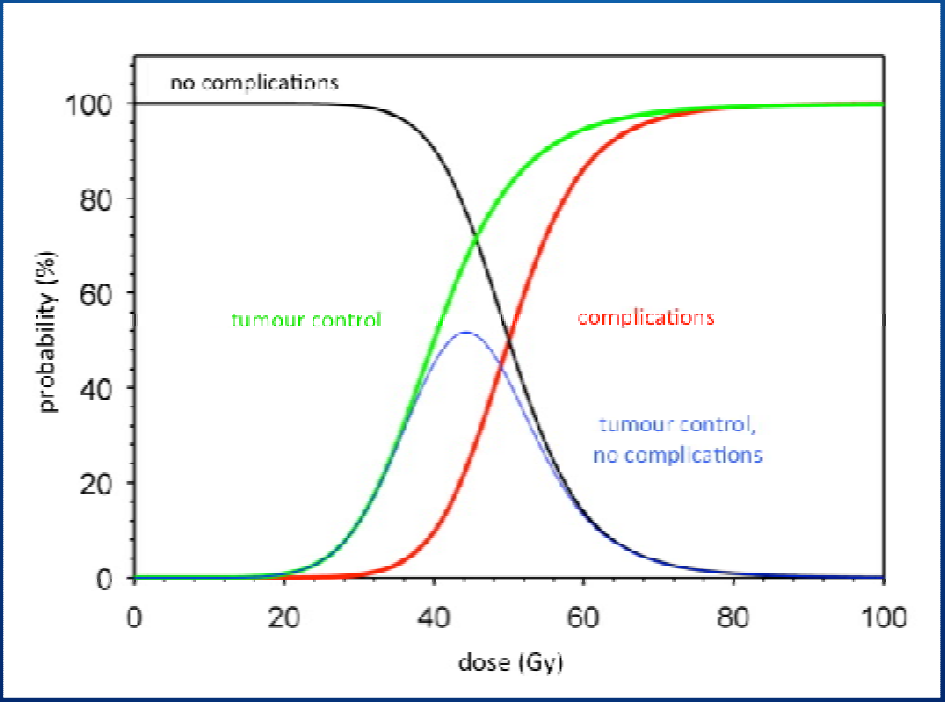
Radiobiology and clinical applications of particle radiations: lessons from large case series

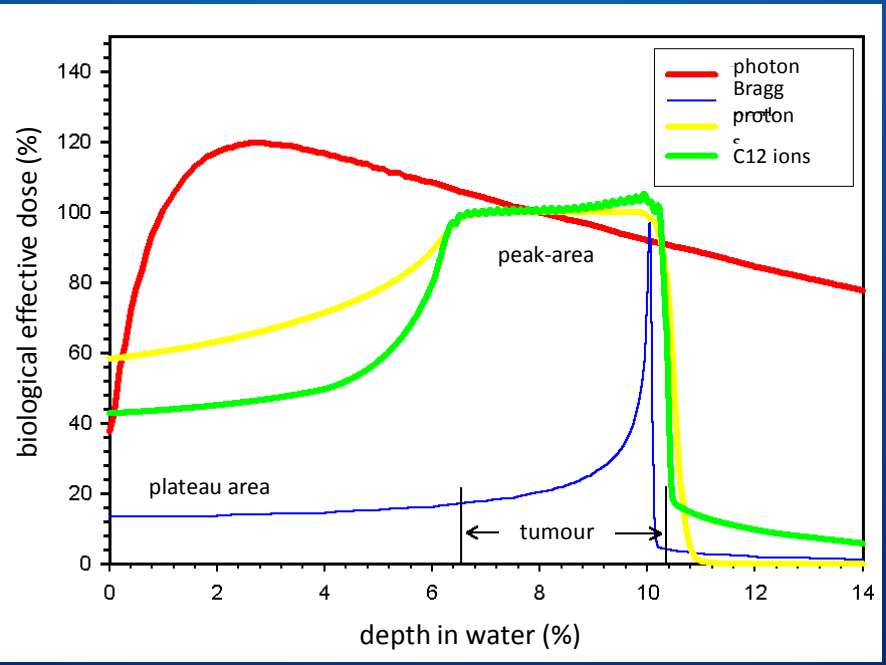
PD Dr. Alexandra Jensen, MSc

Particle Therapy - Rationale



according to Hermann Holthusen, 1933

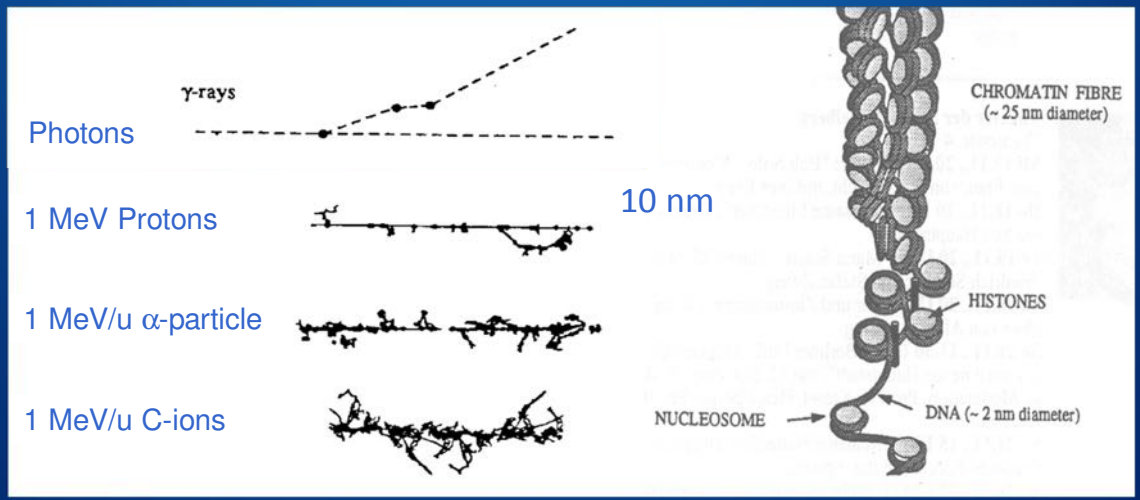
Particle Therapy - Rationale



Particle Radiotherapy: RBE

low LET

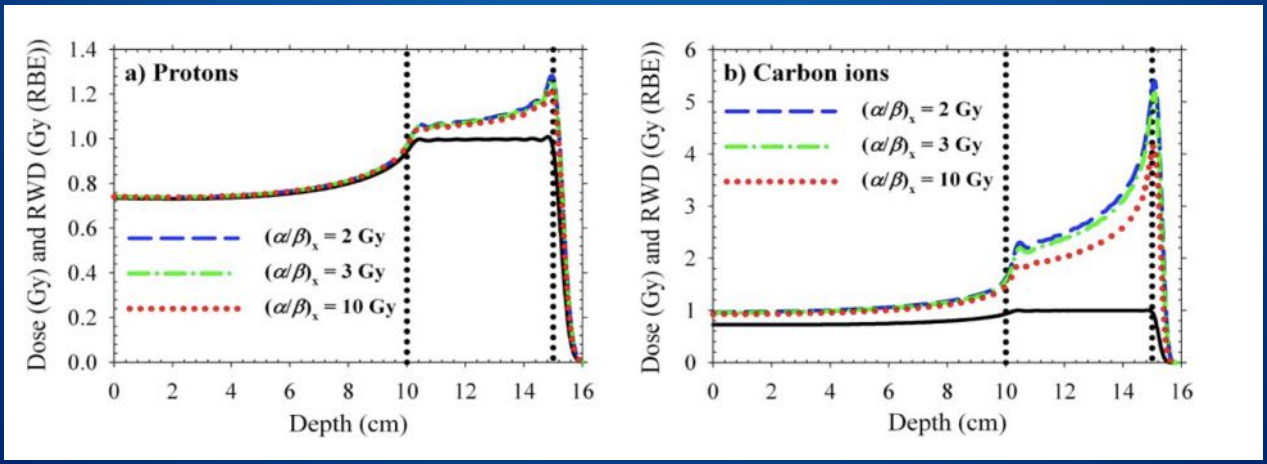
high LET



increased biological effectiveness

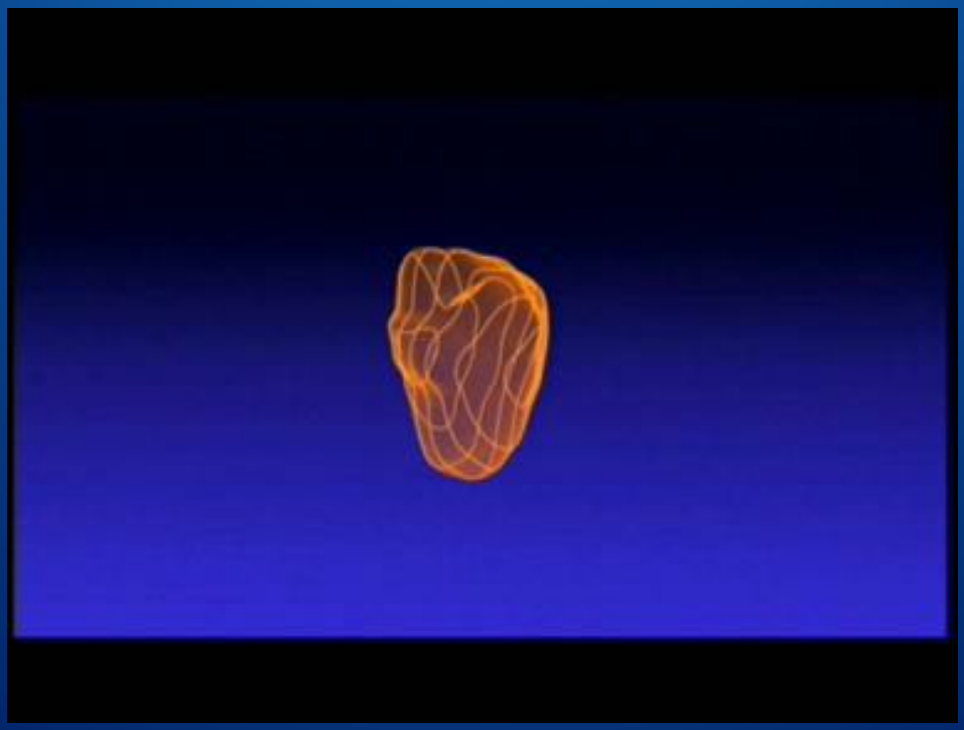
Kraft, 1996

Particle Radiotherapy: RBE



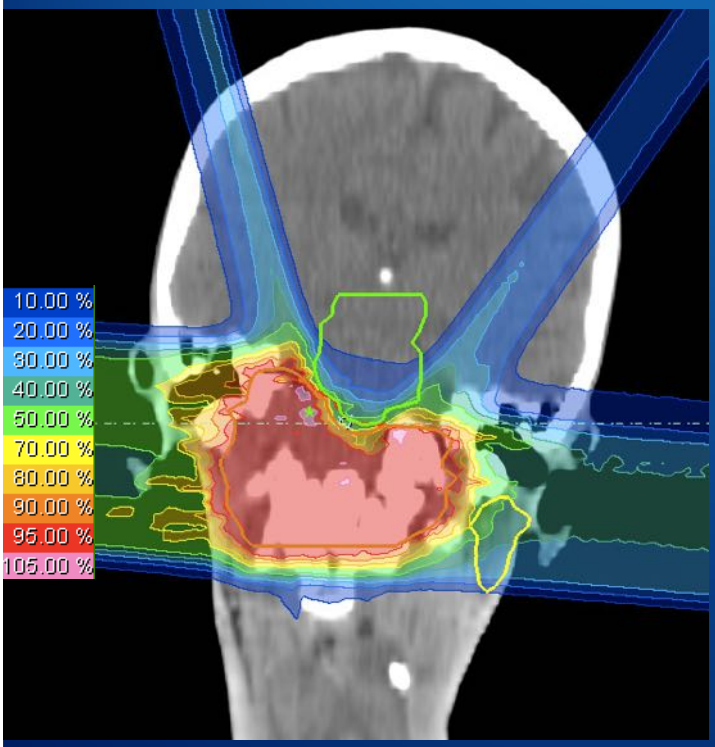
Frese et al, IJROBP 2012

Particle RT: scanning



Dept Radiation Oncology, Heidelberg

Particle RT: scanned beams



5-field IMPT

- varying dose contributions from several beam angles
- varying intensities
- varying energies

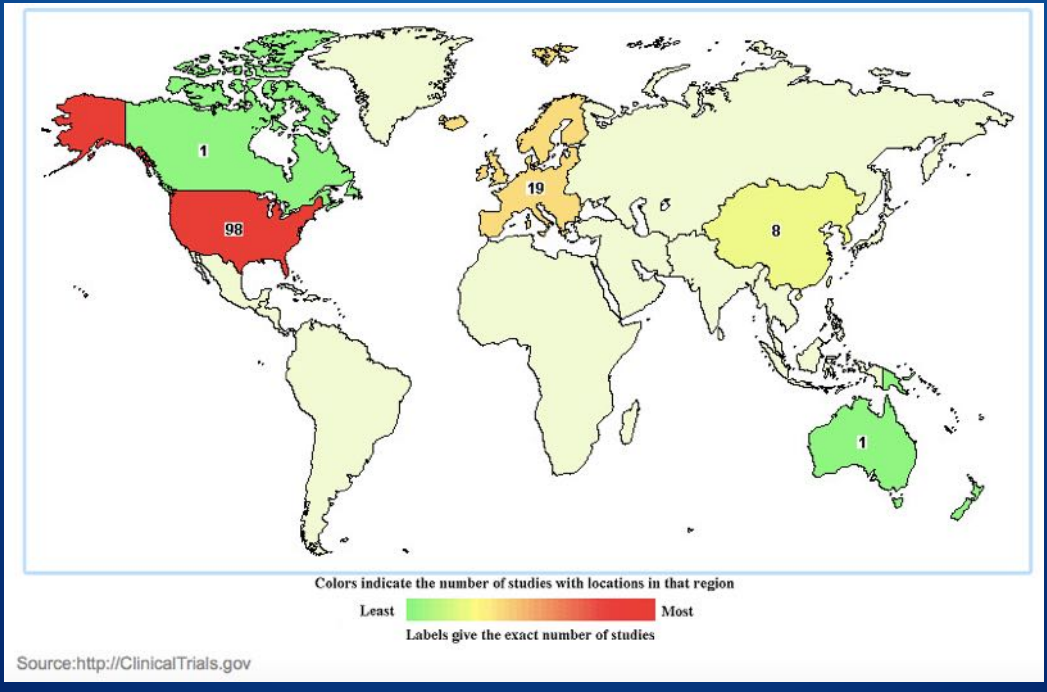
Particle RT: scanned beams

- RBE dependent on
  - location within the particle path
  - particle energy
  - absorbed dose/ local dose
  - particle fluence

biological treatment plan optimisation: integral part of C12 treatment planning systems!

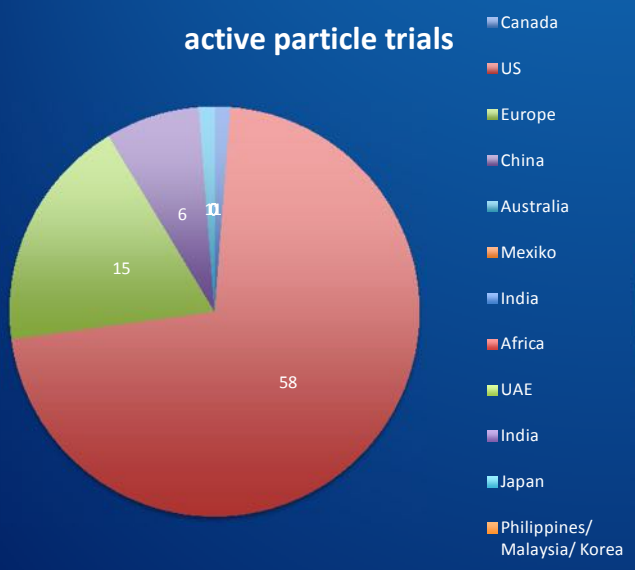
WHAT ABOUT THE EVIDENCE?

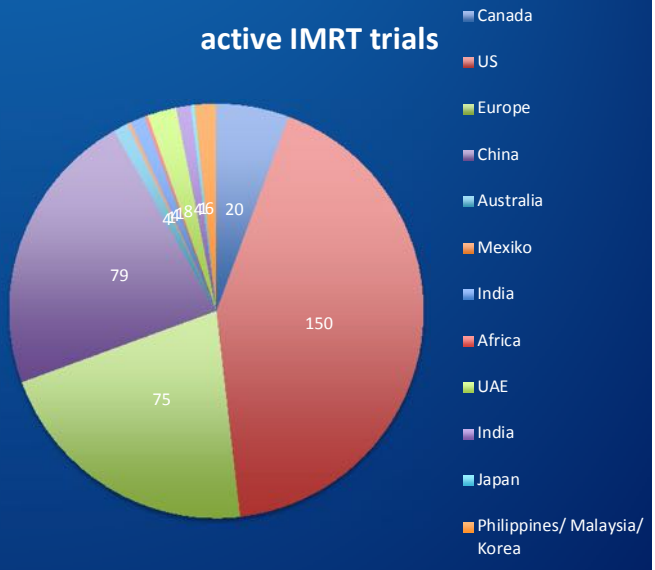
Particle RT: registered clin. trials



clinicaltrials.gov accessed 01.10.2015

Active clin. trials: particles vs IMRT



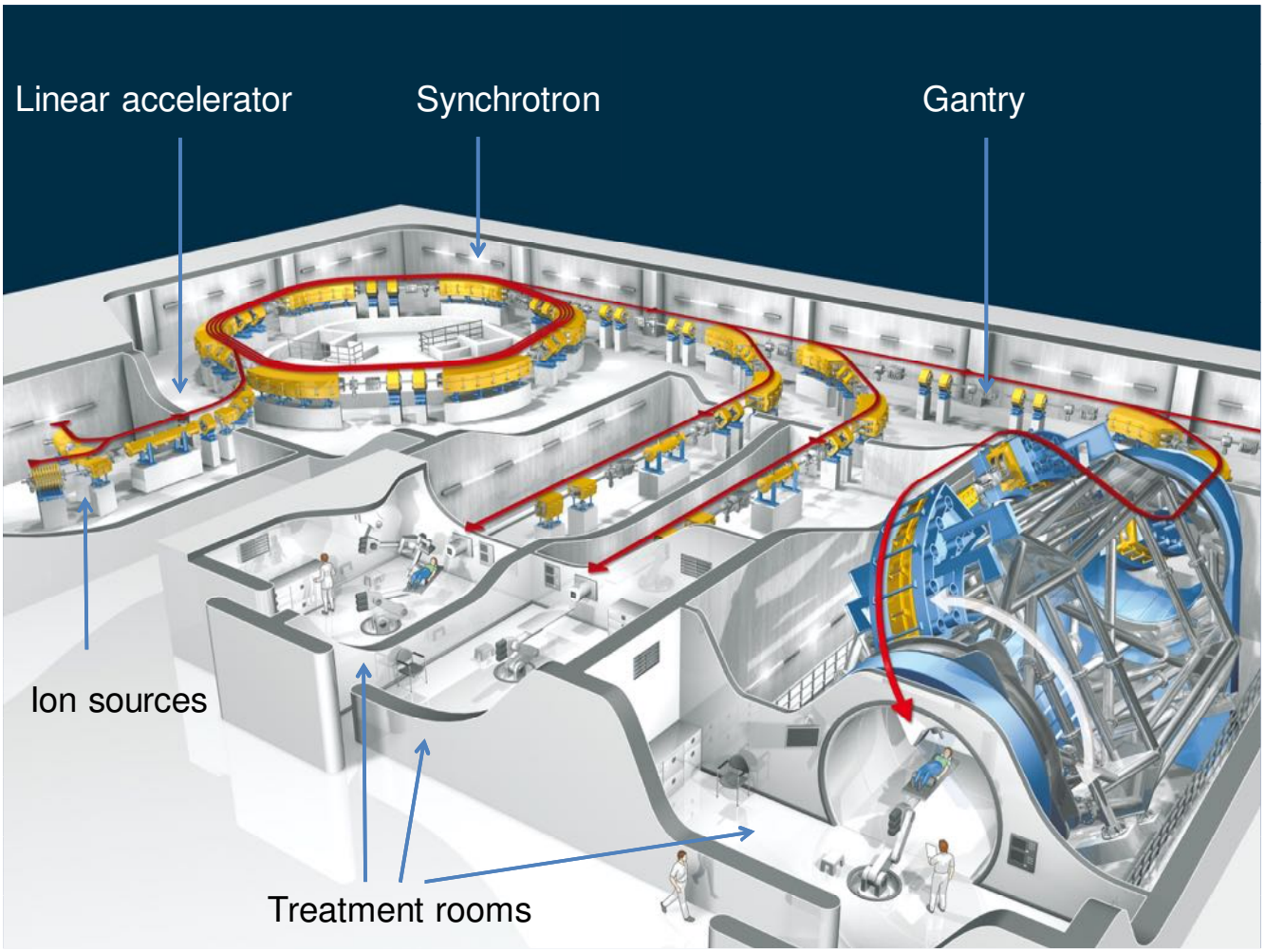


clinicaltrials.gov accessed 01.10.2015

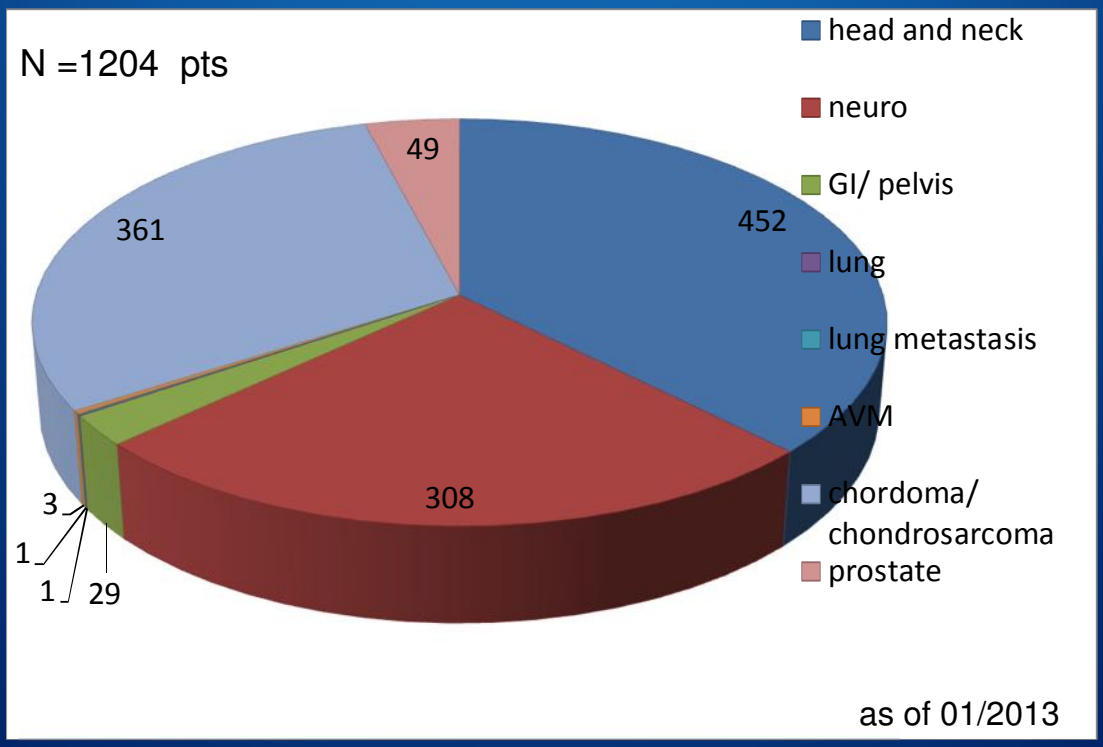
Particle RT: centres >2,000 pts

site	country	Tx start	pt number (12/2014)
Loma Linda	US	1990	18,362
HIMAC	Japan	1994	11,148
MGH Boston	US	2001	8,107
PSI	Switzerland	1984	7,364
Orsay	France	1991	7,004
MD Anderson	US	2006	5,838
UFPTI Jacksonville	US	2006	5,376
Nice	France	1991	5,205
ITEP, Moscow	Russia	1969	4,368
Tsukuba	Japan	2001	3,416
STPTC	Japan	2008	2,797
Clatterbridge	UK	1989	2,626
HIT	Germany	2009	2,547
HZB, Berlin	Germany	1998	2,525
UPenn	US	2010	2,522
PTC Bloomington	US	2004-2014	2,200
HIBMC	Japan	2002	2,146

ptcog.ch, accessed 01.10.2015



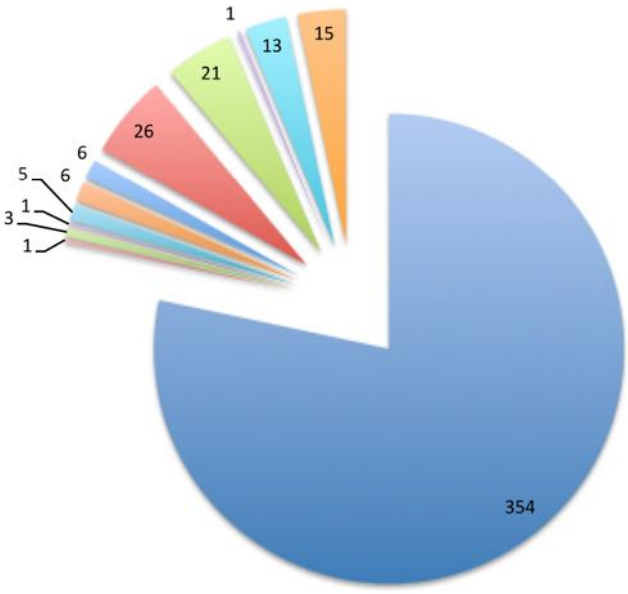
Particle RT indications (HIT)



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

Particle RT indications – head&neck



MSGT

HNSCC and paranasal sinus

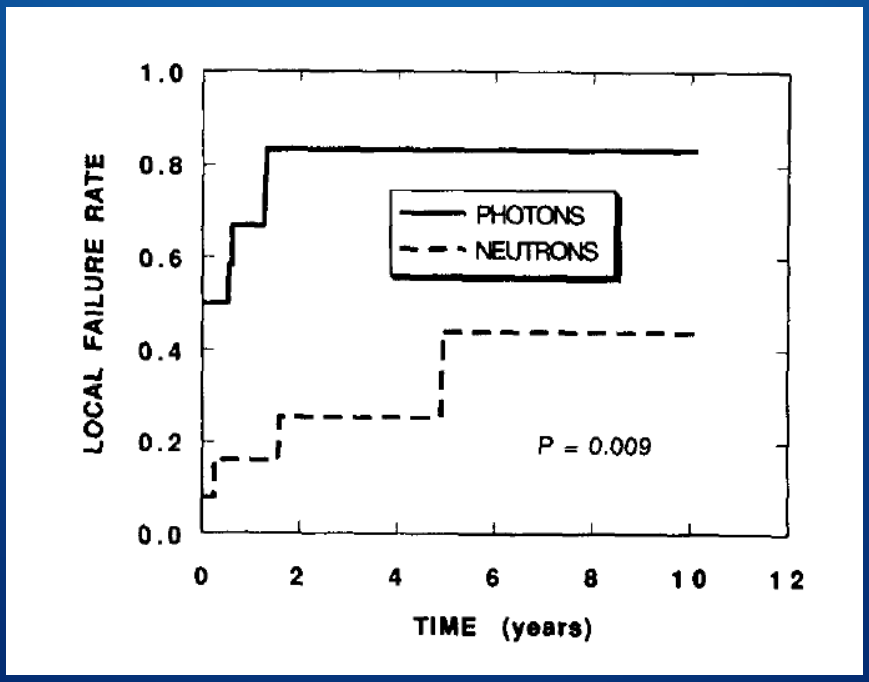
mucosal melanoma

nasopharyngeal carcinoma

misc sarcoma

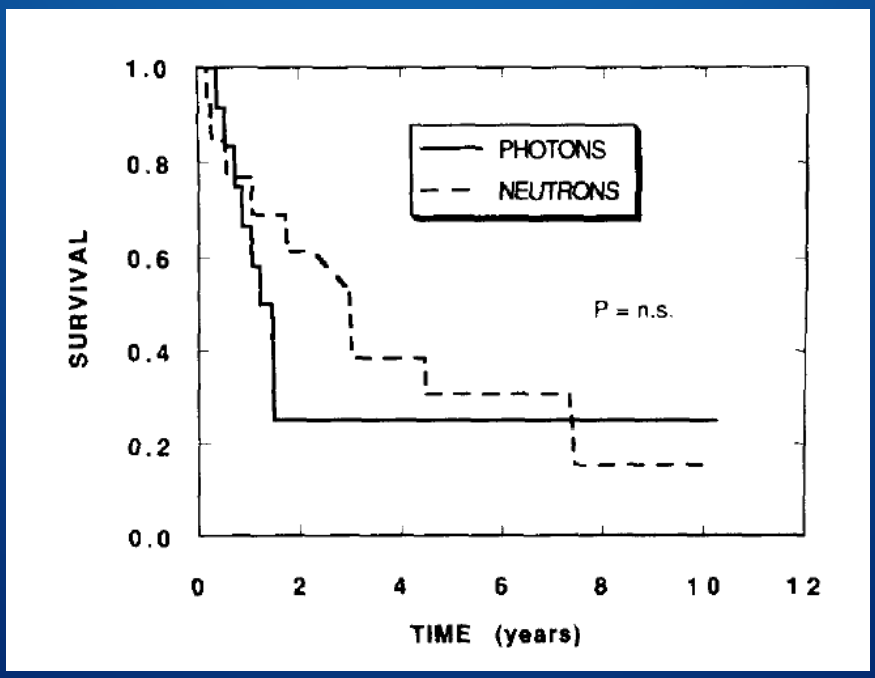
N = 452 pts, as of 01/2013

MSGT: neutrons



Laramore et al, IJROBP 1993

MSGT: neutrons



Laramore et al, IJROBP 1993

MSGT and neutrons: late toxicity

Table 1. Treatment related complications graded "severe or greater" according to the joint RTOG/EOTRC scoring schema

	Photons	Neutrons
Hoarseness	0	1
Dysphagia	1	2
Dehydration	1	2
Malnutrition	1	2
Pain	0	3
Mucosal	1	3
Skin	2	2
Fibrosis	1	2
Necrosis	0	3
Xerostomia	2	1
Impaired taste	1	4
Other	0	1

Note: Some patients exhibited more than one type of complication. There were no fatal complications on either treatment arm.

Laramore et al, IJROBP 1993

Malignant salivary gland tumours

lessons from larger case series so far:

- improved local control by:
  - high-precision radiotherapy techniques
  - dose escalation
  - high-LET radiotherapy
- neutrons:
  - high local control (75% @5 years), but also high toxicity

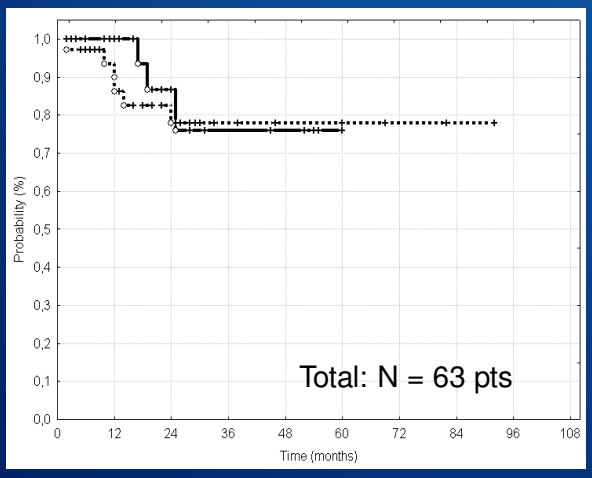
GSI C12 pilot project

Dose concept:

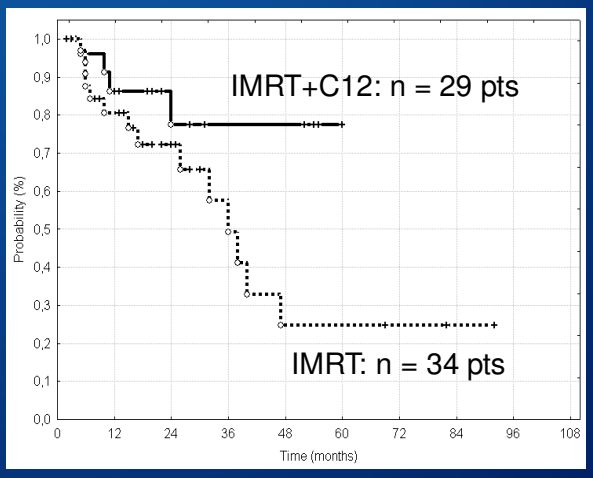
IMRT: 54 Gy (ED 2 Gy) + C_{12}: 18 GyE (6 x 3 GyE)

retrospective comparison regarding control and survival rates

Overall Survival

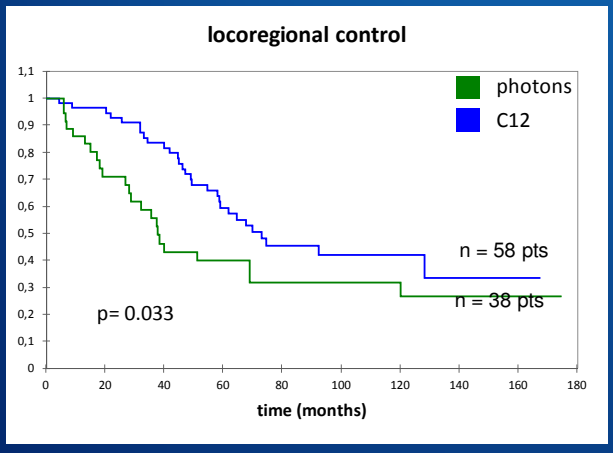


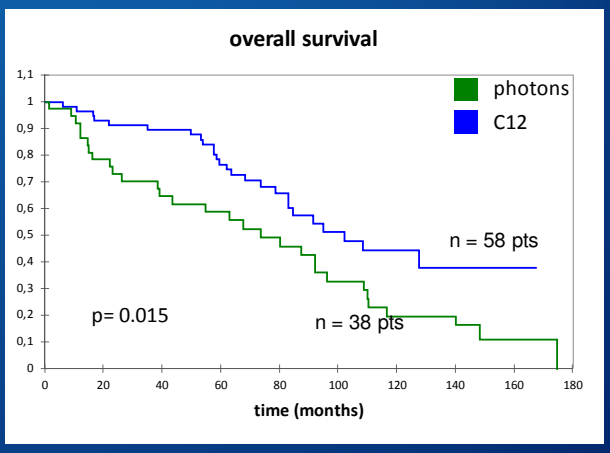
Local control



Schulz-Ertner et al, Cancer 2005

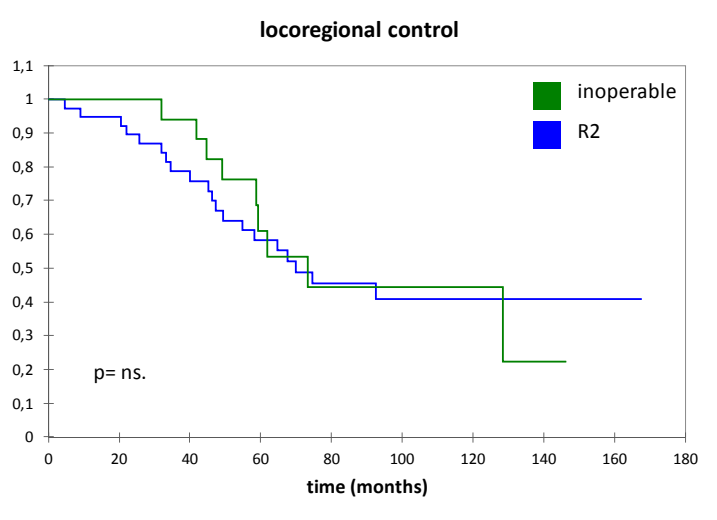
GSI C12 pilot project update





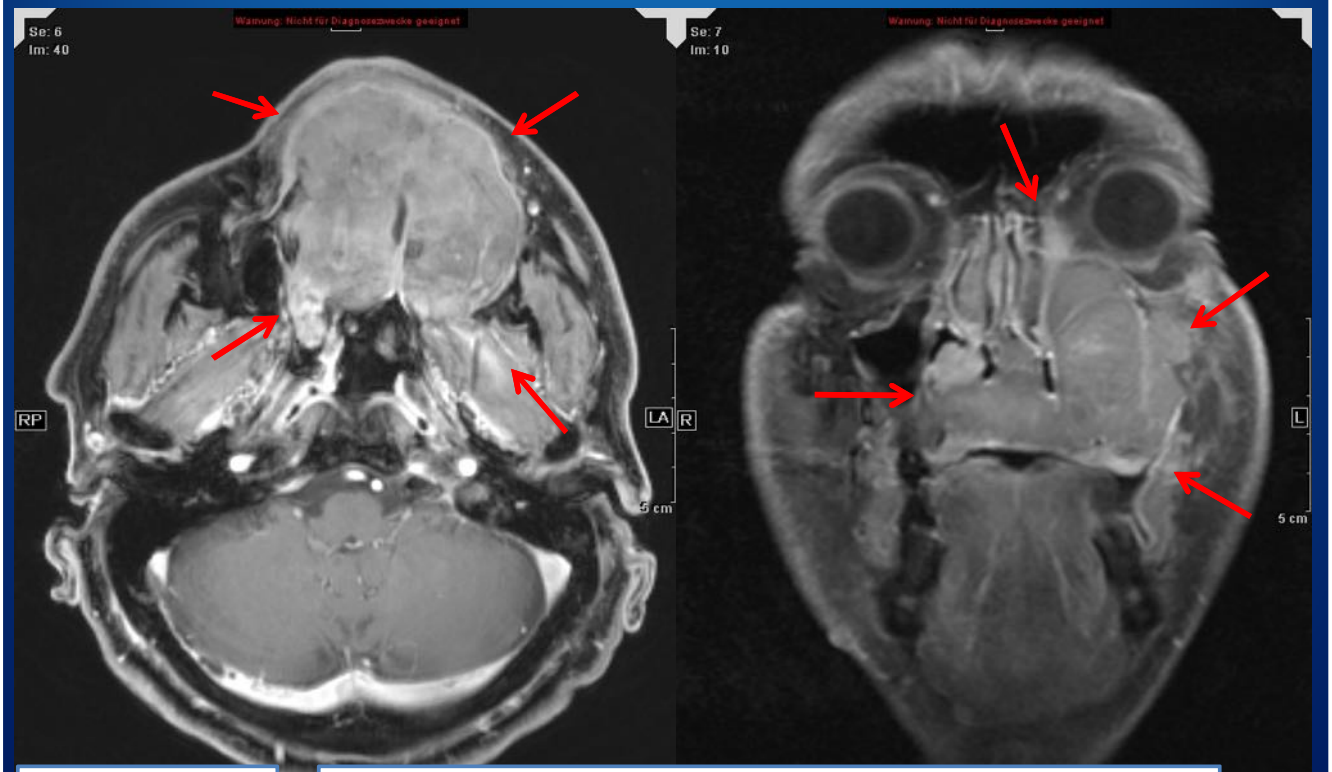
Jensen et al, Cancer 2015

Pilot project update: C12 for ACC



Jensen et al, Cancer 2015

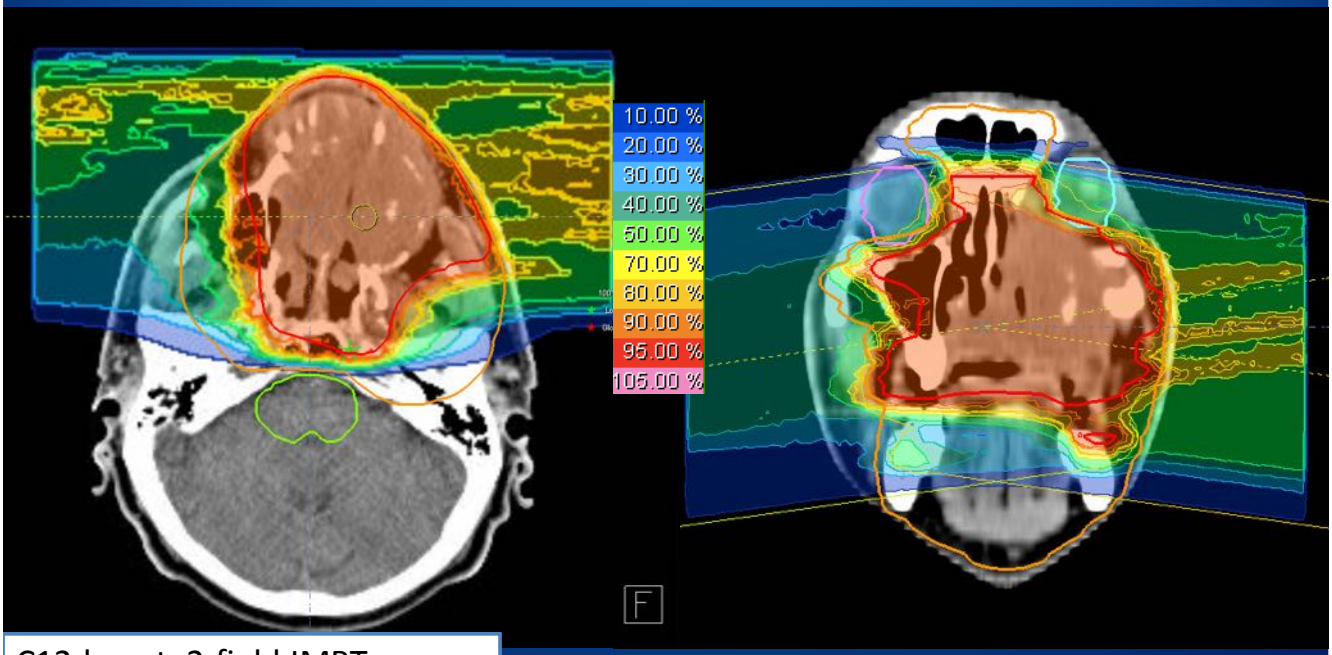
Clinical case: adenoid cystic carcinoma



Prae RT

67 year-old patient with ACC

Clinical case: adenoid cystic carcinoma



C12-boost, 2-field IMPT

Clinical case: adenoid cystic carcinoma

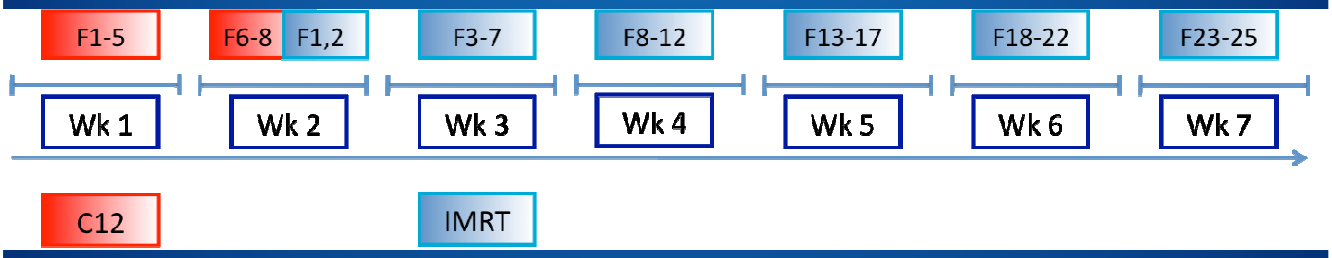
1st follow-up

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

Jensen et al, BMC Cancer 2010

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

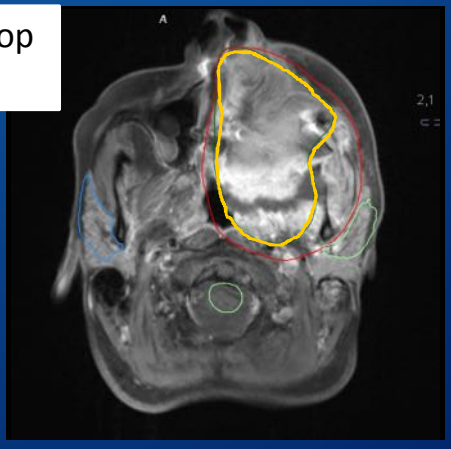
Jensen et al, IJROBP 2015

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%)

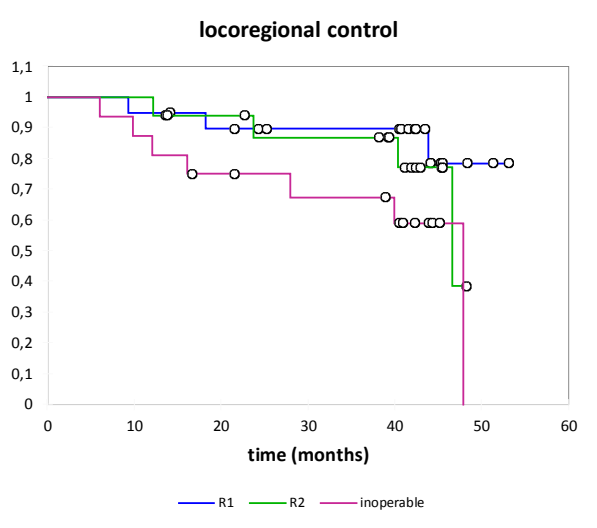
prae-op MRI

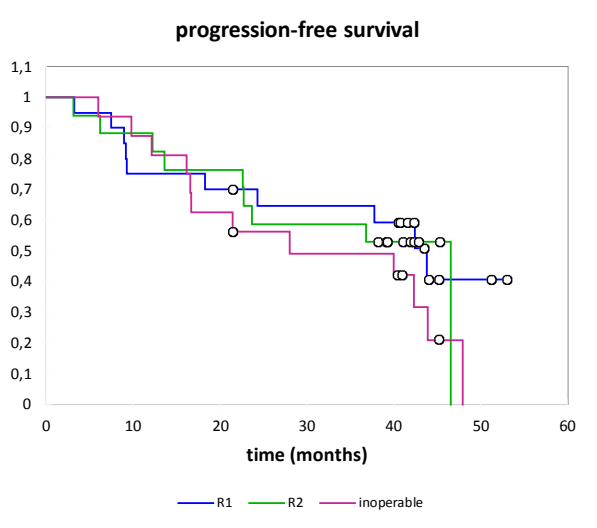
post-op MRI



Jensen et al, ASTRO 2013 & BMC Cancer 2012

Particle RT: COSMIC



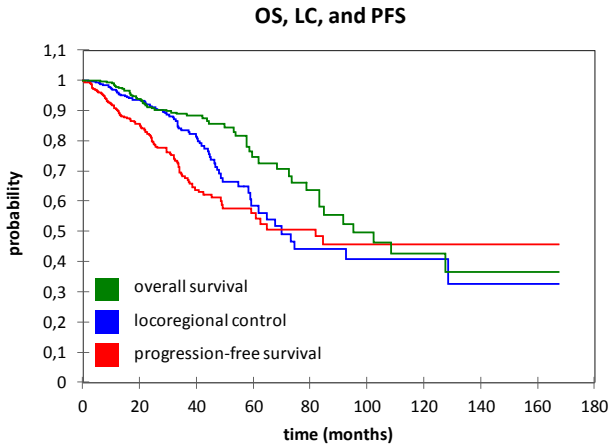


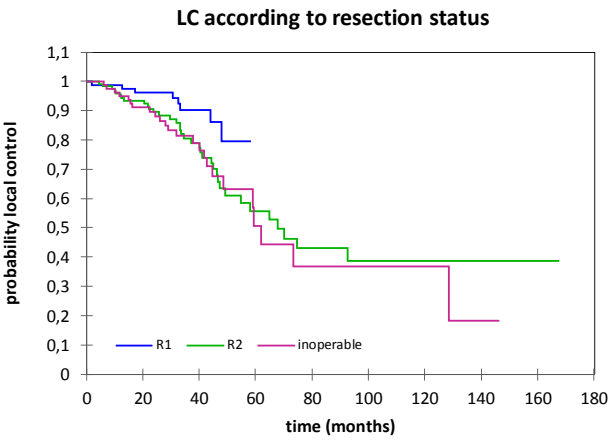
Jensen et al, IJROBP 2015

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

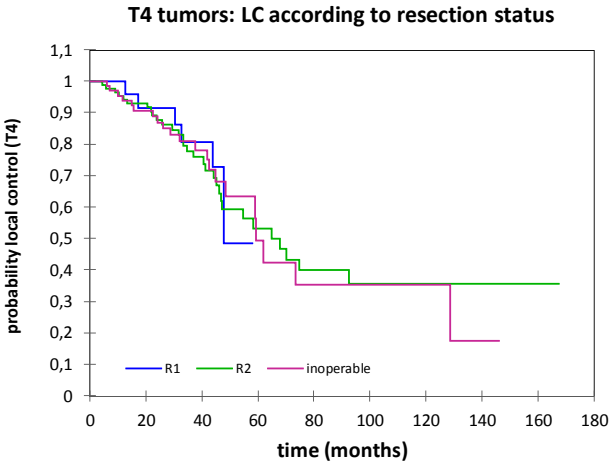




N=309 pts, 1997-2013

Jensen, Radiother Oncol 2015

Validation of project data within larger cohort, 1997-2013



Debulking for ACCs?

Jensen, Radiother Oncol 2015

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)

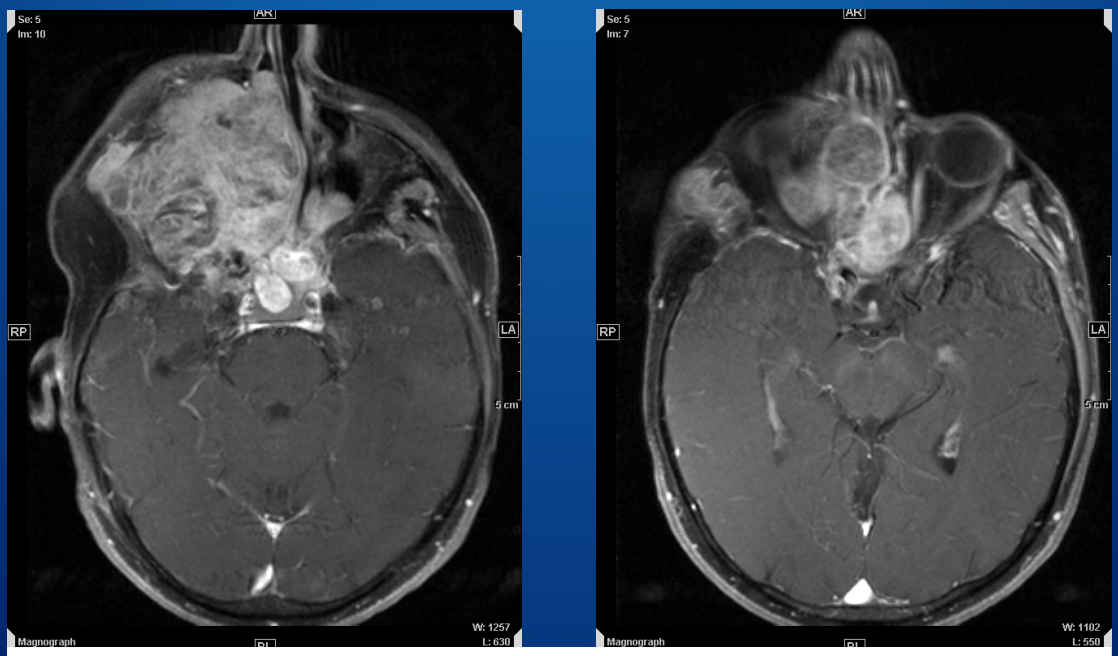
Particle RT: adenoid cystic carcinoma

Author	Journal	patients	indication	radiotherapy	local control at 5a	OS
Douglas et al	IJROBP 2000	159	ACC	neutron, 19.2 Gy; A: R2; B: R1-2	A: 57%; B: 100%	A: 75%; B: 90%
Huber et al	Radiother Oncol 2001	75	ACC	A: neutrons/ 16 Gy; B: photons/ 64 Gy; C: mixed/ 8 Gy neutrons+ photons 32 Gy	A: 75%; B: 32%; C: 32%	
Mizoe et al	IJROBP 2004	36	various, incl ACC	C12/ 48.6 - 52.8 Gy	50%	
Schulz-Ertner et al	Cancer 2005	29	ACC	C12+IMRT/72 GyE	77.5%/ 4a	75.8%/4a
		34	ACC	IMRT/ 66Gy	24.6%/4a	77.9%/4a
Pommier et al	Arch Otolaryngol Head Neck Surg 2006	23	ACC	protons/ 75.9 GyE	93%	
Stannard et al	Radiother Oncol 2013	335 108	various ACC	neutrons/ 20.4 nGy	60.6%	DSS: 66.8%
Mizoe et al	Radiother Oncol 2012	236 69	various ACC	C12/ 48.6 - 52.8 Gy	73%	68%
Jensen et al	Cancer 2015	58	ACC	C12+IMRT/72 GyE	59.6%	76.5%
Jensen et al	IJROBP 2015	54	ACC	C12+IMRT/ 74 GyE	81.9%/ 3a	78.4%/ 3a
Jensen et al	Radiother Oncol 2015	309	ACC	C12+IMRT	58.5%	74.6%

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

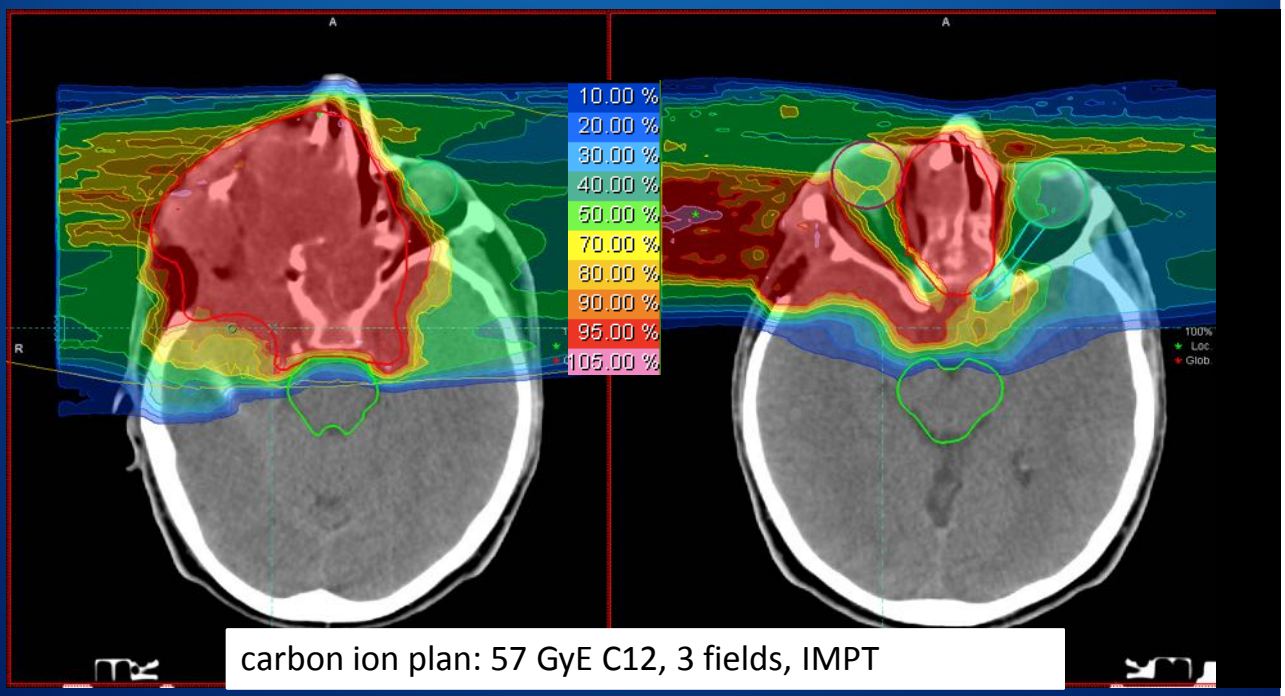
Particle RT: re-irradiation



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

Jensen, PTCOG 2013 & Radiother Oncol 2011

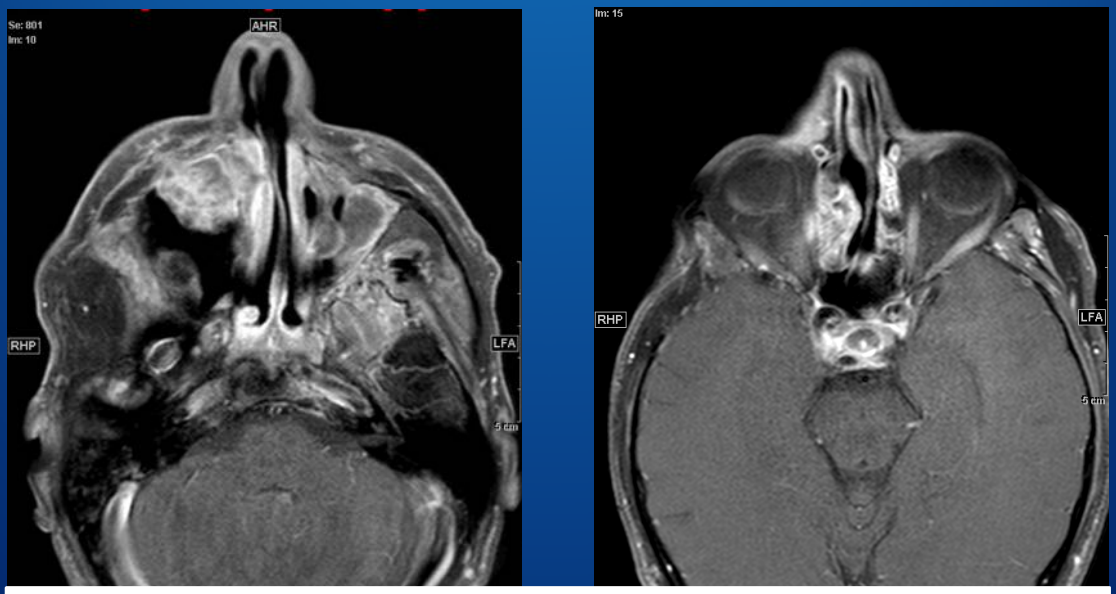
Particle RT: re-irradiation



carbon ion plan: 57 GyE C12, 3 fields, IMPT

Jensen, PTCOG 2013 & Radiother Oncol 2011

Particle RT: re-irradiation

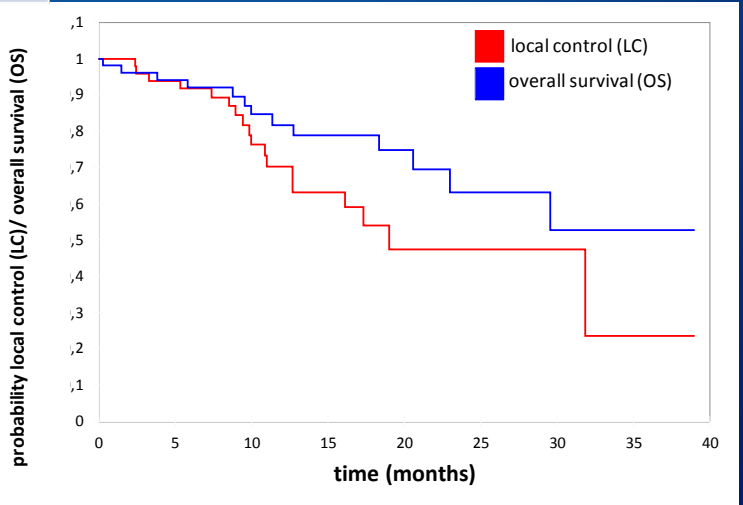


good PR and symptom relief 4 months post re-RT

Jensen et al, PTCOG 2013 & Radiother Oncol 2011

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



Jensen et al, Radiother Oncol 2015

Late toxicity (CTCAE v. 4.03)	Pts	%
Xerostomia °I	4	7.7
Hyperpigmentation °I	2	3.8
Dysphagia °I	3	5.8
Dysphagia °III	*1*	*1.9*
Trismus	6	11.5
CNS necrosis °I	8	15.4
CNS necrosis °III	*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
Tissue necrosis	*2*	*3.8*
ICA haemorrhage (°IV)	*2*	*3.8*
Cranial nerve palsy	1	1.9
Dizziness	1	1.9
Chronic otitis	1	1.9
Symptomatic epilepsy °I	*1*	*1.9*
Dysesthesia	1	1.9
Difficulty in concentration	1	1.9

Jensen, PTCOG 2013 & Radiother Oncol 2015

Particle RT: re-irradiation

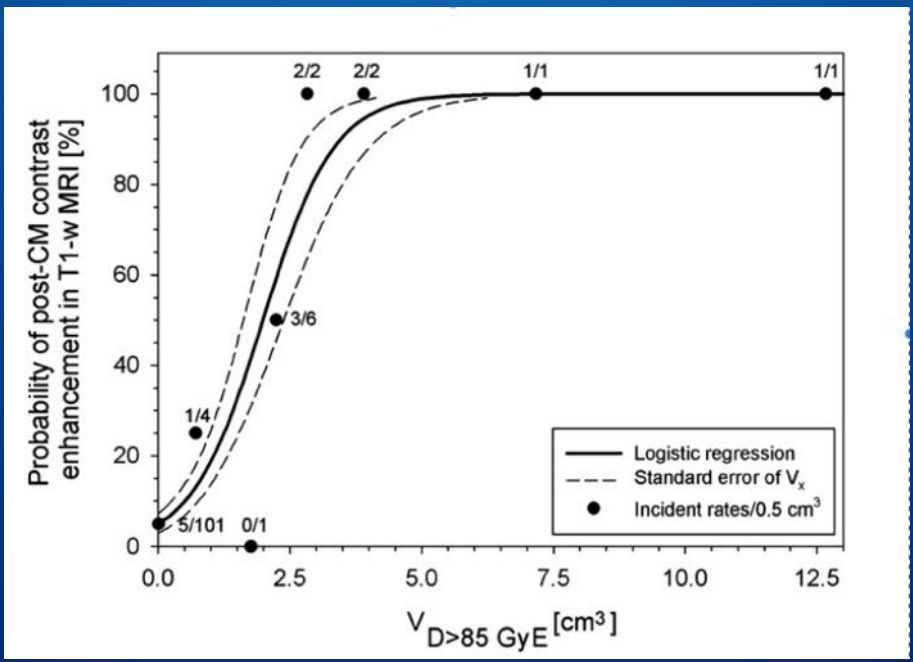
- moderate toxicity
- good treatment response even in heavily pre-treated patients
- good alternative to palliative chemotherapy as local and/ or symptom-oriented measures
- local recurrences still mostly in-field
- role of dose-escalation? use caution!

Jensen et al, Radiother Oncol 2015

Particle RT: bio-optimization

- tumour tissue
- normal tissue

Particle RT: LEM



Schlampp et al, IJROBP 2011

Lessons from large case series

- control/ survival rates in the primary situation
- potential therapy modification: omit surgery in dose escalated treatments?
- control/ survival rates in the recurrent situation
- validation of bio-modelling in the TPS

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 gap

Acknowledgements

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  University of Heidelberg
  Germany