CHEMOTHERAPY AND TARGET THERAPY FOR HEAD AND NECK CANCER
Head and neck cancer

- Heterogeneous disease
  - Oral cavity, oropharynx, larynx, hypopharynx
    - Mostly SCC
      - Common etiology: smoking and drinking (betel nut for oral ca)
      - Similar biological behavior
  - Nasopharynx:
    - WHO class type III: undifferentiate ca (NPC)
  - Nasal and paranasal sinus
  - Salivary gland
NASOPHARYNGEAL CANCER
Pathology – WHO classification

 Nasopharyngeal carcinoma
  • Keratinizing squamous cell ca: type I
    ○ Similar with that in rest of aerodigestive tract
  • Non-keratinizing ca: type II and III
    ○ Differentiated non-keratinizing ca (type II)
    ○ Undifferentiated ca (type III)

 Type I distinct from type II/III
  • Type II/III so called “NPC”
Features of type II/III

- EBV association
  - EBV-encoded RNA in nearly all tumor cells
  - Premalignant lesion also harbor EBV
- Radiation sensitivity
- Tend to distant metastasis
Epidemiology

 Uncommon disease in most countries
  • Incidence 1/100000
 More frequent in
  • Southern China: Hong Kong 15-30/100000
  • Northern Africa
  • Alaska
 Genetic, ethnic, environment factors
Epidemiology

- North America
  - I/II/III: 25/12/63% $\rightarrow$ some are SCCs

- Southern Chinese
  - I/II/III: 2/3/95% $\rightarrow$ almost all typical NPC
Symptoms/signs

- Epistaxis and nasal obstruction/discharge
  - Mass in nasopharynx
- Tinnitus and hearing impairment
  - E-tube dysfunction, lateral extension
- Headache, diplopia, facial pain/numbness
  - Skull-base invasion, nerve palsy (5th/6th)
- Neck mass
- Signs of distant metastasis
  - Lung/bone/liver
Diagnosis and staging

- Endoscopic exam: nasopharynx
  - Punch biopsy
- Plain film: CXR
- Abdominal echo
- Bone scan
- CT and MRI
  - Both for local and distant evaluation
  - MRI better for soft tissue resolution
  - Low-risk( stage I ) may not need
  - After treatment, MRI better
- PET: role to be defined
Prognostic factor

- TNM
- EBV
- Tumor size, age, gender, nerve palsy ....
NPC

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
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<tr>
<td>Stage I</td>
<td>T1</td>
<td>N0</td>
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<tr>
<td>Stage IIa</td>
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<td>Stage IIb</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
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<td></td>
<td>T2a</td>
<td>N1</td>
<td>M0</td>
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<td>T2b</td>
<td>N0, N1</td>
<td>M0</td>
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<td>N2</td>
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</tr>
<tr>
<td></td>
<td>T3</td>
<td>N0, N1, N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>T4</td>
<td>N0, N1, N2</td>
<td>M0</td>
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<tr>
<td>Stage IVB</td>
<td>any T</td>
<td>N3</td>
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<tr>
<td>Stage IVc</td>
<td>any T</td>
<td>any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

T = tumor; N = node; M = metastasis.

Disease status monitored by plasma EBV DNA

Stage I/II over 90% cure rates
EBV and NPC prognosis

**Table 2. Actuarial Survival of Patient Groups With Different UICC Stages and With Different EBV DNA Levels Within UICC Stages**

<table>
<thead>
<tr>
<th>Stage</th>
<th>No. of Patients</th>
<th>5-Year Survival (%)</th>
<th>95% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>36</td>
<td>92</td>
<td>83 to 100</td>
</tr>
<tr>
<td>II</td>
<td>119</td>
<td>80</td>
<td>73 to 88</td>
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<tr>
<td>III</td>
<td>95</td>
<td>73</td>
<td>64 to 82</td>
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<tr>
<td>IV</td>
<td>126</td>
<td>47</td>
<td>38 to 56</td>
</tr>
<tr>
<td>I + II, low DNA*</td>
<td>108</td>
<td>91</td>
<td>85 to 97</td>
</tr>
<tr>
<td>I + II, high DNA*</td>
<td>47</td>
<td>64</td>
<td>53 to 75</td>
</tr>
<tr>
<td>III + IV, low DNA</td>
<td>73</td>
<td>66</td>
<td>50 to 81</td>
</tr>
<tr>
<td>III + IV, high DNA</td>
<td>148</td>
<td>54</td>
<td>44 to 65</td>
</tr>
</tbody>
</table>
Pattern of failure

- T1-2 N0-1: good outcome
- T3-4 N0-1: local failure dominant
- T1-2 N2-3: distant failure dominant
- T3-4 N2-3: both
Treatment

- **RT as the mainstay**
  - Difficult surgical approach
  - Sensitive to radiotherapy

- **RT volume (field) and dose**
  - Primary tumor: 65-75 Gy
  - Involved neck: 65-70 Gy
  - Uninvolved neck: 50-60 Gy
Morbidity from RT

- **Dose-limiting organ**
  - Brain stem
  - Spinal cord
  - Pituitary-hypothalamic axis
  - Temporal lobes
  - Eyes
  - Middle/inner ears
  - Parotid glands
Efficacy of RT

- Control rate
  - T1/T2: 75-90%
  - T3/T4: 50-75%
  - N0/N1: 90%
  - N2/N3: 70%

- Incorporate chemotherapy to RT
Incorporate chemotherapy

- Induction (neoadjuvant)
- Concurrent
- Adjuvant
Adjuvant chemotherapy

Two phase III randomized trial

- **Italian (Non-cisplatin based)**
  - R/T vs R/T + VCA
    - Vincristine/cyclophosphamide/adriamycin
  - No benefit

  *JCO 6: 1401-10, 1988*

- **TCOG**
  - R/T vs R/T + PFL (cisplatin, 5FU, LV)
  - No benefit
    - 6 tx-related mortality

  *Int J Radiat oncol Biol phys 2002;52:1238-44*
Concurrent chemoradiotherapy

Three phase III randomized trial

- U.S.: Intergroup study 0099 trial
  \[\text{JCO 16: 1310-1317, 1998}\]

- Hong Kong
  \[\text{JCO 20: 2038-2044, 2002}\]

- Taiwan: TVGH
  \[\text{JCO 21: 631-637, 2003}\]
Intergroup Study 0099

- Phase III trial
  - CCRT + adjuvant CT
  - RT alone
    - RT: 70 Gy
    - Cisplatin 100mg/m², D1, q3w x 3 (for CCRT)
    - PF x 3
      - Cisplatin 80mg/m², D1 + 5FU 1000mg/m², D1-4, q4w
  - Benefit in RFS and OS

*JCO 16: 1310-1317, 1998*
Hong Kong study

- Ho’s N2, or N3 stage or N1 with node size > 4cm, 1994-1999
- CCRT vs RT alone
  - RT: 66Gy
  - Cisplatin 40mg/m², weekly x 8
- Primary end point: PFS
  - Positive, in T3 group

*JCO 20: 2038-2044, 2002*
Taiwan, VGH

- TVGH, Taiwan, 1993-1999
- CCRT vs RT alone
  - RT: 70-74 Gy
  - Cisplatin $20\text{mg}/\text{m}^2/\text{d} + 5\text{FU} 400\text{mg}/\text{m}^2/\text{d}$ by 96 hrs infusion) $\times 2$
- Benefit: PFS and OS

Neoadjuvant C/T + R/T

Three phase III randomized trial

- Asian-Oceanian Clinical Oncology Association study
  - No benefit, in RFS and OS
    
    *Cancer* 1998; 83: 2270-83

- International Nasopharynx Cancer Study Group
  - Benefit in DFS, not OS
    

- China
  - Benefit in DFS, not OS
    
    *JCO* 2001; 19:1350-7
Incorporate chemotherapy

- Induction (neoadjuvant)
- Adjuvant

- Concurrent → current standard

- Ongoing: induction C/T → CCRT
Meta-analysis-CCRT vs RT

78 randomized controlled trials (9279 patients)

![Meta-analysis of chemoradiotherapy compared to radiotherapy alone for stage III/IV nasopharyngeal cancer](image)

<table>
<thead>
<tr>
<th>Chemotherapy timing</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio [OR], 95% CI</td>
</tr>
<tr>
<td></td>
<td>OS</td>
</tr>
<tr>
<td>Neoadjuvant alone</td>
<td>0.65 (0.51-0.84)</td>
</tr>
<tr>
<td>Concurrent alone</td>
<td>0.72 (0.40-1.30)</td>
</tr>
<tr>
<td>Concurrent + adjuvant</td>
<td>0.30 (0.16-0.55)</td>
</tr>
<tr>
<td>Adjuvant alone</td>
<td>0.49 (0.18-1.31)</td>
</tr>
<tr>
<td>All</td>
<td>0.65 (0.51-0.83)</td>
</tr>
</tbody>
</table>

Proc Am Soc Clin Oncol 2004; 23:491a
Recurrent/residual disease

- **Site**
  - Neck
  - Nasopharynx
  - Distant
    - Bone, lung, liver

- **Treatment option**
  - Surgery
  - Re-irradiation
  - Systemic chemotherapy: palliation
Palliative Chemotherapy

- **Xeloda** 1.25 g/m² bid: PR 17.6%; CR 5.9%; SD 52.9%; PD 23.5%; TTP 4.9 mo, MS 7.6 mo
- **Gemzar** 1250 mg/m², d1,8/21d: RR 48%; TTP 5.1 mo; MS 10.5 mo
- **CPT-11**: RR 14%; MS 11.4 months (28 patients)
- **Vinorelbine** 20 mg/m² followed by Gemzar 1000 mg/m²; d1,8/21d: RR 36%; RD 5.1 mo; PFS 5.6 mo; MS 11.9 mo
- **Gemzar+Vinorelbine**: RR 36% (39 patients); median survival 9 months
- **Carboplatin AUC 5.5+Taxol** (175 mg/m², 3hrs/21d): PR 25%, SD 25%; MS 9.5 mo
- **Ifosfamide plus leucovorin-modulated 5-FU**: RR 56% in a report of 18 patients; although median survival had not been reached, 51% were still alive at one-year
- **Erbitux+Carboplatin**: RR 12%; MS 8 months (50 patients)
Chemotherapy and Target therapy

HEAD AND NECK SCC
Outline

- Introduction, staging
  - Who needs multimodality treatment
- Incorporate chemotherapy to definitive local tx
  - Adjuvant
  - Induction
  - Concurrent
- Organ preservation
  - Laryngeal cancer as an example
Anatomy
Generally, T stage

- Depends on anatomical location, complicate

- General concept of T stage
  - T1, T2: confined, not invade adjacent tissue
  - T3: larger, may invade adjacent tissue
  - T4: deeply invade adjacent tissue/organ
    - 4a, 4b: depends on extend of invasion
    - Critical structure: skull base, pre-veterbral fascia, internal carotid artery, mediastinum
T stage of oropharyngeal cancer

- **T1**: Invade to adjacent tissue, less extensive
- **T2**: ≤2cm
- **T3**: 2-4 cm
- **T4a**: ≥4cm
- **T4b**: Invade to adjacent tissue, more extensive
N1  Single ipsilateral, < 3cm

Ipsilateral  

Contralateral
N2a  Single ipsilateral, 3-6 cm

Ipsilateral  Contralateral

Single, 3-6 cm
N2b  Multiple ipsilateral, < 6cm

Ipsilateral

Contralateral
N2c  Bilateral or contralateral, < 6cm

Ipsilateral

Contralateral
N3 Any LN > 6cm

Ipsilateral

Contralateral
## Staging

<table>
<thead>
<tr>
<th>Stage I</th>
<th>T1</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
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<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVa</td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>N1</td>
<td>M0</td>
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<td></td>
<td>T1</td>
<td>N2</td>
<td>M0</td>
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<td>T2</td>
<td>N2</td>
<td>M0</td>
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<tr>
<td></td>
<td>T3</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>N2</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVb</td>
<td>T4b</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVc</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
Resectability

- Depends on T stage
  - T1, T2: resectable
  - T3: may be resectable
  - T4: mostly unresectable

- Depends on surgical team
  - Wide excision → reconstruction
  - ENT surgeon → plastic surgeon

- Depends on patients
  - Organ preservation
TNM Staging

- Early stage (Stage I – II)
- Locoregionally advanced (Stage III – IVB)
- Metastatic (Stage IVC)

Treatment modality
TNM Staging

- Early stage (Stage I – II)
- Locoregionally advanced (Stage III – IVB)
- Metastatic (Stage IVC)

Treatment modality

- Surgery
- Or
- Radiotherapy
TNM Staging

- Early stage (Stage I – II)
- Locoregionally advanced (Stage III – IVB)
- Metastatic (Stage IVC)

Treatment modality

- Surgery
- Surgery or Radiotherapy
- Radiotherapy
- Chemotherapy
- Target Therapy
Incorporation of chemotherapy

- Before definitive treatment:
  - Induction/neoadjuvant chemotherapy

- After definitive treatment
  - Adjuvant/consolidation chemotherapy

- Concurrent with radiotherapy
  - Concurrent chemoradiotherapy
442 pts, resectable, III/IV, SCC

4 yrs | DFS | OS | LRR | Dist Mets
--- | --- | --- | --- | ---
CT/RT | 46% | 46% | 19% | 15%
RT | 38% | 44% | 24% | 23%
p | NS | NS | NS | 0.03

Compliance of adjuvant C/T: 63%

Cisplatin 100mg/m2, D1
5-FU 1000mg/m2/d IVF 24hrs, D1-D5 q3w
443 pts, resectable, III/IV, SCC

Cisplatin 100mg/m², D1
Bleomycin 15mg/m², D3-D7

C/T x 1

Surgery

XRT

C/T x 1

Surgery

XRT

C/T x 6

Cisplatin 80mg/m², monthly

Compliance:
9% complete 6 cycles
27% complete > 3 cycles
45% received none

Oral 46%
Hypopharynx 35%
Larynx 19%

<table>
<thead>
<tr>
<th></th>
<th>5 yrs</th>
<th>DFS</th>
<th>OS</th>
<th>LRR</th>
<th>Dist Mets</th>
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<tbody>
<tr>
<td>A</td>
<td>55%</td>
<td>35%</td>
<td>41%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>49%</td>
<td>37%</td>
<td>42%</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>64%</td>
<td>45%</td>
<td>30%</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.011 (C vs A)</td>
<td></td>
</tr>
</tbody>
</table>

Cancer 1987; 60: 301-311
J Clin Oncol 1990; 8: 838-847
Adjuvant chemotherapy

- Poor drug delivery
- Decrease distant metastasis
- No effect on locoregional control
- No survival impact
  - Owing to insufficient dose density?
  - Disease nature-related?
**GETTEC, French**

318, HNSCC, oropharynx stage II-IV

Induction C/T

- Cisplatin 100mg/m², D1
- 5-FU 1000mg/m², D1-D5
  - q3w, 3 cycles

Operable: Surgery → RT
Inoperable: RT

Operable: Surgery → RT
Inoperable: RT

---

<table>
<thead>
<tr>
<th>Type of event</th>
<th>Number of events</th>
<th>Relative risk</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loco-regional recurrence or head neck second primary</td>
<td>118</td>
<td>1.15</td>
<td>0.14–1.69</td>
<td>NS</td>
</tr>
<tr>
<td>Metastasis</td>
<td>54</td>
<td>1.36</td>
<td>0.79–2.34</td>
<td>NS</td>
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<tr>
<td>Second primary other than head and neck</td>
<td>25</td>
<td>1.23</td>
<td>0.55–2.75</td>
<td>NS</td>
</tr>
<tr>
<td>Death</td>
<td>165</td>
<td>1.39</td>
<td>1.03–1.88</td>
<td>0.04</td>
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</table>
GETTEC, French

- Chemotherapy vs. No chemotherapy: Overall survival, p = 0.03
- Chemotherapy vs. No chemotherapy: Dz-free survival, p = 0.11
GSTTC, Italy

237, HNSCC, stage III/IV

Induction C/T

Cisplatin 100mg/m2, D1
5-FU 1000mg/m2, D1-D5

q3w, 4 cycles

Operable: Surgery → RT
Inoperable: RT

Operable: Surgery → RT
Inoperable: RT

Oral cavity
Oropharynx
Hypopharynx
Para-nasal sinus

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
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<tr>
<td>Operable</td>
<td>29%</td>
<td>27%</td>
</tr>
<tr>
<td>Inoperable</td>
<td>71%</td>
<td>73%</td>
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</tbody>
</table>
All pts

Overall survival

3-yr distant metastasis rate

<table>
<thead>
<tr>
<th></th>
<th>Inoperable</th>
<th>Operable</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>24%</td>
<td>3%</td>
</tr>
<tr>
<td>B</td>
<td>42%</td>
<td>31%</td>
</tr>
<tr>
<td>p value</td>
<td>0.04</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Operable group

Overall survival

Inoperable group

Overall survival

Log-Rank = 0.12; P = .73

Log-Rank = 4.04; P = .04
158, Head Neck epidermoid carcinoma, stage III/IV

**Induction C/T**

- Cisplatin 50mg/m², D1
- MTX 40mg/m², D1
- Bleomycin 15U/m², D1, D8
- Vincristine 2mg, D1

Q3w, 3 cycles

**Surgery → RT**

Oral cavity 35%
Oropharynx 28%
Hypopharynx 16%
Larynx 21%

4yr | OS | DFS | Local recur | Regional recur | Distant mets
--- | --- | --- | --- | --- | ---
A | 40% | 31% | 40% | 14% | 49%
B | 38% | 23% | 48% | 24% | 28%

p | 0.07

→ No survival benefit

Laryngoscope 1988; 98: 1205
Induction chemotherapy

- Good drug delivery
- Decrease distant metastasis
  - GSTTC, SWOG
- No improvement of locoregional control
- Survival impact??
Concurrent chemoradiotherapy
Sanchiz F et al.

859 pts, HNSCC stage III/IV

Conventional RT
- 60Gy/30fx, 2Gy/d

HFxRT
- 70.4Gy, 1.1Gy bid

CCRT (conventional RT)
- 5FU 250mg/m2, qod

<table>
<thead>
<tr>
<th>Oral cavity</th>
<th>RR</th>
<th>10yr OS</th>
<th>10yr DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>67.8%</td>
<td>17%</td>
<td>17%</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td>90%</td>
<td>40%</td>
<td>31%</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>96.3%</td>
<td>42%</td>
<td>37%</td>
</tr>
<tr>
<td>Larynx</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

p
- <0.01 (A v B)
- <0.01 (A v C)
- <0.01 (A v C)


175 pts, HNSCC T3/T4

RT alone

CCRT

Identical RT in both arms
RT: 60Gy/30fx, conventional
C/T: 5-FU 1200mg/m2/d, infusion
D1-D3, D22-D24

<table>
<thead>
<tr>
<th>Oral cavity</th>
<th>Complete response</th>
<th>3yr PFS</th>
<th>3yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
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<tr>
<td>Oropharynx</td>
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</tr>
<tr>
<td>Hypopharynx</td>
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<td></td>
<td></td>
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<tr>
<td>Larynx</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

More mucositis, weight loss, and skin toxicity in CCRT arm

Browman GP et al
### Patient Information

- **100 pts, HNSCC stage III/IV**

### Treatment Options

- **RT alone**
  - RT: 66-72Gy, conventional, 1.8-2Gy/fx
  - Cisplatin: 20mg/m2/d
  - 5FU: 1000mg/m2/d
  - Infusion, D1-D4, D22-D25

- **CCRT**

### Sites of Tumor

<table>
<thead>
<tr>
<th>Site</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>4%</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>44%</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>16%</td>
</tr>
<tr>
<td>Larynx</td>
<td>36%</td>
</tr>
</tbody>
</table>

### Survival Outcomes

<table>
<thead>
<tr>
<th>5yr</th>
<th>OS</th>
<th>RFS</th>
<th>Dist. Mets-free survival</th>
<th>OS with primary site preserve</th>
<th>Local control without resection</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT</td>
<td>48%</td>
<td>51%</td>
<td>75%</td>
<td>34%</td>
<td>45%</td>
</tr>
<tr>
<td>CCRT</td>
<td>50%</td>
<td>62%</td>
<td>84%</td>
<td>42%</td>
<td>77%</td>
</tr>
<tr>
<td>p value</td>
<td>0.55</td>
<td>0.04</td>
<td>0.09</td>
<td>0.004</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Survival benefit from better local control**

*Aldelstein DJ et al. Cancer 2000; 88: 876-883*
GORTEC

226 pts, oropharynx III/IV

CCRT

RT alone

Identical RT in both arms
RT: 7000cGy/35fx, conventional

Carbo 70mg/m2/d, D1-D4
5FU 600mg/m2/d, D1-D4 q3w, 3 cycles

Dose delivery

<table>
<thead>
<tr>
<th></th>
<th>RT dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT</td>
<td>6920 cGy</td>
</tr>
<tr>
<td>CCRT</td>
<td>6960 cGy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbo</td>
<td>98%</td>
<td>86%</td>
<td>66%</td>
</tr>
<tr>
<td>5FU</td>
<td>98%</td>
<td>88%</td>
<td>67%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>3yr</th>
<th>DFS</th>
<th>OS</th>
<th>Dist. mets</th>
<th>LR control</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCRT</td>
<td>31%</td>
<td>51%</td>
<td>11%</td>
<td>66%</td>
<td></td>
</tr>
<tr>
<td>RT</td>
<td>20%</td>
<td>42%</td>
<td>11%</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.04</td>
<td>0.02</td>
<td>NS</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

Journal of National Cancer Institute 1999; 91:2081-2086
Jeremic B et al, Japan

130 pts, HNSCC stage III/IV

HFxRT alone

CCRT (HFxRT)

Identical RT in both arms
RT: 77Gy/70fx/35d, 1.1Gy bid
C/T: 5FU 6mg/m2/d, 5days/wk

5yr OS PFS Local recur.-PFS Dist. Mets-PFS

<table>
<thead>
<tr>
<th></th>
<th>5yr</th>
<th>OS</th>
<th>PFS</th>
<th>Local recur.-PFS</th>
<th>Dist. Mets-PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCRT</td>
<td>46%</td>
<td>41%</td>
<td>50%</td>
<td>86%</td>
<td></td>
</tr>
<tr>
<td>RT</td>
<td>25%</td>
<td>25%</td>
<td>36%</td>
<td>57%</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.0075</td>
<td>0.0068</td>
<td>0.041</td>
<td>0.0013</td>
<td></td>
</tr>
</tbody>
</table>

Similar stomatitis, esophagitis in both arm, more leukopenia and thrombocytopenia in CCRT arm
ECOG RTOG 295 pts, HNSCC unresectable III/IV

A: RT alone
RT: 7000cGy/35fx, conventional identical in three arms
Cisplatin 100mg/m2, D1, D22, D43

B: CCRT
CR or unresectable CCRT (RT 3000cGy)
PR CCRT (RT 3000cGy)
Cisplatin 75mg/m2, D1
5FU 1000mg/m2/d x 4d q4w x 3

C: CCRT (RT 3000cGy)

Oral cavity 13%
Oropharynx 59%
Hypopharynx 19%
Larynx 9%

<table>
<thead>
<tr>
<th>Treatment</th>
<th>3y OS</th>
<th>Dist. Mets as first site</th>
<th>Treatment compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>23%</td>
<td>17.9%</td>
<td>92.6%</td>
</tr>
<tr>
<td>B</td>
<td>37%</td>
<td>21.8%</td>
<td>85.1%</td>
</tr>
<tr>
<td>C</td>
<td>27%</td>
<td>19.1%</td>
<td>73%</td>
</tr>
<tr>
<td>p</td>
<td>0.014 (A vs B)</td>
<td>NS</td>
<td>0.001(A vs C) 0.05(B vs C)</td>
</tr>
</tbody>
</table>

215 pts, HNSCC stage III/IV, unresectable

**RT 70Gy/35fx**

**C/T → RT (A)**
- Cisplatin 100mg/m2, D1
- 5-FU 1000mg/m2, D1-D5
  - Q3w x 3

**CCRT (B)**
- Cisplatin 60mg/m2, D1
- 5-FU 800mg/m2, D1-D5
  - Qw x 7

---

**Table:**

<table>
<thead>
<tr>
<th></th>
<th>LR recurrence</th>
<th>Dist Mets</th>
<th>3-yr OS</th>
<th>3-yr dz specific survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td>55%</td>
<td>10%</td>
<td>36%</td>
<td>41%</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>41%</td>
<td>7%</td>
<td>42%</td>
<td>55%</td>
</tr>
</tbody>
</table>

**NS**

p=0.011

---

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Cisplatin</td>
<td>97%</td>
<td>88%</td>
</tr>
<tr>
<td>% 5-FU</td>
<td>97%</td>
<td>79%</td>
</tr>
<tr>
<td>% RT(&gt;65Gy)</td>
<td>78%</td>
<td>81%</td>
</tr>
<tr>
<td>% RT delay</td>
<td>No difference</td>
<td></td>
</tr>
</tbody>
</table>
Concurrent chemoradiotherapy

- Enhance locoregional control
- Minimal effect in distant metastasis
- Improve survival
  - Superior than sequential chemoradiotherapy
  - Disease nature: local recurrence predominant
- Enhance RT toxicity
  - Mucositis, skin toxicity, BW loss
  - Leukopenia depends on C/T type
Brockstein B et al

**PFLI**
- Cisplatin 100mg/m², D1
- 5FU 640mg/m²/d, CVI, D1-D5
- Leucovorin 100mg q4h po, D1-D6
- INF-α 2MU/m²/d, D1-D6
- Leucovorin 100mg q4h po, D1-D6
- INF-α 2MU/m²/d, D1-D6
- q3w

164 pts → Induction C/T x 3 → CCRT

**PFLI-FHX**
- 5FU 800mg/m²/d × 5/wk
- Hydroxyurea 1000mg q12h, 11 doses/wk
- RT 6000cGy/30fx

164 pts

**(C/T)HF2X**
- 230 pts → Intensified CCRT

230 pts

- Cisplatin 100mg/m², D1 or Paclitaxel 100mg/m², D1
- q3w × 3
- 5FU 800mg/m²/d × 5/wk
- Hydroxyurea 1000mg q12h, 11 doses/wk
- RT 6000cGy/30fx


C/T impact on failure pattern

- Induction or adjuvant chemotherapy
  - Decrease distant metastasis
    - Related to systemic dose, adequate delivery?

- Chemotherapy concurrent with RT
  - Decrease locoregional recurrence
    - Enhance RT effect

- Add induction chemotherapy to CCRT
  - To reduce distant failure since local control adequate
Yale 6557 protocol

42 pts, HN cancer, stage III/IV resectable/unresectable

C/T: Cisplatin 20mg/m2/d x 4d, 5FU 800mg/m2/d x 4d, LV 500mg/m2/d x 4d
C/T x 2

CCRT: RT: 70Gy/35fx, Cisplatin 100mg/m2, q3w

q4w

Non-responder operation

- Induction C/T: RR 76%
- C/T → CCRT: 67% CR

<table>
<thead>
<tr>
<th>Site</th>
<th>5y PFS</th>
<th>5y OS</th>
<th>2y Local control</th>
<th>2yr Distant control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypopharynx</td>
<td>54%</td>
<td>52.4%</td>
<td>76.3%</td>
<td>79%</td>
</tr>
<tr>
<td>Larynx</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tongue base</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tonsil</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
59 pts, HN cancer, resectable stage III/IV

<table>
<thead>
<tr>
<th>Location</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypopharynx</td>
<td>22 pts</td>
</tr>
<tr>
<td>Tongue base</td>
<td>37 pts</td>
</tr>
</tbody>
</table>

C/T: Cisplatin 100mg/m², 5FU 1000mg/m²/d x 5d  
CCRT: RT: 72Gy/36fx  
Cisplatin 100mg/m², q3w  

C/T x 2  
Non-responder operation

CCRT  
Non-responder operation

• Induction C/T: RR 78%  
• C/T → CCRT: 54% CR

<table>
<thead>
<tr>
<th></th>
<th>3y PFS</th>
<th>3y OS</th>
<th>3y PFS with Organ preservation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>57%</td>
<td>64%</td>
<td>52%</td>
</tr>
</tbody>
</table>

Journal of Clinical Oncology 2005; 23: 88-95
Incorporate Taxane

- Improve response rate in metastatic dz
  - 70% → 90%

- Incorporate to induction regimen
  - Eliminate more micrometastasis
Taxane Cisplatin 5-FU vs. Cisplatin 5-FU
**TAX 324 Phase III Trial of Induction Docetaxel-Cisplatin-5FU (TPF) vs PF in Unresectable HNC: Study Design**

**Patient Population**
- Stage III or IV
- Inoperable SCCHN

**Stratification**
- Center
- N status
- Primary site

**Endpoints**
- Primary: OS
- Secondary: progression-free survival, response rates after induction, toxicity

---

N = 501

- **TPF**
  - q3wk x 3 cycles

- **PF**
  - q3wk x 3 cycles

- RT+CT

- Possible surgery

---

1. Cisplatin: 100 mg/m² D1 – 5FU: 1000 mg/m² D1 – D5
2. Docetaxel: 75 mg/m² D1 - CDDP: 100 mg/m² D1 – 5FU: 1000 mg/m² D1 – D4
3. Weekly Carboplatin (AUC 1.5) x 7 - Conventional radiotherapy = 70 Gy

Induction Chemotherapy

TPF > PF

Median OS: 71M vs. 30M

A

Overall Survival (%)

0 10 20 30 40 50 60 70 80 90 100

0 6 12 18 24 30 36 42 48 54 60 66 72 78

Months

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>TPF</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
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<th></th>
<th></th>
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<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>255</td>
<td>234</td>
<td>196</td>
<td>176</td>
<td>163</td>
<td>136</td>
<td>105</td>
<td>72</td>
<td>52</td>
<td>45</td>
<td>37</td>
<td>20</td>
<td>11</td>
<td>10</td>
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<td>5</td>
<td>4</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>246</td>
<td>223</td>
<td>169</td>
<td>146</td>
<td>130</td>
<td>107</td>
<td>85</td>
<td>57</td>
<td>36</td>
<td>32</td>
<td>28</td>
<td>10</td>
<td>7</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### TAX 324: Toxicity During Induction Chemotherapy

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>TPF (n=251)</th>
<th>PF (n=243)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NCIC-CTC Classification</strong></td>
<td><strong>Grade 3/4</strong></td>
<td><strong>Grade 3/4</strong></td>
</tr>
<tr>
<td>Anemia</td>
<td>12%</td>
<td>9%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>4%</td>
<td>11%*</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>83%</td>
<td>56%*</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>12%</td>
<td>7%*</td>
</tr>
<tr>
<td>Nausea</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>21%</td>
<td>27%</td>
</tr>
<tr>
<td>Lethargy</td>
<td>5%</td>
<td>10%*</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8%</td>
<td>10%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>12%</td>
<td>12%</td>
</tr>
</tbody>
</table>

*Statistically significant (P < .05)

TAX 324 Phase III Trial of Induction TPF: Key Points

- TPF significantly improves survival versus PF
  - 14% absolute improvement in 3-y survival
  - 10% absolute improvement in 5-y survival
  - 26% reduction in mortality (P = 0.014)
- Sequential therapy with TPF is tolerable and safe
  - Toxicity of TPF arguably less than that of PF
  - No significant difference in long-term toxicities (enteral feeding tube and tracheostomy)
- Sequential therapy with TPF followed by carboplatin-based chemoradiotherapy represents an acceptable standard of care for locally-advanced SCCHN
Ongoing trials

**HNSCC, locally advanced**

**Induction C/T**

**CCRT**

**Table 2. Randomized Phase III Trials Comparing Concurrent Chemoradiotherapy With Induction Chemotherapy Followed by Concurrent Chemoradiotherapy**

<table>
<thead>
<tr>
<th>Group</th>
<th>Stages</th>
<th>Sites</th>
<th>Induction Regimen</th>
<th>Concurrent Regimen</th>
<th>Survival End Point</th>
<th>Targeted Improvement (%)</th>
<th>Accrual Goal (No. of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Chicago</td>
<td>N 2-3</td>
<td>All</td>
<td>DPF × 2</td>
<td>DFHX</td>
<td>3 years</td>
<td>50-65</td>
<td>400</td>
</tr>
<tr>
<td>SWOG/ECOG</td>
<td>III-IV*</td>
<td>Oropharynx</td>
<td>DPF × 3†</td>
<td>P</td>
<td>2 years</td>
<td>60-71</td>
<td>398</td>
</tr>
<tr>
<td>Dana-Farber Cancer Institute</td>
<td>III-IV</td>
<td>All</td>
<td>DPF × 3</td>
<td>Various§</td>
<td>3 years</td>
<td>55-70</td>
<td>300</td>
</tr>
</tbody>
</table>

Abbreviations: D, docetaxel; P, cisplatin; F, fluorouracil; H, hydroxyurea; X, hyperfractionated radiation administered on alternate weeks; SWOG, Southwest Oncology Group; ECOG, Eastern Cooperative Oncology Group.

*Resectable patients only, excluding T1-2 N1.
†Nonresponders after first induction course undergo surgery.
§See text.
Post OP RT or CCRT
Risk factors of post-op recurrence

- Primary tumor
  - Positive or close margin
- Neck
  - Multiple LN: >2
  - Extracapsular extension
  - Perineural invasion
  - Vascular embolism
- Both locoregional and distant

Adjuvant RT

- For possible residual disease
  - Positive margin or close margin
  - Multiple neck LN
- Attempt to decrease local failure
  - Decrease subsequent distant failure
- CCRT better than RT?
EORTC 22931

167 pts, HNSCC stage III/IV

Cisplatin 100mg/m², D1, D22, D43
XRT 54Gy/27fx, Boost 12Gy/6fx

Surgery → Cisplatin + XRT
Surgery → XRT

pT3/T4 + any N
pT1/T2 + N2/N3
pT1/T2 + N0/N1 + unfavorable patho

<table>
<thead>
<tr>
<th>Margin</th>
<th>Perineural invasion</th>
<th>Extracapsular spread</th>
<th>Vascular embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>28%</td>
<td>13%</td>
<td>57%</td>
</tr>
<tr>
<td>Negative</td>
<td>71%</td>
<td>85%</td>
<td>43%</td>
</tr>
<tr>
<td>Unknown</td>
<td>1%</td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>

Oral cavity 26%
Oropharynx 30%
Hypopharynx 20%
Larynx 22%
Unknown 1%

## EORTC 22931

<table>
<thead>
<tr>
<th>C/T on time without delay</th>
<th>5yr PFS</th>
<th>5yr OS</th>
<th>LRR</th>
<th>Dist Mets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CCRT</strong></td>
<td>47%</td>
<td>53%</td>
<td>18%</td>
<td>21%</td>
</tr>
<tr>
<td><strong>RT</strong></td>
<td>36%</td>
<td>40%</td>
<td>31%</td>
<td>25%</td>
</tr>
<tr>
<td><strong>p value</strong></td>
<td>0.04</td>
<td>0.02</td>
<td>0.007</td>
<td>0.61</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acute mucosa reaction</th>
<th>Mucosa fibrosis</th>
<th>Xerostomia</th>
<th>Severe leukopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CCRT</strong></td>
<td>41%</td>
<td>10%</td>
<td>14%</td>
</tr>
<tr>
<td><strong>RT</strong></td>
<td>21%</td>
<td>5%</td>
<td>20%</td>
</tr>
<tr>
<td><strong>p value</strong></td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RTOG 9501

416 pts, HNSCC, high risk of recurrence

Cisplatin 100mg/m2, D1, D22, D43
XRT 60Gy/30fx, Boost 6Gy/3fx

Surgery \rightarrow Cisplatin + XRT

Surgery \rightarrow XRT

Positive margin 17%
LN>2 or extracapsular extension 83%

<table>
<thead>
<tr>
<th>Site</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>27%</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>42%</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>10%</td>
</tr>
<tr>
<td>Larynx</td>
<td>21%</td>
</tr>
</tbody>
</table>

**RTOG 9501**

45.9 months follow-up time

<table>
<thead>
<tr>
<th></th>
<th>DFS</th>
<th>OS</th>
<th>LRR</th>
<th>Dist Mets as 1st event</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CCRT</strong></td>
<td>40%</td>
<td>52.5%</td>
<td>19%</td>
<td>23%</td>
</tr>
<tr>
<td><strong>RT</strong></td>
<td>30%</td>
<td>45%</td>
<td>30%</td>
<td>20%</td>
</tr>
<tr>
<td><strong>p value</strong></td>
<td>0.01</td>
<td>0.19</td>
<td>0.01</td>
<td>0.46</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Acute adverse effect</th>
<th>Late adverse effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CCRT</strong></td>
<td>77%</td>
<td>21%</td>
</tr>
<tr>
<td><strong>RT</strong></td>
<td>34%</td>
<td>17%</td>
</tr>
<tr>
<td><strong>p value</strong></td>
<td>0.001</td>
<td>0.29</td>
</tr>
</tbody>
</table>

hematological, mucosa, GI tract

*N Eng J Med 2004; 350: 1937-1944*
Post-op adjuvant CCRT

- Decrease locoregional recurrence
- Not affect distant metastasis
  - Though systemic side-effect
  - Insufficient dose delivery?
  - Single agent not enough?

- Actually improve survival
  - Locoregional recurrence dominant in HNSCC
Table 1. Effect on survival of adding chemotherapy to locoregional treatment: Results from the MACH-NC 2000 analysis [1, 2]

<table>
<thead>
<tr>
<th>Design</th>
<th>n of studies (n of patients)</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value</th>
<th>2 yrs</th>
<th>5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant</td>
<td>8 (1,854)</td>
<td>0.98 (0.85–1.19)</td>
<td>.74</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Induction</td>
<td>31 (5,269)</td>
<td>0.95 (0.88–1.01)</td>
<td>.10</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Induction with platinum and 5-FU [1, 2]</td>
<td>15 (2,487)</td>
<td>0.88 (0.79–0.97)</td>
<td>.01</td>
<td>NA</td>
<td>5%(^b)</td>
</tr>
<tr>
<td>Concurrent</td>
<td>26 (3,727)</td>
<td>0.81 (0.76–0.88)</td>
<td>&lt;.0001</td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td>Total</td>
<td>65 (10,850)(^c)</td>
<td>0.90 (0.85–0.94)</td>
<td>&lt;.0001</td>
<td>4%</td>
<td>4%</td>
</tr>
</tbody>
</table>

\(^a\) Absolute survival benefit

\(^b\) 5% absolute survival benefit in patients with platinum and 5-FU

\(^c\) Total number of patients from all trials

The Oncologist 2010;15(suppl 3):3–7
Organ Preservation

- **Laryngeal cancer as an example**
  - **Supraglottic**
  - **Subglottic**
    - T1: limited, not extend to glottis
    - T2: extend to glottis, but normal cord mobility
    - T3/T4: cord fixation, invade adjacent tissue
  - **Glottic**
    - T1a/b: limited to one/both sides, no cord fixation
    - T2: impair cord motility, to supra- or subglottis
    - T3/T4: cord fixation, invade adjacent tissue/organ
Historically

- Early: T1, T2
  - RT alone, surgical salvage, or
  - Surgical → adjuvant RT
  - Larynx usually preserved

- Advance: T3, T4
  - RT alone not sufficient
  - Surgical resection, usually total laryngectomy
Veterans Affairs Laryngeal Cancer Study Group

332 pts, laryngeal SCC stage III/IV

Surgery → Adjuvant RT
- C/T x 2
- C/T x 1
- Definitive RT

RT: 5000cGy/25fx
RT: 6600-7600cGy

Residual disease

Poor respond

Surgery +/- RT

Cisplatin 100mg/m², D1
5FU 1000mg/m²/d x 5d
q3w

T1/T2 9%
T3 65%
T4 26%

Glottis 37%
Supraglottis 63%

<table>
<thead>
<tr>
<th></th>
<th>2yr</th>
<th>DFS</th>
<th>OS</th>
<th>Recur at primary</th>
<th>Recur at regional</th>
<th>Distant mets</th>
<th>Laryngectomy-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>75%</td>
<td>68%</td>
<td>2%</td>
<td>5%</td>
<td>17%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C/T → RT</td>
<td>65%</td>
<td>68%</td>
<td>12%</td>
<td>8%</td>
<td>11%</td>
<td>39%</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.12</td>
<td>0.98</td>
<td>0.001</td>
<td>NS</td>
<td>0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

QOL assessment

- Veterans Affairs Laryngeal Cancer Study Group

- C/T → RT vs. Surgery → RT
  - “pain”, “mental health”, “bother”

- Laryngectomy vs. Laryngeal preserve
  - “pain”, “mental health”, “bother”
  - “role physical”, “social function”, “emotion”, “response”

- No difference in speech and eating
194 pts, hypopharynx SCC stage II/III/IV

Surgery

C/T x 2

Cisplatin 100mg/m2, D1
5FU 1000mg/m2/d x 5d

q3w

Adjuvant RT

Surgery +/- RT

5yr DFS OS Recur at local Recur at regional Distant mets Laryngectomy-free survival

Surgery 32% 35% 17% 23% 36%

C/T → RT 25% 30% 12% 19% 25% 35%

p value NS NS NS NS 0.041

T2 20%
T3 75%
T4 5%

Pyriform sinus 78%
Aryepiglottic fold 22%
GETTEC, French

68 pts, laryngeal SCC all T3

Surgery → Adjuvant RT

C/T x 3 → Definitive RT

RT: 5000cGy/25fx
RT: 7000cGy

Cisplatin 100mg/m², D1
5FU 1000mg/m²/d x 5d q3w

Supraglottis 31%
Glottis 41%
Unknown 28%

<table>
<thead>
<tr>
<th></th>
<th>2yr DFS</th>
<th>2yr OS</th>
<th>8yr Laryngectomy-free survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>78%</td>
<td>84%</td>
<td></td>
</tr>
<tr>
<td>C/T → RT</td>
<td>62%</td>
<td>69%</td>
<td>42%</td>
</tr>
<tr>
<td>p value</td>
<td>0.02</td>
<td>0.006</td>
<td></td>
</tr>
</tbody>
</table>

Inferior outcome !!
RTOG 91-11

518 pts, laryngeal SCC III/IV

<table>
<thead>
<tr>
<th>T2</th>
<th>12%</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3</td>
<td>78%</td>
</tr>
<tr>
<td>T4</td>
<td>10%</td>
</tr>
</tbody>
</table>

Supraglottis 69%
Glottis 31%

Speech/swallow: similar

RT alone

CCRT

C/T x 2

Cisplatin 100mg/m2, D1
5FU 1000mg/m2/d x 5d q3w

C/T x 1

RT

Residual disease

CCRT: RT 7000cGy/35fx
Cisplatin 100mg/m2, q3w

Surgery +/- RT

<table>
<thead>
<tr>
<th>5yr</th>
<th>DFS</th>
<th>OS</th>
<th>Intact larynx</th>
<th>LR control</th>
<th>Distant mets</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: RT</td>
<td>27%</td>
<td>56%</td>
<td>70%</td>
<td>56%</td>
<td>22%</td>
</tr>
<tr>
<td>B: CCRT</td>
<td>36%</td>
<td>54%</td>
<td>88%</td>
<td>78%</td>
<td>12%</td>
</tr>
<tr>
<td>C: C/T → RT</td>
<td>38%</td>
<td>55%</td>
<td>75%</td>
<td>61%</td>
<td>15%</td>
</tr>
</tbody>
</table>

p
0.02(C v A)
0.006(B v A)
NS
0.005(B v C)
0.001(B v A)
0.004(B v C)
0.001(B v A)
0.03(B v A)

Single-Cycle Induction Chemotherapy Selects Patients With Advanced Laryngeal Cancer for Combined Chemoradiation: A New Treatment Paradigm

Susan Urba, Gregory Wolf, Avraham Eisbruch, Francis Worden, Julia Lee, Carol Bradford, Theodoros Teknos, Douglas Chepeha, Mark Prince, Norman Hogikyan, and Jeremy Taylor

**Individualized Therapy!**

**Patients and Methods**
The chemotherapy was cisplatin 100 mg/m² on day 1 and fluorouracil 1,000 mg/m²/d for 5 days. Patients who achieved less than 50% response had immediate laryngectomy. Patients who achieved more than 50% response went on to concurrent chemoradiotherapy. Histologic complete responders after chemoradiotherapy received two more cycles of chemotherapy. Patients with residual disease after chemoradiotherapy had planned salvage surgery.
Induction Chemotherapy 1 cycle

RR < 50%

Laryngectomy

RR > 50%

CCRT

Residual tumor

Salvage Surgery

CR

Chemotherapy

J Clin Oncol 2006; 24:593-598
Laryngeal preservation

- Chemoradiotherapy becomes standard
  - No negative survival impact, at most series
- Organ preserved, but function?
  - Fibrosis, choking, difficult speech
  - Reconstructed organ followed by rehabilitation
    - Function may be better
    - Loss of organ, psychological stress
Treatment in recurrent or metastatic HNSCC
R/M Head & Neck Cancer

- 20%–30% of patients
- Locoregional recurrence can be salvaged by surgery or re-irradiation.
- Most patients with recurrent or metastatic (R/M) disease only qualify for palliative treatment
Treatment option

- Supportive care
- Single-agent chemotherapy
- Combination chemotherapy
- Targeted therapies either alone or in combination with cytotoxic agents

Goals of treatments

- Symptom control
- Prevention of new cancer-related symptoms
- Improvement in quality of life (QoL)
- Objective tumor response (OR), disease stabilization (SD) or both combined (disease control; DC)
- Prolongation of overall survival (OS) and progression-free survival (PFS).
Factors influence QoL and OS

- Medical conditions (cardiovascular and/or pulmonary diseases)
- Malnutrition
- Infections (local, aspiration pneumonia, systemic)
- Hypercalcemia
- Local pain
- Bleeding (arterial, venous, capillary)

Recurrent / Metastatic HNC

- Median survival 4 months in untreated patients
- Median survival of treated patients with is 6 months and the 1-year survival rate is around 20%.
- These statistics have not been affected by the use of chemotherapy.
- Single agent for R/M HNC: ORR range from 15%-35%

- Cisplatin
- Carboplatin
- Paclitaxel
- Docetaxel
- 5-FU
- Methotrexate
- Ifosfamide
- Bleomycin
- Gemcitabine\textsuperscript{19} (nasopharyngeal)
- Cetuximab\textsuperscript{20}
## Single agent RR with advanced SCCHN

### Table 2. Phase II Trial Single-Agent Response Rates in Patients With Advanced SCCHN

<table>
<thead>
<tr>
<th>Agent</th>
<th>No. of Patients Assessable</th>
<th>Response Rate (%)</th>
<th>Median Survival (months)</th>
<th>Year of Publication</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>8-77 (average 31)</td>
<td></td>
<td></td>
<td>1984</td>
<td>9,8</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>6-45 (average 21)</td>
<td></td>
<td></td>
<td>1977-84</td>
<td>9,89</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>14-41 (average 28)</td>
<td></td>
<td></td>
<td>1983-94</td>
<td>9,34,35,90</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>25</td>
<td></td>
<td></td>
<td>1986</td>
<td>91</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>10</td>
<td></td>
<td></td>
<td>1996</td>
<td>71</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>36</td>
<td></td>
<td></td>
<td>1980</td>
<td>92</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>24</td>
<td></td>
<td></td>
<td>1980</td>
<td>92</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>18</td>
<td>39</td>
<td></td>
<td>1980</td>
<td>10</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>29</td>
<td></td>
<td></td>
<td>1980</td>
<td>10</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>6</td>
<td></td>
<td></td>
<td>1994</td>
<td>74</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>15</td>
<td></td>
<td></td>
<td>1984</td>
<td>9</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>61</td>
<td>13</td>
<td></td>
<td>1994</td>
<td>93</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>14</td>
<td>8</td>
<td></td>
<td>2003</td>
<td>94</td>
</tr>
<tr>
<td>Orzel</td>
<td>42</td>
<td>21</td>
<td></td>
<td>2001</td>
<td>95</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>0-14</td>
<td></td>
<td></td>
<td>2005</td>
<td>72</td>
</tr>
<tr>
<td>Paclitaxel 24-hour infusion</td>
<td>34</td>
<td>40 (4 CRs)</td>
<td>9.2</td>
<td>1998</td>
<td>39</td>
</tr>
<tr>
<td>Paclitaxel 96-hour infusion</td>
<td>Chemotherapy naïve/paclitaxel naïve/paclitaxel exposed</td>
<td>13/0/0</td>
<td>5.5</td>
<td>2004</td>
<td>41</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>21-42</td>
<td></td>
<td></td>
<td>1994-2005</td>
<td>36-38,96</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>35</td>
<td>26</td>
<td>6.4</td>
<td>2001</td>
<td>97</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>26</td>
<td></td>
<td></td>
<td>2003</td>
<td>69</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>103</td>
<td>13</td>
<td></td>
<td>2005</td>
<td>75</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>115</td>
<td>4</td>
<td></td>
<td>2004</td>
<td>73</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>47</td>
<td>11</td>
<td>8.1</td>
<td>2003</td>
<td>70</td>
</tr>
<tr>
<td>Sorafenib (BAY 43-9006)</td>
<td>10</td>
<td></td>
<td>6 SD (60%); 4 SCCHN + 2 NPC; range, 3-6 cycles</td>
<td>2005</td>
<td>87</td>
</tr>
</tbody>
</table>
single-agent chemotherapy

- Methotrexate, Cisplatin, 5-fluorouracil (5-FU) and Bleomycin
- Response of short duration, ~3–5 months, in 15%–30% of cases and only rarely complete response (CR)
- Pemetrexed, vinorelbine, irinotecan, capecitabine, orzel, S-1 and the taxanes paclitaxel and docetaxel
- The taxanes are among the highest scoring agents, with response rates varying between 20% and 43%
Cisplatinum and Bleomycin for advanced or recurrent HNSCC: a randomised factorial phase III controlled trial.

- 31 patients treated with single-agent cisplatin demonstrated prolonged survival compared with 26 patients treated with supportive measures only.

- Patients who respond do quickly. Of the 16 responders, 75% responded after the first cycle and the remaining 25% after the second cycle.

Results of a randomised phase II study comparing docetaxel with methotrexate in patients with HNSCC

- in the randomized phase II study of docetaxel versus methotrexate, the response rate was reported as significantly higher in the docetaxel arm with 27% [95% confidence interval (CI) 21.7% to 32.3%] OR compared with 15% (95% CI 11.2% to 18.8%) in the methotrexate arm.

Other single agent for HNSCC

- Neither vinorelbine, ifosfamide, irinotecan, nor pemetrexed has been evaluated in a randomized phase III study for R/M HNSCC.
Recurrent / Metastatic HNC

Combination therapy

1. Cisplatin or carboplatin + 5-FU\textsuperscript{15,16} \pm cetuximab\textsuperscript{17}
2. Cisplatin or carboplatin + docetaxel or paclitaxel\textsuperscript{15}
3. Cisplatin/cetuximab\textsuperscript{18}

1 & 2 are the most active regimens, result in higher response rate of 30-40%
Combination chemotherapy

- standard platinum-based combinations
- Cisplatin/infusional 5-FU (PF) regimen: a better outcome than what was observed with single-agent treatment, at least with respect to OR rates and CR rates
- Response rates were notably lower for the subsets of patients who had prior surgery and radiation and those who had metastatic disease
Combination chemotherapy

- In a number of randomized phase III trials performed in the 1990s, this PF regimen was shown to be superior to single-agent regimens, in terms of response rates but not meaningful survival advantage.
Phase III PF vs single agent in advanced HNSCC

Randomized Trials: Combinations vs Monotherapy

<table>
<thead>
<tr>
<th>Intergroup</th>
<th>n</th>
<th>RR, %</th>
<th>MS, Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin/5-FU</td>
<td>79</td>
<td>32</td>
<td>5.5</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>83</td>
<td>17</td>
<td>5.0</td>
</tr>
<tr>
<td>5-FU</td>
<td>83</td>
<td>13</td>
<td>6.1</td>
</tr>
</tbody>
</table>

FP > Cisplatin or 5-FU alone!!

Phase III Combinations vs single agent in advanced HNSCC

Randomized Trials: Combinations vs Monotherapy

<table>
<thead>
<tr>
<th>Intergroup</th>
<th>n</th>
<th>RR, %</th>
<th>MS, Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin/5-FU</td>
<td>87</td>
<td>32</td>
<td>6.6</td>
</tr>
<tr>
<td>Carboplatin/5-FU</td>
<td>86</td>
<td>21</td>
<td>5.0</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>88</td>
<td>10</td>
<td>5.6</td>
</tr>
</tbody>
</table>
platinum–taxane combinations

- Regimens with carboplatin and paclitaxel did not seem to be much different from regimens with cisplatin and paclitaxel.
- Docetaxel 65 mg/m(2) and carboplatin (AUC of 6) were given IV in a 21-day cycle to 68 patients. Response probability was 25 percent.
- The major toxicity: neutropenia, with 36 patients (61 percent) experiencing Grade 3 or worse.
- Median PSF was 3.8 months (95%CI, 3.1-4.8) Median OS was 7.4 months (95%CI, 6.2-8.9).
Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395)

- The paclitaxel plus cisplatin (PP) combination was directly compared with the PF regimen in the Intergroup trial E1395.

- Patients received either paclitaxel 175 mg/m² (over 3 h) and cisplatin 75 mg/m², both on day 1, or the classical PF regimen.

- The OR rate was 27% with PP and 26% with PF. The overall grade 3/4 toxicity rate was similar between the two groups.

- However, grade 3/4 mucositis (31%) was only observed in the PF arm, while the occurrence of neurotoxicity was similar in the two groups.

- Median OS was 8.7 months in the PF group and 8.1 months in the PP group.
two-drug and three-drug platinum–taxane combinations.

- The TPF regimen, consists of docetaxel, cisplatin and infusional 5-FU, TAX323/EORTC24971 (Europe) and TAX324 studies (USA)

- Overall response rate: 44%,
- Median time to progression : 7.5 months
- Median OS : 11 months.
- Febrile neutropenia occurred rather frequently (in 15% of patients).
## Recurrent and/or metastatic SCCHN: Phase III chemotherapy results in first line

No improvement in overall survival in recent decades

<table>
<thead>
<tr>
<th>Year</th>
<th>Reference</th>
<th>No. of patients</th>
<th>Regimen</th>
<th>OS</th>
<th>ORR</th>
<th>Grade 3/4 toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1992</td>
<td>Forastiere AA, et al.</td>
<td>277</td>
<td>Cisplatin + 5-FU</td>
<td>NS</td>
<td>32%</td>
<td>Neutropenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Carboplatin + 5-FU</td>
<td></td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Methotrexate</td>
<td></td>
<td>10%</td>
<td>Mucositis</td>
</tr>
<tr>
<td>1992</td>
<td>Jacobs C, et al.</td>
<td>249</td>
<td>Cisplatin + 5-FU</td>
<td>NS</td>
<td>32%</td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5-FU</td>
<td></td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cisplatin</td>
<td></td>
<td>17%</td>
<td>Mucositis</td>
</tr>
<tr>
<td>1994</td>
<td>Clavel M, et al.</td>
<td>382</td>
<td>CABO</td>
<td>NS</td>
<td>34%</td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cisplatin + 5-FU</td>
<td></td>
<td>31%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cisplatin</td>
<td></td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>Gibson MK, et al.</td>
<td>218</td>
<td>Cisplatin + 5-FU</td>
<td>NS</td>
<td>27%</td>
<td>Reduced for cisplatin + paclitaxel</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cisplatin + paclitaxel</td>
<td></td>
<td>26%</td>
<td></td>
</tr>
</tbody>
</table>

CABO = cisplatin, methotrexate, bleomycin, and vincristine; NS = not significant

Combined chemotherapy

- None of the combination chemotherapy regimens demonstrated an OS benefit when compared with single-agent methotrexate, cisplatin or 5-FU.

- Combination chemotherapy should preferably be used in younger patients with good PS and with symptomatic disease who require prompt symptom relief.
Combined chemotherapy

- No combination cytotoxic chemotherapy has shown superiority over another in a randomized prospective trial for patients with R/M HNSCC.

- CP and CF doublets have comparable efficacy as palliative regimens for advanced HNSCC based on randomized clinical trial data.

- Triplet cytotoxic regimens have been less extensively studied and should not be used outside of a clinical trial in the treatment of R/M HNSCC.
The 2\textsuperscript{nd} line Chemotherapy choice in HNSCC


(2) Anthracycline-based regimen: MEPFL (mitomycin, epirubicin, cisplatin, 5-FU, and LV)

(3) High dose ifosfamide and etoposide (IE). Good KPS needed.
ERBITUX + RT IN LOCALLY ADVANCED SCCHN
Mechanisms of action - Erbitux® (Cetuximab) -

High EGFR expression predicts poor survival.

- Erbitux is an IgG1 MAb targeting the EGFR
- Binding blocks EGFR signaling and inhibits proliferation, angiogenesis and metastasis, and stimulates apoptosis and differentiation
  - Fc region may induce antibody-dependent cell-mediated cytotoxicity (ADCC) (immune response)

HNSCC

Courtesy of José Baselga (modified)
Erbitux in locally advanced SCCHN: Bonner Phase III study

Stage III and IV non-metastatic SCCHN

N=424

RT (n=213)

Erbitux + RT (n=211)

Erbitux initial dose (400 mg/m²)
Erbitux (250 mg/m²) + RT (wks 2–8)

Primary endpoint: duration of locoregional control
Secondary endpoints: OS, PFS, RR, QoL, and safety

Bonner et al. NEJM 2006
Erbitux in locally advanced SCCHN: Significant benefit in locoregional control

Erbitux + RT significantly increases median duration of locoregional control vs RT alone by 10 months

HR=0.68 [95% CI: 0.52–0.89]  
p=0.005

3-year control rate

47%

34%

Bonner et al. NEJM 2006
Erbitux in locally advanced SCCHN:
5-year survival update

HR = 0.73 [95% CI: 0.56–0.95]
p = 0.018

Bonner et al. Lancet Oncol 2010
Erbitux in locally advanced SCCHN:
Skin rash correlates with survival

51% reduction in the risk of death (p=0.002)

p=0.002, HR=0.49 (95% CI: 0.34–0.72)

Bonner et al. Lancet Oncol 2010
Adding Erbitux to RT increases survival without compromising QoL

QoL: post-baseline scores for the EORTC QLQ-C30

Curran et al. JCO 2007
CRT: percentage of treatment-related deaths after primary treatment

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Time of occurrence, years median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease progression</td>
<td>1.5 years (0.3–8.6)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>1.9 years (0.07–8.8)</td>
</tr>
<tr>
<td>Treatment-related</td>
<td>0.3 years (0.03–3.4)</td>
</tr>
<tr>
<td>Second primary tumors</td>
<td>3.5 years (1.5–10.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>5.1 years (1.1–9.5)</td>
</tr>
</tbody>
</table>

Forest plot: Subgroup analysis of overall survival – 5-year update

<table>
<thead>
<tr>
<th>Primary tumor site</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oropharynx</td>
<td>Favors RT + Erbitux</td>
</tr>
<tr>
<td>Larynx</td>
<td>Favors RT alone</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>NEJM and ASCO 2010</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor stage</th>
<th>HPV(+) ca:</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1–T3</td>
<td>*Less intensive RT</td>
</tr>
<tr>
<td>T4</td>
<td>*Identified by p16 in biopsy and serum HPV DNA</td>
</tr>
</tbody>
</table>

| RT regimen                   | |
|-------------------------------| |
| Once daily                   | |
| Twice daily                  | |
| Concomitant boost            | |

| Overall stage                | |
|-------------------------------| |
| Stage II/III                 | |
| Stage IV                     | |

| Nodal stage                  | |
|-------------------------------| |
| N0                            | |
| N1–N3                         | |

| KPS                           | |
|-------------------------------| |
| 50–80                         | |
| 90–100                        | |

| Gender                        | |
|-------------------------------| |
| Male                          | |
| Female                        | |

| EGFR status                   | |
|-------------------------------| |
| ≤50% positive                 | |
| >50% positive                 | |
| Unknown                       | |

---

Hazard ratio values for different subgroups are indicated with markers on the plot, with blue markers favoring RT + Erbitux and red markers favoring RT alone. The HPV(+) status (positive, negative, unknown) is indicated by different markers and hazard ratio values.
ERBITUX in locoregionally advanced SCCHN: efficacy summary

- ERBITUX + high-dose RT demonstrated significant efficacy benefits over high-dose RT alone

- 26% reduction in risk of death
- 32% reduction in locoregional relapse
- 20-month increase in median survival
- 10-month increase in median LR control
- 32% reduction in locoregional relapse

Survival of ERBITUX + radiotherapy compared to large randomized trials of chemoradiotherapy vs radiotherapy

<table>
<thead>
<tr>
<th>Activity</th>
<th>n</th>
<th>Median Survival (mo)</th>
<th>Survival Advantage (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERBITUX + RT</td>
<td>211</td>
<td>49</td>
<td>20</td>
</tr>
<tr>
<td>Carboplatin / 5-FU + RT</td>
<td>109</td>
<td>29</td>
<td>14</td>
</tr>
<tr>
<td>Cisplatin + RT</td>
<td>113</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>ERBITUX + radiotherapy</td>
<td>112</td>
<td>36</td>
<td>12</td>
</tr>
<tr>
<td>Carboplatin / 5-FU + RT</td>
<td>113</td>
<td>24</td>
<td>7</td>
</tr>
<tr>
<td>Mitomycin / 5-FU + RT</td>
<td>190</td>
<td>23</td>
<td>7</td>
</tr>
<tr>
<td>Survival advantage with ERBITUX phase III study</td>
<td>2005</td>
<td>a) Bonner et al.</td>
<td></td>
</tr>
</tbody>
</table>

References:
- a) Calais et al. 1999
- b) Huguenin et al. 2004
- c) Staar et al. 2001
- d) Budach et al. 2005
Comparison of overall survival advantage of different combinations (MACH-NC meta-analyses, Bonner study)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Hazard ratio (95% CI)</th>
<th>CT or Erbitux effect (p-value)</th>
<th>Absolute benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>At 2 years&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Adjuvant CT+RT&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.98 (0.85–1.19)</td>
<td>0.74</td>
<td>1%</td>
</tr>
<tr>
<td>Neoadjuvant CT +RT&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.95 (0.88–1.01)</td>
<td>0.10</td>
<td>2%</td>
</tr>
<tr>
<td>Concomitant CT + RT&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.81 (0.76–0.88)</td>
<td>&lt;0.0001</td>
<td>7%</td>
</tr>
<tr>
<td>ERBITUX + RT&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.73 (0.56–0.95)</td>
<td>0.02</td>
<td>7%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Assuming survival rates of 50% at 2 years and 32% at 5 years in control groups

Comparison of the 5-year overall survival benefit (MACH-NC meta-analyses, Bonner study)

ERBITUX+RT improves significantly long-term survival advantage at 5 years

### Development of chemotherapy in R/M SCCHN

1977: cisplatin shows efficacy in 1\textsuperscript{st}-line SCCHN

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Regimen</th>
<th>ORR (%)</th>
<th>Median OS (months)</th>
<th>Significant OS benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grose et al 1985</td>
<td>100</td>
<td>Methotrexate</td>
<td>16</td>
<td>5.0</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cisplatin</td>
<td>8</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Forastiere et al 1992</td>
<td>277</td>
<td>Cisplatin + 5-FU</td>
<td>32*</td>
<td>6.6</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carboplatin + 5-FU</td>
<td>21</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methotrexate</td>
<td>10</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>Clavel et al 1994</td>
<td>382</td>
<td>CABO</td>
<td>34*</td>
<td>7.3</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cisplatin + 5-FU</td>
<td>31*</td>
<td>7.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cisplatin</td>
<td>15</td>
<td>7.3</td>
<td></td>
</tr>
<tr>
<td>Gibson et al 2005</td>
<td>218</td>
<td>Cisplatin + 5-FU</td>
<td>27</td>
<td>8.7</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cisplatin + paclitaxel</td>
<td>26</td>
<td>8.1</td>
<td></td>
</tr>
<tr>
<td>Vermorken et al 2008</td>
<td>442</td>
<td>Platinum + 5-FU</td>
<td>20</td>
<td>7.4</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Platinum + 5-FU + Erbitux</td>
<td>36*</td>
<td>10.1*</td>
<td></td>
</tr>
</tbody>
</table>

CABO, cisplatin, methotrexate, bleomycin, vincristine

*significant

GORTEC TREMPLIN study: Erbitux + RT for larynx preservation

Previously untreated SCC larynx/hypopharynx suitable for total laryngectomy (n=153)

TPF (3 cycles, 1 cycle q3w) → R

- ≥PR: RT (70 Gy) Cisplatin
- <PR: RT (70 Gy) Erbitux (weekly)

Total laryngectomy + postoperative RT

Response evaluation by endoscopy and CT scan

Primary endpoint: larynx preservation 3 months after treatment
Secondary endpoints: larynx function preservation and survival 18 months after treatment

<table>
<thead>
<tr>
<th>Table 1. TREMPLIN trial: Compliance and larynx preservation [6]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-TPF induction treatment</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Radiotherapy + cisplatin ($n = 60$)</strong></td>
</tr>
<tr>
<td><strong>Radiotherapy + cetuximab ($n = 56$)</strong></td>
</tr>
<tr>
<td>Patients starting treatment, $n$</td>
</tr>
<tr>
<td>Patients receiving the full treatment protocol, $n$ (%)</td>
</tr>
<tr>
<td>Larynx preservation rate 3 months after treatment, $n$ (%)</td>
</tr>
</tbody>
</table>

*As a proportion of all randomized patients.
Abbreviations: TPF, docetaxel, cisplatin, and 5-fluorouracil.
Induction PFE (cisplatin and 5-FU + Erbitux) followed by CRT + Erbitux in locally advanced OCSCC, phase II study

2 cycles PFE

- CR
- PR/SD
- CPD

1 cycle PFE

- surgery

CRT

salvage therapy

**PFE:**
- cisplatin: 100 mg/m² day 1 in each induction cycle
- 5-FU: 1000 mg/m² days 1–3 in each induction cycle
- Erbitux: 400 mg/m² day 1, then 250 mg/m² weekly on weeks 2–6

**CRT:**
- RT: 70Gy
- cisplatin: 30 mg/m² weekly on weeks 1–7
- Erbitux: 250 mg/m² weekly on weeks 1–7

Pei-Jen, Alex, Lou, IFHNOS Seoul 2010
RTOG H-0234 phase II trial: Locally advanced resected

N=243
Surgical resection
High risk

RT + ERBITUX (400 ➔ 250 mg/m², qW) + DDP (30 mg/m², qW)

RT + ERBITUX (400 ➔ 250 mg/m², qW) + Docetaxel (15 mg/m², qW)

---

Graph showing tumor size (mm) over days after radiation. The graph includes control and treated groups with different dosages and additional medications.
Erbitux in R/M HNSCC
Platinum-Based Chemotherapy plus Cetuximab in Head and Neck Cancer

Jan B. Vermorken, M.D., Ph.D., Ricard Mesia, M.D., Fernando Rivera, M.D., Ph.D., Eva Remenar, M.D., Andrzej Kawecki, M.D., Ph.D., Sylvie Rottey, M.D., Ph.D., Jozsef Erfan, M.D., Dmytro Zabolotnyy, M.D., Ph.D., Heinz-Roland Kienzer, M.D., Didier Cupissol, M.D., Frederic Peyrade, M.D., Marco Benasso, M.D., Ihor Vynnychenko, M.D., Ph.D., Dominique De Raucourt, M.D., Carsten Bokemeyer, M.D., Armin Schueler, M.S., Nadia Amellal, M.D., and Ricardo Hitt, M.D., Ph.D.
1\textsuperscript{st}-line SCCHN: EXTREME trial

- Randomized, phase III, multicenter study
- 80 sites in 17 European countries
- No prior EGFR testing was required for study entry
- Previously untreated patients with recurrent or metastatic SCCHN
- Patients were stratified according to:
  - Prior chemotherapy
  - KPS (<80 vs ≥80)
- Treatment: platinum (cisplatin or carboplatin) plus 5-FU, with or without Erbitux

Vermorken et al. NEJM 2008
EXTREME Trial: Design

N=442

R/M SCCHN
- Prior CT
- KPS (<80 vs ≥80)

Platinum/5-FU

Platinum/5-FU + Erbitux

Erbitux until PD

Platinum/5-FU
Cisplatin (100 mg/m² IV, day 1) or Carboplatin (AUC 5, day 1) + 5-FU (1000 mg/m² IV, days 1–4)
Every 3 weeks, up to 6 cycles

Erbitux
Initial dose 400 mg/m² then 250 mg/m² weekly until progressive disease (PD)

Primary endpoint: OS
Secondary endpoints: PFS, RR, safety

Vermorken et al. NEJM 2008
## EXTREME Trial: Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PF (n=220)</th>
<th>PF + Erbitux (n=222)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years</td>
<td>57</td>
<td>56</td>
</tr>
<tr>
<td>Male/female, %</td>
<td>92/8</td>
<td>89/11</td>
</tr>
<tr>
<td>Extent of disease, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Locoregionally recurrent</td>
<td>54</td>
<td>53</td>
</tr>
<tr>
<td>Metastasis*</td>
<td>46</td>
<td>47</td>
</tr>
<tr>
<td>KPS score, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;80</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>≥80</td>
<td>89</td>
<td>88</td>
</tr>
</tbody>
</table>

*Metastasis with or without locoregional recurrence

Vermorken et al. NEJM 2008
EXTREME: Overall survival

**PF**
**PF + Erbitux**

HR = 0.80 [95% CI: 0.64–0.99]

*p* = 0.04

Vermorken et al. NEJM 2008
EXTREME: Progression-free survival

**Graph:**
- **Y-axis:** Progression-free survival (%)
- **X-axis:** Months

**Legend:**
- Yellow line: PF
- Blue line: PF + Erbitux

**Key Metrics:**
- At 3 months: PF = 3.3 months, PF + Erbitux = 5.6 months
- HR = 0.54 [95% CI: 0.43 – 0.67]
- p < 0.001

**Source:** Vermorken et al. NEJM 2008
EXTREME: Response

Response rate (%)

OR = 2.33
[95% CI: 1.50–3.60]
p < 0.001

CR; complete response

Vermorken et al. NEJM 2008
RR: Cisplatin vs carboplatin-based CT

RR with cisplatin-based CT
p=0.0035

RR with carboplatin-based CT
p=0.0267

RR:

- Cisplatin
  - vs carboplatin
  - based CT
  - p=0.0035
  - RR with cisplatin
  - based CT
  - p=0.0267

Vermorken et al. NEJM 2008
<table>
<thead>
<tr>
<th>Event</th>
<th>Cetuximab plus Platinum–Fluorouracil (N = 219)</th>
<th>Platinum–Fluorouracil Alone (N = 215)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3 or 4 number of patients (%)</td>
<td>Grade 3 or 4 number of patients (%)</td>
<td></td>
</tr>
<tr>
<td>Any event</td>
<td>179 (82)</td>
<td>164 (76)</td>
<td>0.19</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>49 (22)</td>
<td>50 (23)</td>
<td>0.91</td>
</tr>
<tr>
<td>Anemia</td>
<td>29 (13)</td>
<td>41 (19)</td>
<td>0.12</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>24 (11)</td>
<td>24 (11)</td>
<td>1.00</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>19 (9)</td>
<td>19 (9)</td>
<td>1.00</td>
</tr>
<tr>
<td>Skin reactions‡</td>
<td>20 (9)</td>
<td>1 (&lt;1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>16 (7)</td>
<td>10 (5)</td>
<td>0.31</td>
</tr>
<tr>
<td>Cardiac events§</td>
<td>16 (7)</td>
<td>9 (4)</td>
<td>0.22</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12 (5)</td>
<td>6 (3)</td>
<td>0.23</td>
</tr>
<tr>
<td>Asthenia</td>
<td>11 (5)</td>
<td>12 (6)</td>
<td>0.83</td>
</tr>
<tr>
<td>Anorexia</td>
<td>11 (5)</td>
<td>3 (1)</td>
<td>0.05</td>
</tr>
<tr>
<td>Hypomagnesemia ‡</td>
<td>11 (5)</td>
<td>3 (1)</td>
<td>0.05</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>10 (5)</td>
<td>10 (5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>9 (4)</td>
<td>17 (8)</td>
<td>0.11</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>9 (4)</td>
<td>4 (2)</td>
<td>0.26</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>9 (4)</td>
<td>2 (1)</td>
<td>0.06</td>
</tr>
<tr>
<td>Sepsis (including septic shock)</td>
<td>9 (4)</td>
<td>1 (&lt;1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Tumor hemorrhage</td>
<td>3 (1)</td>
<td>6 (3)</td>
<td>0.33</td>
</tr>
<tr>
<td>Decreased performance status</td>
<td>2 (1)</td>
<td>4 (2)</td>
<td>0.45</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>1 (&lt;1)</td>
<td>5 (2)</td>
<td>0.12</td>
</tr>
</tbody>
</table>
EXTREME: Quality of life

Quality of life of patients receiving platinum-based chemotherapy plus cetuximab first line for recurrent and/or metastatic squamous cell carcinoma of the head and neck

R. Mesía¹, F. Rivera², A. Kawecki³, S. Rottey⁴, R. Hitt⁵, H. Kienzer⁶, D. Cupissol⁷, D. De Raucourt⁸, M. Benasso⁹, P. Koralewski¹⁰, J.-P. Delord¹¹, C. Bokemeyer¹², D. Curran¹³, A. Gross¹⁴ & J. B. Vermorken¹⁵⋆

¹Department of Medical Oncology, Catalan Institute of Oncology, Hospital de Llobregat, Barcelona, Spain; ²Medical Oncology Department, Marqués de Valdecilla University Hospital, Santander, Spain; ³Head and Neck Cancer Department, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland; ⁴Medical Oncology, Ghent University Hospital, Ghent, Belgium; ⁵Medical Oncology Department, University Hospital ‘12 de Octubre’, Madrid, Spain; ⁶3rd Medical Department, Kaiser Franz Josef Spital, Ludwig Boltzmann Institute for Applied Cancer Research, Vienna, Austria; ⁷Department of Medical Oncology, Val d’Aurelle-Paul Lamarque Regional Cancer Centre, Montpellier, France; ⁸Head and Neck Unit, François Baclesse Centre, Caen, France; ⁹Oncology Department, San Paolo Hospital, Savona, Italy; ¹⁰Oncology, Rydzyn Memorial Hospital, Krakow-Nowa Huta, Poland; ¹¹Department of Medical Oncology, Claudius Regaud Institute, Toulouse, France; ¹²Department of Oncology, Hematology, BMT with section Pneumology, Hubertus Wald Tumorzentrum, University Cancer Center Hamburg, University Hospital, Hamburg, Germany; ¹³Statistics, OMEGA Research, Santry, Dublin, Ireland; ¹⁴Global Statistics, Merck KGaA, Darmstadt, Germany and ¹⁵Department of Medical Oncology, Antwerp University Hospital, Edegem, Belgium
EXTREME: Quality of life

Global health status/QoL

Score

baseline

<50% of patients completed a baseline questionnaire; 95% CIs for difference in treatment groups

EORTC QLQ-C30

Mesía et al. Ann Oncol 2010
EXTREME: Symptom control

Mean change from baseline to worst post-baseline score

- Pain: -9.99 (p=0.0027), PF
- Swallowing problems: -9.17 (p=0.0162), PF
- Sense problems: -2.60 (p=0.5702), PF
- Speech problems: -7.81 (p=0.0787), PF
- Social eating problems: -9.98 (p=0.0694), PF
- Problems with social contact: -2.64 (p=0.7732), PF
- Problems with reduced sexuality: -2.55 (p=0.2237), PF

PF + Erbitux:
- Pain: +3.51
- Swallowing problems: +5.21
- Sense problems: +4.42
- Speech problems: +1.33
- Social eating problems: +0.24
- Problems with social contact: -0.43
- Problems with reduced sexuality: +4.37

Modified from Mesía et al. Ann Oncol 2010
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Median Overall Survival (Cetuximab plus Chemotherapy vs. Chemotherapy)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>442</td>
<td>10.1 vs. 7.4</td>
<td>0.80 (0.64–0.99)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>365</td>
<td>10.5 vs. 7.3</td>
<td>0.74 (0.59–0.94)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>77</td>
<td>9.1 vs. 7.8</td>
<td>1.07 (0.65–1.77)</td>
</tr>
<tr>
<td>Karnofsky performance score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;80</td>
<td>52</td>
<td>6.3 vs. 4.4</td>
<td>1.14 (0.64–2.04)</td>
</tr>
<tr>
<td>≥80</td>
<td>390</td>
<td>10.6 vs. 7.9</td>
<td>0.75 (0.60–0.94)</td>
</tr>
<tr>
<td>Platinum regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>284</td>
<td>10.6 vs. 7.3</td>
<td>0.69 (0.53–0.91)</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>149</td>
<td>9.7 vs. 8.3</td>
<td>0.98 (0.69–1.41)</td>
</tr>
<tr>
<td>Previous treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy</td>
<td>57</td>
<td>10.7 vs. 6.3</td>
<td>0.82 (0.46–1.49)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>129</td>
<td>8.6 vs. 7.5</td>
<td>0.90 (0.61–1.34)</td>
</tr>
<tr>
<td>Primary tumor site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral cavity</td>
<td>88</td>
<td>11.0 vs. 4.4</td>
<td>0.42 (0.26–0.67)</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>149</td>
<td>10.9 vs. 7.9</td>
<td>0.85 (0.58–1.23)</td>
</tr>
<tr>
<td>Larynx</td>
<td>111</td>
<td>8.6 vs. 8.4</td>
<td>0.99 (0.65–1.51)</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>62</td>
<td>8.4 vs. 8.9</td>
<td>1.14 (0.64–2.04)</td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well- or moderately differentiated</td>
<td>269</td>
<td>9.5 vs. 6.5</td>
<td>0.72 (0.55–0.94)</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>92</td>
<td>10.8 vs. 9.4</td>
<td>1.00 (0.62–1.60)</td>
</tr>
<tr>
<td>Baseline quality-of-life score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤Median</td>
<td>129</td>
<td>7.4 vs. 5.9</td>
<td>0.86 (0.59–1.24)</td>
</tr>
<tr>
<td>&gt;Median</td>
<td>98</td>
<td>13.9 vs. 9.2</td>
<td>0.70 (0.43–1.12)</td>
</tr>
<tr>
<td>Percentage of EGFR-detectable cells</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0 to &lt;40%</td>
<td>64</td>
<td>10.9 vs. 7.8</td>
<td>0.72 (0.40–1.28)</td>
</tr>
<tr>
<td>≥40%</td>
<td>341</td>
<td>10.1 vs. 7.1</td>
<td>0.75 (0.59–0.95)</td>
</tr>
</tbody>
</table>
EXTREME: EGFR expression and survival

Median OS: PF + Erbitux vs PF

<table>
<thead>
<tr>
<th>EGFR % positive cells</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0% (n=8; 2%)</td>
<td>1.98 [0.32–12.25]</td>
</tr>
<tr>
<td>&gt;0–40% (n=64; 14%)</td>
<td>0.72 [0.40–1.28]</td>
</tr>
<tr>
<td>≥40% (n=341; 77%)</td>
<td>0.75 [0.59–0.95]</td>
</tr>
<tr>
<td>Missing (n=29; 7%)</td>
<td>1.24 [0.51–3.02]</td>
</tr>
</tbody>
</table>

Modified from Vermorken et al. NEJM 2008
<table>
<thead>
<tr>
<th></th>
<th>OS</th>
<th></th>
<th>PFS</th>
<th></th>
<th>RR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PF+</td>
<td>PF</td>
<td>PF+</td>
<td>PF</td>
<td>PF+</td>
<td>PF</td>
</tr>
<tr>
<td>FISH+</td>
<td>10.5 mo</td>
<td>7.2 mo</td>
<td>6.2 mo</td>
<td>3.1 mo</td>
<td>36.0%</td>
<td>11.8%</td>
</tr>
<tr>
<td>FISH-</td>
<td>10.6 mo</td>
<td>7.8 mo</td>
<td>5.7 mo</td>
<td>4.1 mo</td>
<td>34.3%</td>
<td>22.3%</td>
</tr>
<tr>
<td>FISH+ vs FISH-</td>
<td>HR 1.02</td>
<td>HR 1.04</td>
<td>HR 0.86</td>
<td>HR 1.05</td>
<td>OR 1.08</td>
<td>OR 0.46</td>
</tr>
<tr>
<td>95% CI</td>
<td>[0.69–1.51]</td>
<td>[0.71–1.51]</td>
<td>[0.58–1.27]</td>
<td>[0.71–1.54]</td>
<td>[0.54–2.18]</td>
<td>[0.18–1.22]</td>
</tr>
</tbody>
</table>

PF + Erbitux patients: 50 FISH+, 108 FISH-; PF patients: 51 FISH-, 103 FISH-
Adding Erbitux to CT in 1st-line SCCHN: Consistency in outcome

<table>
<thead>
<tr>
<th>Author</th>
<th>Phase</th>
<th>N</th>
<th>Regimen</th>
<th>ORR (%)</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burtness et al. 2005</td>
<td>III</td>
<td>117</td>
<td>Cis + placebo</td>
<td>10</td>
<td>2.7</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cis + Erbitux</td>
<td>26*</td>
<td>4.2</td>
<td>9.2</td>
</tr>
<tr>
<td>Bourhis et al. 2006</td>
<td>I/II</td>
<td>53</td>
<td>PF + Erbitux</td>
<td>36</td>
<td>5.1**</td>
<td>9.8</td>
</tr>
<tr>
<td>Vermorken et al. 2008</td>
<td>III</td>
<td>442</td>
<td>PF</td>
<td>20</td>
<td>3.3</td>
<td>7.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PF + Erbitux</td>
<td>36*</td>
<td>5.6*</td>
<td>10.1*</td>
</tr>
<tr>
<td>Hitt et al. 2007</td>
<td>II</td>
<td>42</td>
<td>Pacli + Erbitux</td>
<td>60</td>
<td>5.0</td>
<td>NR***</td>
</tr>
<tr>
<td>Buentzel et al. 2007</td>
<td>II</td>
<td>23</td>
<td>Pacli/Carbo + Erbitux</td>
<td>56</td>
<td>5.0**</td>
<td>8.0</td>
</tr>
</tbody>
</table>

*Significant; **TTP; ***Median OS not reached after a median follow-up of 5.6 months

Burtness et al. JCO 2005; Bourhis et al. JCO 2006; Vermorken et al. NEJM 2008; Hitt et al. ASCO 2007; Buentzel et al. ASCO 2007
Erbitux in 1st-line SCCHN
A major clinical advance

Highlighted by ASCO:

“... the results of this trial [EXTREME] are particularly noteworthy and are changing clinical practice.”

Petrelli et al. JCO 2009
Platinum/5-FU plus Erbitux in 1st-line SCCHN Summary

- Adding Erbitux to platinum/5-fluorouracil
  - Significantly improves OS
  - Significantly increases PFS
  - Almost doubles RR

- Platinum-based CT + Erbitux is feasible in SCCHN pts

- Erbitux shows benefit regardless of EGFR expression or EGFR gene copy number

- PF + Erbitux is a new standard in 1st-line SCCHN
ESMO clinical recommendations

- This is the first time in >30 years that superiority (in terms of survival) of a new regimen over standard platinum-based combination chemotherapy has been observed.

- Cetuximab and platinum-based chemotherapy is now considered as a new standard for the treatment of R/M-SCCHN for those who are able to tolerate platinum-based combination chemotherapy regimens.
EGFR-targeting therapy in HNSCC

<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase</th>
<th>Reference</th>
<th>Response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab</td>
<td>II</td>
<td>Vermorken 2007 [61]</td>
<td>13</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>II</td>
<td>Soulieres 2004 [77]</td>
<td>4.3</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>II</td>
<td>Cohen 2003 [78]</td>
<td>10.6</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>Cohen 2005 [79]</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>Kirby 2006 [80]</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td>IIIa</td>
<td>Stewart 2009 [81]</td>
<td>7.9</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>II</td>
<td>Abidoye 2006 [82]</td>
<td>0</td>
</tr>
<tr>
<td>BIBW 2992</td>
<td>IIa</td>
<td>Seiwert 2010 [83]</td>
<td>21.7</td>
</tr>
</tbody>
</table>

BIBW 2992

- highly potent inhibitor of EGFR/erbB1 and erbB2. It retains activity for EGFRvIII mutation and provides a sustained blockage of receptor and inhibition of tumor cell proliferation
BIBW 2992 versus cetuximab in patients with metastatic or recurrent HNSCC, a randomized, open-label phase II study

- A randomized, open-label, phase II study of BIBW 2992 versus cetuximab in R/M-SCCHN patients after failure of platinum-containing therapy.
- The primary end point of that study was tumor shrinkage of target lesions before any crossover.
- Diarrhea, dehydration, epistaxis and asthenia occurred more frequently with BIBW 2992, but also tumor shrinkage occurred more frequently with BIBW 2992 than with cetuximab (OR 21.7% versus 13.3%).
- Median PFS with BIBW 2992 was 16 weeks (95% CI 10–19) and 10 weeks (95% CI 8–17) with cetuximab.
- BIBW is the first TKI to demonstrate antitumor activity in SCCHN that appears to be at least comparable to cetuximab.

Gefitinib in SCCHN: Response Data

- Gefitinib 500 mg QD PO
- N = 47 eligible patients
- Half received previous palliative treatments
- ORR: 11% (95% CI: 3.5-23.1)
- Disease control (CR + PR + SD): 53%
- Median survival of 8.1 mos
- 13% had disease control ≥ 6 mos
- Skin toxicity strong predictor of survival

<table>
<thead>
<tr>
<th>Response</th>
<th>n (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>1 (2)</td>
</tr>
<tr>
<td>PR</td>
<td>4 (9)</td>
</tr>
<tr>
<td>SD</td>
<td>21 (45)</td>
</tr>
<tr>
<td>PD</td>
<td>22 (47)</td>
</tr>
</tbody>
</table>

VEGF-targeting therapy in HNSCC

1. Avastin-based chemotherapy combination. Vessel normalization, decreased intra-tumoral pressure, enhanced chemotherapy delivery, and suppression of BM-derived EPC.

Tarceva and Avastin (chemo-naïve or 1st line Tx failure)
*4/48 CR; 3/48 PR; DCR near 50%; PFS 4 months; OS 7.1 months
(Lancet Oncology 2009)
*Response associated with high ratios of tumor pVEGFR2/total VEGFR2 endothelial pEGFR/total EGFR

Avastin and Alimta (chemo-naïve; oral cavity 18%)
*30% RR and 86% stabilization.
Time to progression 4.9 months; OS 11.5 months(JCO 2011)

Avastin-PF or -IE in NTUH

2. Multi-targeted TKI.
Sunitinib

Multi-targeted TKI towards VEGFR1, VEGFR2, PDGFR, c-KIT, and FLT-3.
After sunitinib, tumor necrosis increased and vessel density decreased.
Vessel normalization also seen in sunitinib use.
Sunitinib in advanced HNSCC

*Good response but bleeding events to cause early closure.

*Tumor necrosis/fistula in neck, close to major vessels, and maybe too advanced status. *Too responsive!!!

*PDFGR inhibition to cause pericyte maturation arrest and fragile vessels---rupture.
Carotid artery distance

Necrosis

PR in 1
SD in 18
Unconfirmed PR: 5
Minor response: 6

Disease control rate: 19/38 (50%)

Grade 5 bleeding: 4

Tumor skin ulcers & fistulas: 15
Very similar to NTUH experiences.
GORTEC value

(1) Show activity of sunitinib in advanced HNSCC, even in 2nd line.

(2) Present tumor death patterns of sunitinib and imply bleeding events.

(3) Possible biomarkers choice.

Good patient selection, avoiding bleeding events, and biomarkers development.
HNSCC

(1) Resectable and operable disease: op

(2) Unresectable/inoperable or organ preservation: CCRT

(3) Multiple modality in locally advanced dz
HNSCC

*Resectable disease: operation
After op, high risk P’t(multiple LNs, LVI, PNI, extracapsular invasion, margin +, poor differentiated): adjuvant CCRT

*Locally advanced disease: induction CT (PF, TPF, MEPFL, PF+Erbitux, TPF+Erbitux) followed by op +/- adjuvant CCRT
Unresectable HNSCC or for organ preservation

(1) **CCRT** better than RT or induction CT then RT in organ preservation for larynx/hypopharynx cancers.

(2) CCRT still many pitfalls: choking, poor chest care

(3) **Induction TPF before CCRT:** better survival(TAX 324)

(4) **Erbitux roles in induction and CCRT**
Metastatic HNSCC

(1) PF standard

(2) PF + Erbitux(survival benefit, 10 months)

(3) Taxane, CPT-11, oxaliplatin, gemcitabine, Navelbine, Avastin, Sutent: second line choices

(4) 5-year survival only 50% in stage I-IVB
Still poor outcomes
HNSCC

(1) Prevention most important.

(2) Still poor outcomes.
   Multiple modality Tx strategies and new potential powerful agents needed
THANK YOU!