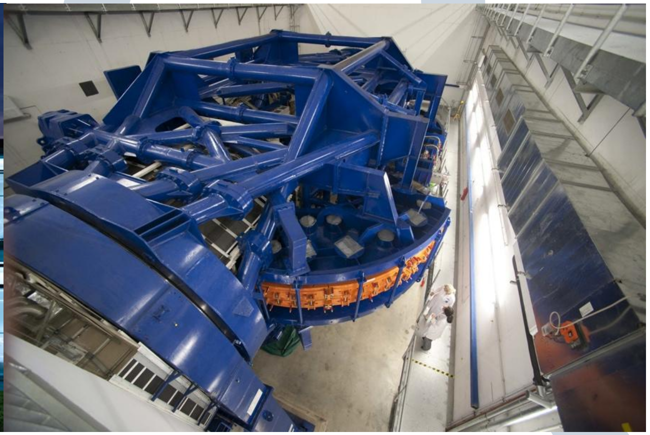
UniversitätsKlinikum Heidelberg

Carbon Ion Radiotherapy: Clinical Concepts and Experience

Jürgen Debus



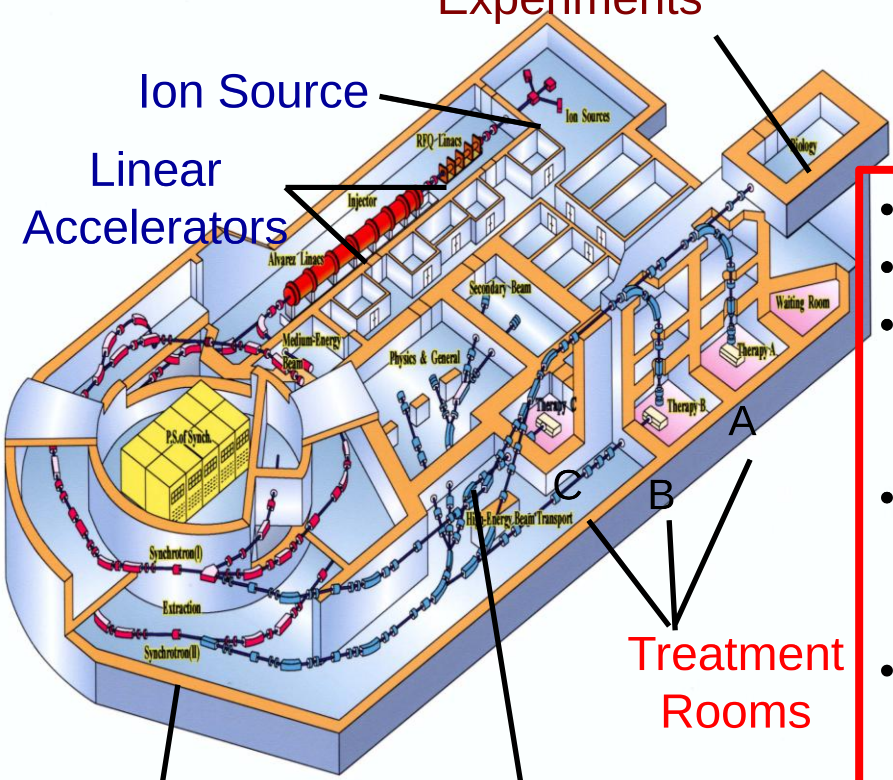
Clinical Use Of Carbon Ions

*** after pionierung work of Berkeley**

Institution	Country	Start of treatment	Patients treated	Date of information
NIRS-HIMAC, Chiba	Japan	1994	7331	01/2013
HIBMC, Hyogo	Japan	2002	788	12/2011
GHMC, Gunma	Japan	2010	537	12/2012
GSI, Darmstadt HIT, Heidelberg	Germany	1997 / 2009	1560	06/2013
CNAO, Pavia	Italy	2012	22	03/2013
IMP-CAS/Lanzhou	China	2006	194	12/2012

centers to go clinical: Shang-hai, Marburg, Vienna

HIMAC(Heavy Ion Medical Accelerator in Chiba)

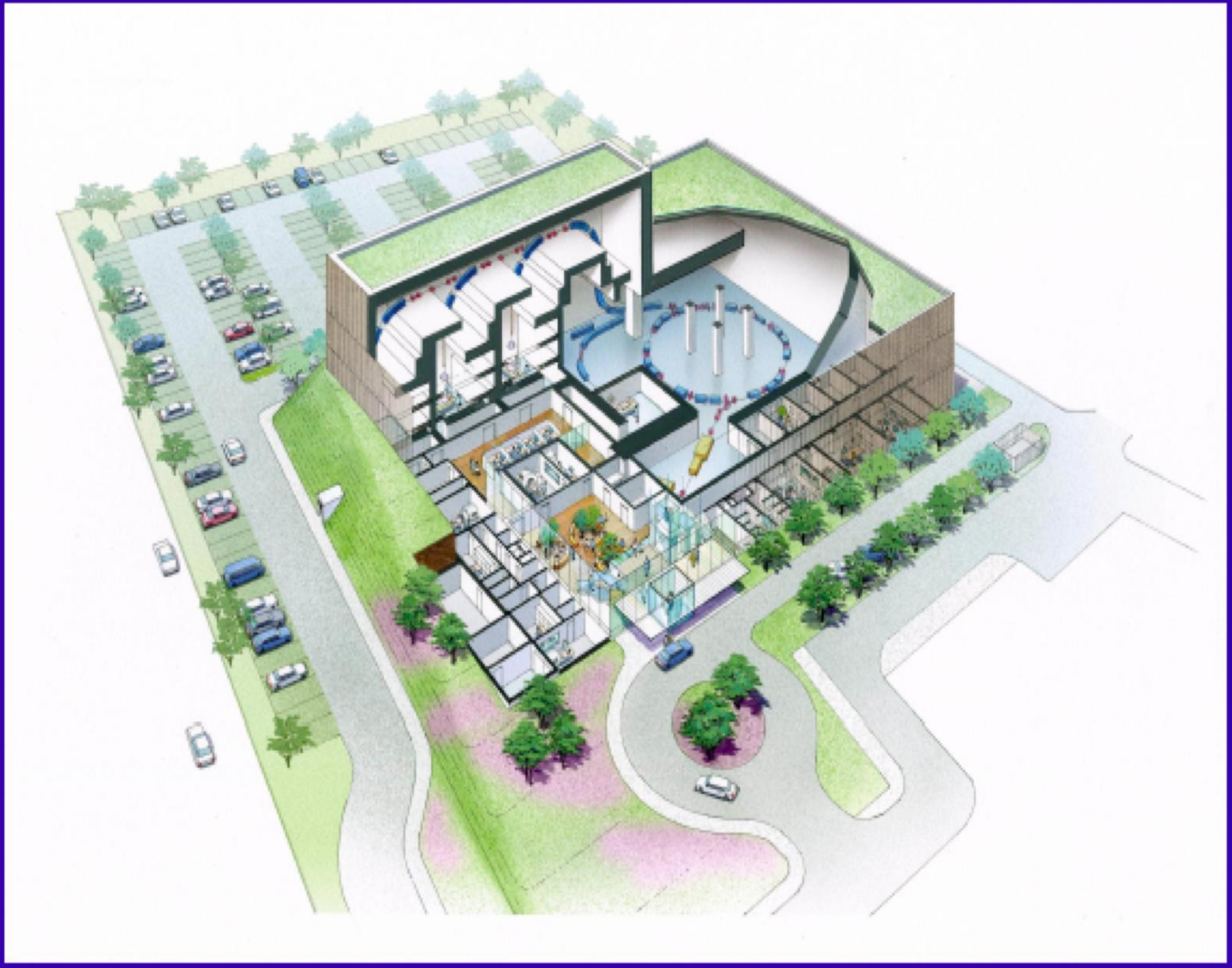


Specification of HIMAC

- Ion : He ~ Ar
- Max energy: ~800Mev/n
- Treatment room(3)
  fixed vertical :A, fixed horizontal :C, V & H :C
- The accelerated energy
  Vertical beam (290 MeV/u, 350 MeV/u)
  Horizontal beam (290 MeV/u, 400 MeV/u)
- The range of C-ion beam in water
  290-MeV/u : 15 cm
  350-MeV/u : 20 cm
  400-MeV/u : 25 cm
- Maximum field size : 15 cm by 15 cm

Sato et al. Nuclear Physics A. 1995; 588: 229—234

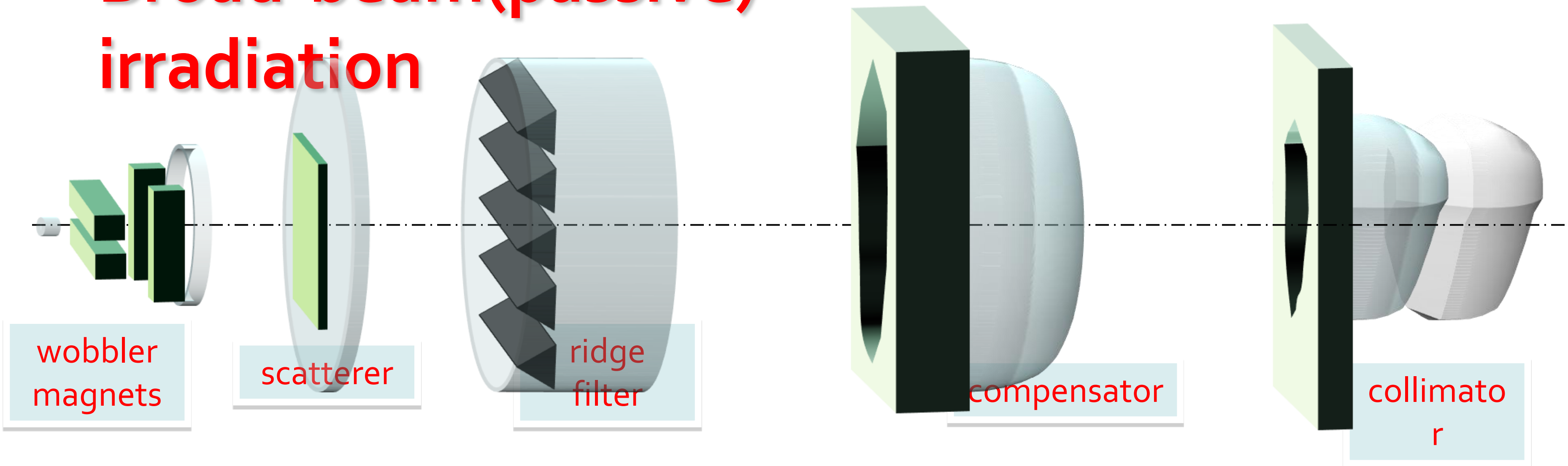
New Compact Accelerator for C-ion RT at Gunma U.



Realized 1/3 cost and size of HIMAC

HIMAC Beam Delivery Techniques

- **Broad-beam(passive) irradiation**



To produce uniform irradiation fields, a passive beam delivery system was employed. We use a pair of wobbler magnets and a scatterer. The range shifter is used for adjusting the residual range of carbon ions in the patient. The ridge filter is used to spread out the Bragg peak in the depth-dose distribution of carbon ions.

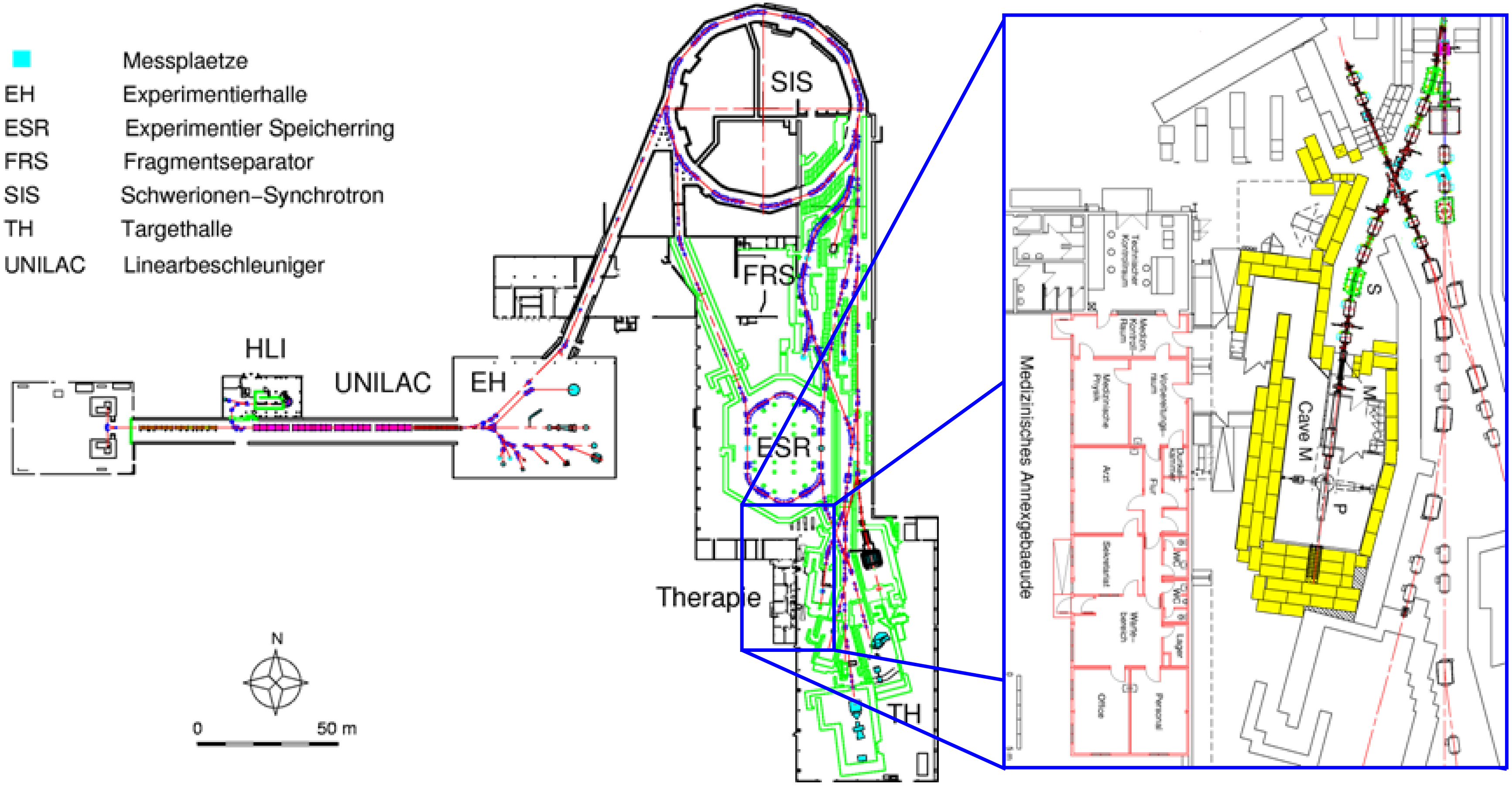
Kanai et al. IJROBP1999, 44:201-21

Technique at HIMAC

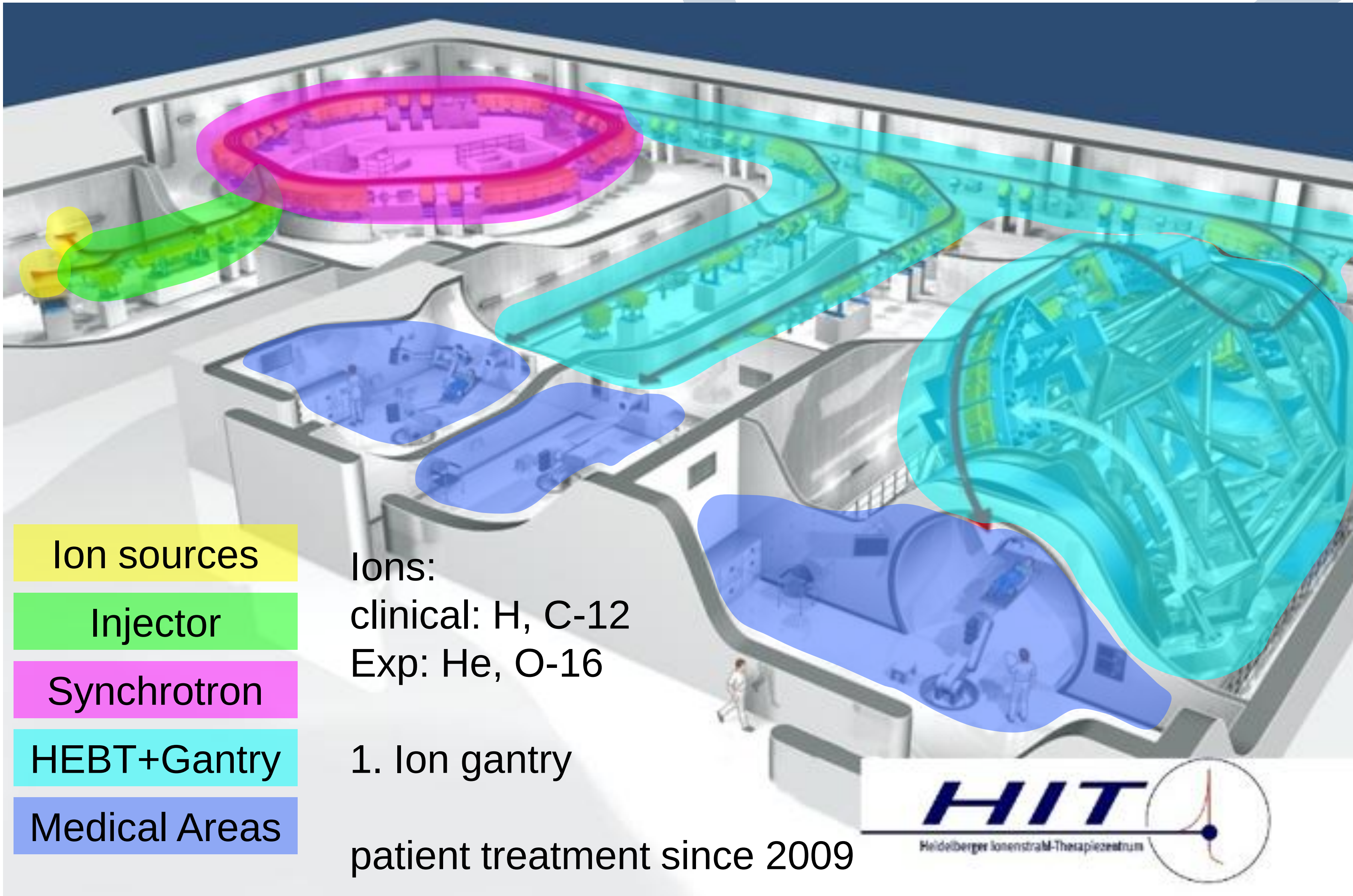
Immobilization
Beam delivery
Targeting
Treatment planning
Gating, patch, and spac

✓ Fixed beam line
✓ Passive beam and raster scanning
✓ Hitting a moving target
✓ SOBP; Dose description

Start Of Carbon Ion Radiotherapy in Heidelberg: Pilot Project At GSI – Medicine in A Physics Lab



HIT Accelerator System



Ions:
clinical: H, C-12
Exp: He, O-16

1. Ion gantry

patient treatment since 2009

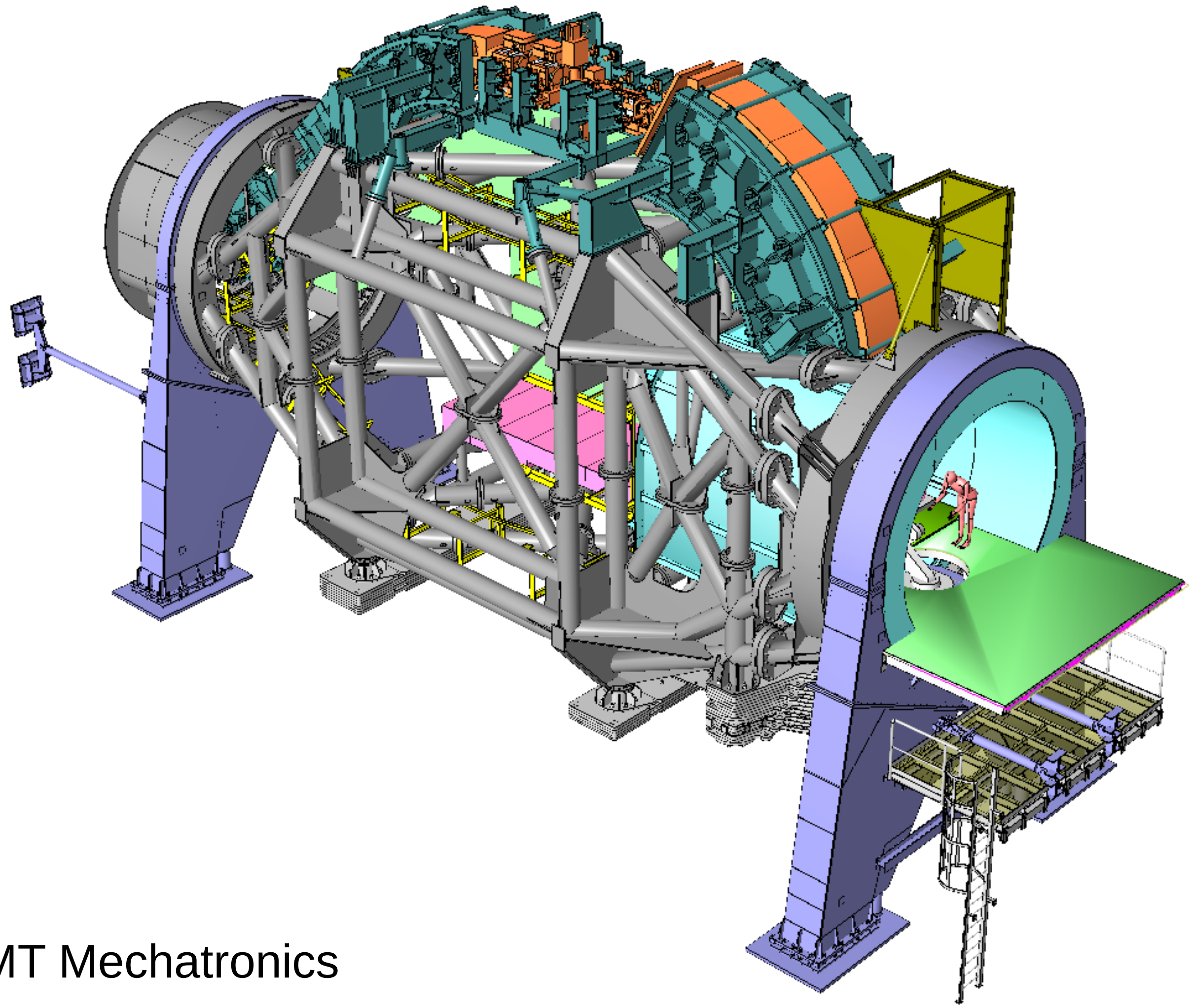
isocentric barrel-type Design for HIT

world-wide first
ion gantry

2D beam scannin
upstream to final
bending, almost
parallel due to edg
focussing

± 180° rotation
3° / second

13m diameter
25m length
600 to rotating
(145 to magnets)

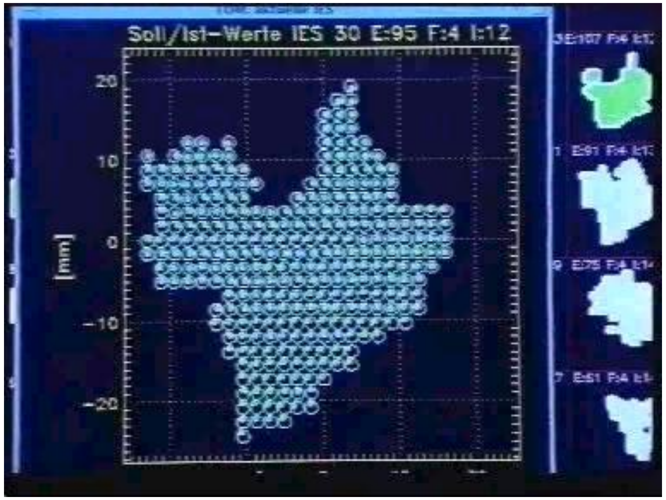


MT Mechatronics

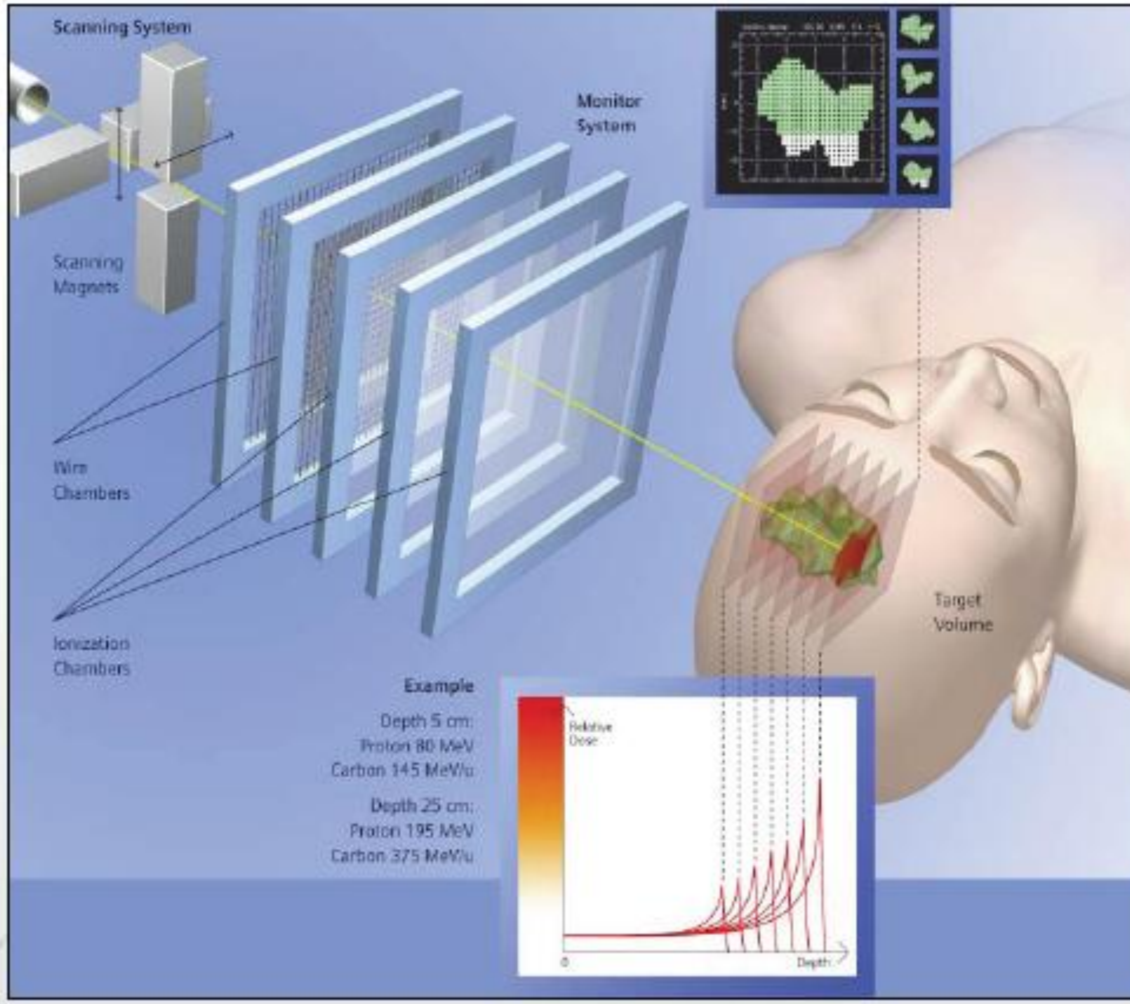
MT Aerospace

Optimized Beam Scanning:

Typically 30-50 energy slices, in total 20000-50000 raster points



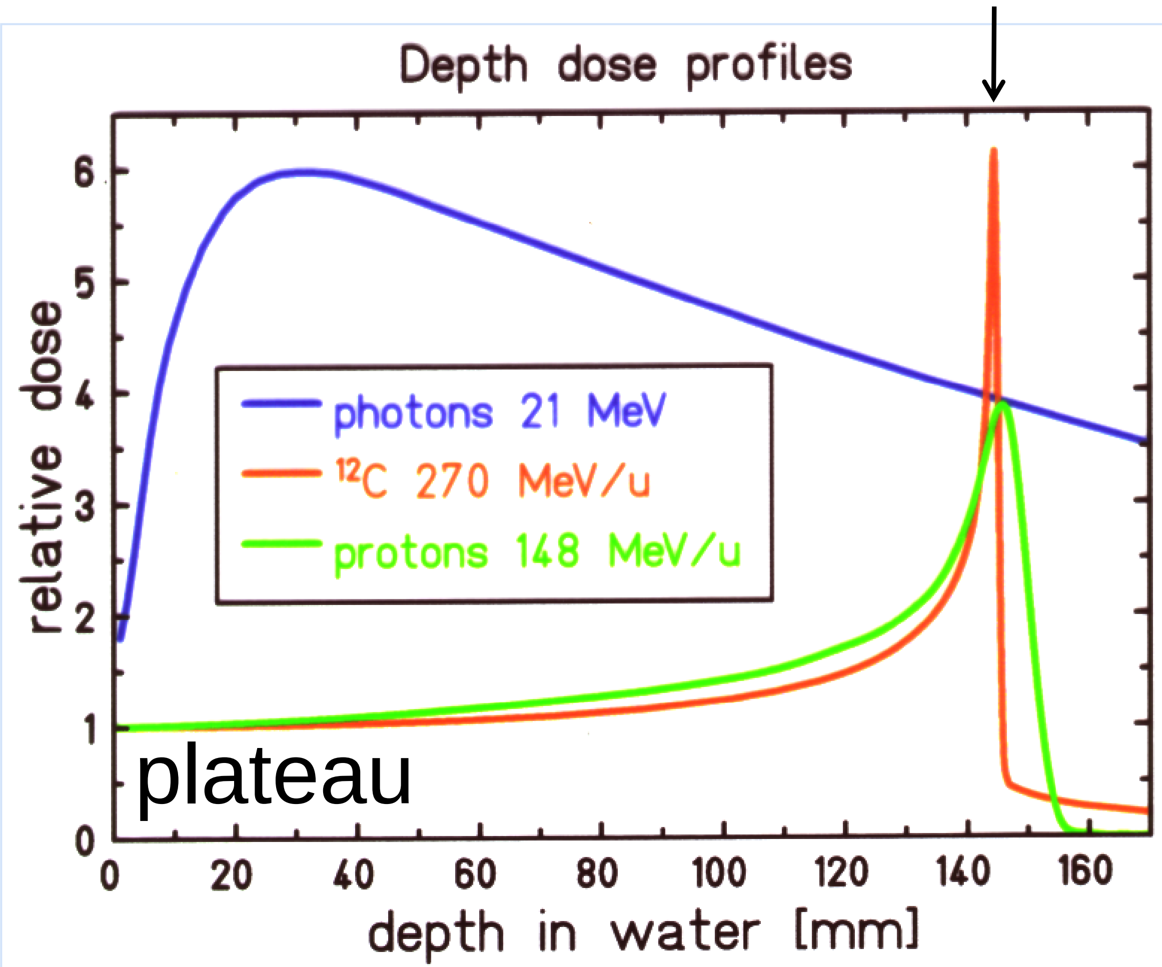
treatment console:
online monitor

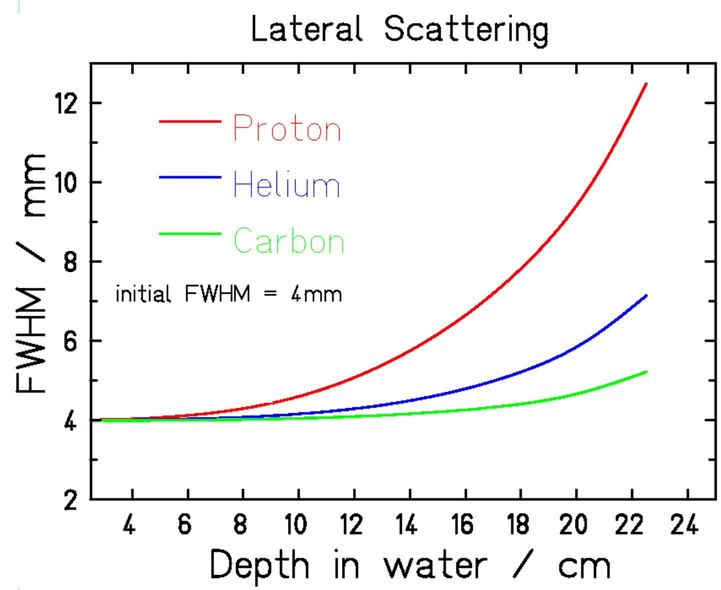


Intensity-Controlled Rasterscan Technique, Haberer et al., GSI, NIM A,1993

Rationale For „Bragg-peak“ Radiotherapy

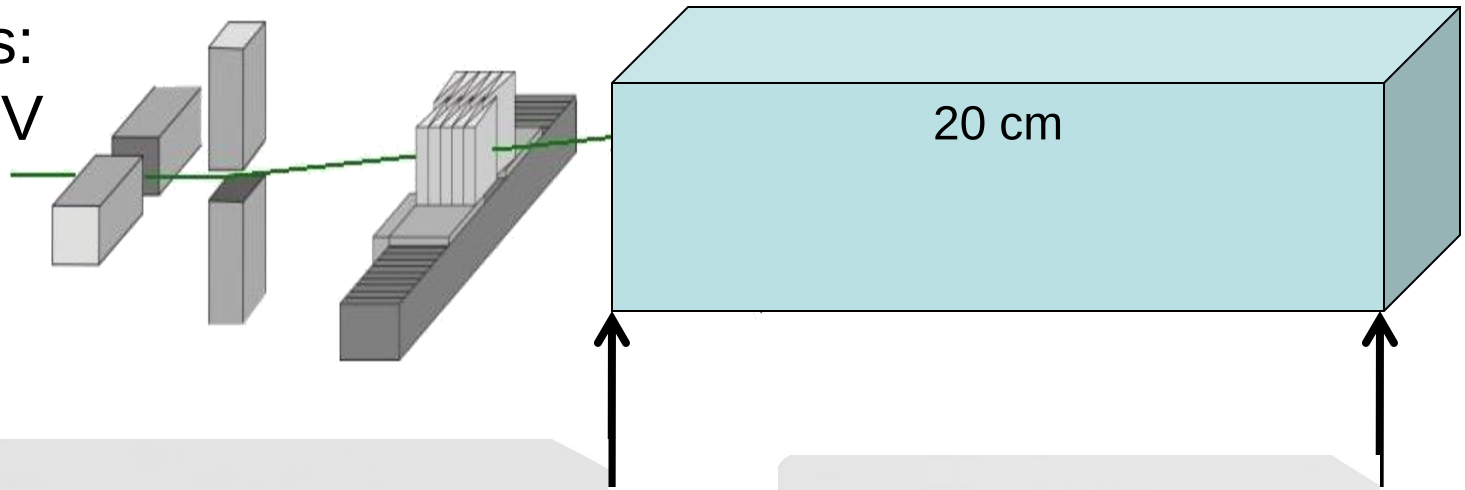
„Bragg“-peak

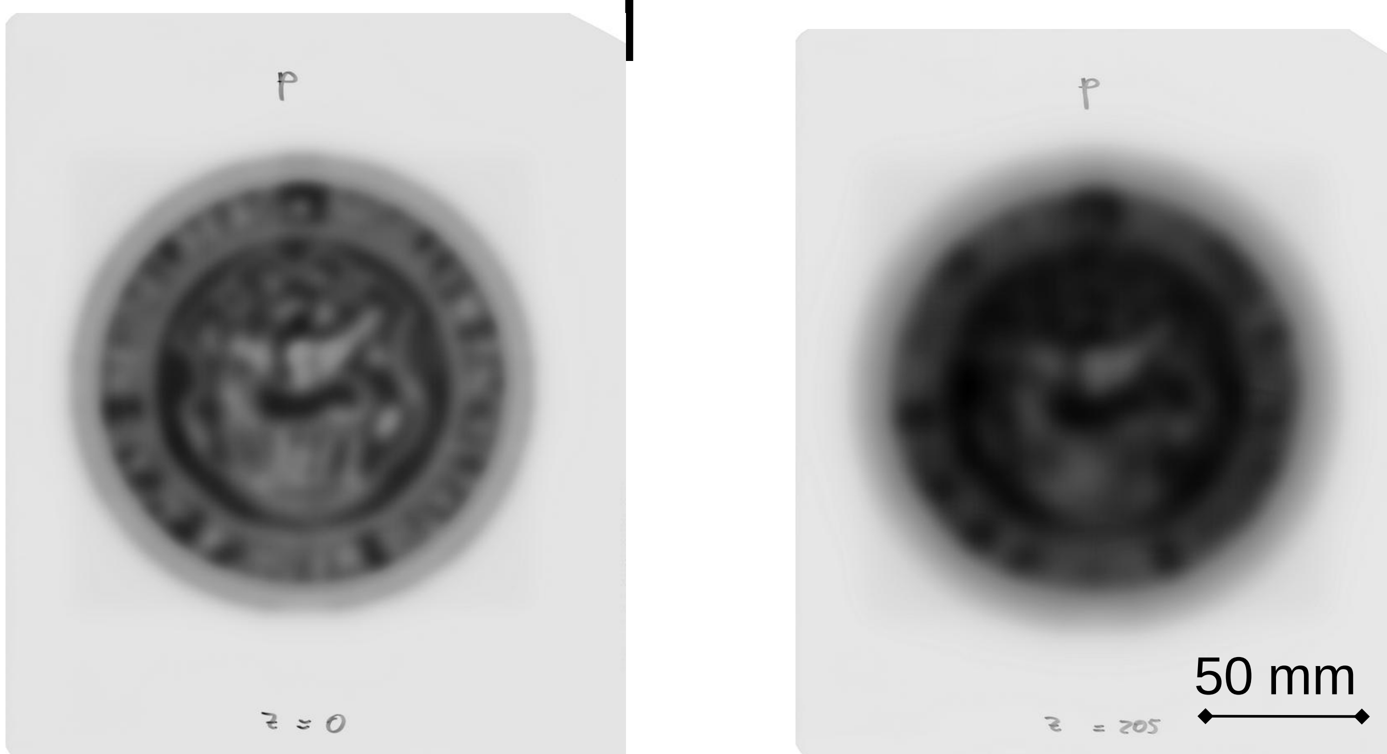




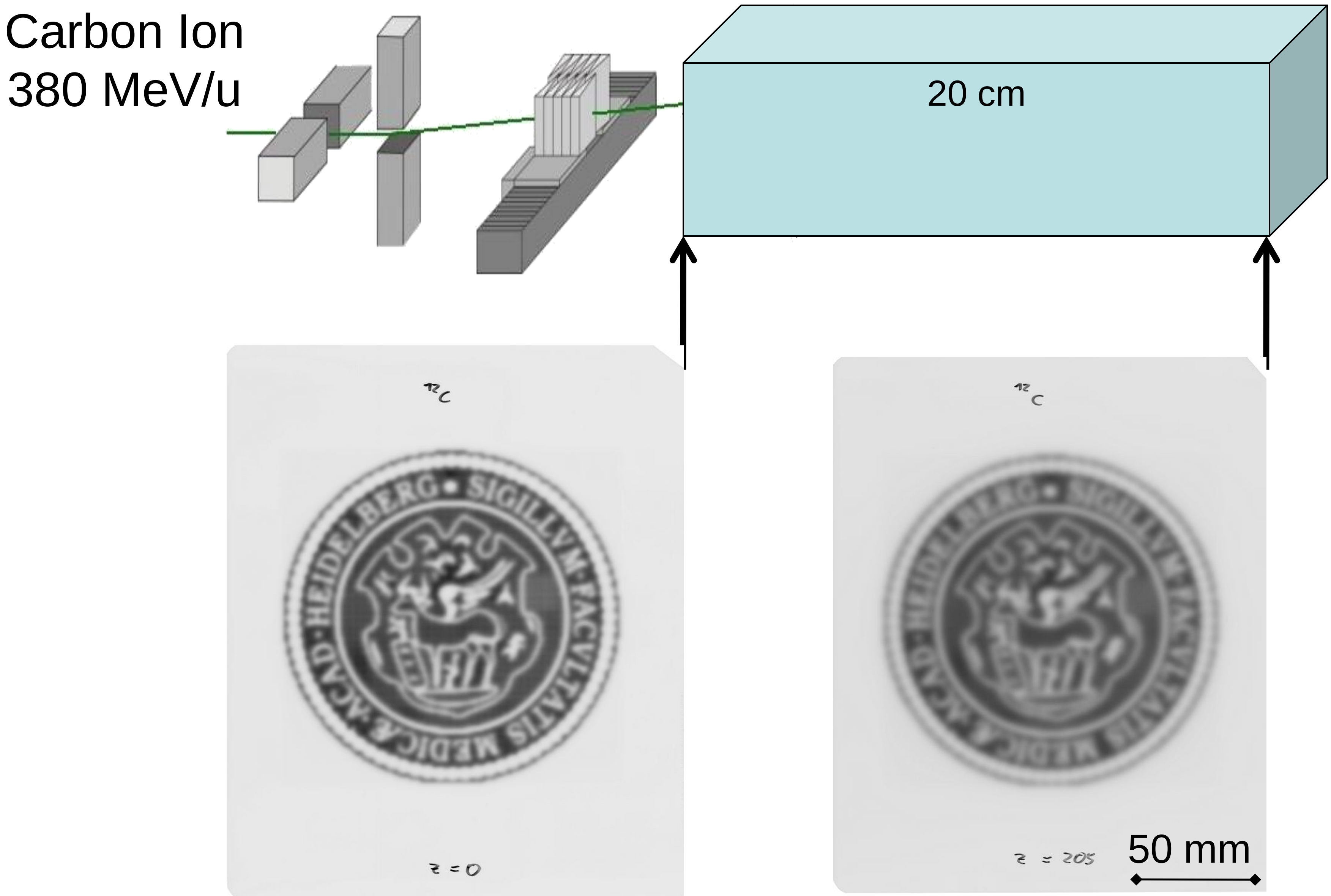
Charged Particle Radiotherapy: Influence of Scattering in Tissue

Protons:
220 MeV





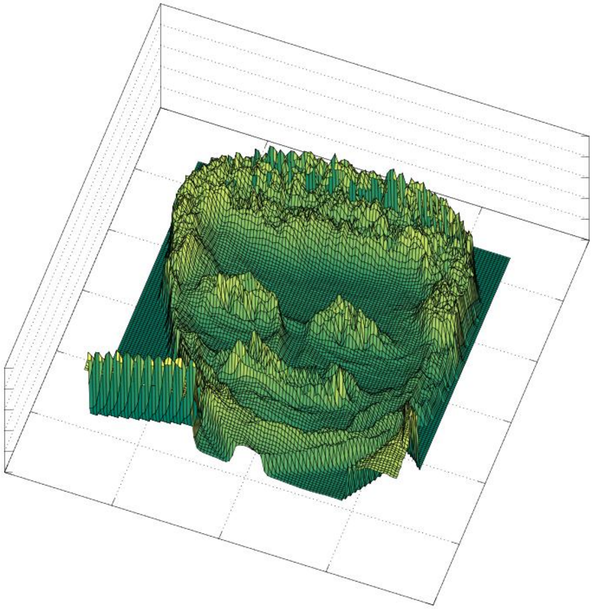
Rasterscanning:
Influence of Scattering in Tissue



Beam Scanning - IMPT

2D-example for fluence (intensity) modulation

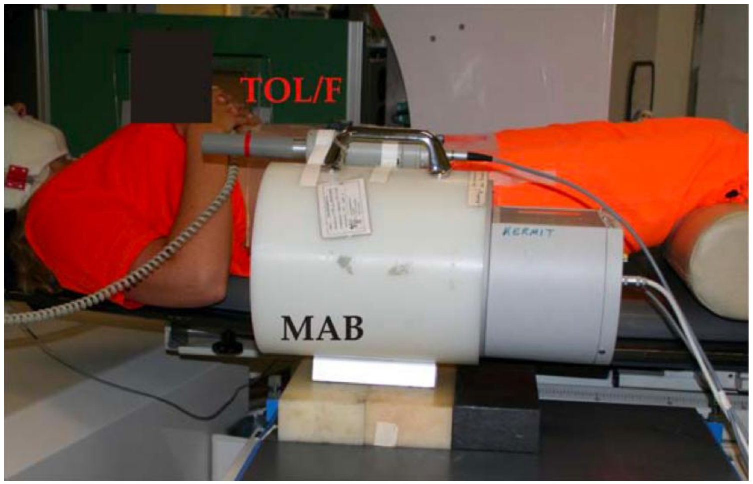
original photograph



fluence map

irradiated radiographic film
rasterscan @ HIT

Carbon Radiotherapy In A Pregnant Patient: low scattered dose to the fetus



	photon dose (μSv/fraction)	neutron dose (μSv/fraction)	Number of fractions	Total dose (μSv)
Normal field	3.0 *	1.4	15	66
Boost field	2.2 **	1.0	5	16
Total treatment			20	**82**

IMRT with 6 MeV photons: $4\ 10^4$ μSv !

Muenter MW, Fertil Steril 2010

Treatment Of Pediatric Patients

Carbon Ion Radiotherapy for Pediatric Patients and Young Adults Treated for Tumors of the Skull Base (n=17)

5 years

8 years

12 years

- **Local control 94% (1 in-field recurrence chordoma, 60 months after C-12)**

exzellent cosmetic outcome

1 pt with hypopituitarism

Combs SE et al., Cancer, 2009

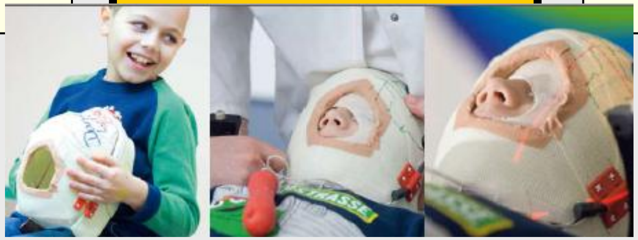
Phase I/II Study Of Carbon Ion Therapy
In Inoperable Osteosarcoma

Neoadjuvant Chemotherapy
(e.g. *EURAMOS1*)
week 1 to 10

Proton / Carbon Ion-radiotherapy (HIT)
(54 GyE +18 GyE),

week11 bis 17

Adjuvant Chemotherapy
(e.g. *EURAMOS1, HR1* (MAP))
week17 bis 34



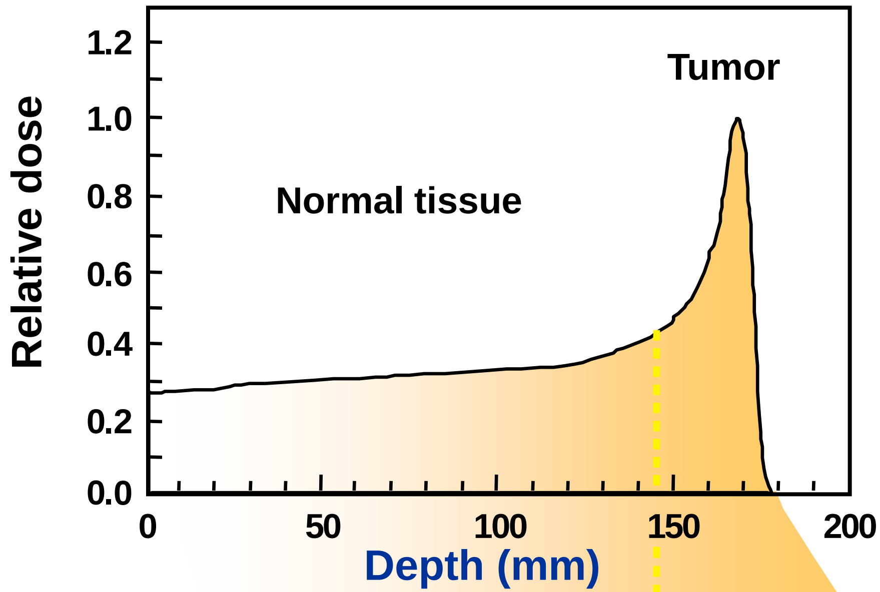
FDG-PET, optional

Inclusion at least 3 weeks before HIT

Required Diagnostics HIT:
✓FDG-PET
✓CT/MRT
✓ Tc99 -scintigramm
Week 7-10

Required Diagnostics after HIT:
✓FDG-PET
Week 17
✓CT/MRI and Tc99 bone scintigramm
Week 19

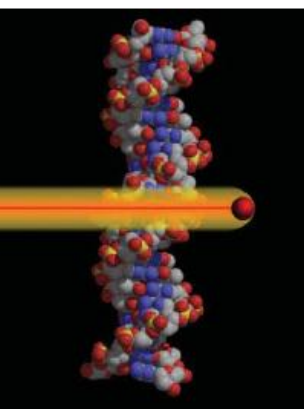
Follow-up Diagnostics
6, 12, 24, 36, 48 and 60 months after HIT



Durante & Loeffler,

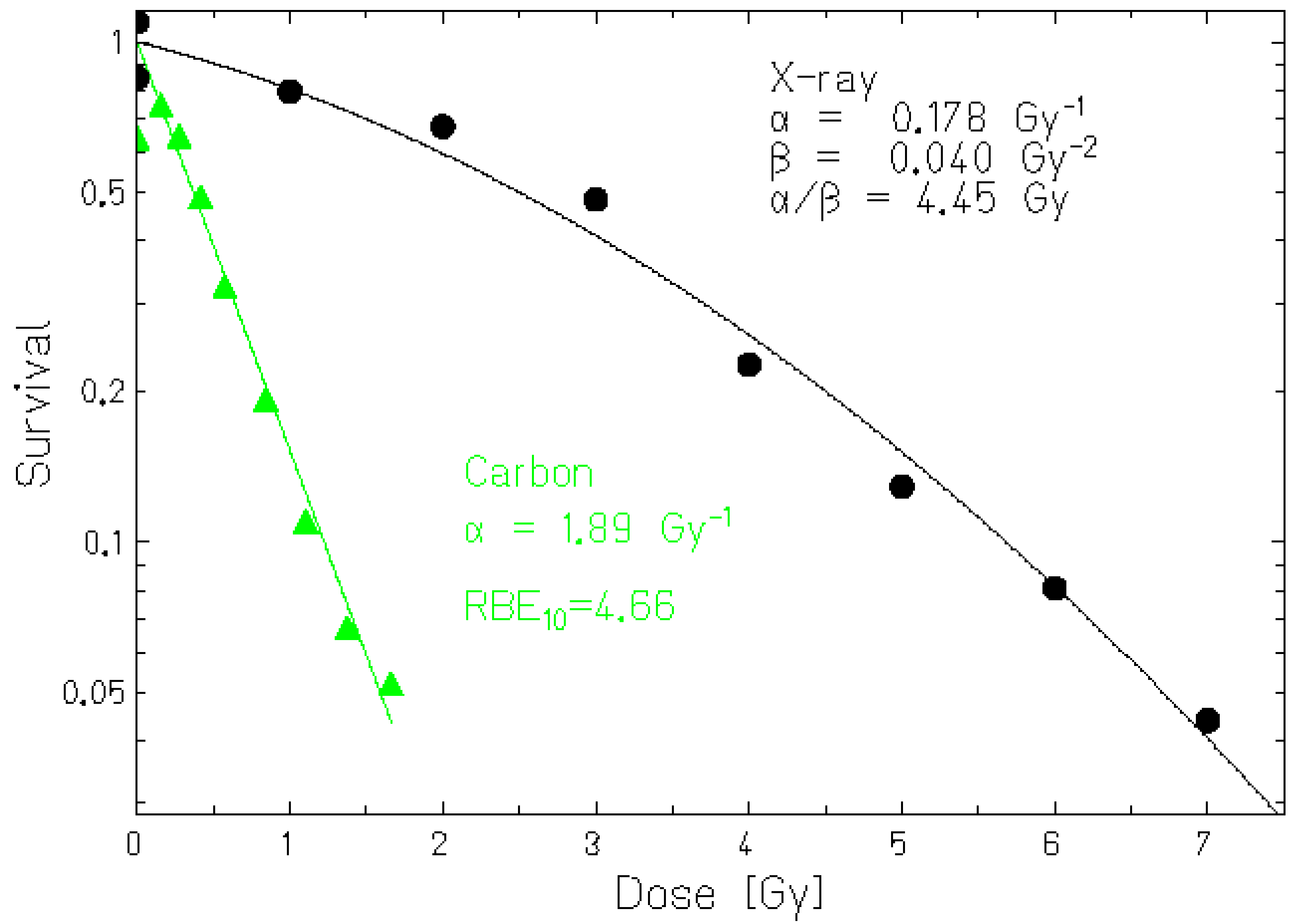
Nature Rev Clin Oncol 2010

Potential advantages of high LET RT



Energy	high	low	
LET	low	high	
Dose	low	high	High tumor dose, normal tissue sparing
RBE	≈ 1	> 1	Effective for radioresistant tumors
OER	≈ 3	< 3	Effective against hypoxic tumor cells
Cell-cycle dependence	high	low	Increased lethality in the target because cells in radioresistant (S) phase are sensitized
Fractionation dependence	high	low	Fractionation spares normal tissue more than tumor
Angiogenesis	Increased	Decreased	Reduced angiogenesis and metastatization
Cell migration	Increased	Decreased	

Increased RBE For High LET Beams:



Combs, Int J Rad Oncol Bio Phys, 2009

Which tumors might be better treated by Ions ?

Tumors, which are refractory to low LET irradiation

Radioresistance

Genetic alterations

upregulated oncogenes
mutated tumor suppresor genes
disregulated apoptosis

Intratumoral micromilieu

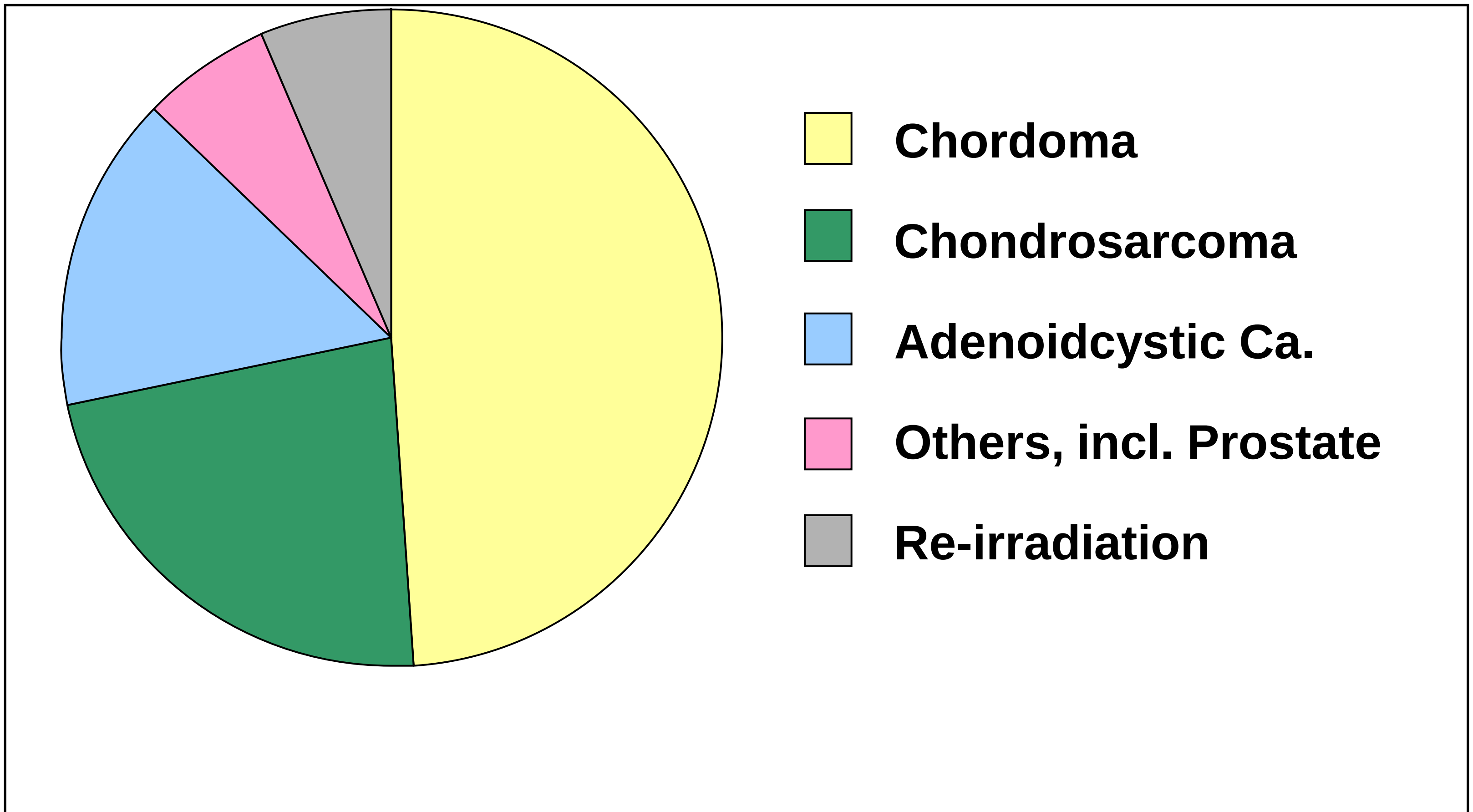
Deprivation of oxygen
Up-regulated defense system
High angiogenic potential

Proliferation status

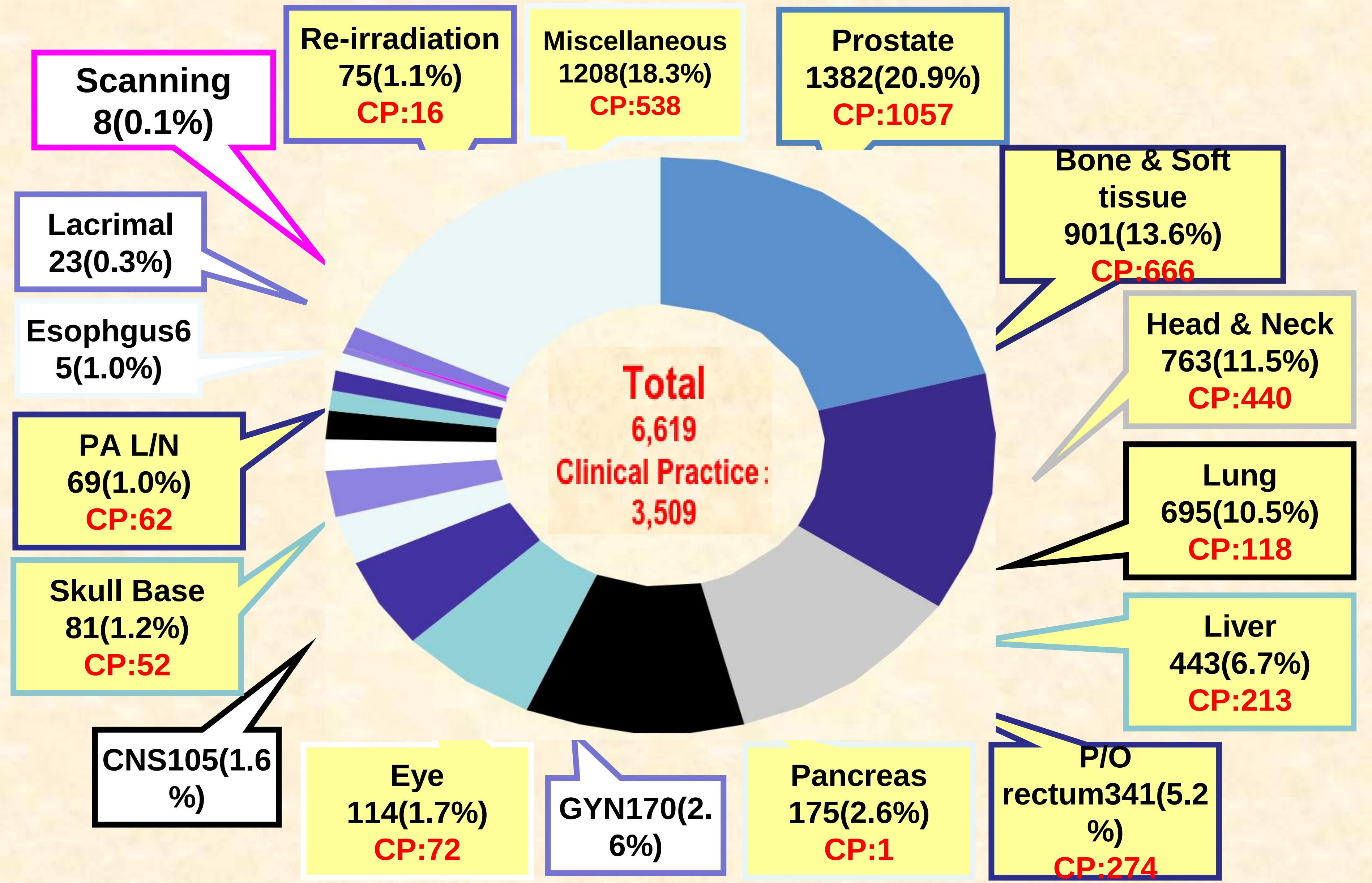
High content of quiescent cell clones
Slow proliferation activity

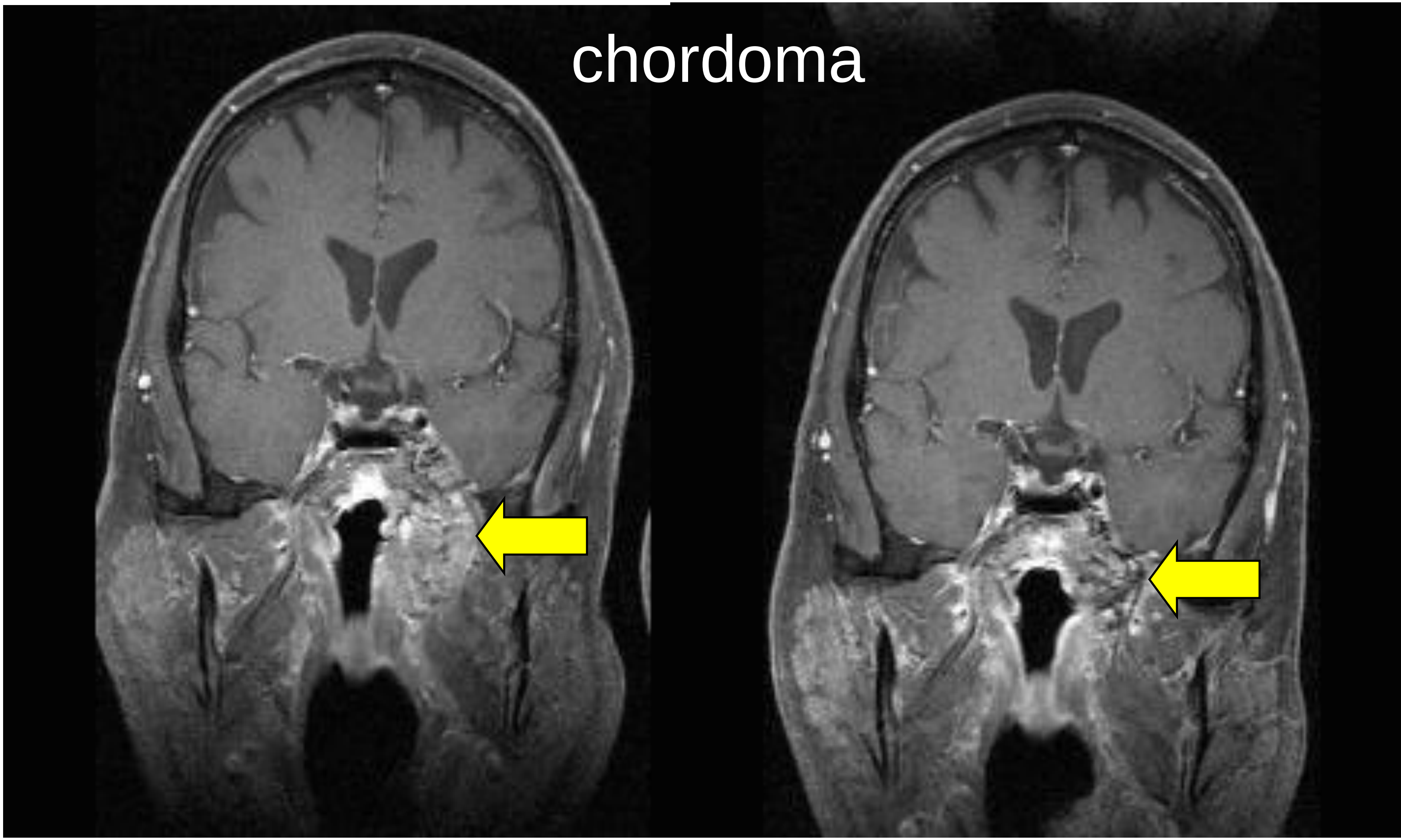
Carbon Ion Radiotherapy At GSI

N=440, 1998-2008



Patient Distribution Enrolled in Carbon Ion Therapy at NIRS (Treatment: June 1994～July 2011)

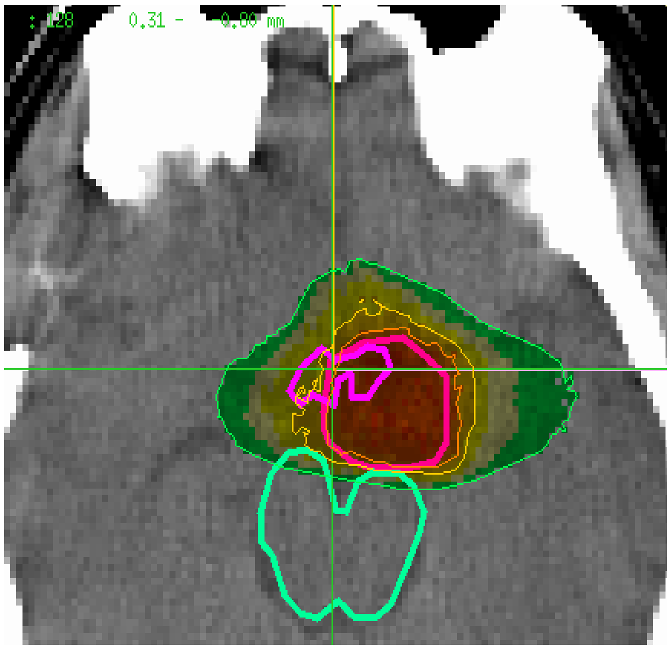


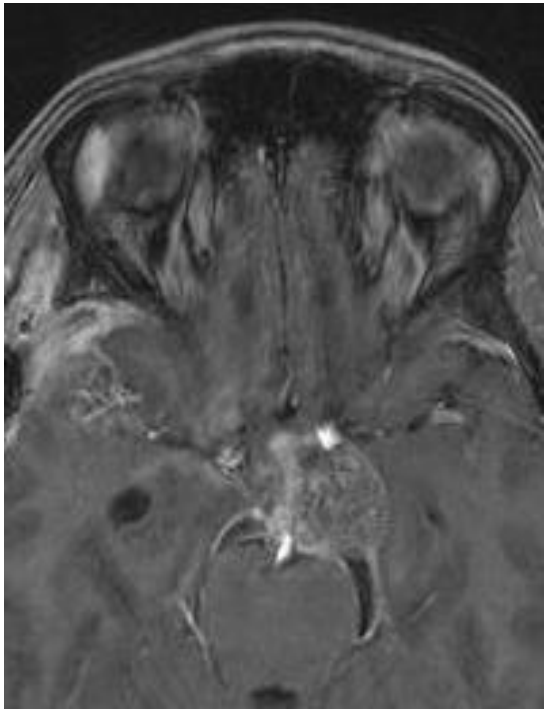


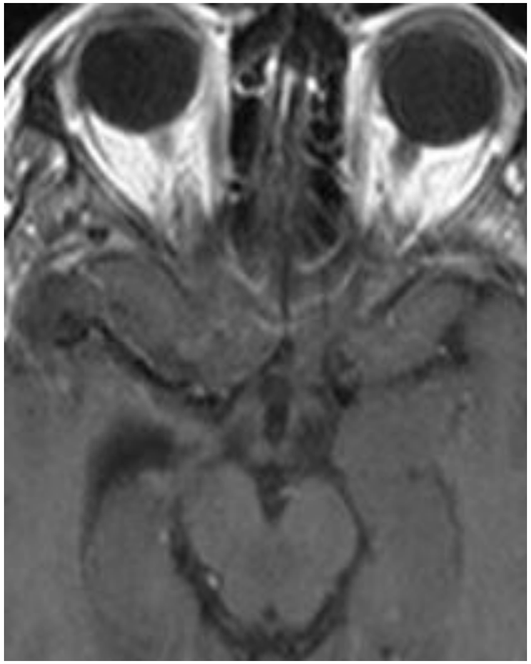
before RT
dose 60 GyE

Follow-up
3 months

Chordoma:
response after carbon ion RT



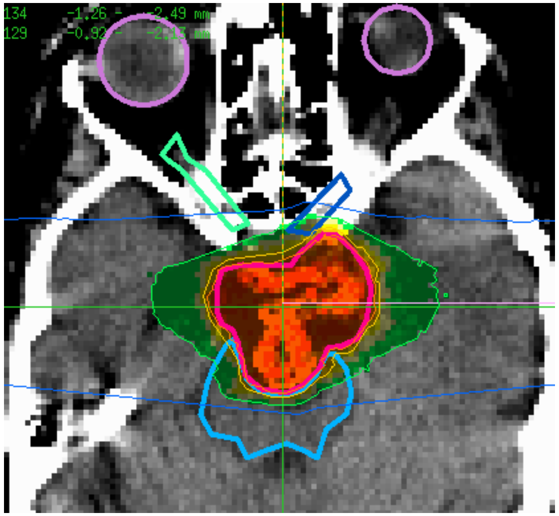


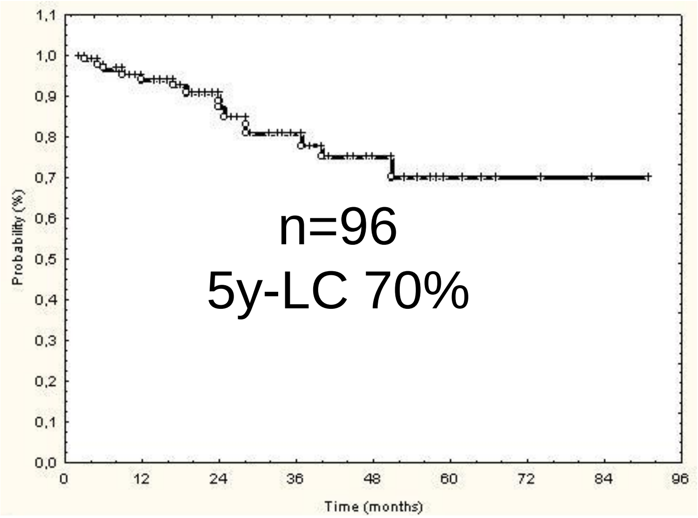


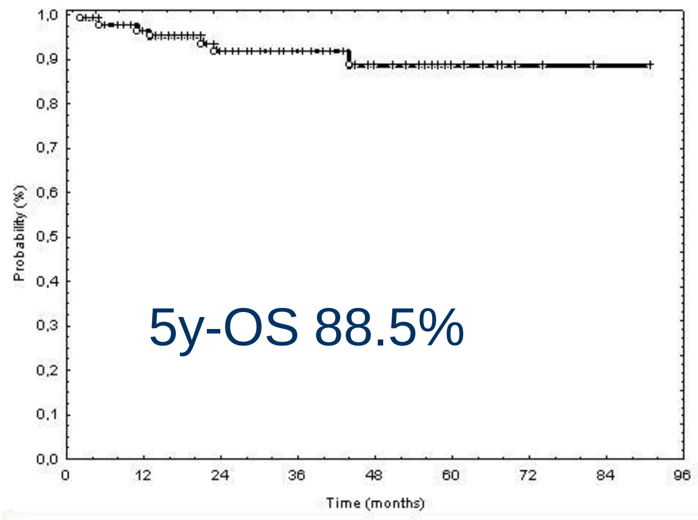
Prior to C12:
rt. hemianopsia
60 GyE

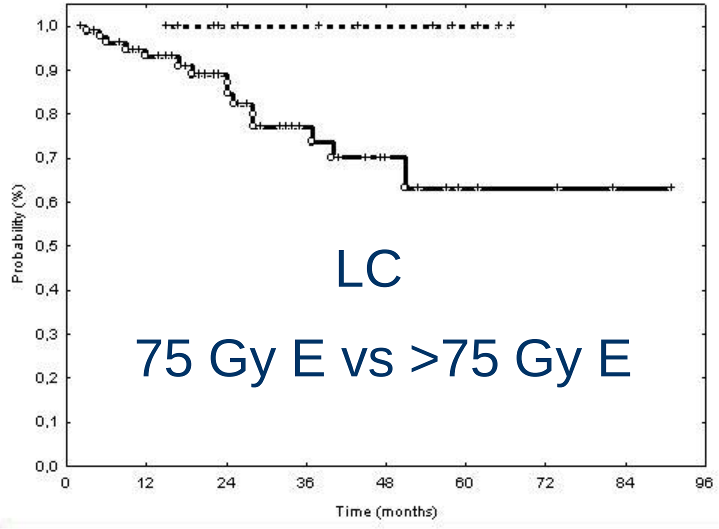
Good partial remission
6 months

Carbon ion RT in skull base chordomas

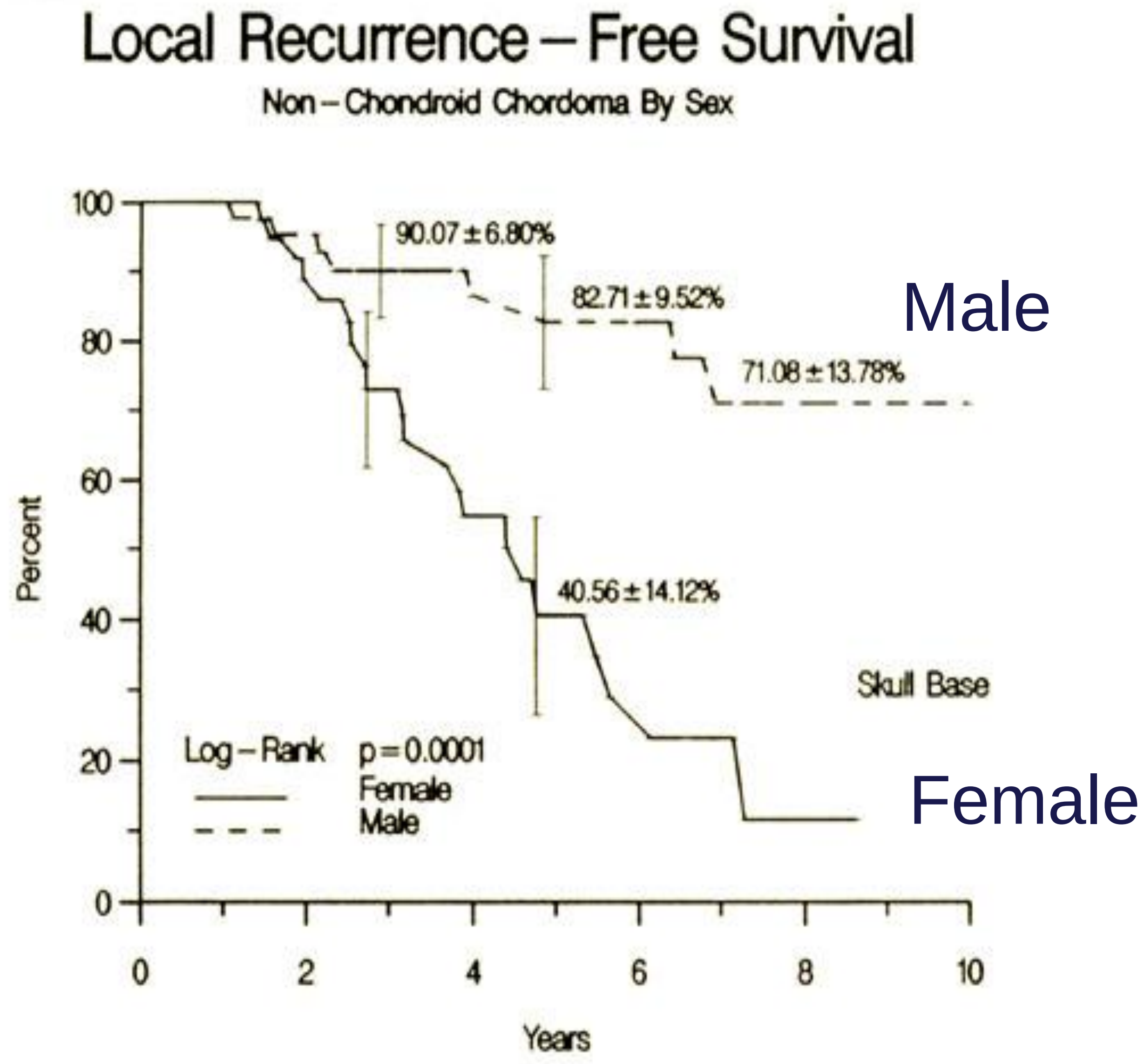








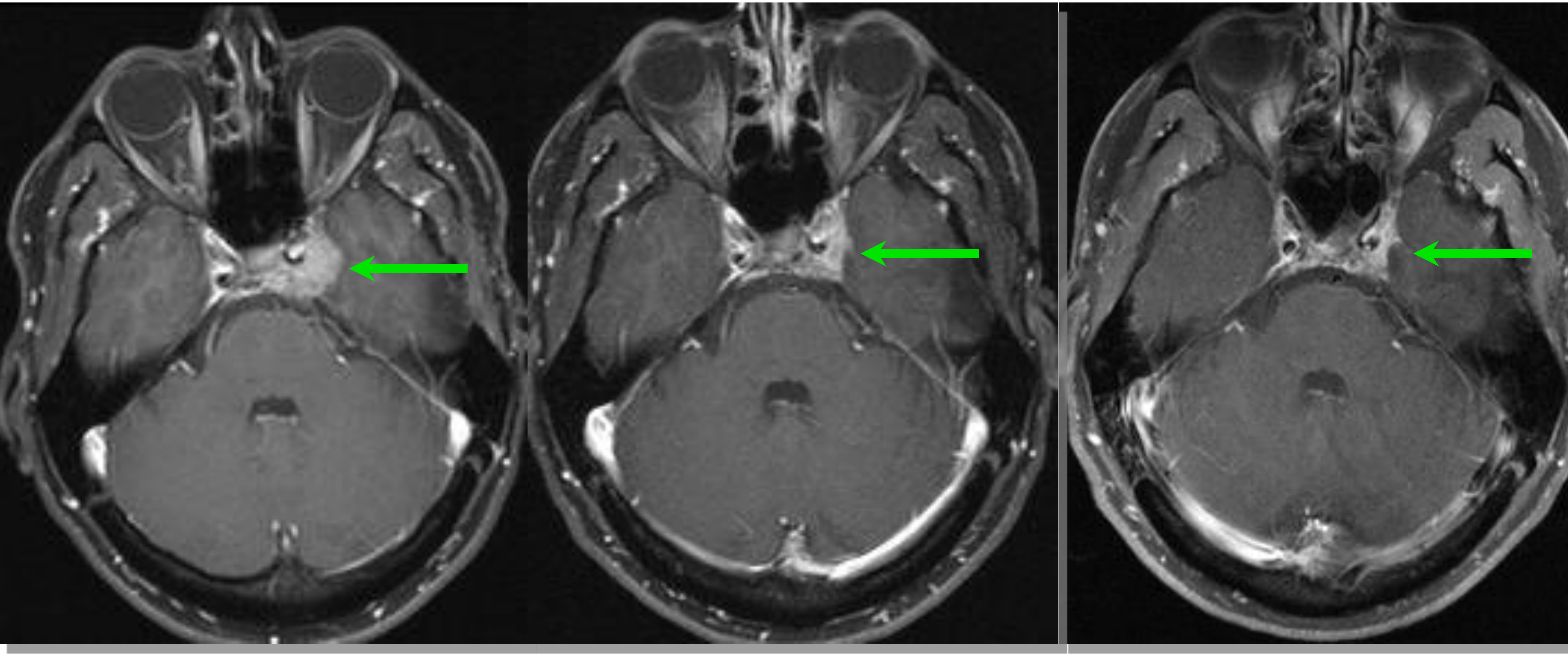
Schulz-Ertner et al. IJROBP 2007



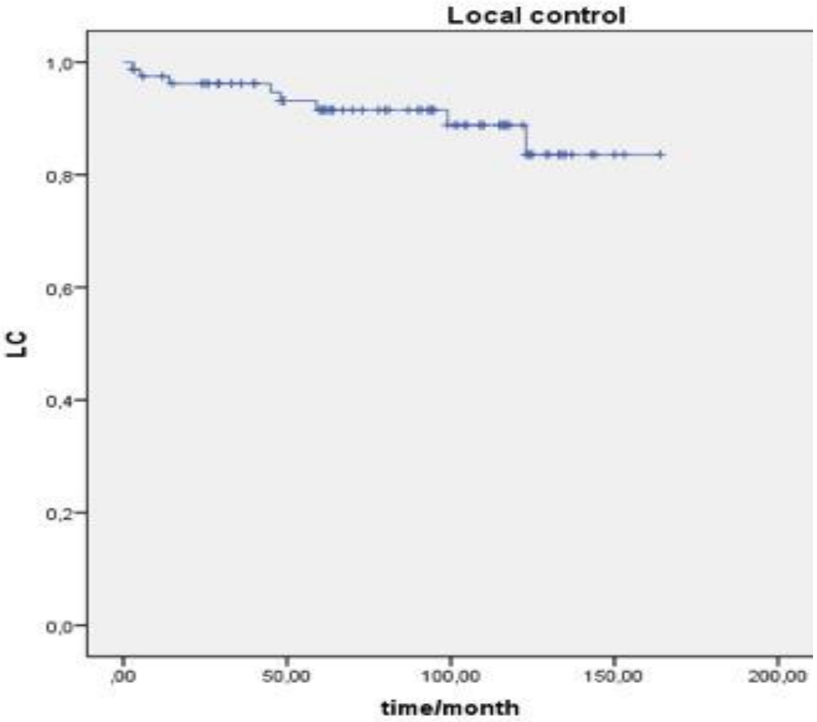
Courtesy John Munzenrider, 1996

Carbon Ion RT: follow-up in low grade chondrosarcoma: slow response

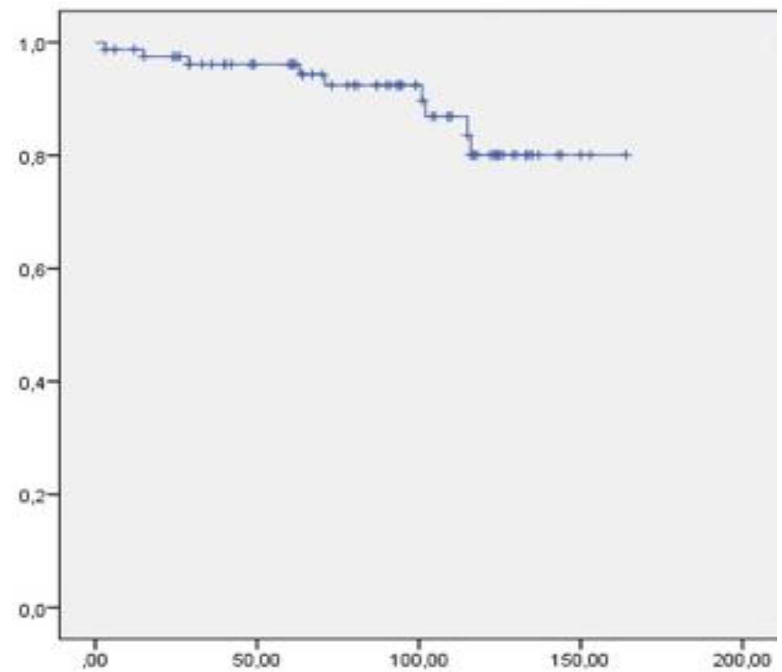
RT in 2005 | 2007 | 2013



^{12}C- therapy in pts. with chondrosarcoma of the skull base (GSI Darmstadt)- <u>Long term follow up of all pts. treated 1998-2008</u>



91.5% (5y) 88.8% (10y)



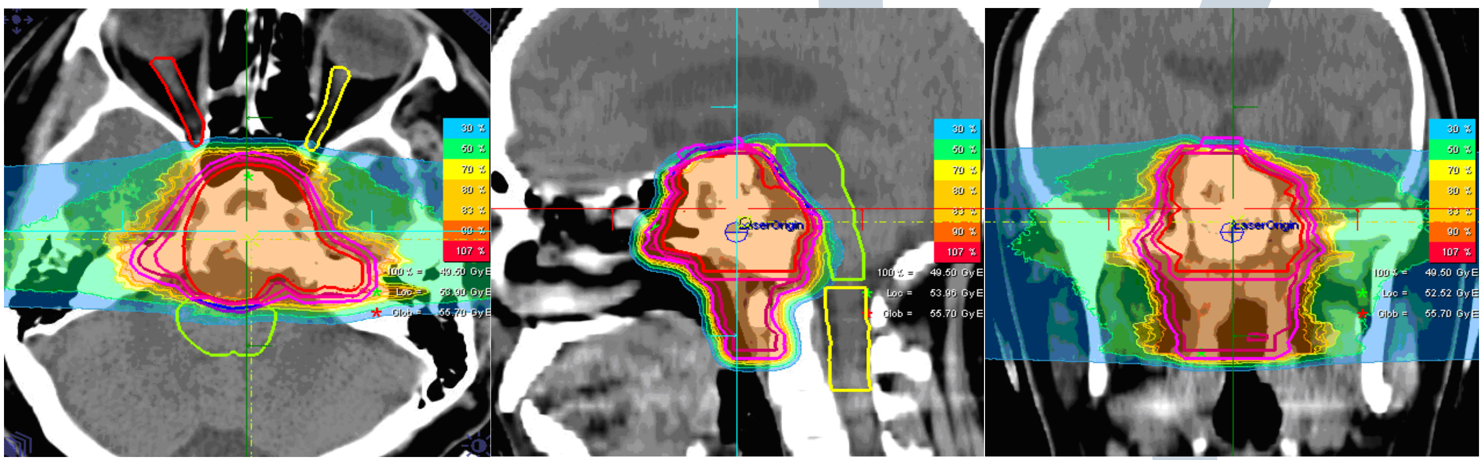
5-year-OS: 96.1% neue Daten

81 patients treated with carbon ion
Median follow-up was 91 months (range, 3-153 months)
8 relapses (still alive)
9 pts. died in the fu-period (cause of dead: „other“)

Unpublished data, in preparation

Assessment of early toxicity and response in patients treated with proton and carbon ion therapy at the Heidelberg Ion Therapy Center (HIT) using the rasterscanning technique

Stefan Rieken MD[1], Daniel Habermehl MD[1], Anna Nikoghosyan MD[1], Alexandra Jensen MD[1], Thomas Haberer Ph D[2], Oliver Jäkel PhD[2,3], Marc W. Münter MD[1], Thomas Welzel MD[1], Jürgen Debus MD PhD[1] and Stephanie E. Combs MDF[1]



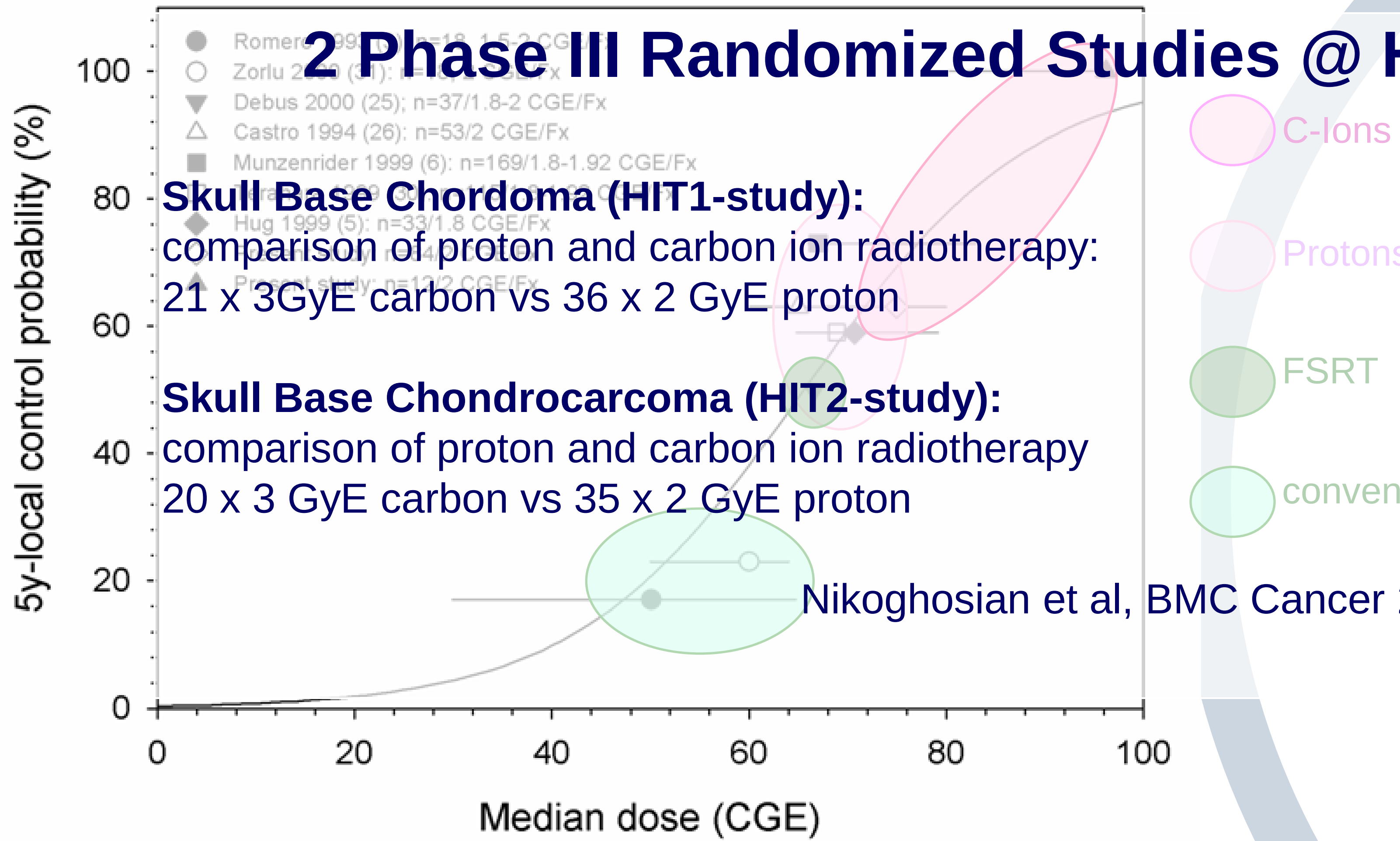
Conclusions

Side effects related to particle treatment were rare and overall tolerability of the treatment could be shown. Initial response is promising. The data confirms safe delivery of carbon ions and protons at the newly opened Heidelberg facility.

Int J Rad Oncol Bio Phys (2011) 81:693

Clinical trials: HIT1,2, CLEOPATRA, MARCIE, MIRANDA, CINDERELLA, PROMETHEUS, …

Hypothesis: Dose Response Relationship Radiotherapy of Skull Base Chordomas



2 Phase III Randomized Studies @ HIT:

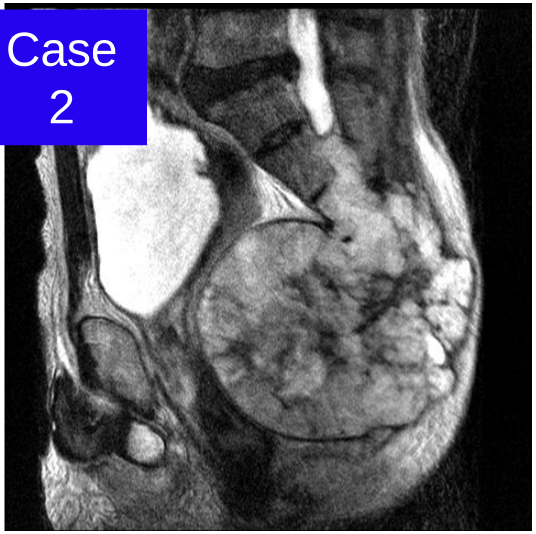
Skull Base Chordoma (HIT1-study):
comparison of proton and carbon ion radiotherapy:
21 x 3GyE carbon vs 36 x 2 GyE proton

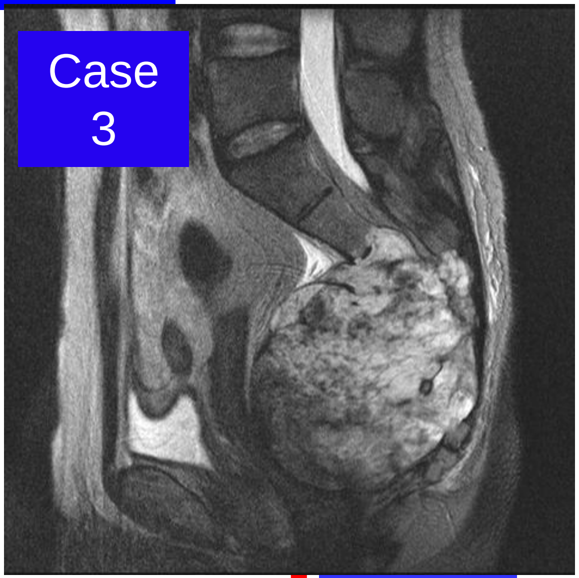
Skull Base Chondrocarcoma (HIT2-study):
comparison of proton and carbon ion radiotherapy
20 x 3 GyE carbon vs 35 x 2 GyE proton

Nikoghosian et al, BMC Cancer 2010, 10:606

[Schulz-Ertner, IJROBP 2007]

Chordoma of the sacrum





6 years

5 years

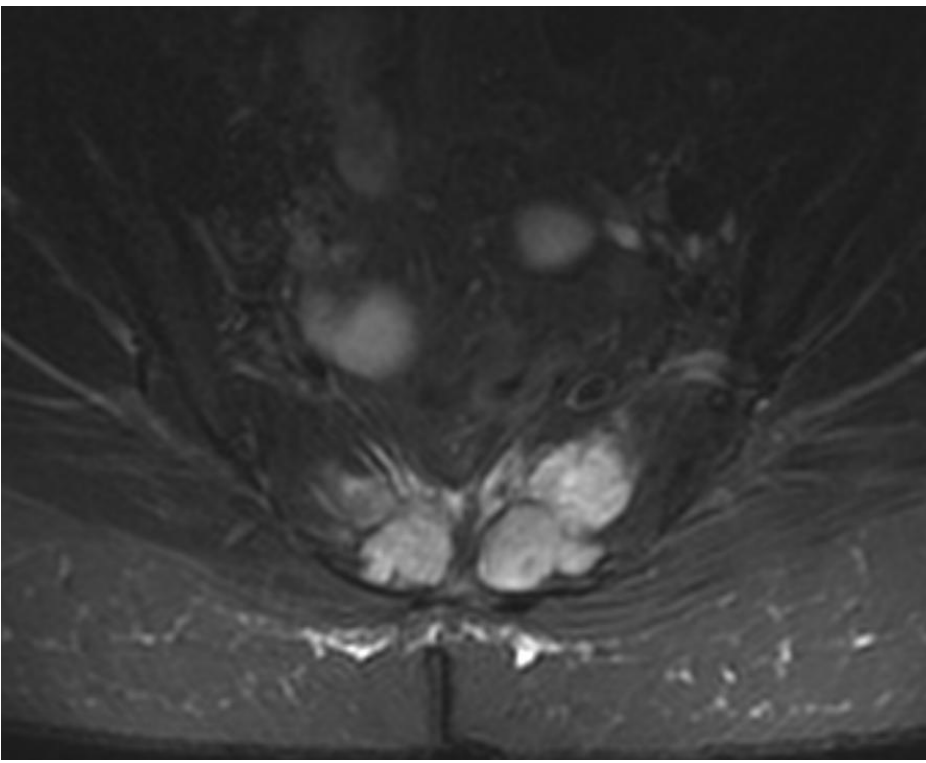
6 years

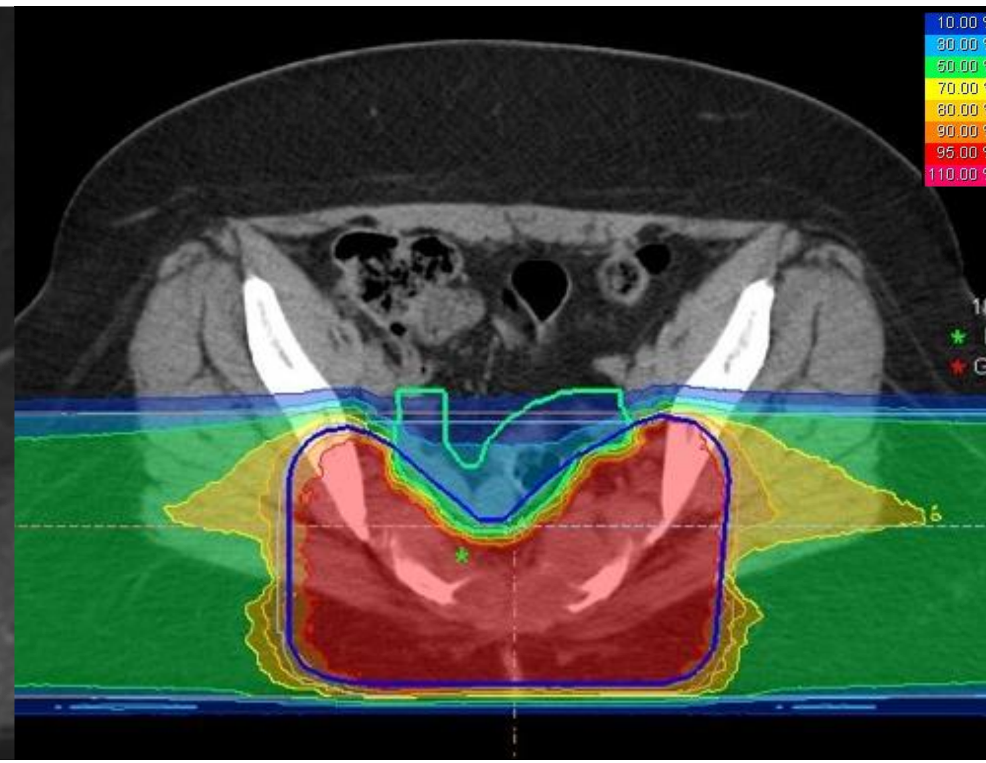
Kamada, Estro teaching course 2011

Sacral Chordomas

ISAC trial

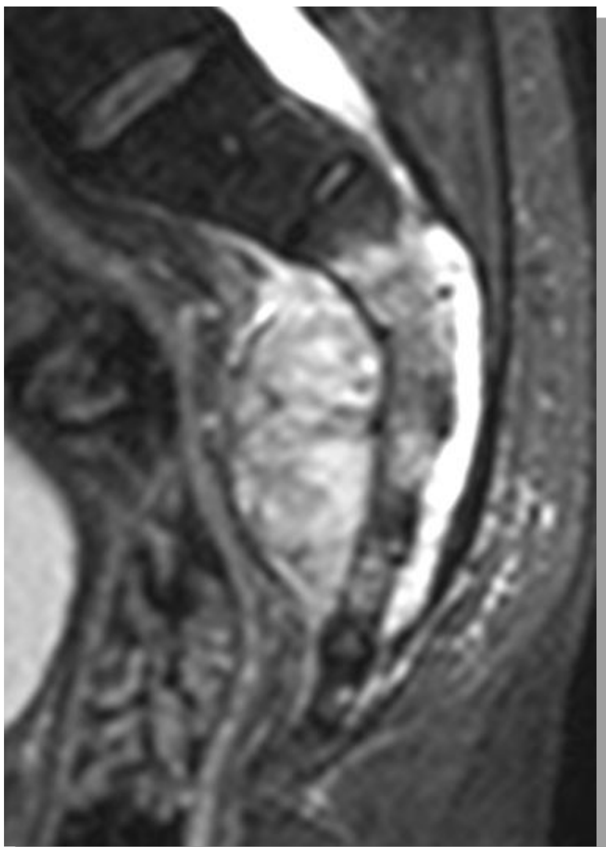
16 x 4 GyE C12 vs. 16 x 4 GyE H1



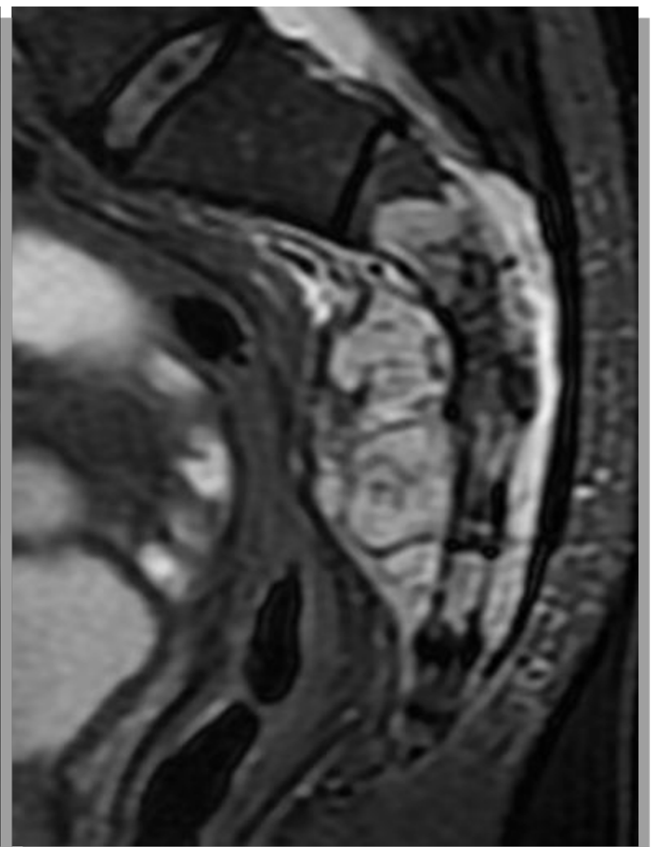


Sacral Chordoma

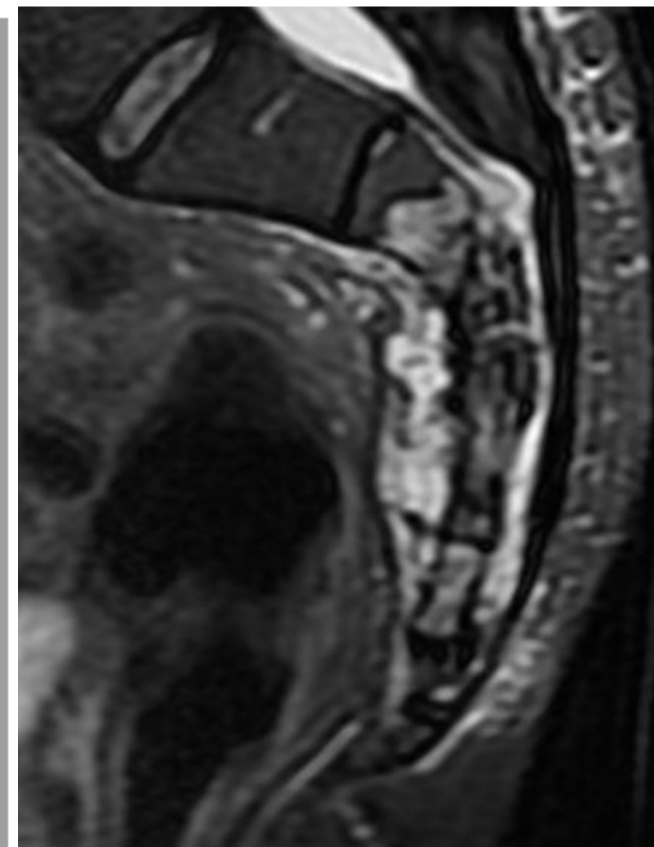
16 x 4 GyE C12



6 /12



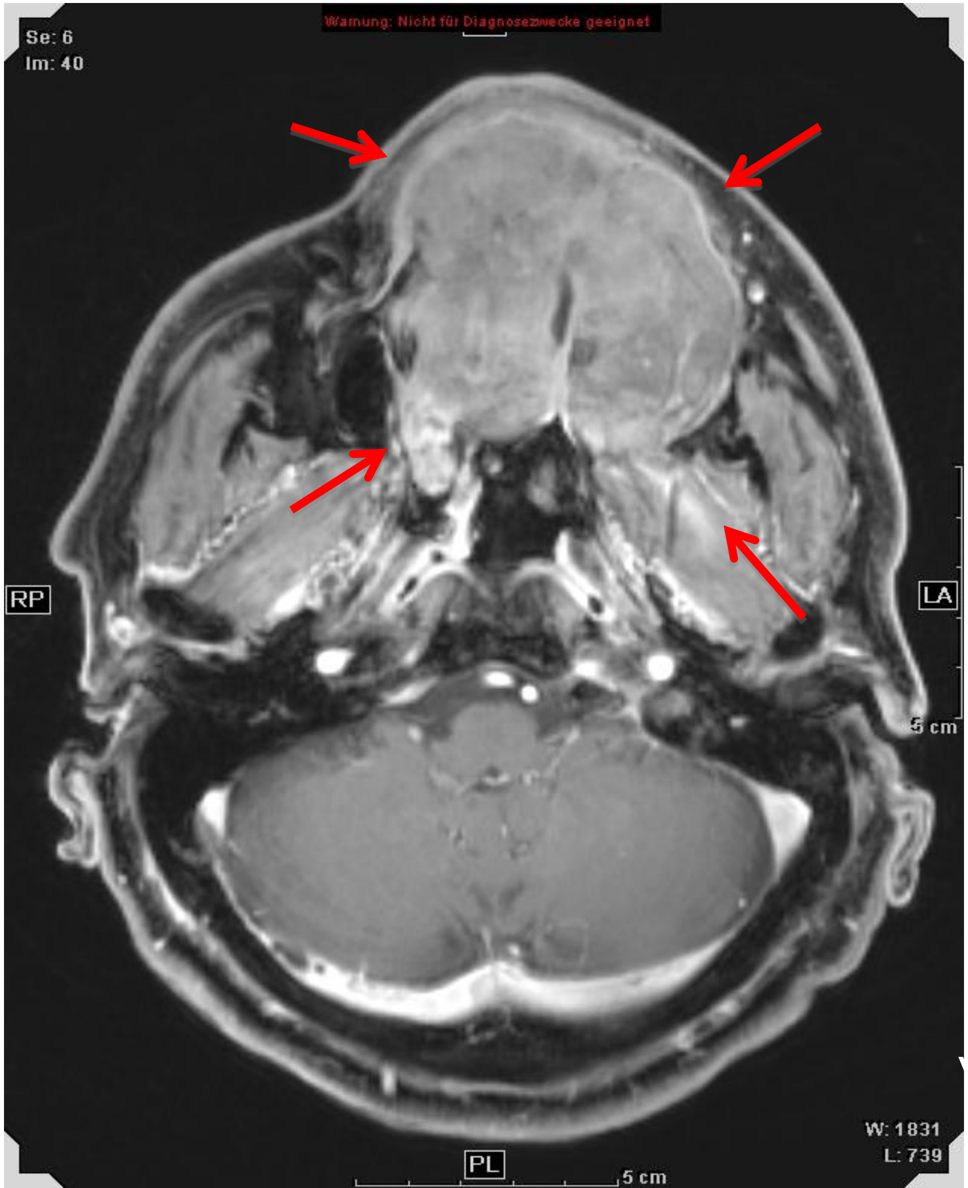
8 /12



2 /13

COSMIC Study: Response

Treatment planning



FU @ 6 weeks after C12

FSRT / IMRT vs. FSRT / IMRT + C12
locally advanced adenoidcystic carcinoma

2 Phase II Studies @ HIT:

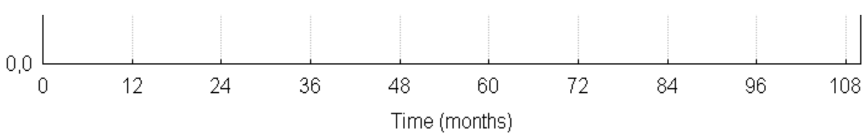
To increase local control:

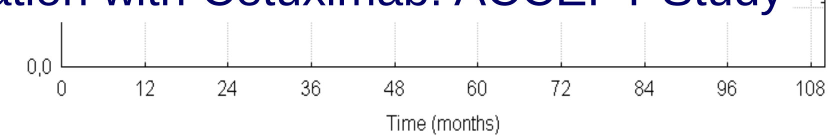
Increase of Boost dose to 24 Gy E – COSMIC-Study

Jensen et al., BMC Cancer 2010

To tackle local control & distant metastases:

Combination with Cetuximab: ACCEPT Study



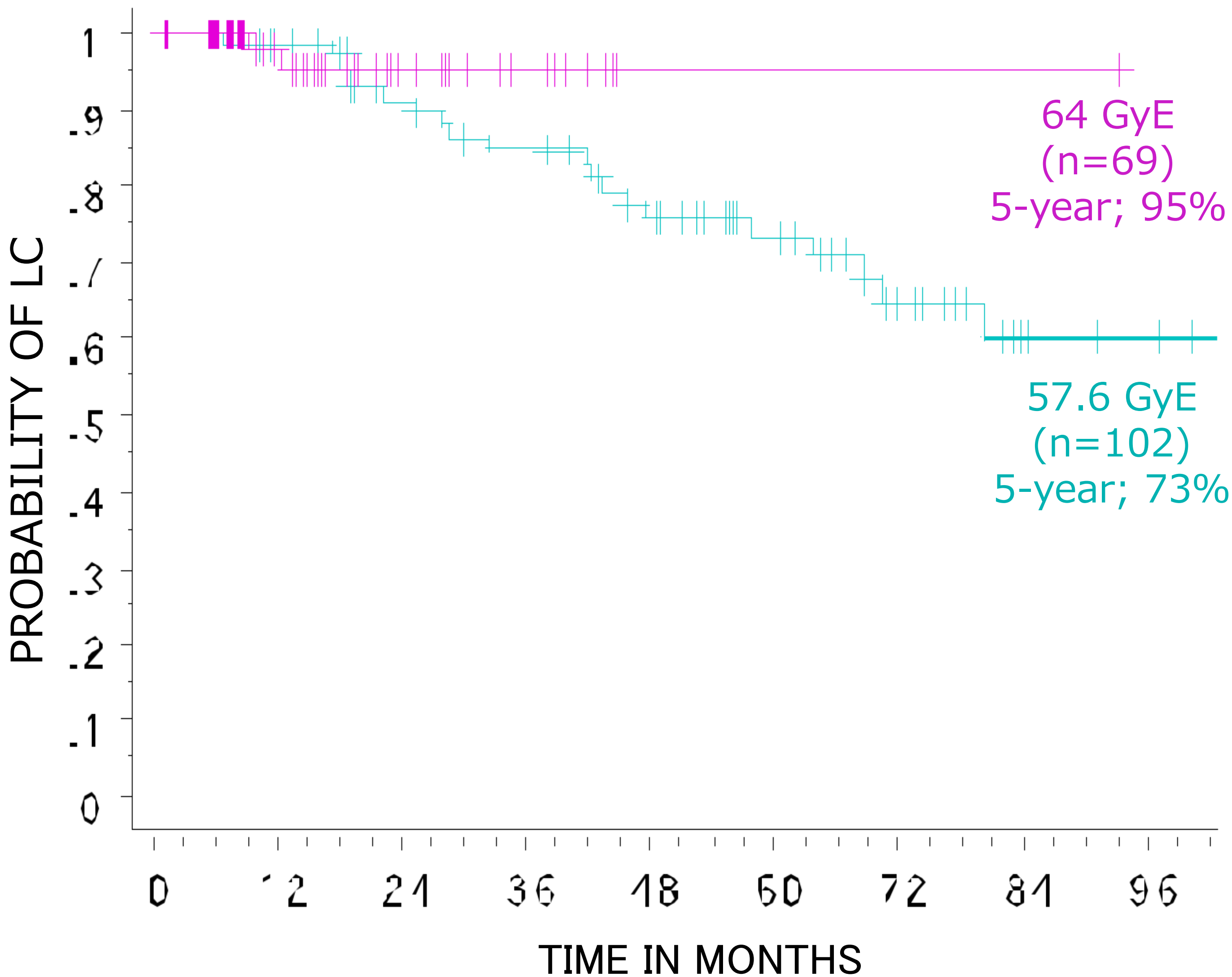


- **no dose limiting acute toxicity**
- **late toxicity > CTC grade 2 < 5%**

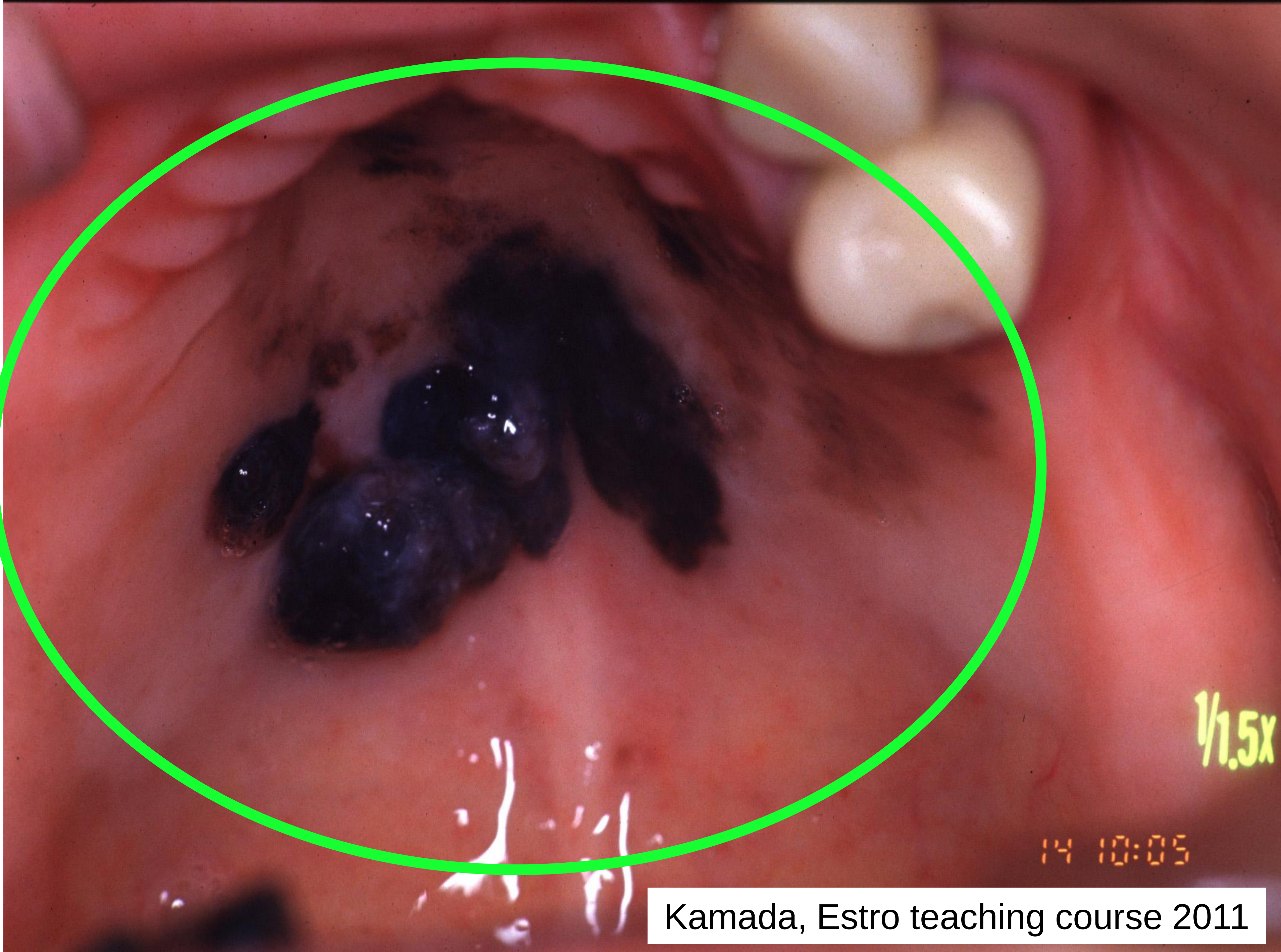
Schulz-Ertner, Cancer. 2005 Jul 15;104(2):338-44

Phase II (9602) for Malignant Head-and-Neck Tumors

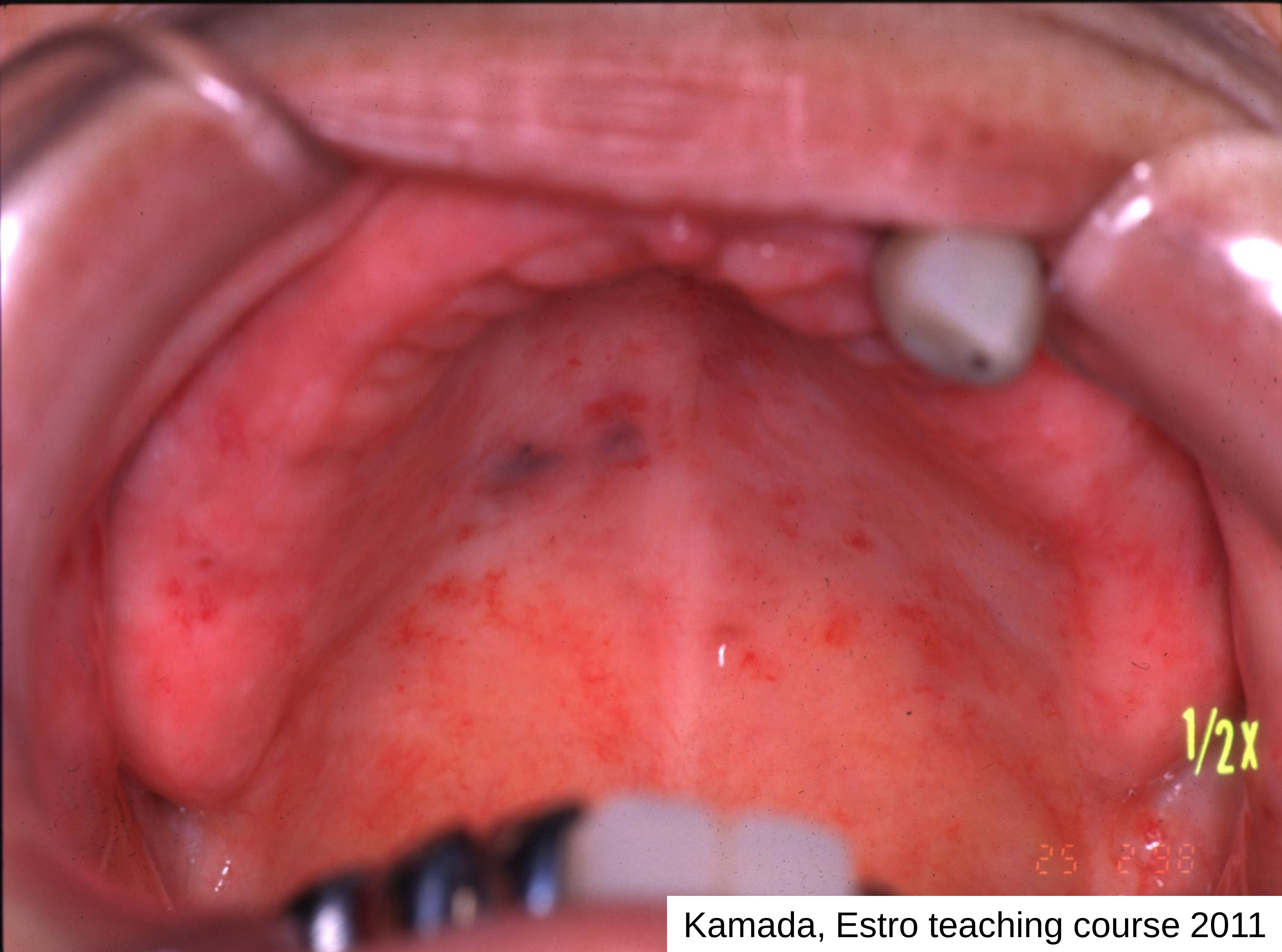
Local Control of ACC (n=129) according to Carbon ion Dose



Kamada, Estro teaching course 2011

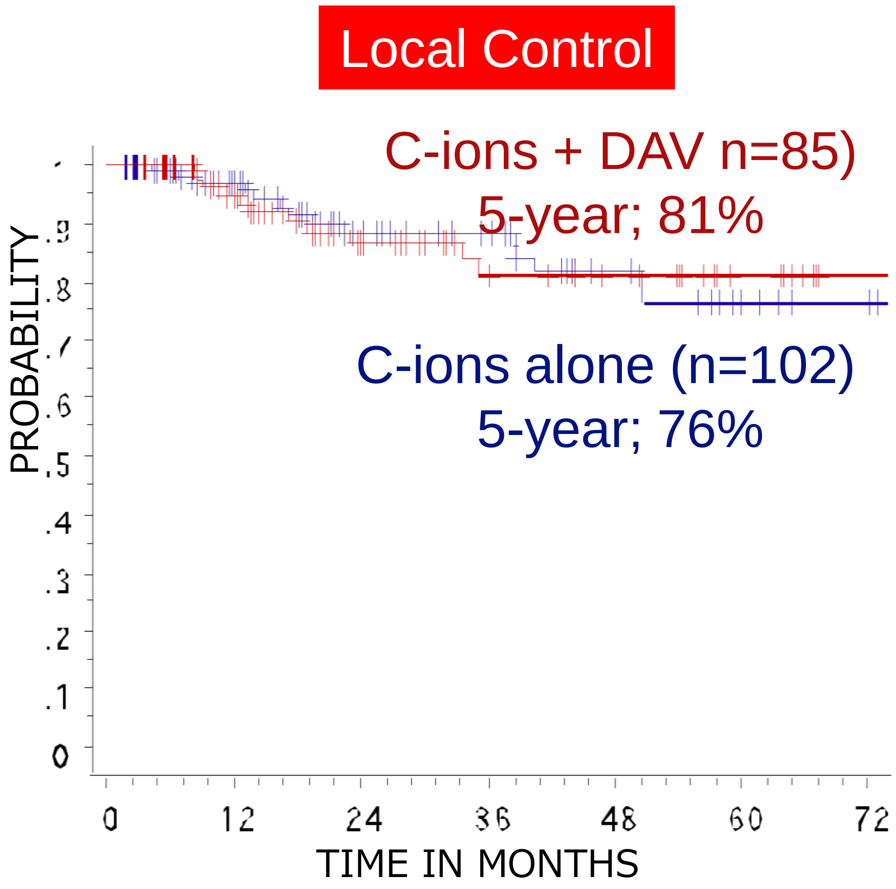


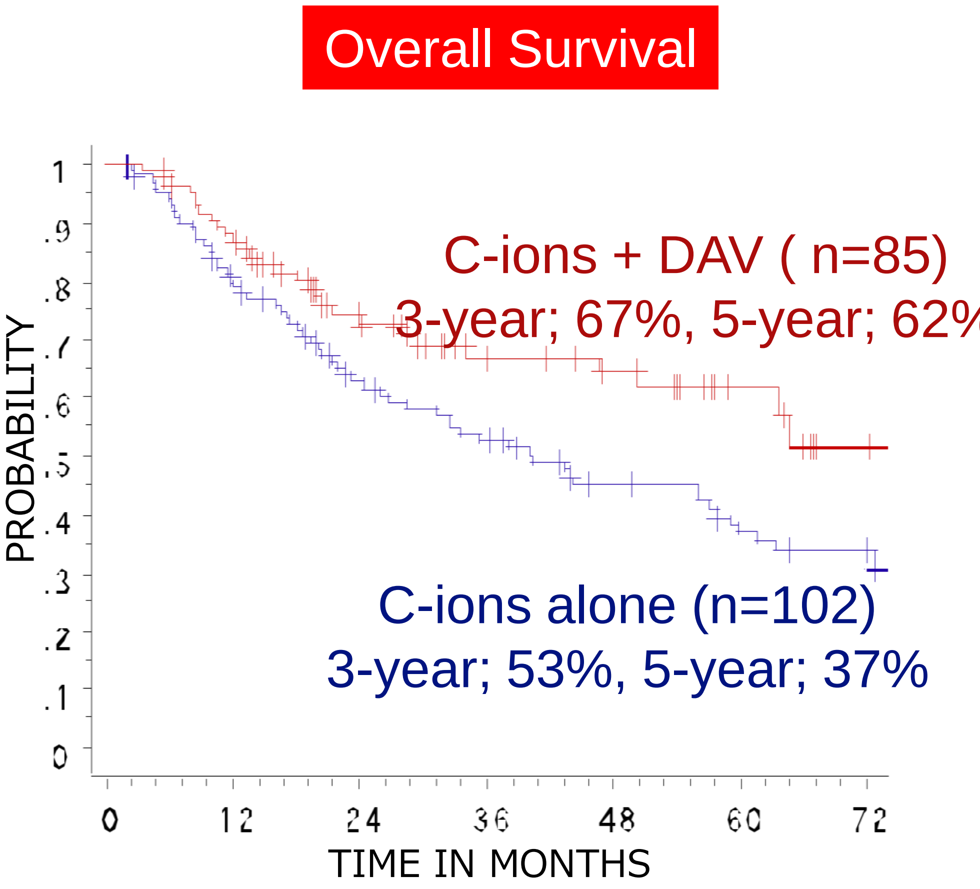
Kamada, Estro teaching course 2011



Kamada, Estro teaching course 2011

Combined Chemotherapy and C-ion RT for MMM





Local Control and Overall Survival of Mucosal Malignant Melanomas

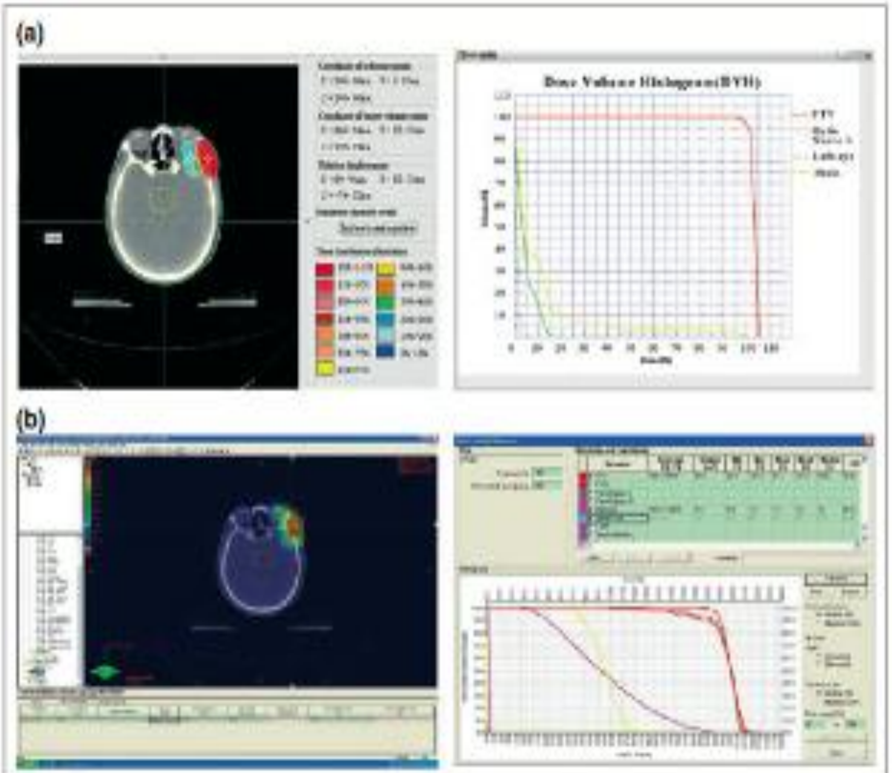
Kamada, Estro teaching course 2011

BJD
British Journal of Dermatology

Results of carbon ion radiotherapy for skin carcinomas in 45 patients

H. Zhang,*†‡ S. Li,†‡§ X.H. Wang,†‡¶ Q. Li,*†‡ S.H. Wei,†‡§ L.Y. Gao,†‡¶ W.P. Zhao,*†‡ Z.G. Hu,*†‡ R.S. Mao,*†‡ H.S. Xu,*†‡ Q.N. Zhang,†‡¶ Y.J. Yue,†‡§ Z.Z. Tian,†‡§ J.T. Ran,†‡¶ G.Q. Xiao*†‡ and W.L. Zhan*†‡

*Department of Heavy Ion Radiation Medicine, Institute of Modern Physics, Chinese Academy of Sciences, Lanzhou 730000, China



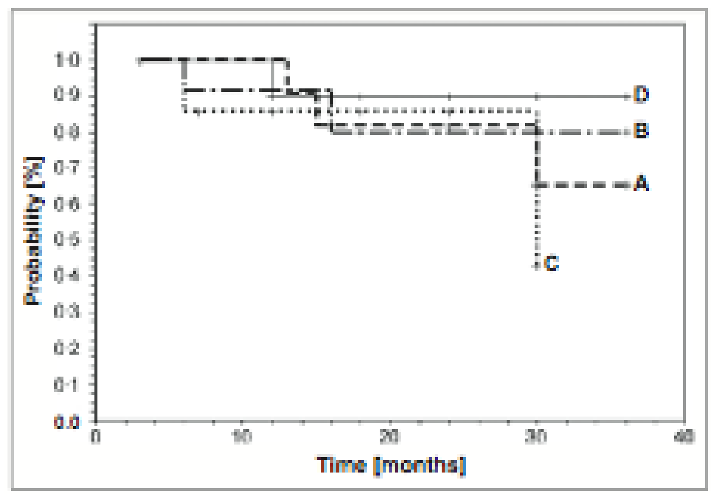
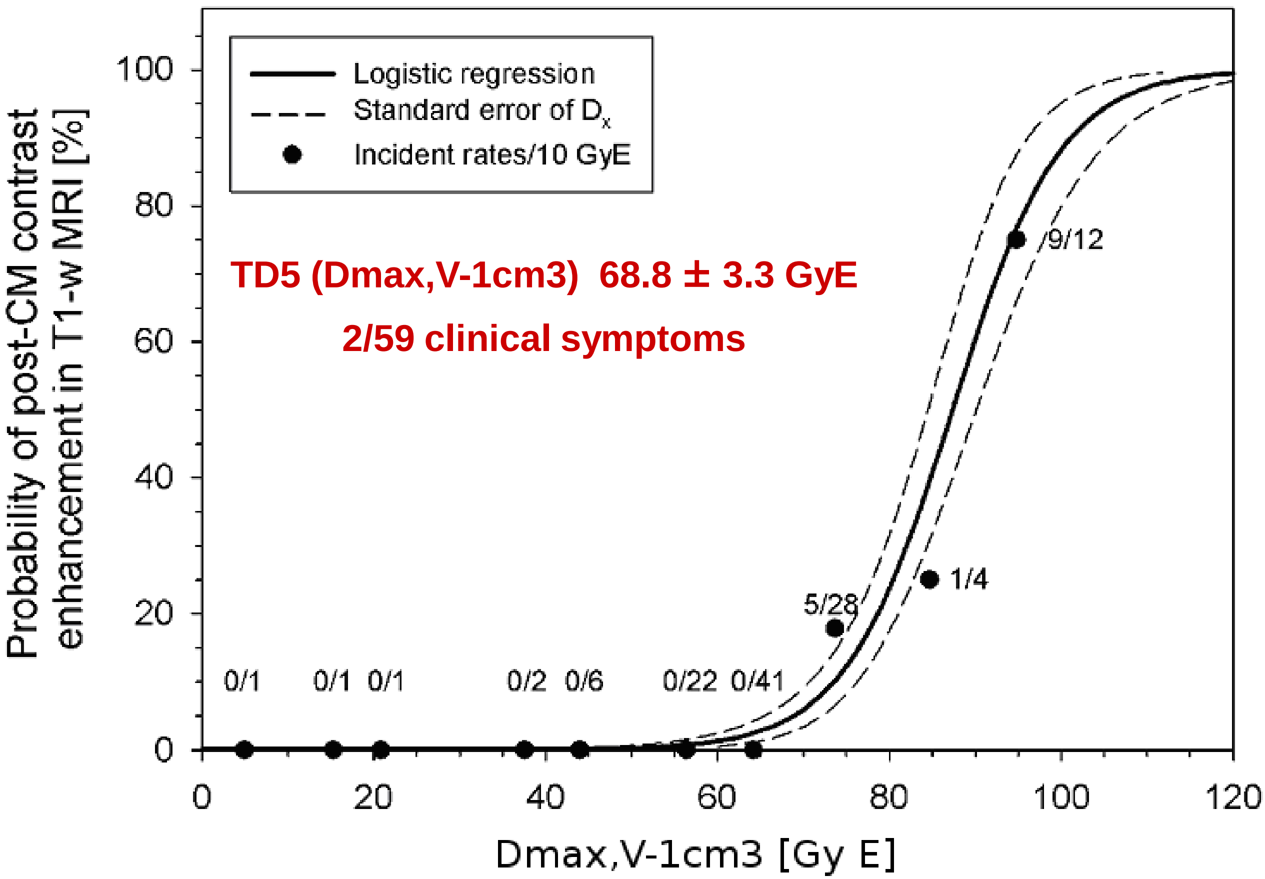


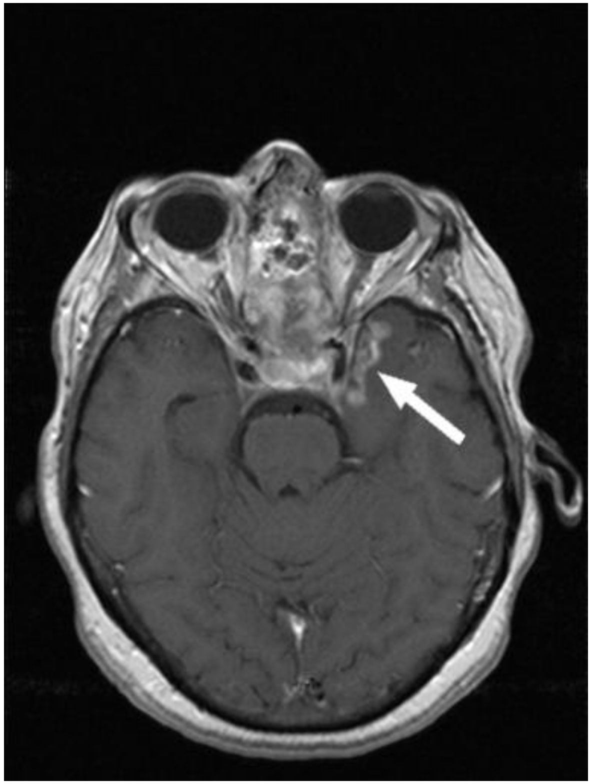
Fig 2. Actuarial local control in 45 skin carcinoma patients with 16 squamous cell carcinoma (A), 12 basal cell carcinoma (B), seven malignant melanoma (C) and 10 Bowen and Paget diseases (D), treated with carbon ion radiotherapy (Kaplan–Meier curve).

Late toxicity after carbon ion RT:

dose response for contrast enhancement in the temporal lobes

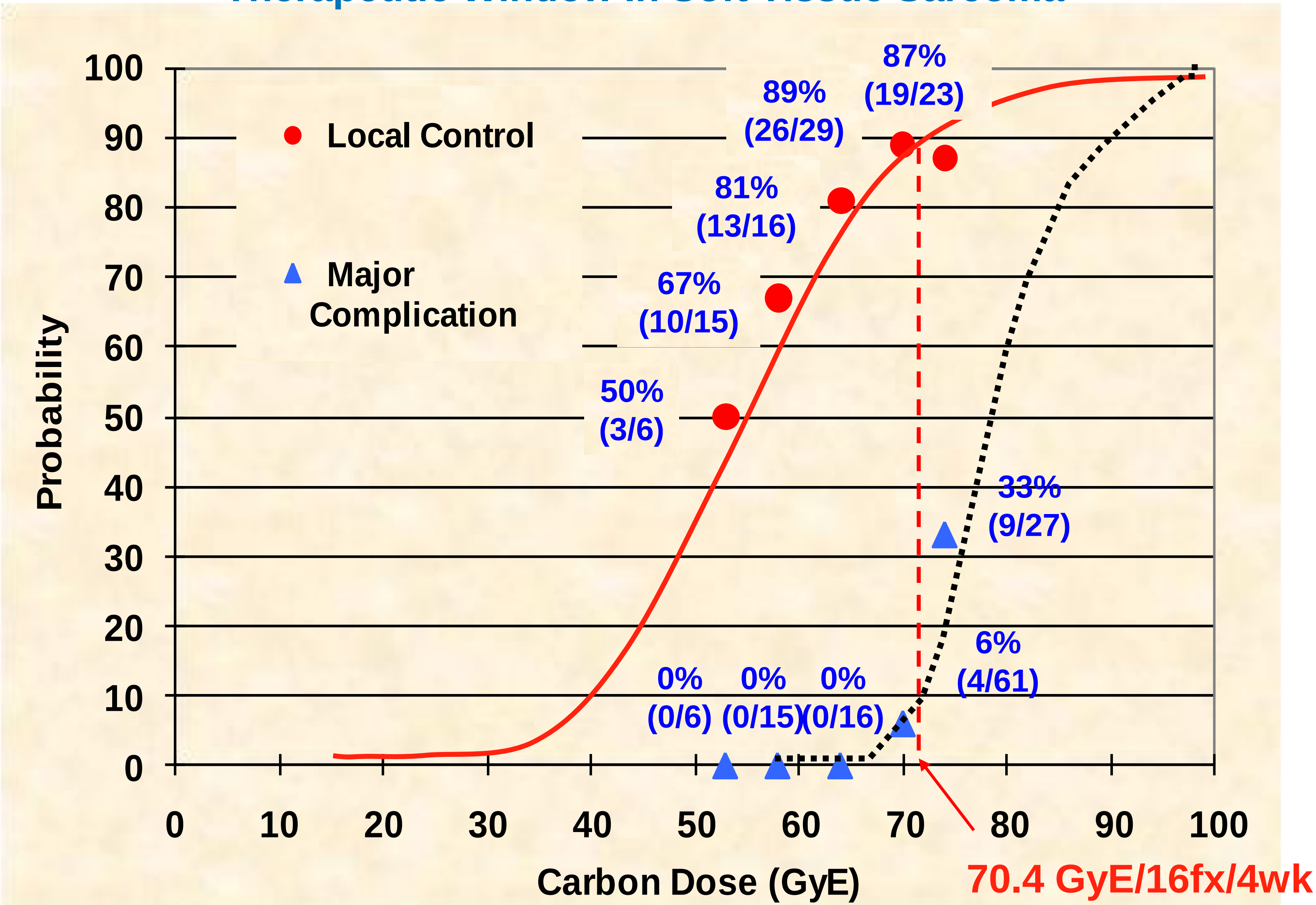
n=59, 2002-2003, FU 2,5 years





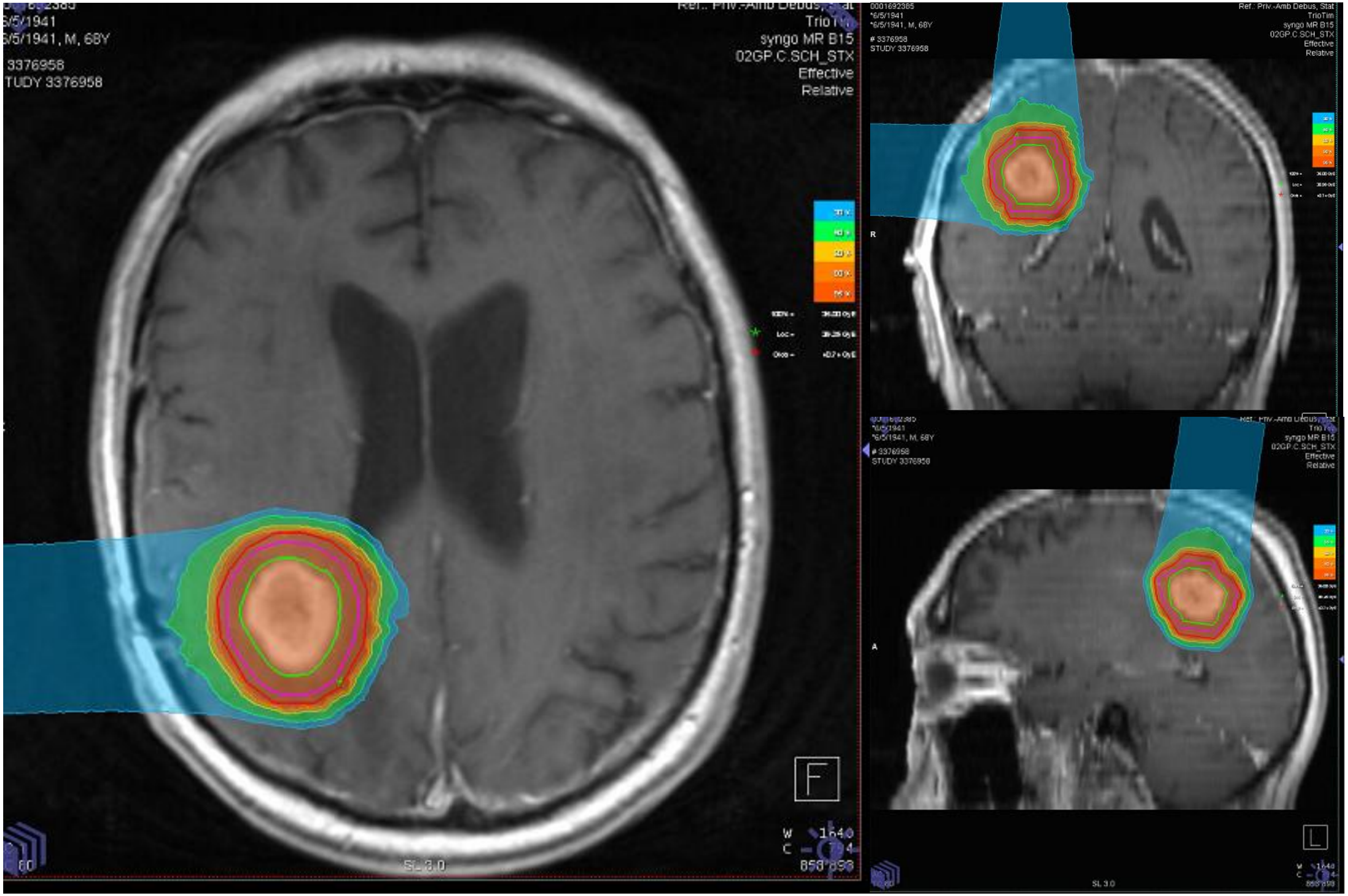
Schlampp et al., Int J Radiat Oncol Biol Phys, (2011) 80: 815ff

Therapeutic Window In Soft Tissue Sarcoma



Kamada et al. , ESTRO teaching course 2011

Carbon ion Radiation Therapy – Recurrent Glioblastoma



Randomised Phase I/II Study to Evaluate ***C****arbon* ***I****o****n*** *Ra****d****iothe****r****apy ve****r****sus Fractionated Stereotactic R****a****diotherapy in Patients with Recurrent or Progressive G****l****iom****a****s:*

The CINDERELLA Trial

- unifocal recurrent glioma post 1 or 2 treatments
- no other re-irradiation performed
- largest diameter of contrast enhancement: 4cm

Phase I:
Dose Escalation

R

Arm A: Experimental Arm

C12

„Best-Dose“ of Phase I

10 x 3Gy E to 16 x 3 Gy E Single Dose

Arm B: Standard Arm

FSRT
Combs SE, JCO 2005
36 Gy / 2 Gy single dose

Study Coordinator: Combs SE
in cooperation with:
Prof. Dr. Wolfgang Wick, Neuroonkology
Prof. Dr. Andreas Unterberg, Neurosurgery
Dr. L. Edler, Dr. I. Burkholder, dkfz-Biostatistics

Combs SE et al., BMC Cancer 2010

Randomized Phase II study Evaluating a Carbon Ion Boost applied after Combined Radiochemotherapy with Temozolomide versus a Proton Boost after Radiochemotherapy with Temozolomide in Patients with Primary Glioblastoma
The CLEOPATRA Trial

- Glioblastoma at primary Diagnosis
- Makroscopic tumor after biopsy or partial resection
- Indication for radiochemotherapy with temozolomide

Radio-

Chemotherapy

Temozolomide

PTV Dose 50 Gy

R

Arm A: Experimental Arm

6 FX C 12 to the macroscopic tumor

T1-contrast enhancement, FET-PET

„Boost“

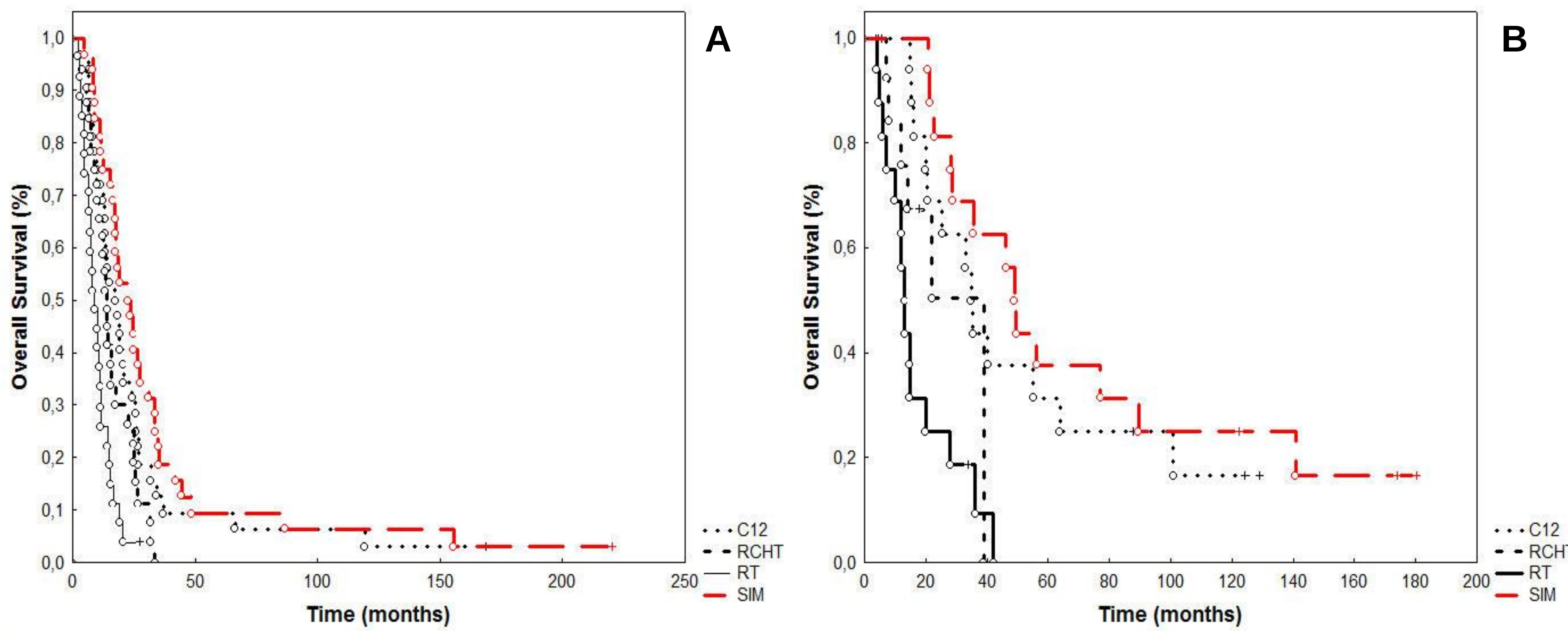
Arm B: Standard Arm

5 FX low-LET up to standard dose of 60 Gy

Study Coordinatior Combs SE
in Cooperation with
Prof. Dr. Wolfgng Wick, Neurooncology
Prof. Dr. Andreas Unterberg, Neurosurgery
Prof. Dr. Meinhard Kieser, Biostatistics
DFG / Klinische Forschergruppe Schwerionentherapie

Combs SE et al., BMC Cancer 2010

Comparison of Heidelberg Radiochemotherapy and NIRS-MIZOE-Study



Simulated OS curves for GBM (A) and AA (B): The SIM-Curves represents a hypothetical population treated with C12 and TMZ. The difference to RCHT with TMZ indicates a potential benefit.

Combs SE et al. Radiother Oncol in Rev.

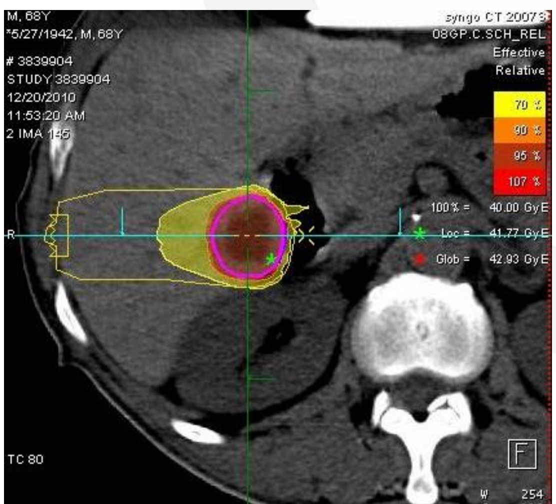
Combs *et al. BMC Cancer* 2011, **11**:67
http://www.biomedcentral.com/1471-2407/11/67

BMC Cancer

STUDY PROTOCOL **Open Access**

Phase i study evaluating the treatment of patients with hepatocellular carcinoma (HCC) with carbon ion radiotherapy: The PROMETHEUS-01 trial

Stephanie E Combs[1*], Daniel Habermehl[1], Tom Ganten[2], Jan Schmidt[3], Lutz Edler[4], Iris Burkholder[5], Oliver Jäkel[6], Thomas Haberer[6], Jürgen Debus[1]



Phase I Study evaluating the treatment of patients with advanced hepatocellular carcinoma (HCC) with Carbon Ion Radiotherapy: *The Prometheus-01 Trial*

• histologically confirmed or imaging-confirmed HCC
• makroscopic tumor, localized, no metastases
•also potential candidates for liver transplantation (bridging therapy)

HCC

C

Arm A: Experimental Arm

Carbon Ion Radiotherapy

Dose Escalation

4 x 10 Gy E 40 Gy E

Increasing fraction size

4 x 14 Gy E 56 Gy E

Arm B: Historical Controls

TACE, Sorafenib-Systemtherapie, HeiLIVCA

Study Coordinator Combs SE
in cooperation with
Prof. Dr. Jan Schmidt, Surgery
Dr. Tom Ganten, Gastroentereology
Dr. L. Edler, Dr. I. Burkholder, dkfz-Biostatistics
DFG Klinische Forschergruppe Schwerionentherapie

Combs SE et al., BMC Cancer 2010

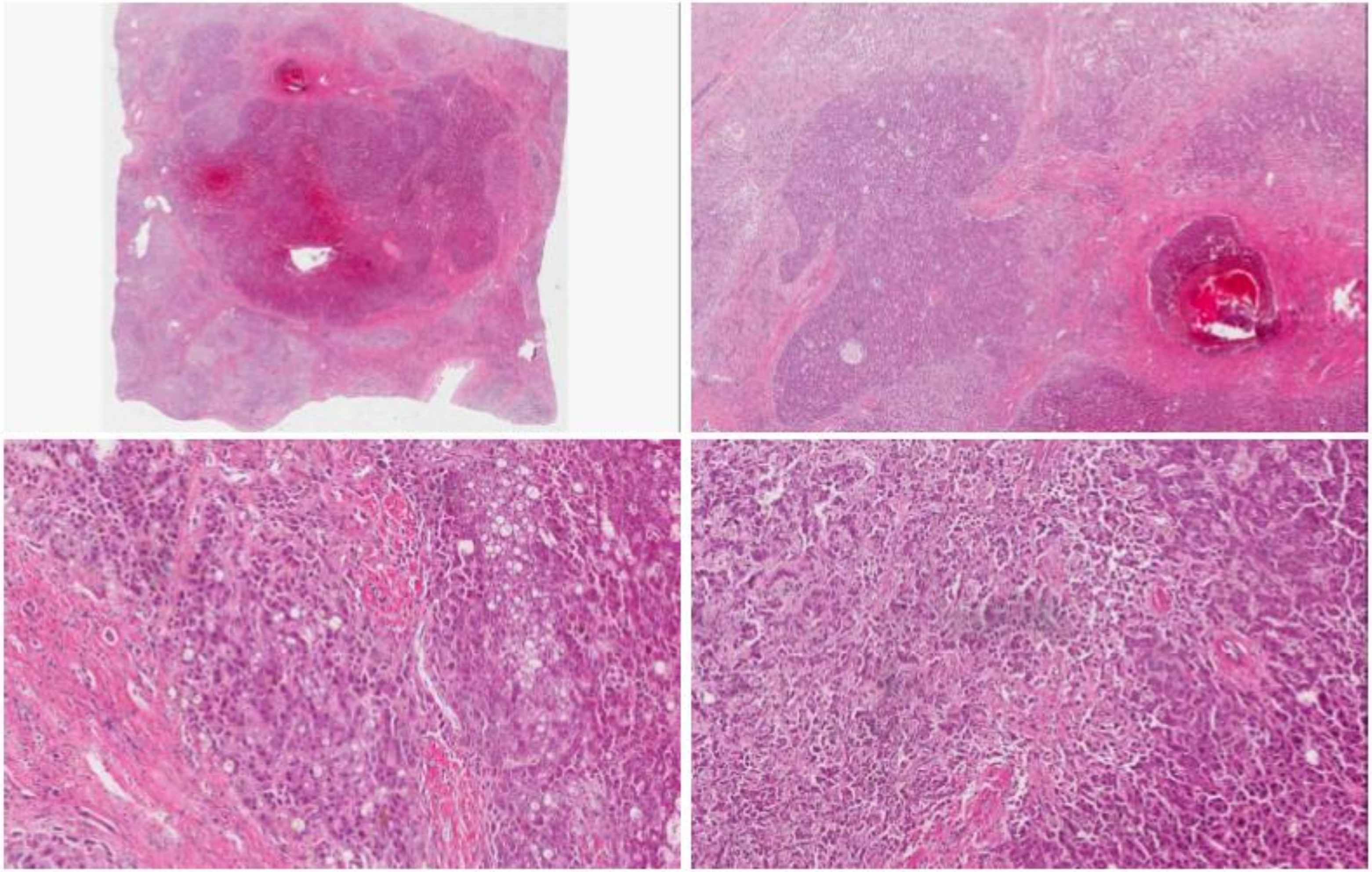
HCC after Carbon Ion RT: Quick Response

initial

4 weeks after RT

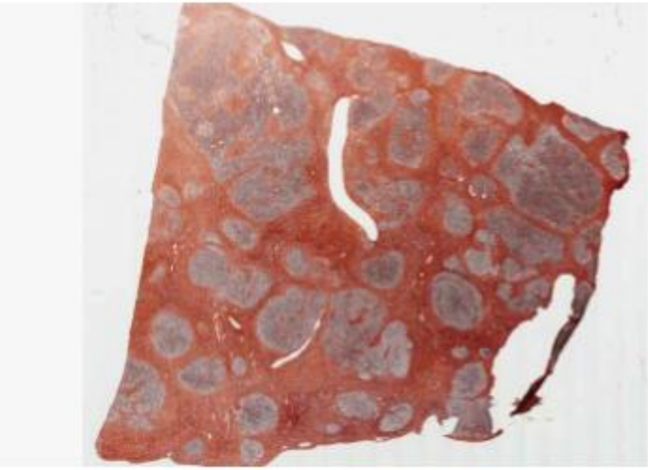
12 weeks after RT

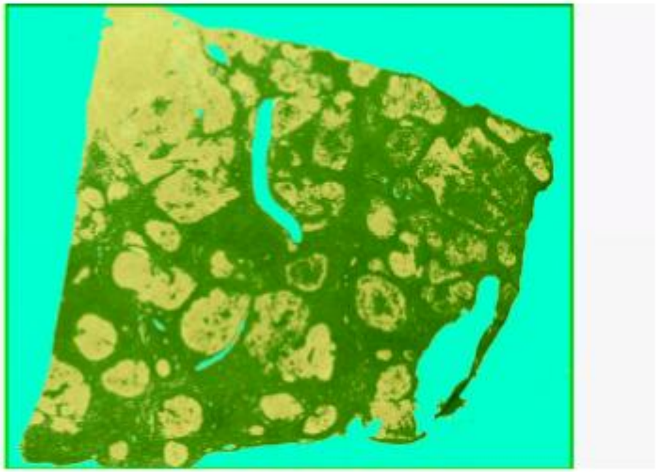
Histological Investigation Of Radiation Effects:
- optimization of targeting
- better understanding of biological effects

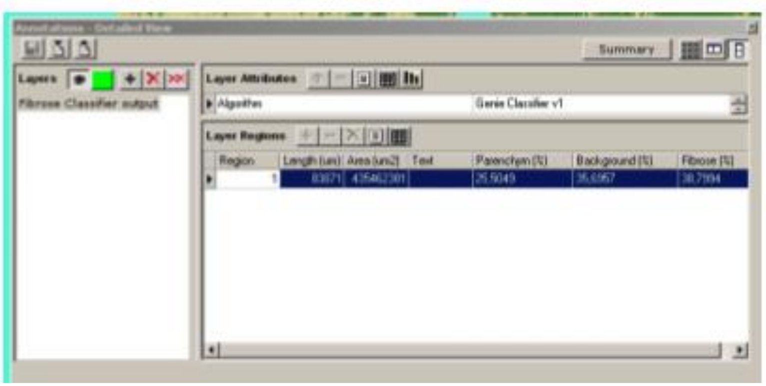


transplantation 63 days after carbon RT

Quantification Of Radiation Effects:
Computerized Analysis Of Fibrosis





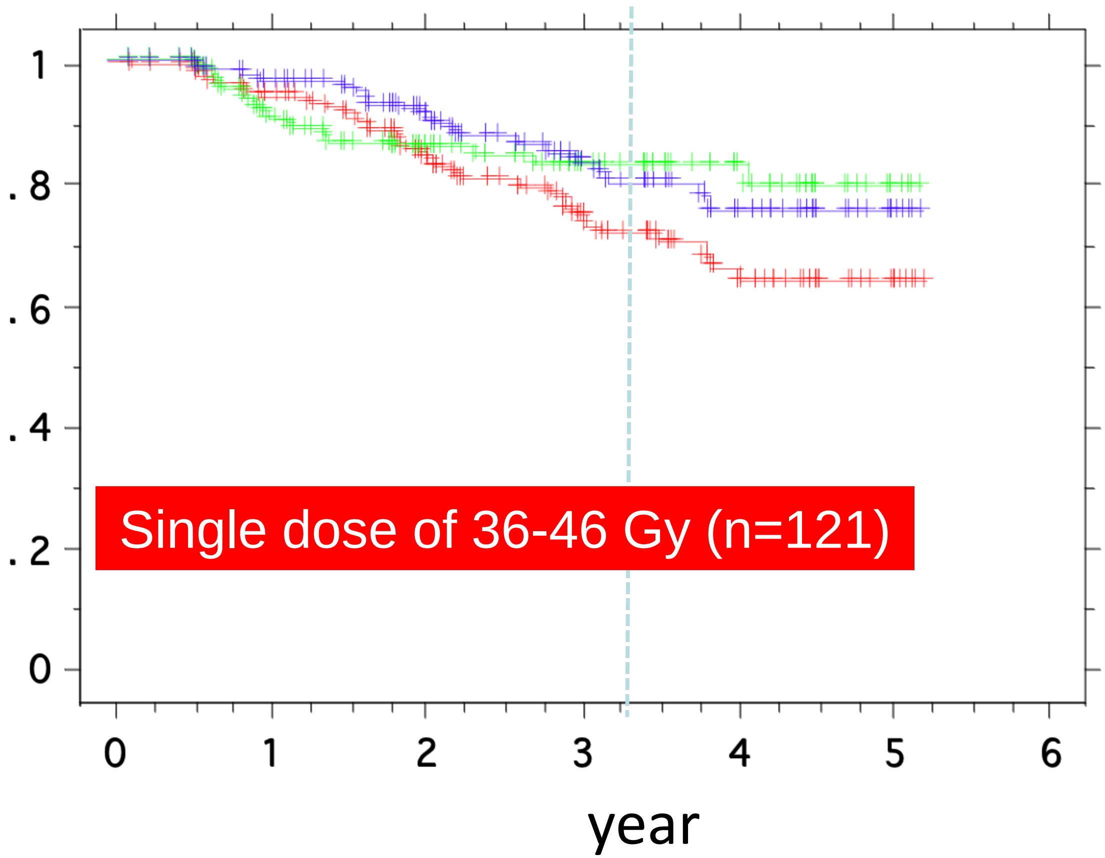


area of fibrosis:

= 38,7994/(25,5049+ 38,7994)*100

= 60,34%

Single Fraction Carbon ion therapy for Stage I non small cell lung cancer

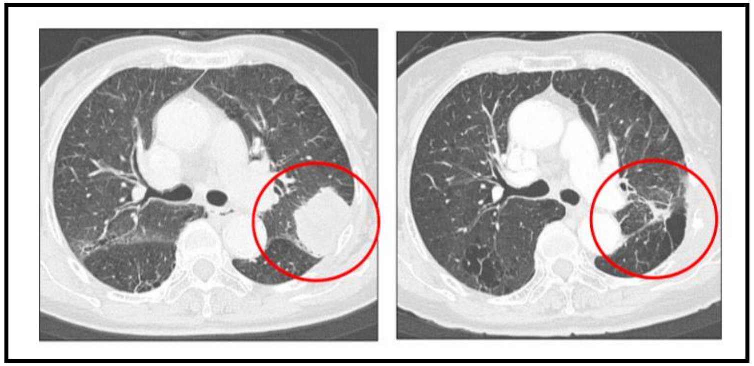


Local control rate(5 y)：79%

Cause-spec. survival rate(5y)：75%

Overall survival rate(5y)：64%

T2N0M0 Sq.CC 71 F



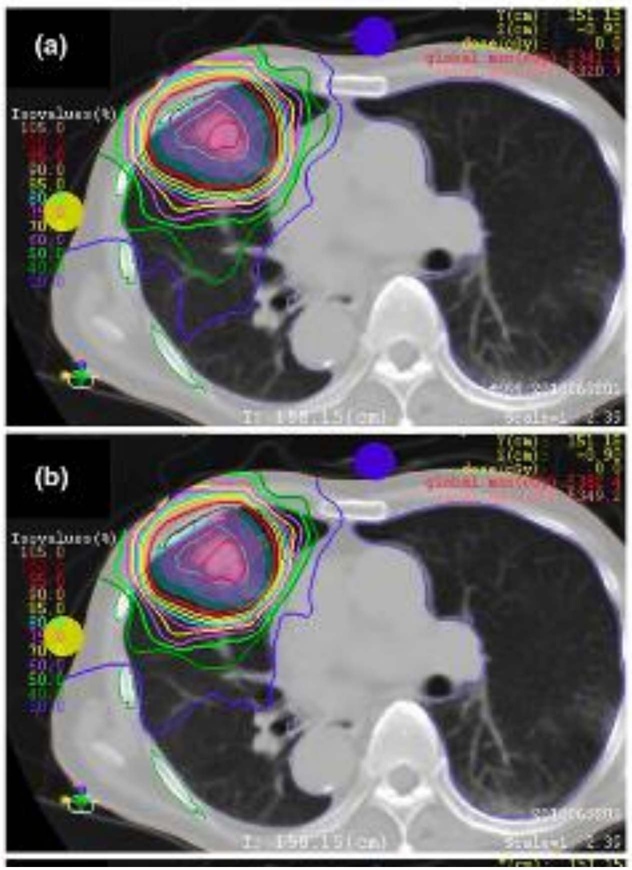
Before After

NO Grade 3 Reactions in this series

Kamada, Estro teaching course 2011

Technical approach to individualized respiratory-gated carbon-ion therapy for mobile organs

Mutsumi Tashiro · Takayoshi Ishii · Jun-ichi Koya · Ryosuke Okada · Yuji Kurosawa · Keisuke Arai · Satoshi Abe · Yoshiaki Ohashi · Hirofumi Shimada · Ken Yusa · Tatsuaki Kanai · Satoru Yamada · Hidemasa Kawamura · Takeshi Ebara · Tatsuya Ohno · Takashi Nakano



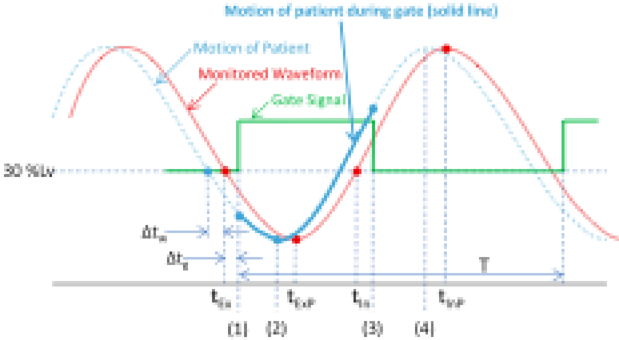


Fig. 2 Relationship among respiratory motion of patient, monitored waveform, and gate signal. Reconstructed 4D CT phases are shown as *numbers*

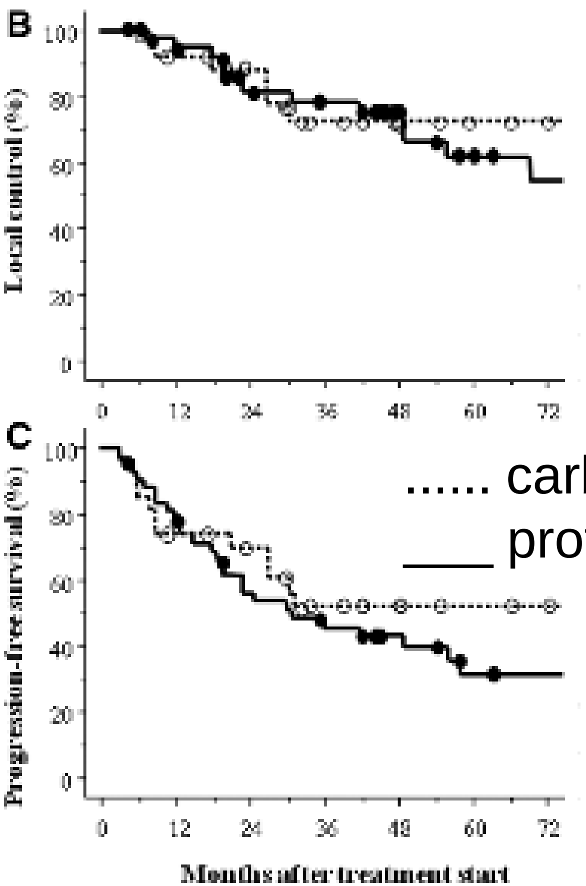
Gunma University

Radio Phys Tech, 2013

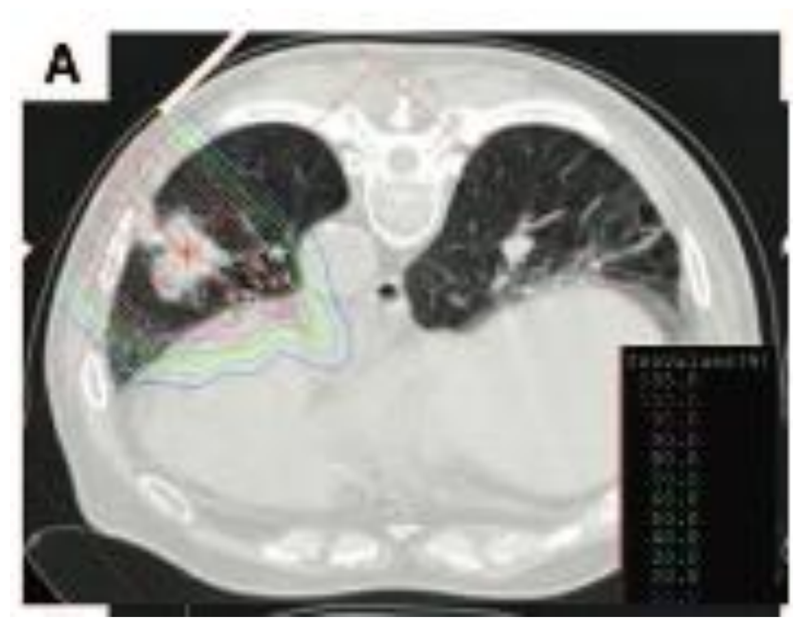
Long-Term Outcome of Proton Therapy and Carbon-Ion Therapy for Large (T2a–T2bN0M0) Non–Small-Cell Lung Cancer

Hiromitsu Iwata, MD, PhD,†‡ Yusuke Demizu, MD, PhD,† Osamu Fujii, MD, PhD,†
Kazuki Terashima, MD, PhD,† Masayuki Mima, MD,† Yasue Niwa, MD,† Naoki Hashimoto, MD, PhD,†
Takashi Akagi, PhD,§ Ryohei Sasaki, MD, PhD,|| Yoshio Hishikawa, MD, PhD,† Mitsuyuki Abe, MD, PhD,†
Yuta Shibamoto, MD, PhD,* Masao Murakami, MD, PhD,¶ and Nobukazu Fuwa, MD, PhD†*

(*J Thorac Oncol.* 2013;8: 726-735)



...... carbon (n =27)
____ proton (n=43)



Nagoya University, Hyogo Ion Beam Center

Hypo-fractionation

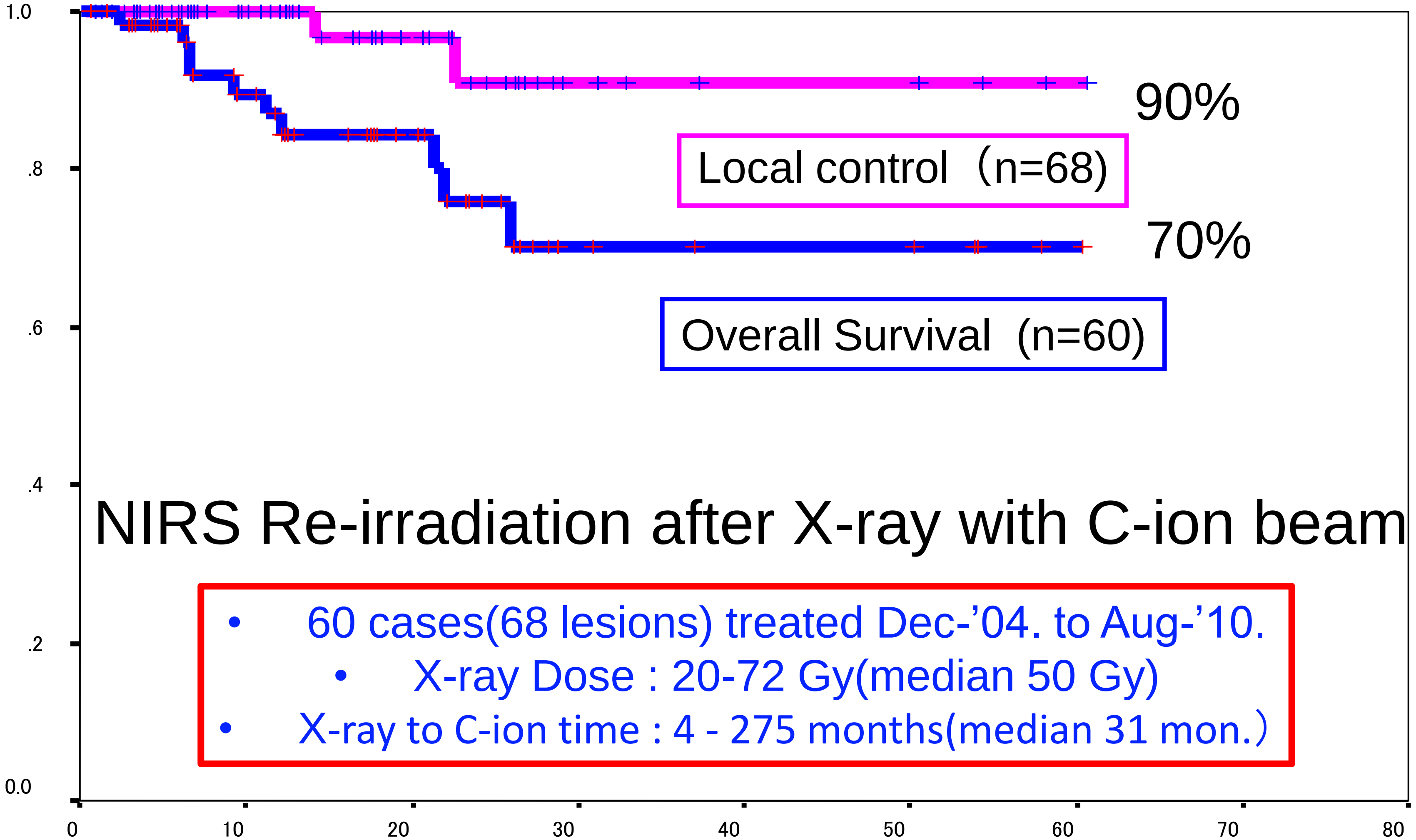
Pros	Cons
Similar effectiveness	Potentially More toxic
Convenient for patient	Less experience
More economic	Less re-oxygenation
More cytokine or bystander effect ?	Less repair…etc
Immumologic effect?	Small therapeutic window

Why Re-irradiation with Carbon?

- Regrowth of a radio-resistant clone often hypoxic
- “different approach”
- Tumor bed effect:

  damage of tumor vasculatures and stromal elements(fibrosis and necrosis) - poor blood supply and impairment of local defense (immune?) system
- Low tolerance of surrounding normal tissue

Local Control and Survival in Re-irradiation with Carbon Ion Therapy



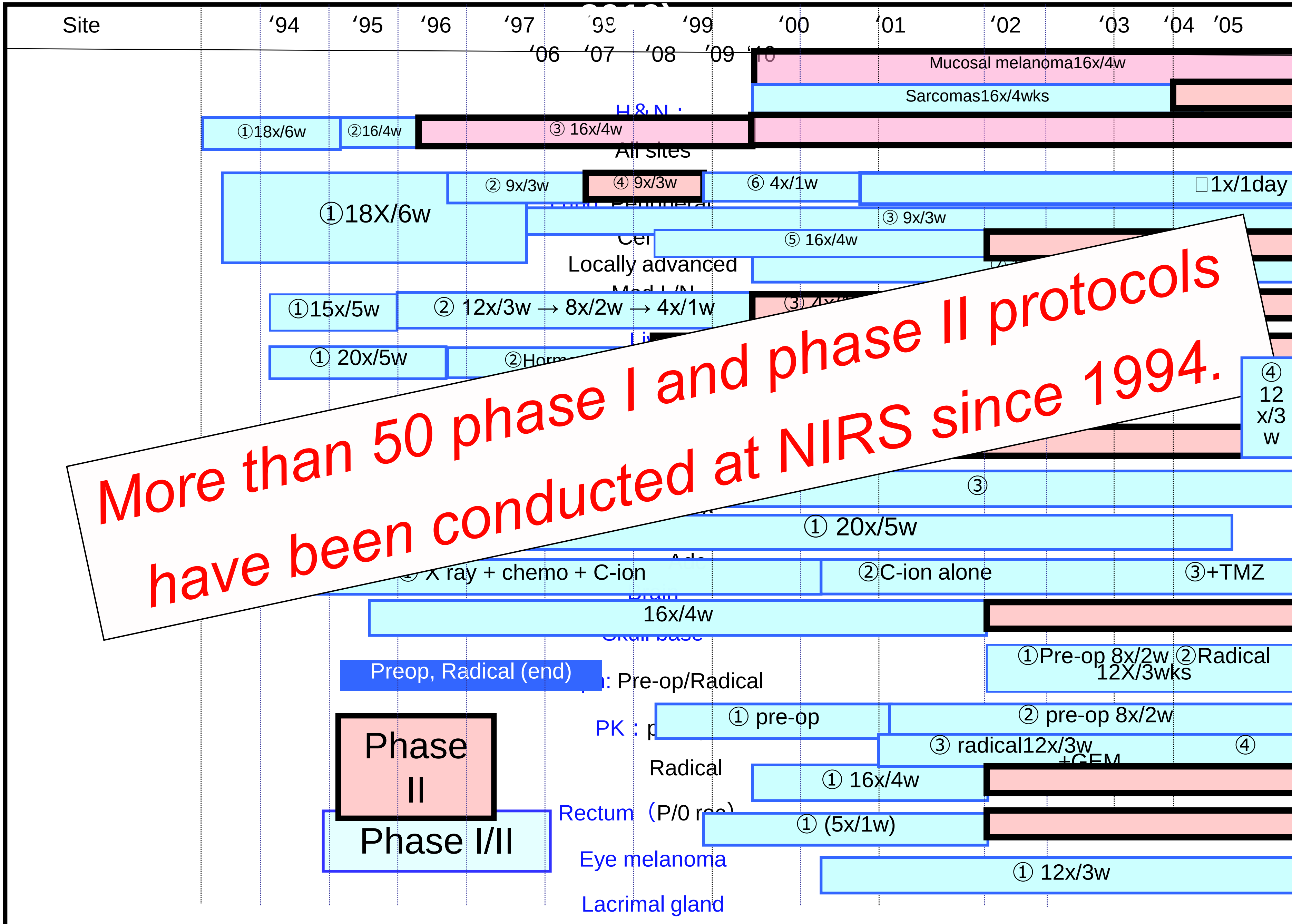
Kamada, Estro teaching course 2011

Months after C-ion

Clinical trials @ HIT

- SB chordomas: H1 vs. C12 recruting
- SB chondrosarcomas: H1 vs. C12 recruting
- CLEOPATRA (H1 vs. C12 boost RT; prim. glioblastoma) recru
- CINDERELLA (C12 recurrent gliobastoma) recruting
- MARCIE (C12 boost RT, meningeomas grade 2) recruting
- COSMIC (C12 boost RT; salivary glands) finished recruiting
- TPF-C HIT (C12 boost RT; head&neck) recruting
- IMRT HIT-SNT (C12 boost RT; sinu-nasal cancer) recruting
- ACCEPT (C12 boost RT + Erbitux for ACC) recruting
- PROMETHEUS (C12 for HCC) recruting
- OSCAR (H1 + C12 boost; inoperable osteosarkoma) recruting
- PANDORA (C12 for recurrent rectal carcinoma) recruting
- IPI (C12/H1 for Prostate cancer) recruting
- ISAC (C12/H1 for sacral chordoma) recruting
- PROLOG (hypofract. H1 for Prostate cancer recurrence) recrut

Protocols and Time Line of Carbon Ion Clinical Trials (1994-2010)



Conclusion

- Clinical data obtained in prospective phase I/II and phase II trials support the hypothesis that there is a role of carbon ions in oncology

- Data of the centers in Europe and Asia are consistent

- Randomized studies are underway

- new indications demand for strong translational research

<u>areas of research:</u>
beam generation,
beam application,
medical physics,
radiation biology,
clinical research

Principles Of Operation:
power and endurance,
balance and harmony

Radiation Oncology

research
teach
treat

University of Heidelberg