

Particle Therapy Centers in Germany

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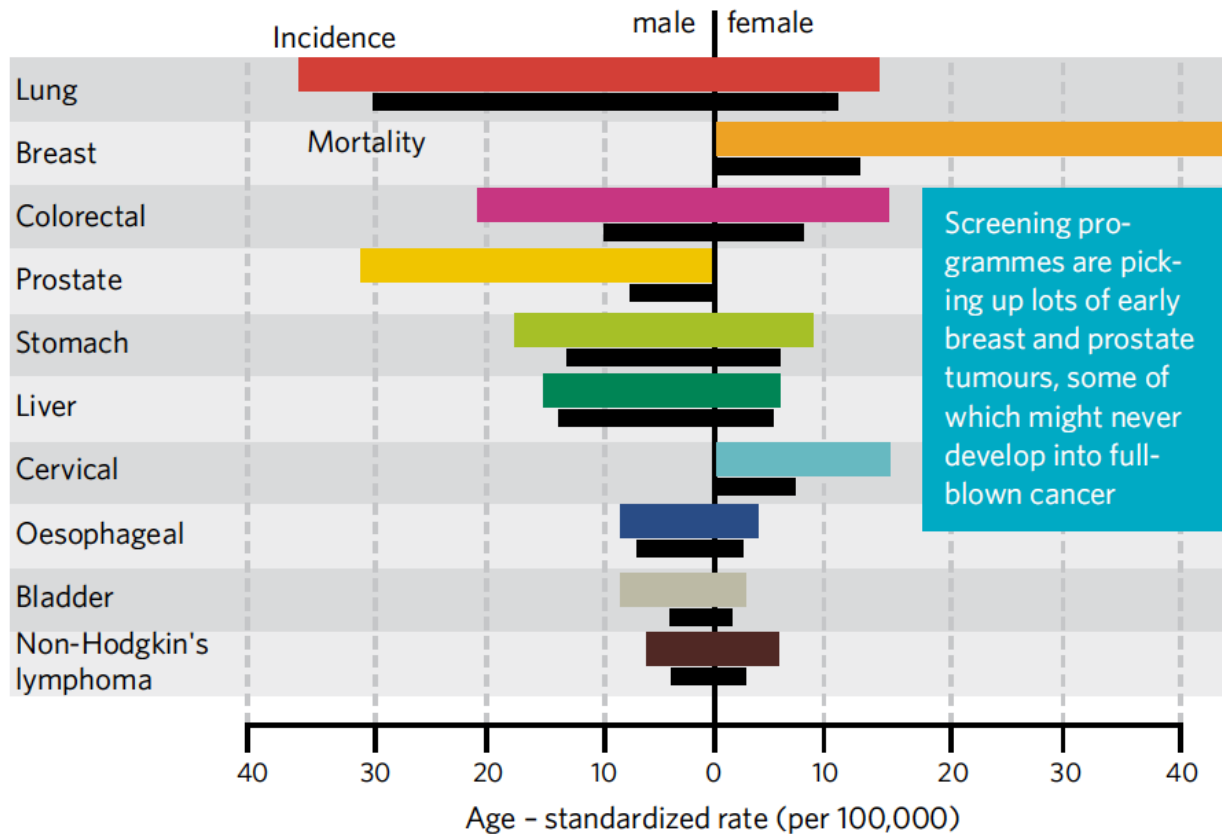
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GERMAN
CANCER RESEARCH CENTER
IN THE HELMHOLTZ ASSOCIATION

Rates of therapy failure today



Screening programmes are picking up lots of early breast and prostate tumours, some of which might never develop into full-blown cancer

Illustration 1: Treatment successes (see the ratio of coloured to black bars) are mainly restricted to prostatic and breast carcinomas. These are, however, treated too frequently, see box. Some of the cancer cells found in the prostate, and to a lesser extent in the breast, would not have become clinically active during the patient's lifetime.

Source: Nature 29.05.2014; Vol. 509; No. 7502; from World Cancer Report 2014

3) Genital carcinomas in women. Guidelines at www.gfmer.ch

4) Wodarz D. et al: Risk factors and random chances. Nature 517 doi:10.1038/517563a

Radiation side-effects

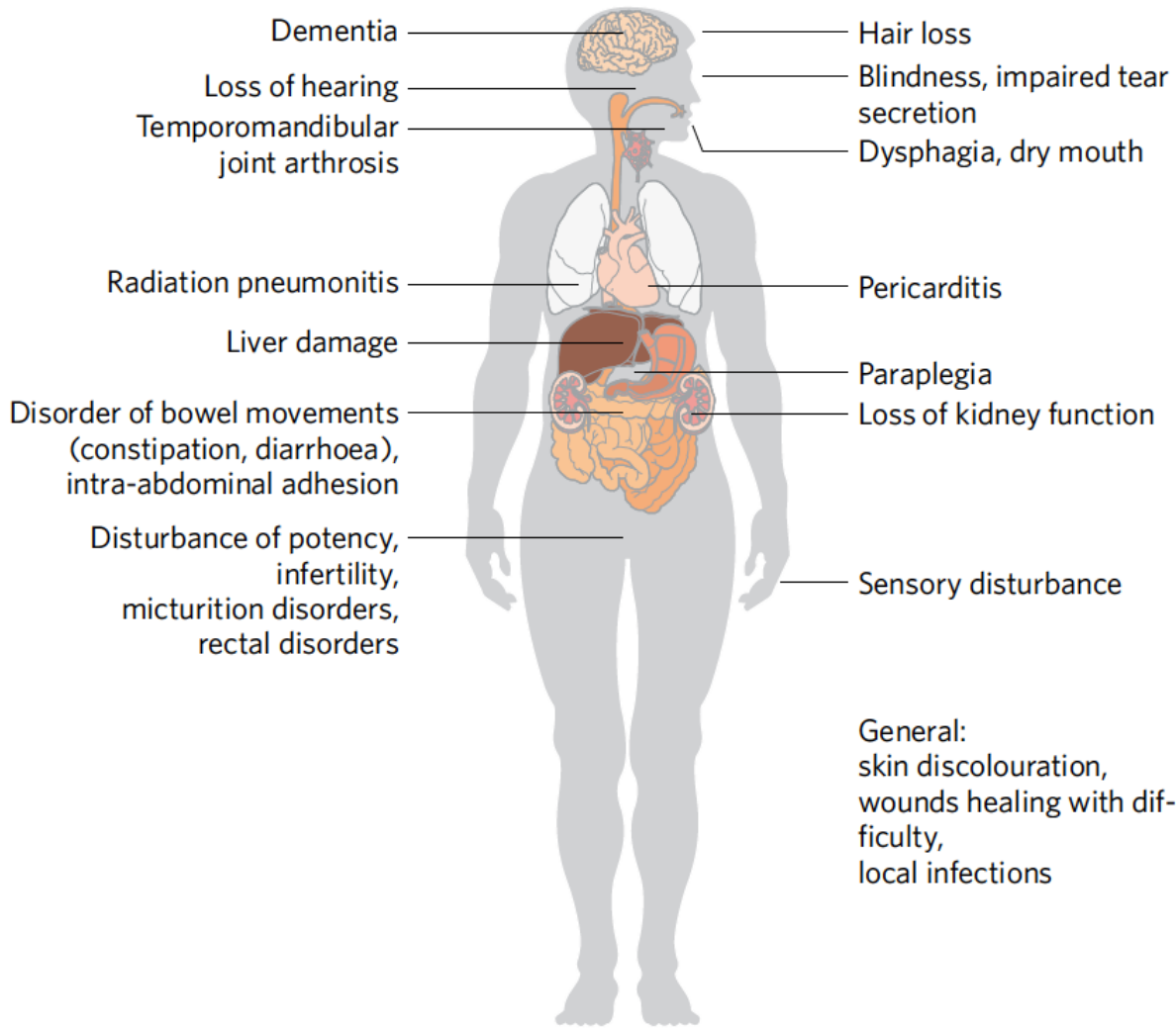
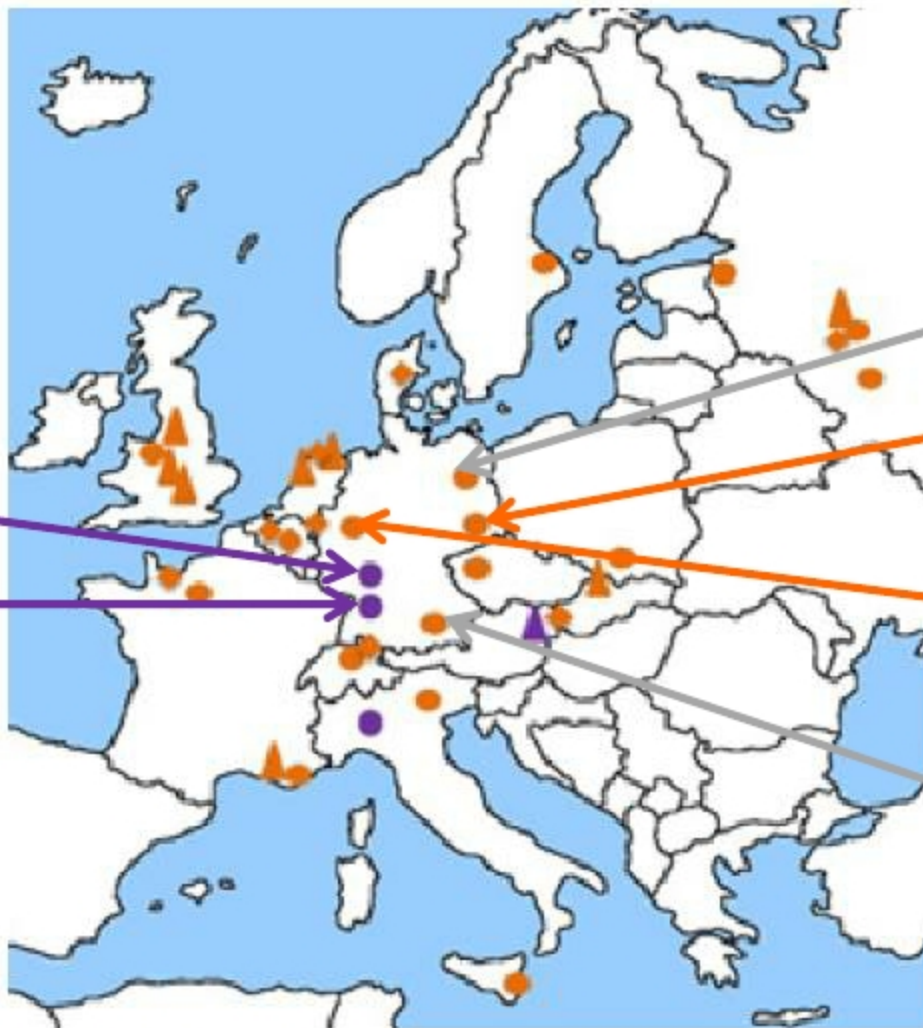


Illustration 4: Organ-specific radiation damage: short-term and long-term damage are grouped together here; the severity always depends on the dose level in the healthy tissue. In addition, there is a generalised risk of secondary carcinomas forming over a longer period of time.

PARTICLE THERAPY CENTRES IN EUROPE - 2015



Protons and carbon ions

- University Hospital Heidelberg
- MIT Marburg
- HIT Heidelberg

Protons

Charité /
Helmholtz-Zentrum
Berlin Protonen

University
Hospital
Dresden

University
Hospital
Essen/ WPE

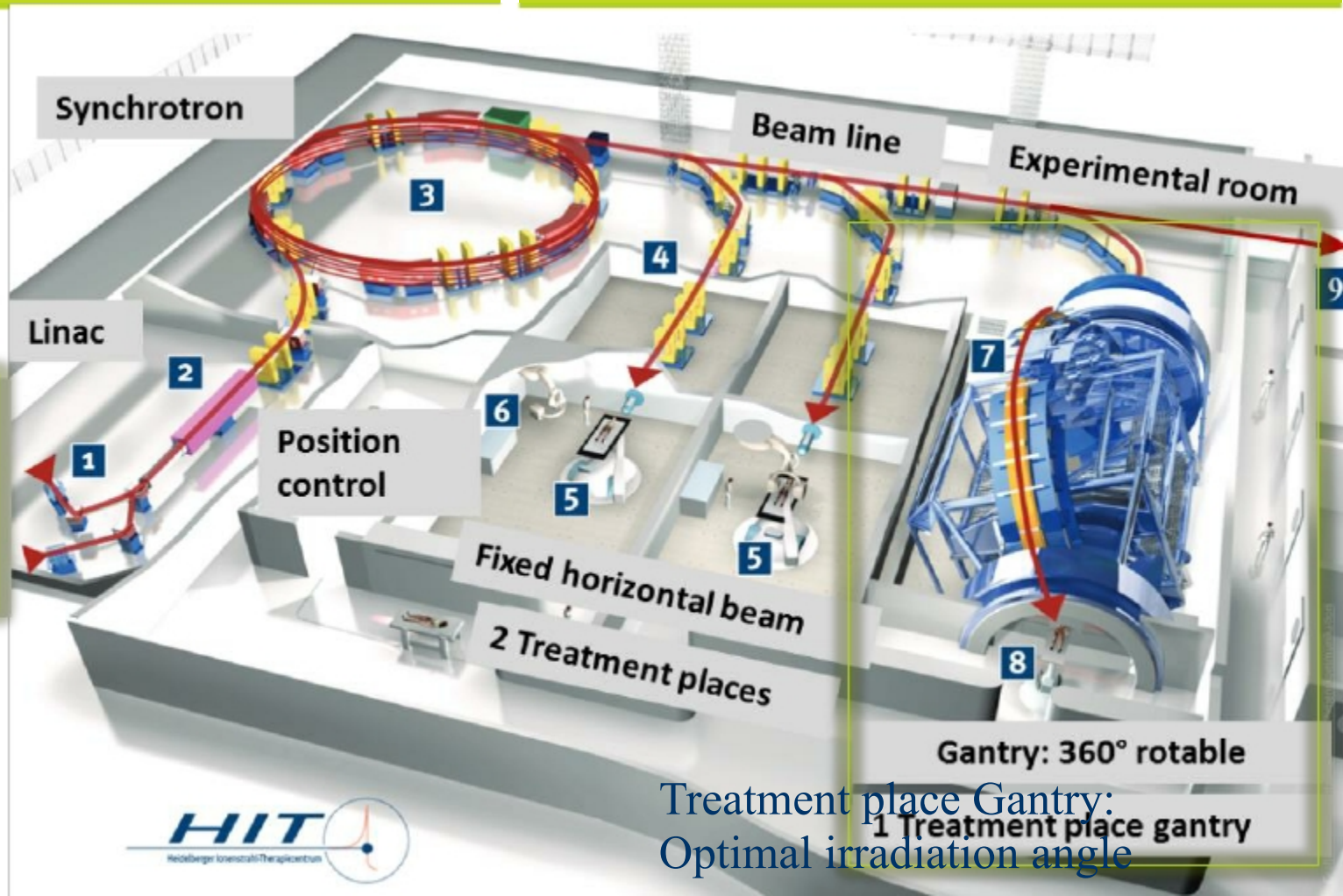
Rinecker Proton
Therapy Center
RPTC

In operation	Under construction	Being planned
● Proton	▲ Proton	◆ Proton
● Dual Ion	▲ Dual Ion	◆ Dual Ion

HIT: Heidelberg Ion Therapy Center

- HIT is Europe's first combined treatment facility using **protons and heavy ions** for radiation therapy.

- HIT is the world's first heavy ion treatment facility with a **360° rotating beam delivery system (gantry)**.

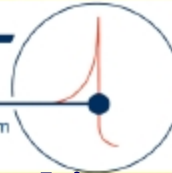


MIT: Marburg Ionbeam Therapy center



MIT

Marburger Ionenstrahl-Therapiezentrum



**Operation started in
10/ 2015
(treated 171 Patients)**



MIT: Marburg Ionbeam Therapy center

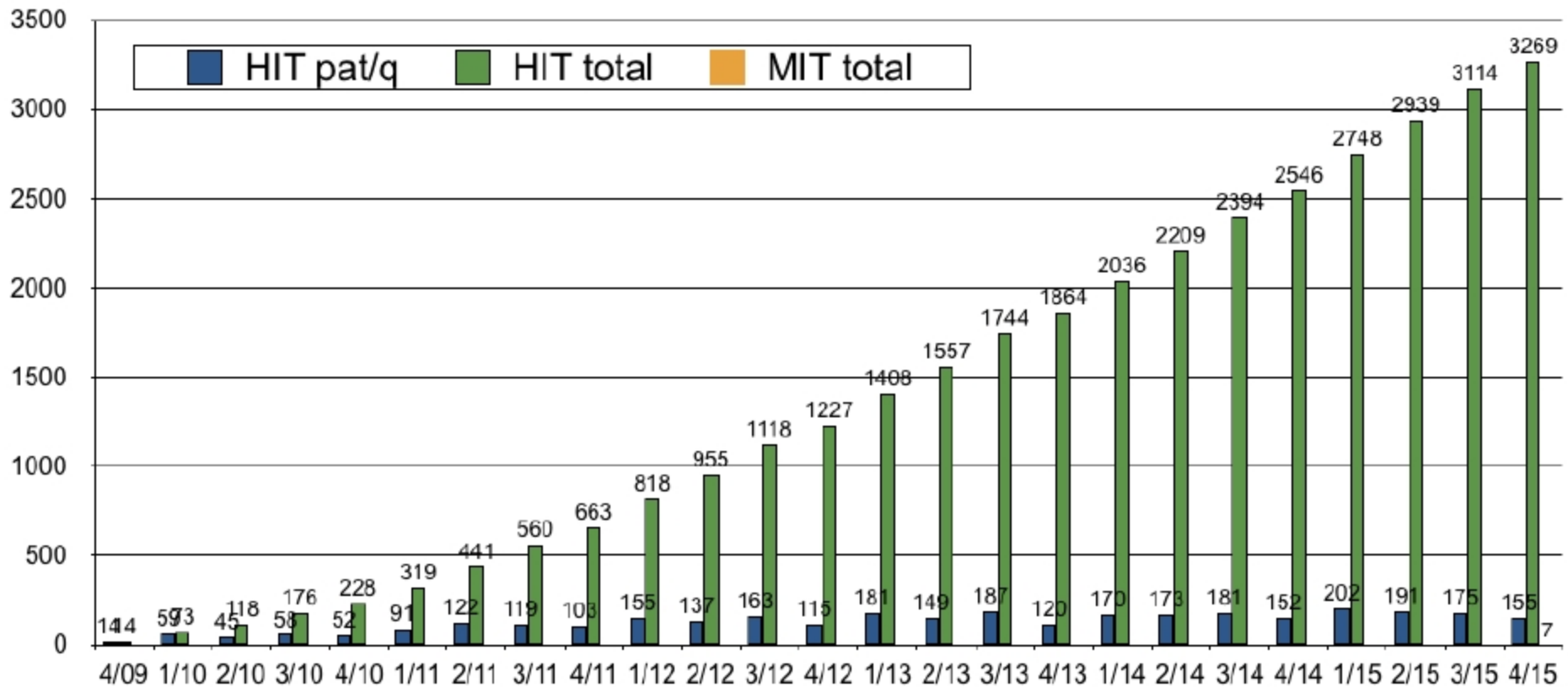
- 3 treatment places at horizontal beam
- 1 treatment places at 45° beam





Patients @ HIT / MIT

Proton therapy since 11/2009, ~3300 patients treated (1200 proton, 2100 Carbon)



2009
14

2010
214

2011
435

2012
570

2013
637

2014
676

2015
723 (HIT)

Clinical trials @ HIT

- • SB chordomas: H1 vs. C12 **recruiting**
- • SB chondrosarcomas: H1 vs. C12 **recruiting**
 - CLEOPATRA (H1 vs. C12 boost RT; prim. glioblastoma) **recruiting**
 - CINDERELLA (C12 recurrent glioblastoma) **recruiting**
 - MARCIE (C12 boost RT, meningiomas grade 2) **recruiting**
- • COSMIC (C12 boost RT; salivary glands) **finished recruiting**
 - TPF-C HIT (C12 boost RT; head&neck)IMRT HIT-SNT (C12 boost F nasal cancer) **recruiting**
- • ACCEPT (C12 boost RT + Erbitux for ACC) **recruiting**
 - PROMETHEUS (C12 for HCC) **recruiting**
- • OSCAR (H1 + C12 boost; inoperable osteosarkoma) **recruiting**
 - PANDORA (C12 for recurrent rectal carcinoma) **recruiting**
 - IPI (C12/H1 for Prostate cancer) **finished recruiting**
 - ISAC (C12/H1 for sacral chordoma) **recruiting**
 - PROLOG (hypofract. H1 for Prostate cancer recurrence) **recruiting**
 - INKA (neoadj. C12 for inop. Sulcus superior tumors) **recruiting**
 - KOLOG (hypofract. C12 for rec. Prostate cancer) **approval pending**



Clinical trial I: chordoma at the base of skull

Primary C-RT in 20Fx (150 patients)

Hypothesis: Existence of dose response relationship

→ 2 prospective randomized phase III studies:

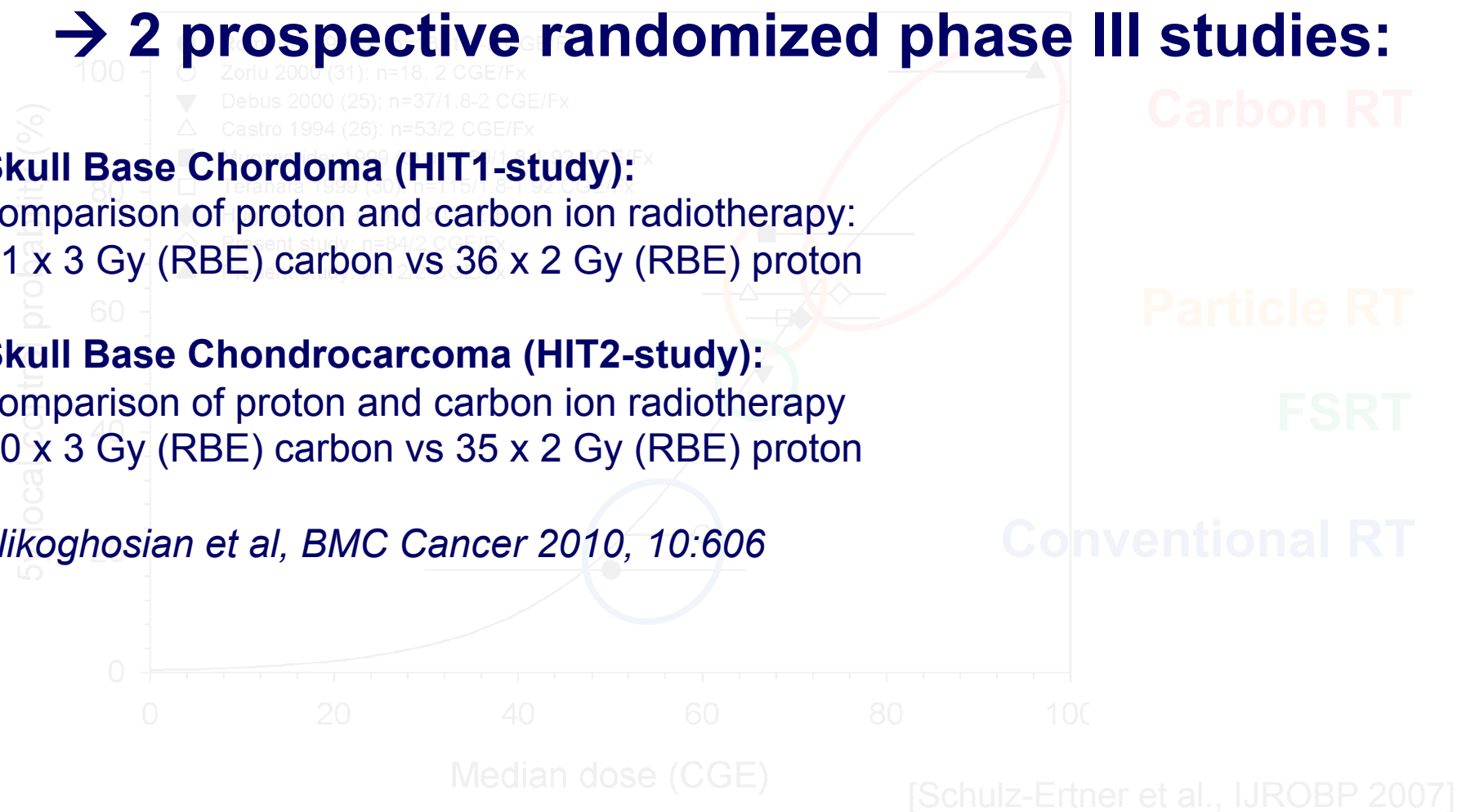
Skull Base Chordoma (HIT1-study):

comparison of proton and carbon ion radiotherapy:
21 x 3 Gy (RBE) carbon vs 36 x 2 Gy (RBE) proton

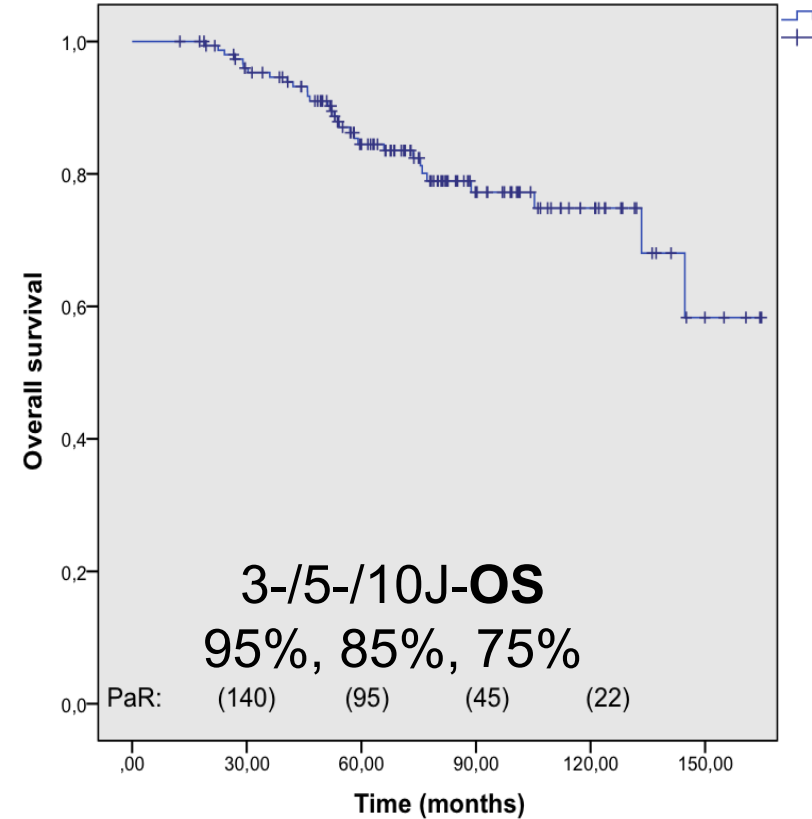
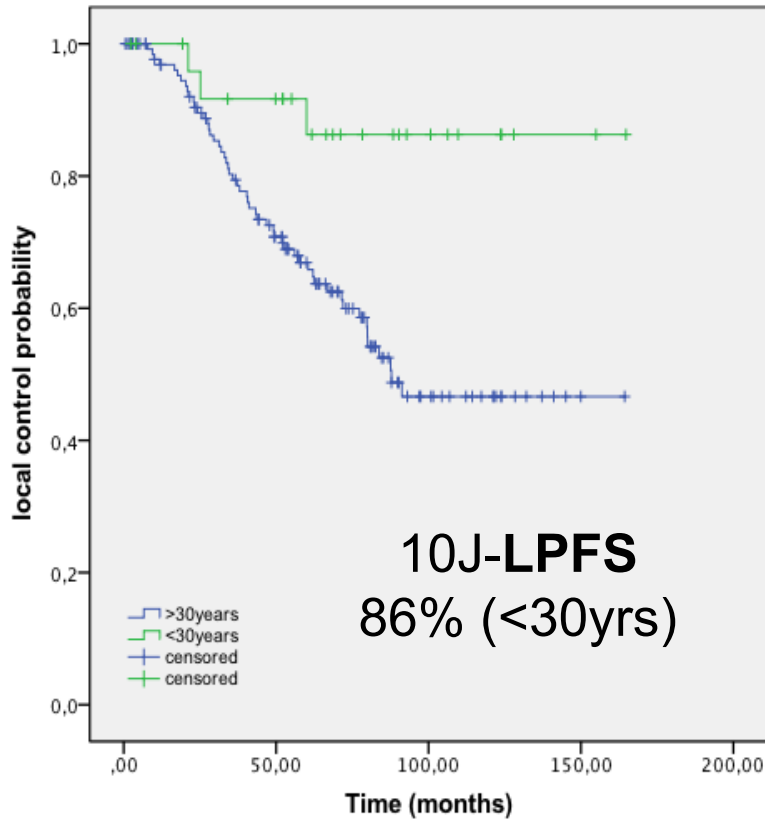
Skull Base Chondrocarcoma (HIT2-study):

comparison of proton and carbon ion radiotherapy
20 x 3 Gy (RBE) carbon vs 35 x 2 Gy (RBE) proton

Nikoghosian et al, BMC Cancer 2010, 10:606



Long term follow up in skull base chordoma



- 155 patients
- median GD: 60 GyE
- median Boost-Volume: 70 ml
- median F/U: 72 months
- No 2nd malignancies

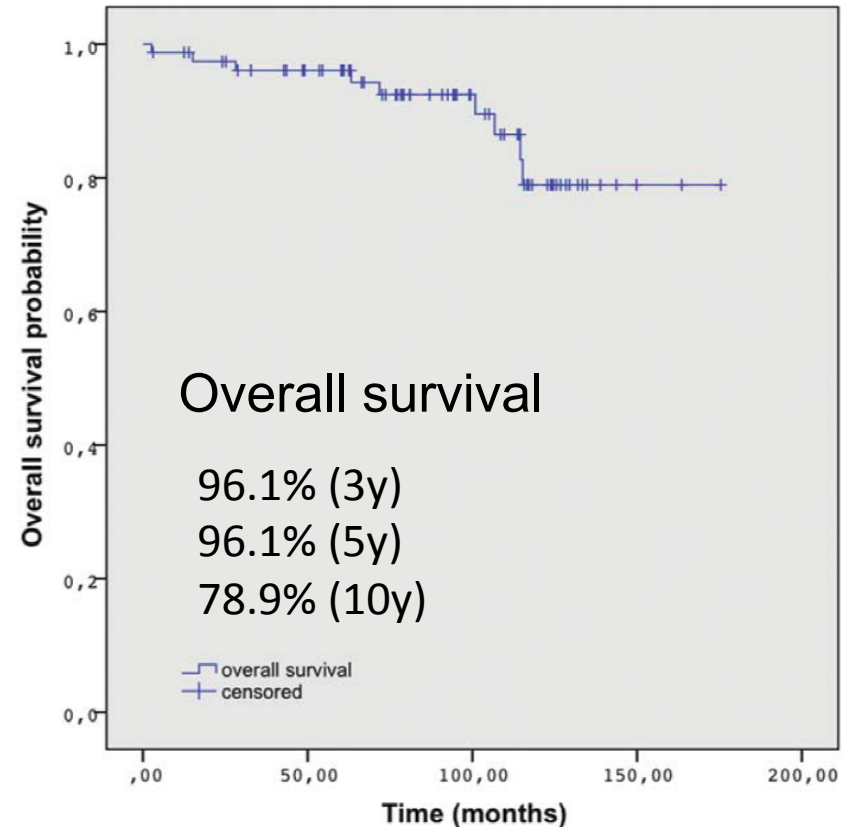
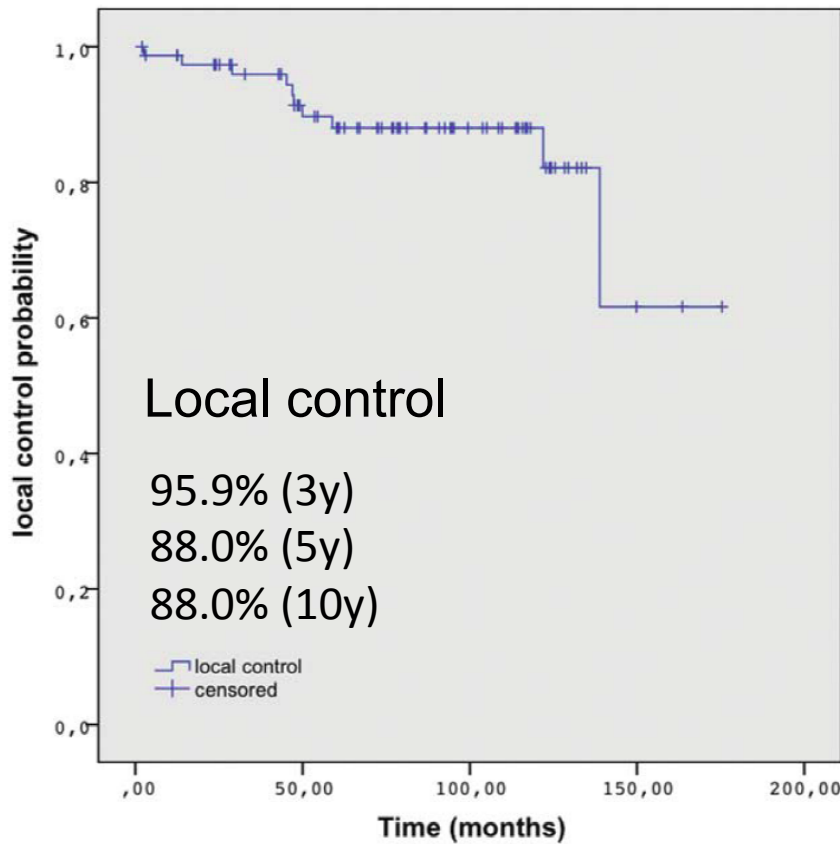
Significant parameters:

Boost-Volume: > vs. < 75 ml

Pat.-Age: LC=86% for < 30 yrs

Long term follow up in skull base chondrosarcoma

Patients treated 1998-2008



- 79 patients treated with carbon ion
- Low and high grade CS
- Median follow-up was 91 months
- No secondary malignancies

Uhl, Cancer 2014

Locally advanced adenoidcystic carcinoma

FSRT / IMRT (n=37) vs. IMRT+¹²C-boost (n=58)

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*)

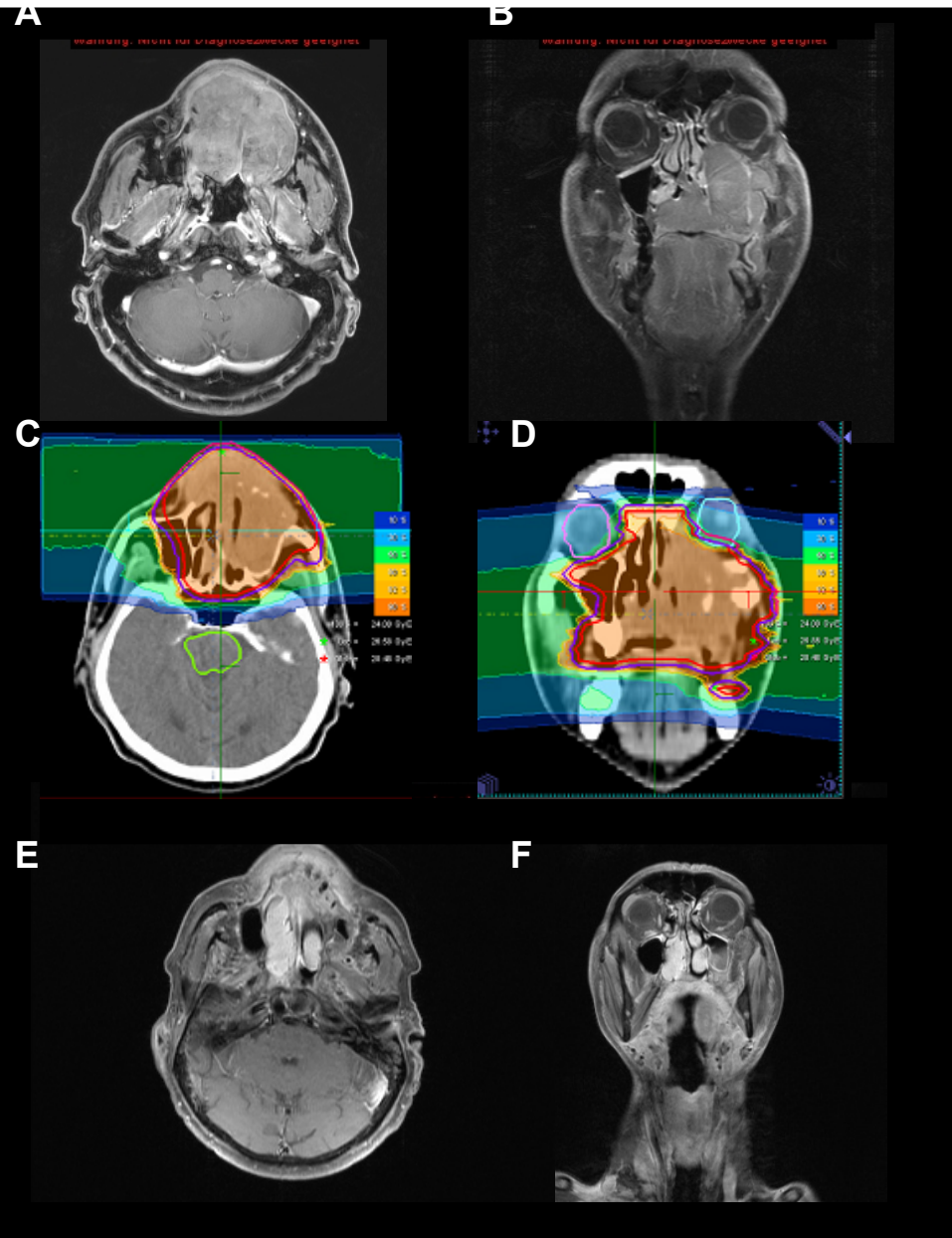
To tackle local control & distant metastases:

Combination with Cetuximab: ACCEPT Study

- 95 patients treated with carbon ion
- Median follow-up 74 (C12) / 63 (photons) months
- 15 yrs follow up
- No dose limiting toxicity

Jensen, Cancer 2014

Treatment response in ACC



Imaging for TP

C-12 RT Boost (18 Gy E),
6 Fx of 3 Gy E
+ IMRT (50 Gy)

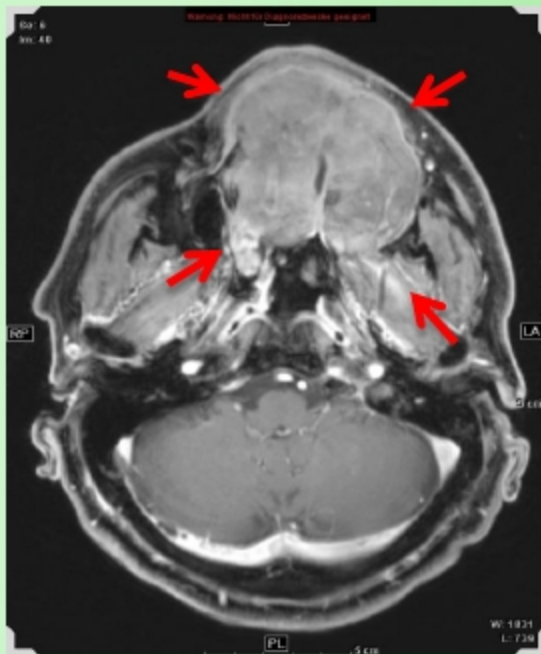
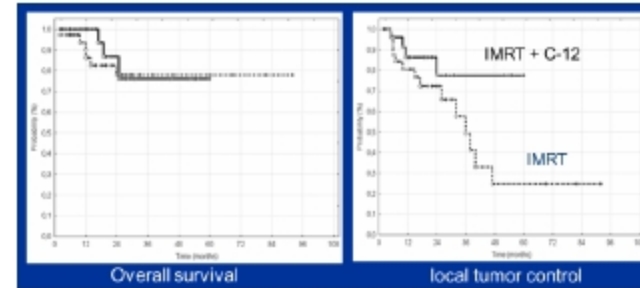
MRI Follow-up 6 weeks
post RT

COSMIC- trial

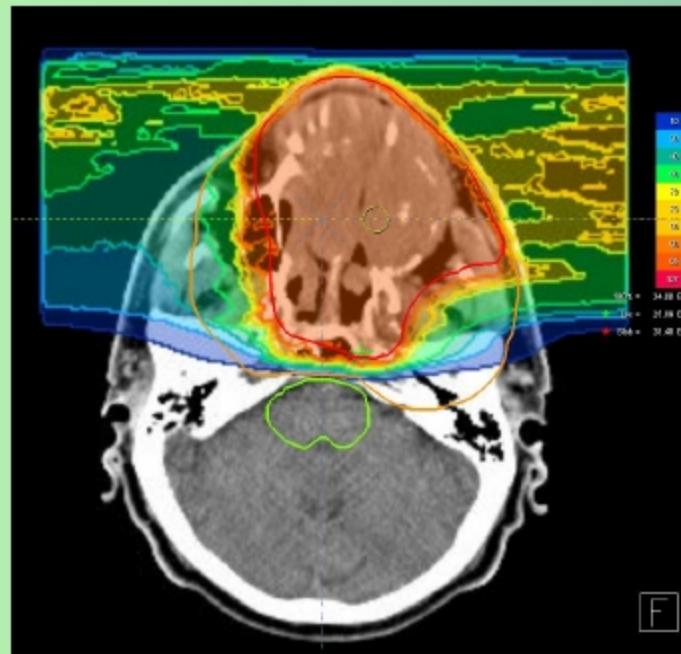
Combined therapy of malignant salivary gland tumors with IMRT and carbon ions

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

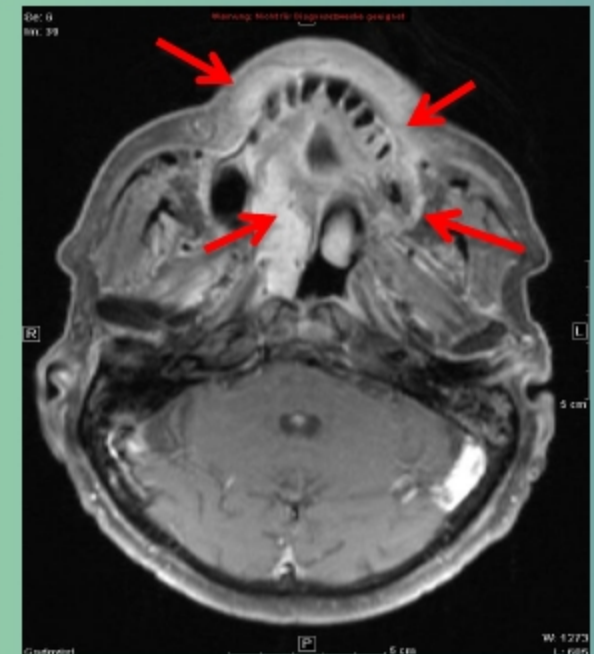
Schulz-Ertner, Cancer. 2005 Jul 15;104(2):338-44



Pre-treatment situation



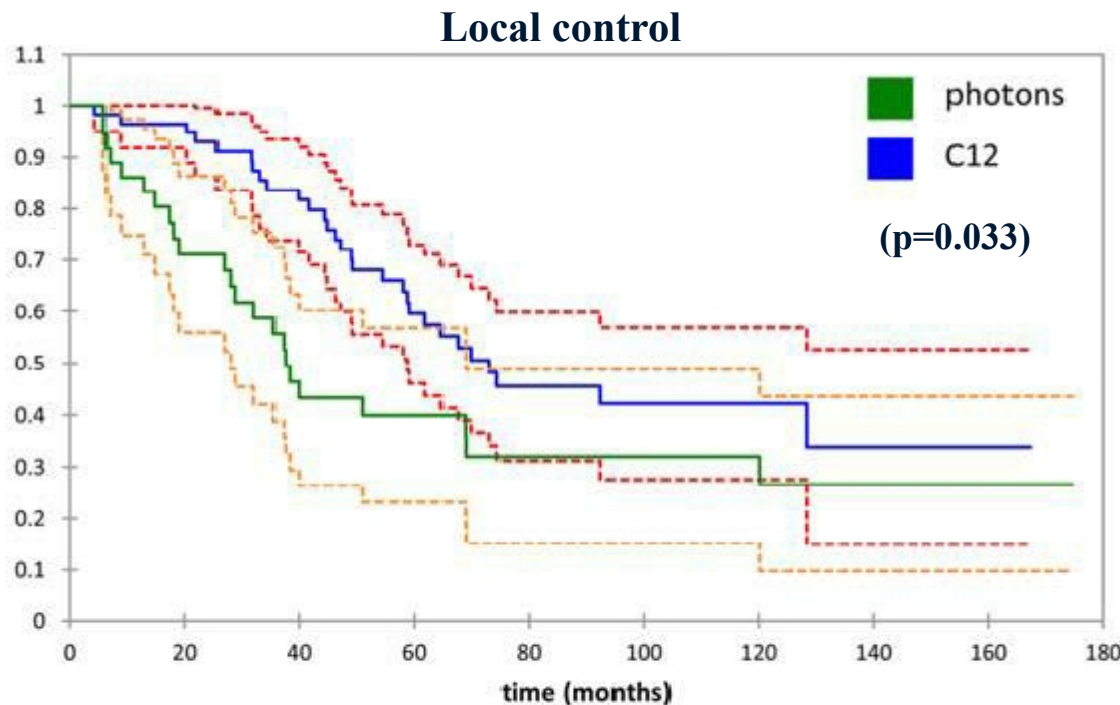
Treatment planning
C-12 boost



6 weeks post RT

COSMIC- trial

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



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

numbers at risk:

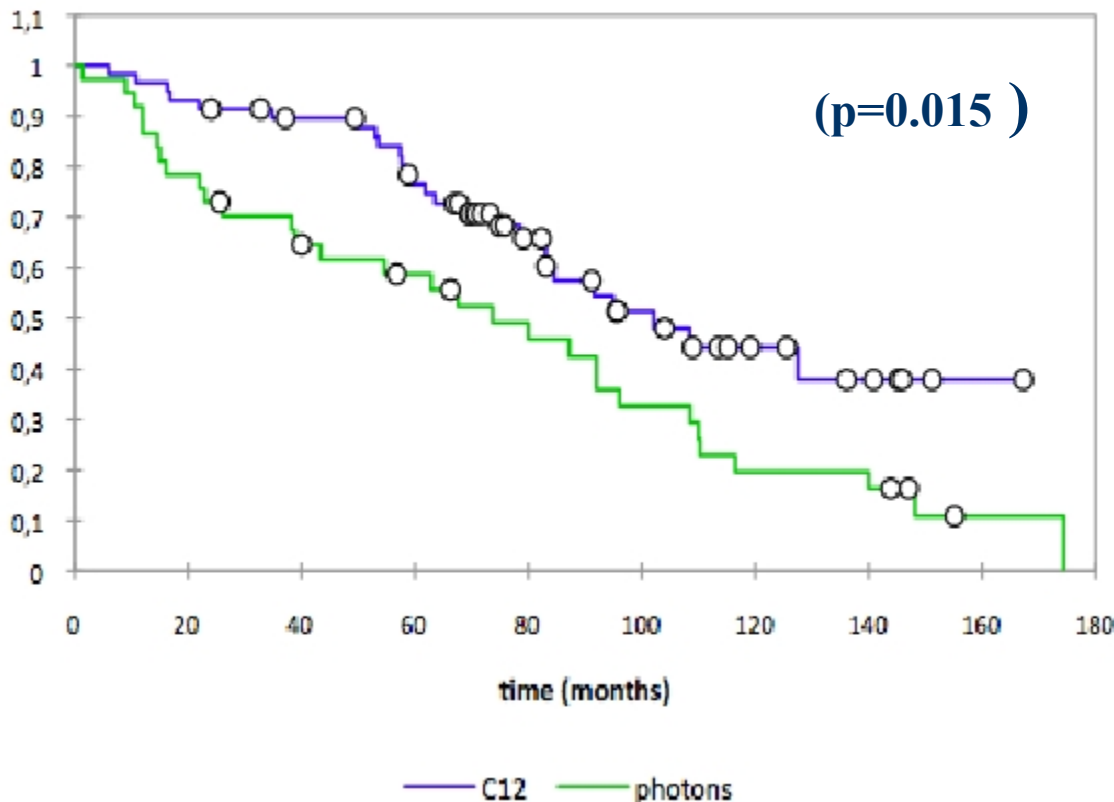
C12:	58	55	43	28	17	11	8	5	2
photons:	37	24	15	12	9	7	7	5	2

Jensen et al. 2015, Cancer

COSMIC- trial

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

Overall Survival



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

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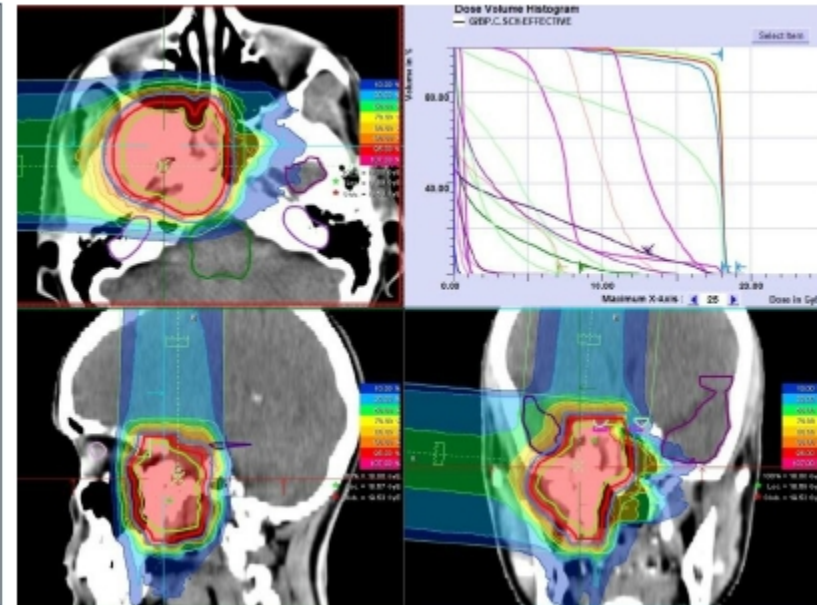
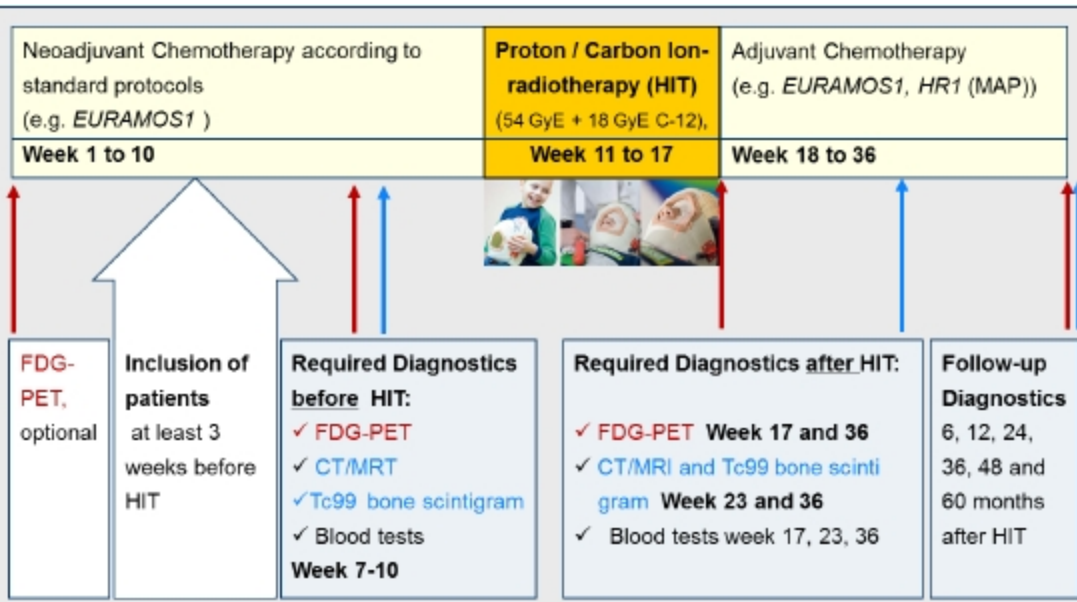
DOI: 10.1002/cncr.29443 View/save citation

Cited by: 0 articles Check for new citations

OSCAR- trial

OSteosarcoma – CARbon Ion Radiotherapy: Phase I/II therapy trial to determine the safety and efficacy of heavy ion radiotherapy in patients with inoperable osteosarcoma

Secondary endpoints: local control disease-free and progression-free survival, Overall survival, role of **FDG-PET** in response monitoring



Future Clinical trials @ HIT

- Pancreatic Carcinoma (C12 only)
- PROCEED (Esophagus Carcinoma (C12 Boost))
- Anal Carcinoma (C12 Boost)

Current clinical studies at Westdeutsches Protonentherapiezentrum Essen (WPE)

Proton therapy since 12/2014, 366 patients treated

- ❖ **Registry study for adult patients** as a basis for future therapy studies
- ❖ **Registry study for pediatric patients** as a basis for future therapy studies
- ❖ **Prospective quality-of-life study** on children with tumors of brain and skull base before and after proton therapy including toxicity and specific side effects; in co-operation with University Hospital Münster
- ❖ **Prospective study on endocrine effects** after cranial irradiation with protons in children



Joint activities: A multicentre explorative study of the German Cancer Consortium Radiation Oncology Group (DKTK-ROG)

Radiobiological profiling for biologically stratified radiochemo-therapy of HNSCC

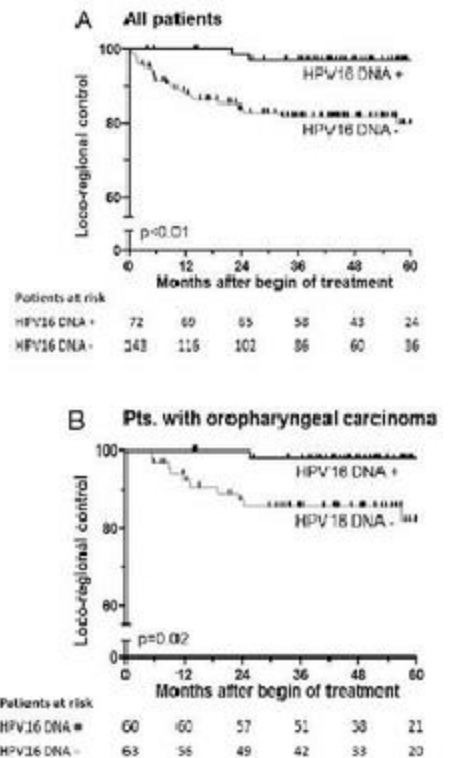
Retrospective
exploratory cohort
(2012 - 15)

Prospective validation
cohort
(2014 - 17)

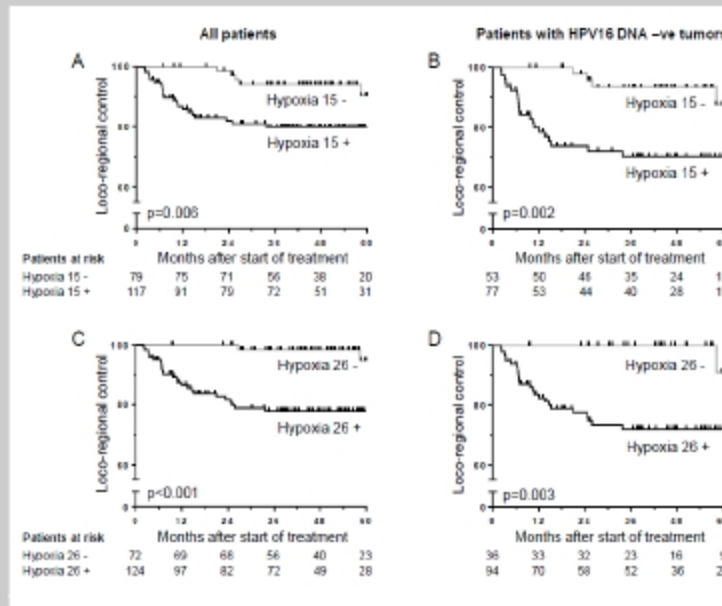
Interventional study
(2016 - ...)

HPV16 DNA status is a strong prognosticator of loco-regional control after postoperative radiochemotherapy of locally advanced oropharyngeal carcinoma :

Low CSC marker expression and low hypoxia identify good prognosis **subgroups in HPV(-) HNSCC**

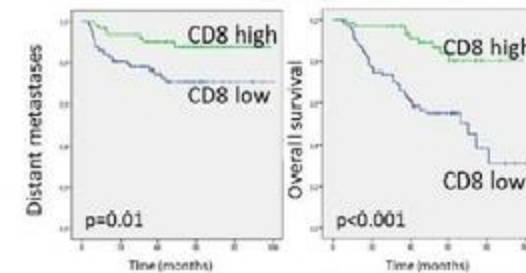


Lohaus et al. Radiother Oncol, 2014



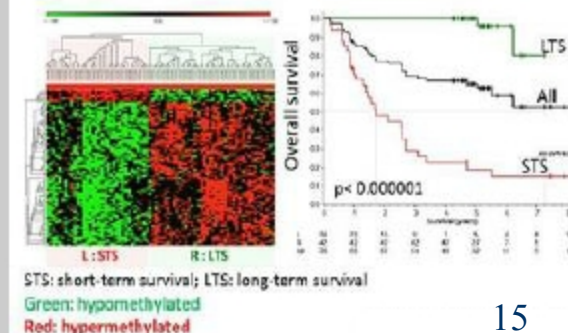
Linge et al. Clin Cancer Res. 2016 Jan 11

Tumour infiltrating lymphocytes (TILs)



Balermipas et al. Int J Cancer. 2016 Jan 1

Methylation patterns in HPV -ve tumours

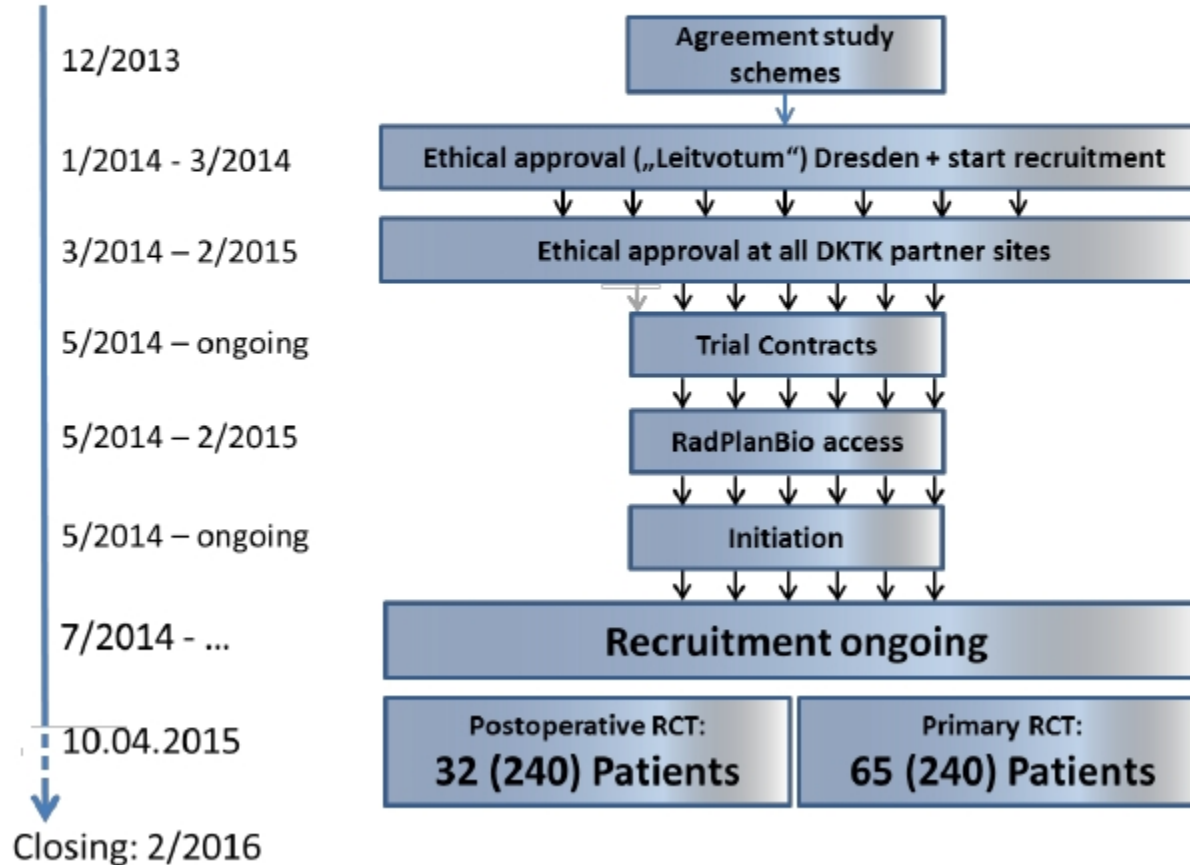


Abdollahi, Debus et al. in preparation



Joint activities: A multicentre explorative study of the German Cancer Consortium Radiation Oncology Group (DKTK-ROG)

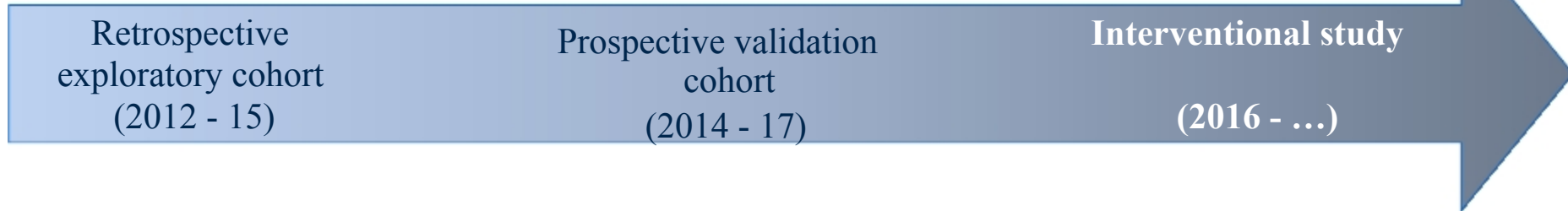
Ongoing and future research: Radiobiological profiling for Biologically stratified radio-chemo-therapy of HNSCC





Joint activities: A multicentre explorative study of the German Cancer Consortium Radiation Oncology Group (DKTK-ROG)

Ongoing and future research: **Radiobiological profiling for Biologically stratified radio-chemo-therapy of HNSCC**



In preparation:

- **Interventional de-escalation study**
(patients with HPV-positive OPSCC)

In planning phase:

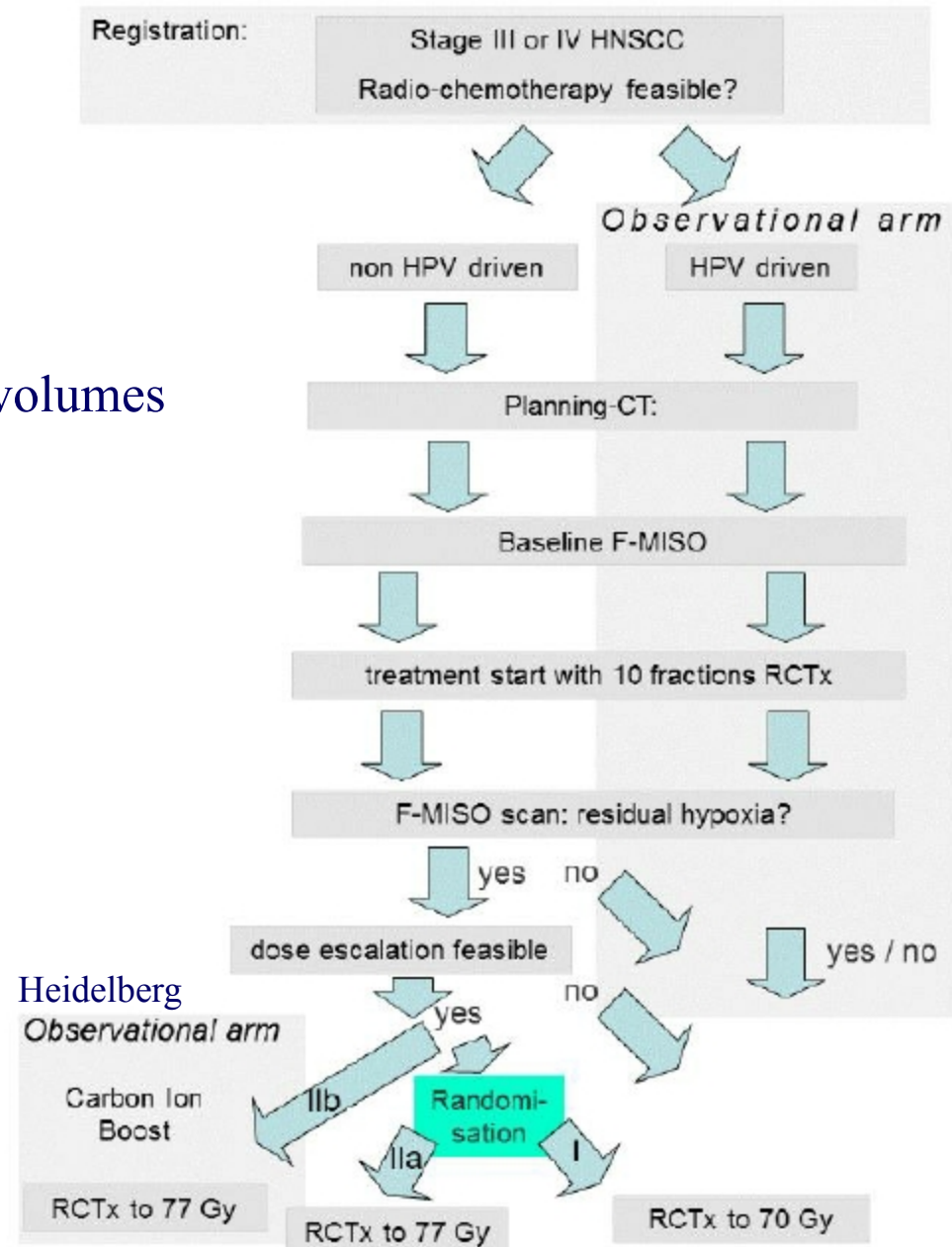
- **Interventional escalation study**
(patients with HPV-negative HNSCC + additional biomarkers, t.b.d.)

Joint activities: A multicentre explorative study of the German Cancer Consortium Radiation Oncology Group (DKTK-ROG) + Rome + Poznan + Vienna

Intervention study :

(waiting for BfS approval)

- in high risk patients
- dose escalation on total GTV,
- non- selective on hypoxic sub-volumes



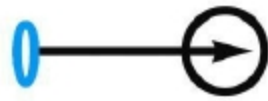
Proton therapy since 12/2014, ~120 patients treated

- First studies in 2015 with non-randomised standard dosing and standard fractionation
- Primary endpoint: chronic toxicity
- Secondary endpoints: Acute toxicities, Quality of life, survival
- ❖ Own study protocol Proto-R-Brain
- ❖ Own study protocol PETra
- ❖ Own study protocol Proto-R-Scull base
- ❖ Proto-Choice Prostate (74-78 Gy RBE) prospective matched pair protons vs. photons
- ❖ ReKo Study (HNSCC, re-RT 60-66 Gy, in high dose pre-irradiated area)
- ❖ Primary Radiochemotherapy of NSCLC: randomised proton vs. photon RT

Future Studies in Dresden

- ❖ PANAMA: Dose escalation in atypical anaplastic meningioma, multicentric

- ❖ Dresden is involved in national studies (GPOH) and national registries (RISK)
- ❖ **Data base** (under construction): data from pediatric patients who received RT with photons **as a reference collective** for comparison with patients irradiated with protons
- ❖ Cooperation with Essen and Heidelberg for follow-up-analysis and quality of life in children (start 2015/16)



Registry for Clinical Trials in Proton and Iontherapy in Germany

www.studien-protonen-ionen.de
 email: contact@studien-protonen-ionen.de

Studien-ID	Studien-Titel	Studien-Status	Studien-Phase	Studien-Ort	Studien-Datum	Studien-Datum	Studien-Datum	Studien-Datum	Studien-Datum	Studien-Datum	Studien-Datum	Studien-Datum	Studien-Datum
00000001	Protonen-Strahlentherapie bei Nasopharynxkarzinom	Rekrutiert	III	Frankfurt	01.01.2010	01.01.2010	01.01.2010	01.01.2010	01.01.2010	01.01.2010	01.01.2010	01.01.2010	01.01.2010
00000002	Protonen-Strahlentherapie bei Harnblasenkarzinom	Rekrutiert	III	Frankfurt	01.01.2010	01.01.2010	01.01.2010	01.01.2010	01.01.2010	01.01.2010	01.01.2010	01.01.2010	01.01.2010
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00000004	Protonen-Strahlentherapie bei Kopf-Hals-Tumoren	Rekrutiert	III	Frankfurt	01.01.2010	01.01.2010	01.01.2010	01.01.2010	01.01.2010	01.01.2010	01.01.2010	01.01.2010	01.01.2010
00000005	Protonen-Strahlentherapie bei Brustkrebs	Rekrutiert	III	Frankfurt	01.01.2010	01.01.2010	01.01.2010	01.01.2010	01.01.2010	01.01.2010	01.01.2010	01.01.2010	01.01.2010
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00000019	Protonen-Strahlentherapie bei Nasopharynxkarzinom	Rekrutiert	III	Frankfurt	01.01.2010	01.01.2010	01.01.2010	01.01.2010	01.01.2010	01.01.2010	01.01.2010	01.01.2010	01.01.2010
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- List of all currently recruiting clinical studies with proton or ion therapy
- Contact information for patients and researchers
- Background information for patients
- In german and english

THE GERMAN PROTON THERAPY CENTER

CANCER THERAPY WITH PROTONS - 2015 “PROTON THERAPY - APPROVED AND OFTEN BETTER”

(Statement by the German Society for Radiation Oncology - DEGRO)



Performance parameters	
Total number of tumour radiation treatments completed*	3,410
Total number of fractions	53,450
Total number of beam directions (fields)	116,521
Total number of single dose-controlled scanning spots	288,505,996
Smallest target area treated	1 ml
Maximum tumour volume treated	5,654 ml

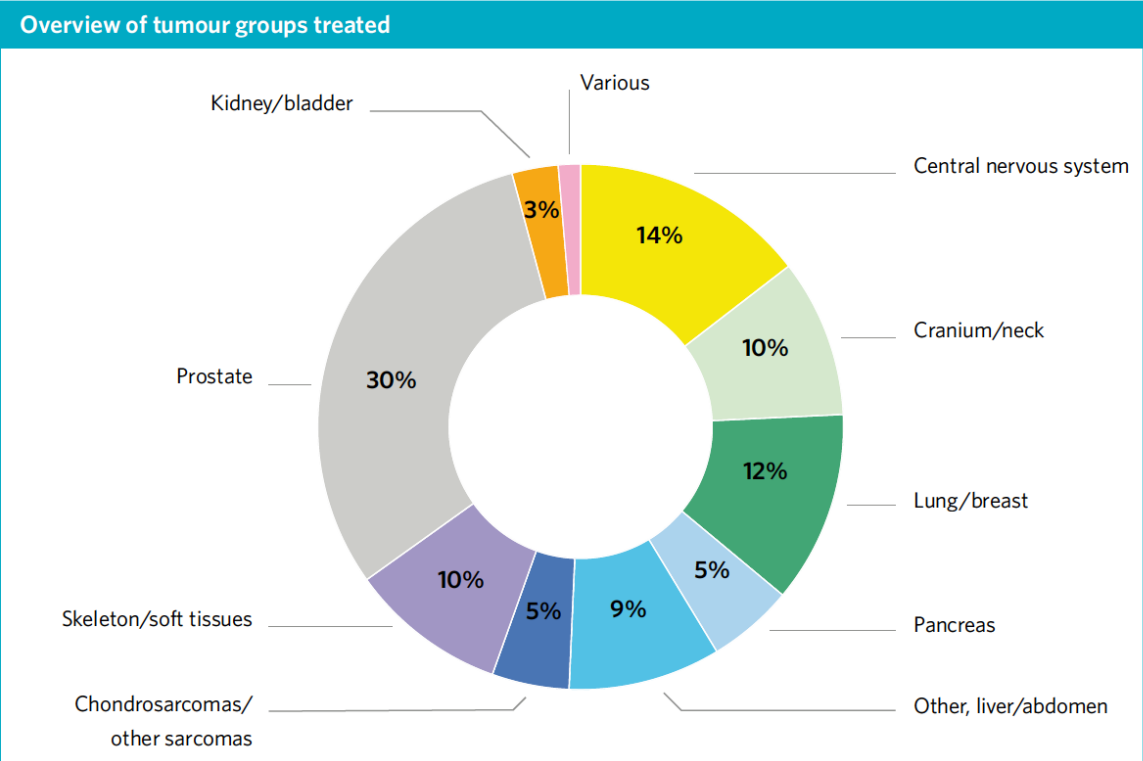


Illustration 1: Average distribution of tumours treated at the RPTC. These and the following statistics are derived from the first 2,500 patients.

Fractions

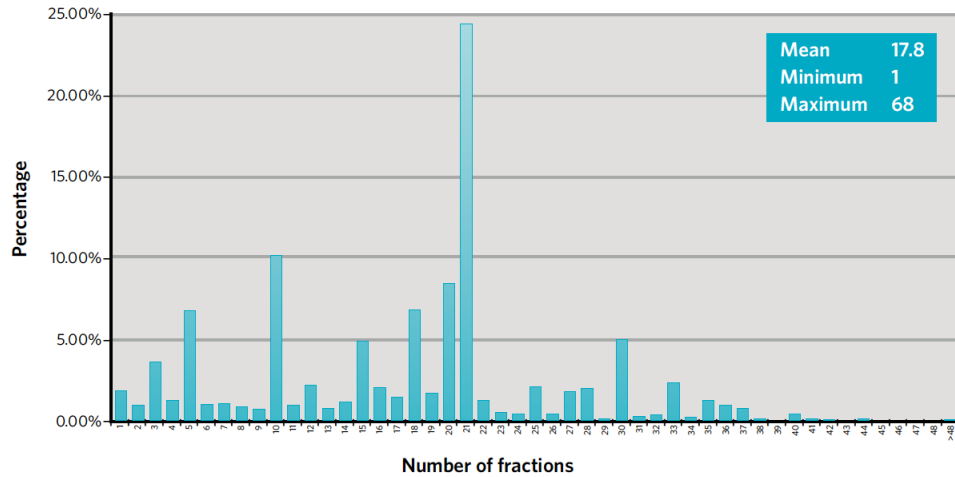


Illustration 4: Frequency distribution of the number of fractions administered at the RPTC (statistics for the entire period of operation).

Fields

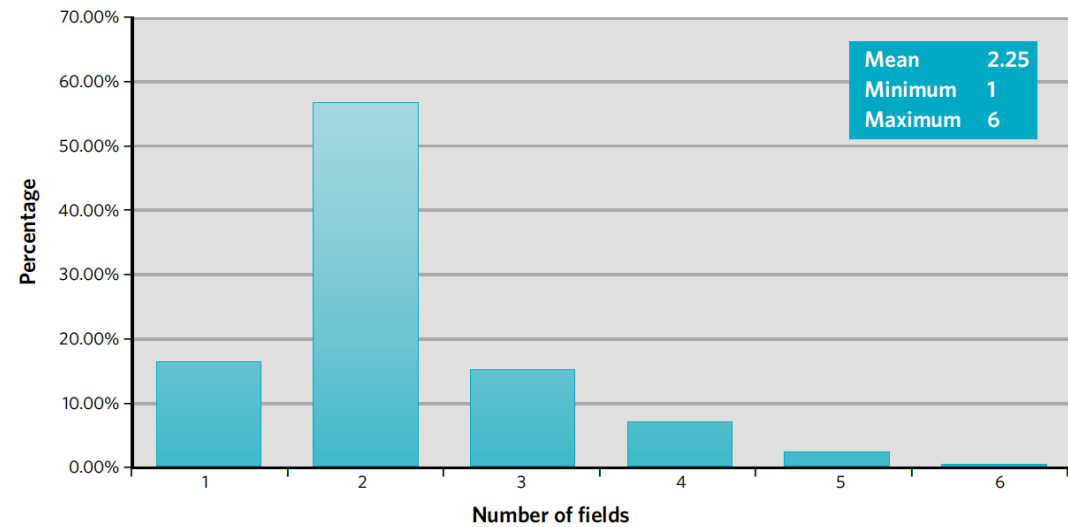


Illustration 5: Frequency distribution of the number of beam directions (fields) used at the RPTC (statistics for the entire period of operation).



Charité / Helmholtz-Zentrum Berlin Protons

Treats ONLY eye tumors
2750 patients treated until Dec-2015
(ptcog.ch)

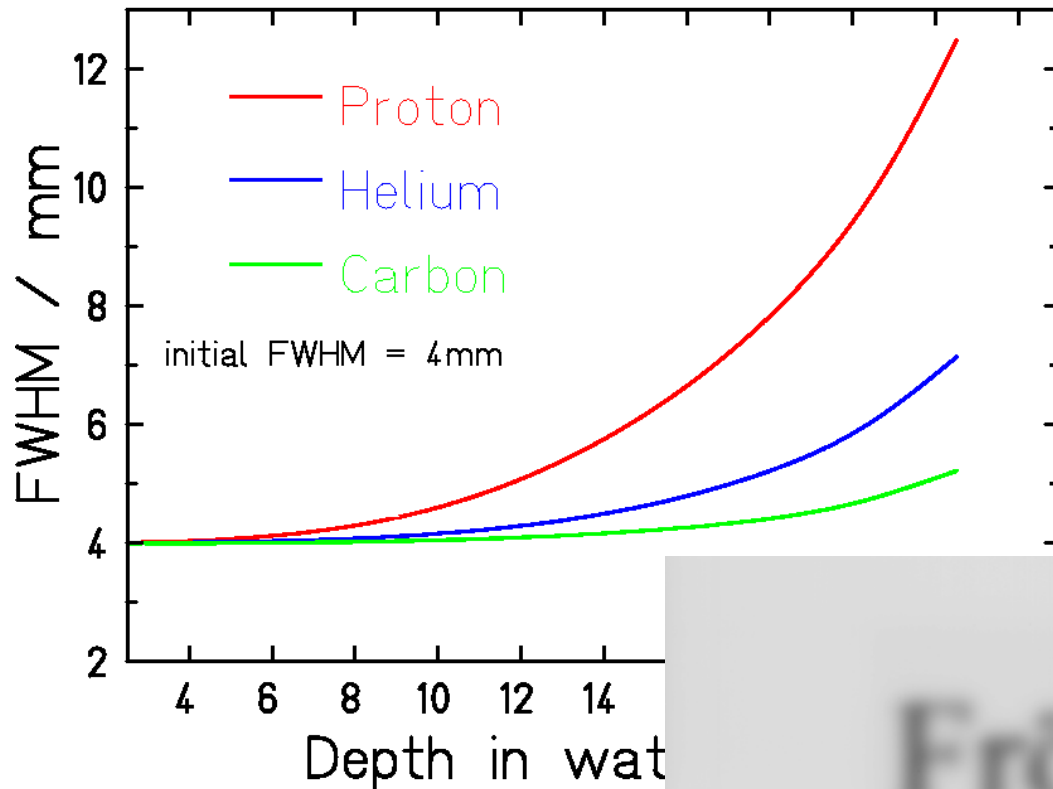
HELIUM beams

to replace

PROTON beams

The Rationale for Helium to replace Protons

Lateral Scattering



He may replace p' s:
-reduced penumbra
-similar biology

Fröhlic⁴He
Weihnacht!

He beams commissioned at HIT in Dec 2013

OXYGEN beams

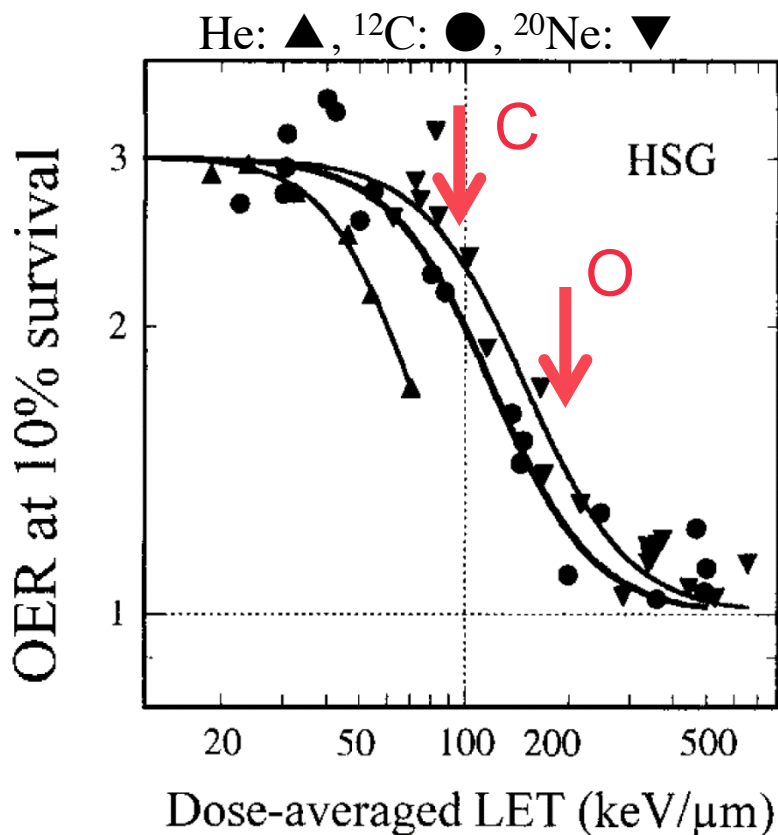
to replace

CARBON beams

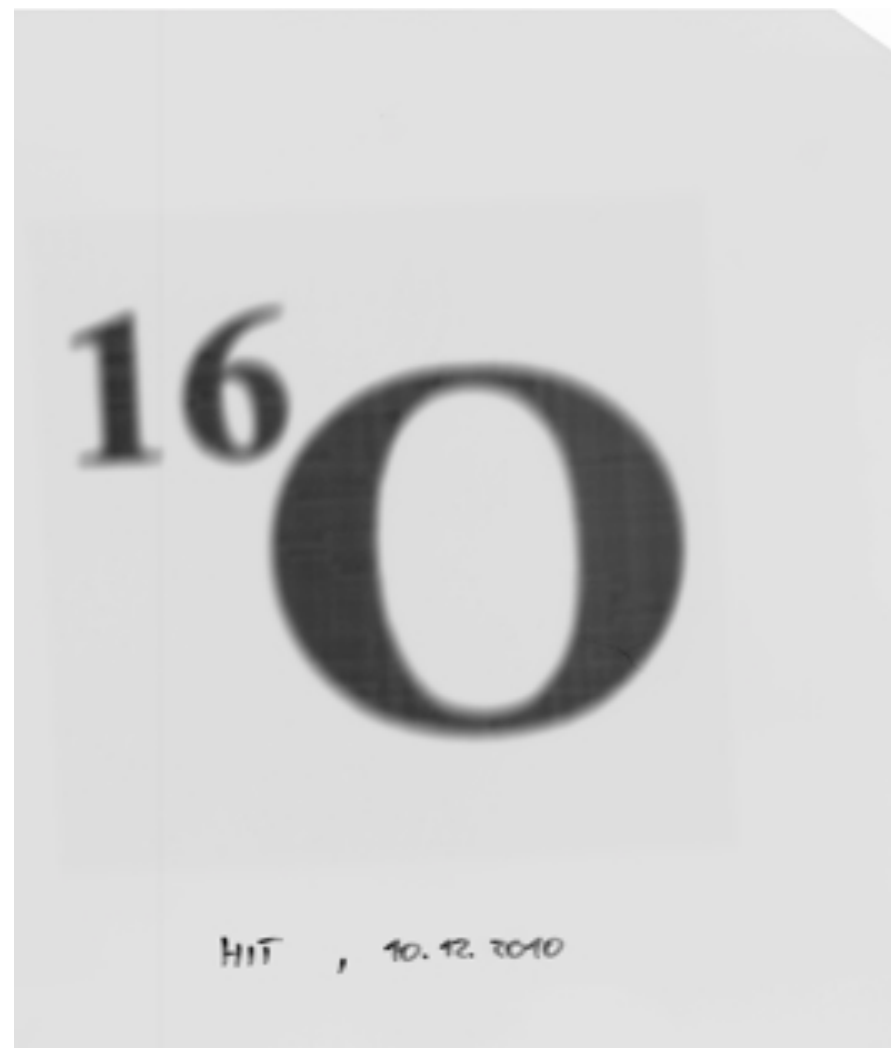
The Rationale for Oxygen: OER

Rasterscan @ HIT-R+D-Room

OER as function of LET



Furusawa et al Rad. Res. (2000)

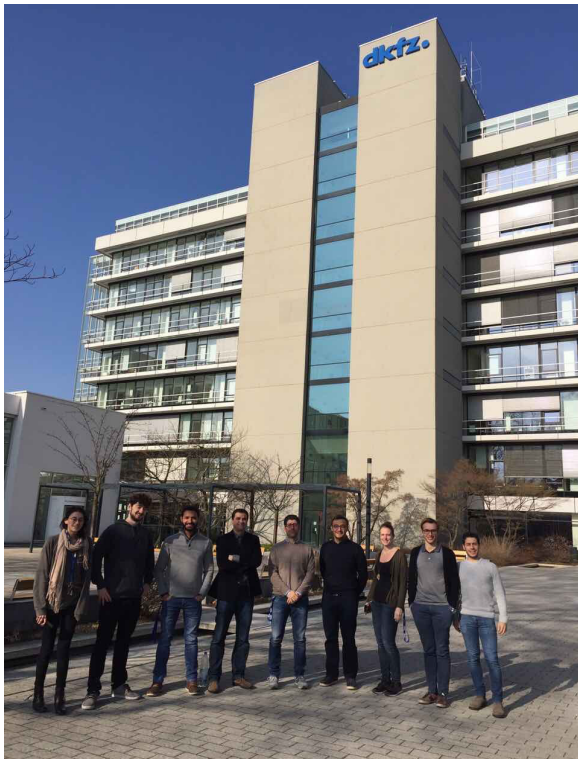


Oxygen maybe more effective esp. for hypoxic tumors

Thank You for Your Attention 😊

DKFZ Group

Relaxing!





UniversitätsKlinikum Heidelberg



QUESTIONS????

HIRO

NCRO

HIRO
Heideler Institut für Radioonkologie

Partners:

