Prognostic Factors and Surgical Approach

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ESO-ESMO Berlin Masterclass 2019
Disclosures

Remuneration for scientific presentations and participation on Advisory Boards: Merck Serono, Roche, Astra Zeneca, MSD, BMS

Research Support: Roche, Merck Serono
Surgery
TLM, TORS

Surgery
TLM, TORS, open + Neck diss.

Surgery + R
TLM, TORS, open + Neck diss.

Surgery + RCH
TLM, TORS, open + Neck diss.

Prim. RCH

Late toxicity,
Late dysphagia

Ralph Gilbert
Toronto

Piero Nicolai
Brescia
Predictive factors

• TNM
• Tumor volume
• Degree of resection margin (R0 versus R+)
• HPV 16, p16
A paradigm shift for HPV (US)

Shatuvedi et al., JCO 2011
266 Patients with oropharyngeal cancer, known tumor HPV status, and known number of pack-years of smoking

178 Had HPV-positive tumors

- 88 Had ≤10 pack-years
- 90 Had >10 pack-years

- 26 Had N0–N2a cancer
- 64 Had N2b–N3 cancer
- 15 Had T2–T3 tumors
- 8 Had T4 tumors

114 of 266 (42.9%) were at low risk
79 of 266 (29.7%) were at intermediate risk
78 of 266 (27.4%) were at high risk

B

Overall Survival (%) vs Years since Randomization

- Low risk
- Intermediate risk
- High risk

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Years since Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk</td>
<td>114  111  106  102  95  46</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>79   70   64    54   44   24</td>
</tr>
<tr>
<td>High risk</td>
<td>73   52   43    33   28   8</td>
</tr>
</tbody>
</table>

K. Kian Ang et al.
Vaccination

The German Vaccination Commission (STIKO) now (28.06.2018) recommends vaccination against HPV not only for girls, but also for all boys aged 9 to 14 years. The vaccination recommendation for girls and young women has been around since 2007. Boys and girls who have not yet been vaccinated against HPV until the age of 15, should catch up with the vaccine as soon as possible - at the latest at the age of 17 years.
WP, male, 59 years

Staging:
• Panendoskopy: < 2 cm left base of tongue tumor
• NMR: T 16 mm; N left Level II (33 mm)
• FDG PET-CT: M0
• Grade 1 HNSCC, p16+/HPV+
WP, male, 59 years

In 2014...

• **UICC/AJCC 7th ed:** T1-N2a-M0 + ECS (stage IV)

**Treatment:**

• primary transoral surgery + adjuvant Concomitant chemo-radiotherapy (60 Gy in 6w + 2 courses of 100 mg/m² cddp)

• Alternatively: Primary treatment: Concomitant chemo-radiotherapy (70 Gy in 6w + 2 courses of 100 mg/m² cddp)
WP, männlich, 59 Jahre

In 2018...

- **UICC/AJCC 8th ed:** T1-N1-M0 (stage I)

**Treatment:**

- primary transoral surgery + adjuvant Concomitant chemo-radiotherapy (60 Gy in 6w + 2 courses of 100 mg/m² cddp)
- Alternatively: Primary treatment: Concomitant chemo-radiotherapy (70 Gy in 6w + 2 courses of 100 mg/m² cddp)
The AJCC/UICC eighth edition for staging head and neck cancers: Is it wise to de-escalate treatment regimens in p16-positive oropharyngeal cancer patients?

Paolo Boscolo-Rizzo and Andreas Dietz

Section of Otolaryngology and Regional Center for Head and Neck Cancer, Department of Neurosciences, University of Padova, Treviso, Italy

Department of Otorhinolaryngology, University Hospital Leipzig, Leipzig, Germany

Current opinion on resection margins

R0 ideal = 5mm
R1, 2 high risk
R0 <5mm intermediate risk
R0 >5mm low risk
principles in therapy

Squamous cell carcinoma head and neck

- resectable
  - Organ preserving surgery
  - Ablative surgery
  - Adjuvant radio-, radiochemo-therapy
- Non resectable
  - Organ preserving chemo-radiation
  - Chemo-radiation
  - Salvage surgery
  - Adjuvant radio-, radiochemo-therapy
- Salvage surgery

First line
Second line

chemotherapy
Transoral vs. open resection
transoral laser microsurgery (TLM)

- Microspot focus CO2-laser < 0.74 mm
- Minimal carbonisation damage of resection margin
- Fiew-beamer axis not bendable
Evidenz und Evidenzlücken zur Chirurgie des Larynxkarzinoms
Evidence-Based Review of Laryngeal Cancer Surgery

Autor: S. Wiegand

ENT Department University Leipzig
Meta-analyzes and systematic reviews to compare local control after radiotherapy and transoral laser surgery of T1 and T2 vocal cord carcinomas.

### Overall survival

<table>
<thead>
<tr>
<th>Autor</th>
<th>Jahr</th>
<th>T-Status</th>
<th>Analyse</th>
<th>Zeitraum</th>
<th>Studien</th>
<th>Patienten</th>
<th>Fazit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higgins [21]</td>
<td>2009</td>
<td>T1, T2</td>
<td>M</td>
<td>?</td>
<td>14</td>
<td>4905</td>
<td>Besseres Gesamtüberleben nach Lasertherapie, OR 1.48 (95%-KI: 1.19–1.85) zugunsten der Laserchirurgie</td>
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<tr>
<td>Abdurehim [23]</td>
<td>2011</td>
<td>T1a</td>
<td>SR + M</td>
<td>1990–2010</td>
<td>7</td>
<td>1067</td>
<td>Trend bezüglich besseren Überleben nach Lasertherapie, OR 1.22 (95%-KI 0.89–1.66) zugunsten der Laserchirurgie</td>
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</tbody>
</table>

SR: systematisches Review, M: Metaanalyse; TL: Transorale Lasertherapie; RT: Radiotherapie

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Meta-analyzes for Comparison of voice quality after Radiotherapy and transoral Laser surgery of T1 and T2 vocal cord cancer.

<table>
<thead>
<tr>
<th>Autor</th>
<th>Jahr</th>
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<th>Zeitraum</th>
<th>Studien</th>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>208 TL</td>
<td></td>
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<tr>
<td></td>
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<td>91 RT</td>
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<tr>
<td>Higgins [21]</td>
<td>2009</td>
<td>T1, T2</td>
<td>?</td>
<td>9</td>
<td>554</td>
<td>Trend zur besseren Stimme nach Radiotherapie</td>
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<tr>
<td></td>
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<td>260 TL</td>
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<td>207 RT</td>
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</table>

SR: systematisches Review, M: Metaanalyse; TL: Transorale Lasertherapie; RT: Radiotherapie
Studies on local control after transoral supraglottic Laser partial resection of the last 10 Years.

<table>
<thead>
<tr>
<th>Autor</th>
<th>Jahr</th>
<th>T-Status</th>
<th>Patientenzahl</th>
<th>Lokalkontrolle in %</th>
<th>Zeitpunkt der Messung der Lokalkontrolle in Monaten</th>
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<tr>
<td>Grant [52]</td>
<td>2007</td>
<td>T1–T4</td>
<td>38</td>
<td>97</td>
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<td>Roh [56]</td>
<td>2008</td>
<td>T1–T3</td>
<td>21</td>
<td>81</td>
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<td>Chijiwa [57]</td>
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<td>161</td>
<td>86</td>
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<td>Peretti [58]</td>
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<td>96</td>
<td>96</td>
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<td>Perez-Delgado [59]</td>
<td>2010</td>
<td>T1–T3</td>
<td>53</td>
<td>81,1</td>
<td>60</td>
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<td>Iro [60]</td>
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<td>137</td>
<td>91</td>
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<td>Csanady [61]</td>
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<td>55</td>
<td>73</td>
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<td>Hutcheson [62]</td>
<td>2012</td>
<td>T1–T3</td>
<td>5</td>
<td>100</td>
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<td>Canis [51]</td>
<td>2013</td>
<td>T1–T2</td>
<td>118</td>
<td>85</td>
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<td>T3</td>
<td>104</td>
<td>82</td>
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<td>T4</td>
<td>55</td>
<td>76</td>
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<td>Canis [49]</td>
<td>2014</td>
<td>T3</td>
<td>226</td>
<td>71,4</td>
<td>60</td>
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<td>To [63]</td>
<td>2015</td>
<td>T1–T4</td>
<td>37</td>
<td>66 late stage</td>
<td>60</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>88 early stage</td>
<td></td>
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<tr>
<td>Wilkie [64]</td>
<td>2015</td>
<td>T1–T3</td>
<td>17</td>
<td>88</td>
<td>36</td>
</tr>
</tbody>
</table>
• Cave: even after ligation of ACE sever beeding possible!
Robotic-Assisted Surgery
Balancing Evidence and Implementation

Jason D. Wright, MD

“Without clear demonstration of improved outcomes associated with robotic-assisted procedures, the complicated issue of the cost will become increasingly important.”

“Both the generation of high quality evidence evaluating new procedures and then the utilization of this evidence to guide practice should remain priorities for surgical disciplines”.
Flex-Robotic System Head and Neck
Smaller, smarter, cheaper
Überleben nach primärer laser resection (TLM)
204 Oropharynx-Karzinompatienten, p16 positiv

ECS ist kein prognostischer Faktor bei p16-positiven Oropharynxkarzinomen

P=0,68

T3/4 OPSCC: transoral/open transpharyngeal resection, reconstruction with free forearm flap, bilat. Selective Neck dissection + adj. PORCT
Advanced OPSCC
Reconstruction with free forearm flab
After having listened to the presentations today – do you have any comments on how you would have liked to receive care in this period of follow-up?
Functional outcome in patients with advanced head and neck cancer: surgery and reconstruction with free flaps versus primary radiochemotherapy: **ICF Core Sets for HNC**

<table>
<thead>
<tr>
<th>ICF category</th>
<th>Title</th>
<th>ProbChiSq</th>
<th>ORE</th>
<th>LowerCL</th>
<th>UpperCL</th>
<th>More problems in group</th>
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<tr>
<td>Body structures (n = 3)</td>
<td>s420 Structures of immune system, e.g. lymph nodes</td>
<td>0.00</td>
<td>0.13</td>
<td>0.03</td>
<td>0.52</td>
<td>MVFF</td>
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<tr>
<td></td>
<td>s7101 Bones of face</td>
<td>0.02</td>
<td>0.15</td>
<td>0.03</td>
<td>0.85</td>
<td>MVFF</td>
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<td></td>
<td>s810 Structure of skin</td>
<td>0.03</td>
<td>0.27</td>
<td>0.08</td>
<td>0.85</td>
<td>MVFF</td>
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<tr>
<td>Body functions (n = 3)</td>
<td>b5150 Oral swallowing</td>
<td>0.04</td>
<td>2.99</td>
<td>1.06</td>
<td>8.42</td>
<td>RCT</td>
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<tr>
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<td>b530 Weight maintenance functions</td>
<td>0.00</td>
<td>10.24</td>
<td>3.02</td>
<td>34.71</td>
<td>RCT</td>
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<td>b640 Sexual functions</td>
<td>0.03</td>
<td>4.728</td>
<td>1.12</td>
<td>19.91</td>
<td>RCT</td>
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<tr>
<td>Activities &amp; participation (n = 6)</td>
<td>d240 Handling stress and other psychological demands</td>
<td>0.04</td>
<td>3.13</td>
<td>1.08</td>
<td>9.04</td>
<td>RCT</td>
</tr>
<tr>
<td></td>
<td>d360 Using communication devices and techniques</td>
<td>0.02</td>
<td>5.47</td>
<td>1.28</td>
<td>23.4</td>
<td>RCT</td>
</tr>
<tr>
<td></td>
<td>d750 Informal social relationships</td>
<td>0.03</td>
<td>3.52</td>
<td>1.11</td>
<td>11.16</td>
<td>RCT</td>
</tr>
<tr>
<td></td>
<td>d760 Family relationships</td>
<td>0.02</td>
<td>5.47</td>
<td>1.27</td>
<td>23.59</td>
<td>RCT</td>
</tr>
<tr>
<td></td>
<td>d845 Acquiring, keeping and terminating a job</td>
<td>0.01</td>
<td>8.01</td>
<td>1.54</td>
<td>41.73</td>
<td>RCT</td>
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<tr>
<td></td>
<td>d870 Economic self-sufficiency</td>
<td>0.01</td>
<td>5.69</td>
<td>1.63</td>
<td>19.83</td>
<td>RCT</td>
</tr>
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</table>

n.s. not significant (p > 0.05)
* Significant with p < 0.05
Neck dissection: Classification of Robbins
Neck Dissection

• radical Neck Dissektion (RND)
  Resection Level I-V incl. Resection of VJI, M.SCCM and N.accessorius

• modified radical Neck Dissektion (mRND) = functional ND
  Resection of Level I-V; preservation of 1 or more non-lymphatic structures of RND

• selektive Neck Dissektion (SND)
  Preservation of 1 or more LK-levels of RND; preservation of VJI, M.SCM and N.accessorius
  new: SND I-III    old: supraomohyoidal SND

• extended Neck Dissektion
Treatment Deintensification in Human Papillomavirus-Positive Oropharynx Cancer: Outcomes From the National Cancer Data Base

Cheraghlou et al. 2017

- retrospектив; all HPV16+ patients

Stage I (T1-2 N0-1) n=3198
Stage II (T1-2 N2, T3N0-2)  
n = 795  AJCC 8. Edition

„CONCLUSION:
Deintensification of treatment from chemoradiotherapy to radiotherapy or surgery alone in cases of HPV16 (AJCC 8. edition) stage I or stage II disease may compromise patient safety.”
Treatment Outcomes for T4 Oropharyngeal Squamous Cell Carcinoma


- retrospektive cohort analysis T4a,b- OPC Patienten
- HPV positive + HPV negative
- HPV 16 + -non-surgery (ICT+RT,CRT) 47 patients
- HPV16 + - surgery 50 patients
Stage III (T1-4 N3, T4 N0-3) n = 450

“CONCLUSION: Treatment intensification to triple-modality therapy for patients with stage III disease may improve survival in this group”
**principles in therapy**

- Squamous cell carcinoma head and neck
  - **resectable**
  - **Organ preserving surgery**
  - **Adjuvant radio-, radiochemo-therapy**
- Non resectable
  - **Ablative surgery**
  - **Organ preserving chemo-radiation**
- **Salvage surgery**
- **Palliative chemotherapy**
  - First line
  - Second line

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Overall survival Laryngektomy vs. multimodal organ preservation T4a-Larynx carcinoma (969 Patients, 64% LP, 36% TL, retrospektive NCDB)

Kaplan-Meier Kurven: Overall survival Laryngektomie vs. multimodaler Organerhalt T4a-Larynxkarzinome (Grover S et al.)
Trends in treatment and survival for advanced laryngeal cancer: A 20-year population-based study in The Netherlands

Adriana J. Timmermans, MD; Bouke A. C. van Dijk, PhD; Lucy I. H. Overbeek, PhD; Marie-Louise F. van Velthuysen, MD, PhD; Harm van Tinteren, PhD; Frans J. M. Hilgers, MD, PhD; Michiel V. M. van den Brekel, MD, PhD

T3

5-year overall survival:
Total laryngectomy: 49%
Radiotherapy: 47%
Radio- and chemotherapy: 45%
p=0.539

Cum Survival

TL
RT
RT-CT
Years
142
215
256
65

324
193
166
573

T4

5-year overall survival:
Total laryngectomy: 48%
Radiotherapy: 34%
Radio- and chemotherapy: 42%
p=0.0001

Cum Survival

TL
RT
RT-CT
Years
123
96
71
380

560
282
195
434

236
64
53
44

Two-thirds of patients ($n = 38$) were not suitable for salvage surgery because of:

- distant metastases ($n = 30$)
- poor general condition of the patient ($n = 3$)
- refusal of surgery by the patient ($n = 1$)
- unresectability of the tumour ($n = 4$)
ORIGINAL ARTICLE

Induction chemotherapy (IC) followed by radiotherapy (RT) versus cetuximab plus IC and RT in advanced laryngeal/hypopharyngeal cancer resectable only by total laryngectomy—final results of the larynx organ preservation trial DeLOS-II

Patient Consort DeLOS-II-trial

Arm A:
- 1x TPF/TP
  - Non-Responder: Laryngectomy (25% non-responders, 60 Responders)
  - Responder: 2x TPF/TP + Cetuximab
  - Non-Responder: Laryngectomy (25% non-responders, 60 Responders)

Arm B:
- 1x TPF/TP + Cetuximab
  - Non-Responder: Laryngectomy (25% non-responders, 60 Responders)
  - Responder: 2x TPF/TP + Cetuximab
  - Non-Responder: Laryngectomy (25% non-responders, 60 Responders)

Endoscopy week 4 for ETSS assessment RT starting week 11

LFS @ 24 months
- 42 (49%) CI 80% 36-48 (43-56%)
- 30 (35%) CI 80% 24-36 (29-42%)
fLFS: survival with functional larynx (fLFS)
FFLED: actuarial freedom from laryngoesophageal dysfunction
Spättoxizität DeLOS-II
Grad ≥ 3
Current discussion regarding functional organ preservation versus LE in St. III/IV-Larynx/Hypopharynx Carcinoma

HNSCC
T3,4a Larynx
T2,3,4a Hypopharynx

Response Evaluation
• Tumorbiology
• Short Induction
• Ex vivo Sensitivity
• PET/CT Response

Laryngektomy
RCH

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WHY ONE-SIZE-FITS-ALL DOESN’T WORK.
DeLOS II: Survival better in high recruiting centers

![Graph showing survival with functioning larynx (fLFS) and overall survival (OS).]

Proportion of survivors

PEG and/or TS censored @731 days

Follow-up (days)

p=0.063

p=0.015
Surgical quality assurance in head and neck cancer trials: an EORTC Head and Neck Cancer Group position paper based on the EORTC 1420 ‘Best of’ and 24954 ‘larynx preservation’ study

Christian Simon a,*, Carmela Caballero b, Vincent Gregoire c, Dietmar Thurnher d, Petri Koivunen e, Philippe Ceruse f, Giuseppe Spriano g, Piero Nicolai h, Lisa Licitra i, Jean-Pascal Machiels j, k, Marc Hamoir l, Guy Andry m, Hisham Mehanna n, Keith D. Hunter o, Andreas Dietz p, q, C. René Leemans q, l
Summary

- Primary surgery is only recommended if R0 resection is possible and reasonable functional outcome available.
- Reconstruction is highly developed and free flap techniques offer a broad spectrum of possibilities.
- Transoral technologies like TORS and TLM are coming more in focus for oropharyngeal and laryngeal/hypopharyngeal HNSCC.
- TORS stimulates a fruitful debate about less mutilating surgery.
- HPV-positivity has no impact on standard treatment (first results of deescalation trials are expected 2021)
- Neck dissection has to be performed by separating the neck levels for better classification of the pathologist.
- Currently the EORTC H&N Group is working on a QA Surgery to standardize quality criteria for H&N institutions regarding future clinical trials.
UPDATE SKILLS IN HEAD AND NECK SURGERY AND ONCOLOGY
26.-28.09.2019 - Leipzig, Germany
Course Director: A. Dietz, DE
www.ukl.xcongress.de/update-skills-2019/home