Head and Neck:
Impact of New Clinical Approaches
AERO in Noordwijk, February 8th 2020

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Agenda

- Latest particle results
- Re-irradiation in head and neck cancers
- Reduced RT-volumes
- Individualized approaches to reduce toxicities
- Immunotherapy
- Future perspectives

escalation

De-escalation
Radiation Oncology in Heidelberg

- ca. 4000 patients/year; 300 patients/day photons
- 6 Linacs – University Hospital
  (3 Elekta, 2 TomoTherapy®, 1 CyberKnife®)
- 1 MR-Linac
- Heidelberg Ion-Beam Therapy Center (HIT)
- 1 Satellite Center with Elekta
- Intraoperative RT with Intrabeam brachytherapy
Combined approaches: Helical IMRT + $^{12}$C-Boost

The Phase 1/2 ACCEPT Trial: Concurrent Cetuximab and Intensity Modulated Radiation Therapy with Carbon Ion Boost for Adenoid Cystic Carcinoma of the Head and Neck
Sebastian Adeberg, MD,*1,2,5,6, Sat Akbaba, MD, *1,2,5,6
Kristin Lang, MD,*1,2,5, Thomas Held, MD, *1,2,5, Vivek Verma, MD, *1,2,5
Anna Nikoghosyan, MD, # Denise Bernhardt, MD, *1,2,5
Marc Münter, MD,** Kolja Freier, MD, ** Peter Plinkert, MD, **
Henrik Hauswald, MD,*1,2,5, Klaus Herfarth, MD, *1,2,5
Stefan Rieken, MD,*1,2,5, Juergen Debus, MD, PhD, *1,2,5,6, and
Alexandra Desire Jensen, MD*1,2,5,6

- 28 patients with ACC
- Def./postOP RT + concomitant Cetuximab
- Toxicity: III°: 16% acute

• 2 y-LC: 84% & 5 y-LRC: 80%
• 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, Astri Heusel, Andreas Mock, Thomas Held, Kristin Lang,
Juliane Hörner-Rieken, Tobias Fronter, Sonja Katayama, Steffen Kargus,
Stefan Rieken, Peter Plinkert, Klaus Herfarth, Juergen Debus, and
Sebastian Adeberg

- 62 pat. with h&n mucoepidermoid CA
- 85% postOP RT vs 15% def. RT
- 5 y-LC: 84% & 5 y-LRC: 80%
- 5 y-DFS: 75% & 5 y-OS: 89%
Toxicity: - no grade IV-V
- Grade 3: 16% acute & 13% late
Carbon Ion Reirradiation for Recurrent Head and Neck Cancer: A Single-Institutional Experience

Thomas Held, MD,*,†,# Paul Windisch, MD,*,†,# Sati Akbaba, MD,*,†,# 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 pat. recurrent H&N tumors
- 54%: ACC, 26% SCC, 8% Adeno
- Median therapy interval: 3.9 years
- Re-RT: 51GyRBE(30-66)/3GyRBE
- mPFS: 24.2m
- mOS: 26.1m

Toxicity:
- acute: IV° = 3.2%
  ≥ III° = 3.0%
- Late: ≥ III° = 14.5%
Clinical randomized Phase-II-Trial

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

- **Screening, Informed Consent, Collecting Trial Relevant Data and History, Staging**
- **Randomization 1:1** stratified for histology and RT-interval
  - Experimental arm: Evaluation of Safety and Toxicity of C12 ion re-irradiation
  - Control arm: Evaluation of Safety and Toxicity of photon re-irradiation
- **Clinical Assessment and Diagnostic Imaging 6 weeks after Completion of Re-Irradiation, then every 3 months (Minimal Follow-Up=12 months)**
- **Total Dose of Carbon Ion or Photon Re-Radiotherapy**
  - RT-interval > 2 years
    - NO
      - 51 Gy(RBE) or 54 Gy
    - YES
      - 54 Gy(RBE) or 60 Gy
- **Adherence to Dose Tolerance of OAR**

* Individual dose prescription can differ (max. 60 Gy or Gy(RBE)) and will be at the discretion of the treating radiation oncologist
<table>
<thead>
<tr>
<th>Organs at Risk</th>
<th>Max. Cumulative BED2Gy (RT-Interval ≤ 2 years)</th>
<th>Max. Cumulative BED2Gy (RT-Interval &gt; 2 years)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain stem (α/β=2)</td>
<td>60 Gy</td>
<td>78 Gy (≒+30%)</td>
<td>Maximum (surface)</td>
</tr>
<tr>
<td>Optic chiasm (α/β=3)</td>
<td>54 Gy</td>
<td>64.8 (≒+20%)</td>
<td>Maximum</td>
</tr>
<tr>
<td>Optic nerves (α/β=3)</td>
<td>54 Gy</td>
<td>64.8 (≒+20%)</td>
<td>Maximum</td>
</tr>
<tr>
<td>Spinal cord (α/β=2)</td>
<td>50 Gy</td>
<td>60 Gy (≒+20%)</td>
<td>Maximum</td>
</tr>
</tbody>
</table>
Clinical Management of Blood–Brain Barrier Disruptions after Active Raster-Scanned Carbon Ion Re-Radiotherapy in Patients with Recurrent Head-and-Neck Cancer

Thomas Held, Sati Akbaba, Kristin Lang, Semi Harrabi, Denise Bernhardt, Christian Freudlsperger, Steffen Kargus, Peter Plinkert, Stefan Rieken, Klaus Herfarth, Jürgen Debus, and Sebastian Adeberg

- 217 pat. with reRT
- RT field boarders CNS
- 16.6% barrier disruptions
- Interval: 9-17m (I-III°)
- Good prognosis with adequate management

Radiotherapy of Head-and-Neck or Brain Cancer

<table>
<thead>
<tr>
<th>Target volume?</th>
<th>Total dose?</th>
<th>Dose distribution?</th>
<th>Systemic therapy?</th>
<th>Regular clinical and radiographic follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Moderate (Grade II)</td>
</tr>
<tr>
<td>No symptoms</td>
<td></td>
<td></td>
<td></td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Observation</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
<td></td>
<td>Life-threatening (Grade IV)</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td></td>
<td></td>
<td></td>
<td>Surgery</td>
</tr>
</tbody>
</table>

(A) (B) (C) (D)
Less is more...

- 414 patients with HNC (1:1)
- PTV-margin reduction 5→3mm
- Toxicity: - III° : 65% vs. 54%, p = 0.032
  - Mucositis III° : 42 to 31%, p = 0.008
- 2y-LC: 79.9% vs 79.2%, n.s.
- 2y-OS: 75.2% vs 75.1%, n.s.

Original article
The impact of margin reduction on outcome and toxicity in head and neck cancer patients treated with image-guided volumetric modulated arc therapy (VMAT)
Arash Navran a, Wilma Heemsebergen a,b, Tomas Janssen a, Olga Hamming-Vrieze a, Marcel Jonker a, Charlotte Zuur a, Marcel Verheij a, Peter Remeijer a, Jan-Jakob Sonke a, Michiel van den Brekel a, Abraham Al-Mamgani a,b

G3 dysphagia
Cumulative incidence

G3 mucositis
Cumulative incidence

Overall Survival

Free from locoregional failure

Margin group
5 mm
7 mm
10 mm
Log Rank p<0.001

Time (months) since start RT

Log Rank p<0.01
Definition of nodal treatment volumes

### Selection of low risk nodal target volumes for p16− oropharyngeal cancers

<table>
<thead>
<tr>
<th>Nodal Category (AJCC/UICC 8th ed.)</th>
<th>Levels to be included in CTV-N-LR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ipsilateral Neck</td>
</tr>
<tr>
<td></td>
<td>Contralateral Neck</td>
</tr>
<tr>
<td>N0-1 (in level II, III, or IV)</td>
<td>(lb)², II, III, IVa, +VIIa for</td>
</tr>
<tr>
<td></td>
<td>posterior pharyngeal wall tumor</td>
</tr>
<tr>
<td>N2a-b</td>
<td>lb, II, III, IVa, Vab, +VIIa, +VIIb²</td>
</tr>
<tr>
<td>N2c</td>
<td>According to N category on each</td>
</tr>
<tr>
<td></td>
<td>side of the neck</td>
</tr>
<tr>
<td>N3</td>
<td>lb, II, III, IVa, Vab, +VIIa, +VIIb²</td>
</tr>
</tbody>
</table>

AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control; CTV-N-LR, low risk nodal clinical target volume.

* Unilateral treatment is recommended for N0-N2a tonsil fossa tumor not infiltrating the soft palate nor the base of tongue; and discussed for N2b patients.
* Any tumor with extension to the oral cavity (e.g., retromolar trigone, mobile tongue, inferior gum, oral side of anterior tonsillar pillar), and/or in case of anterior involvement of level II.
* Level IVa should be included in case of involvement of level IVa.
* Level VIIb should be included in case of bulky involvement of the upper part of level II.

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56y; male; Oropharyngeal CA, right cT2 cN1 (Level IIb) p16−; Def. CRT with individual vs. standard LN-RT
Reduction of elective nodal levels

Eliminating Postoperative Radiation to the Pathologically Node-Negative Neck: Long-Term Results of a Prospective Phase II Study

Jessika A. Contreras, MD; Christopher Spencer, MD, MS; Todd DeWees, PhD; Bruce Haughey, MD, MSc; Lauren E. Henke, MD, MSc; Re-I Chin, MD; Randal Paniello, MD; Jason Rich, MD; Ryan Jackson, MD; Peter Oppelt, MD; Patrik Pipkom, MD; Jose Zevallos, MD, MPH; Rebecca Chemock, MD; Brian Nussenbaum, MD, MHCM; Mackenzie Daly, MD; Hiram Gay, MD; Douglas Adkins, MD; and Wade Thorstad, MD

Single Arm, Phase II
Non-inferiority: LC>90%
n=72; 93% Stage III/IV HNSCC
71% oropharynx + oral cavity
no pN0 PORT
median dose hr-CTV 66Gy/el-CTV 54Gy

Unirradiated neck control: 97%
5-year LC: 84%
5-year RC: 93%
5-year PFS: 60%
5-year OS 64%

QOL measures were not significantly different from baseline at 12 and 24 months post-PORT (p > 05).

Conclusion:
Reduction of elective volumes could play a major role in de-reduction strategies
Individualized 3D-printed retractor

“Every solution to every problem is simple. It's the distance between the two where the mystery lies” – Derek Landy (author)

- 5 sizes: XL, L, M, S, XS
- Inidividual adaption
- material: app. 100 €
61y; male
ACC
cT4 cN1 R2; add. RT
Standard vs. individualized 3-D

Diagnostic CT 2.7.19

Treatment planning 14.8.19
53y; male
Sinonasal carcinoma
pT4 cN0 R2; add. RT
Standard vs. individualized 3-D
GUARD I and II: Randomized Phase-II-trials

Screening

Randomisation (n = 32)

Stratification: systemic therapies

Intervention Arm A (n = 16)
RT with individualized 3D-printed retractor

Control Arm B (n = 16)
RT with regular retractor

Follow-Up

1st study visit 6W; further follow-ups 3M, 6M, 9M und 12M
## Immunotherapy + RT

<table>
<thead>
<tr>
<th>Locally advanced HNSCC</th>
<th>First-line</th>
<th>Second line or higher</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase II</strong></td>
<td></td>
<td></td>
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<tr>
<td>ADRISK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery + CRT + Pembro vs. Surgery + CRT + Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IMPORTANCE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembro + RT vs. Pembro PD-L1 CPS ≥ 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IMPORTANCE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembro + RT vs. Pembro PD-L1 all comor</td>
<td></td>
<td></td>
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<tr>
<td><strong>Phase III</strong></td>
<td></td>
<td></td>
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<tr>
<td>KEYNOTE – 412</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembro + CRT vs. CRT PD-L1 all comor</td>
<td></td>
<td></td>
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<tr>
<td>KEYNOTE – 689</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant / Adjuvant PD-L1 all comor</td>
<td></td>
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</tbody>
</table>
Neoadjuvant Immunotherapy

KEYNOTE-689 (NCT03765918)¹:
Phase-III-Studie, Pembrolizumab Neoadjuvant gefolgt von OP und Pembrolizumab adjuvant

**Primäre Endpunkte**: Rate des deutlichen pathologischen Ansprechens (major pathological response, mPR) laut Beurteilung des zentralen Pathologen zum Zeitpunkt der definitiven Operation, EFS (BICR
**Sekundärer Endpunkt**: Unbekannt

¹. https://clinicaltrials.gov/ct2/show/NCT03765918
Definite Immuno-chemoradiotherapy

KEYNOTE-412 (NCT03040999)\(^1\)
Phase-III-Studie, Pembrolizumab oder Placebo in Kombination mit Radiochemotherapie

**KEYNOTE-412**

<table>
<thead>
<tr>
<th>Haupteinschlusskriterien</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histologisch bestätigtes HNSCC</td>
</tr>
<tr>
<td>Lokal fortgeschrittene Erkrankung</td>
</tr>
<tr>
<td>Evaluierbare Erkrankung basierend auf RECIST 1.1</td>
</tr>
<tr>
<td>ECOG Status 0 - 1</td>
</tr>
<tr>
<td>Geeignetes Gewebe für Biomarker-Testung</td>
</tr>
</tbody>
</table>

\(R \, 1:1\)

- Pembrolizumab\(^a\) 200 mg i.v. Q3W + CRT
- Pembrolizumab-Erhaltungstherapie x 14 Dosen
- Placebo + CRT
- Placebo-Erhaltungstherapie x 14 Dosen

**Geplante Rekrutierung: 780**

**Primärer Endpunkt: EFS**
**Sekundäre Endpunkte: OS, Sicherheit, PRO**

\(^a\) CRT: Chemotherapie
\(^1\) https://clinicaltrials.gov/ct2/show/NCT03040999.
Future perspectives
Future perspectives
Future perspectives
Future perspectives

Machine learning vs. human learning

Computer performance reaching equal to above human performance at narrow task

We are here

Computer performance

Human performance

Performance

Time
Future perspectives

Machine learning vs. human learning

Heron et al., IJROBP 2009
Dank u!