HITRI plus
Heavy Ion Therapy Research Integration

The role of proton and carbon ion therapy in the treatment of osteosarcoma

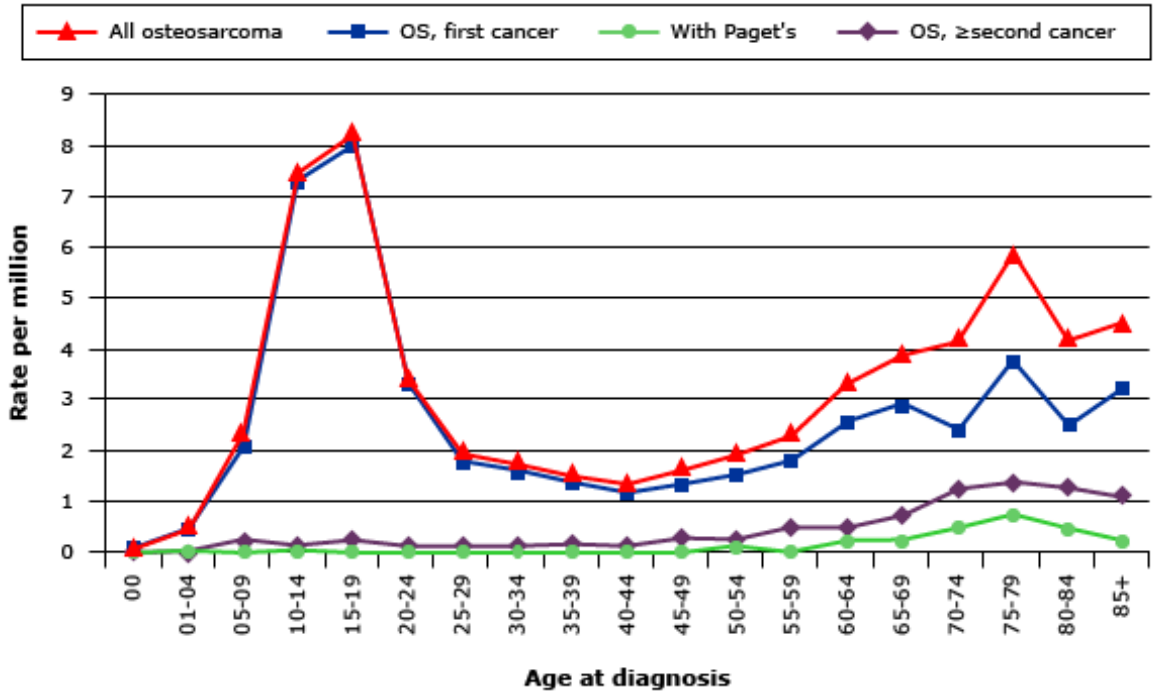
DR. KATHARINA SEIDENSAAL, 04.07.2023

HIT Heidelberger Ionenstrahl-Therapiezentrum

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

Epidemiology of Osteosarcoma

- 1% of all newly diagosed cancers
- 3% of childhood cancers
- Most common primary bone tumor
- 56% of all bone cancer cases under the age of 20
- Children, adolescent and young adults aged 13-16 and over the age of 65



Mirabello, Cancer 2009

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

Risk factors for osteosarcoma

- Genetic conditions (18-28%): Hereditary retinoblastoma (*RB1*), Li-Fraumeni syndrom (*TP53*), Rothmund-Thomson syndrome (RTS), among others
- Radiation therapy: Most common secondary malignant neoplasm, 3% of osteosarcoma
- Chemotherapy (alkylating agents)
- Paget disease

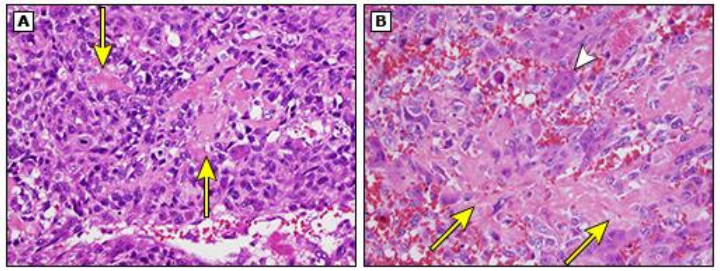
HITRI
Heavy Ion Therapy Research Integration

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

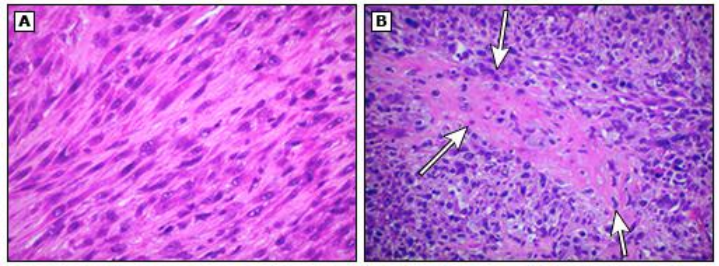
Histologic classification of osteosarcoma (WHO 2020)

- Low-grade central osteosarcoma
- Osteosarcoma NOS:
  - conventional osteosarcoma (>90%)

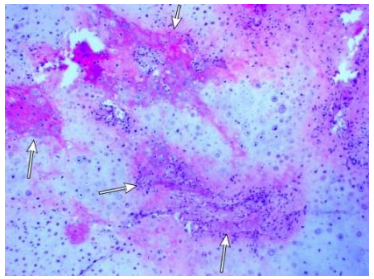
    (osteoblastic (76-80%), chondroblastic, fibroblastic)
  - Telangiectatic osteosarcoma
  - Small cell osteosarcoma
- Parosteal osteosarcoma
- Periosteal osteosarcoma
- High grade surface osteosarcoma
- Secondary osteosarcoma
- Multifocal osteosarcoma
- Craniofacial osteosarcoma



Osteoblastic OS



Fibroblastic OS


Chondroblastic OS

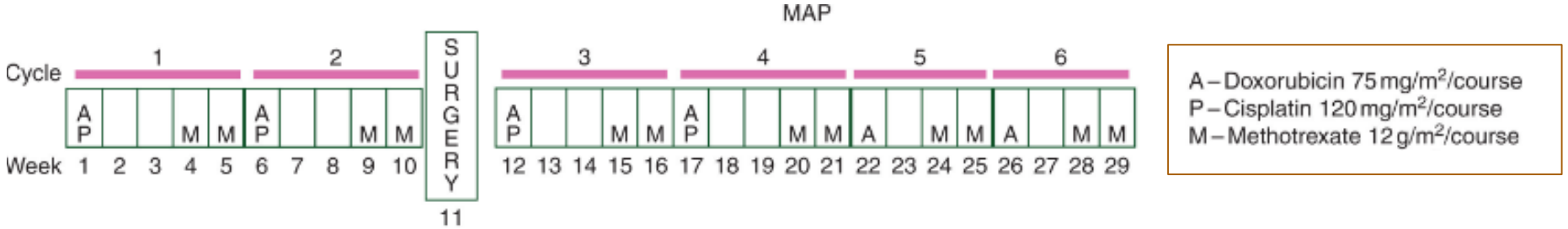
Up to date, 2023

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

Chemotherapy in the management of osteosarcoma

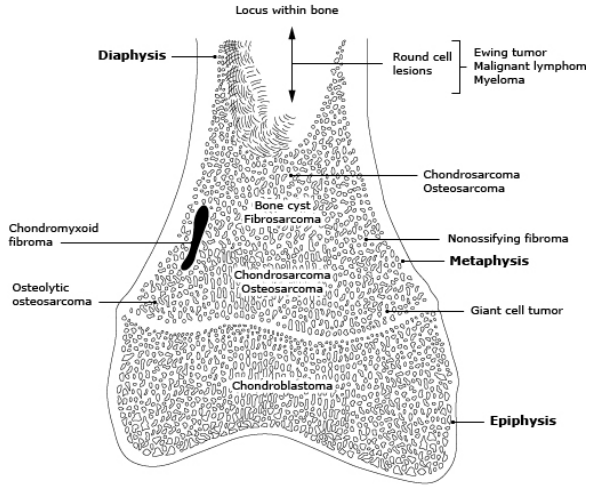
- Survival improved dramatically with chemotherapy
- 80-90% develop metastases prior to the use of systemic treatment for conventional osteosarcoma
- Subclinical metastatic disease at the time of diagnosis
- Long-term survival without chemotherapy: 16%
- Five year survival with chemotherapy: 70%
- ≤ 40a: MAP with methotrexate, doxorubicin, cisplatin (EURAMOS-1 protocol)
- >40a doxorubicin and cisplatin only
- Response assessment: Favorable prognosis with 90% or more tumor necrosis

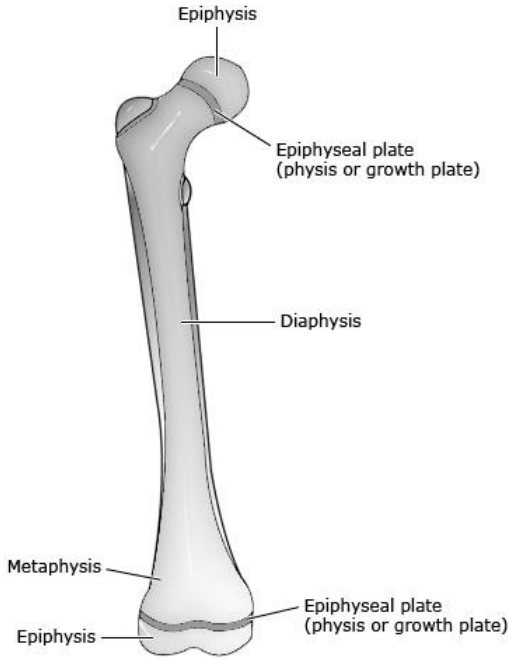


This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Tumor location

- The initial site differs with age at presentation
- Most common site are the metaphyses of long bones
- Distal femur (32 %)
- Proximal tibia (19 %)
- Proximal humerus (10 %)
- Middle and proximal femur (10 %)
- **Other bones, such as the mandible (8 %) and pelvis (8 %)**





Up to date, 2023

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

Remember to wear your **SOCK** (**S**unburst, **O**steosarcoma, **C**odman, **K**nee region).

AMBOSS

Treatment

- Surgery; (definitive resection) with neoadjuvant and adjuvant polychemotherapy (e.g., a combination of methotrexate, doxorubicin, cisplatin, and ifosfamide)
- Histological examination of the resected bone to evaluate the effect of neoadjuvant chemotherapy (major prognostic factor)

Osteosarcomas are usually resistant to radiation therapy.

New radiation therapy techniques (e.g. proton beam and carbon ion therapy) may extend indications.

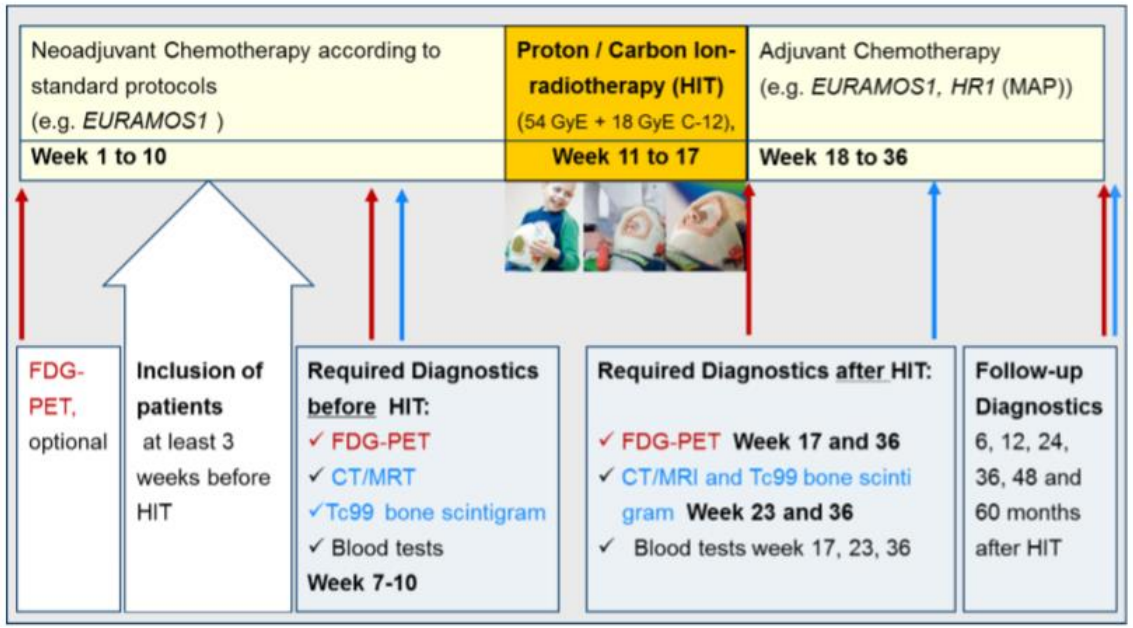
Bone sarcomas: ESMO—EURACAN—GENTURIS—ERN PaedCan Clinical Practice Guideline for diagnosis, treatment and follow-up☆

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

Design of the OSCAR trial

- **OS**teosarcoma- **CA**rbon Ion **R**adiotherapy: Phase I/II therapy trial to determine the safety and efficacy of heavy ion radiotherapy in patients with inoperable high-grade osteosarcoma
- Secondary endpoints: local control, progression-free survival, overall survival, role of FDG-PET in response monitoring
- Treatment with a 54 GyRBE in 27 fractions protons (main plan) and 18 GyRBE in 6 fractions (boost plan)



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

OSCAR trial: study population

- 08/2011-09/2018
- N=20
- Single center
- ≥ 6y
- KPS > 60%
- Adequate blood cell count

Table 1
Patient characteristics.

Country of residence	N	%
Belgium	2	10
United Kingdom	2	10
Netherlands	2	10
France	3	15
Austria	1	5
Germany	10	50
age at treatment (median, range)	20.2	10.8–49.8
Gender	N	%
Female	9	45
Male	11	55
Localization	N	%
Craniofacial	6	30
Pelvic	14	70
Enneking staging for pelvic osteosarcoma	N	%
IIB	10	71
III	3	22
missing	1	7
Grading	N	%
G3	18	90
Missing	2	10
Boost plan clinical target volume (median, range)	415.3	36.70–1727
Base plan clinical target volume (median, range)	1041.9	192.7–3670

Primary/recurrence	N	%
Primary	18	90
Recurrence	2	10
Distant metastases at beginning of hadron therapy	N	%
yes	3	15
no	17	85
Biopsy/Surgery before Treatment	N	%
Biopsy	15	75
Surgery	3	15
Surgery at primary diagnosis and recurrence	1	5
Surgery at primary diagnosis and biopsy at recurrence	1	5
R-Stage after current surgery	N	%
Rx	1	
R2	3	
Chemotherapy protocol	N	%
EURAMOS-1	13	65
EURO-B.O.S.S.	1	5
Carboplatin/VP16 (primary situation EURAMOS-1)	1	5
OS 2006 -API/AI	3	15
EURAMOS-1 plus Carboplatin/Etoposide after PD	1	5
EURAMOS-1 and COSS 96 due to intolerance	1	5

Seidensaal et al, Radiotherapy and Oncology, 2021

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

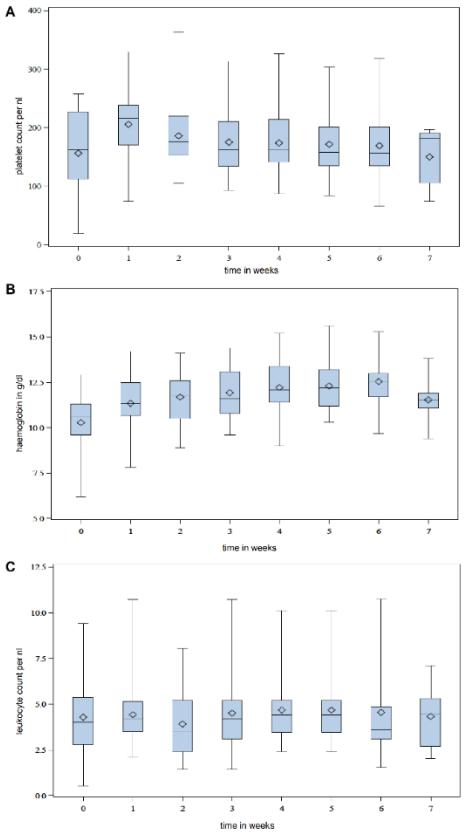
OSCAR trial: primary endpoint toxicity

	Acute Toxicity n=14	all	°I	°II	°III
GI	Intestinal Colic	1		1	
	Diarrhea	3	2	1	
	Meteorism	1	1		
	Constipation	2	2		
	Nausea/Vomiting	2	1	1	
	Soft stool	2	2		
GU	Bladder Infection	1		1	
	Pollakisuria	1	1		
Skin, appendages	Hyperpigmentation	8	6	2	
	Depigmentation	1	1		
	Erythema	11	5	6	
	Ulceration	1	1		
Other	Head aches	1	1		
	Joint discomfort/ Pain	4	4		
	Fatigue	5	4	1	
	Thrombosis	1	1		
	Pain	7	5	1	1
	Sleeping disorder	1	1		
	Herpes	1	1		

	Acute Toxicity	All grades	°I	°II	°III
Nervous system	Visual impairment	2	2		
Skin, appendages and mucosa	Dysphagia	1	1		
	Mucositis	5	3	2	
	Radiodermatitis	6	3	2	1
	Hyperpigmentation	1	1		
	Konjuctivitis	1	1		
	Xerostomia	1	1		
	Dry nasal Mucosa	1		1	
	Epistaxis	2	2		
	Alopecia (focal)	4	2	2	
Ear and labyrith	Ottorhea	1		1	
	Middle ear fluid	1		1	
	Dizziness	3	3		
	Tinnitus	2	2		
Other	Fatigue	3	3		
	Nausea	3	2	1	
	Pain	5	3	2	
	Lymph edema	1	1		

	Late Toxicity n=10	all	°I	°II	°III	°V
GI	Defecation pain	1	1			
Skin, appendages	Hyperpigmentation	2	2			
	Depigmentation	1	1			
	Alopecia	1	1			
	Fibrosis	1	1			
Other	Joint discomfort/ Pain	2	1	1		
	Gait disturbance	1		1		
	Neuropathia	3	2		1	
	Myopathia	1			1	
	Pain	2	1	1		
	Infertility	1			1	
	Herpes reactivation in RT area		1			
	Secondary malignancy	1				1

	Late toxicity	All grades	°I	°II	°IV
Nervous system	Visual impairment	1	1		
	Anosmia	2	2		
	Dysgeusia	3	2	1	
	CNS reaction	4	4		
Skin, appendages and mucosa	Xerostomia	3	1	2	
	Dry nasal Mucosa	1		1	
	Foetor	1	1		
	Alopecia (focal)	5	3	2	
Head and neck	Sinusitis	1	1		
	Trismus	1	1		
Ear and labyrinth	Dizziness	1	1		
	Tinnitus	1		1	
	Hearing impairment	1			1
Other	Fatigue	1	1		
	Pain	3	3		
	Pituary Gland impairment	1		1	



Seidensaal et al, Radiotherapy and Oncology, 2021

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

OSCAR trial: secondary endpoints

- Median Follow up (of Event-free):

  34.5 months [10-87 months]

- Overall survival at 24 months:

  68 % (craniofacial 100 %, pelvic 53 %)

- PFS at 24 months:
  45 % (craniofacial 80 %, pelvic 25 %)

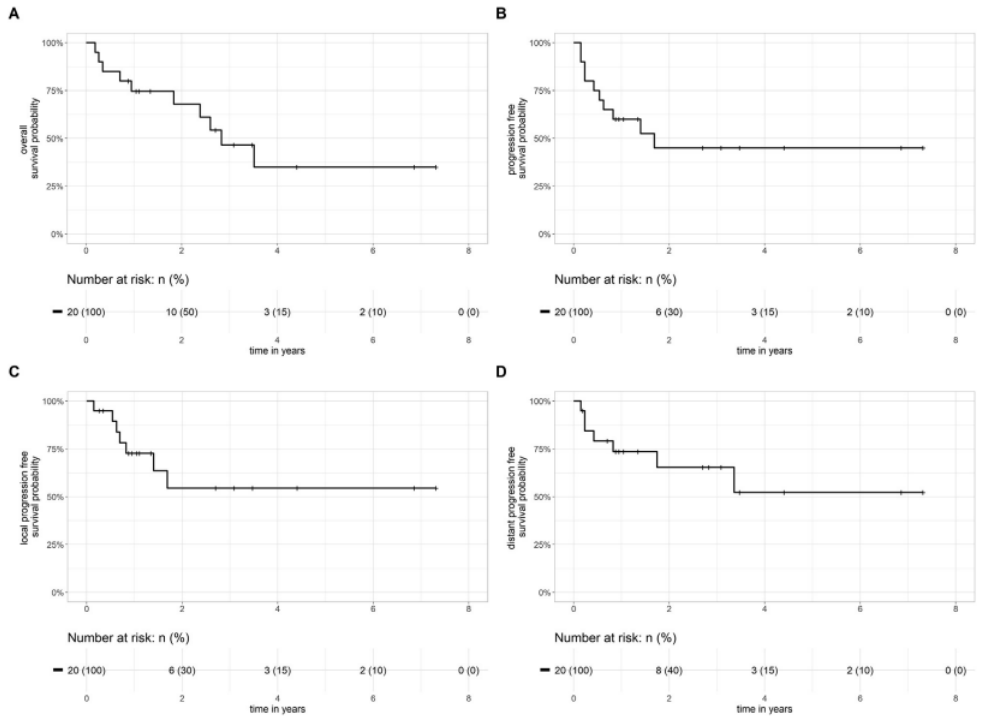


Fig. 2. Kaplan-Meier survival analyses. (A) Overall survival probability with a median OS of 34 months. (B) Progression free survival probability with a median PFS of 20 months. (C and D) both local and distant progression free survival have not yet been reached.

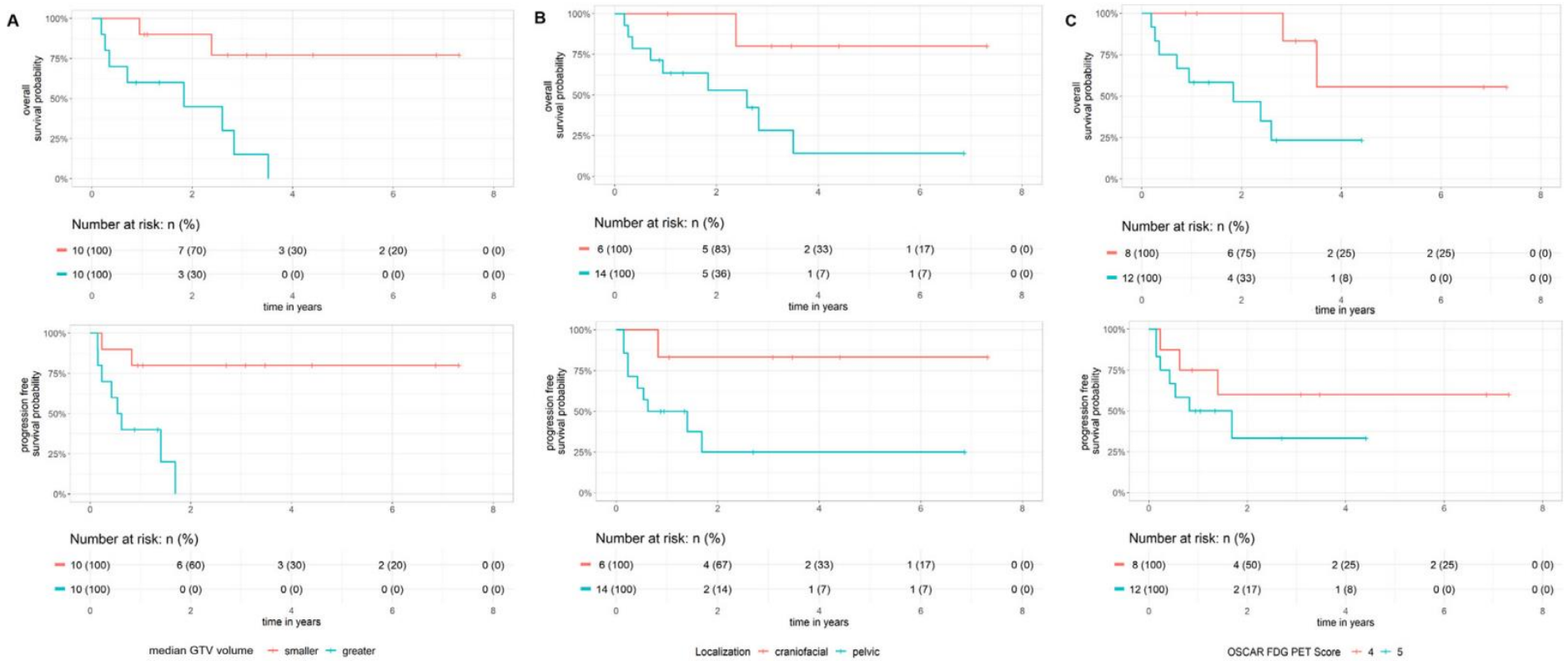
Seidensaal et al, Radiotherapy and Oncology, 2021

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

OSCAR trial: Prognostic factors

<u>Favorable prognosis</u>:

1. Smaller tumor volumes < 415 ml
2. Craniofacial location
3. Lower FDG uptake at beginning of RT

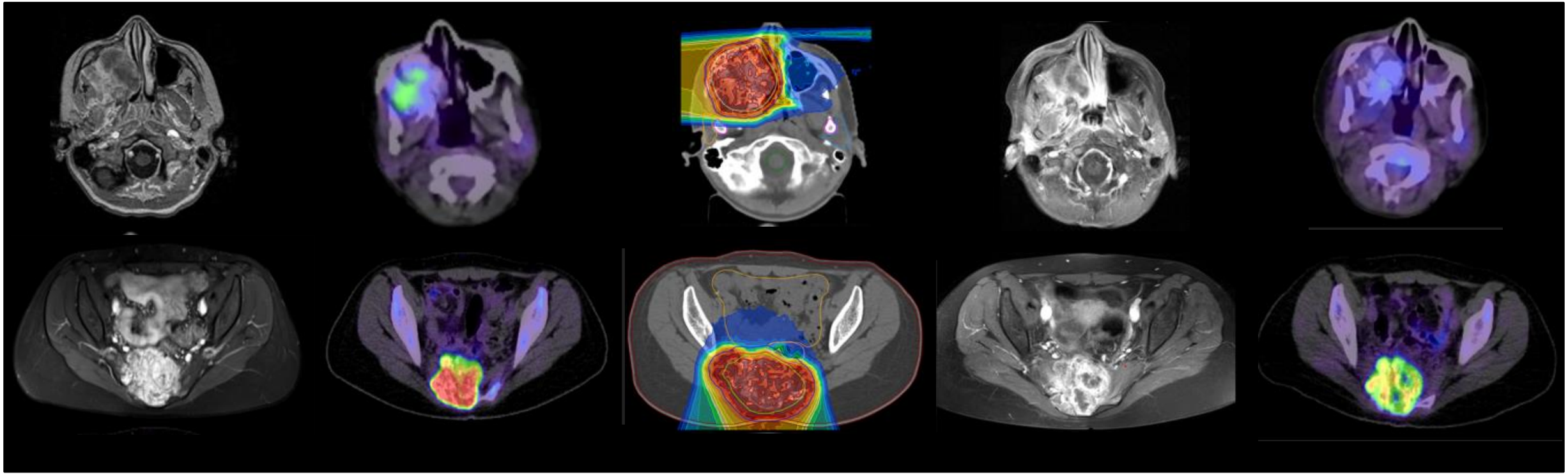


Seidensaal et al, Radiotherapy and Oncology, 2021

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

OSCAR trial: Clinical examples

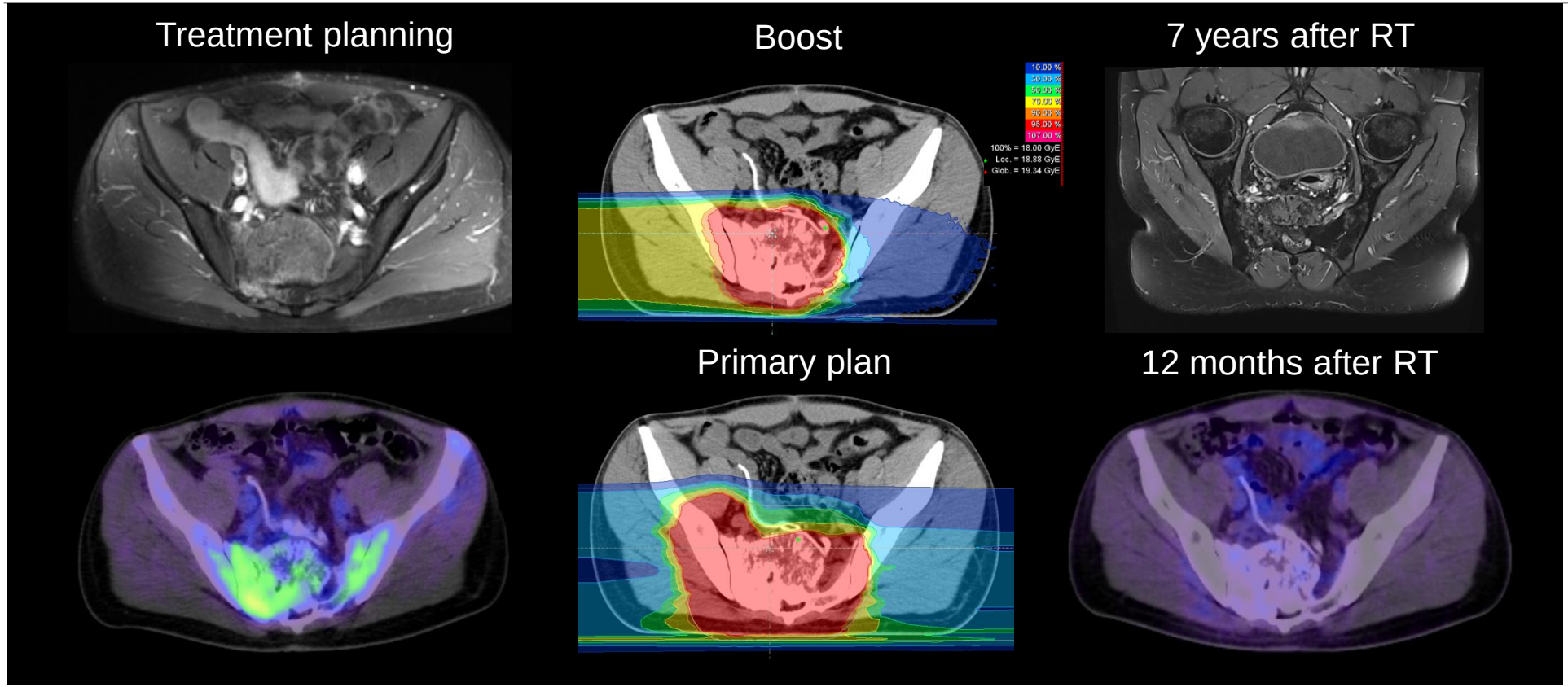
MRT pre RT | PET pre RT | dose distribution | MRT post RT | PET post RT



Seidensaal et al, Radiotherapy and Oncology, 2021

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

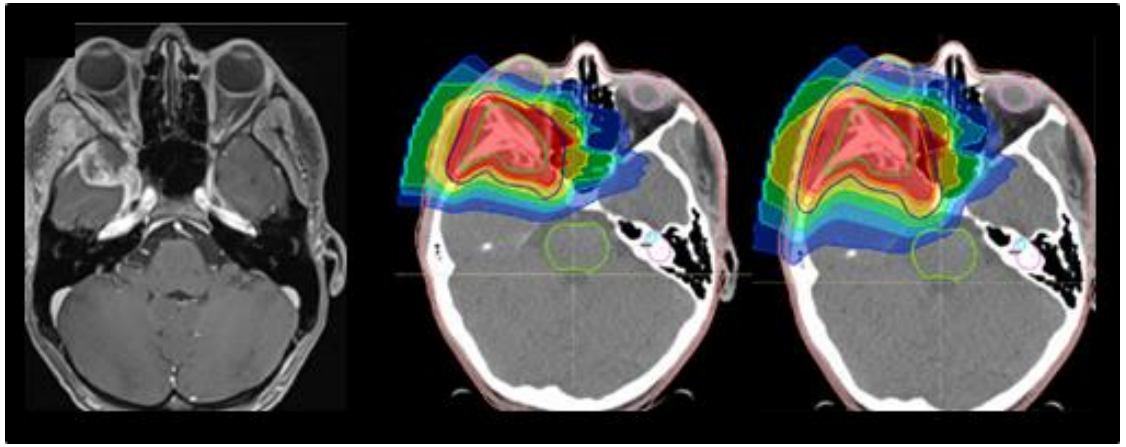
OSCAR trial: Clinical examples



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

Craniofacial Osteosarcoma

- Distinct variant
- Older patients (median age 36)
- May have a more indolent course
- More likely local recurrence (56%)
- Less distant metastases
- 5 year-OS 40-53%
- Most common primary sites: mandibula and maxilla, extragnathic bones
- About 10% of osteosarcoma cases
- Role of neoadjuvant or adjuvant chemotherapy less evident



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

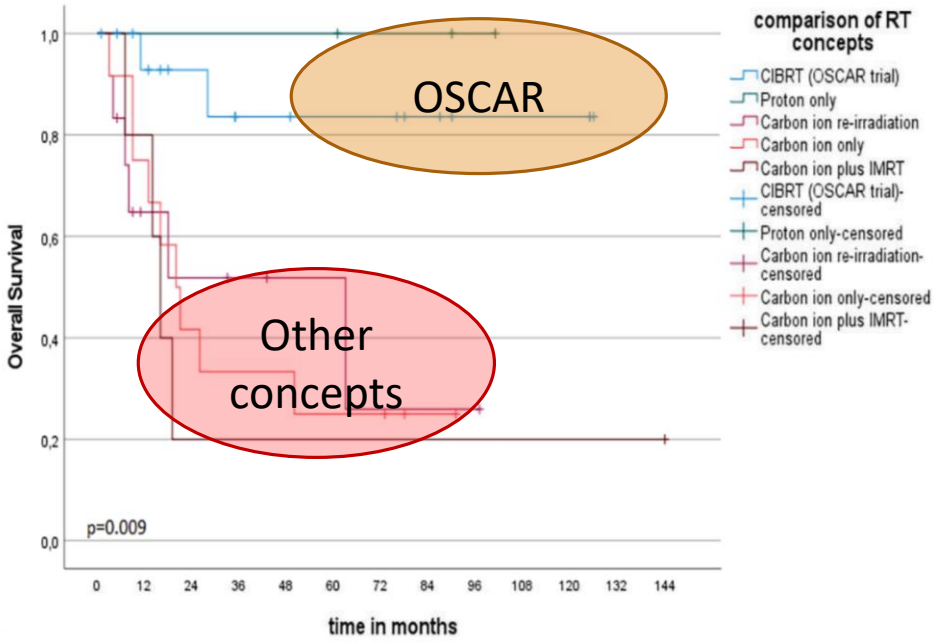
Inoperable or incompletly resected craniofacial osteosarcoma

N=49, thereof *N*=17 treated with protons (54 GyRBE) and ^{12}C (18 GyRBE)

Median FU: 55 months

overall survival (all) 1-year: 83%, 2-years: 60% and 5-years: 52%
overall survival (non-OSCAR) 1-year: 74%, 2-years: 46% and 5-years: 43%
overall survival (OSCAR analog) **1-year: 93%, 2-years: 84% and 5-years: 84%**

3-year local progression free survival 77 % (OSCAR analog)



Seidensaal et al, Frontiers in Oncology, 2022

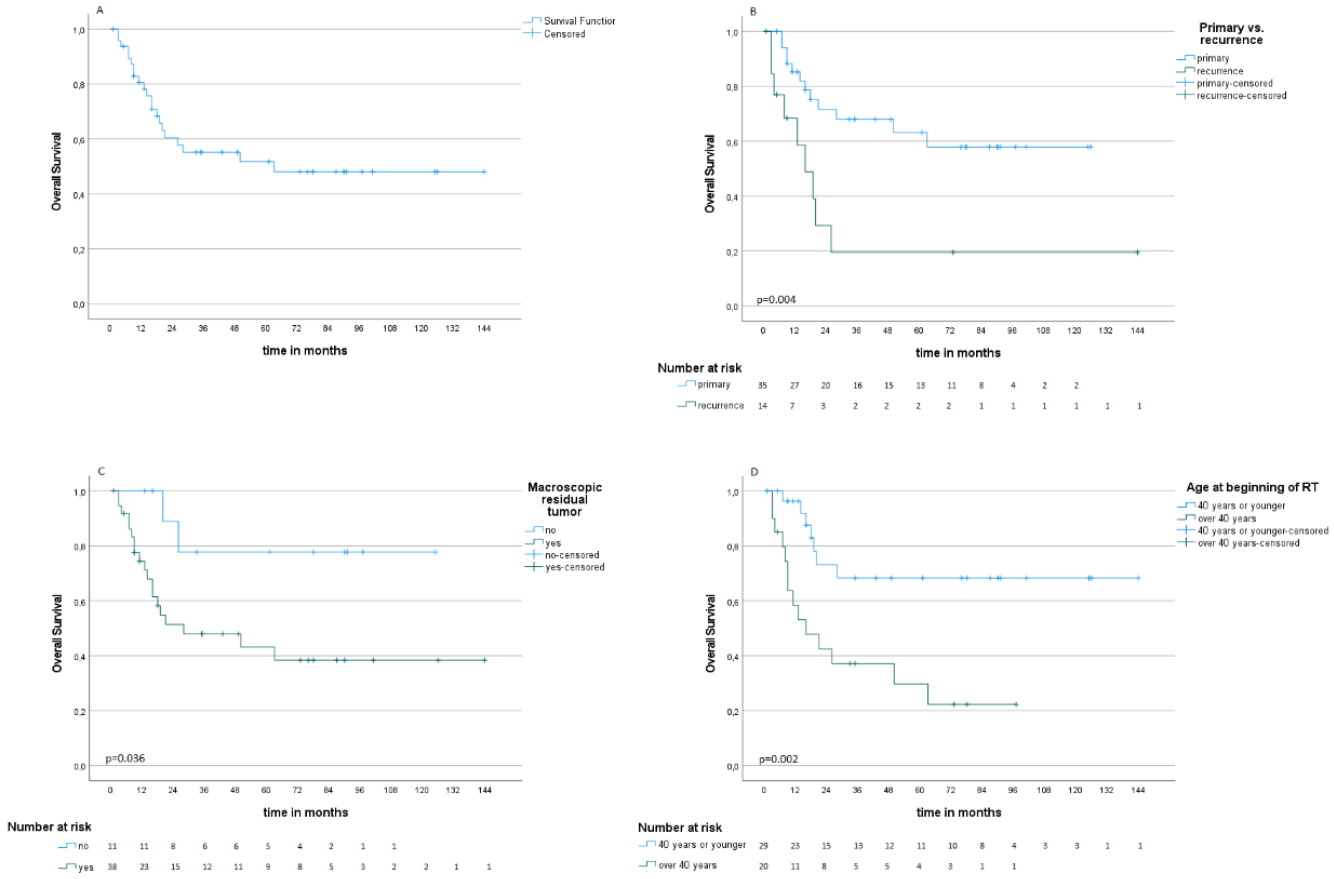
HITRI
Heavy Ion Therapy Research Integration

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

Inoperable or incompletly resected craniofacial osteosarcoma

Favorable factors:

- Age ≤ 40a
- First diagnosis (vs. recurrent disease)
- R1 (no macroscopic residual disease)
- Chemotherapy according to EURAMOS-1



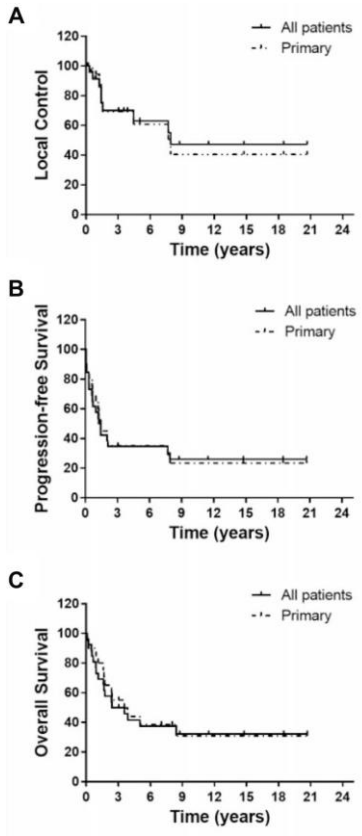
Seidensaal et al, Frontiers in Oncology, 2022

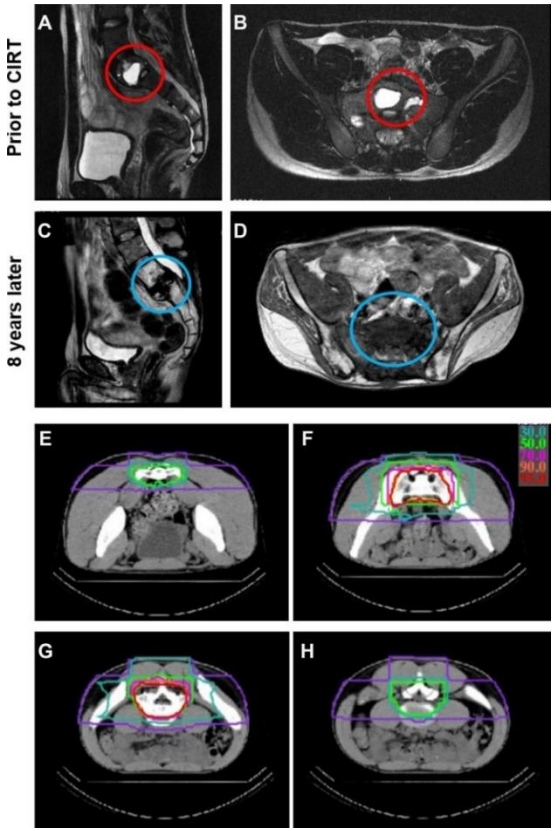
HITRI
Heavy Ion Therapy Research Integration

Carbon ion radiotherapy for inoperable pediatric osteosarcoma

- 26 patients
- Median age 16 (11-20)
- Median FU 32.7 months
- 5-year OS: 42%; 5-year LC: 63%

Characteristic	#patients (%)	Median (range)
Irradiation site		
Pelvic	24	
Spinal/paravertebral	1	
Mediastinum	1	
Target volume (cm^3)		452 (172–1774)
Radiation dose, total (Gy RBE)		70.4 (52.8–73.6)
≤64[a]	5	
70.4	18	
73.6	3	
Dose per fraction (Gy RBE)		4.4 (3.3–4.6)



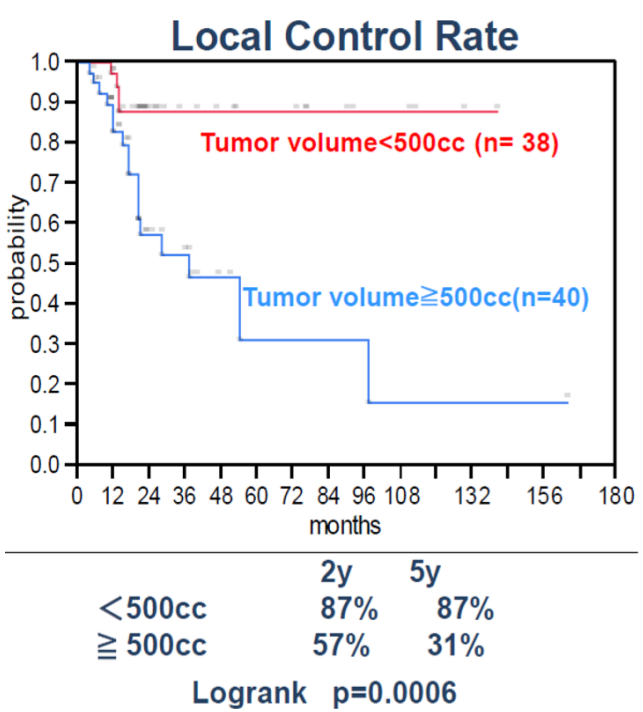


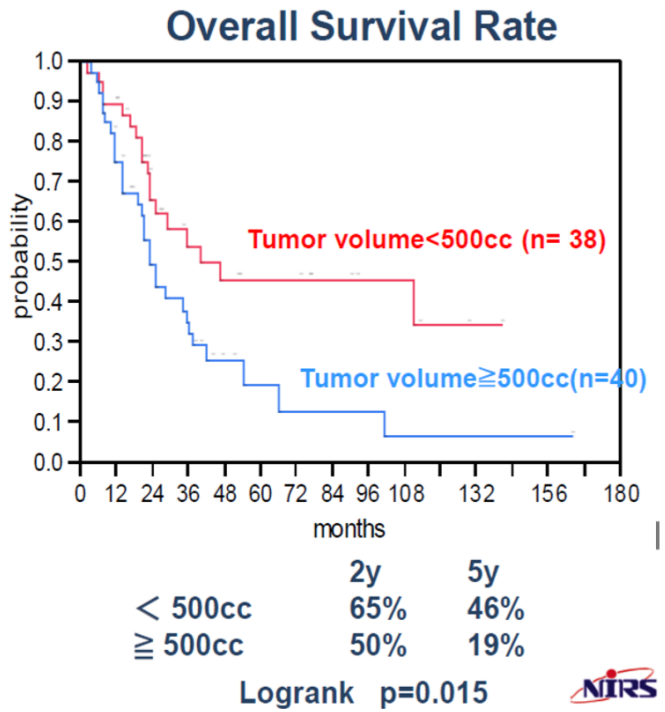
Mohamad, Oncotarget, 2018

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

Osteosarcoma of the trunk

- 78 patients
- 61 located in the pelvis
- 1996 – 2009
- Median dose 70.4 GyE in 16 fractions over 4 weeks
- Minimum follow up: 14 months
- 5-year OS 33%
- 5-year LC 62%
- 3 patients requiring skin grafts due to toxicity



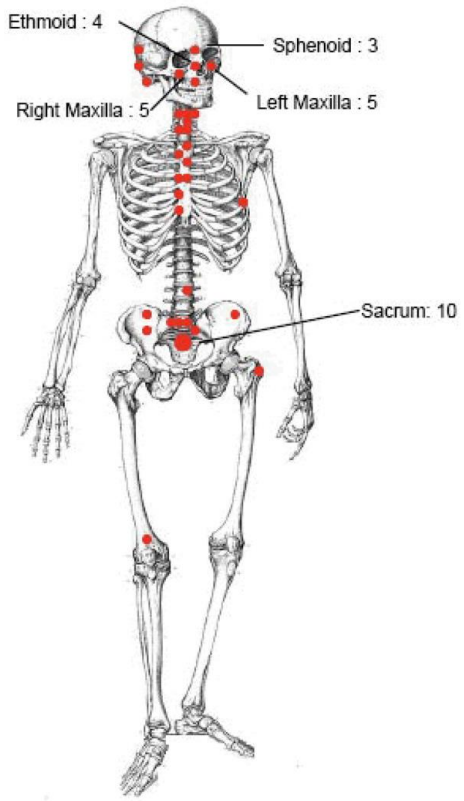


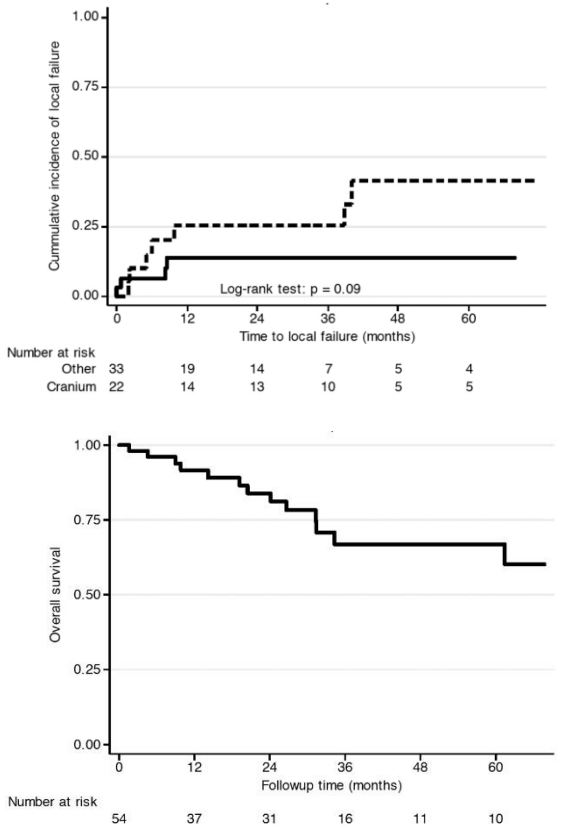
Matsunobu et al., cancer, 2012

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

Proton-Based Radiotherapy for Unresectable or Incompletely Resected Osteosarcoma

- 1983 – 2009
- 55 patients
- Median FU 27 months
- Median age 29 (2-76)
- Cranium 40%, pelvis 24%
- Partially resected 35%
- Grossly resected 43%
- Median boost volume 82 ml (14-1624 ml)
- Mean dose: 68.4 Gy, protons +/- photons
- 5-year LC: 72%
- 5-year OS: 67%
- Grade 3-4 toxicity: 30.1%





Ciernik et al., Cancer, 2011

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

Comparison of osteosarcoma cohorts treated by protons and carbon ions

research group	N	modality	Loc.	Dose (GyRBE)/ Fx	Med. FU (months)	OS	PFS	comment
OSCAR trial	20	P + C	30% craniofacial 70% pelvis	54+18 / 27+6	35	68 % (2 years)	45 % (2 years)	
DeLaney, 2009	41	Ph / P	41% cranium 19 % spine 17% pelvis	66/ -	56	65 % (5 years)	40 % (5 years)	24% significant late complications
Ciernik, 2011	55	P	40% cranium 31% spine 24% pelvic	68.4/ -	27	67 % (5 years)	65 % (5 years)	30 % grade III-IV toxicity
Matsunobu, 2012	78	C	65% pelvis 19 % spine (parasp.)	70.4 /16	42	58 % (2 years)	34 % (2 years)	10 % grade III-IV late skin toxicity
Kamada, 2002	57	C	-	52.8 – 73.6 / 16	21	46 % (3 years)	n/a, 3y-LC 73 %	Mixed cohort, 26% osteosarcoma
Mohamad, 2018	26	C	92% pelvis	70.4 / 16	33	50 % (3 years)	35 % (3 years)	15 % grade III-IV late toxicity

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

Target volume delineation in analogy to OSCAR trial

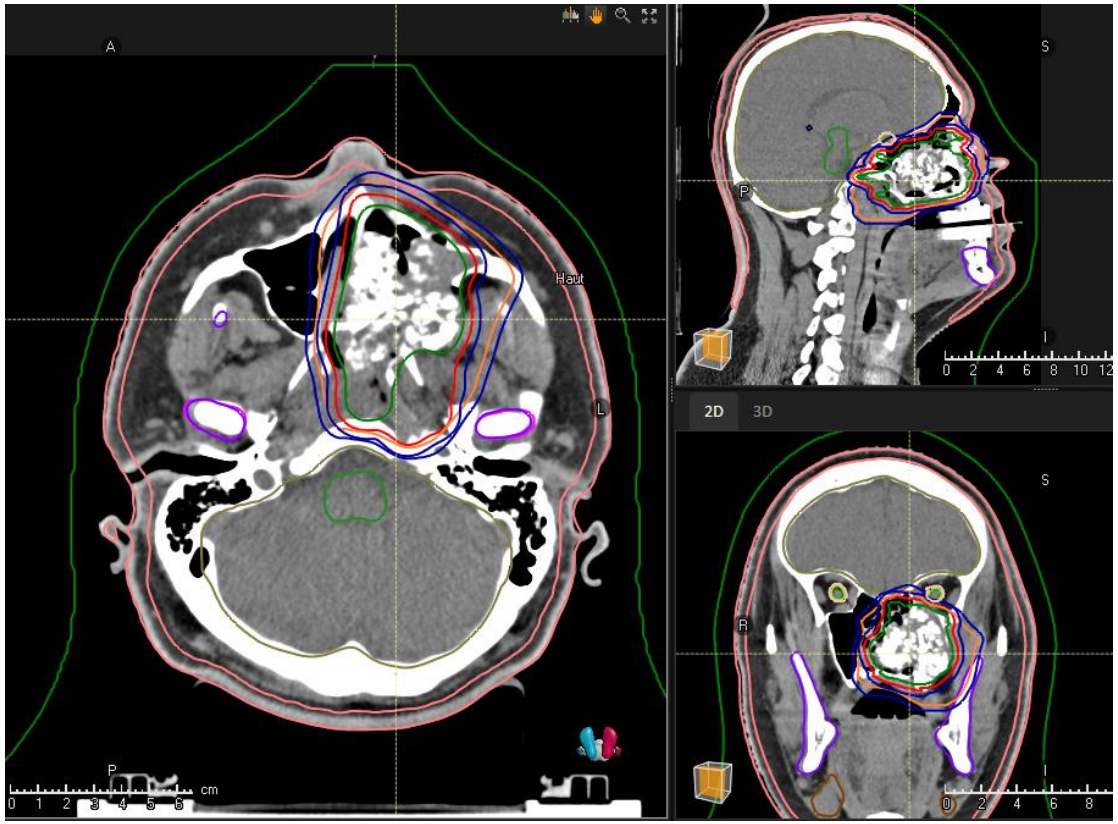
Gross tumor volume (GTV)	Visible tumor at the time of treatment planning (T1w post KM, T2 Stir)
CTV high-risk	GTV + 7 mm (original: 3 mm)
CTV low-risk	Initial pre-chemotherapy, pre-operation extension + 2 cm (including high-risk CTV) Adapt to none infiltrated OAR (brain, bowel, bladder)
PTV	Institution specific. HIT head and neck: 3mm; pelvis 7 mm in beam direction and 5 mm in the remaining directions
Prescribed dose and fractionation	
CTV high-risk	^{12}C 18 GyRBE in 6 fractions, 5-6 fractions per week
CTV low-riks	Protons 54 GyRBE in 27 fractions, 5-6 fractions per week

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

Target volume delineation: craniofacial osteosarcoma

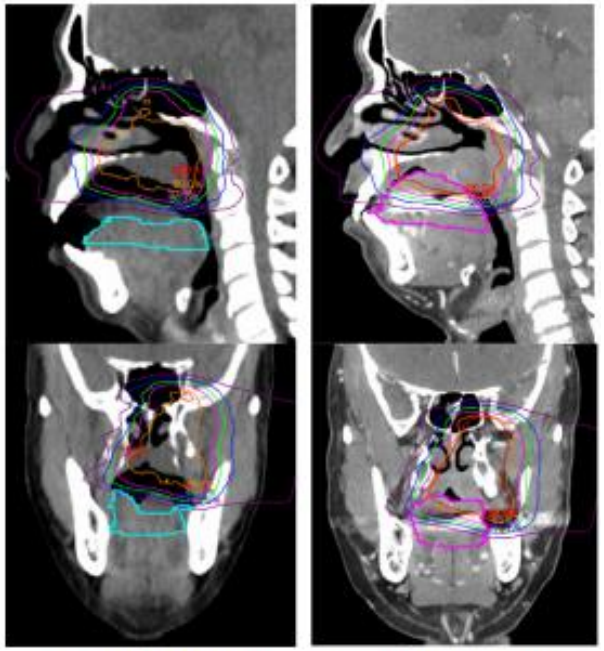
GTV
CTV low risk
CTV high risk
PTVs



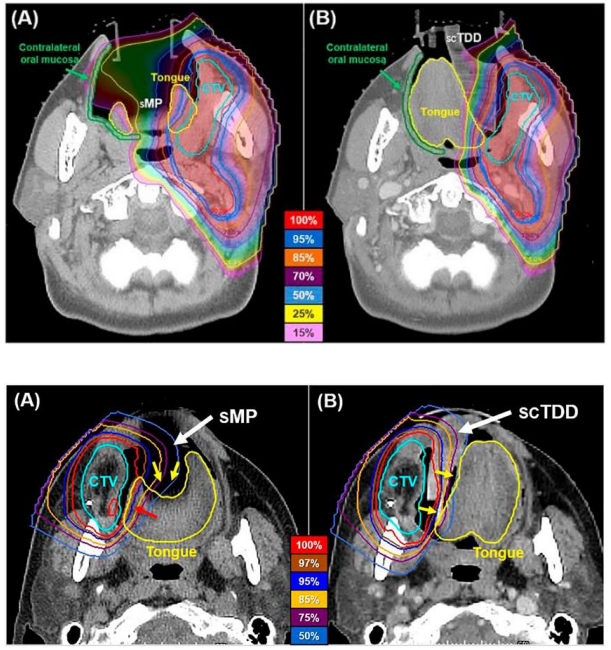
HITRI
Heavy Ion Therapy Research Integration

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

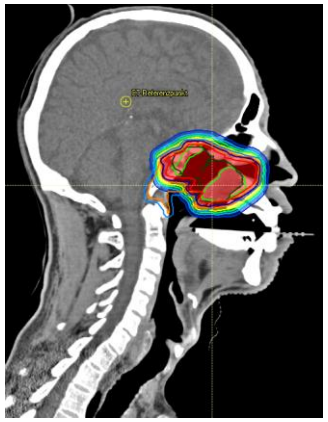
Custom-made tongue devices for protons and carbon-ions



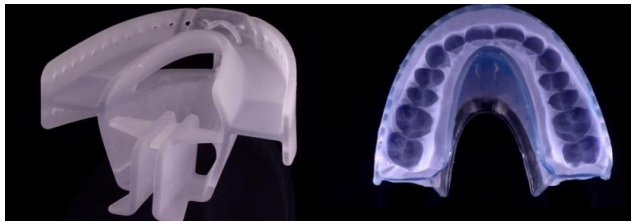
Ikawa et al., Pract Rad Onc, 2017



Hong et al., Front Phys., 2021c



51-year-old patient with incompletely resected chor-doma, boost plan with 21 GyRBE in 3 GyRBE single doses

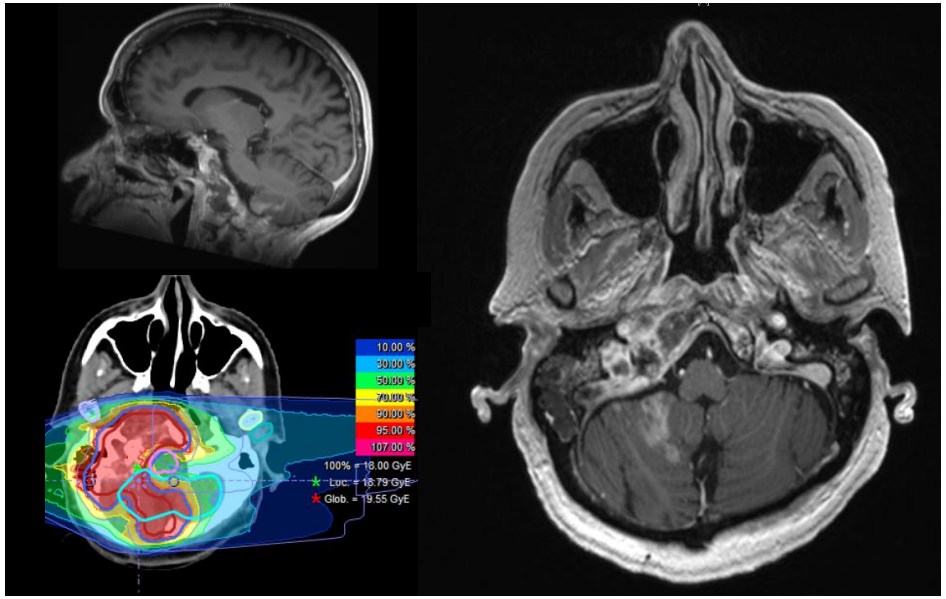


HITRI
Heavy Ion Therapy Research Integration

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

Temporal lobe reactions and radiation CNS necrosis

- TD5% and TD50% 68.8 GyRBE and 87.3 GyRBE
- V50 ≤11 cm3, D2cm3 ≤62 GyRBE



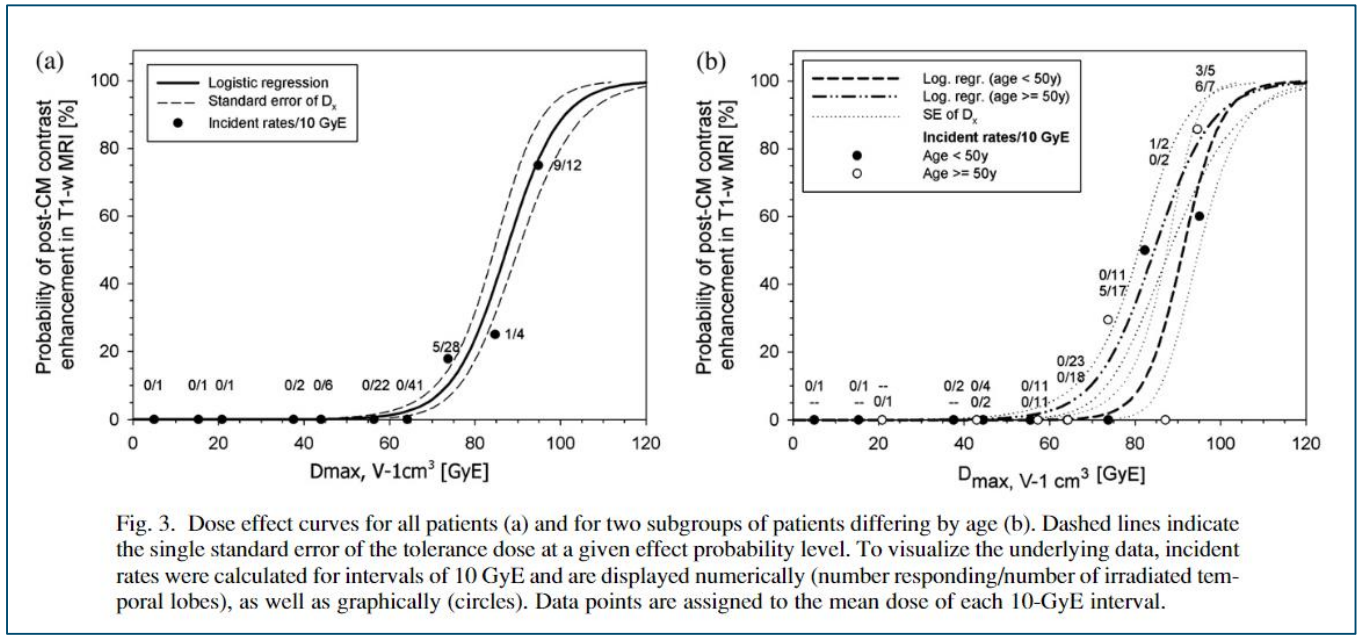


Fig. 3. Dose effect curves for all patients (a) and for two subgroups of patients differing by age (b). Dashed lines indicate the single standard error of the tolerance dose at a given effect probability level. To visualize the underlying data, incident rates were calculated for intervals of 10 GyE and are displayed numerically (number responding/number of irradiated temporal lobes), as well as graphically (circles). Data points are assigned to the mean dose of each 10-GyE interval.

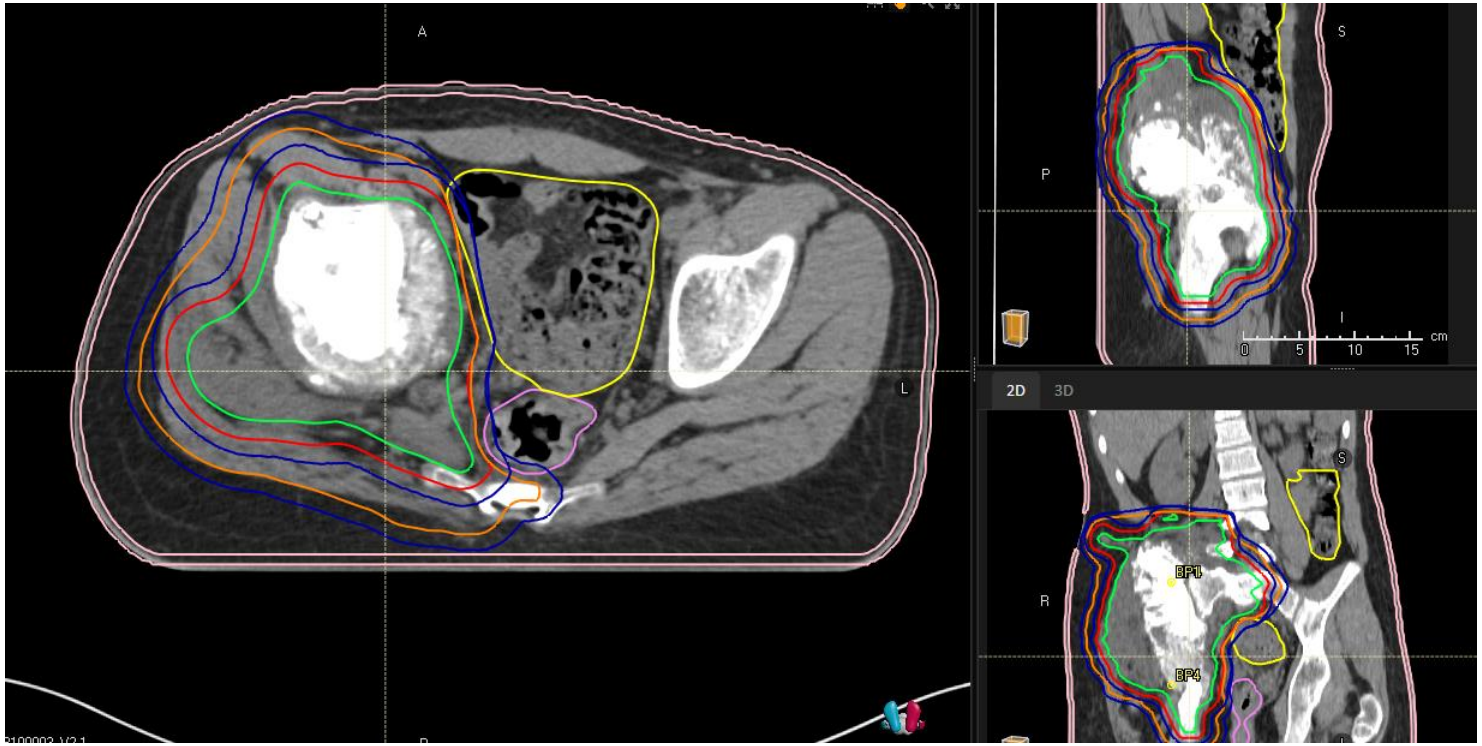
Schlampp et al., J. Rad. Oncol. Biol. Phys., 2011
Kitpanit et al, Int J Particle Therapy, 2020

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

Target volume delineation: pelvic osteosarcoma

GTV
CTV low risk
CTV high risk
PTVs

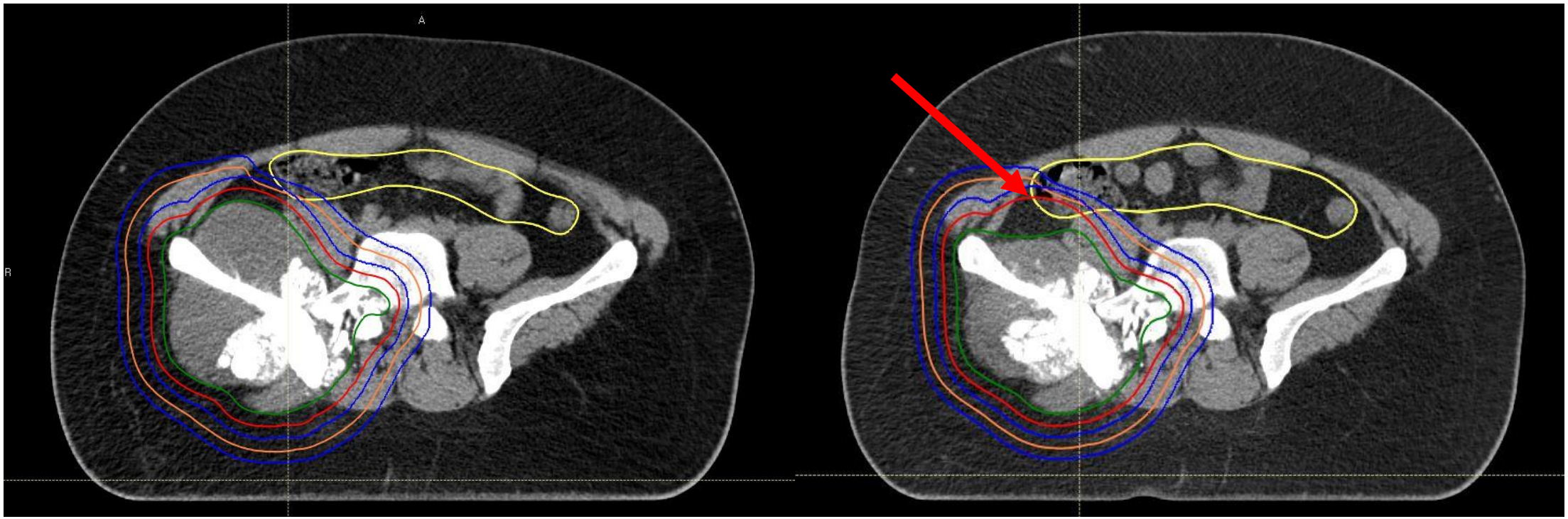


HITRI
Heavy Ion Therapy Research Integration

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

Pelvic osteosarcoma: the need for adaptation

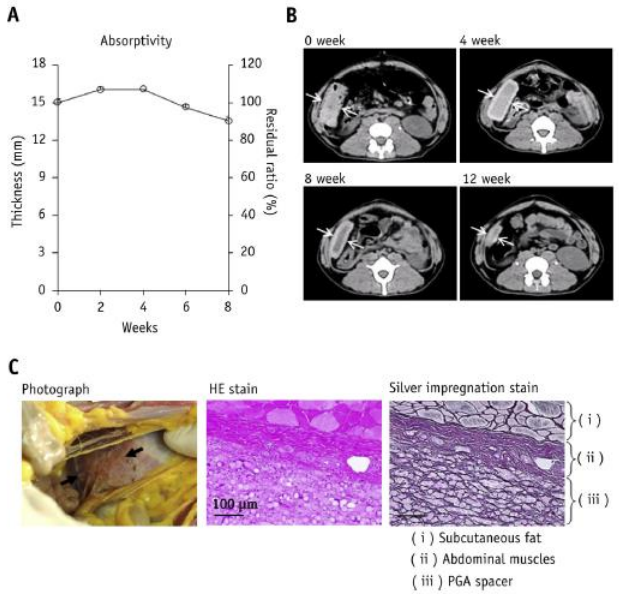
GTV
CTV low risk
CTV high risk
PTVs



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

Bioabsorbable spacer for particle therapy



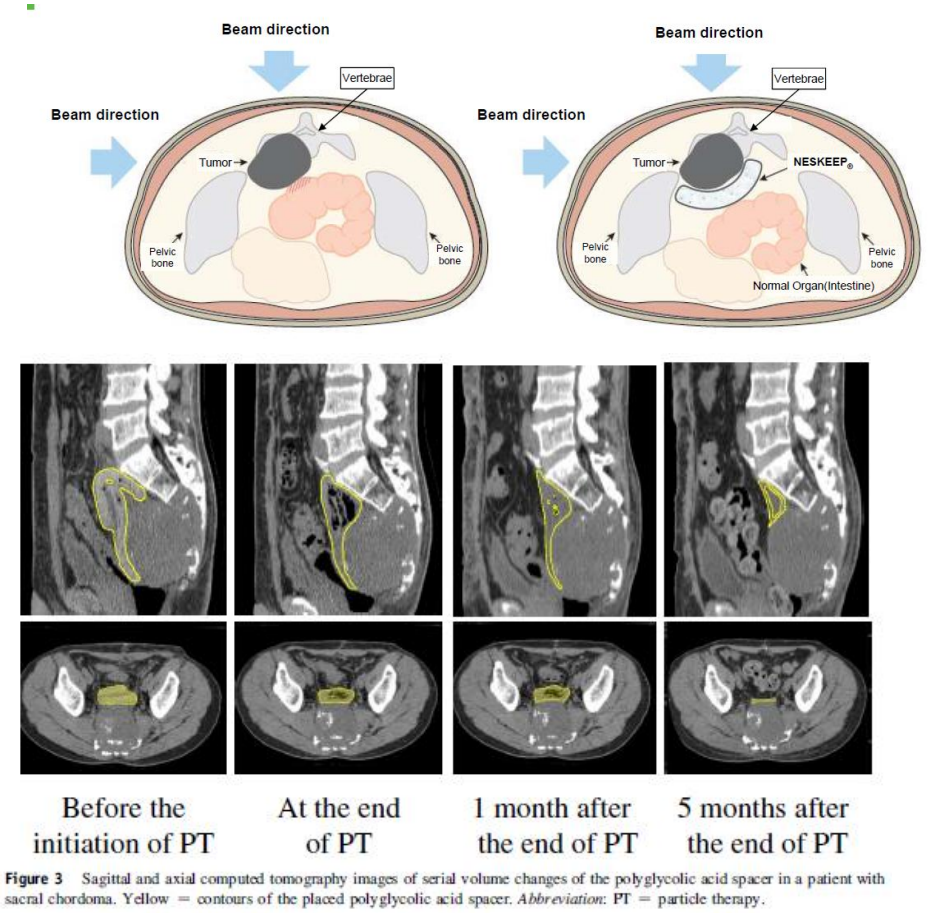


Figure 3 Sagittal and axial computed tomography images of serial volume changes of the polyglycolic acid spacer in a patient with sacral chordoma. Yellow = contours of the placed polyglycolic acid spacer. *Abbreviation*: PT = particle therapy.

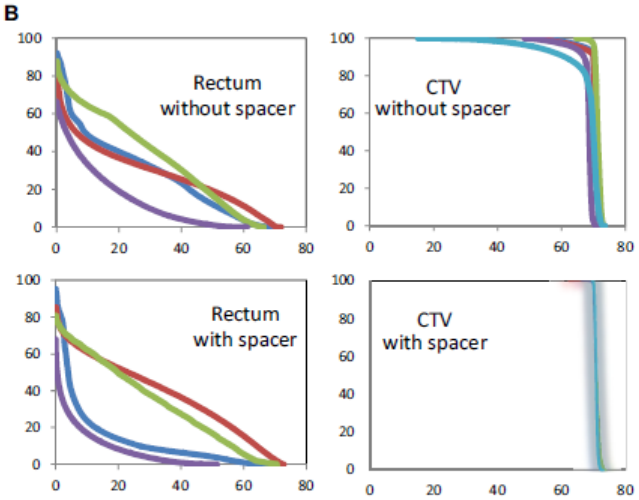


Figure 4 (A) Changes of planning target volume parameters. (B) Comparison of clinical target volume coverage and organ at risk (rectum) with or without the polyglycolic acid spacer in the dose-volume histogram in 4 patients whose tumors were located in the pelvis. *Abbreviations*: D_{95} = dose irradiated to ≥95% of the target volume; PT = particle therapy; SSP = surgical spacer placement; $V_{95\%}$ = volume receiving ≥95% of the prescribed dose.

Sasaki et al., Advances in Radiation Oncology, 2019
Akasaka et al., Red Journal, 2014

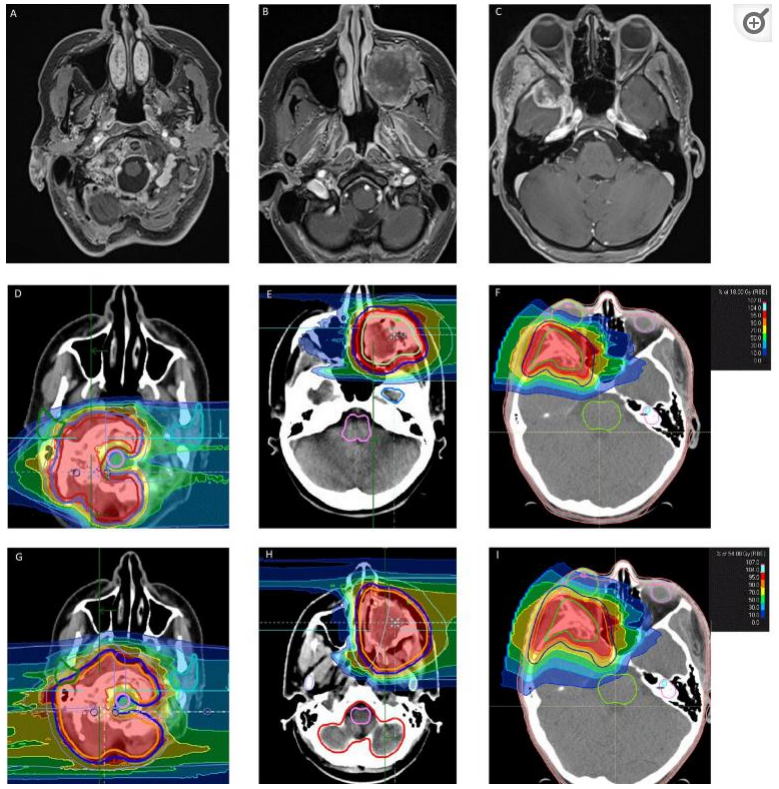
HITRI
Heavy Ion Therapy Research Integration

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

Particle Therapy for inoperable or incompletly resected osteosarcoma

Conclusion:

- Radiotherapy using particles represents a promising alternative in the inoperable situation
- Aim for multimodal therapy including system therapy
- Consider radiotherapy in R1 resected tumors
- Superior OS and LC for craniofacial osteosarcoma
- OS and PFS prolongation for pelvic tumors



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

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