Head and Neck Cancer
Locally Advanced Disease: Treatment Choice Based on Risk Factors

Optimizing Drug Prescription

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Outline of Talk

• Discuss risk stratifications in the multi-modality treatment of localized or locoregionally advanced SCCHN

• Highlight selected recently completed or currently ongoing phase III trials in locoregionally advanced SCCHN
Glossary

• **Sequential therapy:** Induction chemotherapy + concurrent chemo-radiotherapy/bio-radiotherapy

• **Chemo-additive:** Adding another agent (e.g. targeted agent) to a standard chemo-containing regimen

• **Chemo-sparing:** Using another agent (e.g. targeted agent) to replace or reduce chemotherapy in a chemo-containing regimen

• **Radio-sparing:** Using an alternate treatment (e.g. TORS, or systemic agent) to reduce RT dose/intensity
Treatment Algorithm:
Surgery as 1° Modality

Surgery (based on pathological features)

- High risk: ChemoRT
  - Clinical Trials: Chemo-additive, alternate cytotoxic agents
- Intermediate risk: RT
  - Clinical Trials: “Chemosparing”
- Low risk: RT
  - Clinical Trials: Radio-sparing in selected pts?
Post-Operative Adjuvant Therapy

Low Risk: No intermediate or high risk features

Intermediate Risk: LVI, PNI, 1 lymph node >3 cm, ≥2 lymph nodes (all <6 cm), close margins, T3/T4a

High Risk: Extracapsular extension, positive margins

Adjuvant Therapy: High Risk

- **Strategy 1:** Addition of targeted agents to CRT (chemo-additive)
  - Anti-EGFR agents:
    - Lapatinib – NCT004244255 (concurrent + 1 year maintenance)
    - Nimotuzumab – NCT00957086 (concurrent)
    - Afatinib – NCT01427478 (1 year maintenance)
Adjuvant Therapy: High Risk

- **Strategy 2:** Use of non-platinum cytotoxic chemotherapy

  - **RTOG 0234** (randomized phase II trial):
    - N = 238, median follow-up = 2.5 years
    - Compared (A) RT + weekly CDDP (30 mg/m$^2$) + Cetuximab vs (B) RT + weekly Docetaxel (15 mg/m$^2$) + Cetuximab
    - 2-year OS: 69% vs 79%, 2-year DFS: 57% vs 66%
    - Compared to RTOG 9501, absolute improvement in 2-yr DFS = 2% for Arm A and 11% for Arm B, due to improvement in distant control

  - **RTOG 1216** being planned (randomized phase II/III trial):
    - (A) RT + weekly CDDP (40 mg/m$^2$) vs (B) RT + weekly Docetaxel (15 mg/m$^2$) vs (C) RT + weekly Docetaxel (15 mg/m$^2$) + Cetuximab

Kies M et al. ASTRO 2009, abstract A-29, S14
Adjuvant Therapy: Intermediate Risk

- **Strategy:** Addition of targeted agents to RT
  - Anti-EGFR agents (Cetuximab):
    - RTOG 0920 – NCT00956007

N = 700

1° endpt = OS

- RT alone
- RT + Cetuximab starting 5 days prior to RT x 11 doses in total
Treatment Algorithm:
Radiation as 1° Modality

Radiation (based on HPV status, smoking status, stage, comorbidity, etc)

- High risk:
  - ChemoRT
  - Clinical Trials: Sequential strategy, Chemotherapy-additive

- Intermediate risk:
  - ChemoRT
  - Clinical Trials: Sequential strategy, Chemotherapy-sparing

- Low risk:
  - RT or ChemoRT
  - Clinical Trials: Chemotherapy-sparing, Radiotherapy-sparing
Stratification in SCCHN based on Risk of Death (from RTOG 0522): HPV, Smoking, Stage

- 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
    - 26 Had NO–N2a cancer
      - 114 of 266 (42.9%) were at low risk
  - 90 Had >10 pack-years
    - 64 Had N2b–N3 cancer
      - 79 of 266 (29.7%) were at intermediate risk
- 88 Had HPV-negative tumors
  - 23 Had ≤10 pack-years
    - 15 Had T2–T3 tumors
      - 73 of 266 (27.4%) were at high risk
  - 65 Had >10 pack-years

3-year OS
- 93%
- 71%
- 46%

Ang KK et al. NEJM 363:24-35, 2010
Risk stratification: 505 HPV known cases focusing on DM

PMH OPC 2001 – 2009

PMH 2001-2009:
- HPV(+) n=382
- HPV(-) n=123

HPV(+) Low-risk:
- RT-alone: 150
- CRT: 136

O’Sullivan B, Huang S, Siu L et al. JCO (Accepted)
Risk Stratification: HPV(+) Focusing on DM

- HPV(+) Low-risk of DM: not all suitable
  - Results reflect outcome of contemporary treatment
  - Not all low-risk HPV(+) subgroups appear suitable for treatment de-intensification with reduction/omission of chemotherapy
- e.g. N2c is a definite concern

<table>
<thead>
<tr>
<th>STRATA:</th>
<th>Cohort=CRT</th>
<th>Censored Cohort=CRT</th>
<th>Cohort=RT Alone</th>
<th>Censored Cohort=RT Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0-N2a</td>
<td>RT-alone----</td>
<td>CRT-----</td>
<td>N2b</td>
<td>RT-alone----</td>
</tr>
<tr>
<td>N2c</td>
<td>RT-alone----</td>
<td>CRT-----</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3-year DC Rate (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>N0-N2a (n=107)</th>
<th>N2b (n=112)</th>
<th>N2c (n=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT alone</td>
<td>97% (89-99)</td>
<td>89% (75-95)</td>
<td>73% (47-88)</td>
</tr>
<tr>
<td>CRT</td>
<td>88% (66-96)</td>
<td>98% (90-99)</td>
<td>92% (77-97)</td>
</tr>
<tr>
<td>P value</td>
<td>0.07</td>
<td>0.03</td>
<td><strong>0.02</strong></td>
</tr>
</tbody>
</table>

O’Sullivan B, Huang S, Siu L et al. JCO (Accepted)
“Unmet Needs” in Locoregionally Advanced SCCHN

- Localized and locoregionally advanced disease:
  - **High Risk**: Optimization of combined modality therapy for patients with high risk (goal: higher cure rates, less toxicity)
  - **Low Risk**: De-intensification of treatment for patients with favorable risk (goal: equal efficacy, less toxicity)
Sequential Therapy
(Induction Chemotherapy + Concurrent Chem-oradiotherapy or Bio-radiotherapy)
Phase III Trials of Different Sequential Therapies

**TAX 323 (unresectable stage III/IV):**
Median OS for TPF vs PF
= 18.8 mo vs 14.5 mo (HR 0.73, p=0.02)

**TAX 324 (unresectable or organ preservation):**
Median OS for TPF vs PF
= 71 mo vs 30 mo (HR 0.70, p=0.006)

# Phase III Trials of **Sequential Therapy vs CRT**

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>N</th>
<th>Induction Regimen</th>
<th>Concurrent Regimen</th>
<th>CR at end (%)</th>
<th>RSF or PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeCide (Cohen et al) N2, N3 dx</td>
<td>III</td>
<td>280 (400)</td>
<td>Docetaxel, Cisplatin, 5FU (TPF) x 2</td>
<td>Both arms: • Docetaxel, 5FU, Hydroxyurea + hyperfractionated RT</td>
<td>19% vs 15%</td>
<td>3-yr RFS: 67% vs 59%</td>
<td>3-yr OS: 75% vs 73% HR=0.91</td>
</tr>
<tr>
<td>Paradigm (Haddad et al) Stage III or IV</td>
<td>III</td>
<td>145 (300)</td>
<td>Docetaxel, Cisplatin, 5FU (TPF) x 3</td>
<td>Sequential arm: • Docetaxel wkly + Acc. Boost RT • Carboplatin wkly + Standard RT Concurrent arm: • Cisplatin wks 1, 4 + Acc. Boost RT</td>
<td>-</td>
<td>3-yr PFS: 67% vs 69%</td>
<td>3-yr OS: 73% vs 78%</td>
</tr>
</tbody>
</table>

Cohen E et al. ASCO 2012, abstract 5500; Haddad R et al. ASCO 2012, abstract 5501
Ongoing Phase III Trials of Sequential Therapy - 1

- Strategy - Factorial Design: 1) sequential therapy vs concurrent therapy? 2) chemoRT vs bioRT?

– GSTTC (Italian) H&N07 – NCT01086826

N = 320

1° endpt = OS

No Induction

RT + CDDP/5FU

RT + Cetuximab

Induction with TPF x 3

RT + CDDP/5FU

RT + Cetuximab

RT + Cetuximab
Ongoing Phase III Trials of **Sequential Therapy** - 2

- **Strategy:**
  1. sequential therapy vs concurrent therapy?
  2. chemoRT vs bioRT?

  — GORTEC 2007-02 – NCT01233843

- **Randomize**
  - No Induction → RT + Carboplatin/5FU
  - Induction with TPF x 3 → RT + Cetuximab

N = 360

1° endpt = CR rate
Ongoing Phase III Trials of **Sequential Therapy** - 3

- **Strategy:**
  1. sequential therapy vs concurrent therapy?
  2. chemoRT vs bioRT?

  — **GONO INTERCEPTOR — NCT00999700**

```
RANDOMIZE

N = 278
1° endpt = OS

No Induction → RT + CDDP

Induction with TPF x 3 → RT + Cetuximab
```
Chemo-Additive Strategy
## Spectrum Trial – HPV Analysis

<table>
<thead>
<tr>
<th></th>
<th>ITT (n = 657)</th>
<th>HPV+ (n = 83)</th>
<th>HPV- (n = 294)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-MAB + CT vs CT (mo)</td>
<td>11.1 vs 9.0</td>
<td>10.9 vs 12.1</td>
<td>11.8 vs 8.7</td>
</tr>
<tr>
<td>Stratified HR (95% CI)</td>
<td>0.87 (0.73-1.05)</td>
<td>1.02 (0.59-1.77)</td>
<td>0.71 (0.54-0.94)</td>
</tr>
<tr>
<td>Interaction test</td>
<td></td>
<td>p = 0.144</td>
<td></td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-MAB + CT vs CT (mo)</td>
<td>5.8 vs 4.6</td>
<td>5.5 vs 5.3</td>
<td>6.3 vs 5.1</td>
</tr>
<tr>
<td>Stratified HR (95% CI)</td>
<td>0.78 (0.66-0.92)</td>
<td>1.25 (0.74-2.12)</td>
<td>0.64 (0.5-0.83)</td>
</tr>
<tr>
<td>Interaction test</td>
<td></td>
<td>p = 0.018</td>
<td></td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-MAB + CT vs CT (mo)</td>
<td>36 vs 25</td>
<td>41 vs 25</td>
<td>37 vs 27</td>
</tr>
<tr>
<td>P-value odds ratio</td>
<td>0.007</td>
<td>0.21</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Vermorken J et al. ECCO 2011
Ongoing Phase III Trials in Locoregionally Advanced SCCHN (Chemo-Additive) - 1

- Strategy: Following concurrent chemoRT, maintenance PAN-HER inhibition vs placebo?
  - LUX-Head&Neck 2 – NCT01345669 (excludes base of tongue or tonsil and < 10 pack years of tobacco)

N = 669

1° endpt = DFS

2:1

Afatinib maintenance x 18 months

Placebo maintenance x 18 months

ChemoRT
Concurrent Therapy Utilizing Anti-EGFR Therapies
Randomized Phase II Trial of Laryngeal Preservation: TREMPLIN

- Strategy: Sequential therapy + concurrent chemoRT vs sequential therapy + concurrent bioRT (Chemo-Sparing)?
Randomized Phase II Trial of Laryngeal Preservation: TREMPLIN

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CDDP Arm (n = 60)</th>
<th>Cetuximab Arm (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compliance (got all cycles)</td>
<td>43%</td>
<td>71%</td>
</tr>
<tr>
<td>Grade 3-4 mucositis</td>
<td>47%</td>
<td>45%</td>
</tr>
<tr>
<td>Grade 3-4 in-field skin toxicity</td>
<td>26%</td>
<td>57%</td>
</tr>
<tr>
<td>Protocol modification due to acute toxicity</td>
<td>57%</td>
<td>29%</td>
</tr>
<tr>
<td>Late renal toxicity (all grade 1)</td>
<td>22%</td>
<td>0</td>
</tr>
<tr>
<td>Local +/- regional failures at median follow-up of 3 years</td>
<td>11.7%</td>
<td>21.4% (log-rank 0.14)</td>
</tr>
<tr>
<td>1º Endpoint: Larynx preservation at 3 months</td>
<td>95%</td>
<td>93%</td>
</tr>
<tr>
<td>Larynx function preservation at 18 months</td>
<td>87%</td>
<td>82%</td>
</tr>
<tr>
<td>Overall survival at 18 months</td>
<td>92%</td>
<td>89% (log-rank 0.44)</td>
</tr>
</tbody>
</table>

Lefebvre J et al. ASCO 2011 abstract 5501
Recently Completed Phase III Trials in Locoregionally Advanced SCCHN (Chemo-Sparing)

- **Strategy:** Concurrent chemoRT vs concurrent bioRT?
  
  – NCIC CTG (Canadian) HN6 – NCT00820248

\[ N = 320 \]

\[ 1^{\circ} \text{endpt} = \text{PFS} \]

- RT (standard fractionation) + CDDP x 3 cycles
- RT (accelerated fractionation) + Pantitumumab x 3 cycles
Ongoing Phase III Trials in Locoregionally Advanced SCCHN (Chemo-Sparing) - 1

• Strategy: Concurrent chemoRT vs concurrent bioRT?

– RTOG 1016 – NCT01302834 (p16 + oropharyngeal cancer only)

\[ \text{N} = 706 \]
\[ 1^\circ \text{endpt} = \text{OS} \]

\[ \text{RT (accelerated fractionation) + CDDP x 2 cycles} \]

\[ \text{RT (accelerated fractionation) + Cetuximab x 7 wks} \]
Ongoing Phase III Trials
in Locoregionally Advanced SCCHN (Chemo-Sparing) - 2

• Strategy: Following induction chemo, concurrent chemoRT vs concurrent bioRT?

– TTCC (Spanish) 2007-01 – NCT00716391

N = 458
1° endpt = OS

Induction with TPF x 3

RT (standard fractionation) + CDDP x 3 cycles

RT (standard fractionation) + Cetuximab x 7 wks
De-Intensification for Low-Risk Disease
Recently Completed Phase II Trial in Locoregionally Advanced SCCHN (Radio-Sparing)

- Strategy: Following induction chemo, de-intensify RT in combination with cetuximab?
  
  – ECOG 1308 – NCT01084083 (p16 + oropharyngeal cancer only)

- N = 83
- 1° endpt = 2-year PFS

Induction chemo with Paclitaxel, Cisplatin and Cetuximab x 3

- cCR
- cPR or SD

RT (low dose at 54 Gy/27) + Cetuximab

RT (standard) + Cetuximab
Transoral Robotic Surgery (TORS)

- Surgeon sits in a console and controls micromanipulators to move the arms of a robot placed at the patients bedside.
- Highly magnified 3-D view of the surgical field.
- Precise, scaled and filtered motions to the operating arms.
- Needs hands-on course training and quality assurance.
Transoral Robotic Surgery (TORS)

• Advantages:
  – Less invasive, avoids manibulotomy and its associated morbidity
  – Decreased manipulation and dissection of healthy tissues, improved cosmetic outcome
  – Decreased need for tracheotomies
  – Early return to oral intake
  – Shortened hospital stay
Early Stage SCCHN

TORS +/- post op RT vs RT

Low risk e.g. T1-2, N0-1

TORS + post op (C)RT vs CRT

Intermediate risk e.g. T1-3, N2-3, HPV+
Summary: Strategies to Optimize Therapy in High Risk Locoregionally Advanced SCCHN

• Intensification of chemotherapy and radiotherapy – we are at or near limit
• Finding more effective systemic agents to replace or add to current regimens
• Understanding the biology of SCCHN and finding the right drug for the right target
• Targeting primary and acquired resistance mechanisms
Summary: Strategies to Optimize Therapy in **Low Risk** Locoregionally Advanced SCCHN

• De-intensification of chemotherapy and radiotherapy – balance of preserving high cure rates while reducing acute and late toxicities

• Understanding the biology of SCCHN so that patients who relapse despite having low risk can be identified early