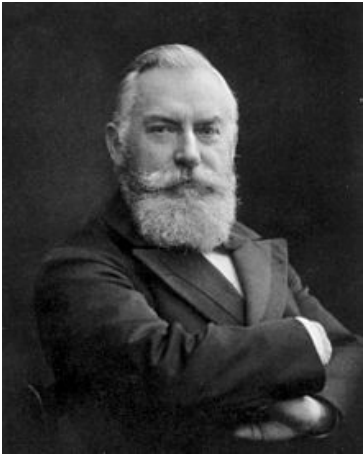


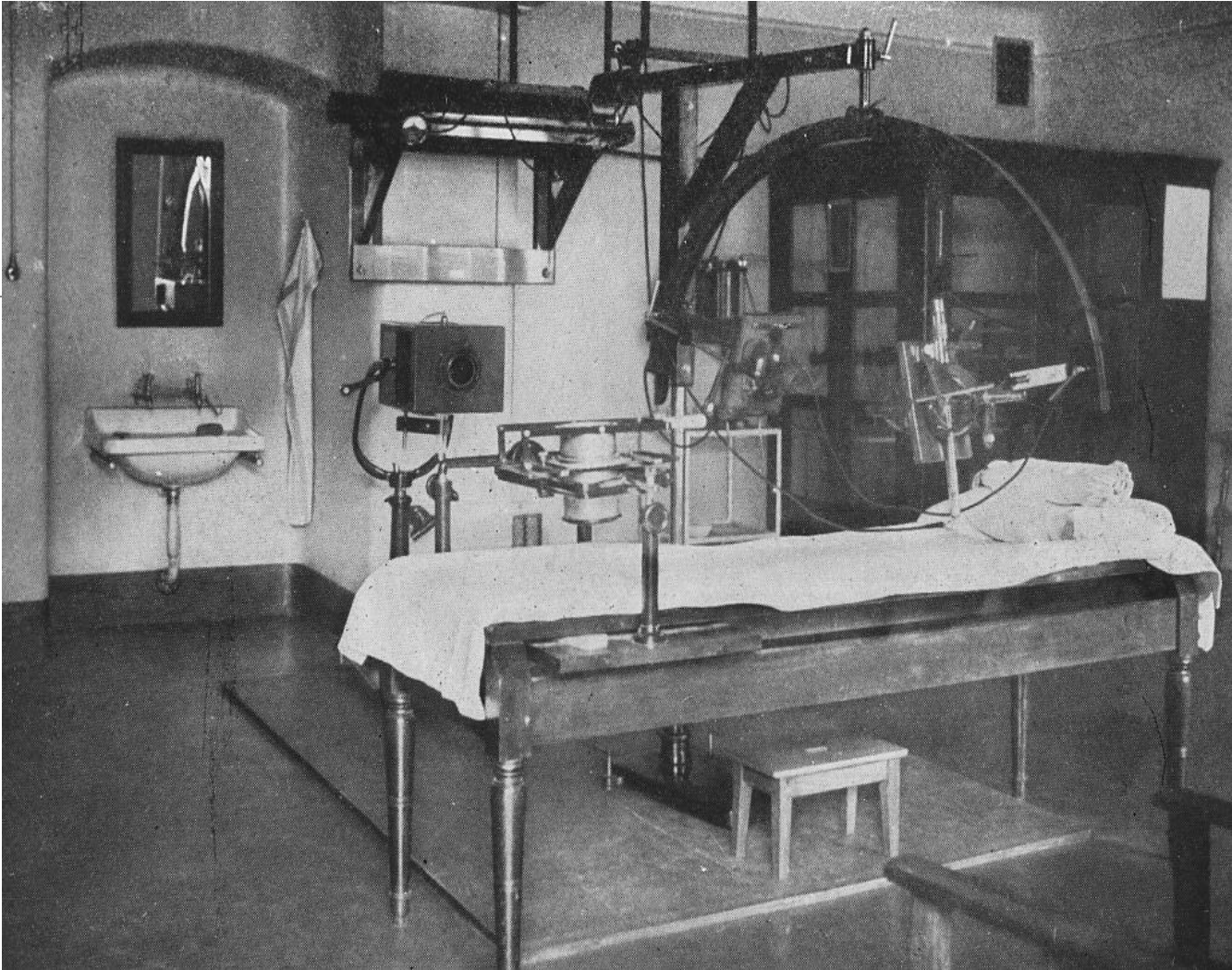
Dr. med. Semi B. Harrabi
University Hospital Heidelberg
Dept. of Radiation Oncology (Prof. Dr. Dr. J. Debus)
Heidelberg Ion Beam Therapy Center (HIT)
Im Neuenheimer Feld 400, 69120 Heidelberg
Germany

clinical trials: The Heidelberg approach

More than 100 years ago...



Vincenz Czerny

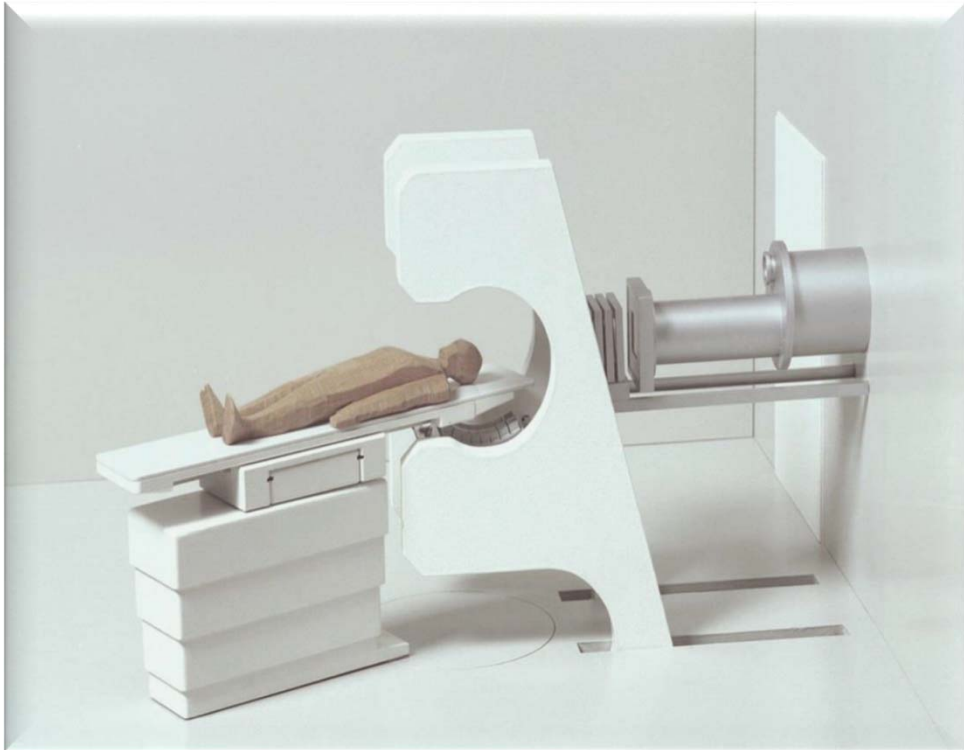


Irradiation device, Heidelberg 1912



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

GSI, MODEL 1994



First patient in Europe treated with C12

December 13th 1997
GSI, Darmstadt, Germany



440 patients treated until 2009



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

GSIC experience (1997 – 2009)

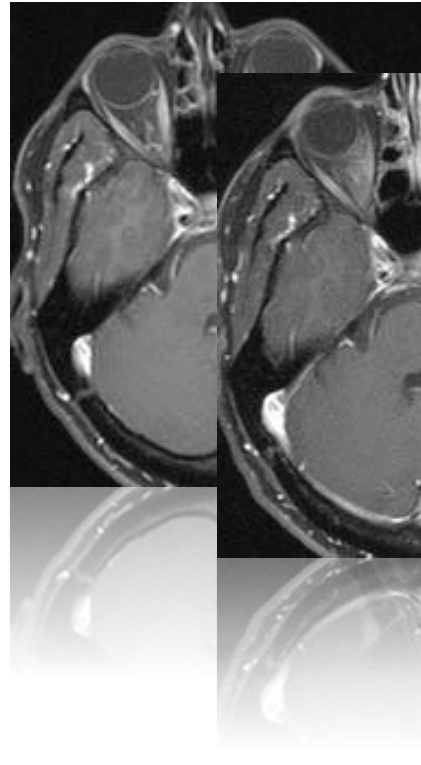
- skull base chondrosarcoma -

before RT

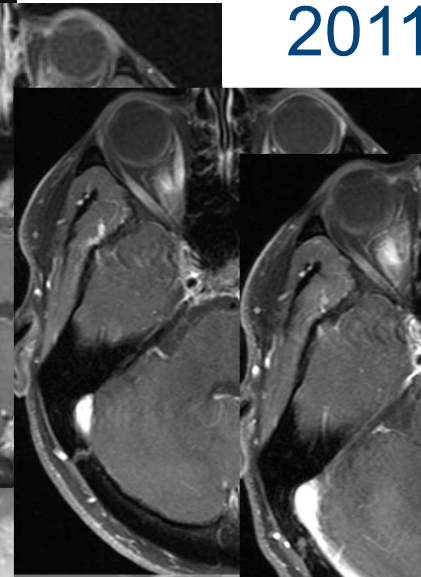
6 weeks after RT



2005

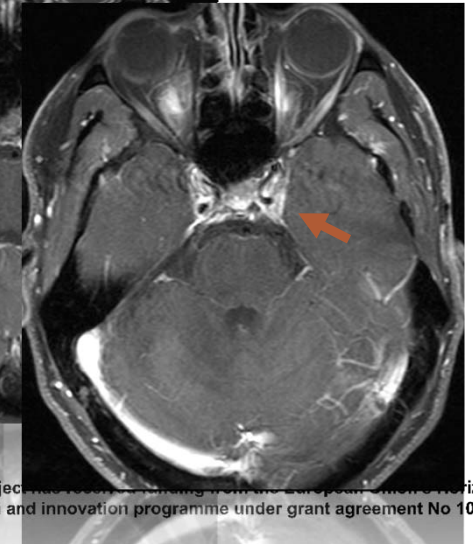


2007



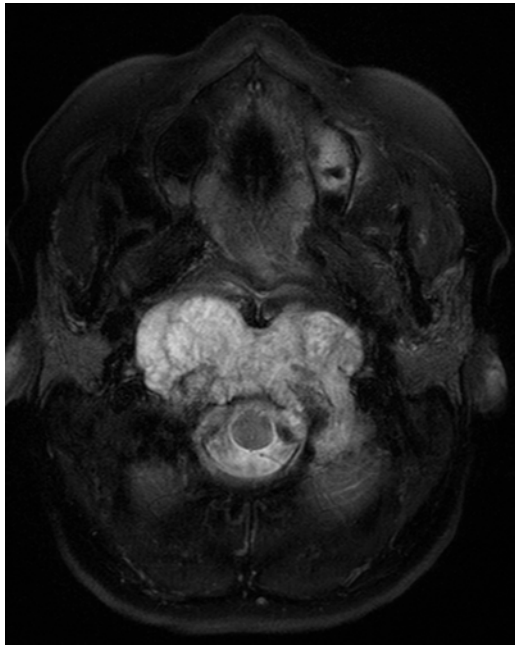
2011

2015

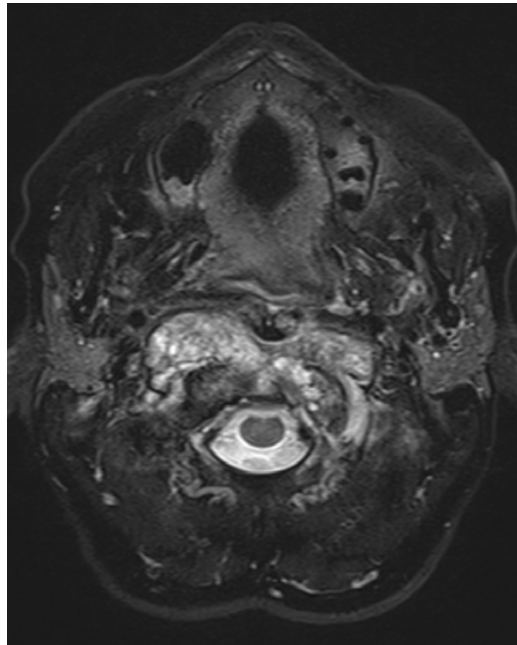


GSIC experience (1997 – 2009)

- skull base & sacral chordoma -

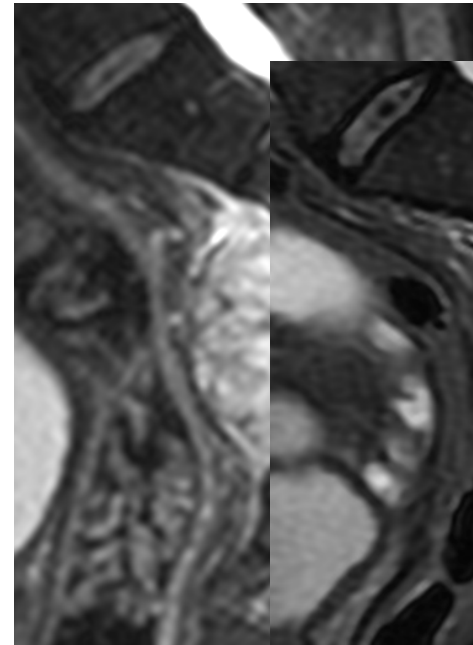


HITRI before RT
Heavy Ion Therapy Research Integration

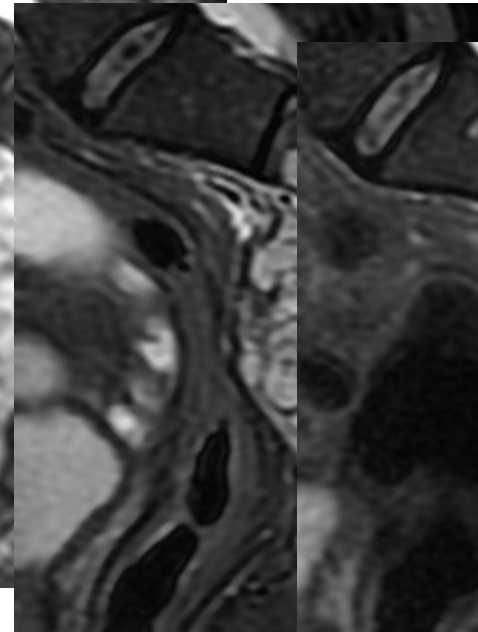


8 months after RT

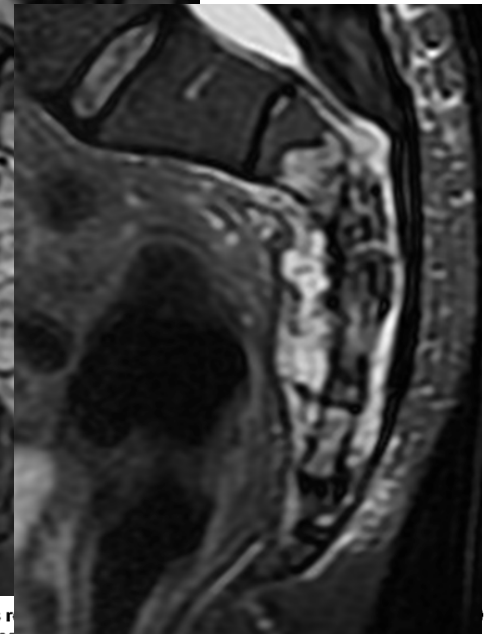
before RT



@3months



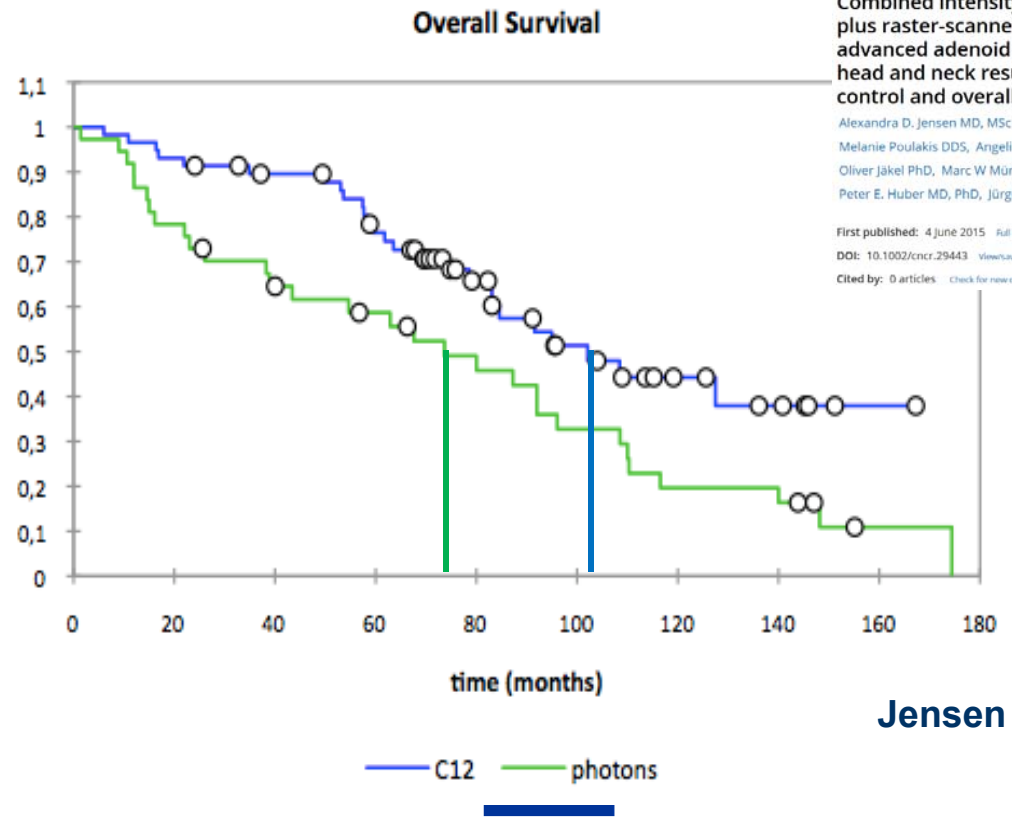
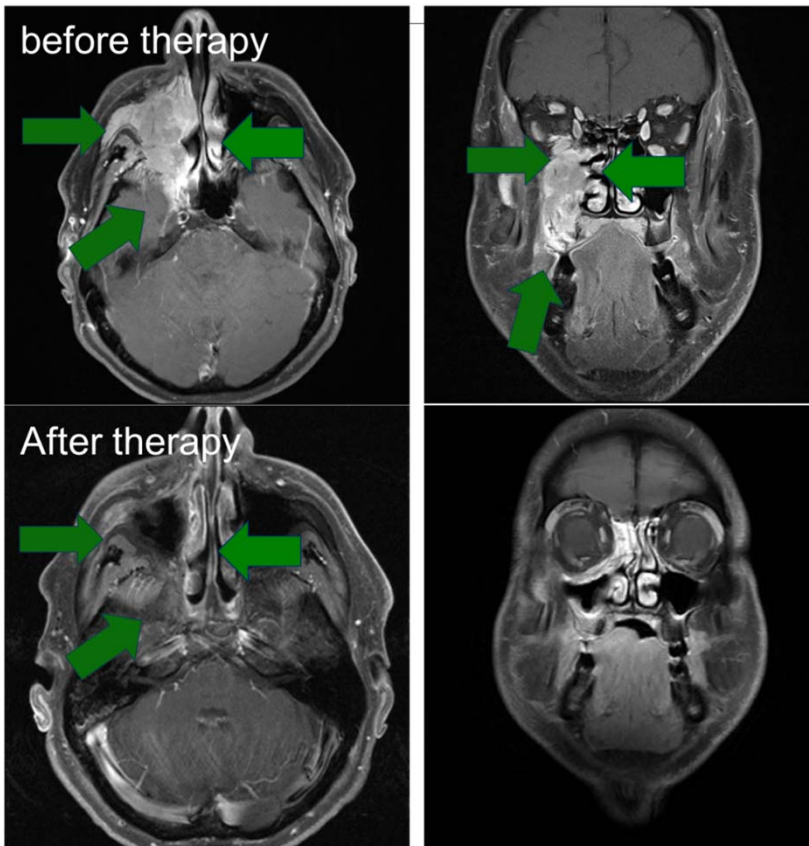
@9months



This project has received funding from the European Union's research and innovation programme under grant agreement No 101019740

GSII experience (1997 – 2009)

- malignant salivary gland tumors -



Cancer

Original Article
Combined intensity-modulated radiotherapy plus raster-scanned carbon ion boost for advanced adenoid cystic carcinoma of the head and neck results in superior locoregional control and overall survival

Alexandra D. Jensen MD, MSc, Anna V. Nikoghosyan MD, Melanie Poulakis DDS, Angelika Höss MSc, Thomas Haberer PhD, Oliver Jäkel PhD, Marc W. Mürter MD, Daniela Schulz-Ertner MD, Peter E. Huber MD, PhD, Jürgen Debus MD, PhD

First published: 4 June 2015 Full publication history
 DOI: 10.1002/cncr.29443 View/Save citation
 Cited by: 0 articles Check for new citations

Jensen et al. 2015

ion's Horizon 2020
 ent No 101008548

GSII experience (1997 – 2009)

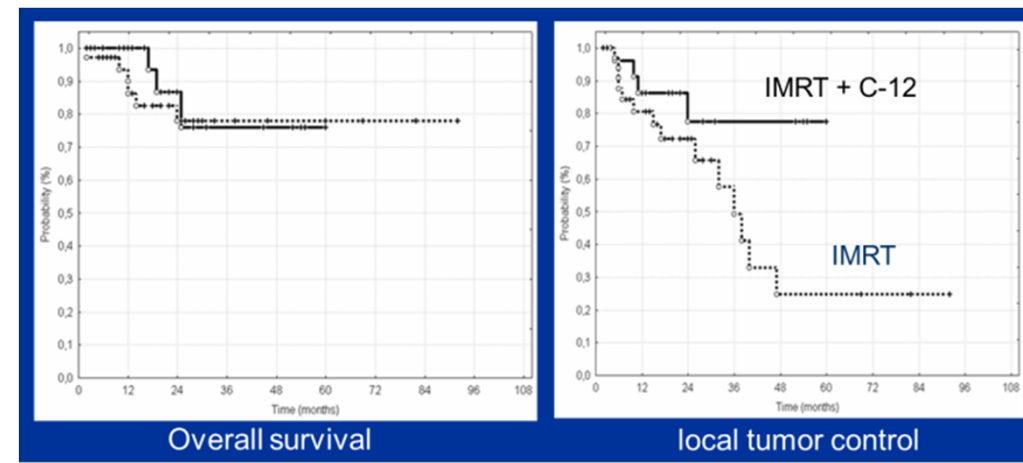
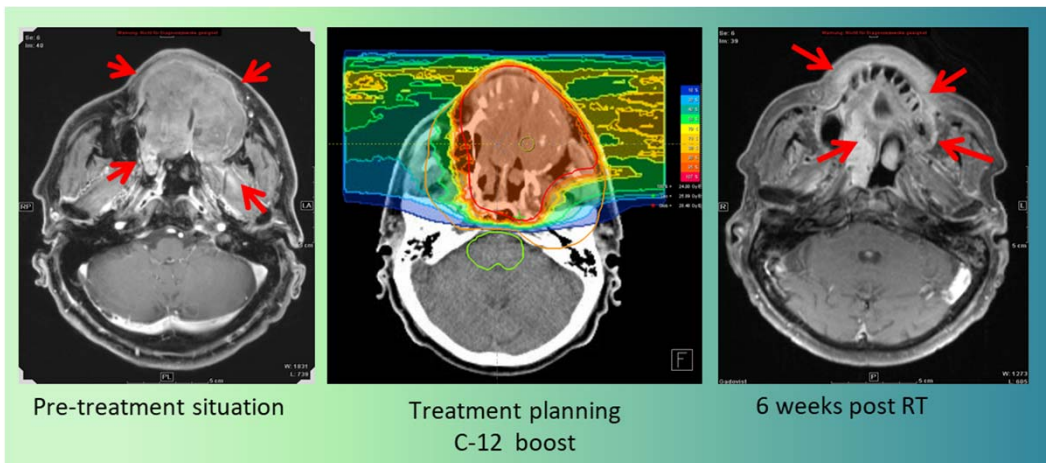
- malignant salivary gland tumors -

COSMIC- trial

Combined therapy of malignant salivary gland tumors with IMRT and carbon ions

- Phase II feasibility study

- No dose limiting acute toxicity
- Late Toxicität G > CTC grade 2 < 5%



CONSTRUCTION OF HIT: 2003-2009, OPENING IN 2009



HIT: Initial Design

2 gantries, 1 horizontal beam (in 2002)

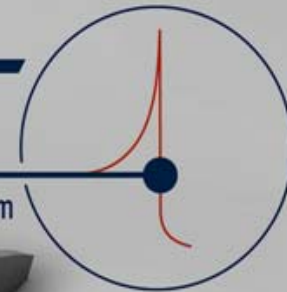


... was changed by hospital administration to :

1 gantry
2 horizontal beam lines

HIT

Heidelberger Ionenstrahl-Therapiezentrum



Ion sources clinical:

- protons
- carbon
- Helium

experimental:

- oxygen

Synchrotron

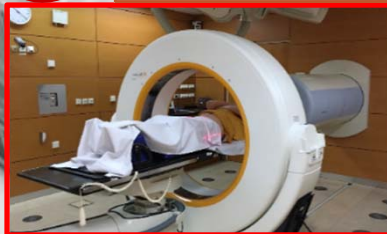
research

X online MRT



1

In room CT



2

MR (shuttle)



3

rotatable Gantry

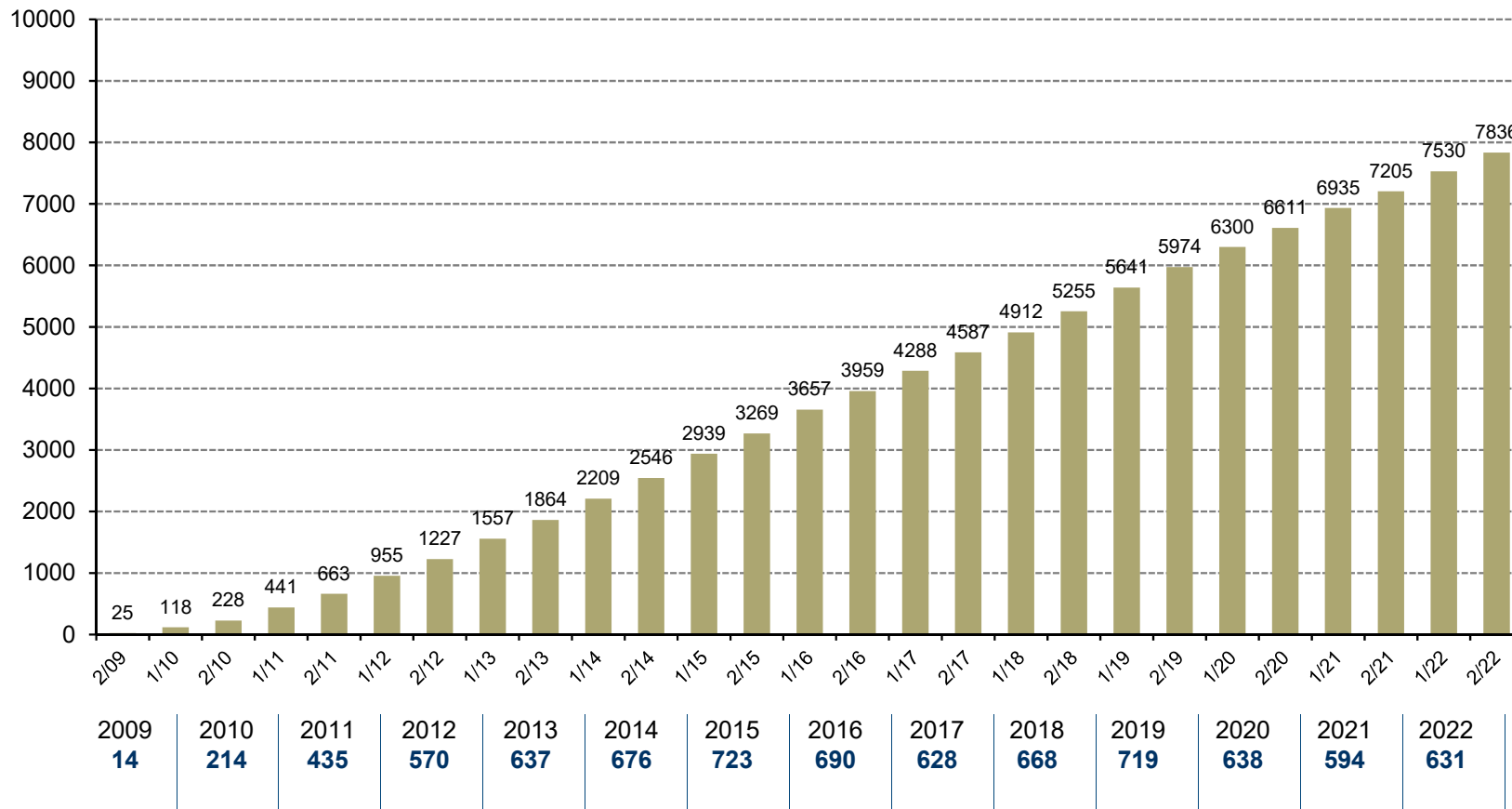


HIT: Operation 24/7



08:00 - 21:00 Uhr Patients /Therapy
21:00 - 24:00 Uhr QA Medical physics
00:00 - 05:00 Uhr Experiments /
Accelerator settings/ Medical physics
05:00 - 06:00 Uhr QA Accelerator
06:00 - 08:00 Uhr QA Medical Physics

Patient numbers @ HIT

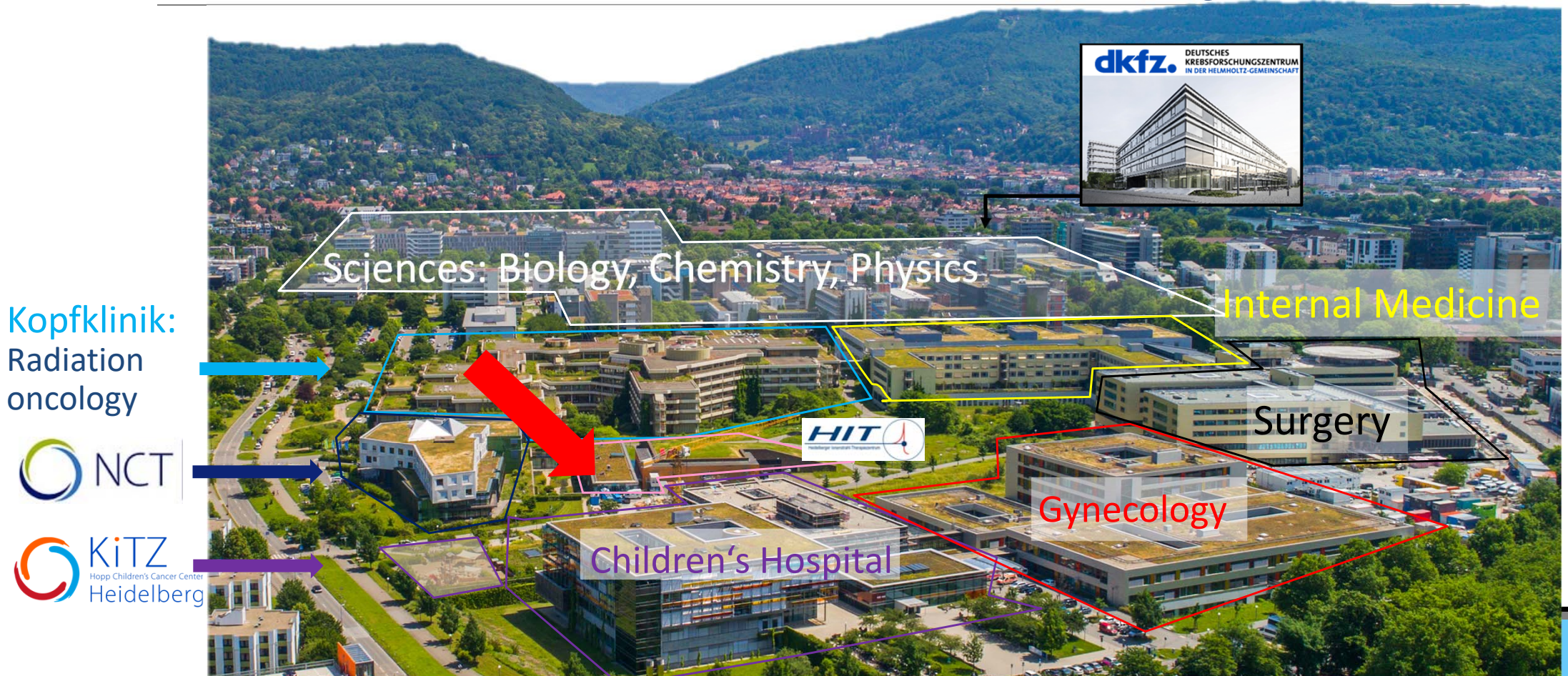


Catchment area:

- 50% local patients (< 50 km)
- 50% national and international patients

Campus Neuenheimer Feld

- ✓ Radiation oncology and HIT is integrated in the clinic ring
- ✓ Translational and academic research are in close neighbourhood



National Center of Tumor diseases (CCC)



Multidisciplinary Care & Translational Research

Multidisciplinary Tumor Boards

27 interdisciplinary tumor boards for each organ system



Members: Experts from medical, surgical and radiation oncology as well as radiology, pathology and nuclear medicine

Tumor Board Types

- **Standard situations** ☑ TUSOP
- **Complex situations** ☑ TUBO
- **Molecular Tumorboards** ☑ MOL-TUBO

Screening for clinical trials

Clinical Cancer Research Programs: Entities

Brain Cancer Program 	Head & Neck Cancer Program 	Breast Cancer Program 	Gynecologic Cancer Program
Genitourinary Cancer Program 	Gastrointestinal Cancer Program 	Endocrine Cancer Program 	Thoracic Cancer Program
Bone and Soft Tissue Sarcoma Program 	Skin Cancer Program 	Hematologic Oncology Program 	Pediatric Cancer Program
Cross-Entity Cancer Program			

Department Radiation Oncology: Staffing



Clinical Study Center

- 2 Scientific coordinators
- 5 Study nurses



Medical data sciences

- 3 Medical data scientists
- 2.5 medical documentalists

Clinical Staff

- 22 Attending physicians
- 26 Resident physicians
- 78 Therapists (MTRA)
- 40 Nurses
- 22 Med. Physicists (photons)
- 12 Med. Physicists (HIT)

Research staff

- Bio-medical Physics
- Data Scientists:
 - AI in medical imaging
- Clinician scientists /trialists
- Medical Scientists
- Translational oncologists
- Biologists



Department Radiation Oncology



Radiotherapy Equipment

- 5 Linear accelerators (Elekta) at Kopfklinik
- 1 TomoTherapy
- 1 MR-Linac (MRIDian)
- 1 CyberKnife
- 1 Brachytherapy unit
- 1 Intraoperative radiotherapy (IOERT) unit
- Ion beam therapy at HIT with 3 treatment places
- 1 Ethos (Varian) at DKFZ

Structure of the Clinic

- ~4500 patients per year
- Ward with 62 beds for in-patients
- Out-patients at NCT
- 27 Tumor conferences
- 14 Specialized consultations



Diagnostic Equipment:

- 2 CT
- 2 MRI
- 1 PET /CT
- Sonography



Coverage of the complete spectrum of radiation therapy treatments
Expansion of therapy options through participation in clinical studies

Indications for protons & carbon ions

Indications

Tumors in children and young adults:

- Ependymoma
- Retinoblastoma,
- Medulloblastoma,
- Glioma,
- Lymphoma,
- Sarkoma,
- Neuroblastoma,
- Teratoma
- Craniopharyngeoma

Chordoma and Chondrosarkoma of skull base

Cerebral Arteriovenous Malformations (AVMs)

Mediastinal lymphoma

Within Phase II clinical trials

Adenoid cystic carcinoma (ACC)

Glioma Grad II/III, Glioblastoma

Paraspinal Sarkoma and Carzinoma, inoperable Osteo- and Chondrosarkomea of the axial skeleton

Meningeoma of the skull base – (> 15 ccm) and atypic and postoperative residual disease or affected sinus cavernosus

Pituitary adenomas (hormonally active and hormone inactive (inoperable, not treatable with radiosurgery/SRS))

Advanced head and neck tumors, non metastasized

Hepatocellular carcinoma

Tumors of the thorax: Lung carcinoma (NSCLC, inoperable stage I-III), and pleura mesothelioma stage I-III

Within Phase II clinical trials

Locally advanced gynecological malignancies that have been pretreated with radiation therapy or are not suitable for brachytherapy.

Esophageal carcinoma not curatively resectable (cT3-4 and cT1-2 inoperable).

Soft tissue sarcomas / chordomas on the trunk of the body (neo) -adjuvant and primarily in the case of inoperability and of the extremities after extremity-conserving surgery

Locally advanced pancreatic carcinoma TxNxM0 with (neo-) adjuvant particle therapy and in the event of inoperability

Craniopharyngeoma

Vestibular schwannoma inoperable, not treatable with radiosurgery / SRS



> 1.000 patients enrolled into clinical trials

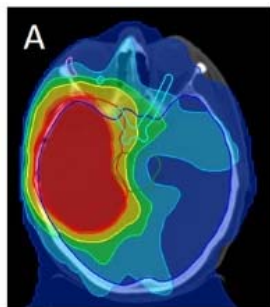
Trial name	Entity treated/investigated	Phase	Ion	Status
ACCEPT	ACC	II	C12 Boost	published
COSMIC	ACC	II	C12 Boost	published
IPI	Prostate	II (random.)	H1 vs. C12	published
OSCAR	Osteosarcoma	II	H1 & C12	published
TPF-C_HIT	Head&Neck	II	C12 Boost	published
MARCIE	atyp. Meningeoma	II	C12 Boost	submitted
CLEOPATRA	Glioblastoma	II	C12 Boost vs. H1 Boost	analysis
CINDERELLA	Glioblastoma (recurrence)	II	C12	analysis
KOLOG	Prostate (recurrence)	II	C12	analysis
PROLOG	Prostate (recurrence)	II	H1	analysis
IMRT HIT-SNT	Paranasal sinus	II	C12 Boost	analysis
PROMETHEUS	HCC	II	C12	analysis
INKA	Pancoasttumor	II	C12	analysis
PANICORA	Rectal cancer (recurrence)	II	C12	analysis
APPROVE	Cervicall Cancer	II	H1	analysis
ISAC	Sacral Chordoma	II (random.)	H1 vs. C12	recruiting
HIT Chordom	Skull Base Chordoma	III	C12 vs. H1	recruiting
HIT Chondrosarkom	Skull Base Chondrosarcoma	III	C12 vs. H1	recruiting
PAROS	Prostate (recurrence)	III	IMRT vs. H1	recruiting
ACCO	ACC	II (random.)	C12 vs. C12 Boost	recruiting
RETRO-ION	Retroperitoneal Sarkoma	II	C12	recruiting
PACK	Pankreatic Cancer	II	C12	recruiting
CARE	Head&Neck (recurrence)	II (random.)	C12 vs. IMRT	recruiting
EXTREM ION	Extremity Sarcoma	II	C12	recruiting
GRIPS	Glioblastoma	III	Protonen vs. IMRT	recruiting



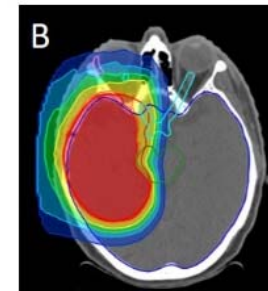
GRIPS: Glioblastoma Radiotherapy with IMRT or Protons

multicentric, prospective, randomized phase III studie, recruiting

funded by



Glioblastoma WHO °4,
gliosarcoma



Standard arm:

R

n = 326

Experimental arm:

30 x 2 Gy
33 x 1,8 Gy
15 x 2,67 Gy } **IMRT**
+/- ChT

30 x 2 Gy(RBE)
33 x 1,8 Gy(RBE)
15 x 2,67 Gy(RBE) } **Protons**
+/- ChT

Endpoint:

Cumulative toxicity rate \geq grade 2 until month 4

Secondary endpoints

- PFS 1 y / 2 y.
- OS 1 y / 2 y
- **Time to additional therapy** due to disease progress (excluding adjuvant therapy)
- **QoL** (QLQ-C30 und QLQ-BN20)
- **Neurocognition** (Hopkins Verbal Learning Test-Revised)
- **Lymphocyte number** (accompanied translational research program)

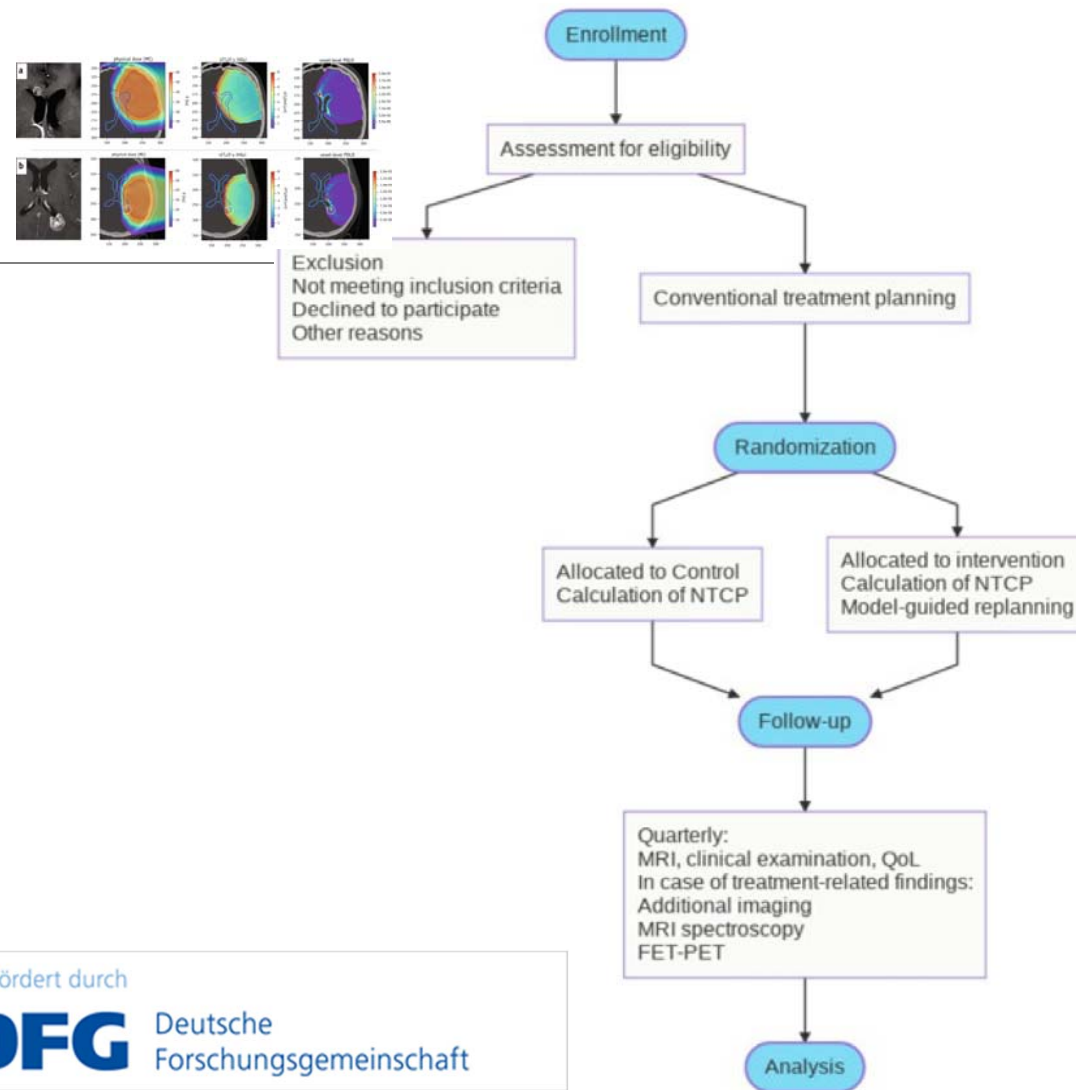


INDIGO: LET and RBE optimization for protons

Key hypothesis:
model-guided risk avoidance reduces the risk for contrast enhancing brain lesions

multicentric, prospective interventional, randomized, observer blind two arm (active control), investigator initiated phase II trial

120 patients to be enrolled (60 per group)

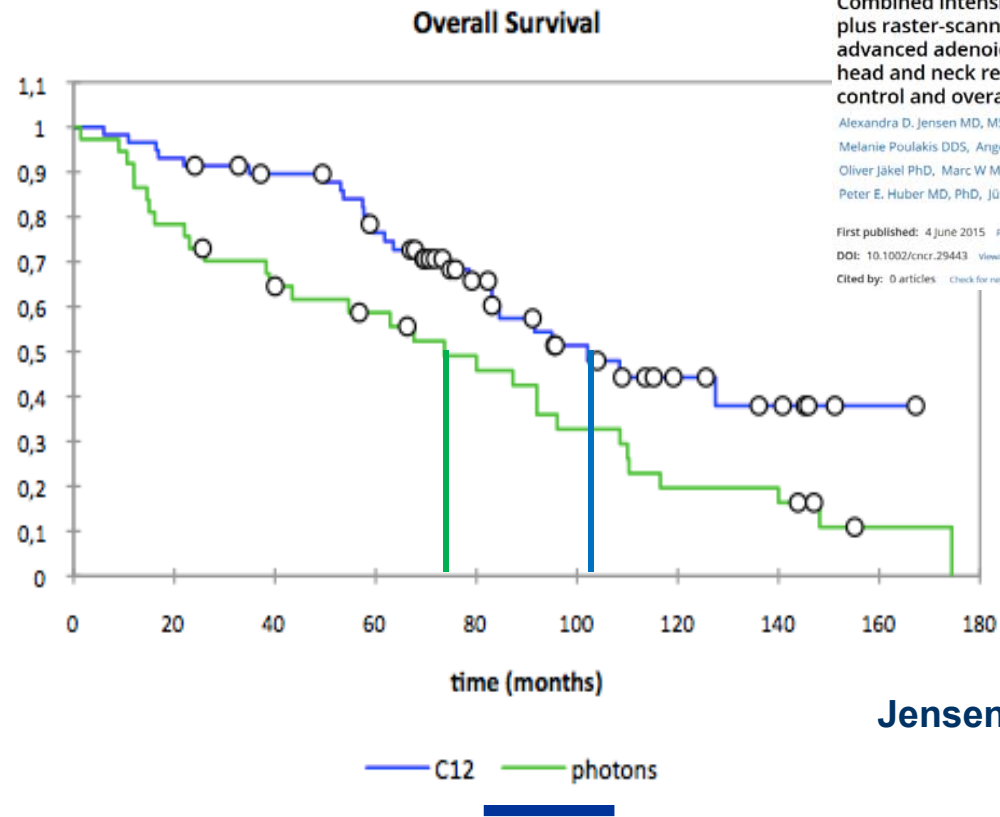
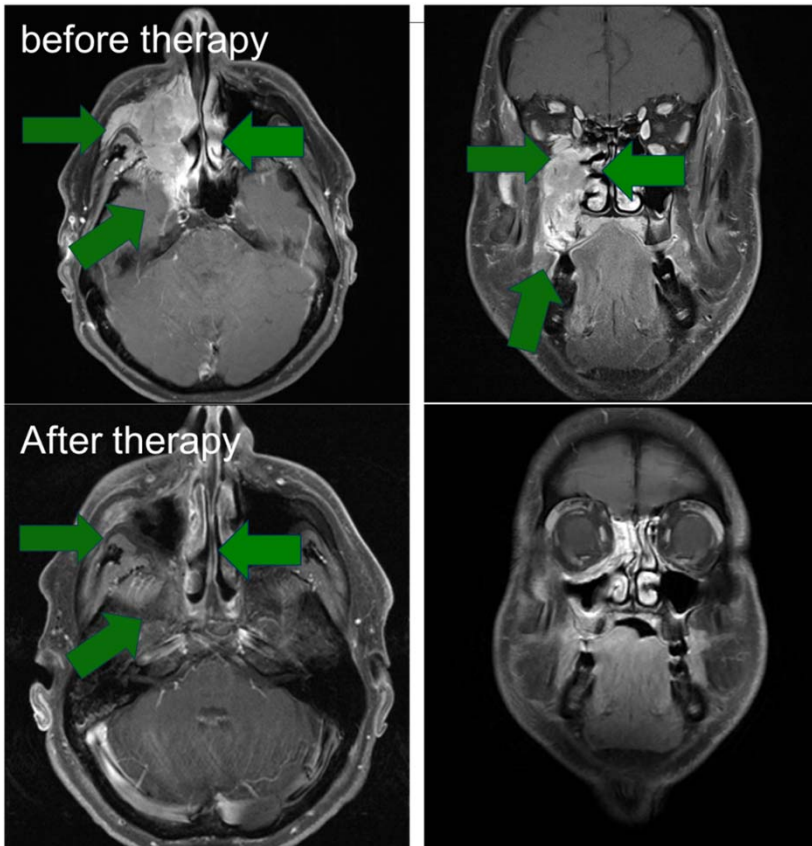


Clinical studies **carbon ions** vs. **photons**

Study Name	Question	Design	Arm A	Arm B	Results
COSMIC <i>Jensen et al. IJROBP (2015)</i> <i>Held et al. Radiat Oncol J (2020)</i> <i>Blattmann et al. BMC cancer (2010)</i>	Combined therapy of malignant salivary gland tumors with IMRT and carbon ions	Phase 2 monocentric randomized	Photon IMRT + ¹² C boost	Photon IMRT	Good tolerability; 3-year LC rate 81.9% no difference regarding resection status
ACCO <i>Lang et al., BMC Cancer. 2021</i>	Adenoid cystic carcinoma and carbon ions only	Phase 2 monocentric randomized	Photon IMRT + ¹² C boost	¹² C RT	Currently recruiting
CARE <i>Held et al. Radiat Oncol. 2020</i>	Carbon ion re-irradiation vs intensity modulated re-radiation therapy for recurrent head and neck cancer	Phase 2 monocentric randomized	¹² C Re-RT	Re-IMRT	Currently recruiting
Cinderella <i>Combs et al. BMC Cancer. 2010;</i>	Carbon ion radiation therapy versus fractionated stereotactic radiation therapy in patients with recurrent or progressive gliomas	Phase 1/2 monocentric randomized	Normo-fractionated ¹² C RT	Fractionated stereotactic photon RT	Results pending

COSMIC- trial

Better local tumor control by C-12 irradiation leads to better long-term survival of locally advanced adenoid cystic carcinoma



Cancer

Original Article
Combined intensity-modulated radiotherapy plus raster-scanned carbon ion boost for advanced adenoid cystic carcinoma of the head and neck results in superior locoregional control and overall survival

Alexandra D. Jensen MD, MSc, Anna V. Nikoghosyan MD, Melanie Poulakis DDS, Angelika Höss MSc, Thomas Haberer PhD, Oliver Jäkel PhD, Marc W. Mütner MD, Daniela Schulz-Ertner MD, Peter E. Huber MD, PhD, Jürgen Debus MD, PhD

First published: 4 June 2015 Full publication history
 DOI: 10.1002/cncr.29443 View/Save citation
 Cited by: 0 articles Check for new citations

Jensen et al. 2015

ion's Horizon 2020
 ent No 101008548

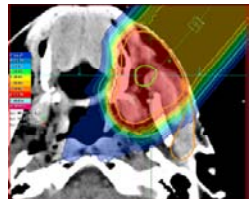
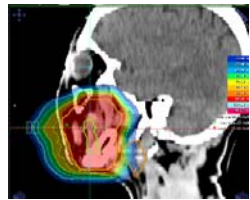
ACCO trial: Adenoid Cystic carcinoma Carbon Only

Design: Prospective, randomized phase II trial, 175 pat. in 4 years

supported by:

Deutsche Krebshilfe
 HELFEN. FORSCHEN. INFORMIEREN.

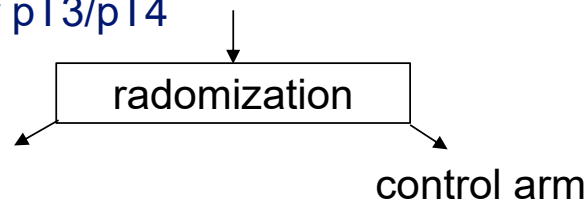
Inclusion: ACC inoperable and/or R1/R2 resected and/or Pn+ and/or pT3/pT4



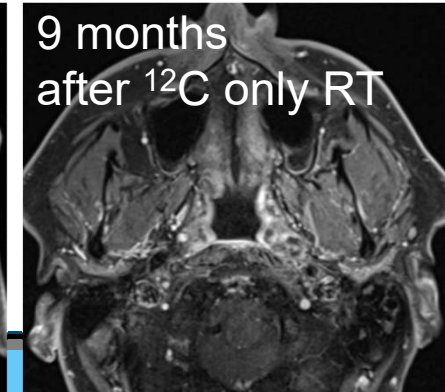
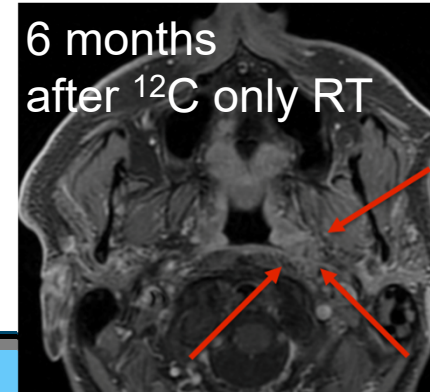
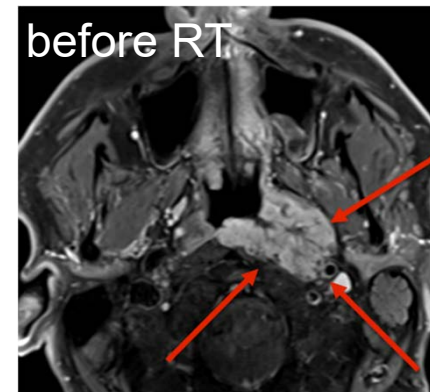
single dose

total dose

BEDd 2Gy*



	carbon ions only		photons + carbon ions	
	initial plan	boost plan	initial plan	boost plan
single dose	3 Gy(RBE)	3 Gy(RBE)	2 Gy	3 Gy(RBE)
total dose	51 Gy(RBE)	15 Gy(RBE)	50 Gy	24 Gy (RBE)
BEDd 2Gy*	61 Gy	18 Gy	50 Gy	29 Gy
	22 FX in 4 weeks 5-6 FX per week		33 FX in ~ 6 weeks	



Primary endpoint: Loco-regional control (5 years)

Clinical trials protons vs carbon ions

Study Name	Question	Design	Arm A	Arm B	Status
Chordoma/HIT-1 <i>Nikoghosyan et al. BMC cancer (2010)</i>	Proton vs carbon ion radiation therapy in patients with chordoma of the skull base	Phase III monocentric randomized	¹² C RT	proton RT	Currently recruiting
ISAC <i>Habl et al. IJROBP (2016)</i>	Ion irradiation of sacrococcygeal chordoma	Phase II monocentric randomized	¹² C RT	proton RT hypo-fractionated	Currently recruiting
Chondrosarcoma <i>Nikoghosyan et al. BMC cancer (2010)</i>	Proton vs carbon ion radiation therapy in patients with low- and intermediate-grade chondrosarcoma of the skull base	Phase III monocentric randomized	¹² C RT	proton RT	Currently recruiting
Retro-Ion <i>Seidensaal et al. Trials (2021)</i>	Neoadjuvant irradiation of retroperitoneal soft tissue sarcoma with ions	Phase II monocentric randomized	¹² C RT	proton RT	Currently recruiting
Retro-Ion <i>Seidensaal et al. Trials (2021)</i>	Neoadjuvant irradiation of retroperitoneal soft tissue sarcoma with ions	Phase II monocentric randomized	¹² C RT	proton RT	Currently recruiting

Skull Base Chordomas treated at GSI

Cohort:

- Between 1998 and 2008 at GSI
- **155 patients (76 m + 79 w)**
- median age 48 years (15y -85y)
- carbon ions using a raster scan technique.
- median total dose **60 Gy (RBE), at 3 Gy (RBE) per fraction.**
- median boost planning target volume 70 mL (2 mL-294 mL).
- **median follow-up 72 mo. (12-165)**

Endpoints:

- local control (LC)
- overall survival (OS)
- long-term toxicity

Results:

- **No higher late toxicity** could be detected after 12 Ctreatment.
- **55 local recurrences (35%)** during f/u

Uhl M et al., Cancer 2014; 120(10): 1579–1585.

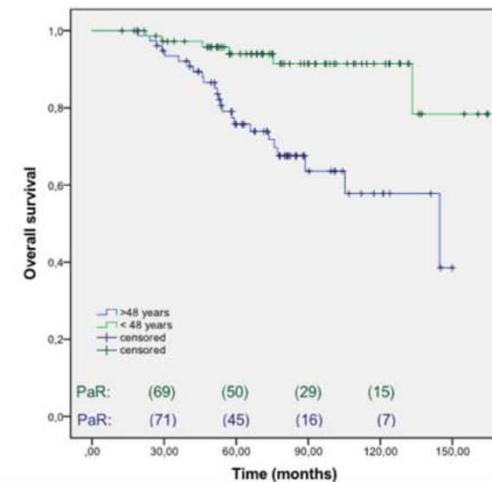
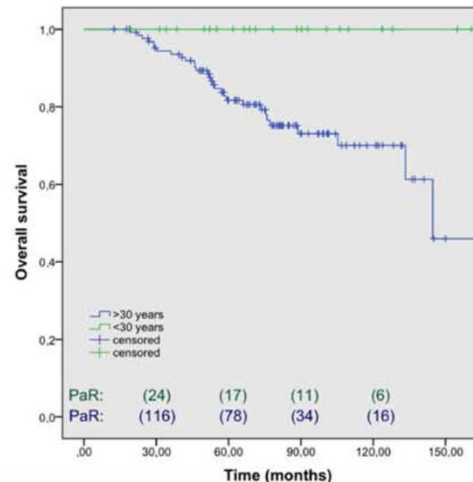
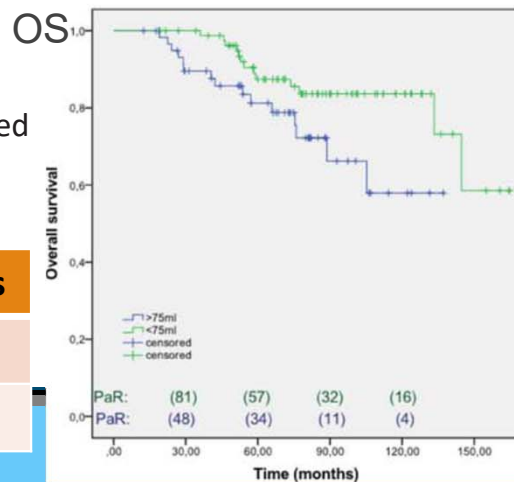
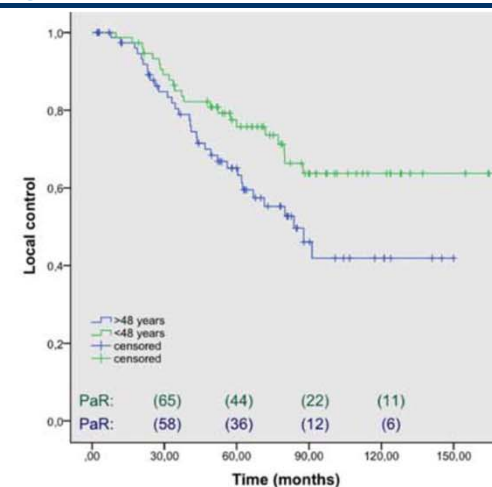
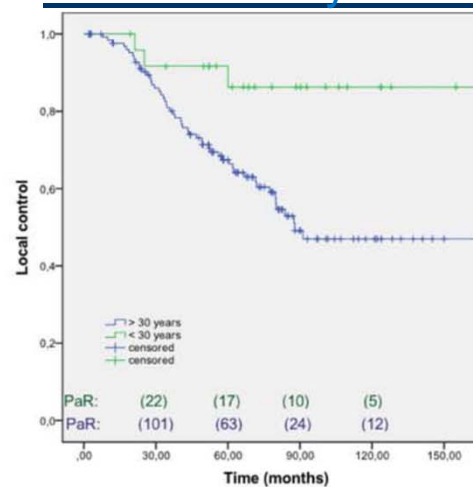
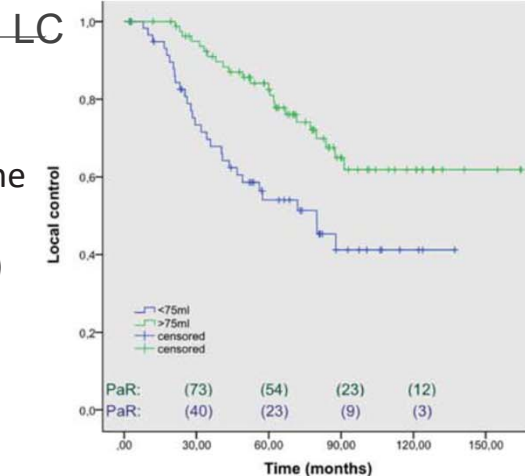
Prognostic factors

< 30 y

age

< 48 y

Boost Volume < 75 ml



	3 years	5 years	10 years
LC	82%	72%	54%
OS	95%	85%	75%

HIT-1 Trial for Skull Base Chordomas

Nikoghosyan et al. BMC Cancer 2010. 10, 607

prospective, randomized phase III superiority trial

Hypothesis: 10% increase in LPFS by using carbon ions

Start: 2010 at HIT

Skull base chordoma
randomization

n = 344

Carbon ions
45 Gy(RBE) ¹²C
+ Boost up to
63Gy (RBE)
3Gy(RBE) / Fx

Protons
50-56 Gy(RBE) ¹H
+boost up to
72 Gy (RBE)
2 Gy(RBE) / Fx

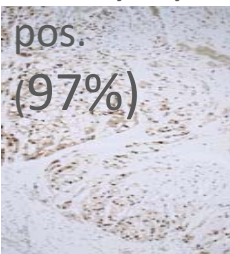
follow-up: 8-13 years

Primary endpoint: 5-y LPFS

Secondary endpoints: Toxicity, prognostic factors

Histology

Chordoma
brachyury

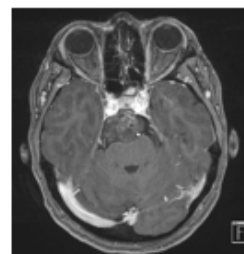


Chondrosarcoma

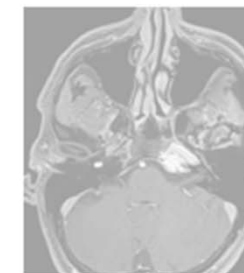
IDH pos.
(50-80%)

T1 + c.a. fatsat

variable
KM-Aufnahme

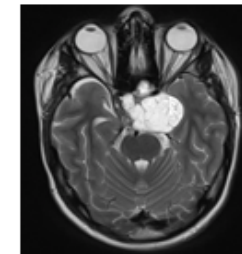


variable
KM-Aufnahme

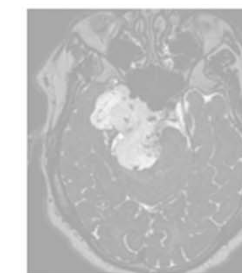


T2 fatsat (STIR, TRIM)

Honigwabenmuster,
Stark hyperintens

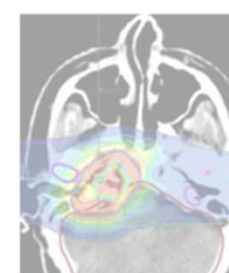


Stark hyperintens



Target volume

+ Clivus+ prävert.
Muskulatur



Ion irradiation of **Sacrococygeal Chordoma**

Pilot trial: **Hypofractionated Protons- vs. C-12-RT**

100 Patients (50 per Arm)
Stratification CTV <1000ml>

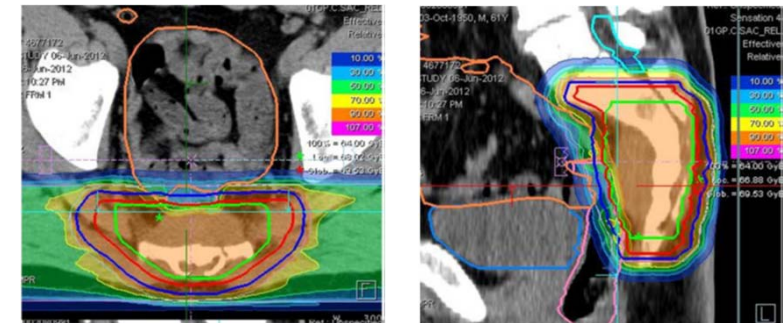
randomization

Arm A (proton therapy):

- Total dose to the PTV : 64 GyE in 4 GyE / Fx
- **BED: 96Gy**

Arm B (12 Ctherapy):

- Total dose to the PTV : 64 GyE in 4 GyE /Fx
- **BED: 96Gy**



	Enrollment	Before irradiation	During irradiation	End of irradiation	6 weeks Post RT	4 months post RT	8 months post RT	12 months post RT
Anamnesis	X		X	X	X	X	X	X
Toxicity	X		X	X	X	X	X	X
MRI		X			X	X	X	X
CT		X						
Quality of life		X		X				X

Primary endpoints:

Feasibility,
Toxicity (Incidence \geq grade 3-5)

Secondary endpoints :

OS, LPFS, QoL

Frequency and clinical relevance of sacral insufficiency fractures (SIFs) after high-dose carbon-ion based irradiation of sacral chordomas

Bostel T, Nicolay NH, Welzel T, Bruckner T, Mattke M, et al. 2018. Radiat Oncol 13: 154

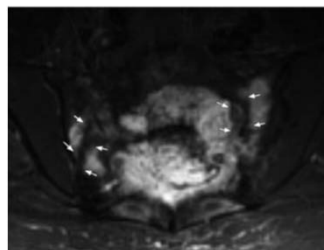
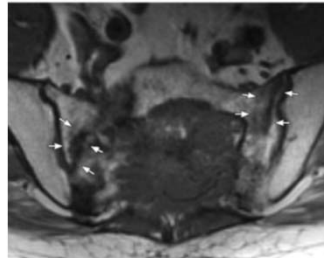
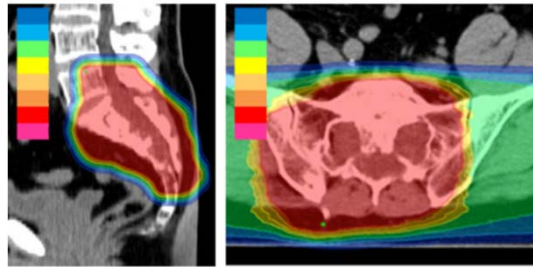
56 patients, retrospective study.

21 patients (37%) definitive radiotherapy
35 patients (63%) postoperative RT using carbon ions, either in combination with photons or as single-modality treatment (median radiation dose 66 Gy RBE, range 60–74 Gy).

Follow-up:

MRI of the pelvis at 3-monthly intervals in the first year and consecutively at 6-monthly intervals.

Median follow-up was **35.5 months** (range 2–83).



Sacral fractures were a considerable radiogenic late effect, affecting about half of the treated patients.

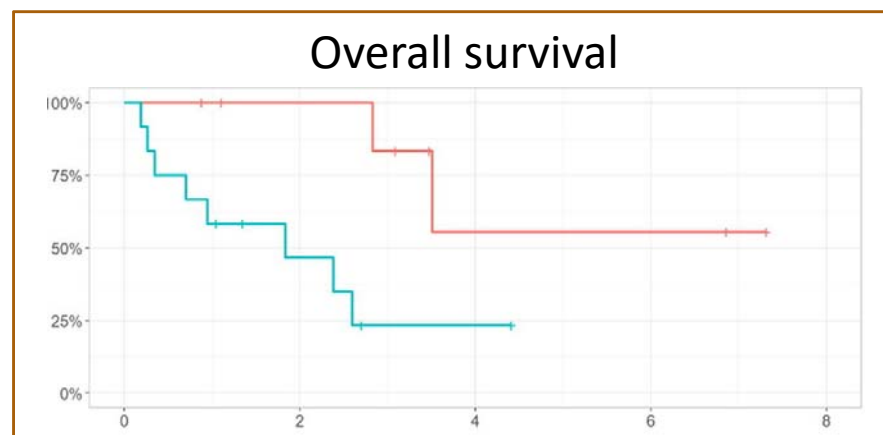
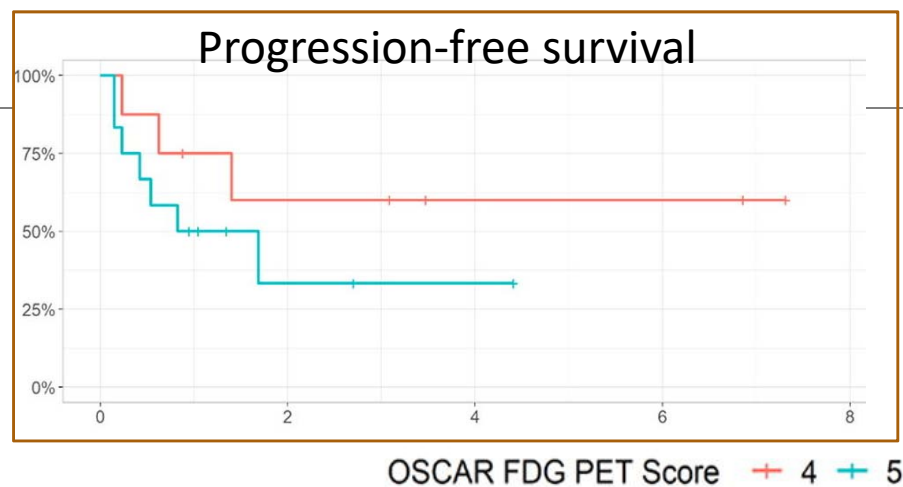
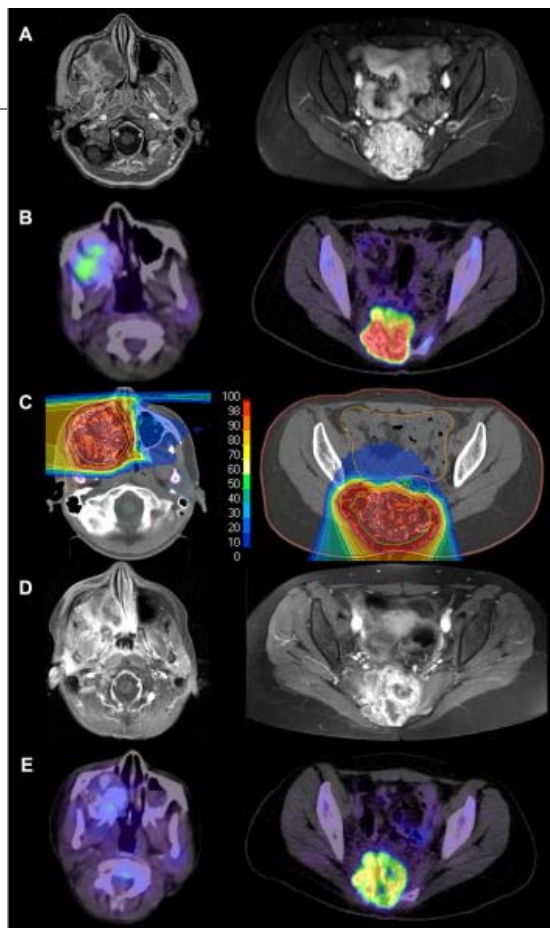
However, only ~32% of these fractures were clinically symptomatic requiring regular medical care and pain therapy.

>> Further hazard factor analysis in the future with larger patient numbers will enable the **identification of high-risk patients** for developing SIFs with the ultimate goal to prevent symptomatic fractures

The role of combined ion-beam radiotherapy (CIBRT) with protons and carbon ions in a multimodal treatment strategy of inoperable osteosarcoma

Seidensaal K, ... Harrabi SB. Radiother Oncol. 2021

- Combined ion-beam radiotherapy for osteosarcoma is a novel local therapeutic approach
- Despite unfavorable size/localization toxicity was moderate and
- Local control promising
- **FDG PET Score** might serve as a surrogate for grading histopathologic regression in future.





NATIONALES CENTRUM
FÜR TUMORERKRANKUNGEN
HEIDELBERG

getragen von:
Deutsches Krebsforschungszentrum
Universitätsklinikum Heidelberg
Thoraxklinik-Heidelberg
Deutsche Krebshilfe



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RadioOnkologie



Behandeln
Forschen
Lehren



HIRO

Heidelberg Institute
for Radiation Oncology

National Center for
Radiation Research in
Oncology Heidelberg

supported by:
German Cancer Research Center (DKFZ)
Heidelberg University Hospital
Heidelberg Ion-Beam Therapy Center (HIT)
Medical Faculty Heidelberg

dkfz.

DEUTSCHES
KREBSFORSCHUNGSZENTRUM
DKFZ KREBSZENTRUM



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