RADIATION THERAPY AND CHEMOTHERAPY
IN LOCALLY ADVANCED CANCER OF THE HEAD AND NECK

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IRRADIACION Y QUIMIOTERAPIA EN CANCER DE CABEZA Y CUELLO LOCALMENTE AVANZADO

- Contenido de Presentacion
- Factores predictivos/ pronosticos
- Quimioterapia Neo-Adyuvante
- Preservacion de Laringe
- Quimioterapia + RT concomitante
- Tumores Irresecables
- Post-operatoria
- Agentes Biologicos
- Secuelas de Tratamiento Combinado
PROGNOSTIC FACTORS FOR CHEMORADIOOTHERAPY IN H&N CANCER

- T and N stage
- Primary tumor site
- Lymphovascular invasion, surgical margins,
- Nodal Extracapsular Tumor Extension
- Therapy factors
  - Radiation Target volume
  - Radiation dose/ fractionation
  - Type of chemotherapy
  - Number of courses given
  - Dose Intensity of chemotherapy
- Performance status, hemoglobin level
- HPV +/-
- Some predictive tumor markers

SURVIVAL IN PATIENTS WITH OROPHARYNGEAL CANCER

Chaturvedi A K et al. JCO 29:4294, 2011

TAX-324

HPV / SMOKING AND OUTCOME WITH CT-RT IN OROPHARYNGEAL CANCER

Gillison M L et al RTOG 0129, 323/433 patients, 2009
PRETREATMENT HEMOGLOBIN LEVELS CORRELATED WITH EFFECTIVENESS OF CT-RT IN ADVANCED HEAD AND NECK CANCER

\[ p = 0.0040 \]

- \(<13 \text{ g/dL} \) (n = 38)
- \(\geq 13 \text{ g/dL} \) (n = 78)

MULTIDISCIPLINARY MANAGEMENT OF HEAD AND NECK CANCER

Disease Stage

- Early stage
  - Curative: Surgery or and Radiotherapy
  - Palliative: Chemotherapy or and Investigational

- Advanced (resectable)
  - Curative: Surgery or and Radiotherapy
  - Palliative: Chemotherapy or and Investigational

- Advanced (nonresectable)
  - Curative: Surgery or and Radiotherapy
  - Palliative: Chemotherapy or and Investigational

- Metastatic, recurrent
  - Palliative: Chemotherapy or and Investigational

60% of presentations
Potential Advantages
Optimal drug delivery (higher doses)
Reduction in tumor burden
Early treatment of micrometastatic disease
Improved treatment tolerance

Potential Disadvantages
Delay in potentially curative therapy
Increased expense and duration of therapy
Noncompliance with curative therapy
Tumor cell accelerated repopulation
Selection of chemo-radiation resistant tumor cells
**Potential Advantages**
- Added antitumor effect from two modalities
- Elimination of tumor cell accelerated repopulation
- Effect on locoregional disease and micrometastatic distant disease
- Decreased overall treatment time

**Potential Disadvantages**
- Increased treatment morbidity
- Interruption of treatment due to toxicity, which may decrease tumor control
Taxanos en Quimioterapia de Inducción
TAX-323

Randomización
Por
Sitio Tumoral
Centro

N- 358
Localmente avanzados (III-IVM0)
Irresecables

X
R
T

P 100 mg/m2
F 1000 mg/m2 1-5
X 4 ciclos

T 75 mg/m2
P 75 mg/m2
F 750 mg/m2 1-5
X 4 ciclos

Seguimiento medio 32,5 meses
Convencional (70 Gy), Acelerada (70 Gy) o Hiperfraccionada (74Gy)
Disección ganglionar cervical considerada antes o después de XRT
Objetivo Primario: Sobrevida libre de Progresión

NEJM 357:17, 2007
Taxanos en Quimioterapia de Inducción.

TAX-323

A

B

No. at Risk
PF 181 112 52 37 25 19 11 5 1
TPF 177 129 79 48 23 16 5 3 1

NEJM 357:17, 2007
Sequential Combined-Modality Therapy
A Phase III Study: TAX 324
TPF vs. PF Followed by Chemoradiotherapy

TPF: Docetaxel $75_{D1}$ + Cisplatin $100_{D1}$ + 5-FU $1000_{CI-D1-4}$ Q 3 weeks x 3
PF: Cisplatin $100_{D1}$ + 5-FU $1000_{CI-D1-5}$ Q 3 weeks x 3
Taxanos en Quimioterapia de Inducción
TAX-324

Figure 2: Progression-free survival for patients with hypopharyngeal and laryngeal primary tumour sites

Figure 3: Overall survival for patients with oropharyngeal cancer

## Table 1. Results Summary for PARADIGM and DeCiDE Trials

<table>
<thead>
<tr>
<th></th>
<th>3-year Overall Survival for Induction Therapy Group</th>
<th>3-year Overall Survival for Non-induction Therapy Group</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARADIGM</td>
<td>73%</td>
<td>78%</td>
<td>Hazard ratio, 1.09; 95% CI: 0.59-2.03; P=0.77, not significant [ns]</td>
</tr>
<tr>
<td>DeCiDE</td>
<td>75%</td>
<td>73%</td>
<td>P=0.70, ns</td>
</tr>
</tbody>
</table>
INDUCTION CHEMOTHERAPY AND CONCURRENT CT-RT IN LOCALLY ADVANCED HEAD & NECK CANCER


CHEMORADIATION THERAPY IN ADVANCED HEAD AND NECK CANCER

NEOADJUVANT CHEMOTHERAPY AND LARYNX PRESERVATION TRIALS
LARYNX PRESERVATION
EORTC Randomized Trial Design

Sequential arm (SEQ)

2 cycles CF* if PD, NC → TL ± PORT
if PR, CR → 2 cycles CF* → RT 70 Gy

Alternating arm (ALT)

1 cycle CF** – RT 20 Gy – 1 cycle CF** – RT 20 Gy →
1 cycle CF** – RT 20 Gy – 1 cycle CF** (RT 60 Gy)

* C: 100 mg/m^2 D1 + 5-FU: 1,000 mg/m^2 D1-5
** C: 20 mg/m^2 D1-5 + 5-FU: 200 mg/m^2 D1-5

RANDOMIZED EORTC TRIAL
CARCINOMA OF THE LARYNX

Larynx Intergroup Study
(RTOG 91-11)

Dx, Staging (excluding T4)

XRT (70 Gy)

XRT (70 Gy)/Cisplatin

CisP-5FU x 3 → XRT (70 Gy) (VA Larynx)

Note: Primary Organ Preservation with surgical salvage accepted for all 3 study arms. Neck dissection included N2 and N3 disease.

Forastiere, NEJM, 2003
Forastiere et al. ASCO 2006. Abstract 5517
Disease-Free Survival (RTOG 91-11)

Forastiere et al. ASCO 2006. Abstract 5517

Failed / Total

- RT + Induction: 120 / 173
- RT + Concomitant: 120 / 171
- RT Alone: 136 / 171

% Alive without Disease

Years from Randomization

Forastiere et al. ASCO 2006. Abstract 5517
Overall Survival
(RTOG 91-11)

Forastiere et al. ASCO 2006. Abstract 5517

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dead / Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT + Induction</td>
<td>89 / 173</td>
</tr>
<tr>
<td>RT + Concomitant</td>
<td>106 / 171</td>
</tr>
<tr>
<td>RT Alone</td>
<td>96 / 171</td>
</tr>
</tbody>
</table>

% Alive vs. Years from Randomization

Forastiere et al. ASCO 2006. Abstract 5517
French (Tour) study- Median follow up, 36 months

3 drugs:
Docetaxel- 75 mg/ m2, day 1
CisPlatin- 75 mg/ m2, day 1
5FU- 750 mg/ m2, days 1-5 continuous infusion
3 cycles, every 21 days

2 drugs:
CisPlatin- 100 mg/ m2, day 1
5FU- 1 gm/ m2, days 1-5, continuous infusion
3 cycles, every 21 days

Concurrent Radiation Therapy
## CHEMO-RT IN LARYNX PRESERVATION
### RANDOMIZED TRIAL, 3 VS 2 DRUGS

<table>
<thead>
<tr>
<th></th>
<th>3 Drugs</th>
<th>2 Drugs</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>110</td>
<td>103</td>
<td></td>
</tr>
<tr>
<td>Larynx Preservation</td>
<td>70.3 %</td>
<td>57.5 %</td>
<td></td>
</tr>
<tr>
<td>Normal Larynx Mobility</td>
<td>42.7 %</td>
<td>29.1 %</td>
<td></td>
</tr>
<tr>
<td>3 yr disease free survival</td>
<td>58 %</td>
<td>44 %</td>
<td>.11</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>60 %</td>
<td>60 %</td>
<td>.57</td>
</tr>
<tr>
<td>Grade 4 Larynx Toxicity</td>
<td>6.2 %</td>
<td>13.6 %</td>
<td>S.N.S.</td>
</tr>
</tbody>
</table>

CHEMO-Radiation in Locally Advanced H&N Cancer

Concurrent Chemotherapy and Irradiation

( unresectable tumors )
Wee, J. et al.
J Clin Oncol 23:6730, 2005

RANDOMIZED TRIAL: RT +/- CONCURRENT AND ADJUVANT CT IN CA. OF NASOPHARYNX

221 patients randomly assigned

110 radiotherapy (R)
- Did not fulfill eligibility criteria:
  - 1 had metastasis
  - 1 had 2nd malignancy
- Noncompliance with treatment:
  - 1 received 2,400 cGy
  - 1 received 5,000 cGy
  - 3 defaulted treatment soon after random assignment
- Completeness of follow-up:
  - 1 lost to follow-up

111 concurrent chemoradiotherapy + adjuvant chemotherapy (C)
- Did not fulfill eligibility criteria:
  - 1 had metastasis
  - 1 had stage II disease
- Noncompliance with treatment:
  - Concurrent chemoradiotherapy
    - 6 RT dose ≤ 6,200 cGy
    - 1 started RT 2 weeks earlier
    - 5 did not have any concurrent chemotherapy
    - 27 had reduced cycles of chemotherapy
    - 7 had delayed cycle(s)
  - Adjuvant chemotherapy
    - 6 had dose reduction
    - 1 dose substitution
    - 38 had no adjuvant therapy

RANDOMIZED TRIAL: RT +/- CONCURRENT AND ADJUVANT CT IN CA. OF NASOPHARYNX

Disease-free / Overall Survival

---

**Disease-Free Survival**

- **P = 0.0093**
- **HR: 0.57**
- **95% CI: 0.4 to 0.9**

<table>
<thead>
<tr>
<th>Years From Random Assignment</th>
<th>C</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>111 (0)</td>
<td>110 (0)</td>
</tr>
<tr>
<td>1</td>
<td>91 (20)</td>
<td>82 (26)</td>
</tr>
<tr>
<td>2</td>
<td>65 (7)</td>
<td>51 (20)</td>
</tr>
<tr>
<td>3</td>
<td>44 (3)</td>
<td>34 (3)</td>
</tr>
<tr>
<td>4</td>
<td>24 (3)</td>
<td>20 (2)</td>
</tr>
<tr>
<td>5</td>
<td>11 (2)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>6</td>
<td>0 (0)</td>
<td>0 (1)</td>
</tr>
</tbody>
</table>

**Overall Survival**

- **P = 0.0061**
- **HR: 0.51**
- **95% CI: 0.3 to 0.8**

<table>
<thead>
<tr>
<th>Years From Random Assignment</th>
<th>C</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>111 (0)</td>
<td>110 (0)</td>
</tr>
<tr>
<td>1</td>
<td>102 (9)</td>
<td>96 (9)</td>
</tr>
<tr>
<td>2</td>
<td>74 (7)</td>
<td>68 (13)</td>
</tr>
<tr>
<td>3</td>
<td>52 (4)</td>
<td>41 (10)</td>
</tr>
<tr>
<td>4</td>
<td>28 (3)</td>
<td>23 (6)</td>
</tr>
<tr>
<td>5</td>
<td>13 (1)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>6</td>
<td>0 (0)</td>
<td>0 (2)</td>
</tr>
</tbody>
</table>
GORTEC 94-01 RT vs CTRT
IN ADVANCED OROPHARYNX CANCER

GORTEC 94-01
ST 3/4 OROPHARYNX CARCINOMAS n=226

Age < 75
Karnofsky index > 60
No metastasis
No synchronous tumour
No previous ttt

Randomisation

Randomized: 115
Eligible: 113
Treated: 112

Control Arm

70 Grays
2 Grays/fraction
7 weeks

Concomitant Arm

70 Grays, 7 weeks
+ Carboplatin 70 mg/m²
days 1, 2, 3, 4
+ 5FU 600 mg/m²
days 1, 2, 3, 4
Weeks 1, 4, 7

Randomized: 111
Eligible: 109
Treated: 108


FRENCH 94-01 RANDOMIZED TRIAL (RT+- CT)
Locoregional (LR) tumor control

$p$ (Mantel-Cox Logrank) = 0.002

$47.6\%$ $24.7\%$

$\rightarrow$ RT / CT
$\rightarrow$ RT

Month After Randomization


JOURNAL OF CLINICAL ONCOLOGY
Overall survival in advanced oropharyngeal cancer

LATE TOXICITY GORTEC 94-01 RT vs CTRT IN ADVANCED OROPHARYNX CANCER

RADIATION THERAPY +/- WKLY CISPLATIN IN UNRESECTABLE H&N CANCER

**Stratification:**
1. Performance Status
   - 0-1
   - 2-3
2. Primary Tumour
   - T1-3
   - T4
3. Nodal Status
   - N0-1
   - N2-3

**Randomize**

**Treatment Arm A:**
- Radiotherapy alone
- 70 Gy in 1.8-2 Gy/day

**Treatment Arm B:**
- 70 Gy in 1.8 Gy/day
- Weekly cisplatin, 20 mg/m², day 1, 8, 15, 22, 29, 36, 43

**Observe**
- No Progression
- Progression
  - Off Study

RADIATION THERAPY +/- WKLY CISPLATIN IN UNRESECTABLE H&N CANCER

Disease free Survival

Overall Survival

CT / RT IN LOCALLY ADVANCED HEAD AND NECK CANCER

POSTOPERATIVE CT/RT VERSUS RT
334 Patients randomized to:

Radiation therapy alone: 66 Gy/33 fractions
or
Chemotherapy plus radiation therapy:
Same radiation therapy
Cisplatin, 100 mg/m² days 1, 22, 43

Progression-free survival.
# HEAD AND NECK CANCER
## POSTOPERATIVE CT/RT VERSUS RT
### EORTC TRIAL 22931

<table>
<thead>
<tr>
<th></th>
<th>RT (n = 167)</th>
<th>CT + RT (n = 167)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-Year disease-free survival</td>
<td>36%</td>
<td>47%</td>
<td>0.0096</td>
</tr>
<tr>
<td>5-Year overall survival</td>
<td>40%</td>
<td>53%</td>
<td>0.007</td>
</tr>
<tr>
<td>Grade 3-4 mucosal reaction*</td>
<td>21.3%</td>
<td>44.5%</td>
<td>0.0004</td>
</tr>
<tr>
<td>Grade 3-4 CT acute toxicity*</td>
<td>1.9%</td>
<td>10.9%</td>
<td></td>
</tr>
</tbody>
</table>

*Note: No difference in late toxicity.*

INTERGROUP PHASE III RTOG 95-01 TRIAL
SURGERY +/- RT IN HIGH RISK H&N CANCER

Completely Resected
High-Risk Pathology
459 patients

STRATIFY

Age:
• <70
• ≥ 70

Risk:
• micro + margin
• ≥ 2 nodes or ECS

RANDOMIZE

RT alone

RT/CT

RT: 60+/- 6 Gy/6 – 6.5 weeks, 2 Gy/fx

Cisplatin: 100 mg/m² IV days 1, 22, & 43
## POSTOPERATIVE CONCURRENT RADIATION THERAPY AND CHEMOTHERAPY FOR HIGH-RISK CARCINOMA OF THE HEAD AND NECK

<table>
<thead>
<tr>
<th></th>
<th>RT (n = 231)</th>
<th>RT/CT (n = 228)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 toxicity</td>
<td>39%</td>
<td>51%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Grade 4 toxicity</td>
<td>14%</td>
<td>25%</td>
<td>0.16</td>
</tr>
<tr>
<td>Fatal toxicity</td>
<td>0</td>
<td>2%</td>
<td></td>
</tr>
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</table>

ECOG 3311 P16+ Trial – Low Risk OPSCC: Personalized Adjuvant Therapy Based on Pathologic Staging of Surgically Excised HPV+ Oropharynx Cancer

**LOW RISK:** T1-T2N0-N1 negative margins
- Transoral Resection (any approach) with neck dissection

**INTERMEDIATE:**
- Clear margins ≤ 1 mm ECS
- 2–3 metastatic LN
- PNI- LVI
- Evaluate for 2-yr PFS
- Local-Regional Recurrence, Functional Outcomes/QOL

**HIGH RISK:**
- Positive Margins > 1 mm ECS or ≥ 4 metastatic LN

**LOW RISK:** T1-T2N0-N1 negative margins
- Radiation Therapy IMRT 50Gy/25 Fx

**INTERMEDIATE:**
- Radiation Therapy IMRT 60 Gy/30 Fx +

**HIGH RISK:** Positive Margins > 1 mm ECS or ≥ 4 metastatic LN
- Radiation Therapy IMRT 66 Gy/33 Fx + CDDP 40 mg/m² wkly

**Assess Eligibility:**
- HPV (p16)+ SCC oropharynx
- Stage III-IV: cT1-3, N1-2b (no T1N1)
- Baseline Functional/QOL Assessment

**Randomize**
- Observation

**Radiation Therapy** IMRT 50Gy/25 Fx
- Evaluate for 2-yr PFS
- Local-Regional Recurrence, Functional Outcomes/QOL

**Low Risk OPSCC:**
- Personalized Adjuvant Therapy Based on Pathologic Staging of Surgically Excised HPV+ Oropharynx Cancer
- ECOG 3311 P16+ Trial
- Low Risk OPSCC: Personalized Adjuvant Therapy Based on Pathologic Staging of Surgically Excised HPV+ Oropharynx Cancer
- Assess Eligibility: HPV (p16)+ SCC oropharynx
- Stage III-IV: cT1-3, N1-2b (no T1N1)
- Baseline Functional/QOL Assessment
CHEMOIRRADIATION IN HEAD AND NECK CARCINOMA

Meta-Analyses
## CHEMOTHERAPY IN HEAD AND NECK CANCER
### META-ANALYSIS (93 TRIALS, 17,346 PATIENTS)


### (a) Hazard ratio of death.

<table>
<thead>
<tr>
<th>Timing</th>
<th>No. Deaths / No. Entered</th>
<th>O-E</th>
<th>Variance</th>
<th>Hazard Ratio</th>
<th>HR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LRT+CT</td>
<td>LRT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant</td>
<td>3171/4824</td>
<td>3389/4791</td>
<td>-326.4</td>
<td>1587.7</td>
<td>0.81 [0.78,0.86]</td>
</tr>
<tr>
<td>Induction</td>
<td>1877/2740</td>
<td>1813/2571</td>
<td>-40.0</td>
<td>900.7</td>
<td>0.96 [0.90,1.02]</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>631/1244</td>
<td>661/1323</td>
<td>17.9</td>
<td>317.4</td>
<td>1.06 [0.95,1.18]</td>
</tr>
<tr>
<td>Total</td>
<td>5679/8808</td>
<td>5863/8685</td>
<td>-348.5</td>
<td>2805.8</td>
<td>0.88 [0.85,0.92]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $\chi^2_{107} = 179.8$ p < 0.0001

Test for interaction: $\chi^2_2 = 26.60$ p < 0.0001

LRT+CT effect: p < 0.0001

LRT+CT better | LRT better

P = 41%
CHEMOTHERAPY IN HEAD AND NECK CANCER
META-ANALYSIS (93 TRIALS, 17,346 PATIENTS)

Integration of Molecular Therapies into First-Line Regimens
PHASE III TRIAL RADIATION THERAPY +/- CETUXIMAB
SQUAMOUS CELL CARCINOMA OF HEAD AND NECK

Stratify by
- Karnofsky score: 90-100 vs. 60-80
- Regional Nodes: Negative vs. Positive
- Tumor stage: AJCC T1-3 vs. T4
- RT fractionation: Concomitant boost vs. Once daily vs. Twice daily

Arm 1
Radiation therapy

Arm 2
Radiation therapy + Cetuximab, weekly
Wk 1: 400 mg/m² IV no RT
Wk 2-8: 250 mg/m² followed by RT

PHASE III TRIAL RADIATION THERAPY +/- CETUXIMAB IN HEAD AND NECK CANCER- 5 YEAR SURVIVAL

Lancet Oncol 11:21, 2010
CHEMOTHERAPY +/- CETUXIMAB
IN HEAD AND NECK CANCER

Randomized study - Arm 1 - CisPlatin (100 mg/m2) or carboplatin, day 1
5FU (1 gm/m2, 4 days) q 3 wks. for 6 cycles
Arm 2 - Same CT + cetuximab (400 mg/m2 initially, 250 mg/m2 per week for 6 cycles)

<table>
<thead>
<tr>
<th></th>
<th>Arm 1</th>
<th>Arm 2</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median overall survival</td>
<td>7.4</td>
<td>10.1</td>
<td>0.04</td>
</tr>
<tr>
<td>(mos.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median progression-free</td>
<td>3.3</td>
<td>5.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>survival (mos.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3-4 anemia</td>
<td>19%</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>1</td>
<td>9</td>
<td>0.02</td>
</tr>
<tr>
<td>Grade 3 skin reactions</td>
<td></td>
<td>9%</td>
<td></td>
</tr>
</tbody>
</table>
There are many new agents directed at important signaling pathways in HNC:
- Survival, metabolism: EGFR, MET
- Cell death: PI3K, PTEN, MTOR
- Vascular support: Bevacizumab
- Differentiation?

Biomarkers are potentially available for some agents, but aside from HPV as a prognostic marker, predictive markers are not ready for prime time.

Personalized cancer therapeutics are close to becoming a reality in HNC.
CHEMORADIATION +/- ERLOTINIB IN LOCALLY ADVANCED HEAD AND NECK CANCER

# Chemoradiation +/- Erlotinib in Locally Advanced Head and Neck Cancer

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Arm A: Chemoradiotherapy (n = 96)</th>
<th>Arm B: Erlotinib + Chemoradiotherapy (n = 95)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>%</td>
<td>No. of Patients</td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade</td>
<td>10</td>
<td>10</td>
<td>65</td>
</tr>
<tr>
<td>Grade 3</td>
<td>2</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade</td>
<td>54</td>
<td>56</td>
<td>50</td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td>18</td>
<td>19</td>
<td>18</td>
</tr>
</tbody>
</table>

RTOG 0522
Phase III Trial for Stage III-IV HNSCC
Schema – Sample Size: 720

Stage III & IV* SCC of:
• Oropharynx
• Hypopharynx
• Larynx

Stratify:
• Larynx ~ Others
• N0~N1,2a,2b~N2c-3
• KPS
  60-80 ~ 90-100
• 3-D vs IMRT

*Exclude T1 any N or T2N1

1. Accelerated FX +
   CDDP: 100 mg/m², q3W X 2

2. Accelerated FX +
   CDDP: 100 mg/m², q3W X 2
   C225: 400 mg/m² Pre-RT, then
   250 mg/m²/wk x 7

One of Nine Protocols Covered Under the Medicare Anti-Cancer Drug National Coverage Decision.

http://www.cancer.gov/clinicaltrials/developments/NCD179N
Concurrent Chemoradiotherapy
RTOG 0522: A Phase III Trial of Cisplatin CRT
With or Without Cetuximab

CisPl: 100 mg/m²

XRT

Cetuximab 400/250 mg

XRT

Stratify: XRT as Standard or IMRT on DAHANCA

Ang et al, 2011.
CHEMO-RADIATION IN OROPHARYNGEAL CANCER

Feng FY et al J Clin Oncol 28:2732, June 1, 2010
Randomized Comparison Concomitant Boost RT Alone vs Concurrent Chemo-RT in Locally Advanced Oropharyngeal Cancer

**Assessed for eligibility**

- Enrolled (n = 216)
- Excluded (n = 214)
- Not meeting inclusion criteria (n = 156)
- Refused to participate (n = 58)

**Enrollment**

**Randomization**

**Chemoradiation Arm:**
- 66 Gy in 33 Fr over 6½ wks (conventional fractionation) with concurrent Cisplatin (100 mg/m²) on D₁, D₂₂ and D₄₃

**Concomitant Boost Arm:**
- (67.5 Gy in 40 Fr over 5 weeks
  - Phase -1, 45 Gy in 25 Fr and phase-2, 22.5 Gy in 15 fractions)

Rishi A et al. Radiother & Oncol ePubl June 2013
RANDOMIZED COMPARISON CONCOMITANT BOOST RT ALONE VS CONCURRENT CHEMO-RT IN LOCALLY ADVANCED OROPHARYNGEAL CANCER

Rishi A et al
Radiother & Oncol ePubl June 2013
### RANDOMIZED COMPARISON CONCOMITANT BOOST RT ALONE VS CONCURRENT CHEMO-RT IN LOCALLYA ADV. OROPHARYNGEAL CANCER- Grade 3-4 Toxicity

<table>
<thead>
<tr>
<th></th>
<th>Chemo RT (N=106)</th>
<th>Conc Boost RT (N=110)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucositis</td>
<td>40 (38%)</td>
<td>60 (55%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>32 (31%)</td>
<td>87 (79%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>44 (42%)</td>
<td>38 (34%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Pain</td>
<td>13 (12%)</td>
<td>13 (12%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Xerostomia</td>
<td>20 (34%)</td>
<td>12 (18%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>4 (7%)</td>
<td>1 (4%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Weight loss</td>
<td>18 (17%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Fistula</td>
<td>0</td>
<td>2 (2%)</td>
<td></td>
</tr>
</tbody>
</table>

Rishi A et al Radiother & Oncol ePubl June 2013
CHEMOTHERAPY AND RADIATION THERAPY IN H&N CANCER: QUESTIONS

- What are the most reliable prognostic/predictive factors for benefit of combined chemo-radiation?
- What chemotherapy schema is best, when combined with RT?
- Are biological modifiers more effective and less toxic?
- Is hyperfractionated or accelerated radiation fractionation more effective than conventional fractionation?
- What are optimal schemas of chemotherapy and radiation therapy?

- Need additional trials on targeted therapies and EGFR inhibitors
CHEMO-RADIATION IN H & N CANCER
Future Directions

Better Patient Selection

Altered Fractionation CRT vs. CF CRT
RTOG 0129, NCI G99-1657

Innovative Surgery, Reconstruction & Rehabilitation
CO₂ Laser Surgery, Microvascular Reconstruction

Better Chemotherapy & Adjuvant Biological Modifiers
Taxanes, Cetuximab, Iressa

Normal Tissue Radioprotectants
Amifostine - IMRT

IMRT ± Chemotherapy
Conclusions:

Minimal benefit with neoadjuvant chemotherapy

- Improved local regional tumor control and small benefit in overall survival with concurrent chemo-radiation therapy
- Increased toxicity with concurrent irradiation and chemotherapy

- Addition of cetuximab improves outcome, more toxicity
- Additional clinical trials necessary

- Amifostine may be helpful in reducing treatment toxicity according to some studies
MUCHAS GRACIAS POR VUESTRA ATENCION Y MUY BUENA SUERTE !
Treatment Toxicity
MUCOSITIS WITH IMRT AND CONCOMITANT CHEMOTHERAPY

SEVERE TOXICITY AFTER CONCURRENT CT-RT IN HEAD AND NECK CANCER (RTOG (TRIALS))

230 patients in studies. 99 (43%) developed toxicity, 131 controls no toxicity

<table>
<thead>
<tr>
<th></th>
<th>91-11</th>
<th>97-03</th>
<th>99-14</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeding tube &gt; 2 yrs post- RT</td>
<td></td>
<td></td>
<td></td>
<td>29 (12.6%)</td>
</tr>
<tr>
<td>Grade 3+ late</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharyngeal dysfunction</td>
<td>16</td>
<td>28</td>
<td>19</td>
<td>63 (27.3%)</td>
</tr>
<tr>
<td>Laryngeal dysfunction</td>
<td>22</td>
<td>6</td>
<td>0</td>
<td>28 (12.1%)</td>
</tr>
<tr>
<td>Death</td>
<td>11</td>
<td>9</td>
<td>2</td>
<td>22 (9.6%)</td>
</tr>
<tr>
<td>Other (fistula, infection, etc)</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Any toxicity</td>
<td>38</td>
<td>40</td>
<td>21</td>
<td>99 (43%)</td>
</tr>
<tr>
<td>No severe late toxicity</td>
<td>50</td>
<td>62</td>
<td>19</td>
<td>13</td>
</tr>
</tbody>
</table>

Machtay M et al J Clin Oncol 26: 3582, June 2008
SEVERE TOXICITY AFTER CONCURRENT CT-RT IN HEAD AND NECK CANCER (RTOG TRIALS)

Subgroup analyses based on patient/treatment characteristics

## Thyroid Size After RT for Laryngeal Cancer

### Treated with Ext RT for Larynx Cancer

<table>
<thead>
<tr>
<th></th>
<th>Euthyroid</th>
<th>Hypothyroid</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>42</td>
<td>19</td>
<td>.20</td>
</tr>
<tr>
<td>Average width change (mm)</td>
<td>4.1 (11%)</td>
<td>6.1 (20%)</td>
<td></td>
</tr>
</tbody>
</table>

### Also Receiving Chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>31</td>
<td>30</td>
</tr>
<tr>
<td>Average width change (mm)</td>
<td>5.5 (16%)</td>
<td>3.9 (11.5%)</td>
</tr>
</tbody>
</table>

CHEMO-IMRT DOSE TO PHARYNGEAL CONSTRUCTORS AND DYSPHAGIA IN H & N CANCER

Bhide S A et al Radiother & Oncol 93: 539, 2009
HEAD & NECK CANCER CT-RT
LATE TOXICITY- DYSPHAGIA
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Bilateral Neck IMRT</th>
<th>Unkn Primary Neck IMRT</th>
<th>Salivary Gland IMRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporary</td>
<td>48% (183/380)</td>
<td>None (0/15)</td>
<td>12% (3/24)</td>
</tr>
<tr>
<td>Permanent</td>
<td>20% (75/380)</td>
<td>None (0/15)</td>
<td>None (0/24)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>40% (153/380)</td>
<td>40% (6/15)</td>
<td>12% (3/24)</td>
</tr>
</tbody>
</table>
ELECTIVE GASTROSTOMY-TUBE IN HEAD & NECK CHEMO-RADIATION

Chen AM et al Int J Rad Oncol Bio Phys 78: 1026, 2010

Weight Loss
ELECTIVE GASTROSTOMY-TUBE IN HEAD & NECK CHEMO-RADIATION

Permanent G-tube

Esophageal Stricture

G-tube- 30%

No G-tube- 6%

(p < 0.001)

Chen AM et al Int J Rad Oncol Bio Phys 78: 1026, 2010
Amifostine
• Lower delivery of drug in tumors
• Higher delivery in normal tissues
• Alkaline phosphatase is required for activation of drug
• Alkaline phosphatase activity is higher in normal tissues
Amifostine: Mechanism of Action

Amifostine (WR-2721)

NH₂-(CH₂)₃-NH-(CH₂)₂-S-PO₃H₂

WR-1065

NH₂-(CH₂)₃-NH-(CH₂)₂-SH

alkaline phosphatase

ionizing radiation

generating radicals

radicals

oxygen

nucleus

PHASE III TRIAL OF RT ± AMIFOSTINE IN HEAD AND NECK CANCER

Arm 1 (n = 150)
Amifostine:
- 200 mg/m² IV over 3 min
- 15-30 min before RT

RT
- 1.8-2.0 Gy/d
- Total: 50-70 Gy x 5 d/wk

Arm 2 (n = 153)
RT alone
- 1.8-2.0 Gy/d
- Total: 50-70 Gy x 5 d/wk

STRATIFY
- Treatment center
- 1° tumor site
- Definitive vs post-operative adjunctive radiation
- N+ vs N0
- Karnofsky performance status

RANDOMIZE
DOSE AT ONSET OF GRADE 2 XEROSTOMA
MEDIAN RT DOSE

Median RT dose
- Amifostine + RT: 62 Gy
- RT: 42 Gy

Log-rank: p < 0.0001
Hazard ratio: 1.878 (1.404-2.507)
PATIENTS WITH NO SALIVA PRODUCTION AT ONE YEAR

- Amifostine + RT (n = 42)
- RT (n = 42)

19% vs. 38%

p = 0.08
Phase III Trial of RT ± Amifostine for H&N Cancer: Antitumor Efficacy at 18 M

- Locoregional control: 58% (RT + Amifostine) vs. 64% (RT - Amifostine)
- Disease-free survival: 63% (RT + Amifostine) vs. 64% (RT - Amifostine)
- Overall survival: 81% (RT + Amifostine) vs. 73% (RT - Amifostine)

*Significant difference

Brizel DM, et al. JCO, 2000
DISEASE-FREE SURVIVAL

Events total

- Amifostine + RT: 34/157
- RT: 36/158

p = 0.98
Hazard ratio: 0.99 (0.62-1.59)
Bardet E et al
J Clin Oncol Jan 10, 2011: 119