Welcome to Master Class for Oncologists

Session 1:
1:00 PM – 1:45 PM
Head and Neck Cancer:
Update on Comprehensive Management
Robert Haddad M.D.
Clinical Director/Head and Neck Oncology Program
Dana Farber Cancer Institute
Harvard Medical School
Boston, MA

Presenter Disclosure Information
The following relationships exist related to this presentation:
• Dr Haddad serves as a consultant for Bristol-Myers Squibb and sanofi-aventis.

Off Label/Investigational Discussion
In accordance with Pri-Med Institute policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Update on Head and Neck Cancer Outline
• Introduction:
  Epidemiology, Clinical Features, Prevention, Treatment Modalities
• Concurrent Chemoradiotherapy
• Sequential Chemoradiotherapy
• Adjuvant Chemoradiotherapy
• Palliative Therapy

Head and Neck Cancer Primary Disease Sites
Oral Cavity
Pharynx
Larynx
Nasal Cavity
Paranasal Sinuses

Epidemiology
• 47,500 new cases, 11,000 deaths estimated for 2008
• Median age of diagnosis: ~60 years
• African American > White/Hispanic/Asian
• Male: Female 4:1
• Strongly associated with tobacco and alcohol
• Epstein-Barr virus risk factor for nasopharynx cancers
• Human papillomavirus risk factor increasingly appreciated as a risk factor
1. A patient is found on exam to have a clinical T2N2B tonsil tumor. Biopsy of the tonsil yields a diagnosis of basaloid squamous cell cancer. The pathologist reports that in situ hybridization testing using a probe with affinity for high risk human papillomavirus (HPV) genotypes was positive. Which statement is false regarding the relationship between HPV infection and head and neck cancer?

1. HPV 16 is the viral subtype in the majority of these tumors.
2. HPV-positive tumors are associated with better survival rates.
3. Associated with ↑ number of sexual partners and certain sexual practices.
4. Lip cancers have a higher association with prior HPV infection than do tonsil cancers.

1. HPV 16 is the viral subtype in the vast majority of patients.
2. Half of oropharynx cancers will have HPV 16 DNA.
3. Often occurs in non-smokers, non-drinkers.
4. Median age younger than HPV-negative patients; incidence increasing.
5. Men and women at more similar risk.
6. Associated with ↑ number of sexual partners and certain sexual practices.
7. Favorable prognosis

**Human Papillomavirus (HPV)-Positive Head and Neck Cancer**

- HPV 16 is the viral subtype in the vast majority of patients.
- Half of oropharynx cancers will have HPV 16 DNA.
- Often occurs in non-smokers, non-drinkers.
- Median age younger than HPV-negative patients; incidence increasing.
- Men and women at more similar risk.
- Associated with ↑ number of sexual partners and certain sexual practices.
- Favorable prognosis

**Human Papillomavirus (HPV) Prognosis**

<table>
<thead>
<tr>
<th>Response</th>
<th>HPV (+)ve</th>
<th>HPV (-)ve</th>
<th>p-value</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>82%</td>
<td>55%</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protocol</td>
<td>84%</td>
<td>57%</td>
<td>0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival - all sites</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS (2yrs)</td>
<td>86%</td>
<td>53%</td>
<td>0.02</td>
<td>0.28</td>
<td>0.07-1.0</td>
</tr>
<tr>
<td>OS (2yrs)</td>
<td>56%</td>
<td>42%</td>
<td>0.005</td>
<td>0.21</td>
<td>0.06-0.74</td>
</tr>
<tr>
<td>Survival - OP cancers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PFS (2yrs)</td>
<td>85%</td>
<td>50%</td>
<td>0.06</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS (2yrs)</td>
<td>94%</td>
<td>58%</td>
<td>0.004</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion:** HPV positive tumors are associated with enhanced sensitivity to treatment and better outcome.

**Head and Neck Cancer: Clinical Features**

- Squamous cell cancer or variant
- Locoregional character
- M1 uncommon at presentation
- Medical comorbidity
- Second primary cancers: “field cancerization”; “condemned mucosa”

**Lymphatic Drainage**

Each anatomic site has a predilection for spreading to different lymph node level

I: oral cavity
II/III/IV: larynx/pharynx
I/IV: nasopharynx
V: scalp
III/IV/V: thyroid
IV/V: below the clavicles
Premalignant Lesions

Leukoplakia

Erythroplakia

Screening/Prevention

• United States Preventive Services Task Force: no definitive recommendations with regard to screening for head and neck cancers.
• Direct inspection and palpation of oral cavity during dental examinations most commonly applied screening procedure.
• Counsel regarding tobacco and alcohol use.
• Human papillomavirus vaccine – not standard practice for prevention of head and neck cancer.
• No proven standard chemopreventive agent.

Evaluation and Staging

• Clinical exam of the head and neck
• Endoscopy
  – Fiberoptic flexible laryngopharyngoscopy
  – Exam under anesthesia: laryngoscopy, esophagoscopy, bronchoscopy
• Biopsy
  – Fine needle aspiration of a neck node
  – Punch/core biopsy
  – Excisional biopsy
• Computed axial tomography/Magnetic resonance imaging of primary site and neck
• Chest imaging
• Positron emission tomography
• Tumor-Node-Metastasis system applied

Head and Neck Cancer Prognosis

Survival (yrs)

Percentage (%)

Local
Regional
Metastatic
Unknown

SEER registry

Treatment Approach

<table>
<thead>
<tr>
<th>Disease Extent</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_1N_0$ or $T_2N_0$</td>
<td>Surgery or RT</td>
</tr>
<tr>
<td>$T_3N_0$ or $T_3N_1$ or $N_2N_3$</td>
<td>Combined modality</td>
</tr>
<tr>
<td>Recurrent or $M_1$</td>
<td>Surgery and/or RT</td>
</tr>
<tr>
<td></td>
<td>Combined modality</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy</td>
</tr>
</tbody>
</table>

Surgical Therapy: General Principles

• Oncologically adequate resection
• Comprehensive versus selective neck dissection
• Factors suggesting disease unresectable for cure:
  – Massive skull base infiltration
  – Involvement of prevertebral fascia
  – Invasion of the cervical vertebrae or brachial plexus
  – Encasement of the carotid artery
  – Skin infiltration
  – Rapid local or regional recurrence after surgery
Radiation Therapy
Standard Fraction Dosage

<table>
<thead>
<tr>
<th>Treatment Setting</th>
<th>Dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitive RT</td>
<td></td>
</tr>
<tr>
<td>Primary &amp; gross lymph nodes</td>
<td>≥ 70 Gy</td>
</tr>
<tr>
<td>Neck: low-risk nodal stations</td>
<td>≥ 50 Gy</td>
</tr>
<tr>
<td>Adjuvant RT (4-6 weeks after surgery)</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>≥ 60 Gy</td>
</tr>
<tr>
<td>Neck: high-risk nodal stations</td>
<td>≥ 60 Gy</td>
</tr>
<tr>
<td>Neck: low-risk nodal stations</td>
<td>≥ 50 Gy</td>
</tr>
</tbody>
</table>

*Ratios are 80 Gy/day
NCCN Guidelines

RTOG 90-03: Altered Fraction RT

<table>
<thead>
<tr>
<th>#</th>
<th>LRC</th>
<th>DFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>QD</td>
<td>268</td>
<td>46%</td>
<td>32%</td>
</tr>
<tr>
<td>BID</td>
<td>263</td>
<td>54%</td>
<td>38%</td>
</tr>
<tr>
<td>BID (split)</td>
<td>274</td>
<td>48%</td>
<td>33%</td>
</tr>
<tr>
<td>CBRT</td>
<td>268</td>
<td>55%</td>
<td>39%</td>
</tr>
</tbody>
</table>

Conclusion: Continuous course, altered fractionation schedules delivering higher total dose associated with improved disease control.

Toxicities of Radiation Therapy

- Mucositis/edema → dysphagia → feeding tube
- Xerostomia and loss of taste
- Hypothyroidism
- Lhermitte’s syndrome
- Long term induration and fibrosis
- Osteoradionecrosis of the jaw
- Cervical myelopathy

Treatment Approach

<table>
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<th>Treatment</th>
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<td>Surgery or RT</td>
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<tr>
<td>T_3N_0 or T_3N_1 or N_2</td>
<td>Combined modality</td>
</tr>
<tr>
<td>Recurrent or M_1</td>
<td>Surgery and/or RT Combined modality Chemotherapy</td>
</tr>
</tbody>
</table>

Audience Response Question

A patient is diagnosed with a squamous cell cancer of the right supraglottic larynx T3N1M0, and is interested in a primary chemoradiotherapy approach to avoid total laryngectomy. In a patient without significant medical comorbidity, what initial therapy is preferred by the National Comprehensive Cancer Network (NCCN) practice guidelines panel?

1. High-dose cisplatin x 3 cycles with concurrent standard fractionation (SF) radiation therapy (RT)
2. Induction docetaxel/cisplatin/5-fluorouracil followed by chemotherapy with concurrent SFRT
3. Weekly cetuximab with concurrent SFRT
4. Weekly paclitaxel and cisplatin with concurrent SFRT
Concurrent Chemoradiotherapy

MACH-NC = Meta-Analysis of Chemotherapy in Head and Neck Cancer; PF = cisplatin + fluorouracil.


<table>
<thead>
<tr>
<th>Design (No. of Studies/No. of Subjects)</th>
<th>Hazard Ratio (95% CI)</th>
<th>Chemotherapy Effect (P Value)</th>
<th>Absolute Benefit 2 Years</th>
<th>Absolute Benefit 5 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard Ratio (PF induction)</td>
<td>0.98 (0.85-1.19)</td>
<td></td>
<td>0.74</td>
<td>1%</td>
</tr>
<tr>
<td>Hazard Ratio (PF induction)</td>
<td>0.95 (0.88-1.01)</td>
<td></td>
<td>0.10</td>
<td>2%</td>
</tr>
<tr>
<td>Hazard Ratio (PF induction)</td>
<td>0.81 (0.76-0.88)</td>
<td>&lt; 0.0001</td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td>Hazard Ratio (PF induction)</td>
<td>0.90 (0.85-0.94)</td>
<td>&lt; 0.0001</td>
<td>4%</td>
<td>4%</td>
</tr>
</tbody>
</table>

RTOG 91-11 Induction Cisplatin/5-FU vs Concomitant Cisplatin vs RT Alone in Resectable SCC

<table>
<thead>
<tr>
<th>Arm</th>
<th>Stomatitis*</th>
<th>LP rate (5yrs)</th>
<th>DFS (5yrs)</th>
<th>OS (5yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT</td>
<td>24%</td>
<td>66.7%</td>
<td>27.3%</td>
<td>53.5%</td>
</tr>
<tr>
<td>Chemo →RT</td>
<td>24%</td>
<td>70.5%</td>
<td>38.6%</td>
<td>59.2%</td>
</tr>
<tr>
<td>ChemoRT</td>
<td>43%</td>
<td>83.6%</td>
<td>39.0%</td>
<td>54.6%</td>
</tr>
</tbody>
</table>

Conclusion: Concomitant chemoradiation is superior to induction chemotherapy followed by RT and RT alone for laryngeal preservation. There is no difference in overall survival between the 3 arms.

RTOG 91-11 Larynx Preservation (LP) Trial

<table>
<thead>
<tr>
<th>Grade 3-5 Toxicity</th>
<th>RT Alone (N=132)</th>
<th>RT + Cetuximab (N=248)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucositis</td>
<td>50%</td>
<td>50%</td>
<td>0.44</td>
</tr>
<tr>
<td>Acneiform Rash</td>
<td>17%</td>
<td>9%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Infusion Reaction</td>
<td>0%</td>
<td>0%</td>
<td>0.01</td>
</tr>
<tr>
<td>Anemia</td>
<td>2%</td>
<td>1%</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Phase III Trial: Cetuximab + RT for SCC

For glottic or supraglottic cancer
Previously untreated
N=515

- Primary endpoint: larynx preservation
- Secondary endpoint: LFS

LFS=laryngectomy-free survival.

Intergroup Phase III Trial: Cisplatin/5-FU/RT vs Cisplatin/RT vs RT Alone in Unresectable SCC

<table>
<thead>
<tr>
<th>Outcome</th>
<th>A (N=102)</th>
<th>B (N=102)</th>
<th>C (N=102)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-Year OS</td>
<td>23%</td>
<td>33%</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>Median OS</td>
<td>12.6 mos</td>
<td>18 mos</td>
<td>13.8 mos</td>
<td></td>
</tr>
<tr>
<td>3-Year DFS</td>
<td>33%</td>
<td>51%</td>
<td>41%</td>
<td></td>
</tr>
</tbody>
</table>


Advanced SCC
• Stage B/Iv
• N=424

Grade 3-5 Toxicity

Phase III: Cetuximab + RT for SCC: Results

Locoregional Control
OS

47% vs 59% at 2 years
55% vs 65% at 3 years

RTOG 0522 Phase III Trial: Concomitant CRT ± Cetuximab in Advanced SCC

Cisplatin
(40 mg/m²)
3-D Conformal or IMRT
(once or twice daily,
5 or 6 days/week, 6 wks)

Cetuximab
(wks 0–7)

Expected N=720

Phase III: Cetuximab + RT for SCC: Results

47% vs 34% at 3 years
P <0.01 at 3 years

55% vs 45% at 3 years
P =0.05 at 3 years

Stage III/IV SCC
• Oropharynx, larynx, hypopharynx
(oral cavity, nasopharynx, sinuses,
salivary glands)
• No distant metastases
• No synchronous, concurrent head
and neck cancers
• No prior anti-EGFR therapy
• No prior chemotherapy for SCC
• No prior RT with overlapping fields
• No initial surgical treatment
(excluding biopsy)
• No prior RT with overlapping fields

Locoregional Control
OS

Audience Response Question

A patient is diagnosed with a squamous cell cancer of the right supraglottic larynx T3N1M0, and is interested in a primary chemoradiotherapy approach to avoid total laryngectomy. In a patient without significant medical comorbidity, what initial therapy is preferred by the National Comprehensive Cancer Network (NCCN) practice guidelines panel?

1. High-dose cisplatin x 3 cycles with concurrent standard fractionation (SF) radiation therapy (RT)
2. Induction docetaxel/cisplatin/5-fluorouracil followed by chemotherapy with concurrent SFRT
3. Weekly cetuximab with concurrent SFRT
4. Weekly paclitaxel and cisplatin with concurrent SFRT

TAX 324: Sequential Combined Modality Therapy
TPF vs PF Followed by Chemoradiotherapy

TPF: Docetaxel 75D1 + Cisplatin 100D1 + 5-FU 1000 CI-D1-4 Q 3 weeks x 3
PF: Cisplatin 100 D1 + 5-FU 1000 CI-D1 Q 3 weeks x 3

Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>TPF (N=256)</th>
<th>PF (n=246)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), y</td>
<td>65 (20-84)</td>
<td>66 (20-84)</td>
</tr>
<tr>
<td>NC status</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>ECOG PS, % of pts</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>F0</td>
<td>50%</td>
<td>39%</td>
</tr>
<tr>
<td>F1</td>
<td>44%</td>
<td>49%</td>
</tr>
<tr>
<td>Primary tumor size, % of pts</td>
<td>62%</td>
<td>39%</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>18%</td>
<td>13%</td>
</tr>
<tr>
<td>Lymph node</td>
<td>12%</td>
<td>18%</td>
</tr>
<tr>
<td>Vascular space invasion</td>
<td>17%</td>
<td>14%</td>
</tr>
<tr>
<td>Clinical stage, % of pts</td>
<td>11%</td>
<td>19%</td>
</tr>
<tr>
<td>N0</td>
<td>84%</td>
<td>86%</td>
</tr>
<tr>
<td>Reason for inoperability, % of pts</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Localized invasion</td>
<td>31%</td>
<td>39%</td>
</tr>
<tr>
<td>Margin involvement</td>
<td>25%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Overall Survival

Survival Probability (%)

Survival Time (months)

3-year survival: TPF 42%, PF 38%

Hazard ratio: 0.70
95% CI: [0.54-0.90]

Log-rank test: \( P = 0.0058 \)

TPF: median survival 30.1 months
PF: median survival 70.6 months

TAX 324 Phase III Trial: Docetaxel/Cisplatin/5-FU vs Cisplatin/5-FU
Sequential Therapy in Advanced SCCHN: Toxicity

<table>
<thead>
<tr>
<th>Grade 3/4 Toxicity</th>
<th>TPF</th>
<th>PF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomatitis</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>5%</td>
<td>12%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>64%</td>
<td>50%</td>
</tr>
<tr>
<td>Neutropenic infection</td>
<td>12%</td>
<td>9%</td>
</tr>
</tbody>
</table>

During ICT
N=251 TPF, 243 PF

During CRT
N=203 TPF, 184 PF


Taxane + PF Phase III Trials


<table>
<thead>
<tr>
<th></th>
<th>Chemo</th>
<th>PF</th>
<th>DPF</th>
<th>PF</th>
<th>PaPF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>181</td>
<td>177</td>
<td>193</td>
<td>189</td>
<td></td>
</tr>
<tr>
<td>Med PFS*</td>
<td>8.2 mo</td>
<td>11.0 mo</td>
<td>12 mo</td>
<td>20 mo</td>
<td></td>
</tr>
<tr>
<td>Med OS*</td>
<td>14.5 mo</td>
<td>18.8 mo</td>
<td>37 mo</td>
<td>43 mo</td>
<td></td>
</tr>
<tr>
<td>RR*</td>
<td>54%</td>
<td>68%</td>
<td>68%</td>
<td>80%</td>
<td></td>
</tr>
</tbody>
</table>

\* P<0.05 for all comparisons, except P=0.06 for OS in Hitt study

Conclusions

• Overall survival advantage >3 years with TPF sequential therapy
  – 40.5 month improvement in median overall survival at 3 years
  – 30% reduction in the risk of mortality (\( P = 0.0058 \))
  – Consistent with prior phase III trial (TAX 323)
• Patients received a median of 3 cycles of induction chemotherapy in the TPF and PF arms
• In the TPF arm, 81% of patients went on to receive CRT
• Grade 3/4 treatment-emergent adverse events
  – Less stomatitis, thrombocytopenia, and lethargy in the TPF arm
  – More neutropenia and febrile neutropenia (any grade) in the TPF arm

Impact of Induction Chemotherapy (CT):
Reconciling Opposing Views

• Pro: allows time to optimize patient medical status; customization of RT dosing based on response to treatment; provides early treatment of distant micrometastatic disease.
• Con: Induction CT may affect adversely compliance to subsequent concurrent CT/RT or choice of CT/RT regimen; adds 2-4 months to treatment.
• Synthesis: Important RCTs in progress that deserve support; in the interim, Risk-based therapy is appropriate

What to do?

• Clinical scenarios in which to consider it:
  1. Potential Distant metastasis
  2. Delay in radiation simulation
  3. Impending local issue (eg, airway)
  4. Markedly advanced disease (eg, bulky, N2c, N2b, N3, low neck, dermal infiltration)
  5. organ preservation strategy in patients with markedly advanced disease.
Neck Dissection (ND) After Chemoradiotherapy

- Indicated for gross residual disease.
- Not indicated for pretreatment N1 disease that has achieved clinical complete response.
- For pretreatment N2-3 disease, opinions vary.
  - When pretreatment neck disease is N2-3, some centers recommend routine ND regardless of response to chemoradiotherapy.
  - However, others will observe if a clinical complete response on PET scan 12 weeks post therapy is achieved with chemoradiotherapy.

Concurrent Chemoradiotherapy Trials for Nasopharynx Cancer

<table>
<thead>
<tr>
<th>Arm</th>
<th>Al-Sarraf 1998</th>
<th>Lin 2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT/RT</td>
<td>ORT</td>
<td>ORT</td>
</tr>
<tr>
<td>RT</td>
<td>OS* 78%</td>
<td>47%</td>
</tr>
<tr>
<td>DFS*</td>
<td>69%</td>
<td>24%</td>
</tr>
</tbody>
</table>

*All differences P <0.05; outcomes are at 3 yrs for Al-Sarraf study, 5 yrs for Lin study

Locoregionally Advanced

A patient underwent surgery to the primary site and neck for a clinical T3N2bM0 left oral tongue tumor. Pathology is notable for a moderately-differentiated squamous cell cancer; a microscopically positive tongue margin and evidence of vascular invasion; 1/35 lymph nodes positive for cancer - extracapsular nodal spread is present. In a patient without significant medical comorbidity, what adjuvant therapy is most supported by available data from randomized trials?

1. Standard-fractionated (SF) radiation (RT) alone
2. Hyperfractionated RT alone
3. High-dose cisplatin x 3 cycles with concurrent SFRT
4. Cisplatin/5-fluorouracil x 3 cycles with concurrent SFRT

Adjuvant Chemoradiotherapy

EORTC 22931 and RTOG 9501 Phase III Trials: Adjuvant RT ± Concomitant Cisplatin

- Resectable SCC
  - Oral cavity, oropharynx, hypopharynx, larynx
  - Stage IV (EORTC), high risk (RTOG)
  - Previously untreated
    - N=334 (EORTC)
    - N=459 (RTOG)

Surgery → Cisplatin (100 mg/m², d1, 22, 43) → EORTC: 66 Gy over 6.5 wks
→ RTOG: 60-66 Gy over 6-6.6 wks
**Poor Risk Criteria**

**RTOG 9501**
- ≥ 2 nodes
- ECE
- +Margins

**EORTC 22931**
- Level IV/V (OC/OP)
- ECE
- +Margins
- Perineural disease
- Vascular emboli

ECE = extracapsular nodal extension; OC = oral cavity; OP = oropharynx

**EORTC 22931 and RTOG 9501: Adjuvant RT ± Concomitant Cisplatin: Results**

**OS (EORTC)**

**OS (RTOG)**

**RTOG 9501/EORTC 22931**

Which prognostic risk factors are most important?

- Extracapsular nodal extension and +margins - significant benefit from chemoradiotherapy.
- Trend toward benefit for stage III-IV disease, perineural invasion, vascular embolisms, and/or clinically enlarged level IV/V lymph nodes secondary to tumors in oral cavity or oropharynx.
- No benefit in patients with 2 or more nodes but no extracapsular extension.

**Audience Response Question**

1. Standard-fractionated (SF) radiation (RT) alone
2. Hyperfractionated RT alone
3. High-dose cisplatin x 3 cycles with concurrent SFRT
4. Cisplatin/5-fluorouracil x 3 cycles with concurrent SFRT

**Follow Up**

- Assess for Recurrence/2nd Primary/Premalignant Lesions
  - 1st year: Q 1-3 mos
  - 2nd year: Q 2-4 mos
  - 3rd – 5th year: Q 4-6 mos
  - > 5 years: Q 6-12 mos
- TSH q 6-12 mos if neck irradiated.
- Chest imaging as indicated.
- Speech/Swallowing evaluation/rehabilitation as indicated.
- Counsel regarding tobacco and alcohol use.
- Integrate general medical care.
- Once felt disease free, imaging of primary and neck not routinely indicated unless suspicious signs or symptoms.

**Treatment Approach**

<table>
<thead>
<tr>
<th>Disease Extent</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>T_N1 or T2N0</td>
<td>Surgery or RT</td>
</tr>
<tr>
<td>T2N1 or T3N0</td>
<td>Combined modality</td>
</tr>
</tbody>
</table>
| Recurrent or M1| Surgery and/or RT

 Adapted from NCCN
**Palliative Chemotherapy**

- Treatment for recurrent disease without surgical or radiotherapy option
- 1st line therapy:
  - historically platinum-based doublet
  - overall RR 30-40%
  - median survival 6-9 months regardless of treatment
  - randomized controlled trials fail to demonstrate clear improvement in OS compared to RX with single agents
- Active agents: cisplatin, carboplatin, 5-FU, taxanes, methotrexate, cetuximab, ifosfamide, gemcitabine (for nasopharynx cancer) and others

---

**EXTREME: Study Design**

- **5-FU 1000 mg/m² d1-4 with**
  - Cisplatin 100 mg/m² d1 or
  - Carboplatin AUC 5 d1
  - 6 cycles maximum
- **Cetuximab 250 mg/m²/week**
  - q 3 weeks
  - Loading dose of 400 mg/m² on week 1

**Patients at Risk:**

<table>
<thead>
<tr>
<th>Tablular</th>
<th>First Line</th>
<th>Second Line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platinum/5-FU</td>
<td>220</td>
<td>222</td>
</tr>
<tr>
<td>Cetuximab + Platinum/5-FU</td>
<td>173</td>
<td>184</td>
</tr>
</tbody>
</table>

**Survival Probability**

- **HR (95% CI)=0.797 (0.644-0.986)**
- Strat. log-rank test: 0.0362

**Conclusion:** Addition of cetuximab to standard first-line platinum-based chemotherapy improves overall survival.

---

**EXTREME: First-Line Platinum/5-FU ± Cetuximab in Recurrent/Metastatic SCC: Survival**

**Phase II Trial: Cetuximab Monotherapy in Platinum-Refractory Recurrent/Metastatic SCC**

- **Platinum-refractory SCC**
  - Stage III/IV recurrent and/or metastatic SCC not suitable for local therapy
  - Documented PD within 30 days of cisplatin- or carboplatin-based chemotherapy (≥2 cycles)
  - Tumor tissue available for IHC of EGFR expression
  - No nasopharyngeal carcinoma
  - No nonplatinum chemotherapy or RT within past 3 wks
  - No prior/concomitant surgery within 30 days of enrollment

**Cetuximab (400 mg/m² then by 250 mg/m²/week) LVEF**

- CR, PR, or SD Continue cetuximab and PD
- Optional: cisplatin or carboplatin + cetuximab

**Monotherapy (continued if CR, PR, SD)**

**Vermorken. J Clin Oncol. 2007;25:2171; Trigo. ASCO. 2004 (abstr 5032).**
### Phase II: Cetuximab Monotherapy in Platinum-Refractory Recurrent/Metastatic SCC: Results

<table>
<thead>
<tr>
<th></th>
<th>Monotherapy Phase (95% CI); N=103</th>
<th>Combined Therapy Phase* (95% CI); N=53</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ITT: N=103</td>
<td>IRC-PD: N=68</td>
</tr>
<tr>
<td></td>
<td>IRC-PD: N=68</td>
<td>ITT: N=53</td>
</tr>
<tr>
<td></td>
<td>IRC-PD</td>
<td>IRC-PD</td>
</tr>
<tr>
<td>OR</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>PR</td>
<td>13%</td>
<td>12%</td>
</tr>
<tr>
<td>SD</td>
<td>33%</td>
<td>26%</td>
</tr>
<tr>
<td>PD</td>
<td>37%</td>
<td>27%</td>
</tr>
<tr>
<td>DCR</td>
<td>46% (36-56)</td>
<td>46% (33-58)</td>
</tr>
<tr>
<td>Median Time to Response</td>
<td>49 days</td>
<td>52 days</td>
</tr>
<tr>
<td>Median DOR</td>
<td>5.9 mos</td>
<td>4.2 mos</td>
</tr>
<tr>
<td>Median TTP</td>
<td>2.1 mos</td>
<td>1.8 mos</td>
</tr>
<tr>
<td>Median Survival</td>
<td>5.9 mos</td>
<td>5.5 mos</td>
</tr>
</tbody>
</table>

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**Key Points:**
- DCR= disease control rate; DOR= duration of response; IRC-PD= ITT patients with PD determined by Independent Review Committee; ITT= intention to treat; TTP= time to progression.
- 53 patients progressing while receiving cetuximab monotherapy continued with combined therapy (cetuximab plus cisplatin or carboplatin).

### Re-Irradiation

- Feasible in full doses either alone or concurrently with chemotherapy.
- Better survival outcomes for new primaries than for recurrent disease.
- Evidence for improvement in PFS (but not OS) when adjuvant CT/Reirradiation is done after salvage surgery compared to observation alone.
- Compared to chemotherapy alone:
  - Median OS similar
  - Selected pts have more durable responses
  - RTSG 0421 comparing CT/Reirradiation versus CT alone, closed due to poor accrual.

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### EGFR-TK Inhibitors

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Agent</td>
<td>Gefitinib</td>
<td>Gefitinib</td>
<td>Gefitinib</td>
<td>Erlotinib</td>
</tr>
<tr>
<td>Median PFS</td>
<td>3.4mo</td>
<td>1.8mo</td>
<td>2.6</td>
<td>2.2</td>
</tr>
<tr>
<td>Median OS</td>
<td>8.1mo</td>
<td>5.5mo</td>
<td>4.3mo</td>
<td>6.0mo</td>
</tr>
<tr>
<td>1yr OS</td>
<td>29.2%</td>
<td>19%</td>
<td>~0%</td>
<td>20%</td>
</tr>
<tr>
<td>ORR</td>
<td>10.6%</td>
<td>1.4%</td>
<td>8%</td>
<td>4.3%</td>
</tr>
</tbody>
</table>

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**Notes:**
- EGFR-TK Is in metastatic disease trials:
- RCT of Gefitinib vs MTX – no significant survival improvement (Proc AACR 2007).