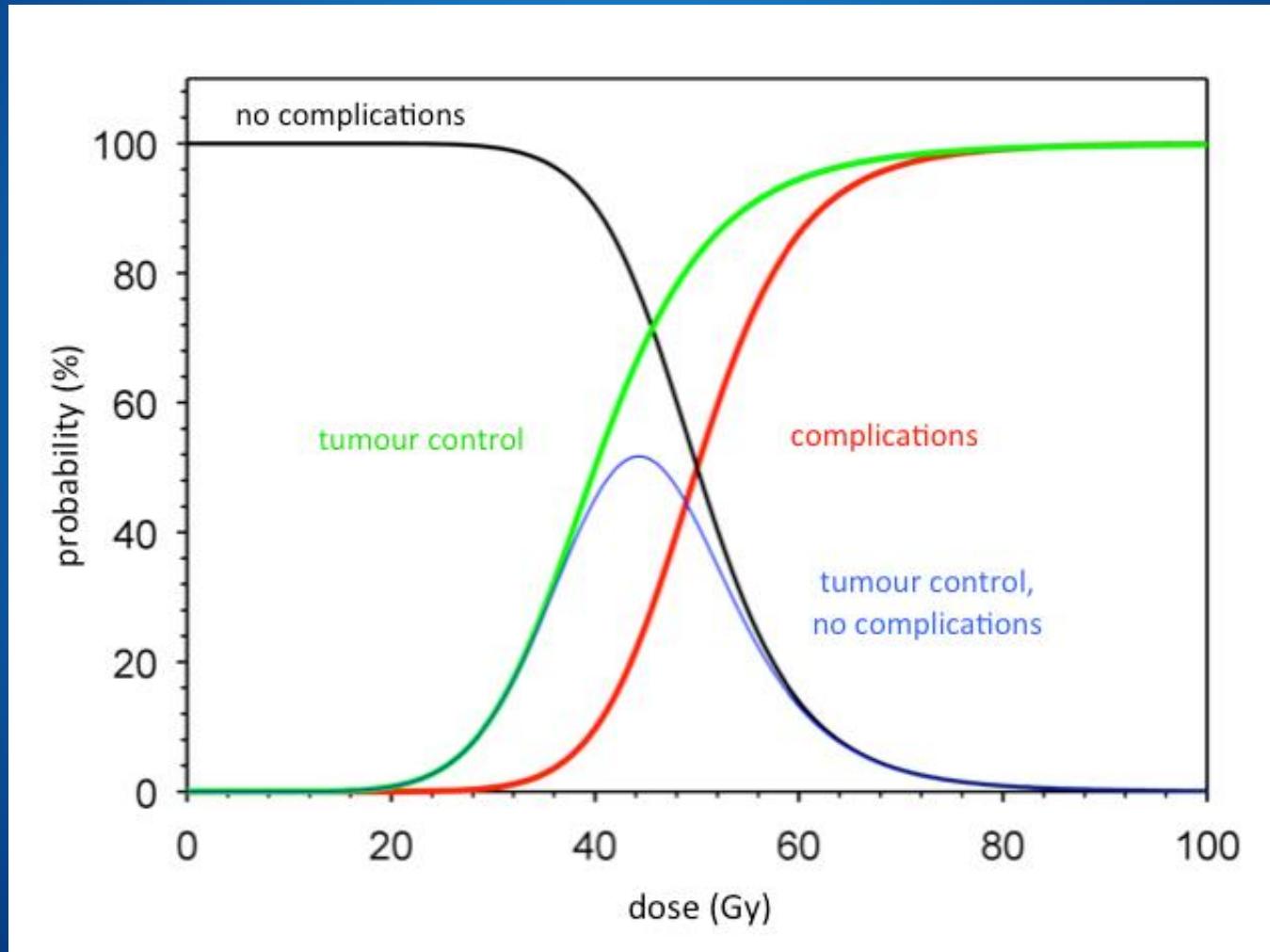




Clinical indications for carbon ion radiotherapy

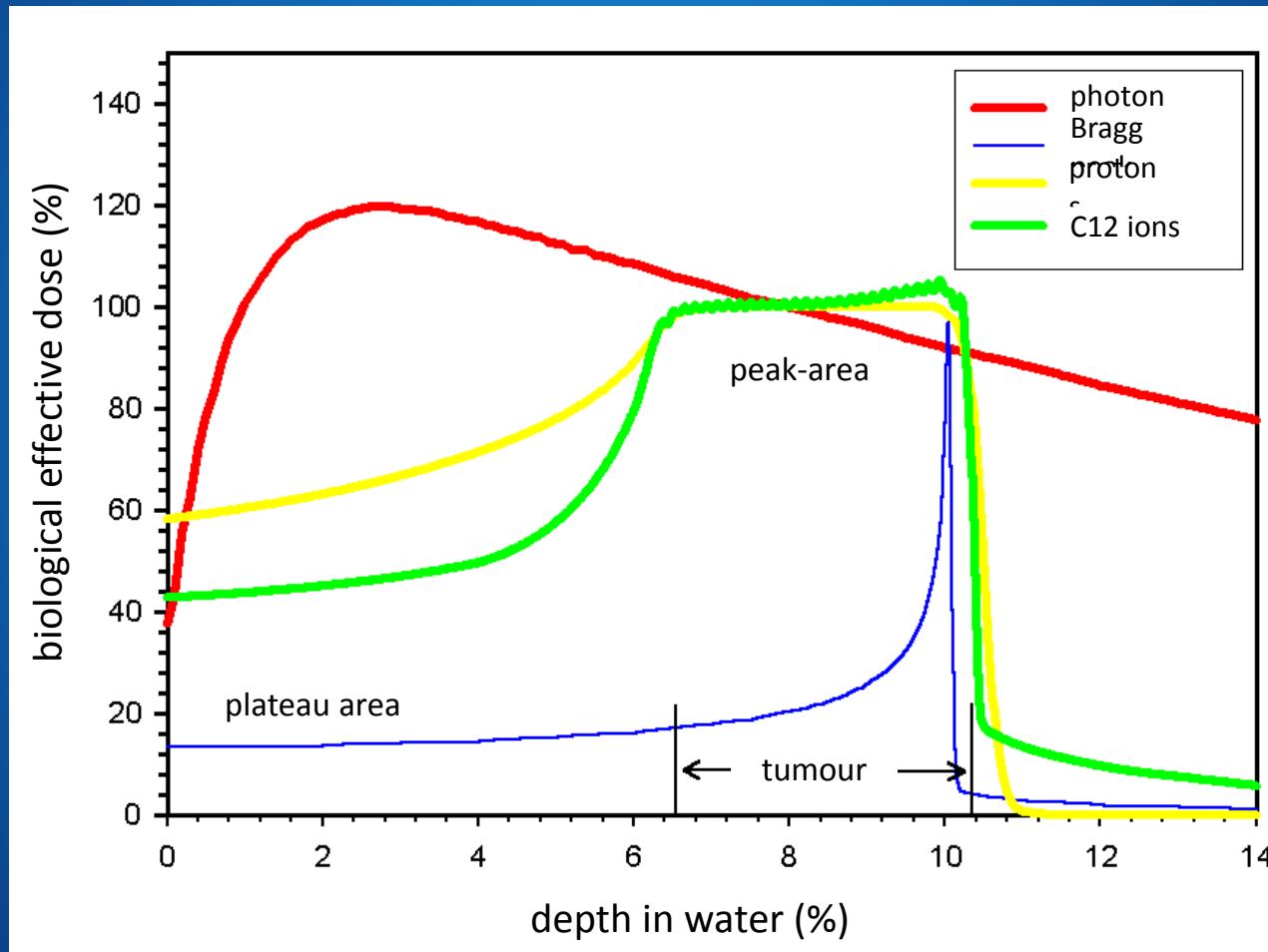
PD Dr. Alexandra Jensen, MSc

Particle Therapy - Rationale

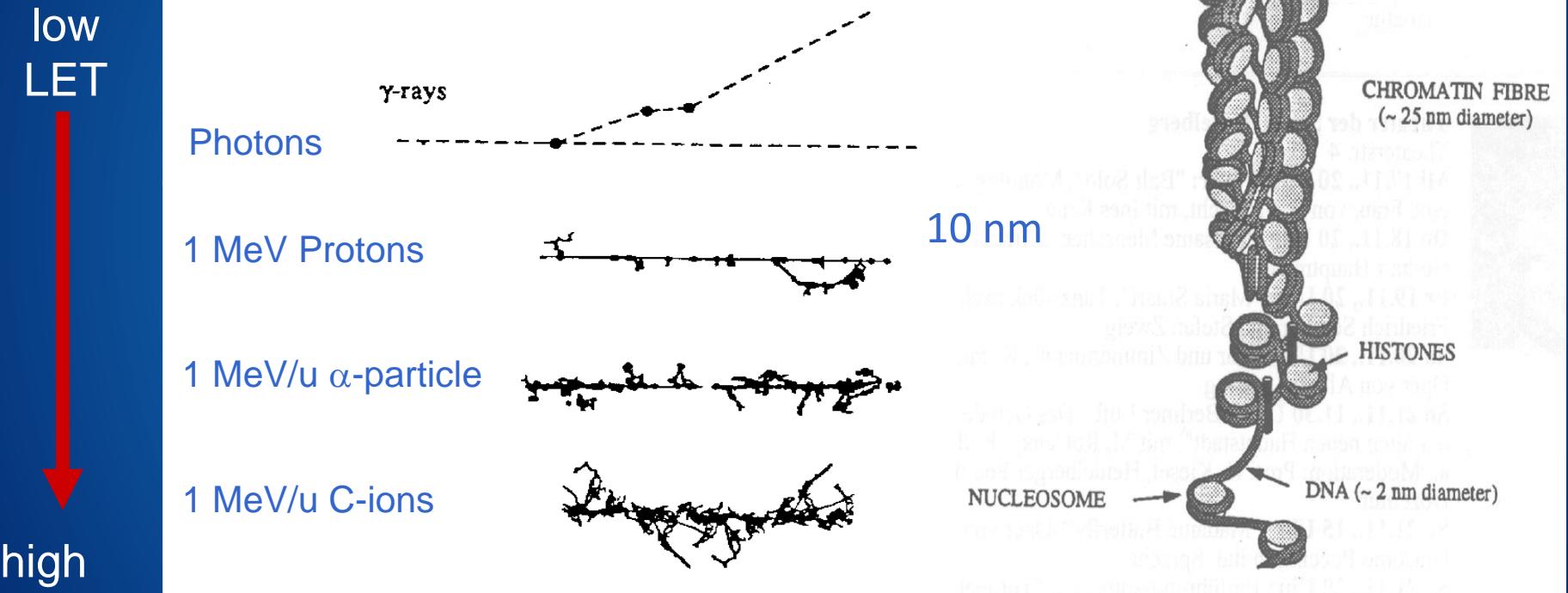


according to Hermann Holthusen, 1933

Particle Therapy - Rationale



Particle Radiotherapy: RBE



increased biological effectiveness

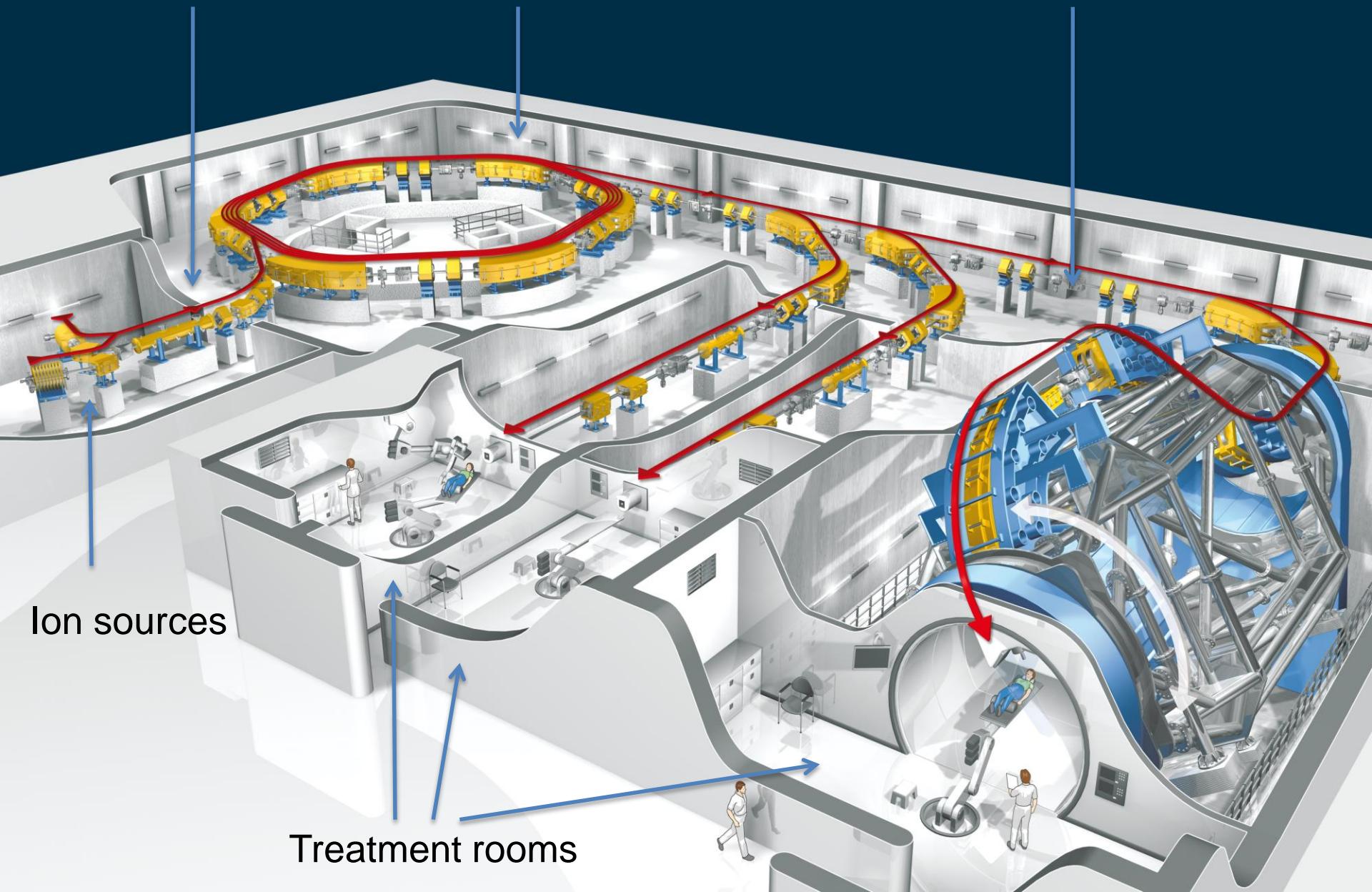
Particle RT: common indications

- adenoid cystic carcinoma:
 - incidence: 1.31/ 100,000/ year
- chordoma
 - incidence: 8.4/ 10,000,000/ year
- chondrosarcoma
 - incidence: 2/ 1,000,000/ year

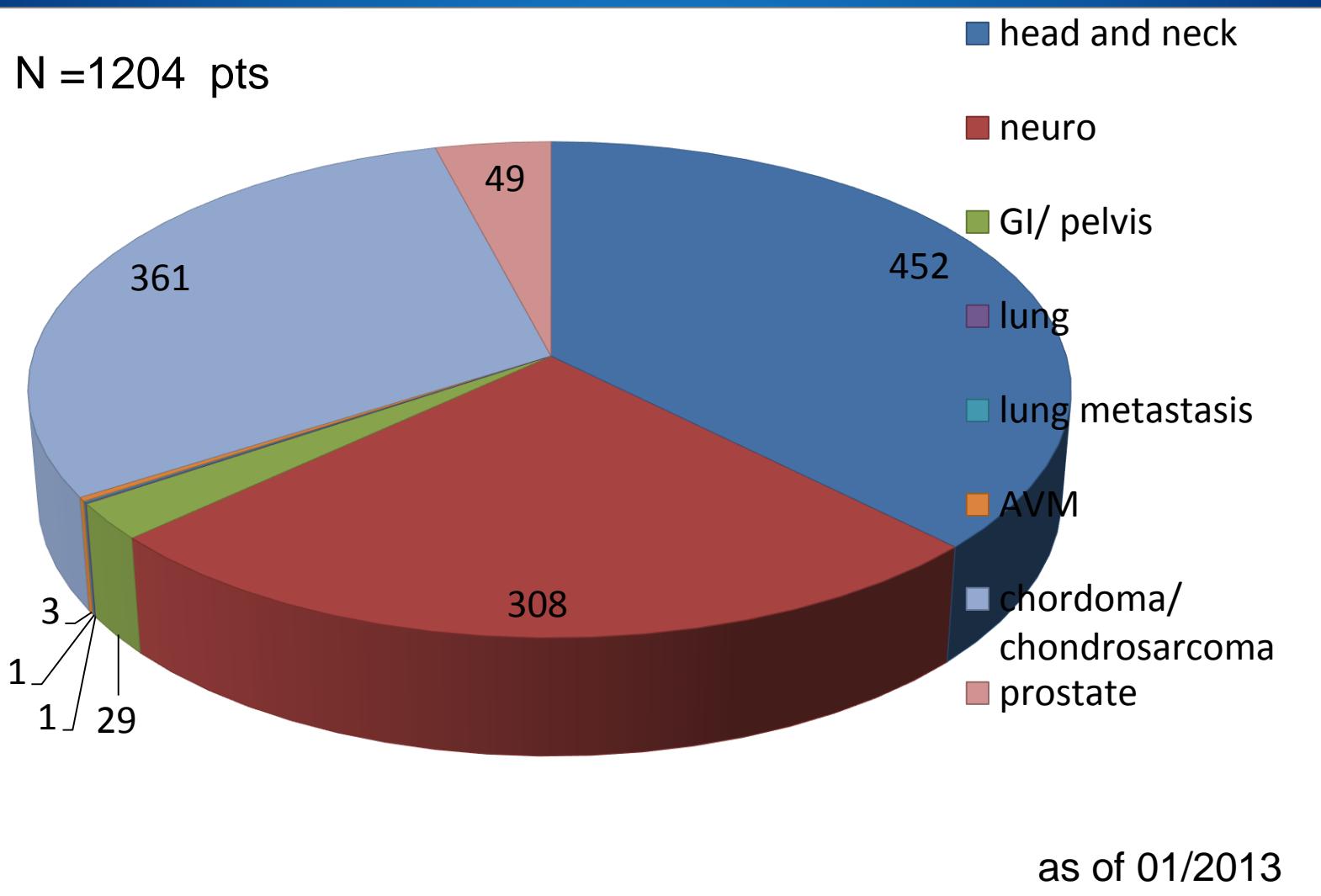
Linear accelerator

Synchrotron

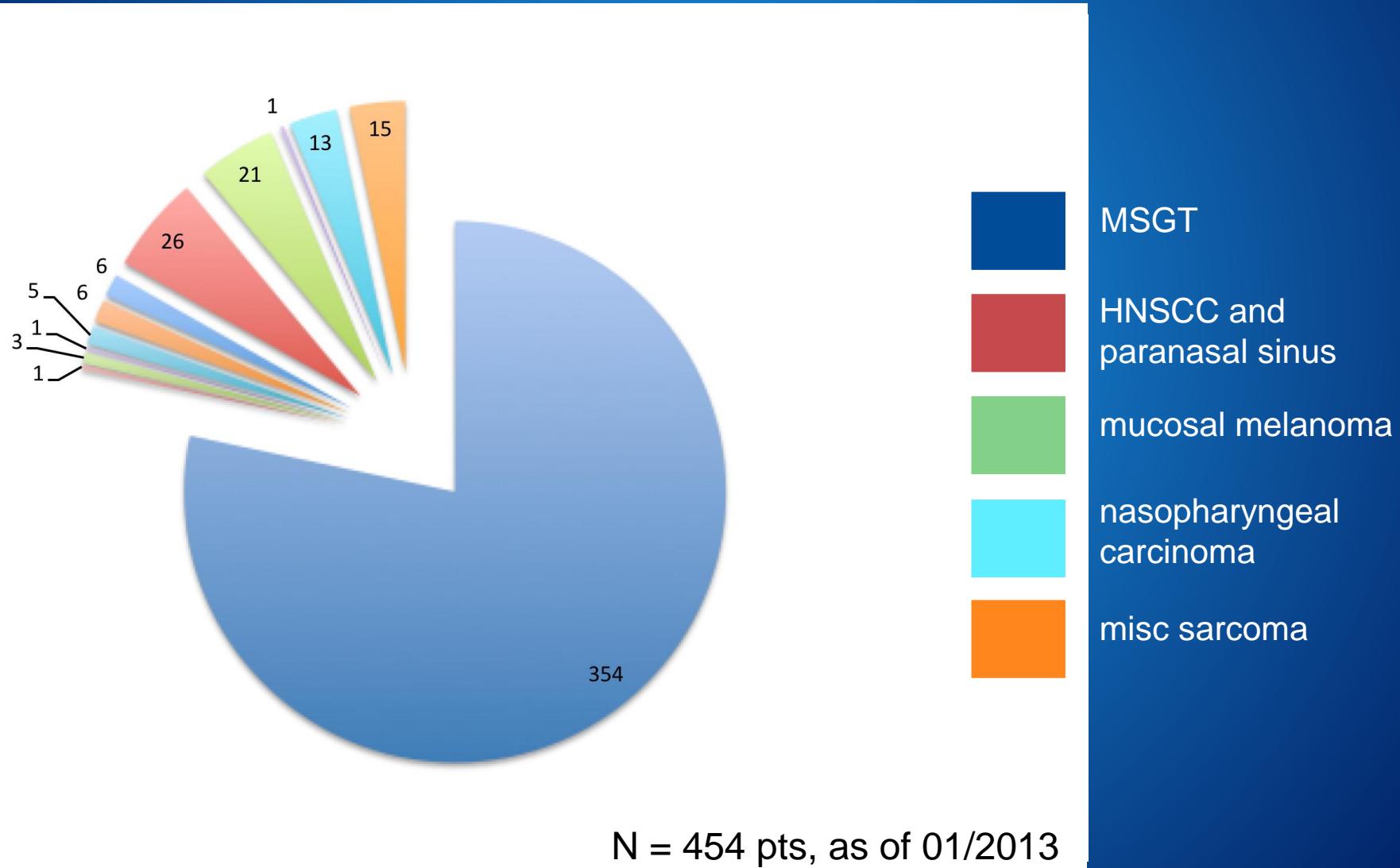
Gantry



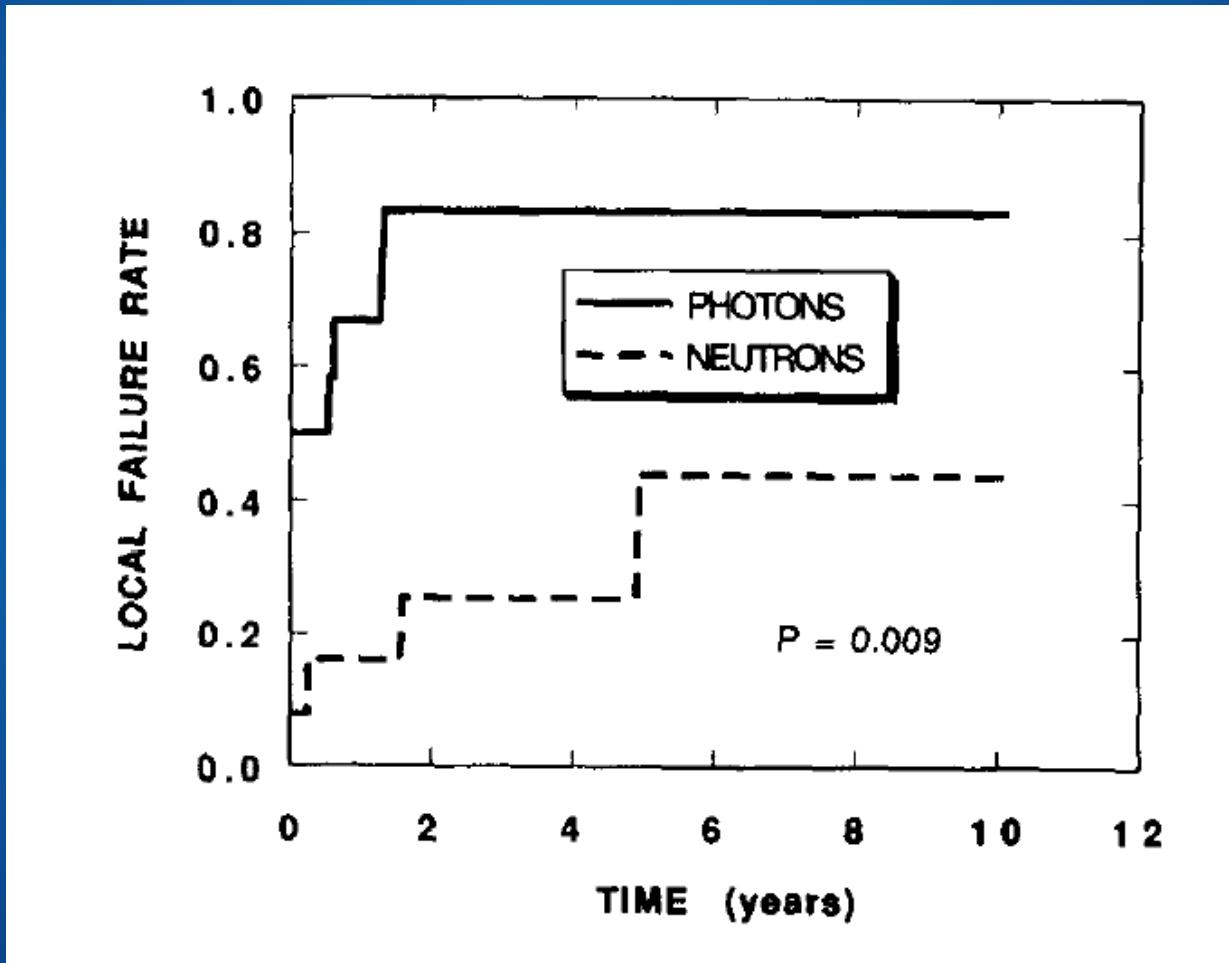
Particle RT indications (HIT)



Particle RT indications – head&neck



MSGT: neutrons



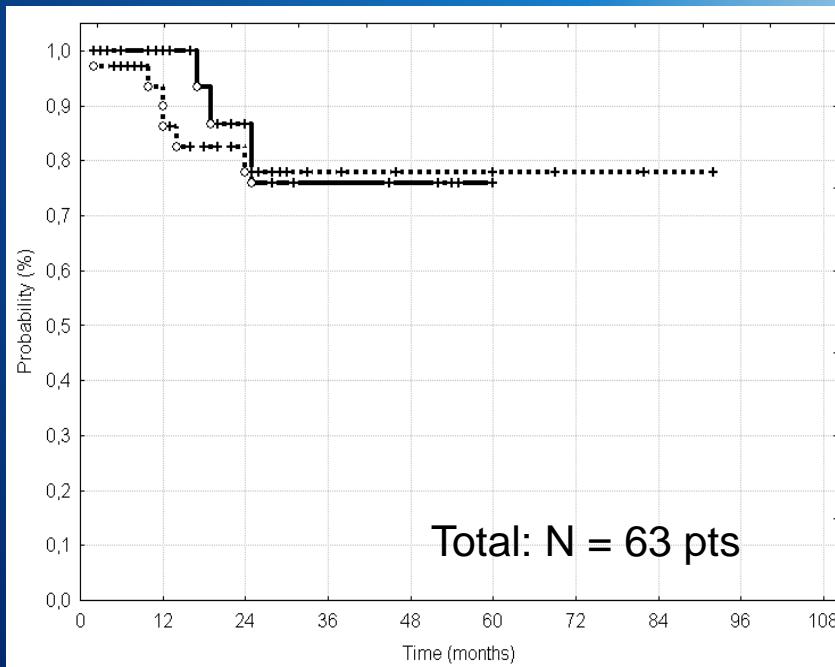
GSI C12 pilot project

Dose concept:

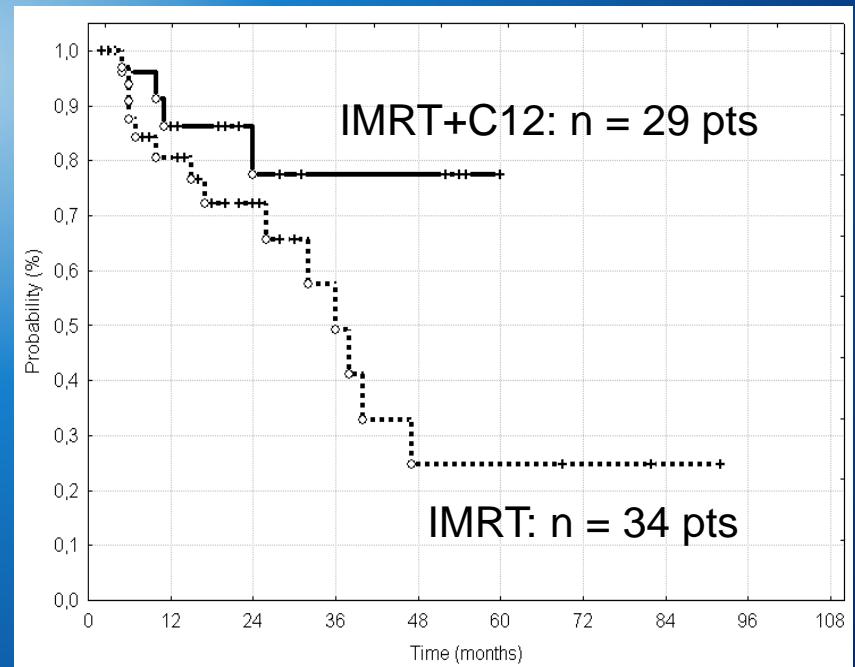
IMRT: 54 Gy (ED 2 Gy) + C₁₂: 18 GyE (6 x 3 GyE)

retrospective comparison regarding control and survival rates

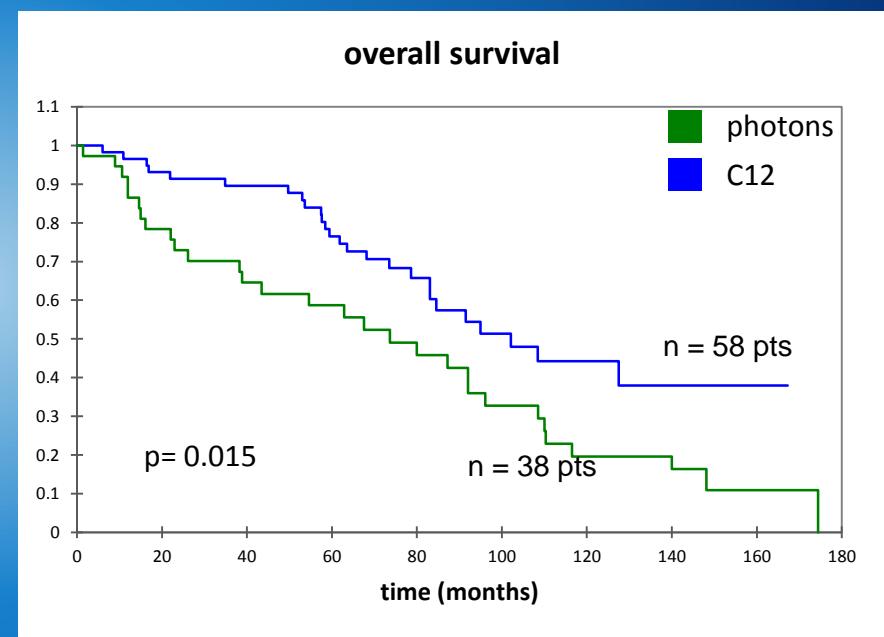
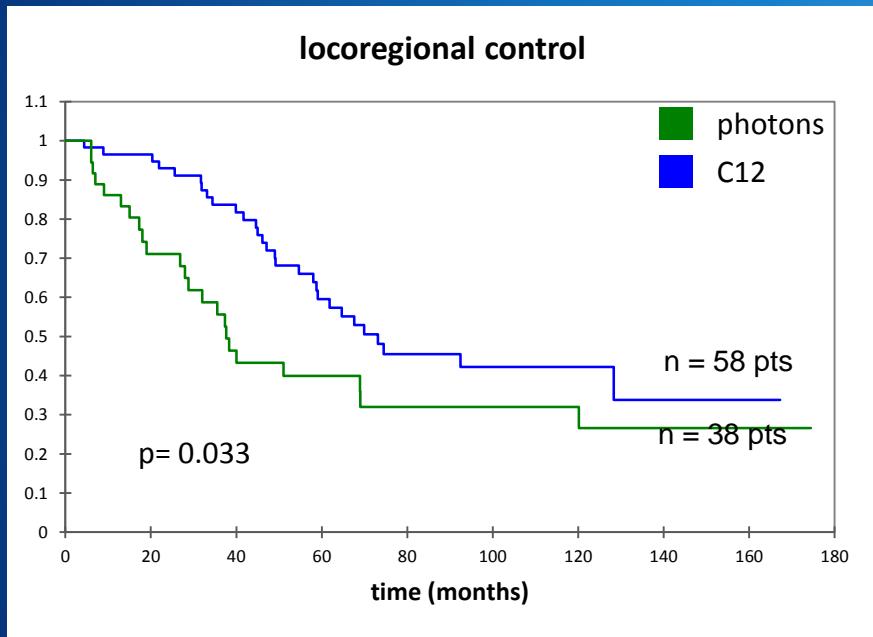
Overall Survival



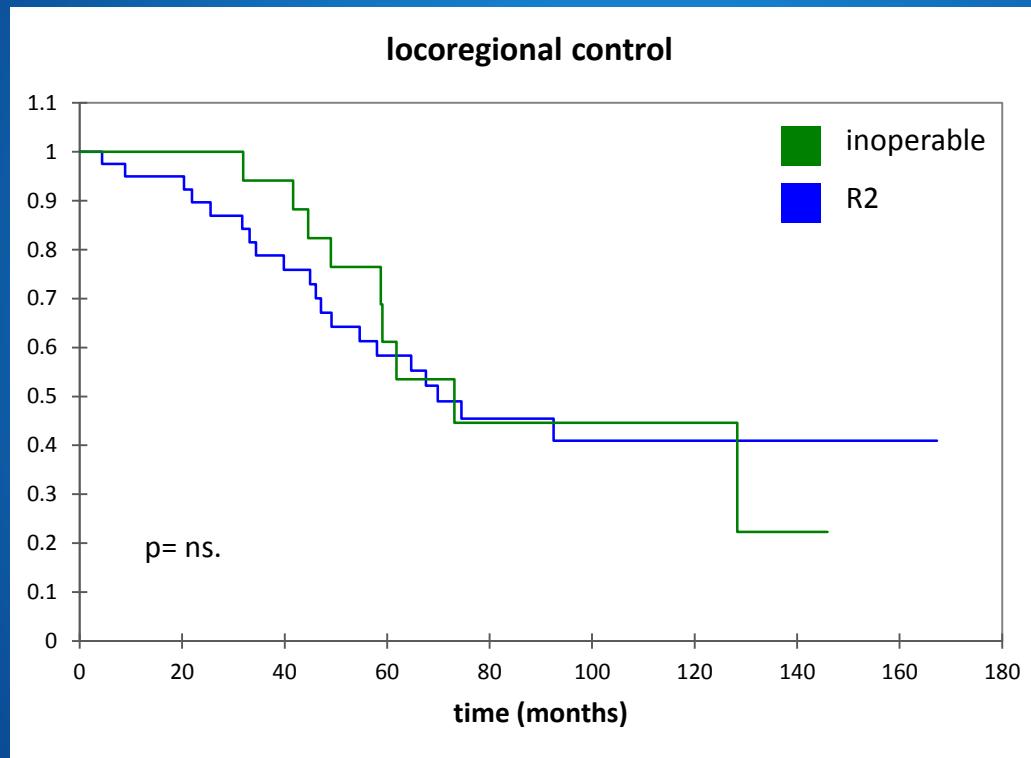
Local control



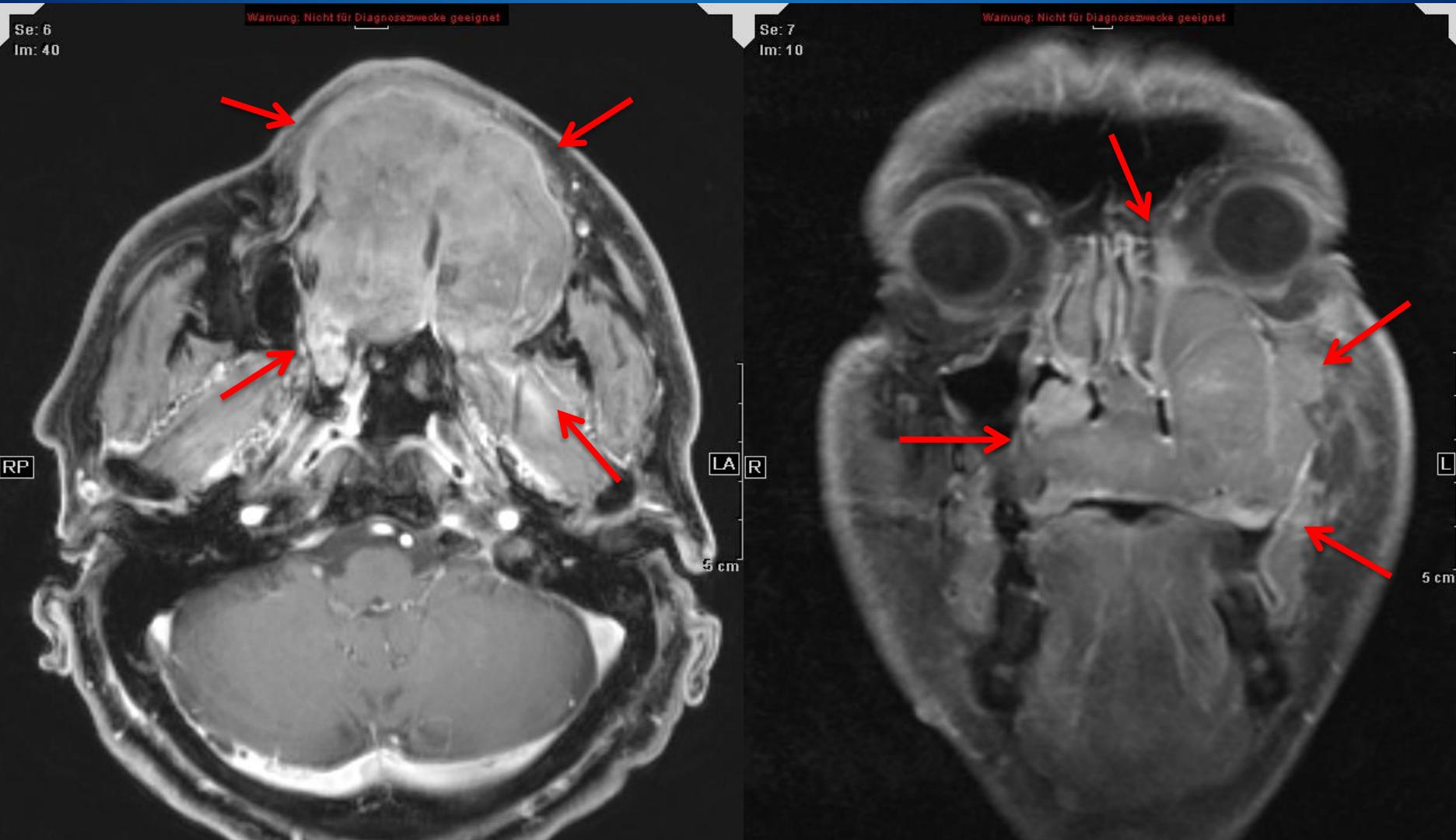
GSI C12 pilot project update



GSI C12 pilot project update



Clinical case: adenoid cystic carcinoma

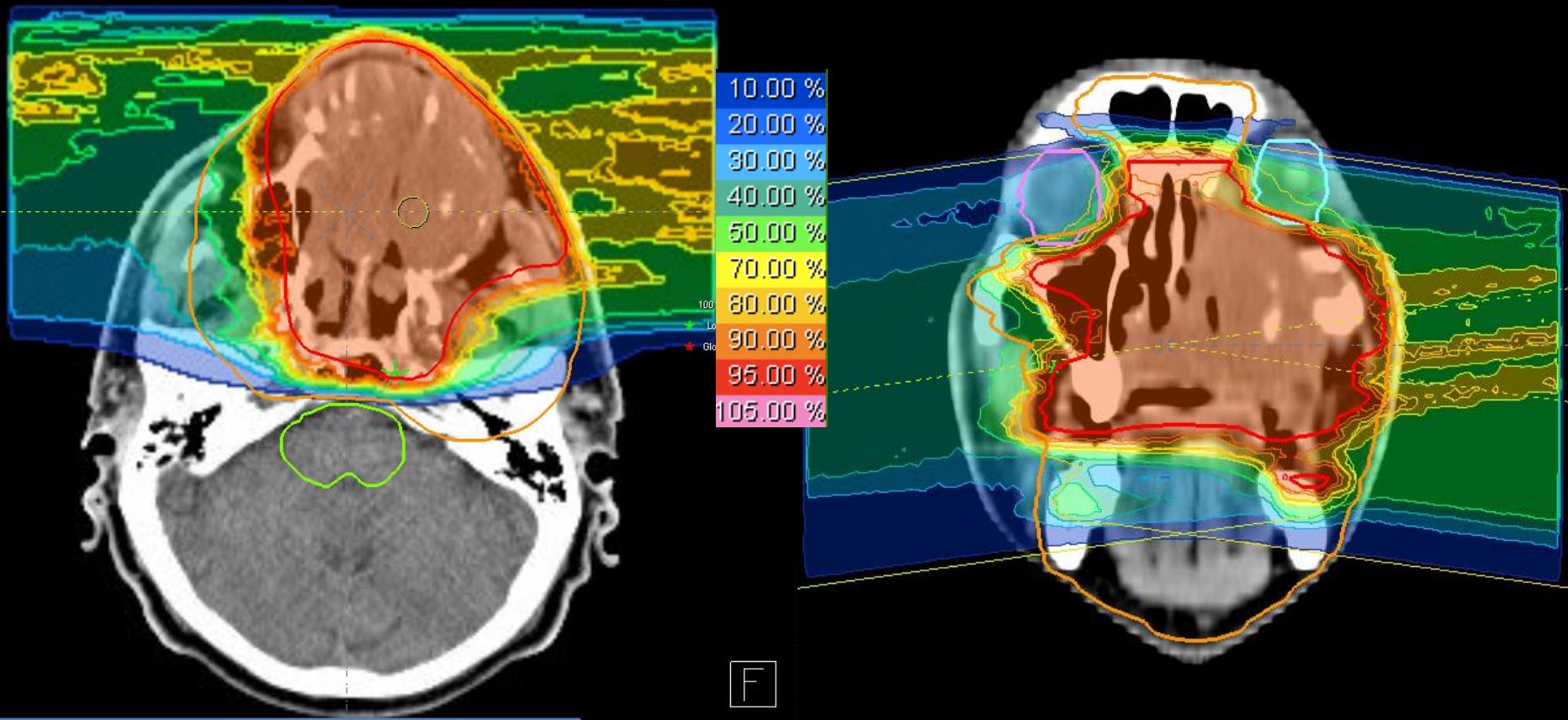


Prae RT

67 year-old patient with ACC

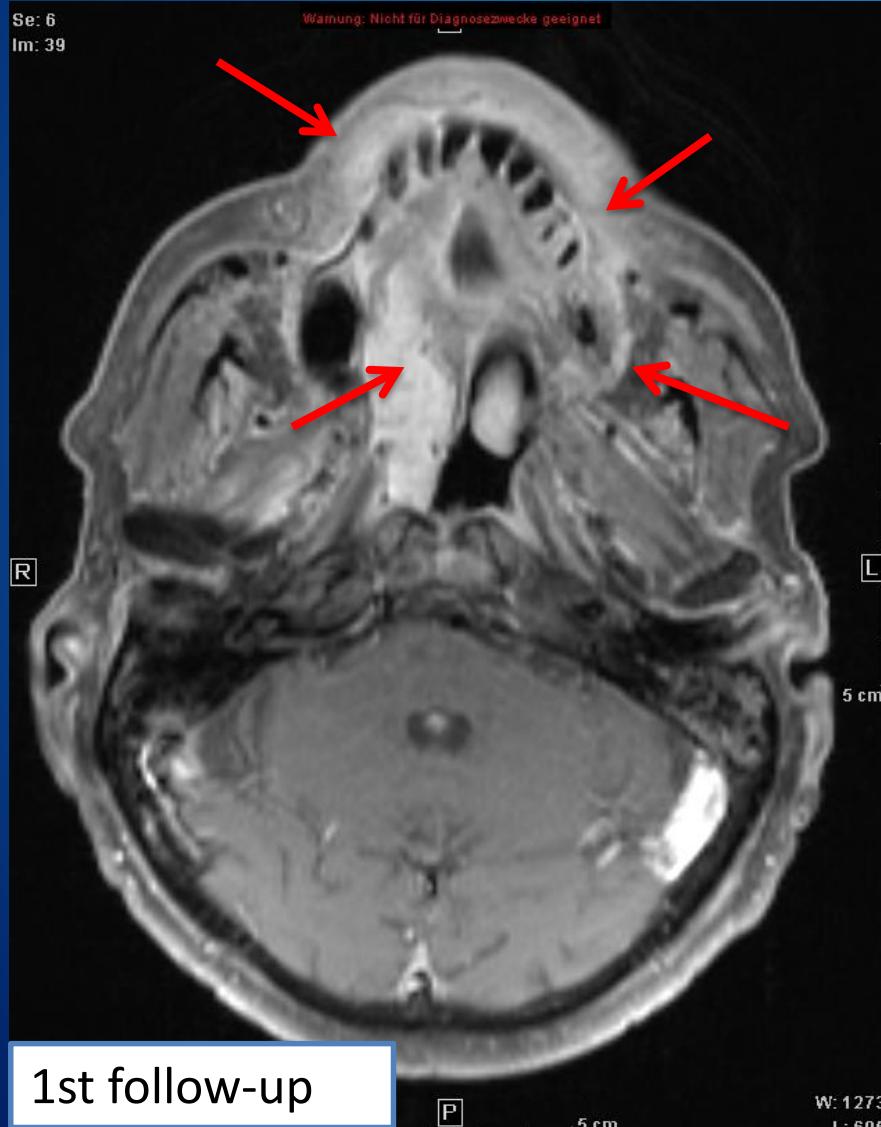
W: 1284
L: 583

Clinical case: adenoid cystic carcinoma



C12-boost, 2-field IMPT

Clinical case: adenoid cystic carcinoma



1st follow-up

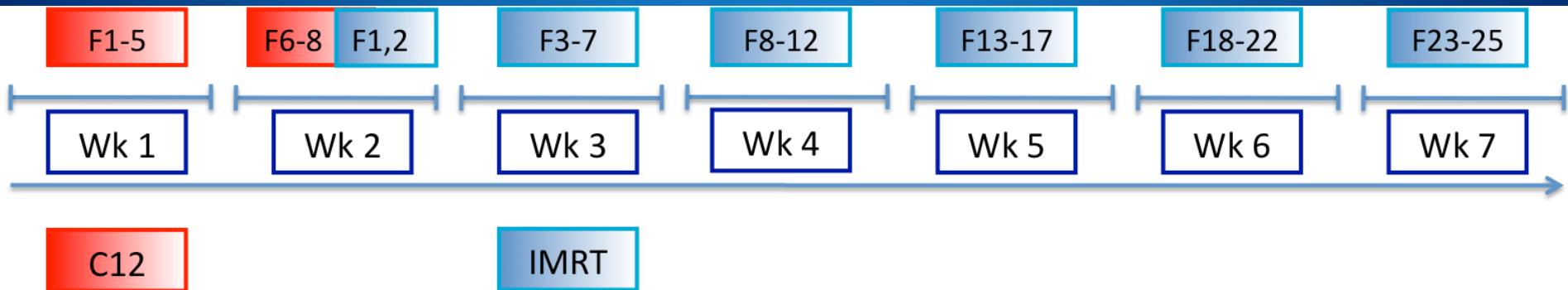


W: 1090

Pilot project update: C12 for ACC

- local control comparable to neutron data
- toxicity profile mild
- role of surgery in extensive tumours?
- local relapse predominantly in-field
=> dose escalation?

Particle RT: C12 phase-II-trial



- IMRT:
 - dose: 50 Gy a 2 Gy
 - target volume: primary tumour/ locoregional nodal levels
- C12-Boost:
 - dose: 24 GyE a 3 GyE C12 (biolog. optimized)
 - target volume: primary tumour/ tumour bed and positive nodes

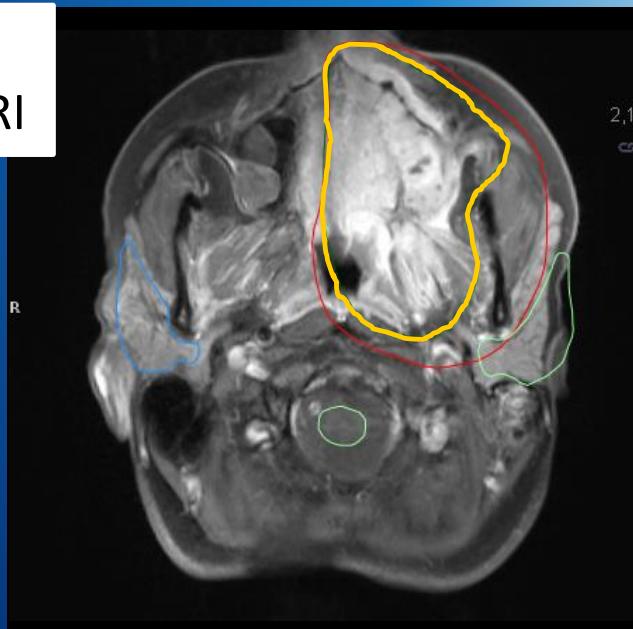
Particle RT: COSMIC

- accrual: 07/2010 – 08/2011
- N= 54 pts
- n= 53 pts available for evaluation
- median age: 58 years [25 – 74 years]
- median follow-up:
 - 42 months

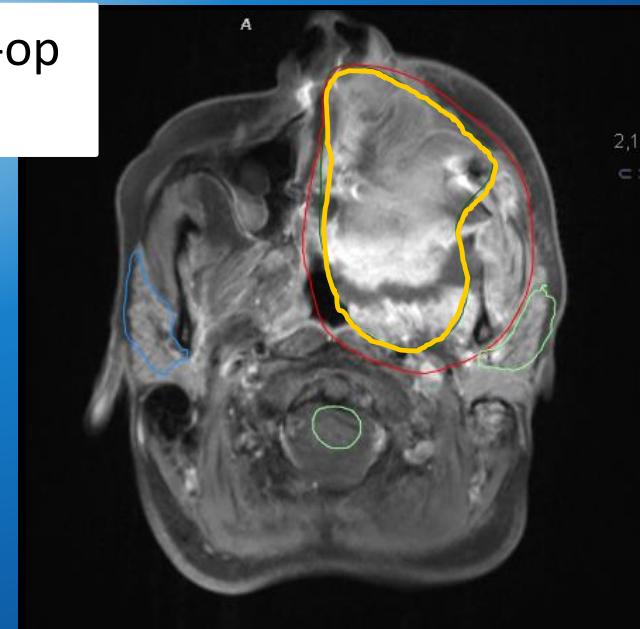
Particle RT: COSMIC

	R1 (20 pts)	R2/ inoperable (34 pts)
mucositis °III	12 (60%)	2 (5.9%)
dysphagia °II	5 (25%)	10 (29.4%)
trismus	8 (40%)	2 (5.9%)

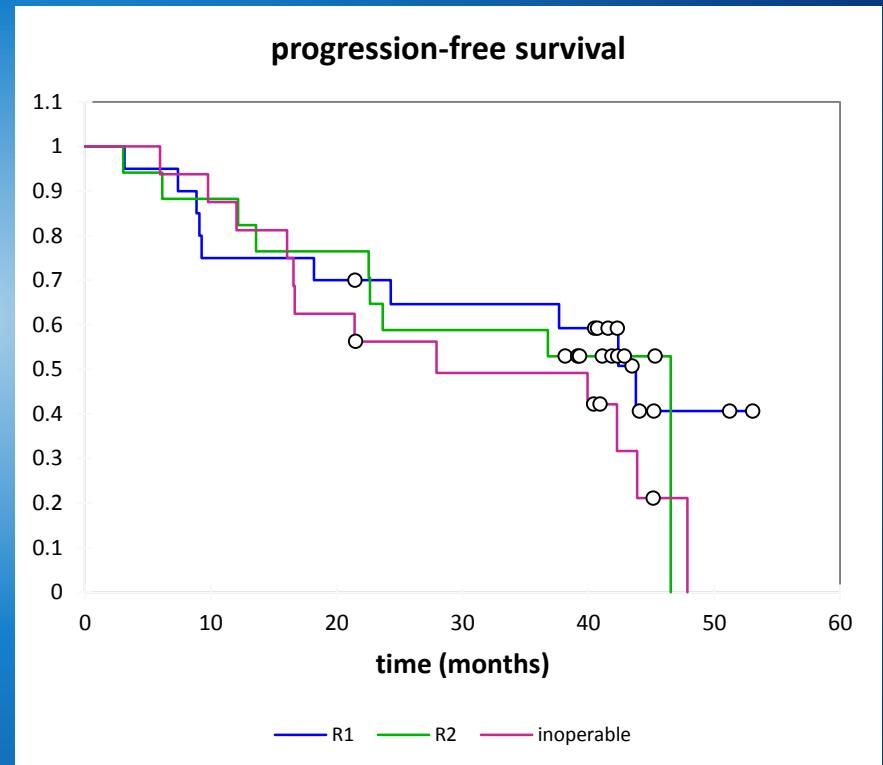
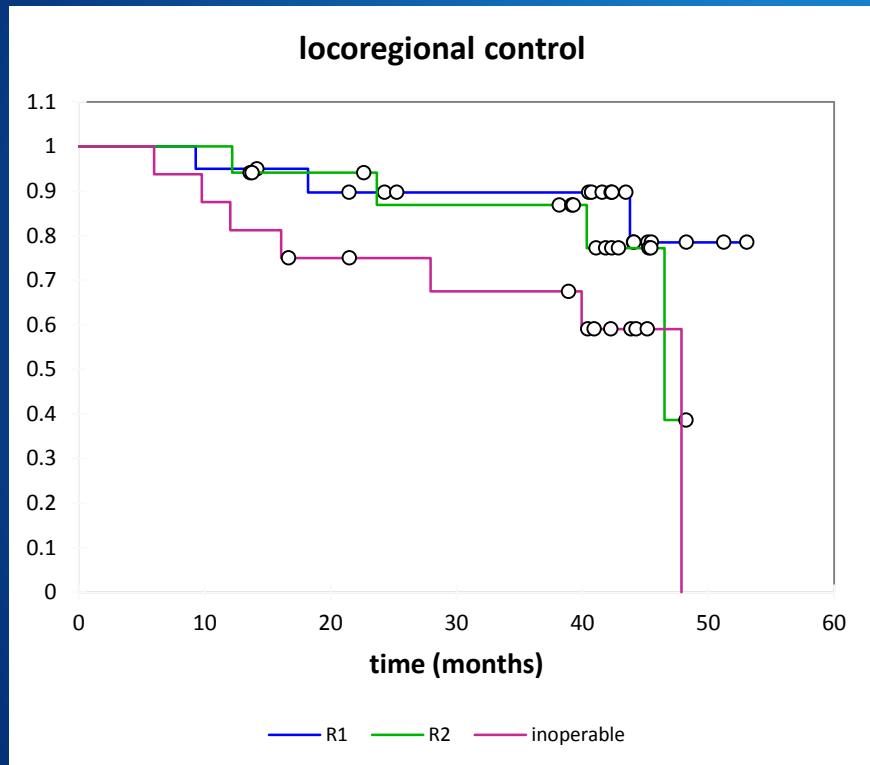
prae-
op MRI



post-op
MRI



Particle RT: COSMIC

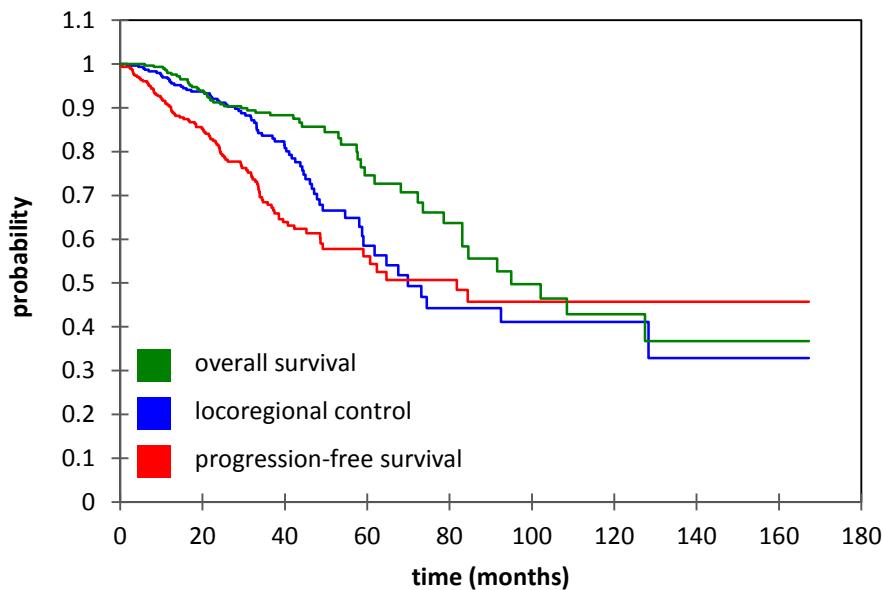


Particle RT: COSMIC

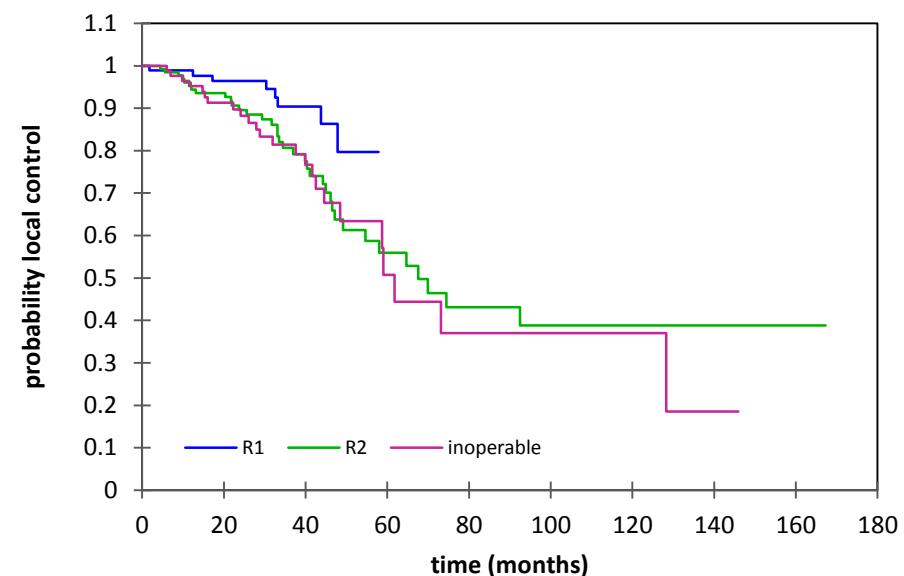
- no unexpected toxicity
- most common tox: xerostomia ° I (39.6%) und hearing problems (11.3%).
- initial treatment response promising
- no significant difference in control between R1 and R2-resected patients
- increased acute toxicities in the surgical groups
- **role of surgery in extensive tumours?**
- **needs validation in larger cohort**

Validation of project data within larger cohort, 1997-2013

OS, LC, and PFS

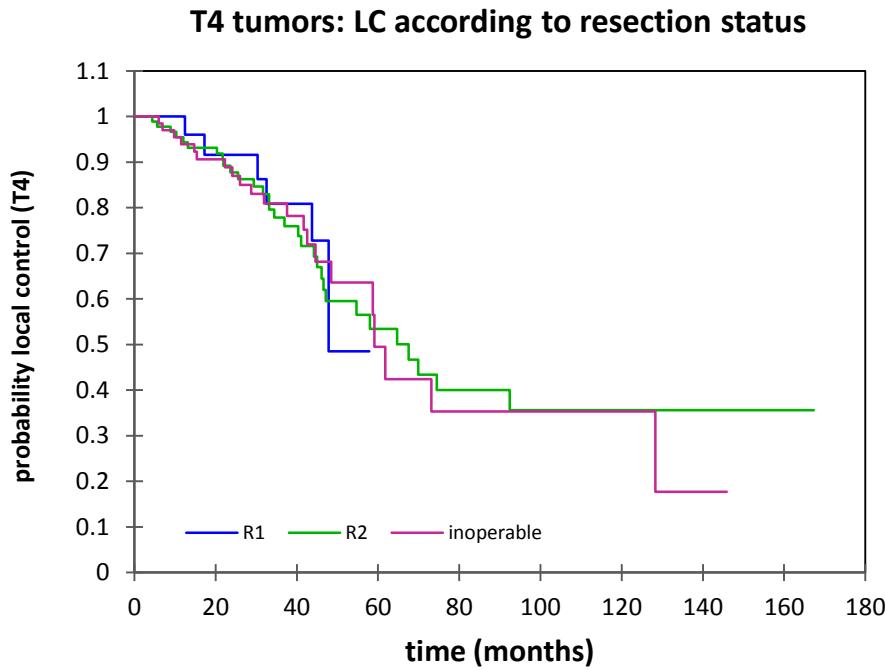


LC according to resection status



N=309 pts, 1997-2013

Validation of project data within larger cohort, 1997-2013



Debulking for ACCs?

Validation of project data within larger cohort, 1997-2013

- consistently mild toxicity profile in the primary treatment
 - mucositis °II/ °III: 37.9% / 8.7%
 - dermatitis °II: 20.4%
(Radiat Oncol 2011)
- good treatment response (RECIST):
 - primary tumours: 63.3%
(Radiat Oncol 2011/ Radiother Oncol 2015)
- consistently high control rates
(Radiother Oncol 2015)

ACC: ongoing trial

- ACCEPT-trial

Jensen et al. BMC Cancer 2011, 11:70
<http://www.biomedcentral.com/1471-2407/11/70>



STUDY PROTOCOL

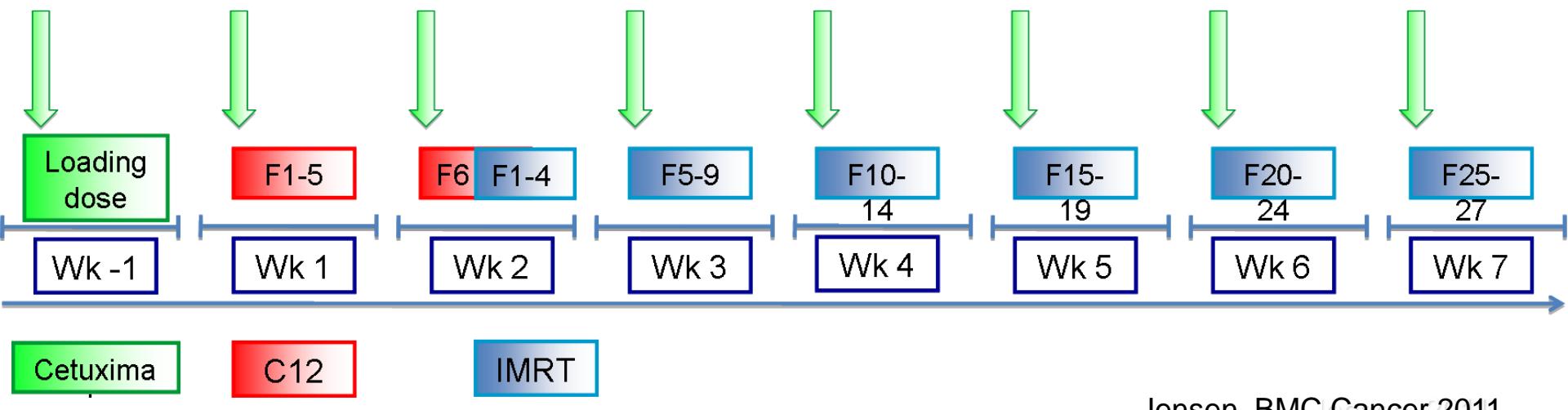
Open Access

Combined treatment of adenoid cystic carcinoma with cetuximab and IMRT plus C12 heavy ion boost: ACCEPT [ACC, Erbitux[®] and particle therapy]

Alexandra D Jensen^{1*}, Anna Nikoghosyan¹, Axel Hinke², Jürgen Debus¹, Marc W Münter¹

ACCEPT

- Phase II
- ACC: R2 or inoperable
- radiotherapy:
 - C12-Boost: **18 GyE** a 3 GyE C12
 - IMRT: 54 Gy a **1,8 Gy**



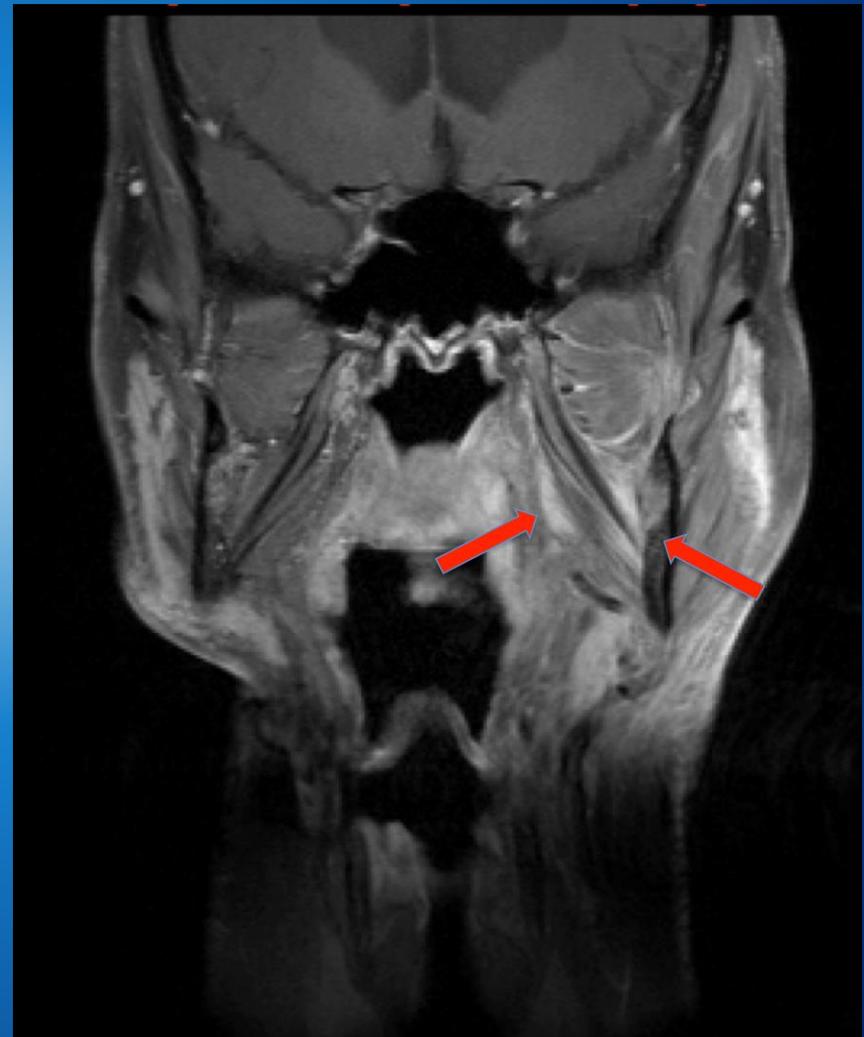
ACCEPT – response



Planning scan

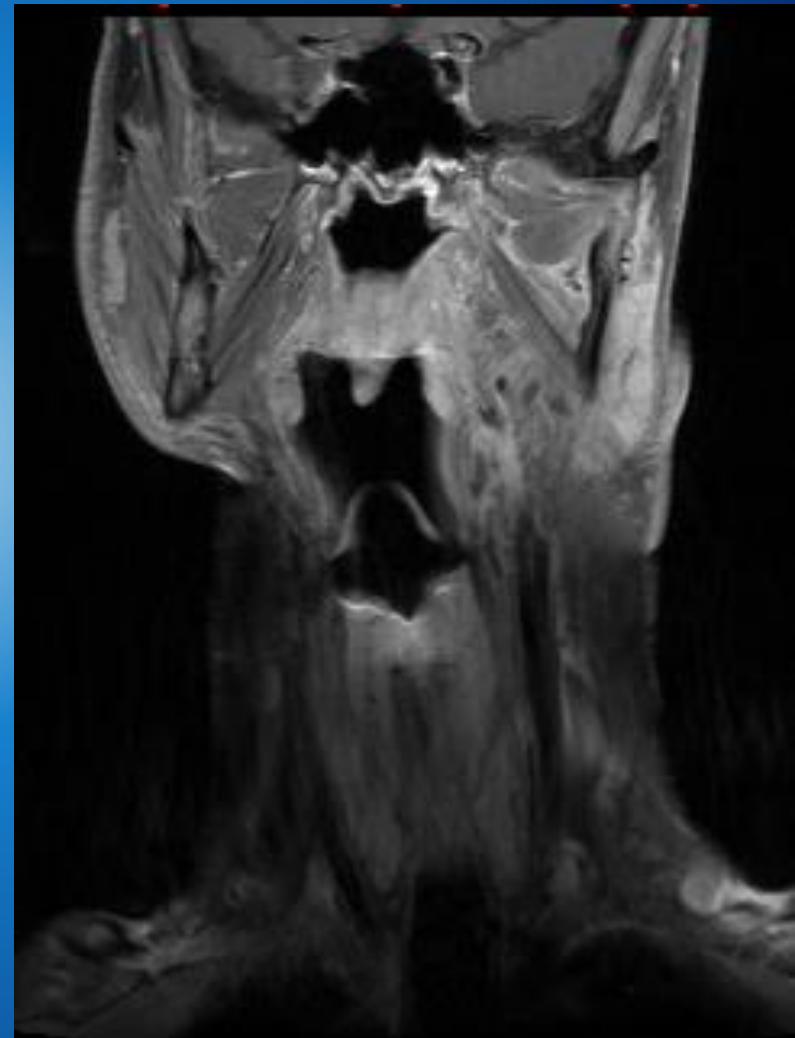


ACCEPT – response



6 wks post completion of RT

ACCEPT – response

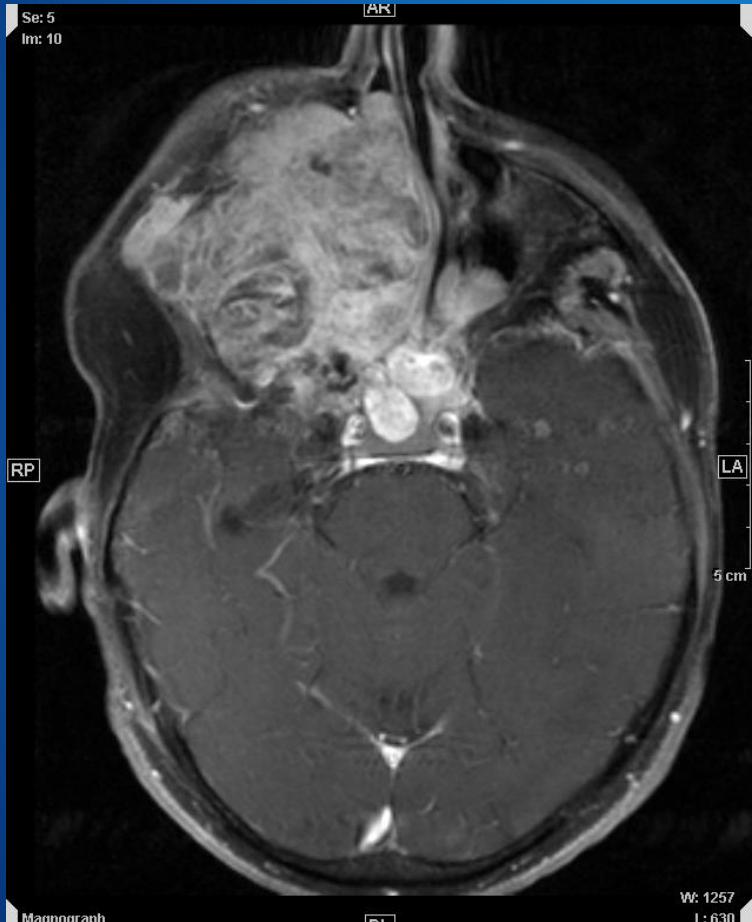


4 months post completion of RT

TREATMENT OF LOCAL RELAPSE?

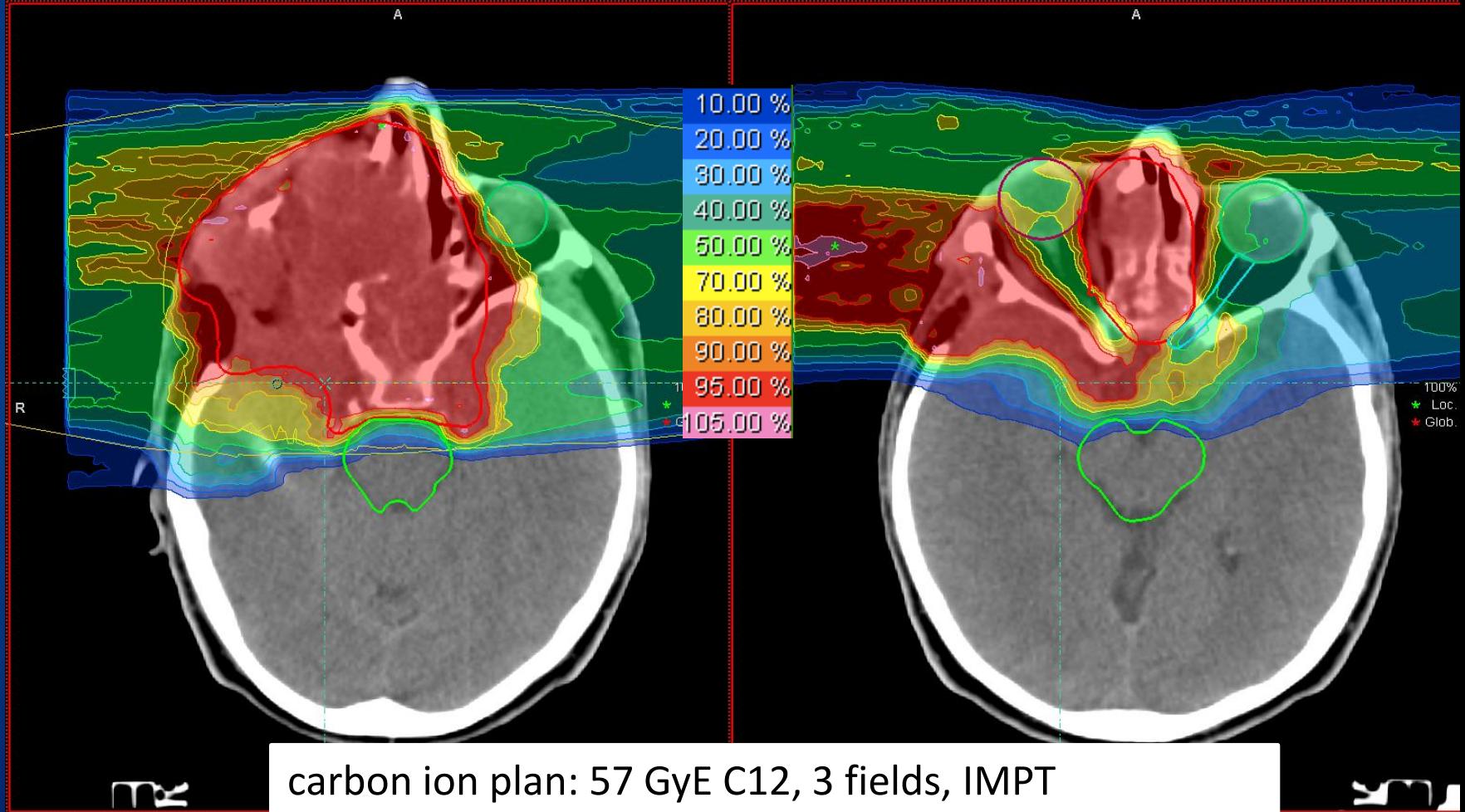
active agent	# of pts (ACC)	CR/ PR	SD	1st author	publication year	journal
Lapatinib	19	0	79%	Agulnik	2007	JCO
Bortezomib	25	0	64%	Argiris	2006	Proc ASCO
Sunitinib	14	0	77%	Chau	2012	Ann Oncol
Gefitinib	21	0	67%	Glisson	2005	Proc ASCO
Imatinib	15	0	60%	Hotte	2005	Proc ASCO
Cetuximab	30	0	87%	Locati	2009	Oral Oncol
Paclitaxel	14	0		Gilbert	2005	Head Neck
Vinorelbine	20	0/ 20%		Airoldi	2001	Cancer
Cisplatin/ Vinorelbine	16	19%/ 25%		Airoldi	2001	Cancer
Platin/ Gemcitabine	30	3%/ 23%		Laurie	2010	Cancer
CAP	13	23%/ 23%		Dreyfuss	1987	Cancer

Particle RT: re-irradiation



46-year old pt; recurrence approx. 10a post initial treatment

Particle RT: re-irradiation



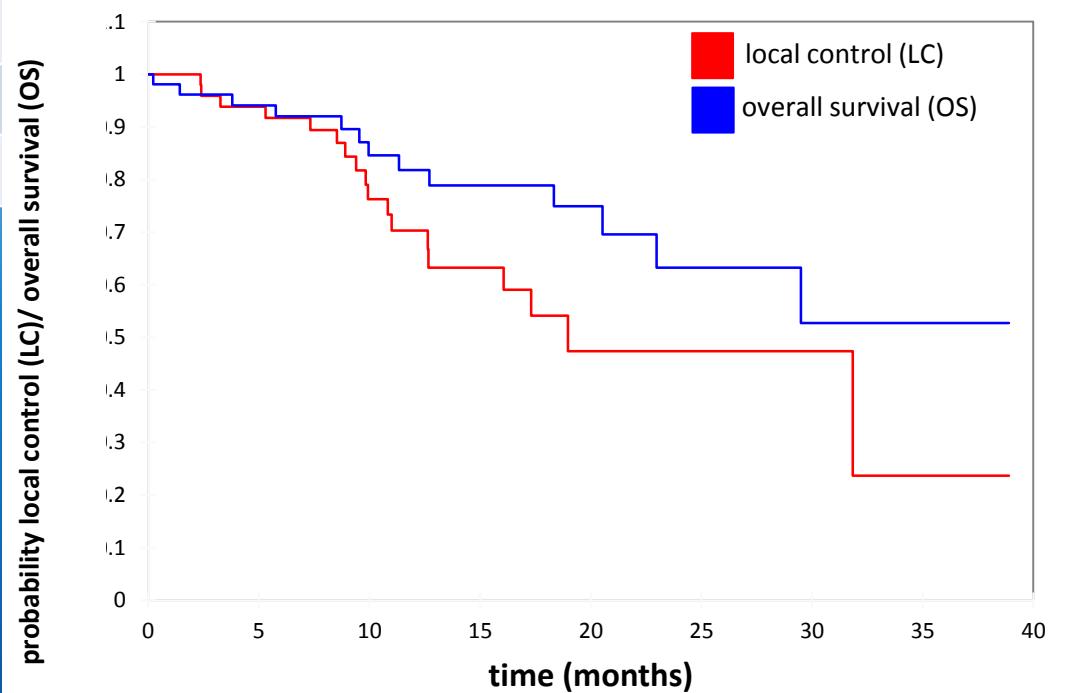
Particle RT: re-irradiation



good PR and symptom relief 4 months post re-RT

Particle RT: re-irradiation

N=52 pts	6 wks post RT (%)	best response (%)
CR	3.8	5.8
PR	34.6	48.1
SD	46.2	36.5
PD	0	0
dna	7.7	7.7
lost to f/u	0	1.1



Late toxicity (CTCAE v. 4.03)

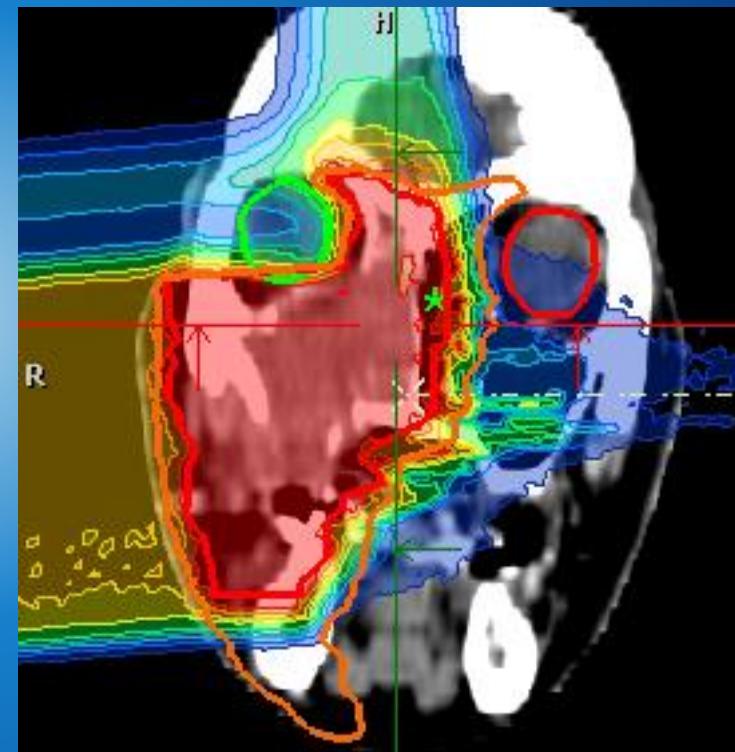
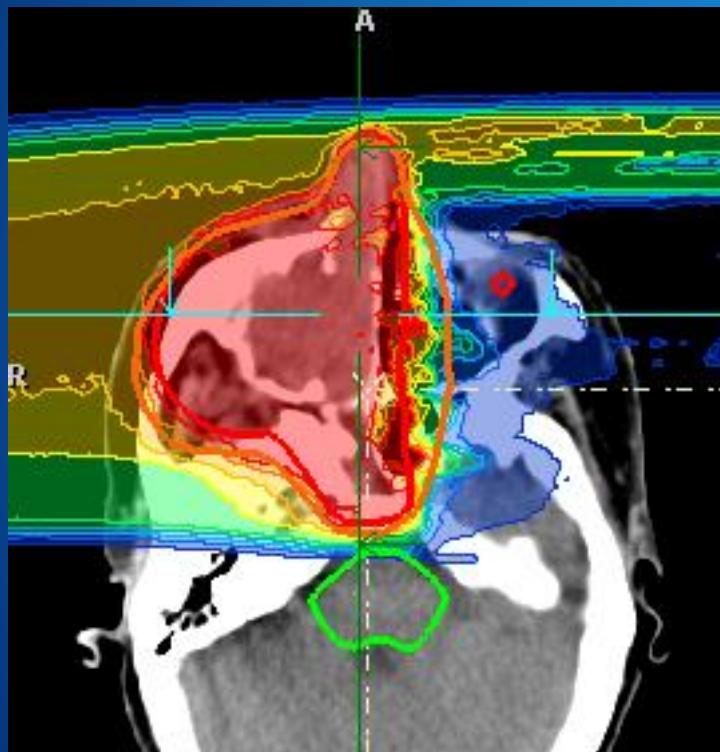
	Pts	%
Xerostomia °I	4	7.7
Hyperpigmentation °I	2	3.8
Dysphagia °I	3	5.8
<i>Dysphagia °III</i>	1	1.9
Trismus	6	11.5
CNS necrosis °I	8	15.4
<i>CNS necrosis °III</i>	2	3.8
Osteoradionecrosis	3	5.8
Tinnitus	1	1.9
Xerophthalmia	2	3.8
Corneal ulcer	1	1.9
Rhinoliquorrhea	1	1.9
Conjunctivitis	1	1.9
Lymphedema	3	5.8
<i>Tissue necrosis</i>	2	3.8
<i>ICA haemorrhage (°IV)</i>	2	3.8
Cranial nerve palsy	1	1.9
Dizziness	1	1.9
Chronic otitis	1	1.9
<i>Symptomatic epilepsy °I</i>	1	1.9
Dysesthesia	1	1.9
Difficulty in concentration	1	1.9

Particle RT: re-irradiation

- moderate toxicity
- good treatment response even in heavily pre-treated patients
- good alternative to palliative chemotherapy as local and/ or symptom-oriented measures
- local recurrences still mostly in-field
- role of dose-escalation? use caution!

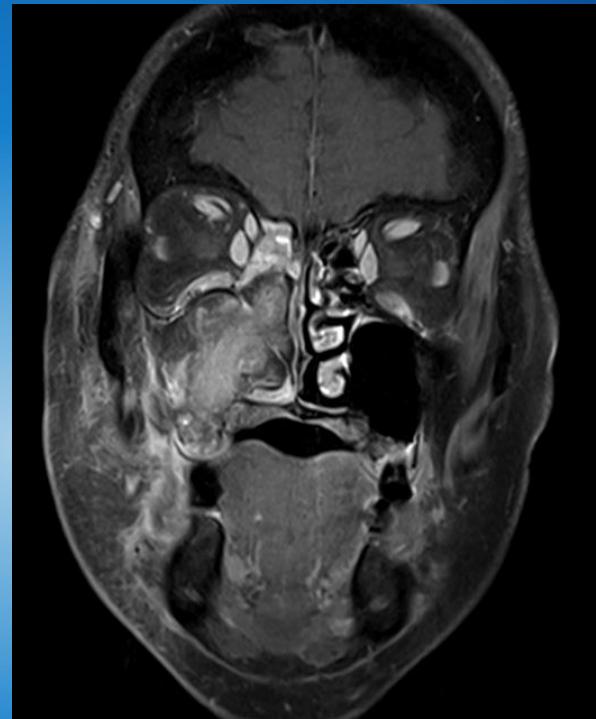
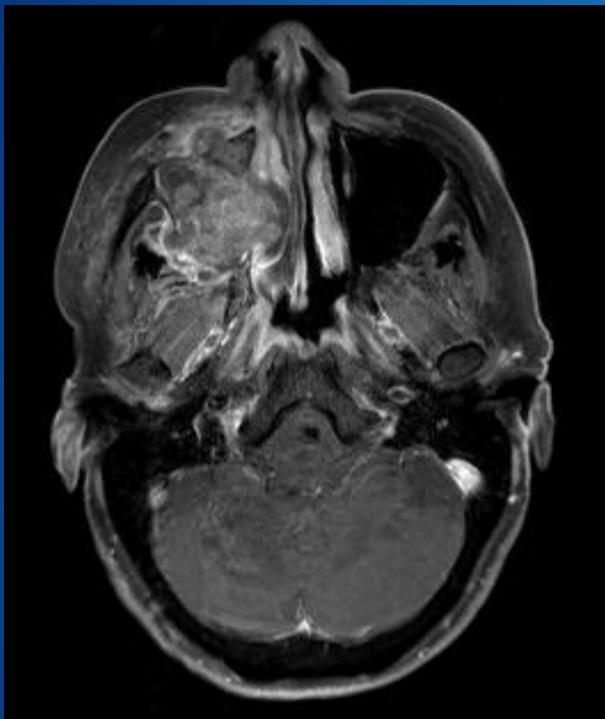
OTHER INDICATIONS

C12: Mucosal melanoma

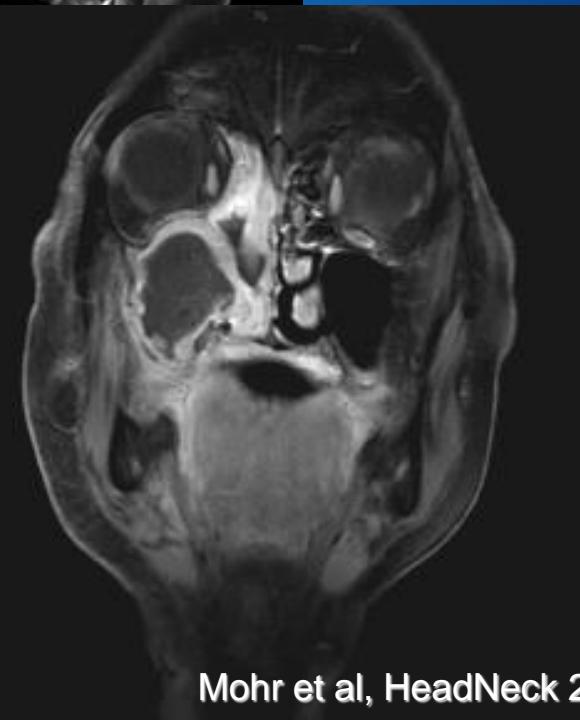
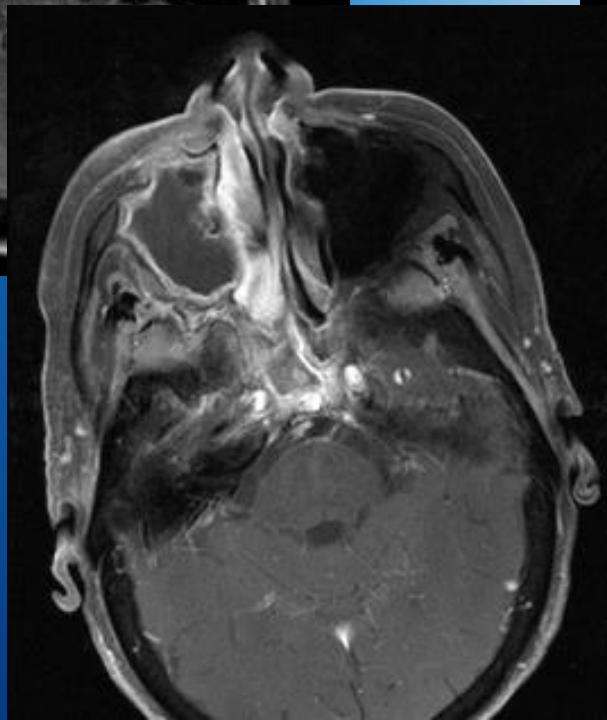
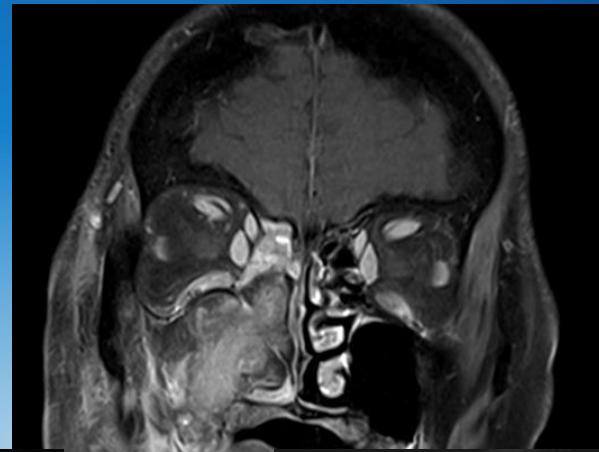
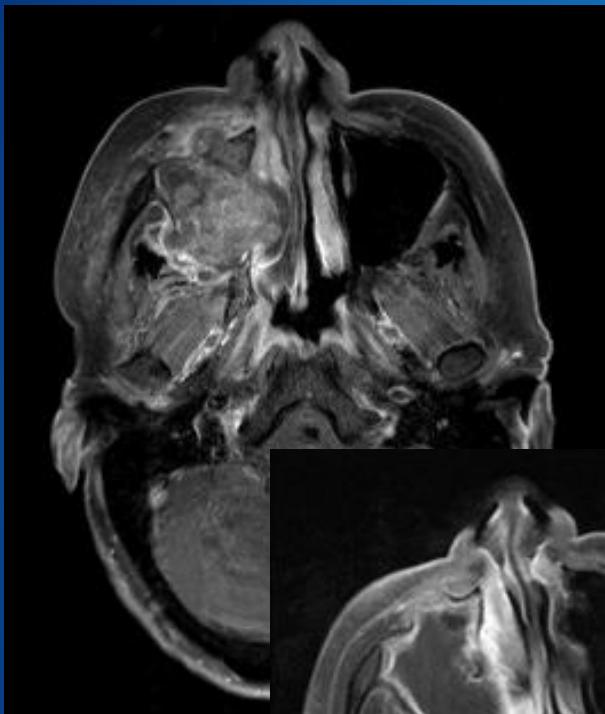


C12- boost, 2 fields, IMPT, 8 x 3 GyE

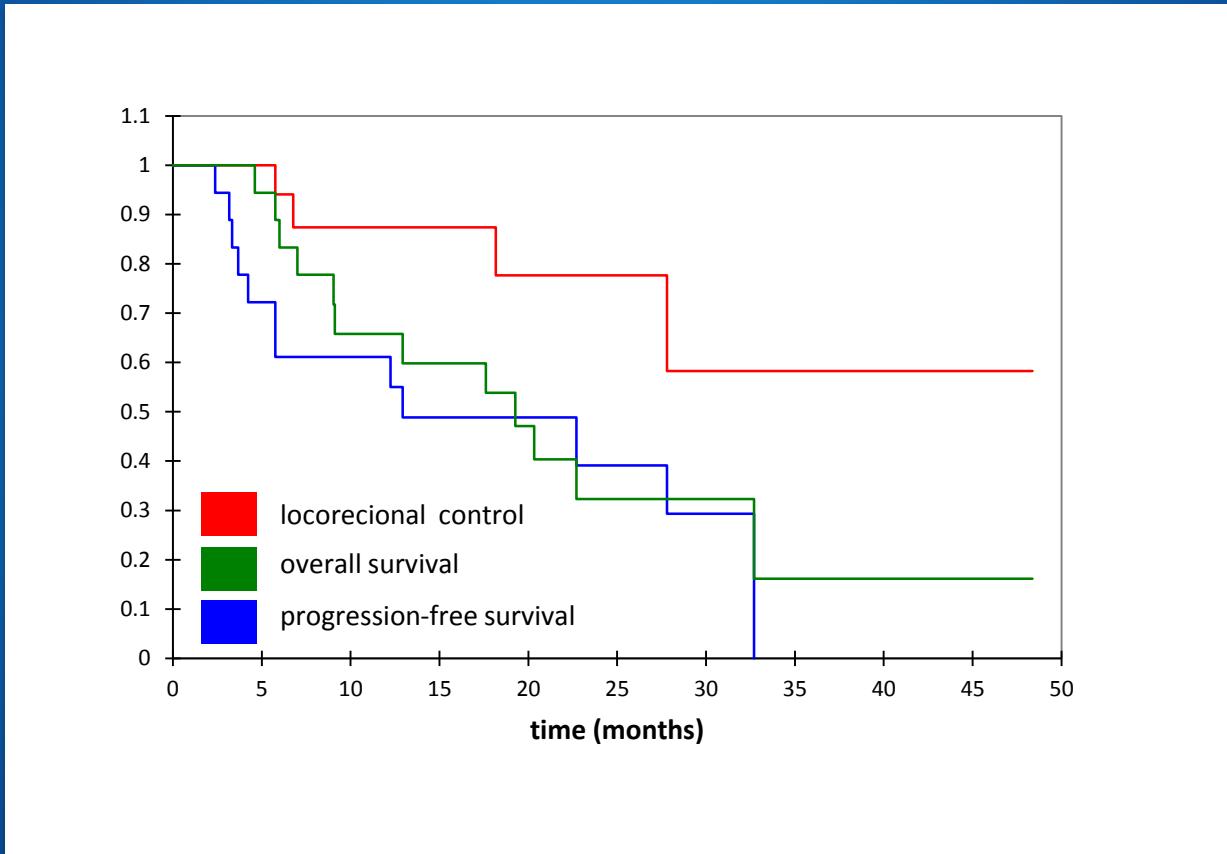
C12: Mucosal melanoma



C12: Mucosal melanoma



C12: Mucosal melanoma



HNSCC: Dose escalation

Jensen et al. BMC Cancer 2011, 11:182
<http://www.biomedcentral.com/1471-2407/11/182>

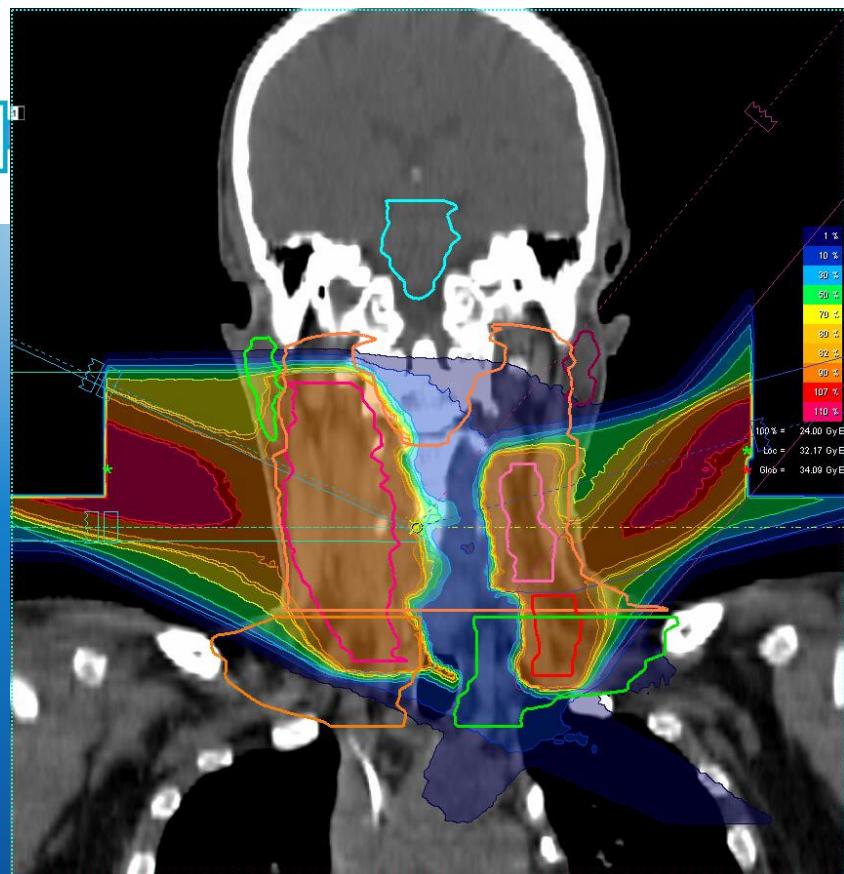
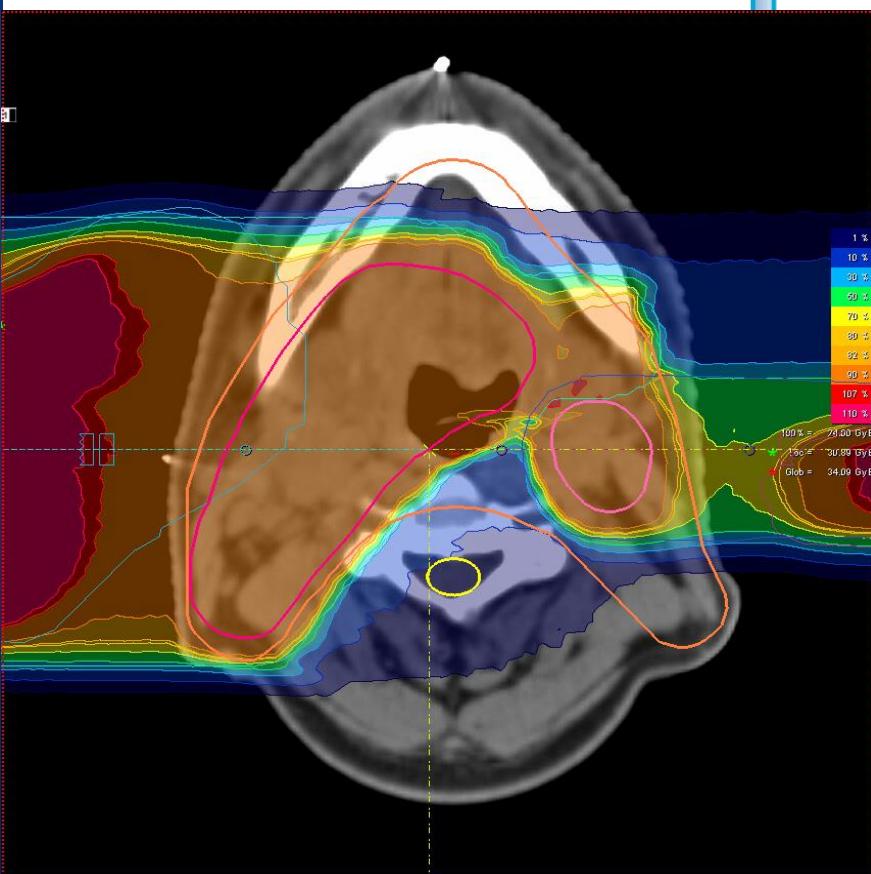
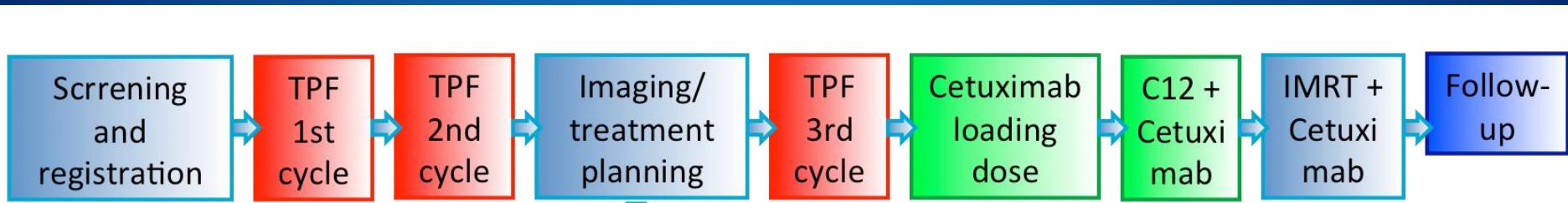


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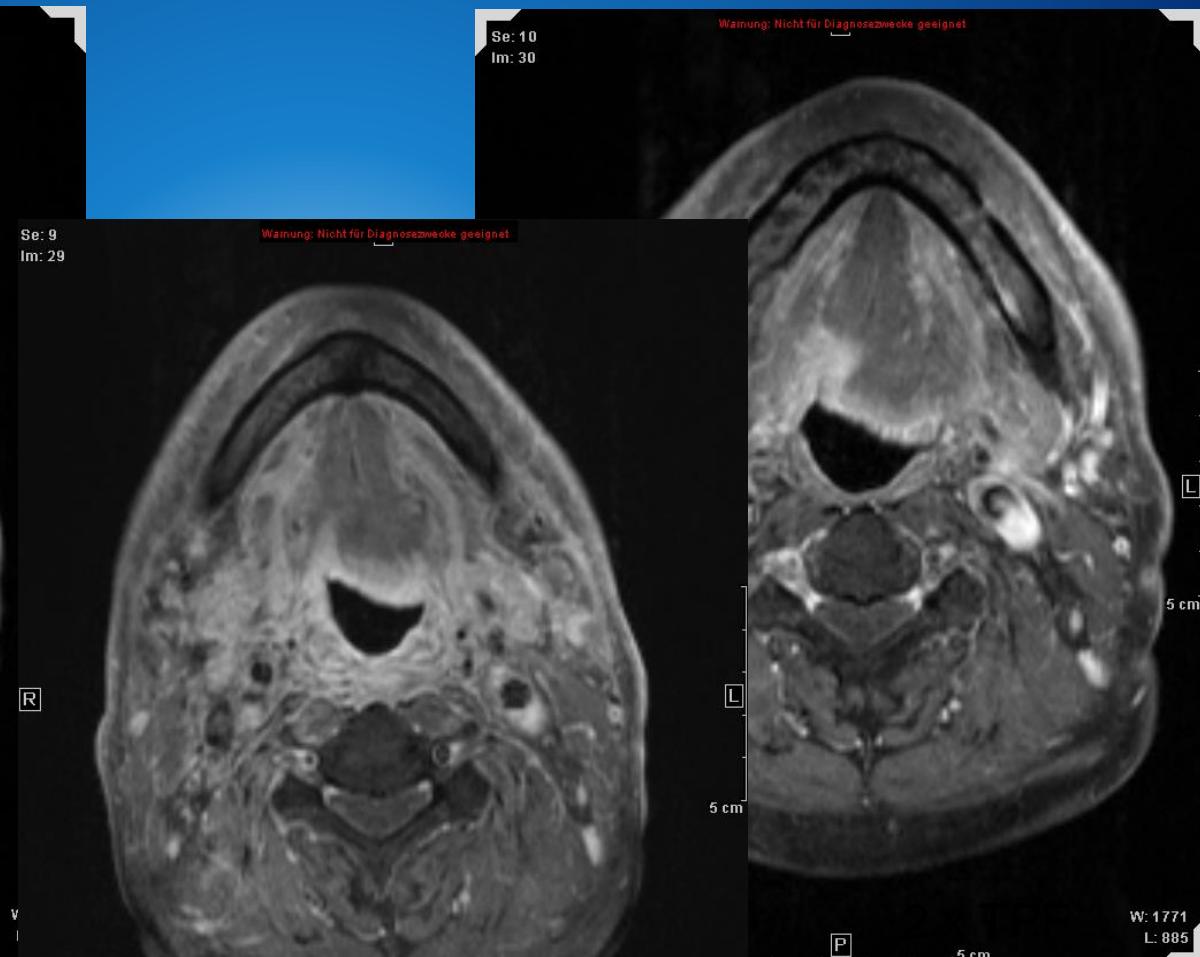
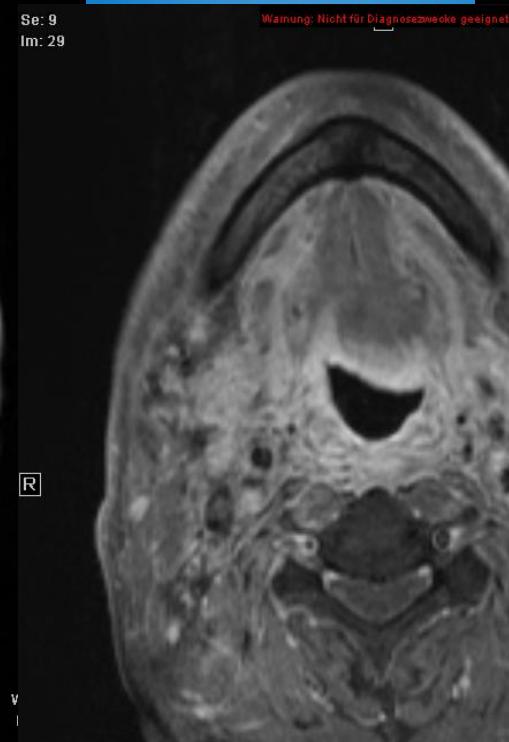
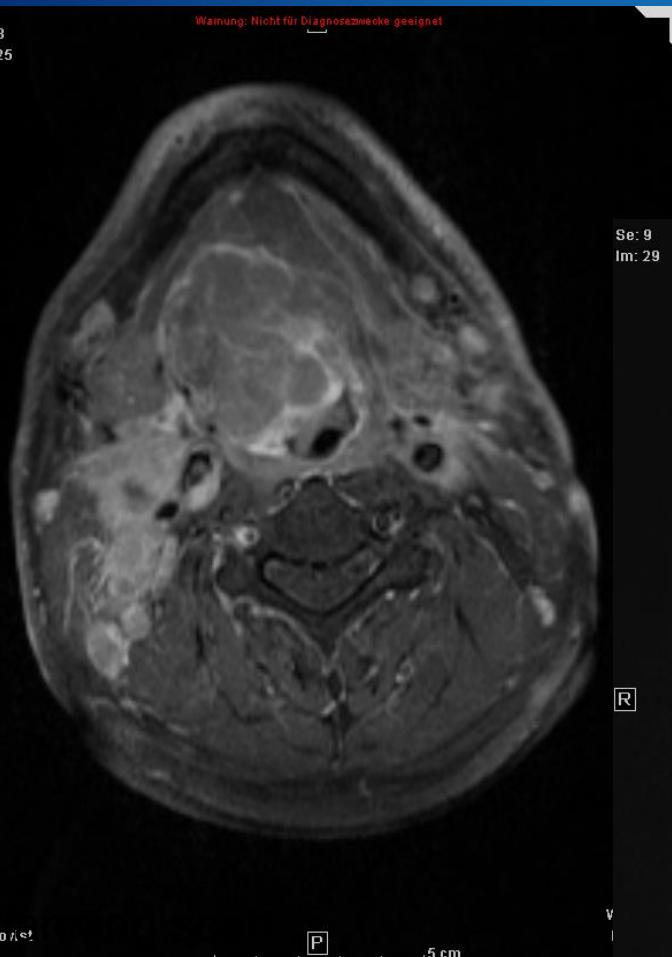
Phase II study of induction chemotherapy with TPF followed by radioimmunotherapy with Cetuximab and intensity-modulated radiotherapy (IMRT) in combination with a carbon ion boost for locally advanced tumours of the oro-, hypopharynx and larynx - TPF-C-HIT

HNSCC: Dose escalation?



TPF-C-HIT: response?

Se: 8
Im: 25



1st follow-up TPF-C-HIT

Gadovist

W: 2383
L: 1084

Jensen et al, DEGRO 2014

C12: trial and potentials

- „radioresistant tumours“
 - malignant salivary gland tumours
 - debulking surgery in T4 tumours?
 - re-irradiation
- challenging anatomical sites
 - i.e. mucosal melanoma
- tumour hypoxia
 - HNSCC with large nodal disease
 - nasopharyngeal carcinoma?
- open trials:
 - ACCEPT
 - IMRT-HIT-SNT

Do not stop there!!!

- further characterisation of particle cohorts:
 - subgroup analyses
 - characteristics of patients with
 - early relapse?
 - long local control?
- hypothesis generation for prospective trials
- cooperation between particle centres
 - create meaningful results
 - bridge evidence gaps

Acknowledgements

- Dept. Radiation Oncology

University of Heidelberg
Germany



Thank you!