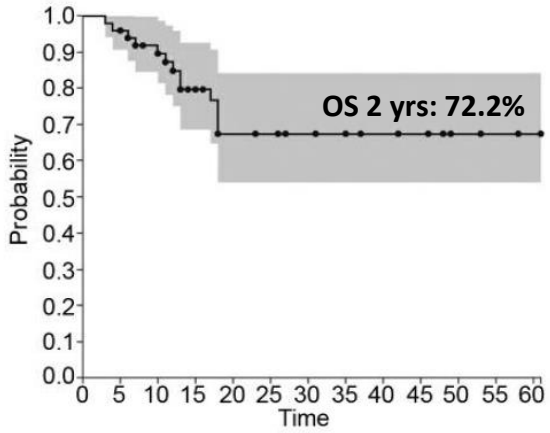
CNAO experience

Outcome and Toxicity of Carbon Ion Radiotherapy for Axial Bone and Soft Tissue Sarcomas

Anticancer Research (2020)

Patients=54	N (range or %)
M:F	32:22
Age	50 (19-79)
Histologic subtypes	
Osteosarcoma	13 (24%)
Solitary fibrous tumor	3 (6%)
Chondrosarcoma	21 (39%)
Other	17 (31%)
Grading	
G1	11 (20%)
G2	12 (22%)
G3	23 (43%)
Gx	8 (15%)
Disease presentation	
De novo	41 (76%)
Recurrent	13 (24%)
Tumor site	
Pelvis	27 (50%)
Cervical spine	8 (15%)
Thoracic spine + Chest wall	13 (24%)
Lumbar spine	6 (11%)
Surgery	
Unresectable	37 (68%)
Subtotal resection	17 (32%)
Chemotherapy Pre-RT	22 (40%)
Median total dose	73.6 Gy RBE (70.4-76.8)





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Spine chordoma preliminary outcome @CNAO

Unpublished data

40 patients:

- 34 (85%) CIRT after R2 surgery
- 6 (15%) unresectable: definitive CIRT
- Total dose range was 66-70.4 GyRBE
- Follow-up: median 35 months (12 – 85)

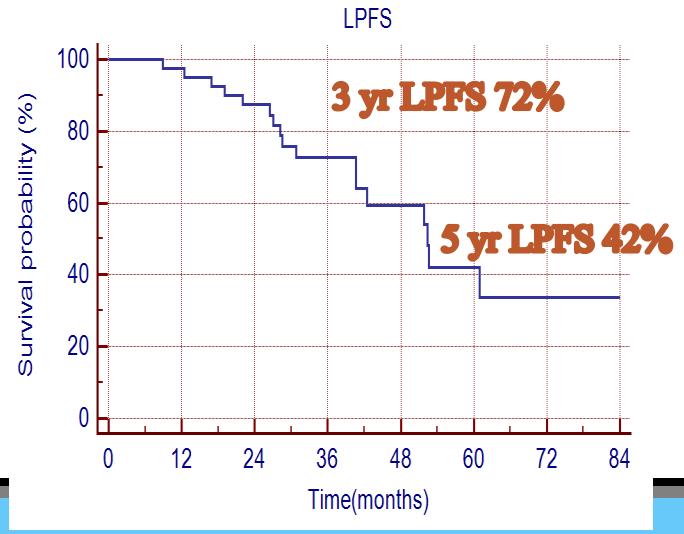
Median TTR 26.4 months (12.4- 84.2)

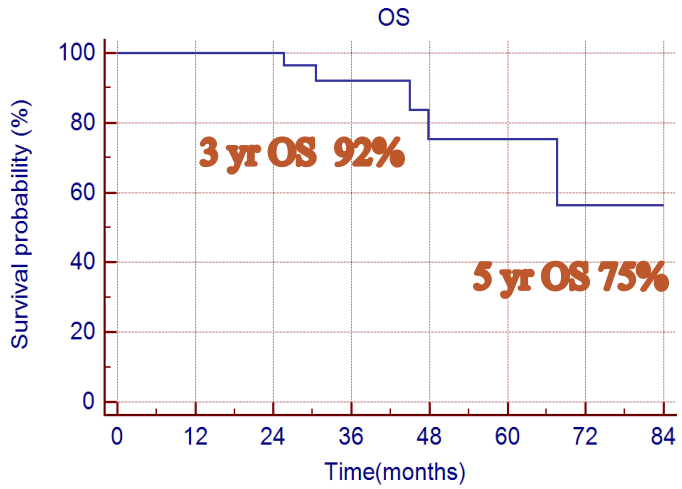
Late toxicity

G1-G2 neuropathy 20 (50%) pts

G2 dysphagia 2 (4%)

No G3





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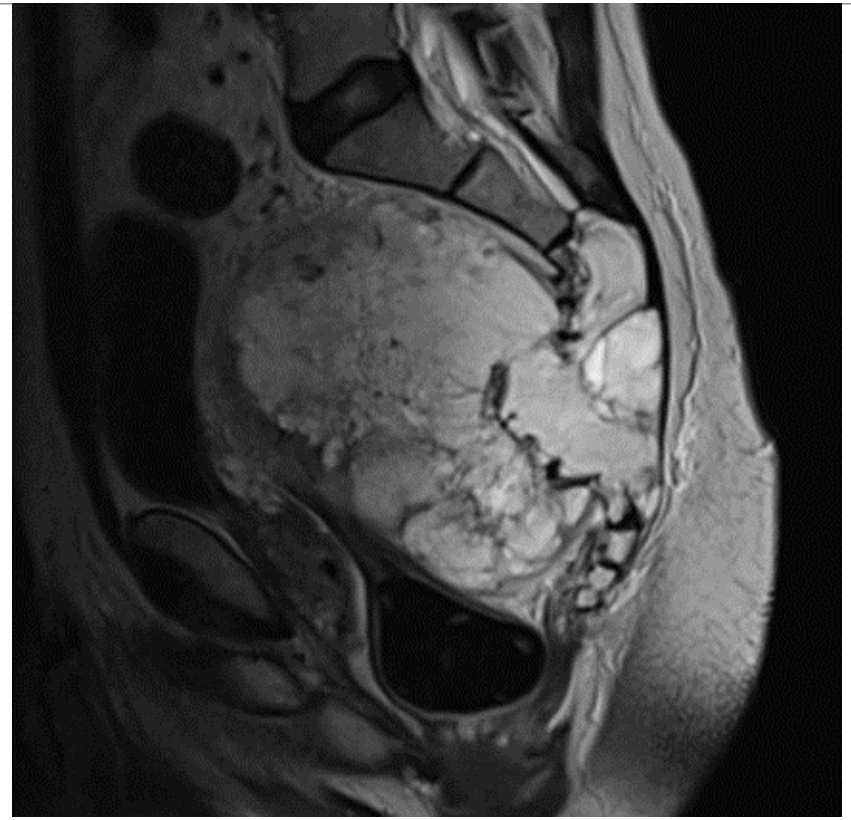
Sacral chordoma

Still a challenging treatment for surgeons and radiation oncologist

Typical presentation with large mass strictly close to the OaR (rectum, nerve roots, cauda….)

Radioresistant tumor: poorly responds to traditional radiotherapy



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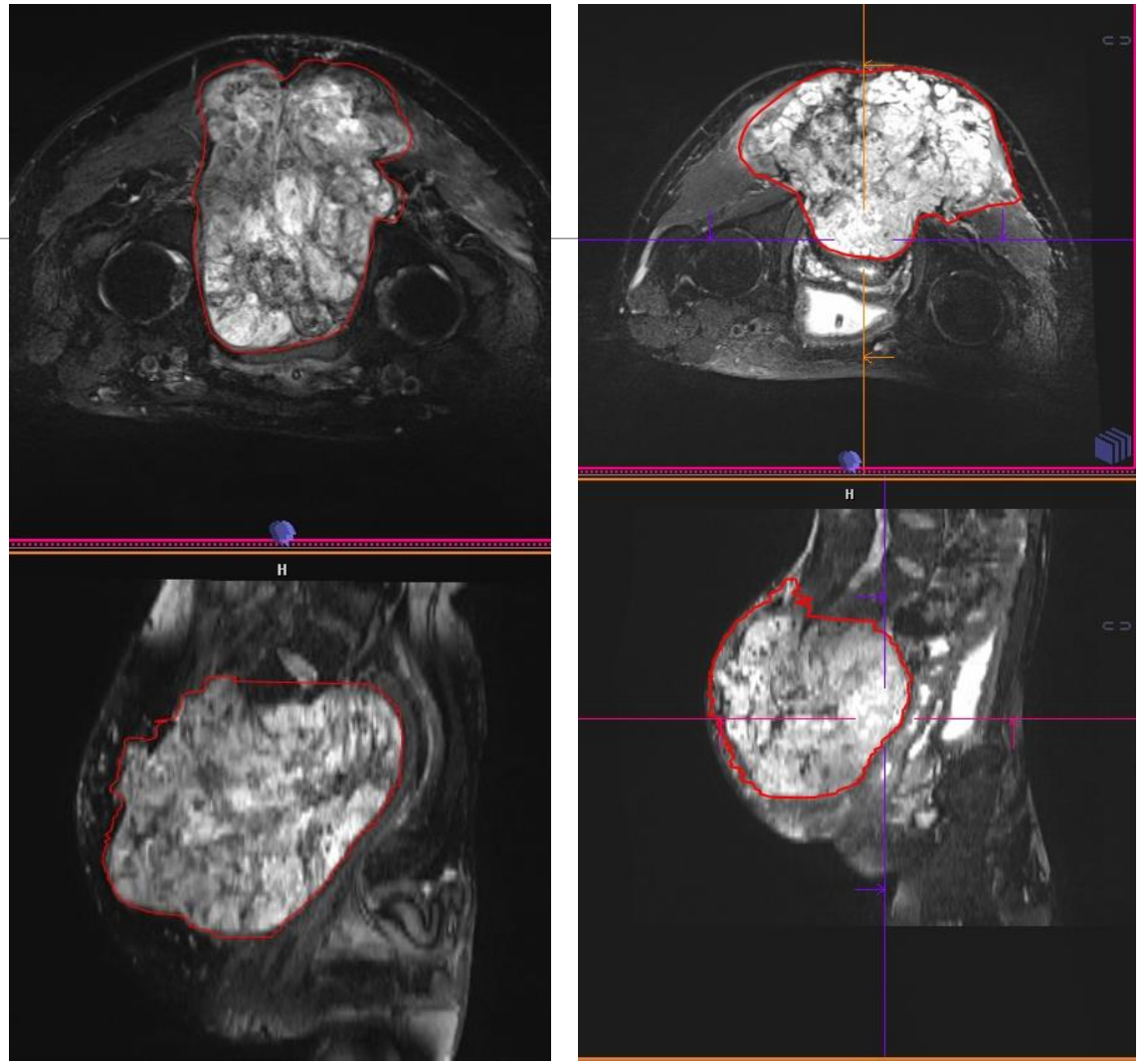
Sacral chordoma

Surgery with wide margins still remains the main therapy

What about when wide margins are not achievable….?



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Local and Distant Recurrence in Resected Sacral Chordomas: A Systematic Review and Pooled Cohort Analysis

Global Spine Journal
1-11

DOI: 10.1177/2192568217741114
journals.sagepub.com/home/gsj
SAGE

Daniel Kerekes, BS[1,*], C. Rory Goodwin, MD, PhD[2,*], A. Karim Ahmed, BS[1,*], Jorrit-Jan Verlaan, MD, PhD[3], Chetan Bettegowda, MD, PhD[1], Nancy Abu-Bonsrah, MD[1], and Daniel M. Sciubba, MD[1]

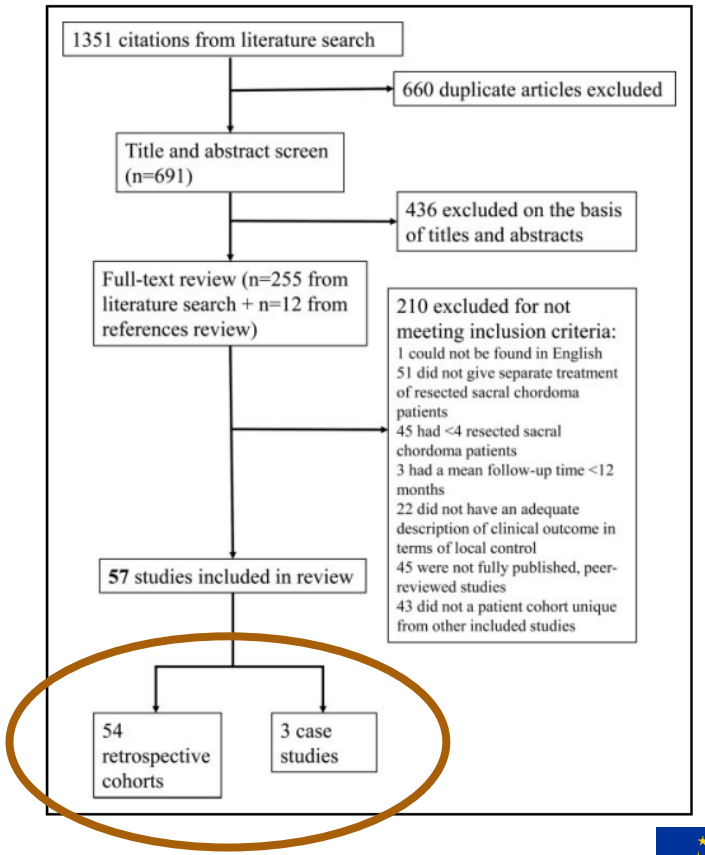

Table 1. Characteristics of Patients in Pooled Cohort[a].

Characteristic	% (n) of Patients
Total patients, n	1235
Sex, n = 1081	
Male	62.0% (670)
Female	38.0% (411)
Ratio (male to female)	1.6
Age, n = 800	
Mean	56.1 ± 5.4
Range	13-85
Previous sacral surgery, n = 601	20.5% (123)
Symptoms at presentation	
Pain, n = 308	86.7% (267)
Mass/swelling, n = 177	50.3% (89)
Bowel dysfunction, n = 171	27.5% (47)
Bladder dysfunction, n = 180	18.9% (34)
Neuropathic pain, n = 124	16.1% (20)
Neurologic symptoms: unspecified or other, n ==190	21.1% (40)
Follow-up, n = 956	
Mean (months)	72.0 ± 27.5
Range (years)	0-34

Abbreviation: n, number of patients at risk (in studies reporting characteristic).
[a]A total of 1235 surgical sacral chordoma patients were included. Among the patients for whom gender was known, 62% were male, giving a male-to-female ratio of 1.6:1. The mean age at diagnosis of sacral chordoma was 56.1 ± 5.4 (range 13-85).

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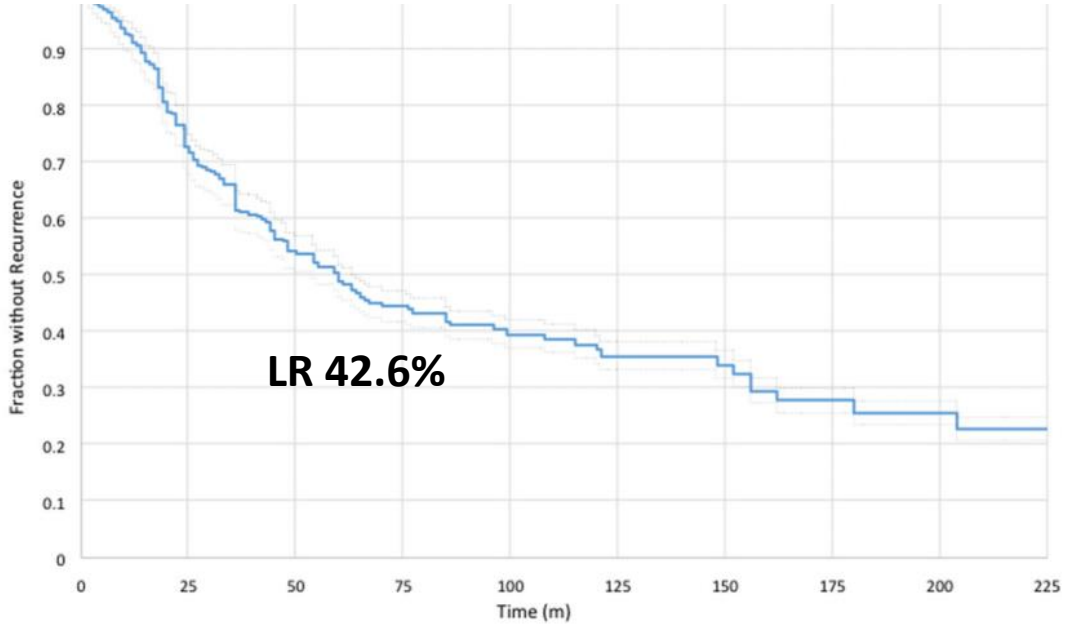

349 pts specific recurrence data available

Median FUP 59 months

Variable	Local Recurrence Event % (LR/Total)	P	Time to LR (Months)	P	Distant Recurrence Event % (DR/Total)	P	Time to DR (Months)	P
Surgical margin								
Wide	25.6% (80/313)	<.0001	47	.1034	16.4% (23/140)	<.0001	66	.6724
Marginal	44.4% (59/133)		37		40.0% (24/60)		56	
Wide-contaminated	64.7% (11/17)		44		75.0% (3/4)		39	
Intralesional	57.0% (73/128)		35		52.5% (32/61)		52	

[a]Patients who were treated with a surgery with wide margins had very significantly lower rates of both local and distant recurrence compared with patients with any other surgical margin classification.

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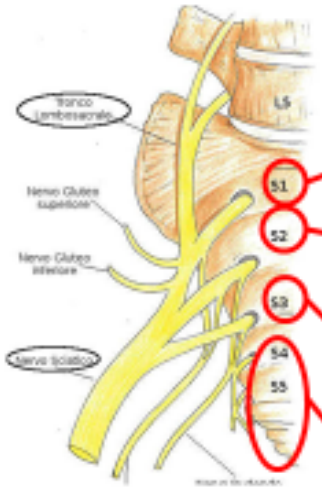
ıe European Union's Horizon 2020
research and innovation programme under grant agreement No 101008548

CHORDOMA FOUNDATION

2018

Vertebra sacrale	Trattamento raccomandato	Effetti collaterali dell'intervento chirurgico
S1	La radioterapia rappresenta un'alternativa consigliabile alla chirurgia	Gli effetti collaterali sono molto gravi
S2	In base alle preferenze del paziente e a considerazioni riguardanti la qualità della vita	Sono probabili gravi effetti collaterali
S3	Intervento chirurgico	Se le radici nervose di S2 non sono danneggiate, circa il 40 percento delle persone si riprende da eventuali effetti collaterali
S4 o inferiore	Intervento chirurgico	È possibile preservare le funzioni più importanti

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



Permanent urinary/rectal disfunction → RT

High risk of severe sequelae → patients preference based on expected QoL

Low risk of severe sequelae,
40% of recovering possibility
Depending on S2 nerve roots
Involved → surgery

Not expectd severe sequelae → surgery

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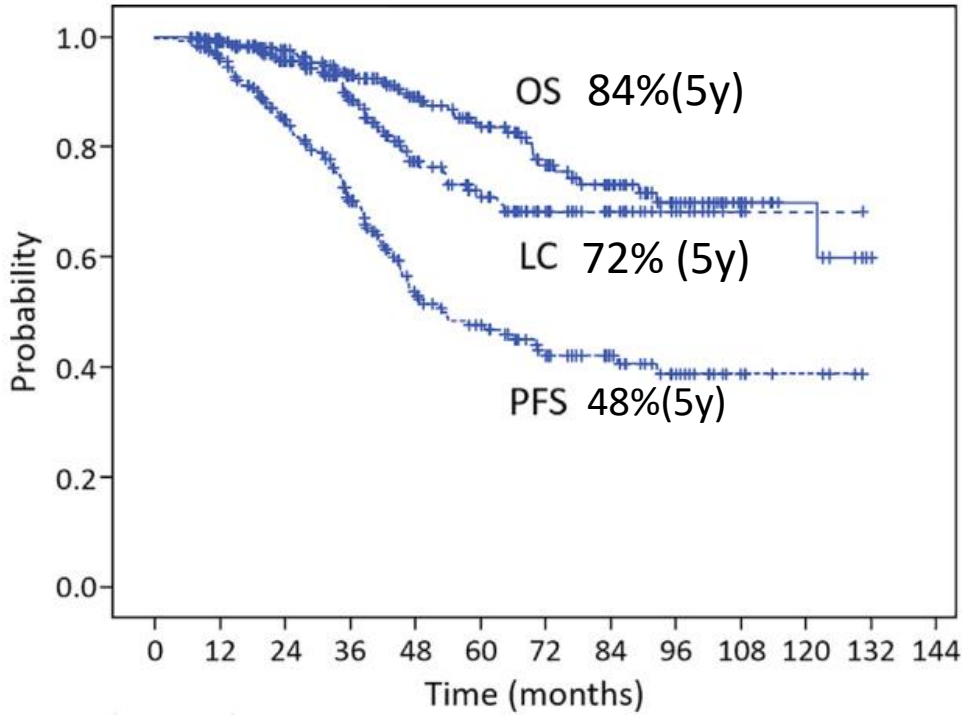
Carbon ion radiotherapy for sacral chordoma: A retrospective nationwide multicentre study in Japan ☆

Yusuke Demizu [a,b], Reiko Imai [c], Hiroki Kiyohara [d], Akira Matsunobu [e], Masahiko Okamoto [f], Tomoaki Okimoto [b], Hiroshi Tsuji [c], Tatsuya Ohno [f], Yoshiyuki Shioyama [e], Kenji Nemoto [g], Takashi Nakano [h], Tadashi Kamada [i,*], theJapan Carbon-Ion Radiation Oncology Study Group

Radiotherapy and Oncology 2021

4 CIRT centres in Japan

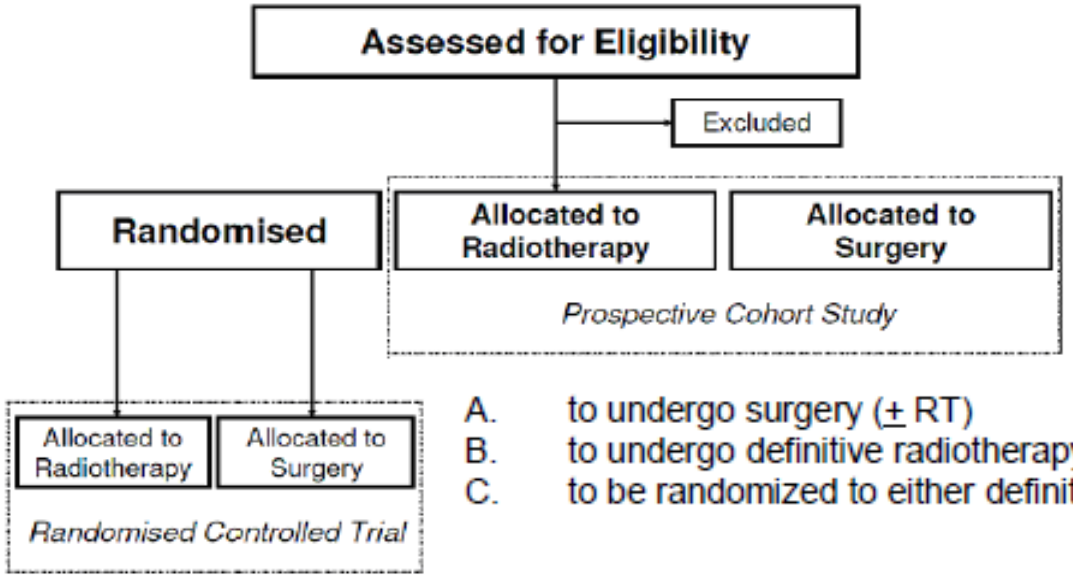
Characteristic		n = 219
Age (years), median (range) n (%)		67 (26–87)
	<67	108 (49)
	≥67	111 (51)
Sex n (%)	Male	151 (69)
	Female	68 (31)
Performance status n (%)	0	4 (2)
	1	189 (86)
	2	26 (12)
Surgery n (%)	None	211 (96)
	Postoperative recurrence	7 (3)
	Incomplete resection	1 (1)
Chemotherapy n (%)	None	219 (100)
	Yes	0 (0)
SSP or colostomy n (%)	None	188 (86)
	SSP	19 (9)
	Colostomy	12 (5)
PTV (mL) n (%)	<100	15 (7)
	100–500	143 (65)
	≥500	61 (28)
Dose-fractionation (Gy [RBE]/fr) n (%)	67.2/16	143 (65)
	70.4/16	70 (32)
	70.4/32	5 (2)
	79.2/18	1 (1)



Toxicity >G3: 13 pts

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

Schematic flow-chart



A. to undergo surgery (± RT)
B. to undergo definitive radiotherapy
C. to be randomized to either definitive radiotherapy or surgery (± RT).

From 2018 CNAO: ARM B definitive CIRT

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Sacral chordoma preliminary outcome @CNAO

From March 2013: **136 pts treated with definitive CIRT**

43 pts enrolled in international protocol from March 2018, were excluded

28 pts with FUP < 12 months were excluded

65 pts analised

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

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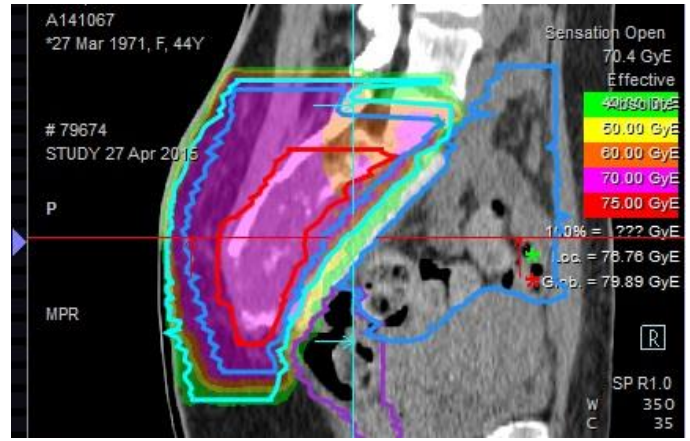
Tumors , treatments characteristics of 65 patients

Median follow-up months (range)	48 (12-115)
Median GTV ml (range)	**401,6 (10,6-2002,7)**
Anatomical Disease extension n (%)	**S1-S2 36 (55%)** S3-S4-S5 29 (44%)
Distant / loco-regional metastasis	0
Spacer n (%)	18 (28%)
Dose GyRBE (range)	70,4 (70,4-73,6) 16 Fractions



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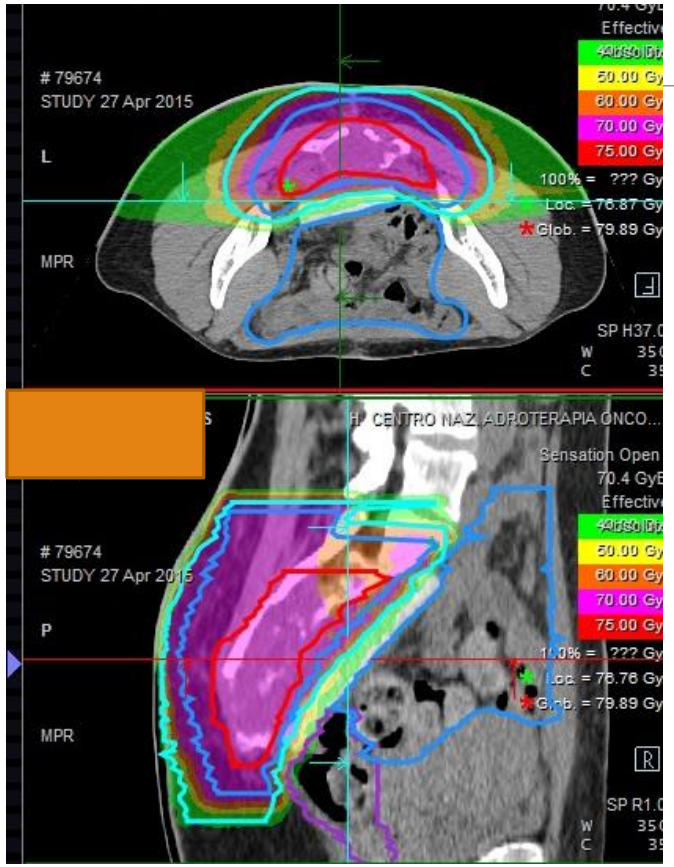
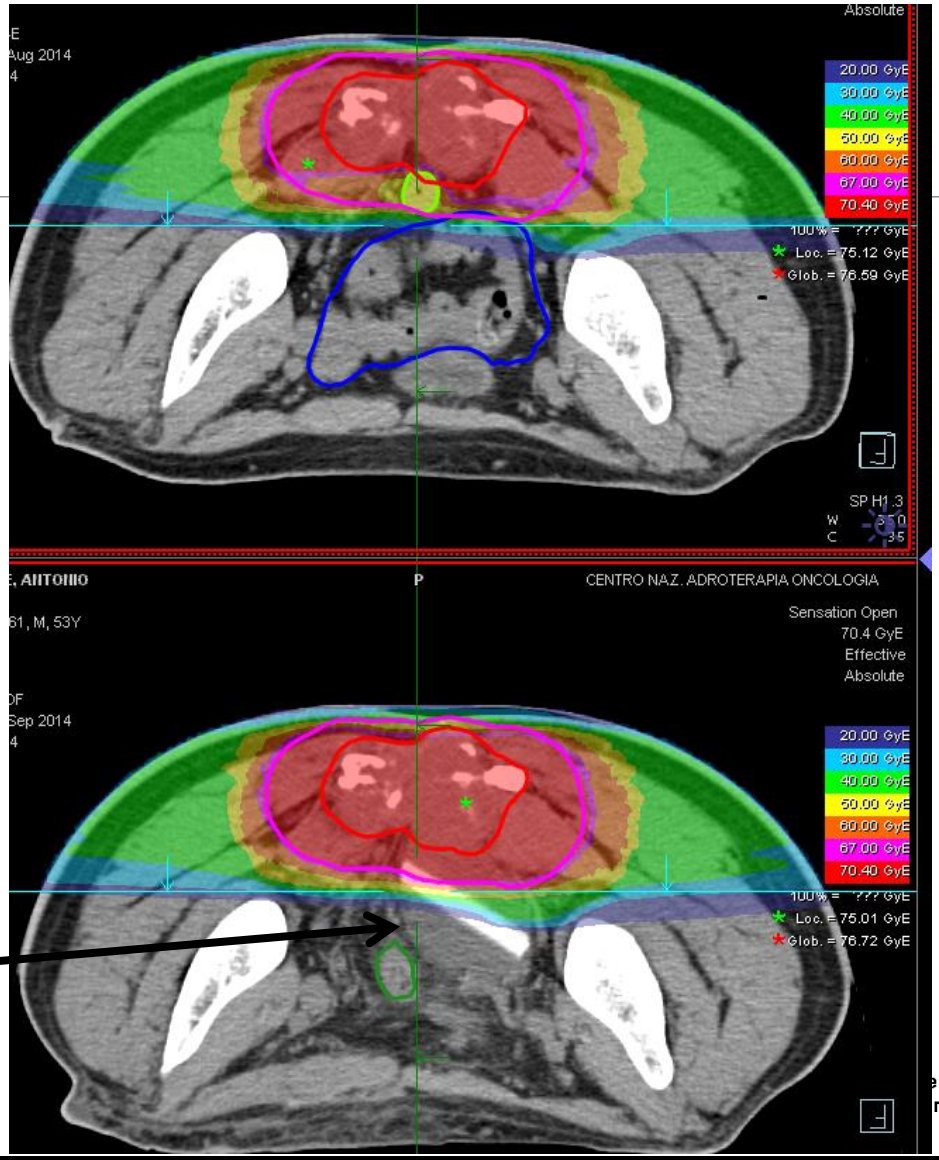
Bowel displacement
With spacer surgical implant



spacer



Cobianchi et al World J Surg Oncol. 2016

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r grant agreement No 101008548

Sacral chordoma preliminary outcome @CNAO

Outcome: 65 patients

Local control 41 pts 63%

Local progression 24 pts 36%

Median Time to Relapse
30 months [12 – 115]

Distant metastasis 8 pts 12%

- In Field 18 pts
  - **2 pts** Simultaneously lung metastasis
  - **1 pt** liver, lung, lumbar tract metastasis
- Out Field 6 pts
  - **2 pts** lung metastasis
  - **2 pt** lumbar tract metastasis

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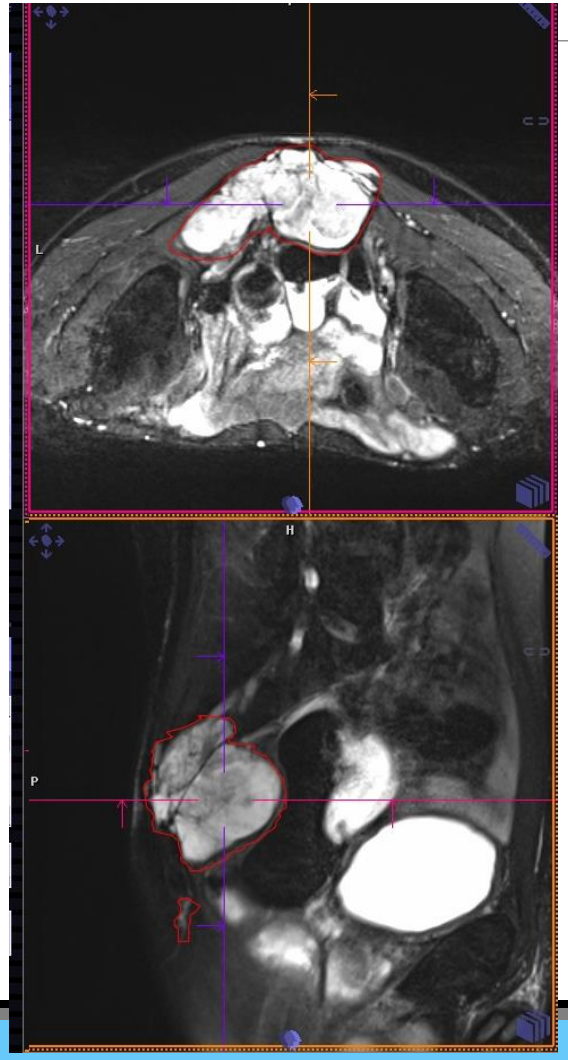
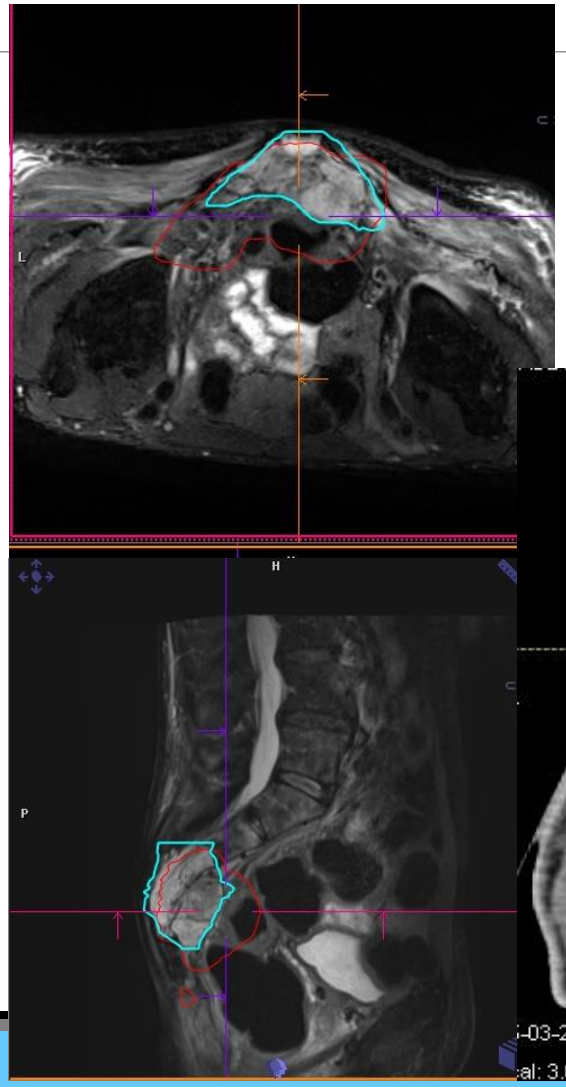
In Field relapse: pararectal site, concomitant L4, liver, lung metastasis

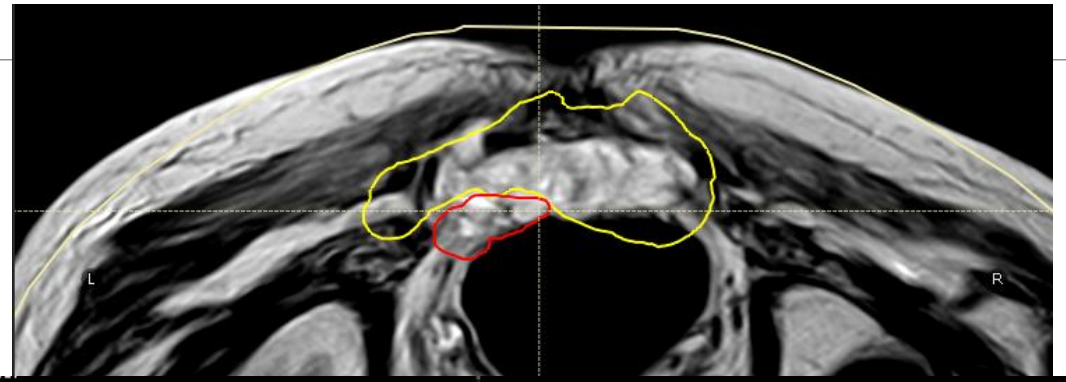
Baseline 03.2018

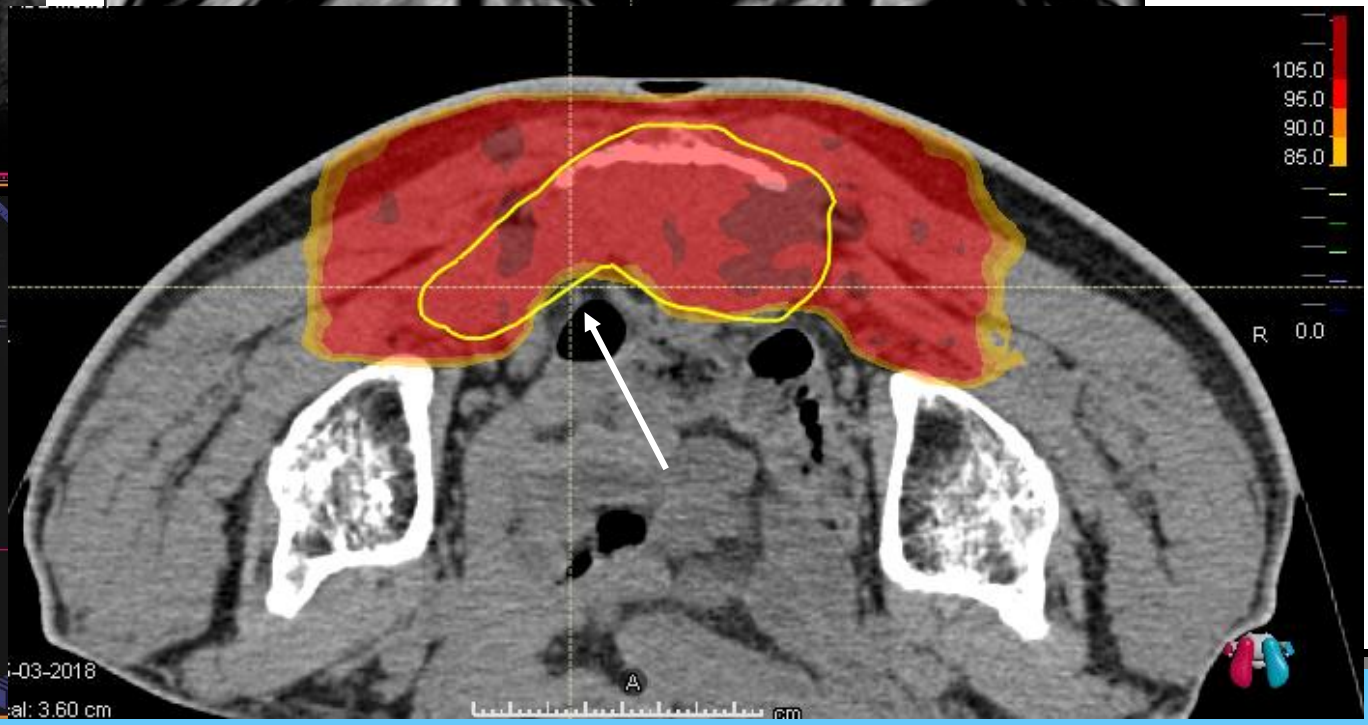


FUP 11 m, 04.2019



FUP 2 years 05.2020

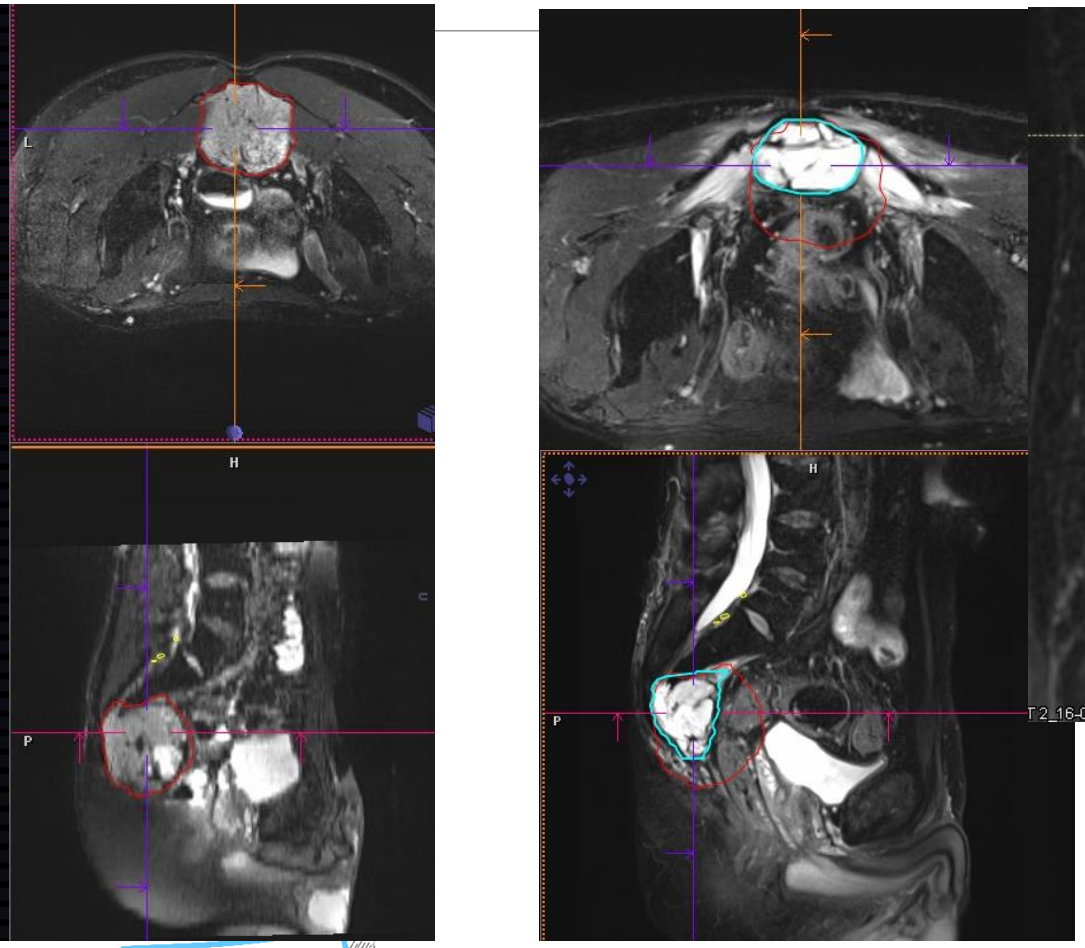




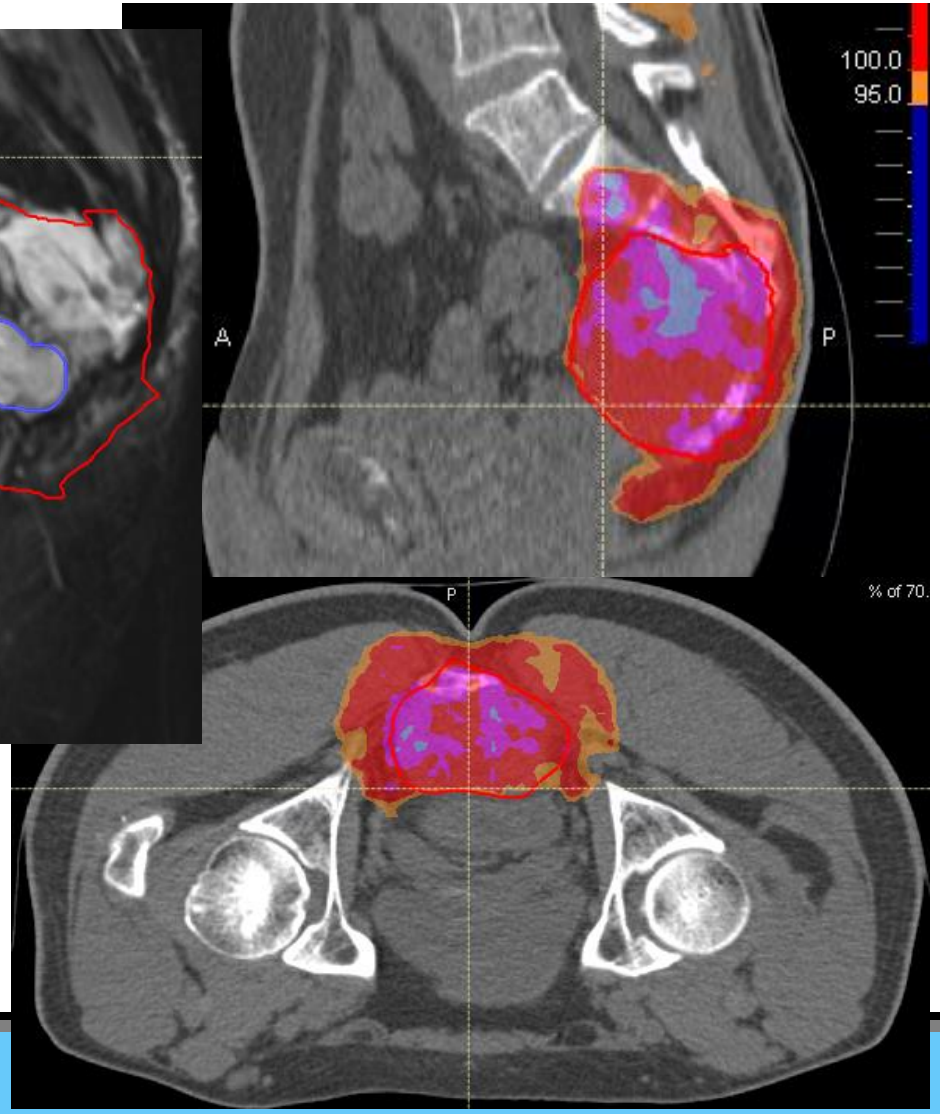
Dose
< 80%

In Field relapse : pararectal site

FUP 29 m, 08.2019
baseline 03.2017

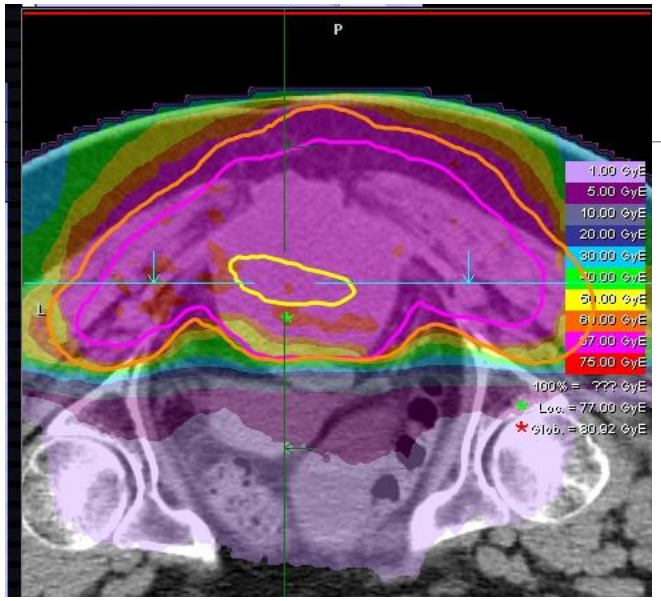


FUP 5 years, 06.2022



F, 67y
FUP 25m →LR in high dose volume

→ LET Distribution?....



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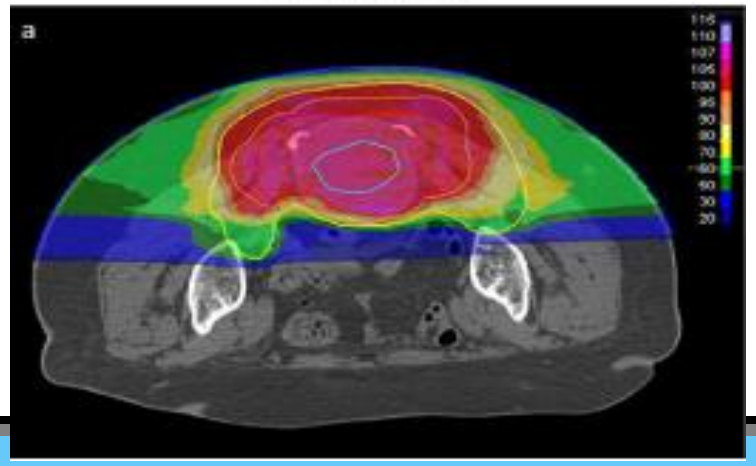
Original Article

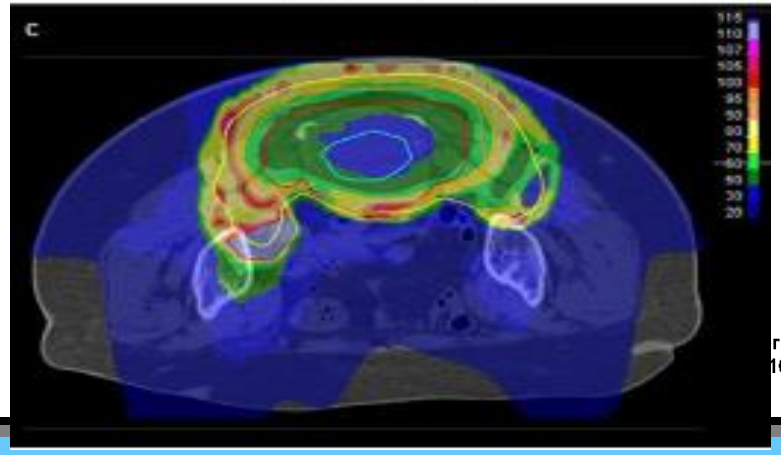
How LEM-based RBE and dose-averaged LET affected clinical outcomes of sacral chordoma patients treated with carbon ion radiotherapy

Silvia Molinelli [a,*], Giuseppe Magro [a], Andrea Mairani [b], Albina Allajbej [c], Alfredo Mirandola [a], Agnieszka Chalaszczyk [a], Sara Imparato [a], Mario Ciocca [a], Maria Rosaria Fiore [a,1], Ester Orlandi [a,1]

LEM-based D_{RBE}



Dose-averaged LET



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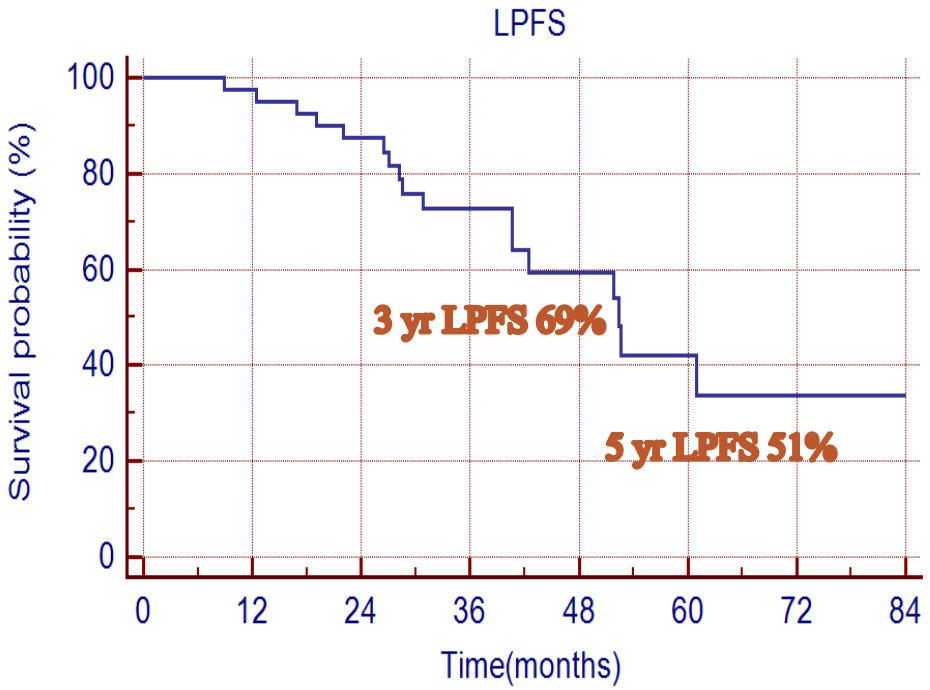
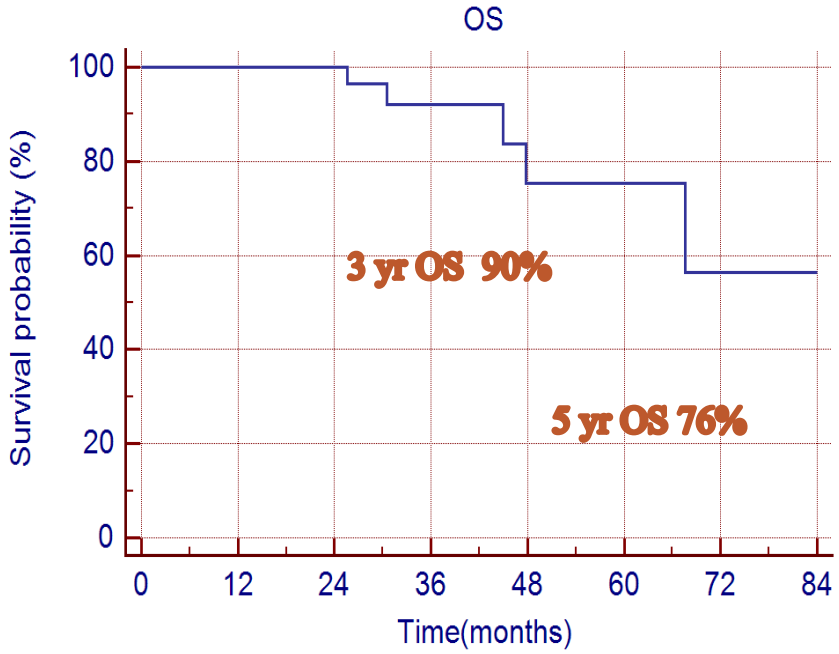
101008548

Sacral chordoma preliminary outcome @CNAO





Late toxicity > G3 7pts (11%)

	events
1	bone fractures
2	skin ulceration
3	M-S neuropathy
1	urinary retention

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CONCLUSIONS and considerations

Well dose coverage is important for LC improvement

To overcome the limits of constraints spacer placement should be planned for all pts ….not always possible for technical problem or patient refusing

Unexpected relapse in high dose/well covered area……..Work in progress the optimization of LET distribution → radiobiological model LEM *vs* MKM

Definitive high dose CIRT could be a favorable strategy with acceptable toxicity for chordoma and chondrosarcoma where surgery is expected to be disabling.

More prospective studies are required to investigate the potentiality of CIRT

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Thank you !

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