Particle Therapy Experience on Head and Neck Cancers

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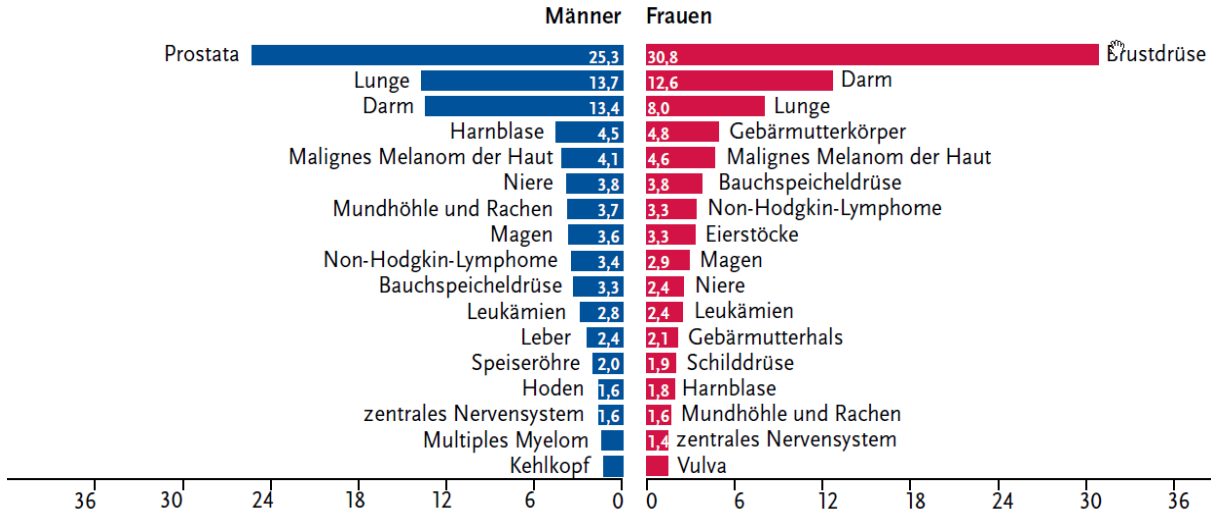
This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008548

Oncological diseases in Germany – Status Quo

- Incidence: ~450.000 new cases per year
- Mortality: ~ 250.000 per year
- ~55% of patients are cured
- Of which ~75-90% through local measures
- ~ 60% of patients receive radiotherapy



RKI Krebs in Deutschland für 2015/2016

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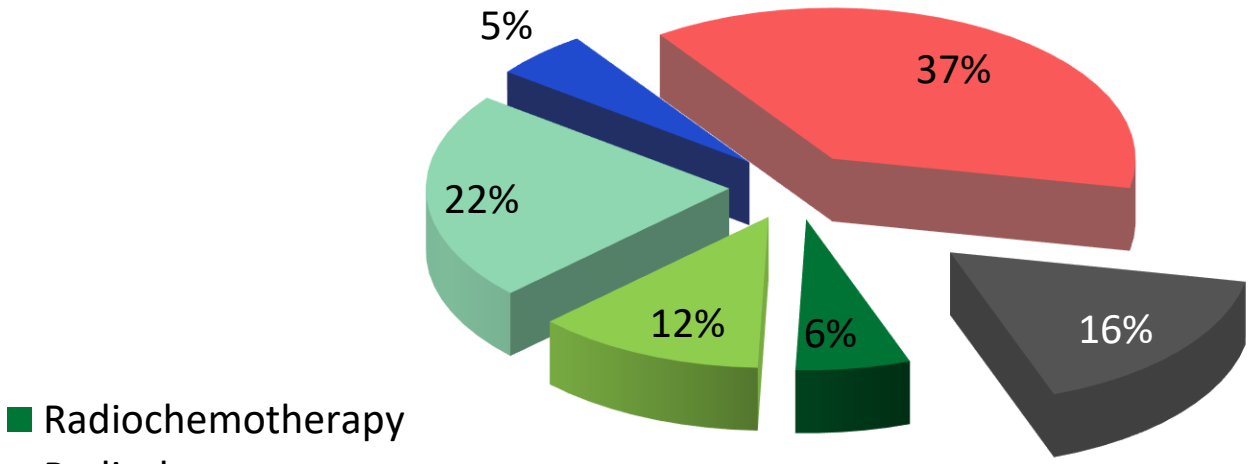
Oncological diseases in Germany – Status Quo



- ~16% of all tumor patients die from locally uncontrollable progression without evidence of distant metastases
- Benefit of local therapy escalation
- Potential for particle therapy

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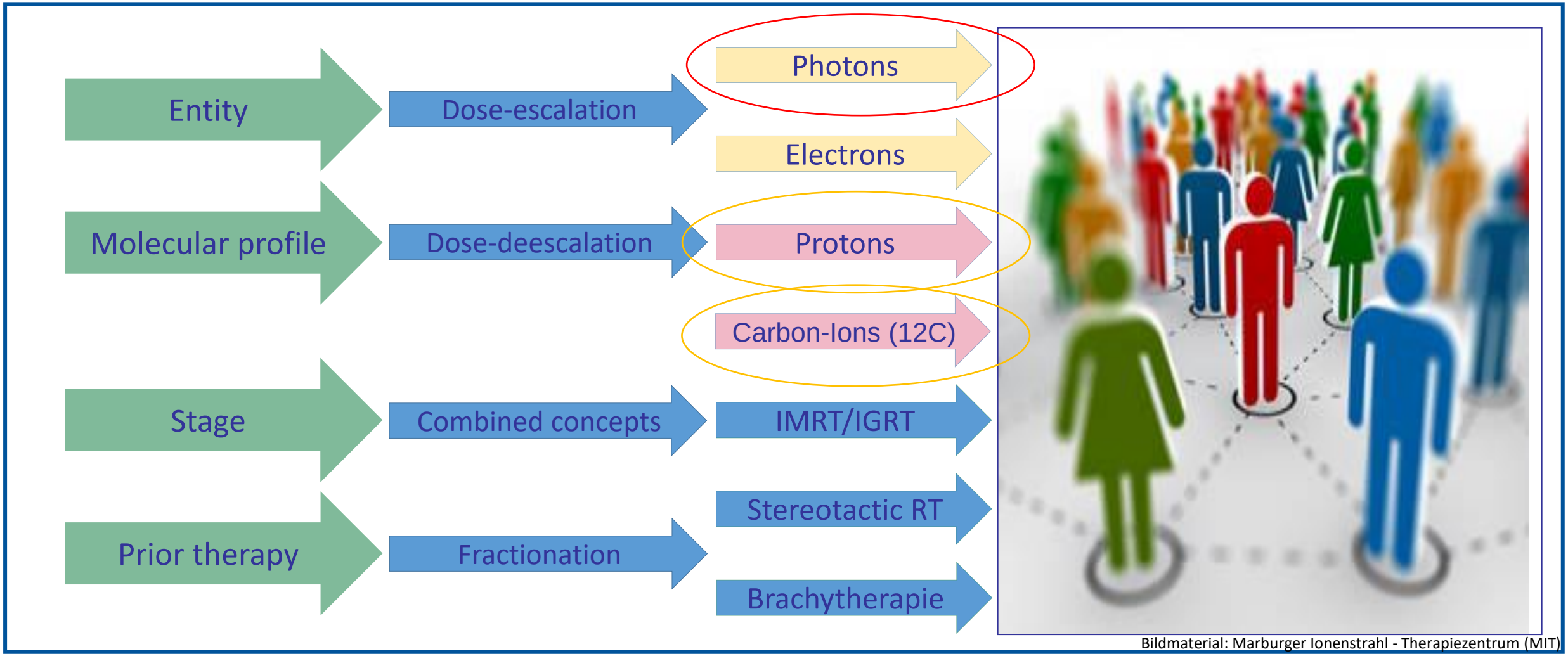
Radiotherapy for H&N tumors – Individual therapy planning



Bildmaterial: Marburger Ionenstrahl - Therapiezentrum (MIT)

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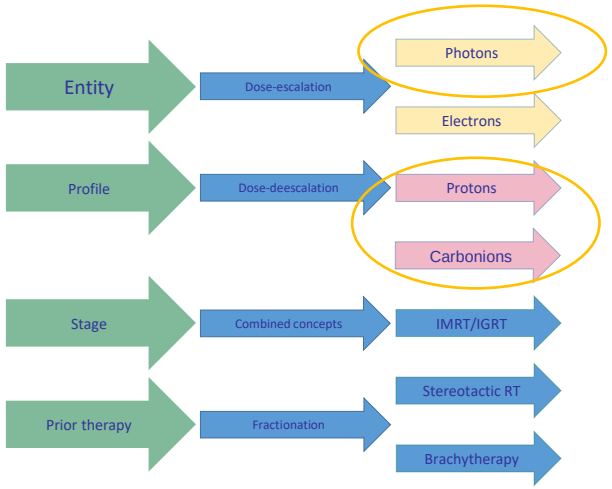
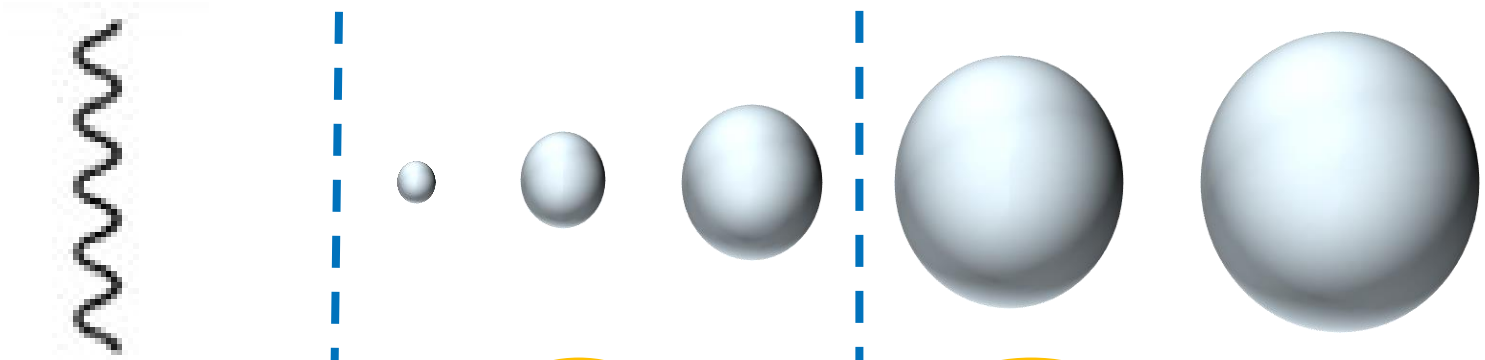
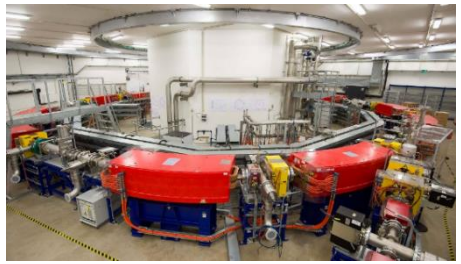
Radiotherapy for H&N tumors – Types of radiation



Types of radiation (radiation qualities)

Conventional RT | **Particle therapy**





Heavy Ions

Bildmaterial: Marburger Ionenstrahl - Therapiezentrum (MIT)

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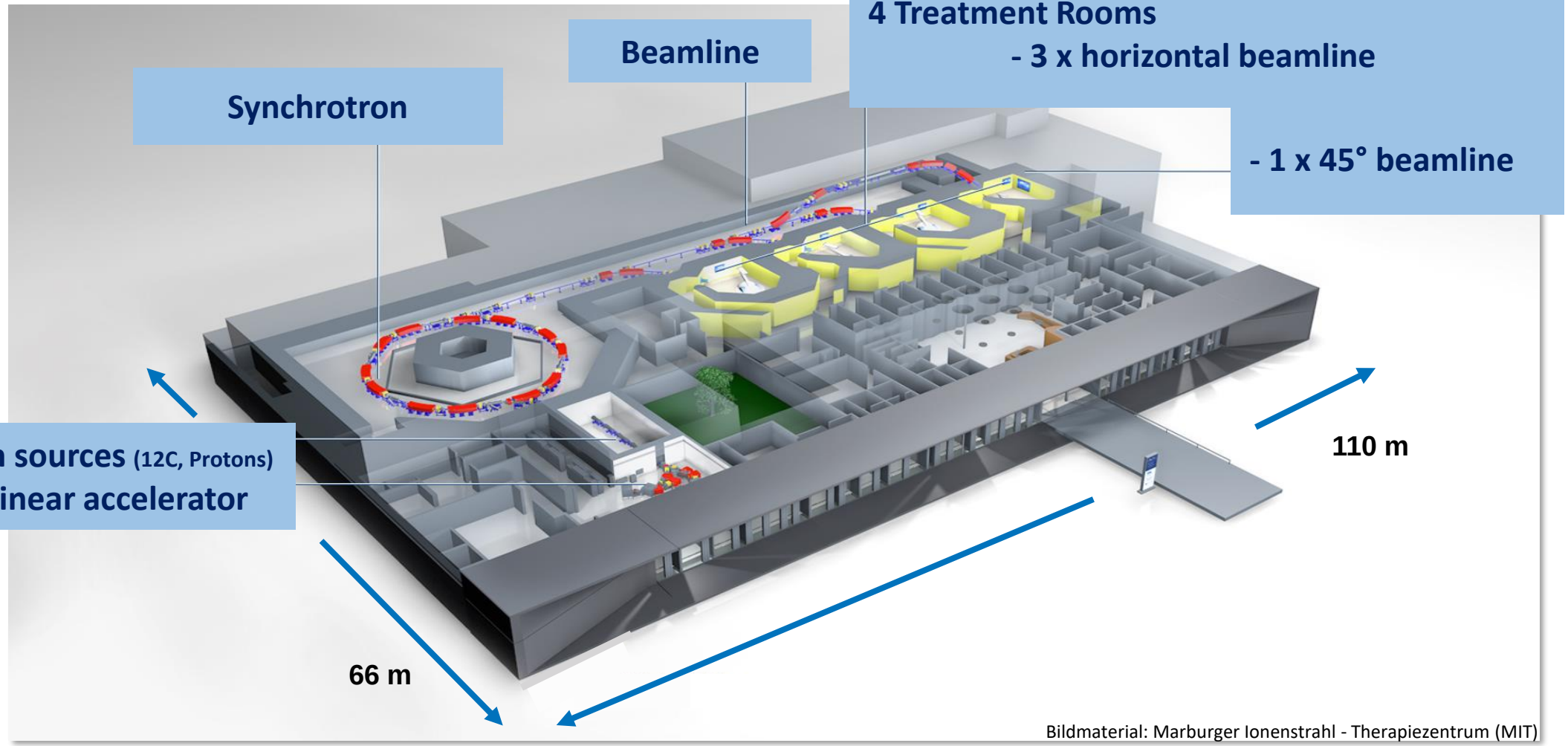
Radiotherapy for H&N tumors – Technical setup MIT



Bildmaterial: Marburger Ionenstrahl - Therapiezentrum (MIT)

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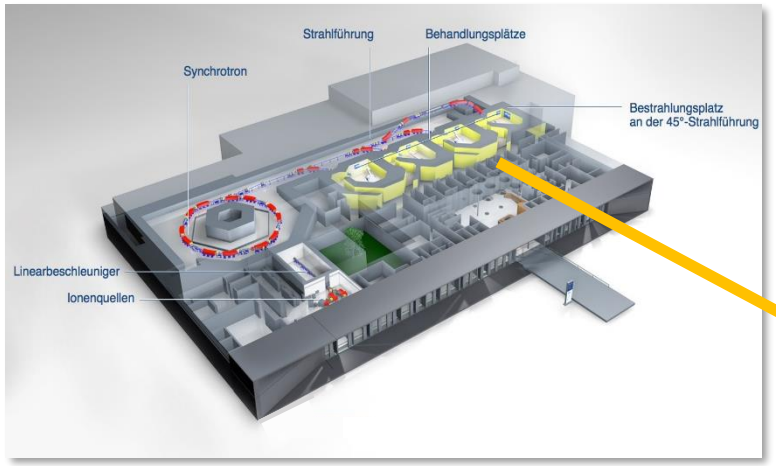
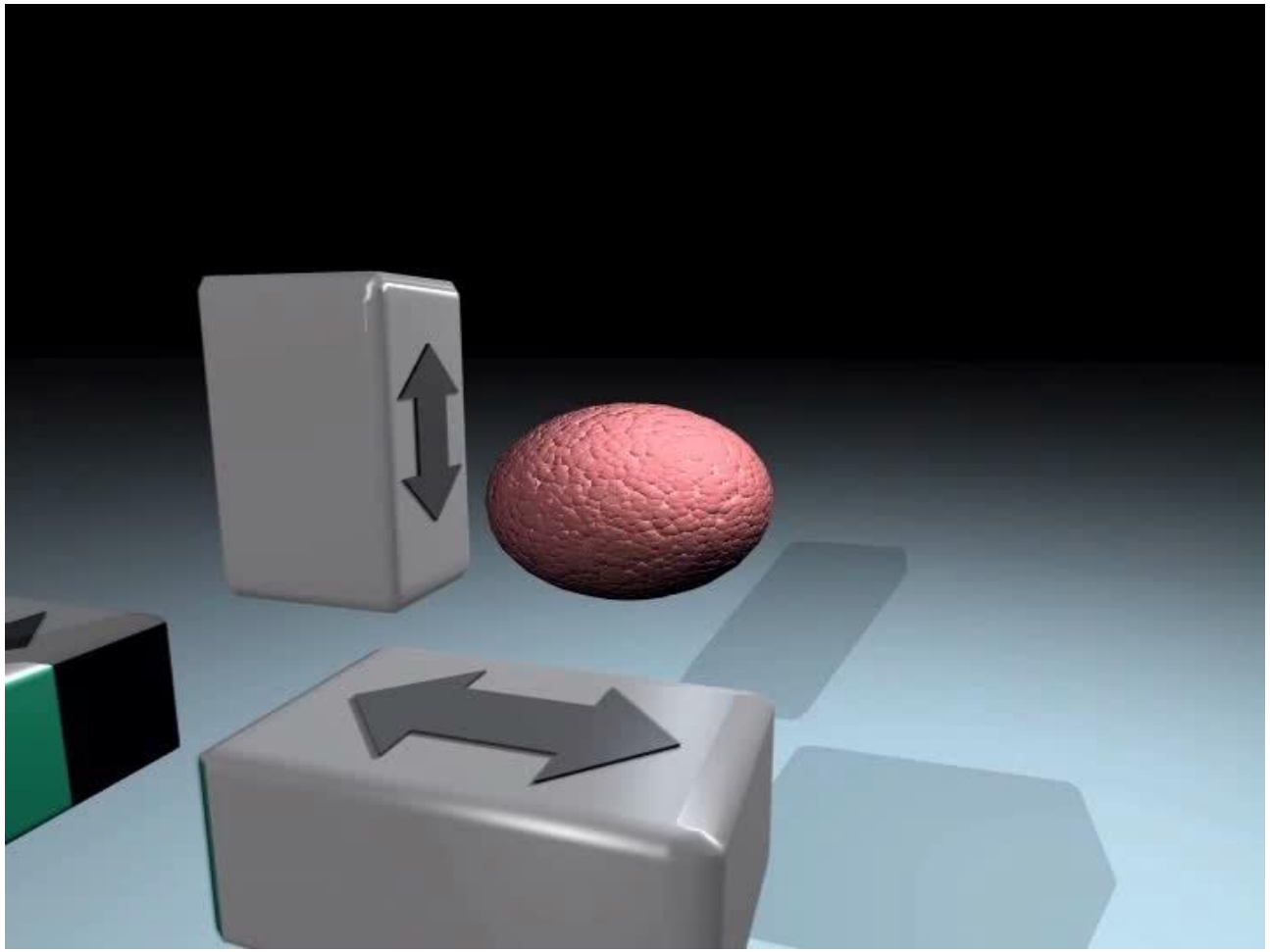
Radiotherapy for H&N tumors – Technical setup MIT / active Rasterscanning



- Active beam guidance
- Scanning of energy layers



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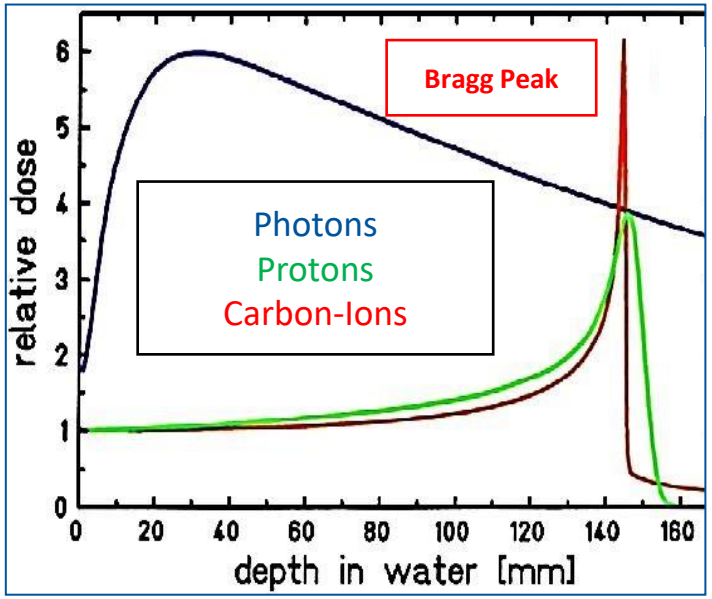
Radiotherapy for H&N tumors – physical aspects / advantage

Depth-dose-profile

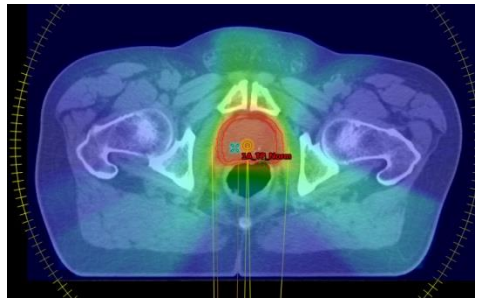


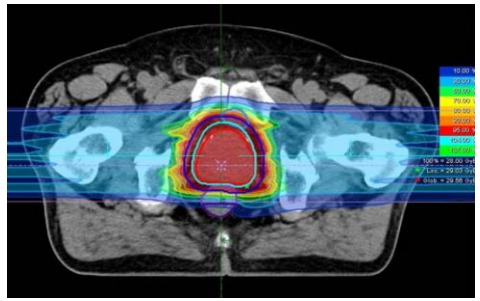
Treatment with

Photons

Protons

Dose distribution (prostate RT)





12C / protons

- high conformity
- steep dose falloff
- low integral dose

Pugh et al. 2014

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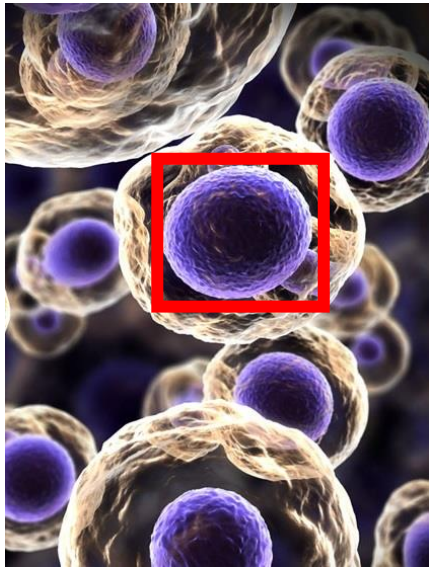
Radiotherapy for H&N tumors – biological aspects / advantage

Cells

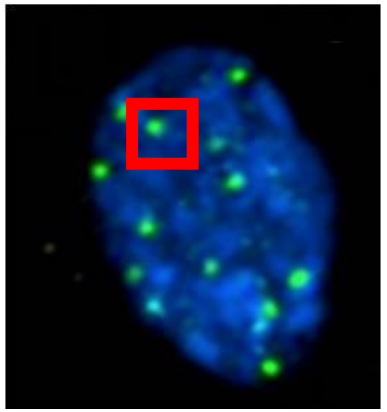


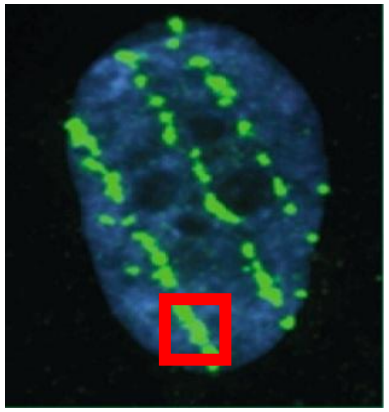
treatment with

Photons

Carbon-Ions

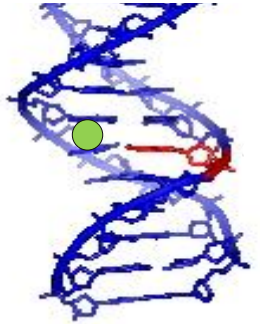
cell nucleus with DNA-damage (green)

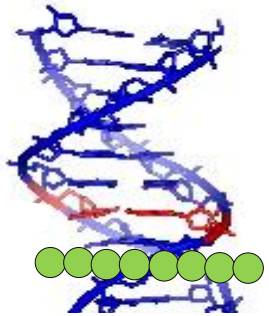




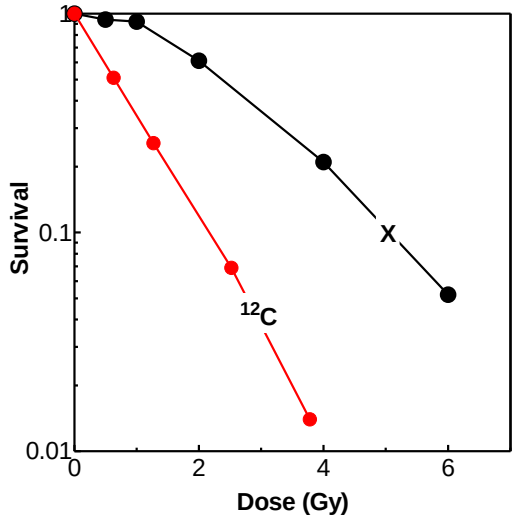
DNA-damage pattern

simple





complex



Carbon-Ions

- high damage density
- complex damage
- increased cell death

Averbeck et al. 2014

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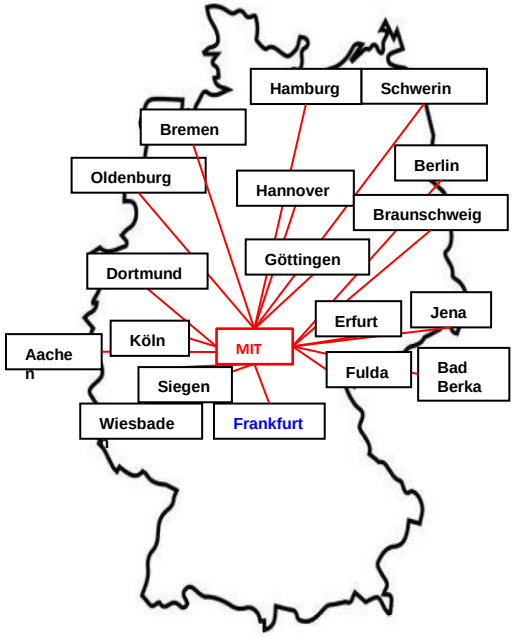
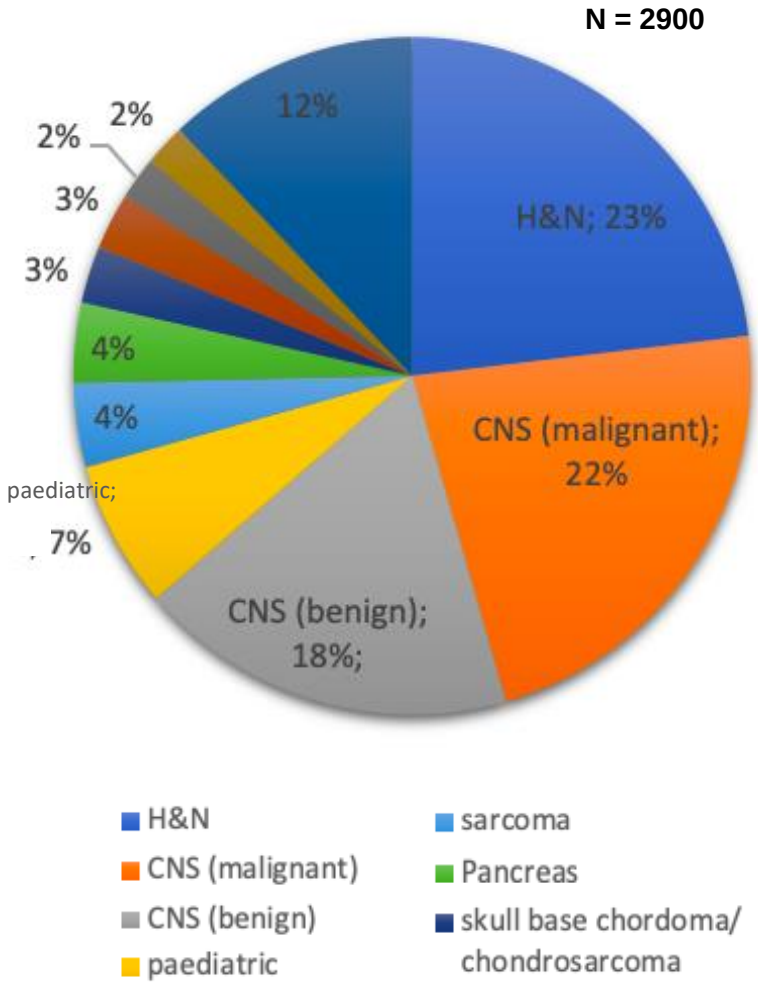
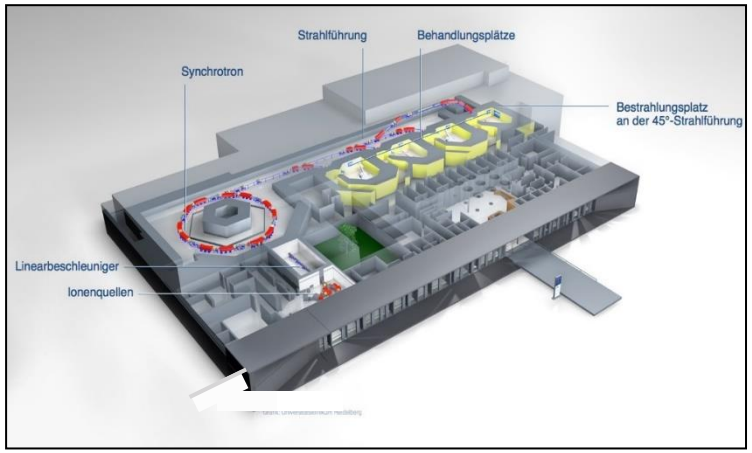
Radiotherapy for H&N tumors – treated patient population

- 4 particle therapy centers in Germany
- 2 centers with carbon ions in Germany







Bildmaterial: Marburger Ionenstrahl - Therapiezentrum (MIT)

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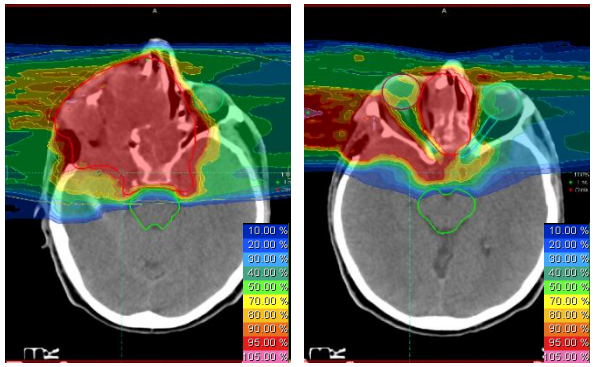
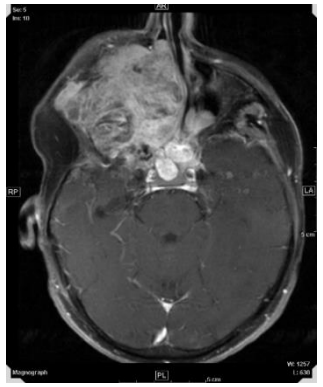
Radiotherapy for H&N tumors – Clinical considerations / indications

- Radioresistant tumors
- Hypoxic tumors
- Pre-irradiated tumors
- Locally advanced tumors
- Critical localization





Adenoidcystic Carcinoma (ACC)

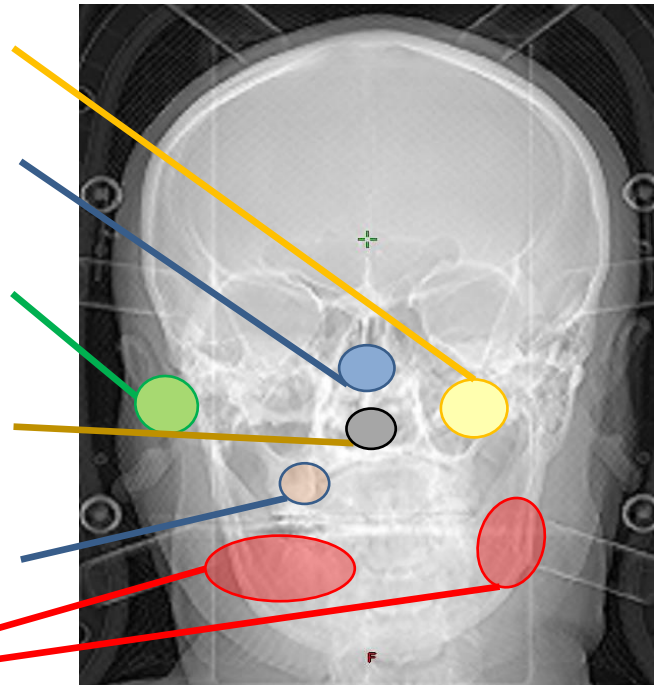
Advanced H&N malignancies

Salivary Gland- / Salivary Duct malignancies

Nasal vestibule malignancies

Sinunasal malignancies /

Recurrent / pre-irradiated disease



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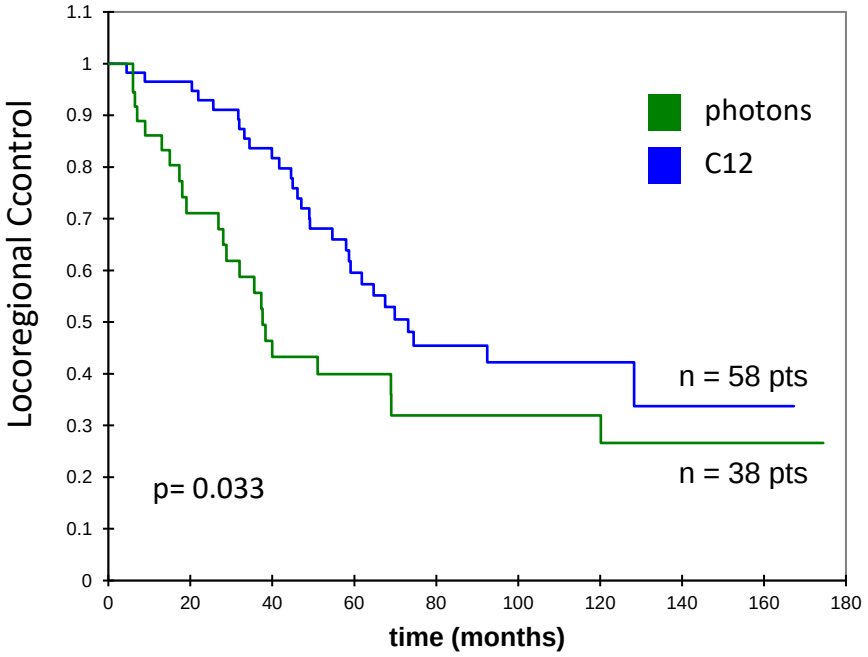
Radiotherapy for H&N tumors – Adenoidcystic Carcinoma (ACC)

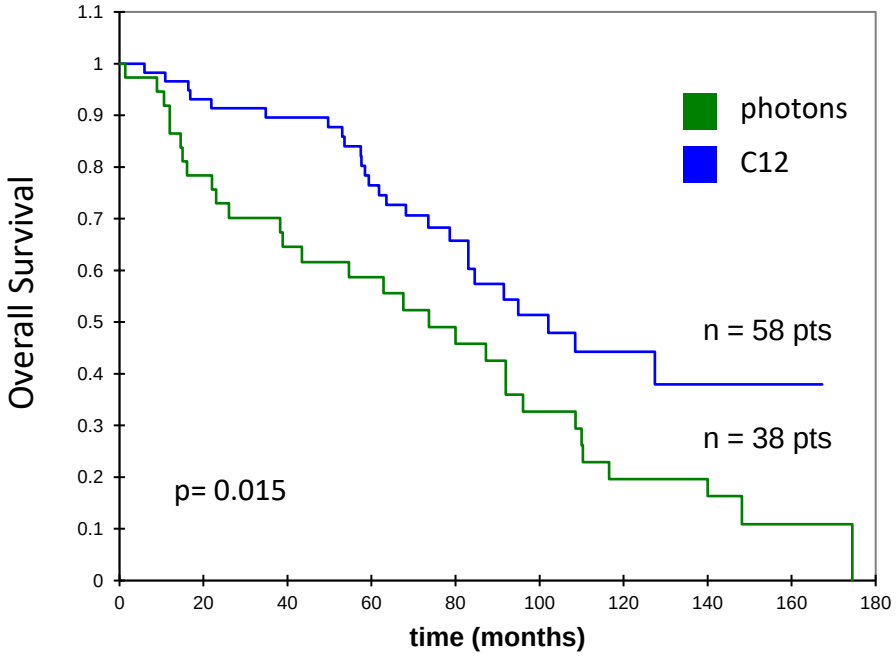
Cancer

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[1]; Anna V. Nikoghosyan, MD[1]; Melanie Poulakis, DDS[1]; Angelika Höss, MSc[2]; Thomas Haberer, PhD[3]; Oliver Jäkel, PhD[3]; Marc W. Münter, MD[1]; Daniela Schulz-Ertner, MD[1]; Peter E. Huber, MD, PhD[4]; and Jürgen Debus, MD, PhD[1]

- 96 patients with ACCs
- Carbon ions vs photons
- 3y-LC: 84% vs. 56%
- 3y-OS: 89% vs. 70%
- Comparable toxicity rates





Jensen et al., J Rad Oncol, 2014
Jensen et al., Cancer , 2015
Jensen et al., J Rad Oncol, 2015

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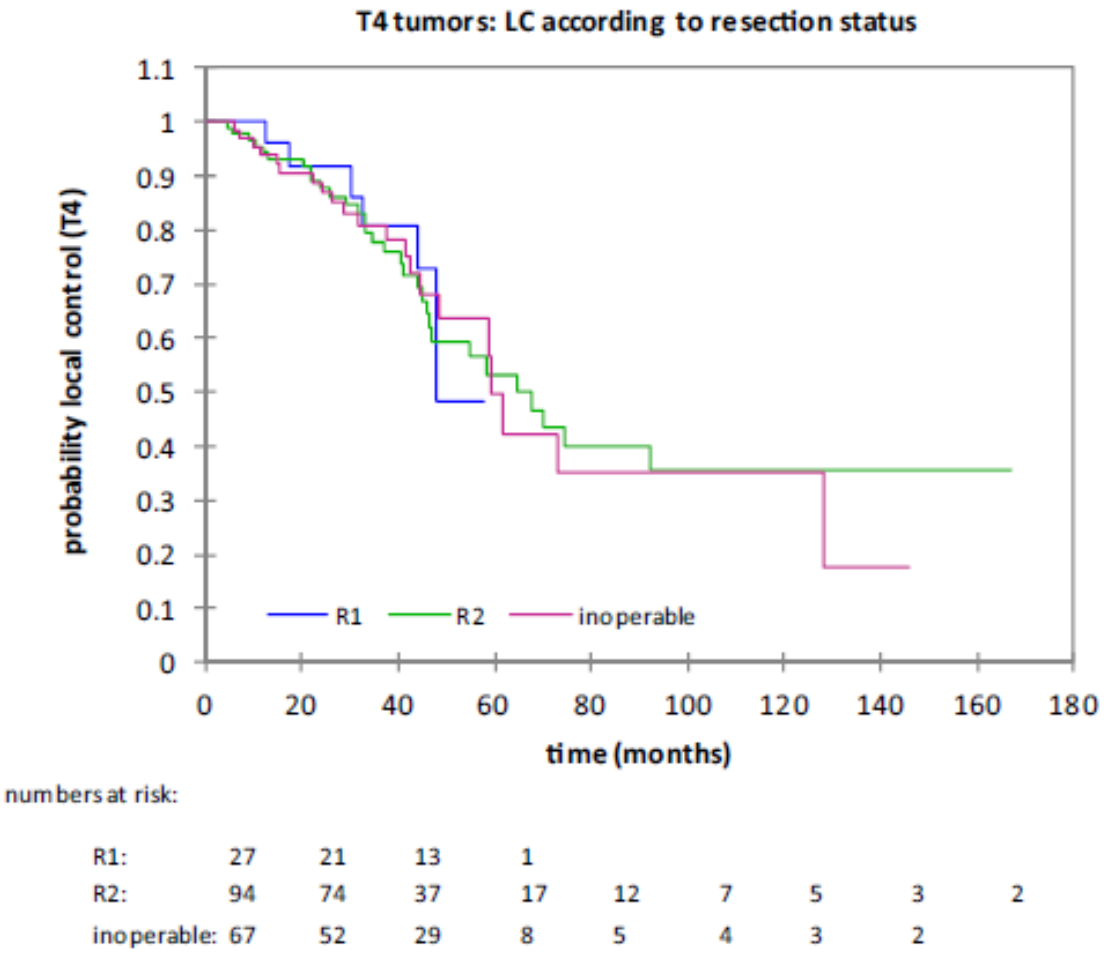
Radiotherapy for H&N tumors – Adenoidcystic Carcinoma (ACC)



Particle therapy in head and neck cancer

High-LET radiotherapy for adenoid cystic carcinoma of the head and neck: 15 years' experience with raster-scanned carbon ion therapy

Alexandra D. Jensen [a,*], Melanie Poulakis [a], Anna V. Nikoghosyan [a], Thomas Welzel [a], Matthias Uhl [a], Philippe A. Federspil [b], Kolja Freier [c], Jürgen Krauss [d], Angelika Höss [e], Thomas Haberer [f], Oliver Jäkel [f], Marc W. Münter [a], Daniela Schulz-Ertner [a], Peter E. Huber [g], Jürgen Debus [a]

[a] Dept of Radiation Oncology, University of Heidelberg; [b] Dept of Otorhinolaryngology, University of Heidelberg; [c] Dept of Dental and Oro-maxillofacial Surgery, University of Heidelberg; [d] Dept of Medical Oncology, National Center for Tumor Disease (NCT), Heidelberg; [e] Medical Informatics and Regulatory Affairs, Heidelberg Ion Beam Therapy Centre; [f] Heidelberg Ion Beam Therapy Centre; and [g] Molecular Radiation Oncology (E055), German Cancer Research Centre (DKFZ), Heidelberg, Germany

- 188 Patienten mit ACCs
- 67 Pat nur Biopsie
- 94 Pat mit R2 Resektion
- 27 Pat mit R1 Resektion

- 3y-LC:

  R1: 89%

  R2: 80%

  Biopsie: 81%

Jensen et al., RO, 2016

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

Radiotherapy for H&N tumors – Adenoidcystic Carcinoma (ACC)

- ACCs – Locoregional control after local therapy (particles vs. photons)

	3J	4J	5J
IMRT (Jensen et al. 2015)	56%	43%	40%
Neutrons (Huber et al., 2001)	75%	75%	75%
12C (Mizoe et al., 2004)	75%	65%	60%
12C (Ikawa et al., 2017)	89%	82%	69%
IMRT + 12C (Jensen et al. 2015)	84%	70%	60%

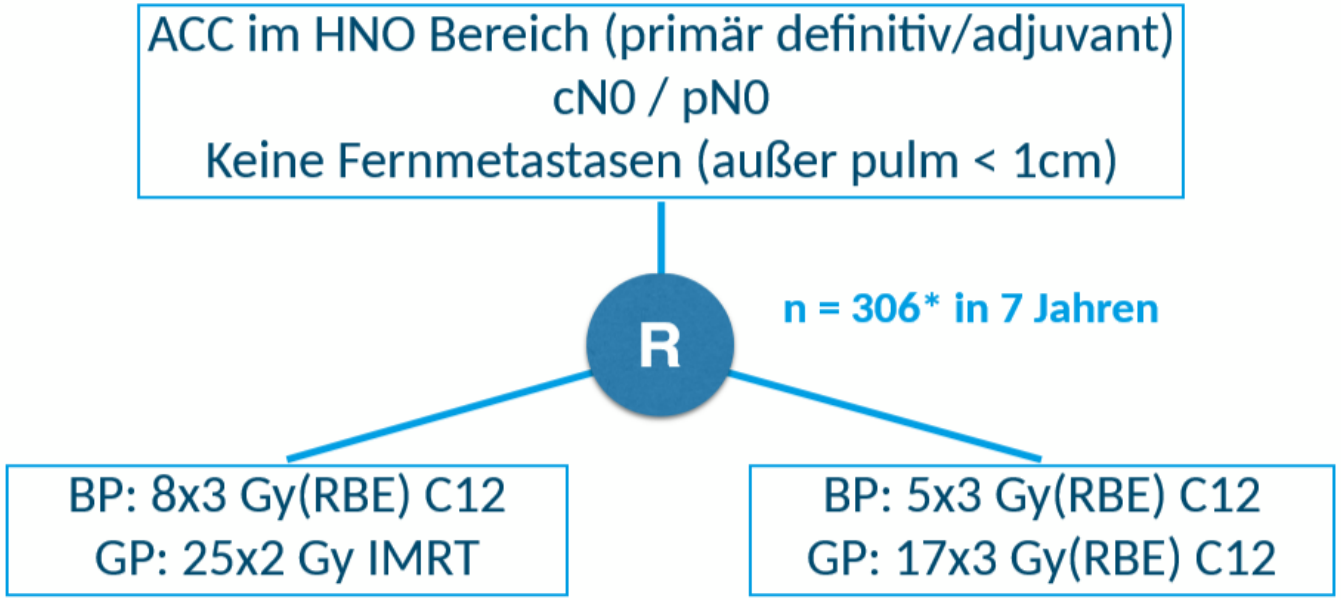
- Patients with ACCs benefit from the use of carbon ions (LC / OS)

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

Radiotherapy for H&N tumors – Adenoidcystic Carcinoma (ACC)

Clinical randomized Phase-II-Trial

Adenoid **C**ystic carcinoma **C**arbon **O**nly (*ACCO*-Trial)



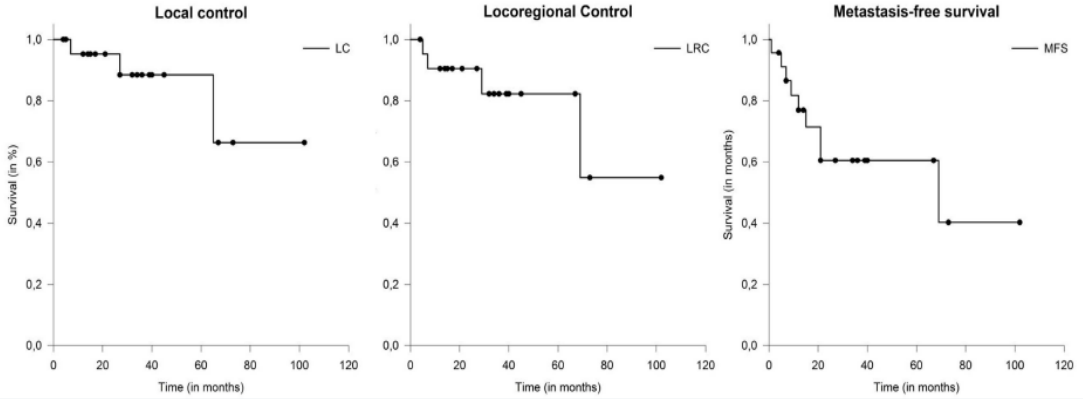
Lang et al., BMC Cancer , 2021

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

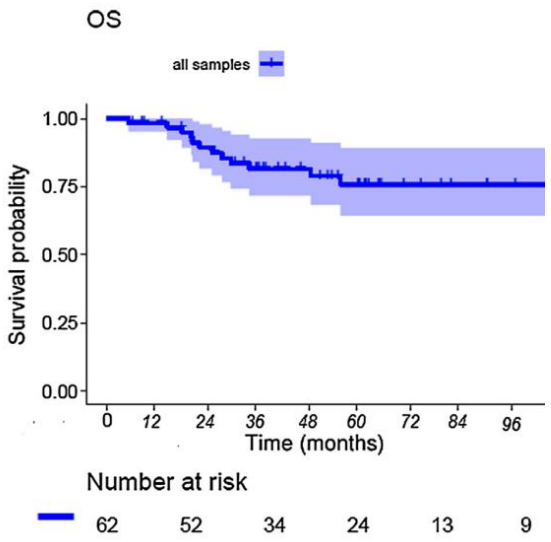
Radiotherapy for H&N tumors – Salivary duct / salivary gland malignacies

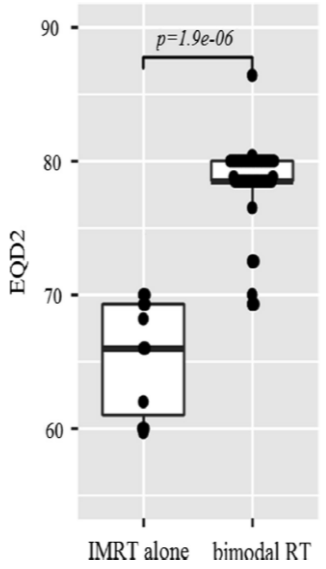
Intensity Modulated Radiotherapy (IMRT) With Carbon Ion Boost in the Multimodal Treatment of Salivary Duct Carcinoma

Sebastian Adeberg[1,2,3,4], Paul Windisch[1], Felix Ehret[1], Melissa Baur[1], Sati Akbaba[1,2], Thomas Held[1,2], Denise Bernhardt[1,2], Matthias F. Haefner[1,2], Juergen Krauss[5], Steffen Kargus[6], Christian Freudlsperger[6], Peter Plinkert[7], Christa Flechtenmacher[8], Klaus Herfarth[1,2,4], Juergen Debus[1,2,3,4,5] and Stefan Rieken[1,2,4]*



- 28 patients with salivary duct malignancies
- Def./adj. RT
- 2y-LC: 96% & 2y-LRC: 93%
- 2y-DMFS: 27m
- Toxicity ° III: 16% acute





The impact of age on the outcome of patients treated with radiotherapy for mucoepidermoid carcinoma (MEC) of the salivary glands in the head and neck: A 15-year single-center experience

Sati Akbaba[a,b,c,d,*,1], Astrid Heusel[a,b,1], Andreas Mock[e,f,g], Thomas Held[a,b,c,d], Kristin Lang[a,b,c,d], Juliane Hoerner-Rieber[a,b,c,d,h], Tobias Forster[a,b,c], Sonja Katayama[a,b,c], Steffen Kargus[i], Stefan Rieken[a,b,c,d,h], Peter Plinkert[j], Klaus Herfarth[a,b,c,d,h], Juergen Debus[a,b,c,d,g,h], Sebastian Adeberg[a,b,c,d]

- 62 patients with mucoepidermoid carcinoma
- 85% adj. RT , 15% def. RT
- 5y-LC: 84% & 5y-LRC: 80%
- 5y-DFS: 75% & 5y-OS: 89%
- Toxicity: no ° IV-V, grade III: 15% acute & 13% late

Adeberg et al., RO, 2016
Akbaba et al., Oral Oncol, 2019

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

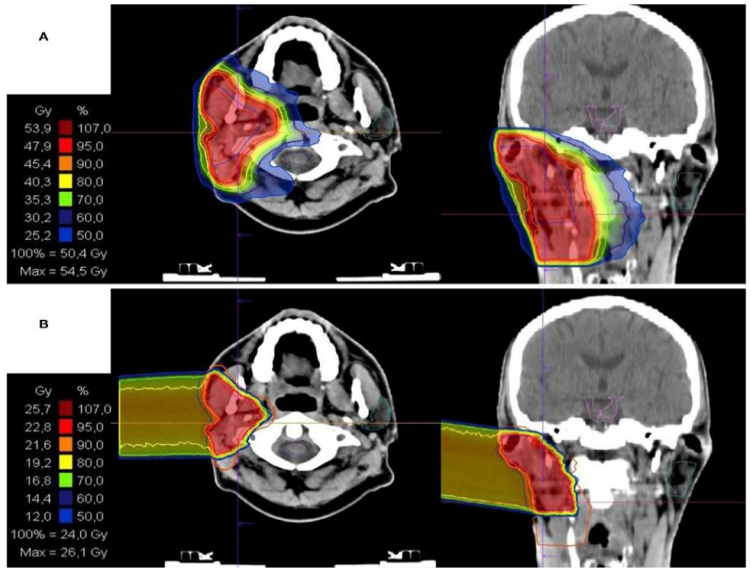
Radiotherapy for H&N tumors – H&N Adenocarcinoma

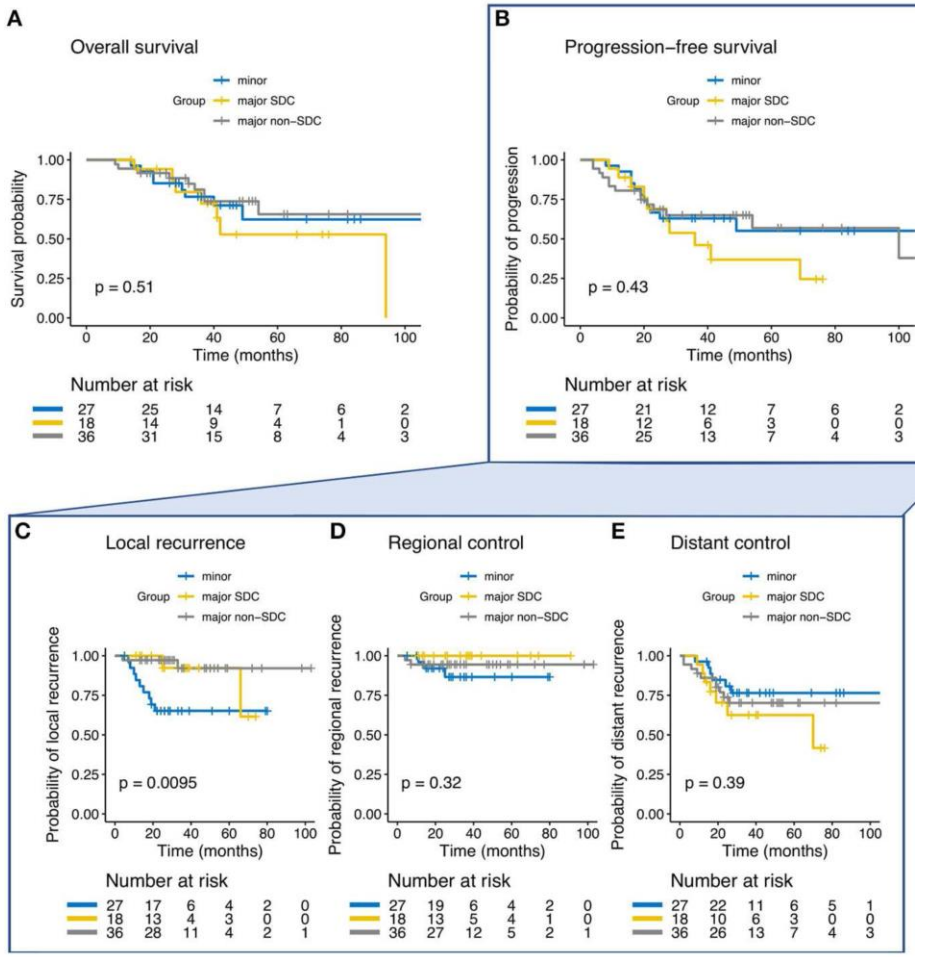
Treatment Outcome of a Combined Dose-Escalated Treatment Regime With Helical TomoTherapy® and Active Raster-Scanning Carbon Ion Boost for Adenocarcinomas of the Head and Neck

*Sati Akbaba [1,2,3,4], Andreas Mock [5,6], Juliane Hoerner-Rieber [1,2,3,4,7], Thomas Held [1,2,3,4], Sonja Katayama [1,2,3,4], Tobias Forster [1,2,3,4], Christian Freudlsperger [8], Stefan Rieken [1,2,3,4], Klaus Herfarth [1,2,3,4,5], Peter Plinkert [9], Juergen Debus [1,2,3,4,5] and Sebastian Adeberg [1,2,3,4]**

- 81 patients with H&N Adeno-Ca
- ~50% macroscopic tumor
- 3y-LC: 83% & 5y-LC: 75%
- 3y-PFS: 60% & 5y-PFS: 50%
- Toxicity: keine ° IV-V

  ≥° 3: 21% acute & 25% late





Akbaba et al., Oral Oncol, 2019

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

Radiotherapy for H&N tumors – Mucosal melanoma

Raster-scanned intensity-controlled carbon ion therapy for mucosal melanoma of the paranasal sinus

Angela Mohr, MD,[1] Naved Chaudhri, PhD,[2] Jessica C. Hassel, MD,[3] Philippe A. Federspil, PhD,[4] Valentina Vanoni, MD,[1] Jürgen Debus, MD, PhD,[1] Alexandra D. Jensen, MSc, PhD,[1]*

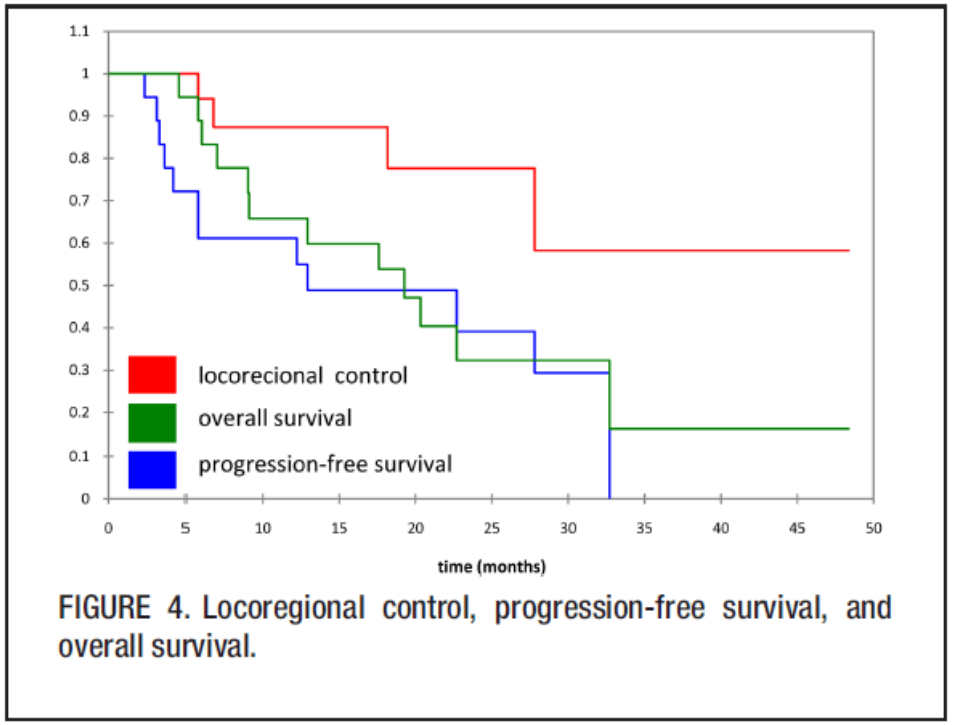
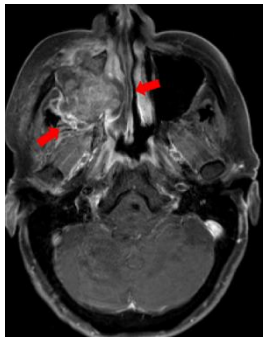
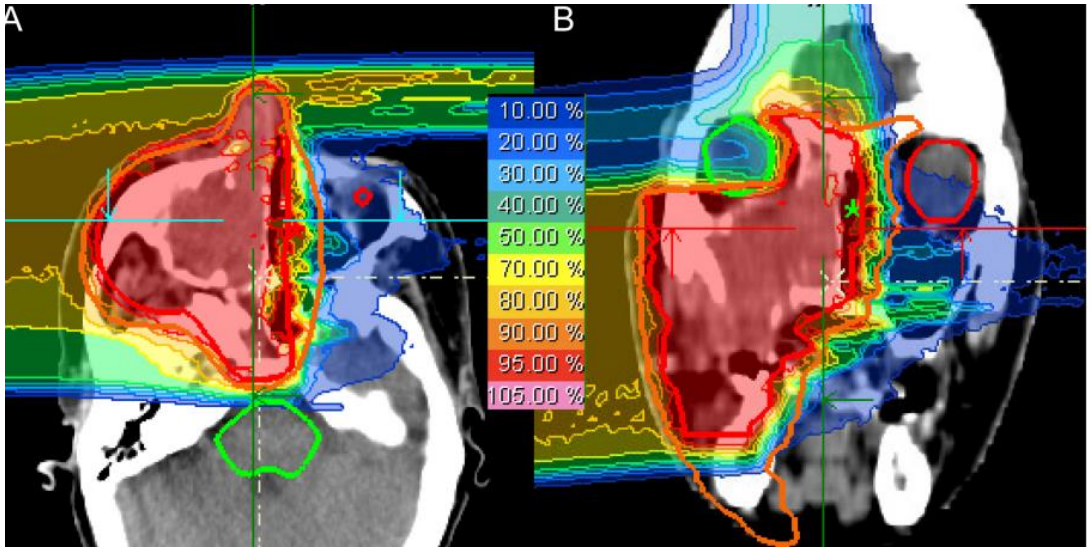


FIGURE 4. Locoregional control, progression-free survival, and overall survival.

- 28 patients with mucosal melanoma of the paranasal sinus
- 94% T4 tumors
- 2y-LC: 81%
- 2y-OS: 34%
- Toxicity: no ° IV-V
  - ≥° 3: 28% acute & 18% late





Mohr et al., Head and neck, 2016

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

Radiotherapy for H&N tumors – Malignancies of the Nasal Vestibule

frontiers in Oncology

Carbon Ion Beam Boost Irradiation in Malignant Tumors of the Nasal Vestibule and the Anterior Nasal Cavity as an Organ-Preserving Therapy

- Standard treatment is resection +/- radiochemotherapy
- Even in early tumor stages, organ-preserving resection is often not possible
- Nasal ablation as a mutilating therapeutic procedure
- Radio(chemo)therapy with C12 boost as an organ-preserving therapeutic approach

Eberle et al., Front Oncol, 2022
Bildmaterial Klinik für HNO UKGM GI

HITRI Heavy Ion Therapy Research Integration

MIT Marburger Ionenstrahl-Therapiezentrum

Philipps Universität Marburg

UKGM

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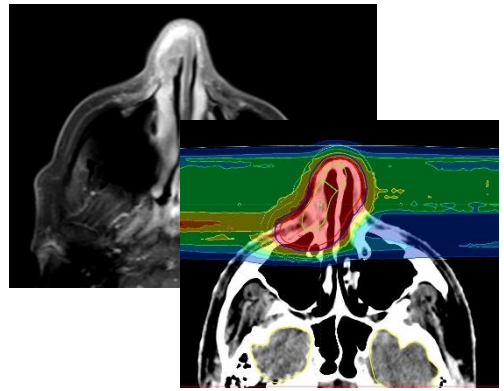
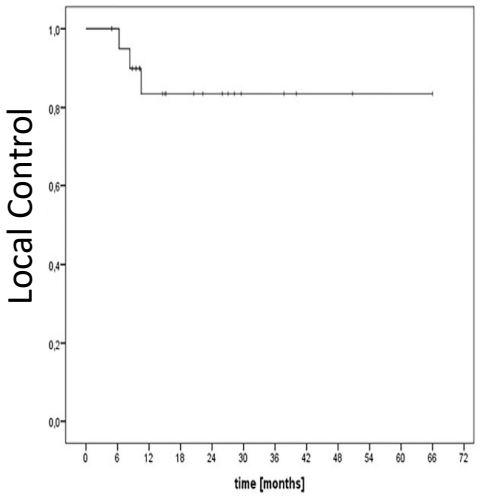
Radiotherapy for H&N tumors – Malignancies of the Nasal Vestibule

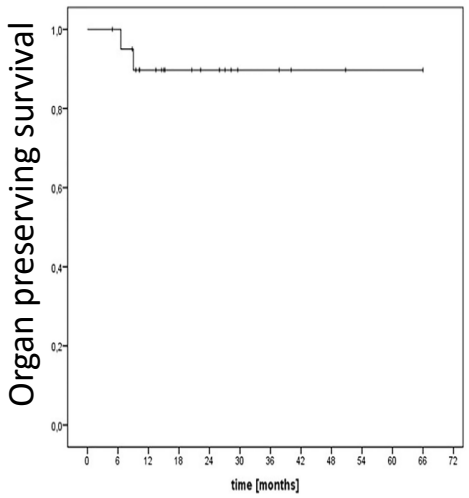
frontiers in Oncology

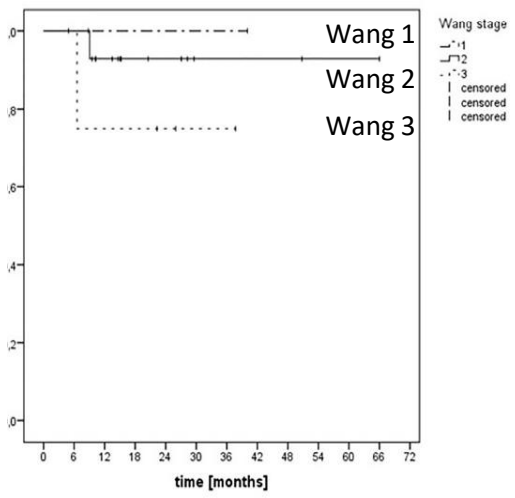
Carbon Ion Beam Boost Irradiation in Malignant Tumors of the Nasal Vestibule and the Anterior Nasal Cavity as an Organ-Preserving Therapy

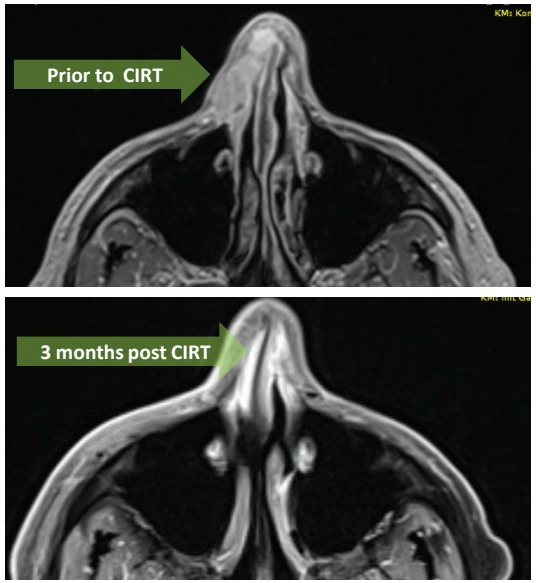
- 21 Patienten with malignancies of the nasal vestibule
- 2y-LC: 84%
- 2y-OPS: 90%
- Wang 3 2y-OPS: 75%
- Toxicity: no ° IV-V / ≥° 3: 60% acute & 14% late











Eberle et al., Front Oncol, 2022

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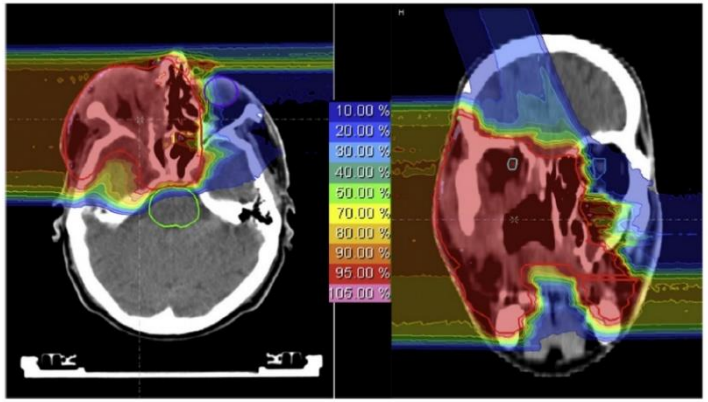
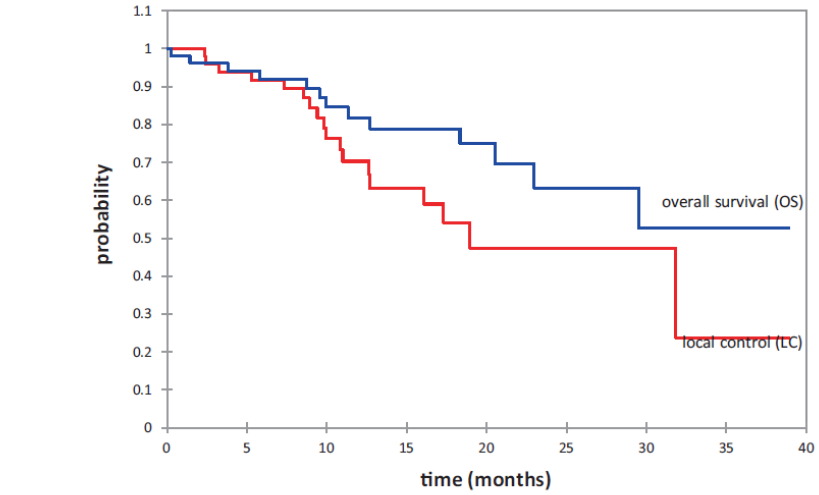
Radiotherapy for H&N tumors – Recurrent disease / pre-irradiated tumors (ACC)

- 52 patients with ACC recurrence
- 86% definitive re-RT with 12C
- Interval to pre-RT: median 61 months

- 70% of recurrences in SB, NNH, orbit
- 80% of patients with T4 tumors
- Median CTV volume ~100ml

- RT dose median 51Gy(RBE), ED 3Gy(RBE)
- Cumulative total dose EQD2 median 128Gy(RBE)

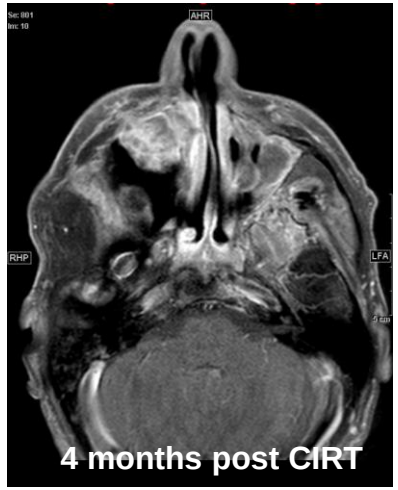




numbers at risk:

OS:	52	47	35	24	17	9	6	4
LC:	52	46	28	17	8	4	4	2

- 1y-LC: 70.3%
- 1y-OS: 81.8%
- No acute Toxicity >°3
- Moderate Late Toxicity (≥°III ~6%)
- Necrosis and bleeding in 2 patients (~3.8% (BED 150/180GyRBE)
- No °V Toxicity



Jensen et al., RO, 2015

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Radiotherapy for H&N tumors – Recurrent disease / pre-irradiated tumors (non ACC + ACC)

Carbon Ion Reirradiation for Recurrent Head and Neck Cancer: A Single-Institutional Experience

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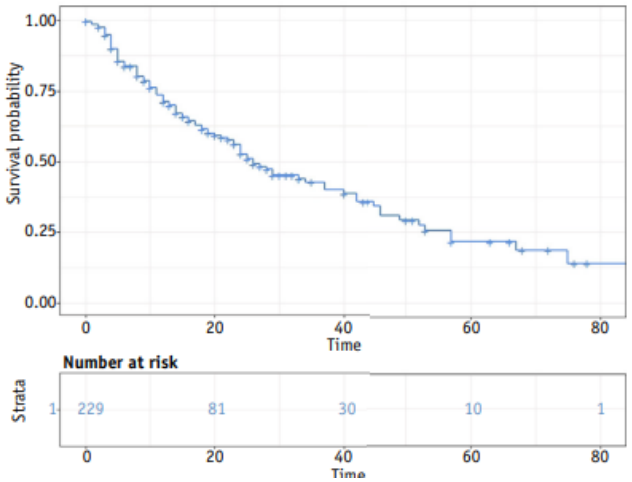
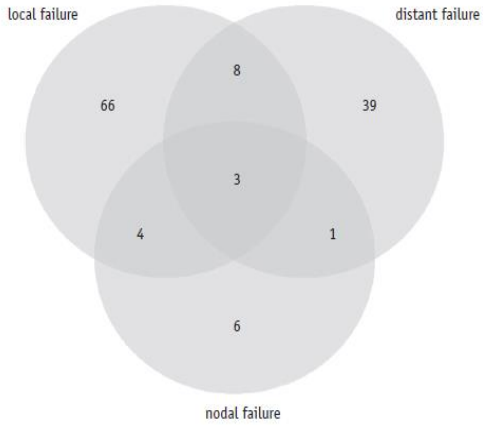
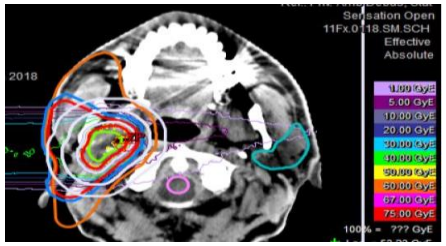
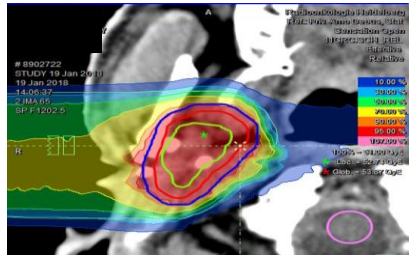
Kristin Lang, MD,*,†,‡ Rami El Shafie, MD,*,†,‡
Denise Bernhardt, MD,*,†,‡ Peter Plinkert, MD,§ Steffen Kargus, MD,‖
Stefan Rieken, MD,*,†,‡,¶,#,** Klaus Herfarth, MD,*,†,‡,¶,#,**
Jürgen Debus, MD, PhD,*,†,‡,¶,#,**
and Sebastian Adeberg, MD*,†,‡,¶,#,**

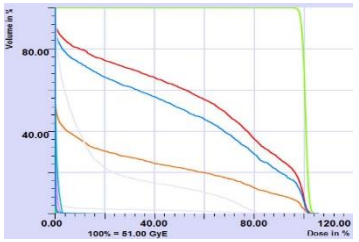




- 229 patients with H&N recurrences
- 54%: ACC, 26% SCC, 8% Adeno-Ca
- Interval to pre-RT: median 4 years
- Re-RT: 51Gy(RBE), ED 3Gy(RBE)
- 1y-LC: 65%, mLC: 24.2m
- 1y-OS: 72%, mOS: 26.1m
- Moderate Toxicity:
  - acute: ° IV = 3.2%
    ° III = 3.0%
  - late: ≥ ° III = 14.5%







Held et al., IJROBP, 2019

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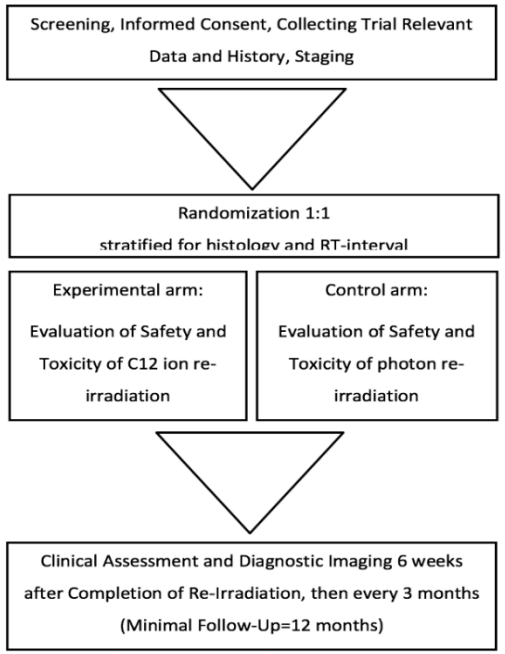
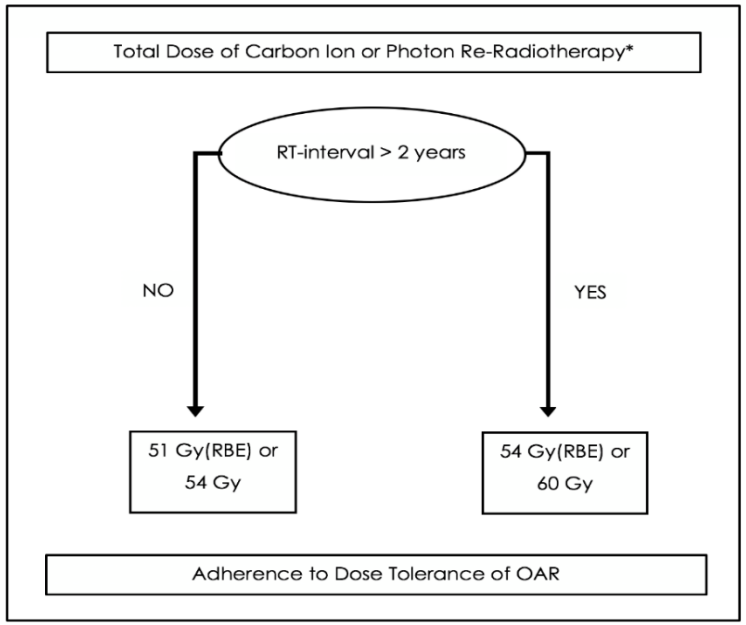
Clinical randomized Phase-II-Trial

Carbon Ion **Re**-Radiotherapy for Recurrent Locally Advanced Head-and-Neck Cancer (*CARE*-Trial)





* Individual dose prescription can differ (max. 60 Gy or Gy(RBE)) and will be at the discretion of the treating radiation oncologist

Held et al., RO, 2020

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Radiotherapy for H&N tumors – Summary

- The treatment of patients with head H&N malignancies continues to represent an interdisciplinary challenge
- The optimal treatment sequence must be coordinated between surgeons, radiotherapy and oncology
- Radio(chemo)therapy is an important component of treatment
- The optimal treatment technique is selected on a patient-specific basis

- Adenoid cystic carcinomas and recurrences of adenoid cystic carcinomas are considered proven indications for particle therapy
- Possible advantages of particle therapy: salivary gland-, sinunasal malignancies, mucosal melanoma, locally advanced tumors, recurrences

- Prospective, randomized data largely not available
- Patient treatment in clinical trials required

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