4th ESO-ESMO Latin-American Masterclass in Clinical Oncology

18-22 April 2018
Mexico City, Mexico

Chairs:
A. Cervantes, ES - N. Pavlidis, GR
R.A. Stahel, CH

Scientific Co-ordinators:
M. Aapro, CH - F. Cardoso, PT

Under the auspices of
CMO - SMEO

LATIN-AMERICA PROGRAMME
Head & Neck Cancer: When to Irradiate...

ESO-ESMO Latin-America 2018

Talented students... colleagues
> 15 different diseases for RT strategies...
## HPV – Prognostic Marker >2010

<table>
<thead>
<tr>
<th>Trial</th>
<th>Cases</th>
<th>Marker</th>
<th>Survival</th>
<th>First author</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG</td>
<td>323</td>
<td>HPV</td>
<td>82% vs. 57% (3-year)</td>
<td>Ang, 2010</td>
</tr>
<tr>
<td>TROG</td>
<td>185</td>
<td>p16^INK4A</td>
<td>91% vs. 74% (2-year)</td>
<td>Rischin, 2010</td>
</tr>
<tr>
<td>DAHANCA</td>
<td>794</td>
<td>p16^INK4A</td>
<td>66% vs. 28% (5-year)</td>
<td>Lassen, 2011</td>
</tr>
<tr>
<td>TAX 324</td>
<td>111</td>
<td>HPV</td>
<td>82% vs. 35% (5-year)</td>
<td>Posner, 2011</td>
</tr>
</tbody>
</table>
De-escalation treatment protocols for human papillomavirus-associated oropharyngeal squamous cell carcinoma (Review)


Main results

We did not identify any completed randomised controlled trials that could be included in the current version of this systematic review. We did, however, identify seven ongoing trials that will meet our inclusion criteria. These studies will report from 2014 onwards. We excluded 30 studies on methodological grounds (seven randomised trials with post hoc analysis by human papillomavirus status, 11 prospective trials and 12 ongoing studies).

No data yet…
The MARCH-HPV project

Prognostic impact of HPV-associated p16-expression and smoking status on outcomes following radiotherapy for oropharyngeal cancer: The MARCH-HPV project

Pernille Lassen, Benjamin Lucas, Jean-Pierre Pignon, Andy Trotti, Bjorn Zackrisson, Q Jens Ovegaard, Pierre Blanchard, on behalf of the MARCH Collaborative Group

<table>
<thead>
<tr>
<th>Table 1: Baseline patient and tumor characteristics stratified by p16-status.</th>
</tr>
</thead>
<tbody>
<tr>
<td>p16-positive</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>&lt;50</td>
</tr>
<tr>
<td>50-59</td>
</tr>
<tr>
<td>60-69</td>
</tr>
<tr>
<td>&gt;70</td>
</tr>
<tr>
<td>Median (range)</td>
</tr>
<tr>
<td>Performance status</td>
</tr>
<tr>
<td>T1</td>
</tr>
<tr>
<td>T2</td>
</tr>
<tr>
<td>T4</td>
</tr>
<tr>
<td>Missing/unknown</td>
</tr>
<tr>
<td>N-stage</td>
</tr>
<tr>
<td>N0</td>
</tr>
<tr>
<td>N1</td>
</tr>
<tr>
<td>N2</td>
</tr>
<tr>
<td>N3</td>
</tr>
<tr>
<td>Smoking status</td>
</tr>
<tr>
<td>Nonsmoker</td>
</tr>
<tr>
<td>Current</td>
</tr>
<tr>
<td>Treatment arm</td>
</tr>
<tr>
<td>Conventional RT</td>
</tr>
<tr>
<td>Altered fractioned RT</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

RT, radiotherapy.
Prognostic impact of HPV-associated p16-expression and smoking status on outcomes following radiotherapy for oropharyngeal cancer: The MARCH-HPB project

Pernille Lassen a, Benjamin Lacas b,c, Jean-Pierre Pignon b,c, Andy Trotti d, Bjorn Zackrisson e, Q Jens Overgaard a, Pierre Blanchard f, on behalf of the MARCH Collaborative Group

Table 3
Causes of death and type of failure by p16-status and smoking status.

<table>
<thead>
<tr>
<th>Type of failure</th>
<th>p16-positive</th>
<th>p16-negative</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Former/current smokers</td>
<td>Never smokers</td>
<td>Never smokers</td>
</tr>
<tr>
<td>Cancer related death</td>
<td>74</td>
<td>29.4</td>
<td>13</td>
</tr>
<tr>
<td>Non-cancer related death</td>
<td>56</td>
<td>22.2</td>
<td>13</td>
</tr>
<tr>
<td>Status at last follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>122</td>
<td>48.4</td>
<td>60</td>
</tr>
<tr>
<td>Locoregional failure</td>
<td>40</td>
<td>51.5</td>
<td>5</td>
</tr>
<tr>
<td>Distant failure</td>
<td>27</td>
<td>10.5</td>
<td>7</td>
</tr>
<tr>
<td>Locoregional and distant failures</td>
<td>9</td>
<td>3.6</td>
<td>0</td>
</tr>
<tr>
<td>No failure</td>
<td>176</td>
<td>69.8</td>
<td>74</td>
</tr>
<tr>
<td>Total</td>
<td>252</td>
<td>100</td>
<td>86</td>
</tr>
</tbody>
</table>
Selected topics for talented... When RT?

Locally advanced stages
Nasopharynx
Postoperative RT
Laryngeal preservation
Oligo-recurrence
New concepts, new trials

How? and what? (to expect)...)
2012-2016
Highest level of clinical evidence
Australian National Health and Medical Research Council

48% all cancer pts indication of RT
73% chemoradiation level I-II
34% curative
14% palliative

<table>
<thead>
<tr>
<th>Radiation type</th>
<th>LC benefit @ 5y</th>
<th>OS benefit @ 5y</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT</td>
<td>10% all pts</td>
<td>2.4% all pts</td>
</tr>
<tr>
<td>CRT</td>
<td>0.6% all pts</td>
<td>0.3% all pts</td>
</tr>
<tr>
<td>Head &amp; Neck CRT</td>
<td>32%</td>
<td>16%</td>
</tr>
<tr>
<td>Cervix CRT</td>
<td>33%</td>
<td>18%</td>
</tr>
</tbody>
</table>
Principles of RT technique/target delineation

- Simulation
  - Head extended
  - Supine
  - Arms down
  - IV contrast
  - 5-pt mask
  - Thin cut (2-3 mm)

- Technique: **IMRT** (except for early stage glottic cancer)
• Target delineation (elective nodes)
  • Primary echelon
    • Location/drainage of primary
    • Lateralized (ipsilateral) vs. midline
      » (bilateral)
  • Secondary echelon
    • At risk if primary echelon contains bulky or high-volume disease

Dose-Volume Histograms DVH
Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial

Christopher M Nutting, James P Morden, Kevin J Harrington, Teresa Guerrero Urbano, Shreerang A Bhide, Catharine Clark, Elizabeth A Miles, Aisha B Miah, Kate Newbold, MaryAnne Tanay, Fawzi Adab, Sarah J Jefferyes, Christopher Strase, Beng K Yap, Roger P A Hem, Mark A Sydenham, Marie Emson, Emma Hall, on behalf of the PARSPORT trial management group

H&N IMRT Practice Heterogeneity

T2 N1 M0 Tonsil Cancer

P. Harari: Radiotherapy & Oncology 2012

Courtesy of Dr. Harari
Isodoses or Heterodoses: 3D!
IMRT: decisions

boost & fractionation: sequential vs SIB

Gross Disease 70 Gy in 33-35 daily fractions

“High-Risk” 59-63 Gy in 30-35 daily fractions

“Risk” 50-56 Gy in 25-35 daily fractions

Macro… micro… nano… level of risk
Importance of Radiation Oncologist Experience Among Patients With Head-and-Neck Cancer Treated With Intensity-Modulated Radiation Therapy

Isabel J. Boero, Anthony J. Paravati, Beibei Xu, Ezra E.W. Cohen, Loren K. Mell, Quynh-Thu Le, and James D. Murphy

Fig 2. Overall survival for patients with head-and-neck cancer receiving intensity-modulated radiation therapy stratified by high- versus low-volume providers.
Selected topics for talented... When RT?

Locally advanced stages
Nasopharynx
Postoperative RT
New concepts, new trials

How? and what? (to expect)...
Loco-regional Advanced

when, how and what to expect

- **Unresectable**: radical chemoradiation
- **Consolidation**: post-induction CT
- **Oligo-recurrent**: radical rescue
Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients

Jean-Pierre Pignon *, Aurélie le Maître *, Emilie Maillard *, Jean Bourhis *, on behalf of the MACH-NC Collaborative Group

*Department of Biostatistics and Epidemiology, Institut Curie-Assay, Villejuif, France;
**Department of Radiotherapy, Institut Curie-Assay, Villejuif, France.
<table>
<thead>
<tr>
<th>Type of chemotherapy</th>
<th>No. Deaths / No. Entered</th>
<th>O-E</th>
<th>Variance</th>
<th>Hazard Ratio</th>
<th>HR [95% CI]</th>
<th>p of interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(a) Poly chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-FU and Platin</td>
<td>602/940</td>
<td>-92.2</td>
<td>317.6</td>
<td>0.75</td>
<td>[0.67;0.84]</td>
<td>0.41</td>
</tr>
<tr>
<td>5-FU or Platin</td>
<td>495/743</td>
<td>-45.8</td>
<td>250.0</td>
<td>0.83</td>
<td>[0.74;0.94]</td>
<td></td>
</tr>
<tr>
<td>Neither 5-FU nor Platin</td>
<td>62/115</td>
<td>-11.1</td>
<td>35.0</td>
<td>0.73</td>
<td>[0.52;1.01]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (a)</td>
<td>1159/1798</td>
<td>-149.0</td>
<td>602.6</td>
<td>0.78</td>
<td>[0.72;0.85]</td>
<td></td>
</tr>
<tr>
<td><strong>(b) Mono chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mono Platin</td>
<td>703/1151</td>
<td>-102.6</td>
<td>341.8</td>
<td>0.74</td>
<td>[0.67;0.82]</td>
<td><strong>0.006</strong></td>
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<tr>
<td>Mono Other</td>
<td>1309/1875</td>
<td>-74.8</td>
<td>643.3</td>
<td>0.89</td>
<td>[0.82;0.96]</td>
<td></td>
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<tr>
<td>Subtotal (b)</td>
<td>2012/3026</td>
<td>-177.4</td>
<td>985.1</td>
<td>0.84</td>
<td>[0.78;0.89]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (a ... b)</strong></td>
<td>3171/4824</td>
<td>-326.4</td>
<td>1587.7</td>
<td>0.81</td>
<td>[0.78;0.86]</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2 = 1.69$, p = 0.19
Selected topics for talented...

Locally advanced stages: randomized trials

RT FRACTIONATION altered vs standard
RTOG 90-03

Standard fractionation
7000 cGy/35 fx
7 weeks

Hyperfractionation
8160 cGy/68 fx
7 weeks (1.2 Gy Bid)

Accelerated fractionation, split course
6720 cGy/42 fx
6 weeks (1.6 Gy Bid)

Accelerated fractionation, concomitant boost
7200 cGy/42 fx
6 weeks
Overall survival

<table>
<thead>
<tr>
<th>Fractionation RT</th>
<th>OS @ 5y</th>
<th>OS @ 10 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hiperfractionation</td>
<td>8.1%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Very accelerated</td>
<td>1.3%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

33 trials and 11,423 patients
Role of radiotherapy fractionation in head and neck cancers (MARCH): an updated meta-analysis

Progression-free survival

Figure 4. Progression-free survival curves for trials comparing altered fractionation and conventional fractionation radiotherapy

Any Hiperfractionation
Moderately accelerated Very accelerated
Selected topics for talented...

Locally advanced stages: randomized trials

FRACTIONATION +/- CRT
No form of acceleration can potentially compensate fully for the lack of concurrent chemotherapy.
updated meta-analysis, Jan 1, 2009, and July 15, 2015

conventional fractionation RT
vs
altered fractionation radiotherapy

conventional fractionation CRT
vs
altered fractionation radiotherapy alone

Eligible trials had to start randomisation on or after Jan 1, 1970, and completed accrual before Dec 31, 2010

33 trials and 11,423 patients
RT radical vs Cetuximab-RT

OS

LR failures

Figure 1. Conditional Probability of Locoregional Failure after Radiotherapy plus Cetuximab as Compared with Radiotherapy Alone.

Figure 2. Kaplan–Meier Estimates of Overall Survival among All Patients Randomly Assigned to Radiotherapy plus Cetuximab or Radiotherapy Alone.
Cetuximab and Radiotherapy Versus Cisplatin and Radiotherapy for Locally Advanced Head and Neck Cancer: A Randomized Phase II Trial

Stefano Maria Magrini, Michela Buglione, Renzo Corvò, Luigi Pirtoli, Fabiola Paiar, Pietro Ponticelli,

Fig. 1. Weight loss, feeding tube dependency, and acute toxicity resolution over time. EOT, end of treatment. Blue bars, cisplatin arm; gold bars, cetuximab arm.
The addition of an anti-EGFR agent to RT or CRT do not improve outcomes compared with CRT in LA-HNSCC.

Except for patients with coexisting medical conditions or decreased performance status, concurrent CRT should remain the standard of care for patients with LA-HNSCC.
Loco-regional Advanced

when, how and what to expect

- **Unresectable**: radical chemoradiation

- **Consolidation**: post-induction CT

- **Oligo-recurrent**: radical rescue
Why to Still Consider Induction Chemotherapy

• **Pros:**
  • Salvage subclinical M1 disease and OS benefit
  • **Assessment of response**
  • Reduce dose/volume of RT

• **Cons:**
  • Prolongs treatment time/cost
  • Increases toxicity
  • No clinical benefit
SCREENING/BIOPSY
Please see Section 12 for details regarding the research biopsy

RANDOMIZATION

Arm A

Arm B

INDUCTION CHEMOTHERAPY
(DURATION 6 WEEKS)

Induction Chemotherapy:
Docetaxel (75 mg/m² on day 1) in 250 ml D5W over 60 minutes (Dexamethasone 4 mg x 3 doses taken orally the night before, the morning of, and the evening after docetaxel administration) + Cisplatin (75 mg/m² on day 1) administered in 250 ml NS over 60 min after completion of docetaxel + 5FU (750 mg/m²/day on days 1-5).
Resume chemotherapy for cycle 2 on Day 22 (two cycles of 3 weeks duration).

Pegfilgrastim or other white blood cell growth factor support (6 mg SQ once per chemotherapy cycle)
Chemoradiation will begin after induction (i.e. day 43 of therapy).

CONCOMITANT CHEMORADIATION
(DURATION 10 WEEKS)

Concomitant Chemoradiation:
Chemotherapy should be administered during all 5 weeks of radiotherapy.
EACH CYCLE:
Day 0: In PM: Start hydroxyurea at 500 mg PO q 12 hours on 6 days (11 doses).
The first daily dose of hydroxyurea on Days 1 – 5 is given 2 hours prior to the first fraction of daily radiotherapy.
Day 0: 6:00 P.M.: Start continuous infusion of 5-fluorouracil 600 mg/m²/day x 5 days (120 Hours).
Dexamethasone 4mg PO (or IV?)
Day 1 8AM: Dexamethasone 4 mg PO
Docetaxel 25 mg/m² in D5W or NS over 15-30 minutes.
Dexamethasone 4mg PO the evening after docetaxel administration
Days 1 – 5: RT 150 cGy (twice daily)
Days 6 – 12: No chemoradiotherapy (see Section 5.2 for supportive care guidelines)
Chemoradiotherapy cycles are repeated every 14 days until completion of radiotherapy.

CONCOMITANT CHEMORADIATION
(DURATION 10 WEEKS)

Unless contraindicated, every patient should undergo node dissection. Specific surgical procedure is at the discretion of the investigator within 8 weeks of completing chemoradiotherapy.
Responders...
Phase III Randomized Trial of Induction Chemotherapy in Patients With N2 or N3 Locally Advanced Head and Neck Cancer
Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial.

Lancet Oncol. 2013 Mar;14(3):257-64

- Study terminated early due to poor accrual (145 enrolled)
- Median f/u 49 mos
- 3-yr OS: (73% ICT vs 78% CRT, NS)
- Febrile neutropenia (23% ICT vs 1% CRT)
Induction chemotherapy prior to surgery with or without postoperative radiotherapy for oral cavity cancer patients: Systematic review and meta-analysis

Gustavo N. Marta a,*, Rachel Riera b, Paolo Bossi c, Lai-ping Zhong d, Lisa Licitra c, Cristiane R. Macedo e, Gilberto de Castro Junior f, André L. Carvalho g, William N. William Jr. h, Luis Paulo Kowalski i

European Journal of Cancer (2015) 51, 2596–2603

Induction CT → Surgery +/- RT

LRC

DFS

OS

Graphical data showing outcomes and risk ratios for chemotherapy versus control.
5 randomized trials
1022 patients
TPF induction CT
Pt / Tx CRT

Meta-analysis TPF in HNSCC

TPF→RT-CHX vs. RT-CHX in locally advanced head and neck cancer

Meta-analysis of randomized controlled trials: PFS

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>HR</th>
<th>95% CL-</th>
<th>95% CL+</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paccagnella et al.</td>
<td>101</td>
<td>0.718</td>
<td>0.424</td>
<td>1.217</td>
<td>0.187</td>
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<tr>
<td>Cohen et al.</td>
<td>273</td>
<td>0.840</td>
<td>0.560</td>
<td>1.260</td>
<td>0.390</td>
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<tr>
<td>Haddad et al.</td>
<td>145</td>
<td>1.070</td>
<td>0.590</td>
<td>1.920</td>
<td>0.820</td>
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<tr>
<td>Hitt et al.</td>
<td>283</td>
<td>0.912</td>
<td>0.692</td>
<td>1.202</td>
<td>0.513</td>
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<tr>
<td>Takácsi-Nagy et al.</td>
<td>60</td>
<td>1.315</td>
<td>0.663</td>
<td>2.607</td>
<td>0.506</td>
</tr>
<tr>
<td>Total</td>
<td>862</td>
<td>0.908</td>
<td>0.751</td>
<td>1.098</td>
<td>0.319</td>
</tr>
</tbody>
</table>
Clinical Investigation

Final Results of a Randomized Phase 2 Trial Investigating the Addition of Cetuximab to Induction Chemotherapy and Accelerated or Hyperfractionated Chemoradiation for Locoregionally Advanced Head and Neck Cancer

Tanguy Y. Seiwert, MD, James M. Melotte, MD

Methods and Materials: Patients with LA-HNSCC were randomized to receive 2 cycles of weekly IC (cetuximab, paclitaxel, carboplatin) and either Cetux-FHX (concurrent cetuximab, 5-fluorouracil, hydroxyurea, and 1.5 Gy twice-daily radiation therapy every other week to 75 Gy) or Cetux-PX (cetuximab, cisplatin, and accelerated radiation therapy with delayed concomitant boost to 72 Gy in 42 fractions).
Clinical Investigation

Final Results of a Randomized Phase 2 Trial Investigating the Addition of Cetuximab to Induction Chemotherapy and Accelerated or Hyperfractionated Chemoradiation for Locoregionally Advanced Head and Neck Cancer

Tanguy Y. Seiwert, MD, * James M. Melotek, MD, **

---

A

Overall Survival (%)

Time (months)

---

B

Progression-Free Survival (%)

Time (months)

---

C

Cumulative Incidence

P<.01

Time (months)

---

D

Cumulative Incidence

P=.53

Time (months)

---

LRR

Distant failure
ECOG 1308: Phase II trial of IC followed by cetuximab + 54 Gy vs 69 Gy IMRT in HPV-associated resectable oropharyngeal SCCA

**Induction Chemotherapy**

- N=90 patients, 80 analyzable

**Key Eligibility**
1. OPSCC
2. HPV16 ISH + and/or p16+
3. Resectable stage III, IVA

**Concurrent Chemoradiation**

**Response**

- Low dose IMRT 54Gy/27fx** + Cetuximab weekly
- Full dose IMRT 69.3Gy/33fx** + Cetuximab weekly
Loco-regional Advanced

when, how and what to expect

- Unresectable: radical chemoradiation

- Consolidation: post-induction CT

- Oligo-recurrent: radical rescue
bio-guided IMRT for oligo-recurrences
22 articles
1105 patients
published 1976 and 2014

The **5-year OS** improved over time:

- 18% pre-2000
- 35% mixed pre-2000 and post-2000
- 51% in the post-2000

(p < .001).
16 publications
919 patients

522 patients P OreRT

- Re-RT after salvage surgery,
- to highly selected patients with high-risk features (R+)
- Re-irradiation with highly conformal techniques and only when a dose > 50 Gy can be delivered
- LC from 21% to 100%
- 2-years-OS of 48% (range, 24–81%);
- mucositis and/or dysphagia/pharyngitis (11–52%)
- late fibrosis (range, 2–44%)
- pharynx dysfunction (range, 2–70%)
- death up to 6.8%
Selected topics for talented... When RT?

Locally advanced stages
Nasopharynx
Postoperative RT
New concepts, new trials

How? and what? (to expect)...
Nasopharynx: Anatomy
Treatment Approach

• Stage I
  • RT alone (10 yr LC and DSS > 90%)

• Stage II-IVb
  • Concurrent chemoradiation + adjuvant chemotherapy

• Stage IVc (M1 disease)
  • Chemotherapy
  • RT for symptom palliation
RT Treatment planning

- IMRT
  - LC > 90%

- Gross disease (primary + nodes): ~70 Gy

- High-risk CTV (bilateral RP, II-V, subclinical nasopharynx): 59-63 Gy

- Low-risk CTV: 56-59 Gy
NPC: Imaging
Chemotherapy and radiotherapy in nasopharyngeal carcinoma: an update of the MAC-NPC meta-analysis

Induction

Concomitant CRT + adjuvant

Adjuvant

Experimental arm

… all combinations
EBV: Prognostic Marker

Pre-RT

1 wk post-RT

NRG HN001: Phase II/III Trial of Individualized

Basic Eligibility: Stage II-IVB NPC; detectable EBV-DNA pre-treatment

Control: Consolidation 5-FU/cisplatin X 3
Consolidation Gemcitabine/Paclitaxel X 4

Stratify:
N-stage N0-1 vs. N2-3
T-stage T1-2 vs. T3-4
PS 0 vs. 1

Assess EBV-DNA

All Pts Receive RT/cisplatin

Re-Assess EBV-DNA

"Detectable"

R (Ph II)

"Undetectable"

R (Ph III)

Basic Statistical Design:
- Phase IIIR sub-study (detectable EBV after chemo-RT): 1-year PFS 55% vs. 40% superiority design. 120 analyzable pts, 4.2 yr
- Phase III sub-study (undetectable EBV after chemo-RT): 2-year OS 91% both arms noninferiority. 600 analyzable pts, 7.7yr

Quality of Life: FACT-NP, HHIE-S (audiometry), FACT-Taxane, EQ-5D
Nasopharynx: Summary

• RT is the curative modality
  • RT alone: stage I
  • CRT: stage II-IVb
  • IMRT: standard of care
    • High rates of local control (> 90%)
    • Failures predominantly systemic

• Approaches to address to systemic relapse warranted
  • Role of adjuvant chemotherapy?
    • Risk stratification via EBV
Selected topics for talented... When RT?

Locally advanced stages
Nasopharynx
Postoperative RT
New concepts, new trials

How? and what? (to expect)...

Do not duplicate or distribute without permission from the author and ESO.
Poor / Imposible Volume Definition
Ipsilateral Level 3 Failure

T2N1 oral tongue cancer, postoperative radiation

Submental Failure

Postoperative IMRT for Laryngeal Cancer

Stoma ≥ 60 Gy
Postop RT: Indications

- Multiple lymph nodes involved
- Extracapsular extension (ECE)
- Positive/close surgical margins
- Perineural invasion
- Lymphovascular invasion
- Deep (>5mm) invasion
Postop RT: Treatment Decisions

- May deliver RT as soon as the wound is healed
- Ideally initiate within 6 weeks after surgery
- Intermediate Risk: 60 Gy / 30 fractions
- High Risk (Positive margin / ECE): 66 Gy / 33 fx
- Concurrent systemic therapy in high risk patients
Combined RTOG/EORTC Analysis

Bernier, Cooper. Head Neck 2005;27:843
Long Term Follow Up of RTOG 9501 Patients with Positive Margin and/or ECE

Cooper et al. IJROBP 2012
Differences in Survival With Surgery and Postoperative Radiotherapy Compared With Definitive Chemoradiotherapy for Oral Cavity Cancer
A National Cancer Database Analysis

58755 Patients aged ≥18 years with tongue, floor of mouth, or other oral cavity tumors received at least part of the initial treatment at the reporting facility and definitive surgery followed by radiotherapy with or without chemotherapy or definitive concurrent chemoradiotherapy

51855 Excluded
- 2121 Evidence of in situ disease
- 31571 Clinical stage I, II, or IVB
- 3958 Distant metastatic disease
- 3223 Treated with palliative intent
- 2902 Discordant clinical and pathologic staging
- 8080 Status unknown

6900 Included in analysis

A total of 6900 patients were identified with clinical stage III to IVA oral cavity squamous cell carcinoma treated with surgery and postoperative radiotherapy or definitive chemoradiotherapy.
All patients

Overall Survival, %

Time, mo

Δ 17.8%
(95% CI, 14.9% to 20.7%)

<table>
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<tr>
<th>Treatment</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
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<tr>
<td>CRT</td>
<td>2082</td>
<td>1328</td>
<td>818</td>
<td>570</td>
<td>414</td>
<td>295</td>
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<tr>
<td>S+RT</td>
<td>2324</td>
<td>1840</td>
<td>1286</td>
<td>893</td>
<td>607</td>
<td>420</td>
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<tr>
<td>S+CRT</td>
<td>2462</td>
<td>1876</td>
<td>1234</td>
<td>828</td>
<td>540</td>
<td>330</td>
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</tbody>
</table>
Loco-regional

Disease free

Survival

CRT vs RT alone: postoperative
Selected topics for talented... When RT?

Locally advanced stages
Nasopharynx
Postoperative RT
Laryngeal preservation
New concepts, new trials

How? and what? (to expect)...
Anatomy

• Supraglottis
  – Epiglottis
  – Arytenoids
  – AE folds
  – False cords
  – Ventricles

• Glottis
  – True vocal cords

• Subglottis
  – 5mm below glottis to bottom of cricoid
Treatment Approach

- Glottic, early stage: single modality
  - RT: limited field
  - Surgery: partial laryngectomy, cordectomy, laser

- Supraglottic, early stage: single modality
  - RT: include regional nodes (bilateral levels II-IV)
  - Surgery: partial laryngectomy + neck dissection

- Advanced stage: combined modality
  - Organ preservation (concurrent chemoradiation): VA larynx, RTOG 91-11
  - Surgery + adjuvant RT (+/- chemo)
    - Selection: need to consider disease and patient characteristics
Dose and fractionation: T1 glottis (Yamazaki et al. IJROBP 2006)

- Prospective, Randomized Trial, 1993-2001
- 180 pts with T1N0 Glottic Cancers
- Randomized to
  
  A) 2.00 Gy/fraction
    1) 60 Gy in 30 fractions (<2/3 VC)
    2) 66 Gy in 33 fractions (>2/3 VC)

  B) 2.25 Gy/fraction
    1) 56.25 Gy in 25 fractions (<2/3 VC)
    2) 63 Gy in 28 fractions (>2/3 VC)

- No significant increase in acute or chronic toxicity

Conclusion: Use 225 cGy per fraction to 63 Gy for T1 Glottic Ca
RTOG 91-11 LARYNX TRIAL


Median F/U 3.8 years

84%  
72%  
67%
Long Term Update of RTOG 91-11

Forastiere et al, JCO 2013

LARYNGEAL PRESERVATION

OVERALL SURVIVAL
**EORTC 24891 Laryngeal Preservation Trial**

- **Randomize**
  - Induction Chemotherapy (3 Cycles)
  - Complete Responders*
- PR/NR
  - Surgery
  - XRT
- Surgery
  - RT
- RT

**Induction Chemotherapy:** Cisplatin and 5 FU

J.L. Lefebvre et al, JNCI 88:890-899, 1996
EORTC 24891 Laryngeal Preservation Trial

<table>
<thead>
<tr>
<th></th>
<th>S + RT</th>
<th>CT + RT+ S</th>
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</thead>
<tbody>
<tr>
<td><strong>No. of patients</strong></td>
<td>94</td>
<td>100</td>
</tr>
<tr>
<td><strong>10-yr. PFS</strong></td>
<td>8.5%</td>
<td>10.5%</td>
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<tr>
<td><strong>10-yr. Survival</strong></td>
<td>13.8%</td>
<td>13.1%</td>
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<tr>
<td><strong>Distant Mets.</strong></td>
<td>36%</td>
<td>25%</td>
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<tr>
<td><strong>10 yr. Alive w/Larynx</strong></td>
<td>8.7%</td>
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</tr>
</tbody>
</table>

J.L. Lefebvre et al, JNCI 88:890-899, 1996; Annals Oncology, 2012
T4a Laryngeal Cancer
Patient selection/Patients of care/T4a
(Grover et al. IJROBP 2015)

- NCDB
  - 969 pts RT for T4a larynx cancer from 2003-2006
  - Patterns of care/survival

- Results
  - 2/3 treated with OP, 1/3 with initial TL
Organ Preservation for Advanced Larynx Cancer: Issues and Outcomes
Arlene A. Forastiere, Randal S. Weber, and Andy Tratti

Results
There are data from clinical trials to support induction chemotherapy, followed by radiotherapy (preferred approach in Europe) and concomitant cisplatin plus radiotherapy (preferred in North America) for nonsurgical preservation of the larynx. Treatment intensification by a sequential approach of induction, followed by concomitant treatment, is investigational. Transoral laryngeal microsurgery and transoral robotic partial laryngectomy have application in selected patients.

Conclusion
The management of locally advanced larynx cancer is challenging and requires an experienced multidisciplinary team for initial evaluation, response assessment, and support during and after treatment to achieve optimal function, quality of life, and overall survival. Patient expectations, in addition to tumor extent, pretreatment laryngeal function, and coexisting chronic disease, are critical factors in selecting surgical or nonsurgical primary treatment.
Selected topics for talented... When RT?

Locally advanced stages
Nasopharynx
Postoperative RT
Laryngeal preservation
Re-irradiation
New concepts, new trials

How? and what? (to expect)
22 retrospective studies

>550 pts

14% - 54% OS @ 5y
51% post-2000

OS @ 3y  OS @ 5y  Time recruitment 2.000
FDG-PET/CT in detecting nodal disease within 6 months after treatment

Systematic review + meta-analysis 20 studies (1293 patients)

**Sensitivity 83%, specificity 91%**

**HPV positive** tumors were associated with lower
sensitivity (75% vs 89%; p=0.01)
specificity (87% vs 95%; p < 0.005).

FDG-PET/CT within 6 months after (chemo)radiotherapy in HNSCC patients is a reliable method for ruling out residual/recurrent nodal disease

(less reliable in HPV positive tumors)

optimal surveillance strategy remains to be determined.
Ongoing RT practice oriented research...2017

ECOG 1308: HPV + Induction CT + Cetuximab +IMRT/Cetuximab

RTOG 1016: HPV + IMRT/CDDP vs IMRT/Cetuximab

RTOG 1216: > 60 Gy + CDDP vs Docetaxel vs Docetaxel/Cetuximab

ECOG 3311: HPV + risk adapted IMRT 50 vs 60 vs 66 Gy/CDDP

RTOG 1221: HPV + IMRT 70 Gy vs surgery (PORT)

RTOG 1305: IMRT 70 Gy/CDDP plasma EBV +/- Chemo/adjuvant
MOLECULAR IMAGE GUIDED RT (M-IGRT)

GTV... smaller
Nodes... more
Mis-match GTV... 20-40%
Macroscópic

TAC

\(^{18}\text{F-FDG}\) PET

Daisne et al, 2004
T3 N2c oropharynx: target adapted to M-IGRT
DOSE-ESCALATION BASED ON HIPOXIA M-IGRT

A: GTV Hipoxia

B: STANDARD PLAN

C: Dose-escalation based on HIPOXIA gradients

D: Dose-escalation based on HIPOXIA presence
TIME-IMAGE GUIDED RT (T-IGRT)

4D = time = movement = changes = adaptation = ART
Potential Target Deformations during Tx T-IGRT implications
Potential Dosimetric Changes

INCREASED MEAN DOSE TO PAROTID  5 Gy

Nishi et al, Radiother and Oncol 106 (2013) 85–89
Head and Neck Cancers: Very Advanced Head and Neck Cancer

NCCN Guidelines

- Cancer of the Lip
- Cancer of the Oral Cavity
- Cancer of the Oropharynx
- Cancer of the Hypopharynx
- Cancer of the Nasopharynx
- Cancer of the Glottic Larynx
- Cancer of the Supraglottic Larynx
- Ethmoid Sinus Tumors
- Maxillary Sinus Tumors
- Very Advanced Head and Neck Cancers
- Occult Primary
- Salivary Gland Tumors
- Mucosal Melanoma
MULTIDISCIPLINARY TEAM

The management of patients with head and neck cancers is complex. All patients need access to the full range of support services and specialists with expertise in the management of patients with head and neck cancer for optimal treatment and follow-up. Outcomes are improved when patients with head and neck cancers are treated in high-volume centers.

- Head and neck surgery
- Radiation oncology
- Medical oncology
- Plastic and reconstructive surgery
- Specialized nursing care
- Dentistry/prosthodontics
- Physical medicine and rehabilitation
- Speech and swallowing therapy
- Clinical social work
- Clinical nutrition
- Pathology (including cytopathology)
- Diagnostic radiology
- Adjunctive services
  - Neurosurgery
  - Ophthalmology
  - Psychiatry
  - Addiction services
  - Audiology
  - Palliative care

SUPPORT SERVICES

Follow-up should be performed by a physician and other health care professionals with expertise in the management and prevention of treatment sequelae. It should include a comprehensive head and neck exam. The management of head and neck cancer patients may involve the following:

- General medical care
- Pain and symptom management
  - Nutritional support
    - Enteral feeding
    - Oral nutrition
- Dental care for RT effects
- Xerostomia management
- Smoking and alcohol cessation
- Speech and swallowing therapy
- Audiology
- Tracheotomy care
- Wound management
- Depression assessment and management
- Social work and case management
- Supportive care

(See NCCN Guidelines for Adult Cancer Pain)
(See NCCN Guidelines for Distress Management)
(See NCCN Guidelines for Palliative Care)
Selected topics for talented... when, how and what

HPV and RT !... De-escalation? Not yet... but...
Locally advanced stages... CRT + dose-escalation + AFX?
   induction CT?
Nasopharynx... CRT tailored volume
Larynx preservation: CRT supra-tailored strategy
Postoperative RT... risk adapted CRT
Oligo-recurrent: 50% OS radical rescue (40% 2y OS re-RT)
New concepts... M-IGRT / T-IGRT
New trials ... Induction CT, viral status tailoring