Sequencing Chemo with Radiation therapy
Locally Advanced Head and Neck Cancer

Dr P Vijay Anand Reddy
Director
Apollo Cancer Hospital
H&N Ca - Disease Burden

- 15-20% of all cancers in India, 8% worldwide
- 60% presents with locally advanced disease
- Average 3yr survival – 30%-50%
HNSCC - Goals of Rx

- Survival - Cure
- Preserving Organ & Function
- Minimizing the morbidity

*Quantity and Quality of life!*
LAHNSCC - How best we can achieve?

- Surgery vs Radiotherapy
- Radiotherapy vs RT + Chemo
- What drugs? Two vs Three drugs
- Neoadj Chemo vs Concurrent
- Conclusions
Surgery vs Radiotherapy
Can we preserve the Organ & Function?
Without compromising the survival?

Locally advanced Laryngeal & Hypo-pharyngeal ca
Dept of Veterans Affairs Laryngeal Study
*NEJM ’91*

VA study: 332 pts

- **Experimental arm** Larynx Preservation
  - 2 cycles of chemo (Cispllt and 5 FU)
  - PR or CR had 3rd cycle of chemo followed by XRT
  - Non-responders - TL+PORT

- **Control arm** Total Laryngectomy
  - TL + PORT
Dept of Veterans Affairs Laryngeal Study Group, *NEJM '91*

**VA study**
Stage III/IV
Glottic/supraglottic larynx
N=332

- **Experimental arm**
  - 3 cycles PF in responders RT

- **Control arm**
  - Non Responders TL + RT

✓ Neo adj Chemo ---→ RT alone
Veterans Affairs Laryngeal Cancer Study Grp

OS at 2 yrs - 68 % both groups

332 pts.
Surgery vs Radiotherapy

VA study: results

- 2 & 10yr f.u. show no significant diff in survival
- Overall laryngeal preservation rate = 64%

NEJM ’91
Larynx Preservation in Pyriform Sinus Ca EORTC Phase III Trial

Hypopharynx 78%
Larynx 22%
T2(19%), T3(75%), T4(6%)
N= 202

PF (3#) followed by RT
(in only CR pts)
Sx + RT

RANDOMIZE

OS : chemo (57%) > surgery (43%) at 3 yr, equal at 5 yrs
No difference in Loco-regional failure
Increase in distant mets in surgery (36%) Chemo (25%)
Surgery vs Radiotherapy
VA and EORTC studies

- Overall survival is similar
- Organ preservation is feasible
- Better QOL with CT + RT
- Exact role of CT not certain!

Neo adj CT => RT alone is equally good to Surg!

Terrell JE, Arch Otolaryngol Head Neck Surg ‘98
RT alone or RT + CT ?

Defining the role of chemo..

- Does it make a diff?
- Neo adjuvant? or
- Concurrent?
Defining the role of Chemotherapy...

- RTOG 91-11

Determine role of induction vs concurrent chemo vs radiation alone in Laryngeal preservation for pts with Stage 3 & 4, SCC of Larynx
RTOG 91-11
Larynx: stage III-IV

**Randomization**

- **RT** (n=170)
  - 70 Gy
  - 2 Gy/F
  - 7 weeks

- **Ind. CT =>RT or S** (n=171)
  - CDDP 100mg/m²d1
  - 5FU 1g/m², d1-5
  - X 2-3
  - ≥ PR: 70 Gy
  - < PR: surgery

- **Conc CT+RT** (n=169)
  - 70 Gy, 2Gy/F, 7 w
  - CDDP 100 mg/m², D 1, 22, 43

Karnofsky ≥ 60
Glottic or supra-glottic SCC
No metastasis
No synchronous T
No previous RT

*Forastiere, NEJM 2003, JCO 2006*
RTOG 91-11 study: results

- OS did not differ @ 3 & 5 year
  - 76% at 2 years overall

- Local-regional control
  - Conc Chemo / RT > induction chemo or XRT

- Laryngeal preservation at 3.8 yrs median f/u
  - 84% conc CT/RT > 72%induc > 67% XRT

✔ Concurrent Chemoradiotherapy

Forastiere, NEJM 2003, JCO 2006
Role of Chemotherapy

Neo-adj vs Concurrent?
Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data

Pignon group for MACH-NC collaborative Grp

J P Pignon, J Bourhis, C Domenge, L Designé, on behalf of the MACH-NC Collaborative Group*

No. of patients analyzed = 10,741
63 Randomised trials 1965-1993

<table>
<thead>
<tr>
<th>Trial Category</th>
<th>No. of Trials</th>
<th>No. Patients</th>
<th>Absolute Benefit at 5 years</th>
<th>p value</th>
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<tbody>
<tr>
<td>All trials</td>
<td>65</td>
<td>10850</td>
<td>+4</td>
<td>&lt;0.0001</td>
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<tr>
<td>Adjuvant</td>
<td>8</td>
<td>1854</td>
<td>+1</td>
<td>0.74</td>
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<td>Induction</td>
<td>31</td>
<td>5269</td>
<td>+2</td>
<td>0.10</td>
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<tr>
<td>Concomitant</td>
<td>26</td>
<td>3727</td>
<td>+8</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Pignon et al Lancet 2000
Conclusions

- ICT inferior to Conc CTRT in terms of Organ preservation, Loco-regional control
- No survival benefit with NACT
- Cisplatin + 5-FU most effective combination

*Data for conc CT+RT more robust & consistent*

Pignon et al Lancet 2000
New Neo adjuvant trials……
Addition of Doce/pacli?

- TAX323,
- TAX 324,
- Hitt 2005,
- Paccognella 2006,
- Hitt 2009….
Unresectable SCC - Head and Neck Ca (excluding NP, nasal and paranasal cavities)

Stage III or IV, Mo
Age 18 to 70
Median f/u 32.5 mths
Study Design

Unresectable SCCHN

Stratification: Institution Primary Site

TPF – 181 pts, PF – 177 pts
Response assessment at end of cycles 2&4

Vermorken et al, EORTC 24971, TAX 323
Chemotherapy Regimens

Standard arm (PF)
- Cisplatin 100 mg/m², day 1
- 5-FU 1000 mg/m²/day, day 1 to 5

Experimental arm (TPF)
- Docetaxel 75 mg/m², day 1
- Cisplatin 75 mg/m², day 1
- 5-FU 750 mg/m²/day, day 1 to 5
<table>
<thead>
<tr>
<th>End point</th>
<th>TPF (mths)</th>
<th>PF (mths)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>11</td>
<td>8.2</td>
<td>0.007</td>
</tr>
<tr>
<td>Median OS</td>
<td>18.8</td>
<td>14.5</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Median fu 38 months
**Drop outs!....**

<table>
<thead>
<tr>
<th></th>
<th>TPF</th>
<th>PF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protocol</td>
<td>75.7%</td>
<td>65.7%</td>
</tr>
<tr>
<td>completed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemo</td>
<td>38 pts (21%)</td>
<td>60 pts (34%)</td>
</tr>
<tr>
<td>discontinued</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

......Significant!
Vermorken et al, EORTC 24971, TAX 323

- CR significant in TPF arm
- Overall RR significant in TPF arm in induction & RT phase
- 28% reduction in rate of progression or death

Toxicity
- Alopecia, infections more in TPF arm
- Severe leucopenia more in TPF
- Vomiting, stomatitis, diarrhea, hearing loss more in PF arm
- Anemia, thrombocytopenia more in PF?
Cisplatin and Fluorouracil Alone or with Docetaxel in Head and Neck Cancer

TAX 324: study design

**Locally advanced SCCHN:**
organ preservation, resectable with low curability, unresectable

- **3 x TPF q3w**
  - T  Taxotere  75 mg/m²  D1
  - P  Cisplatin  100 mg/m²  D1
  - F  5-FU  1000 mg/m²  D1–5

- **3 x PF q3w**
  - P  Cisplatin  100 mg/m²  D1
  - F  5-FU  1000 mg/m²  D1–5

**Carboplatinum**
AUC 1.5 weekly

**Daily radiotherapy**
<table>
<thead>
<tr>
<th></th>
<th>TAX 324</th>
<th>TPF</th>
<th>PF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>71mths</td>
<td>30mths</td>
<td></td>
</tr>
<tr>
<td>3yr OS</td>
<td>62%</td>
<td>48% (p=.002)</td>
<td></td>
</tr>
<tr>
<td>Median PFS</td>
<td>36 mths</td>
<td>13 mths</td>
<td></td>
</tr>
<tr>
<td>LRF</td>
<td>30%</td>
<td>38% (p=.04)</td>
<td></td>
</tr>
<tr>
<td>Dist mets</td>
<td>5%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>Grade3/4 neutropenia</td>
<td>83%</td>
<td>56%</td>
<td></td>
</tr>
<tr>
<td>Grade3/4 thromboytopenia</td>
<td>4%</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>Rx delays</td>
<td>29%</td>
<td>65% (p=.001)</td>
<td></td>
</tr>
</tbody>
</table>
Sequential therapy for the locally advanced larynx and hypopharynx cancer subgroup in TAX 324: survival, surgery, and organ preservation


<table>
<thead>
<tr>
<th>TAX 324</th>
<th>TPF</th>
<th>PF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>59 mths</td>
<td>24 mths</td>
</tr>
<tr>
<td>Median PFS</td>
<td>21 mths</td>
<td>11 mths</td>
</tr>
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</table>
**Drop outs!**

<table>
<thead>
<tr>
<th>Patients</th>
<th>TPF</th>
<th>PF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo discontinuation</td>
<td>68 pts (27%)</td>
<td>79 pts (32%)</td>
</tr>
</tbody>
</table>


Induction chemotherapy with cisplatin and fluorouracil alone or in combination with docetaxel in locally advanced squamous-cell cancer of the head and neck: long-term results of the TAX 324 randomised phase 3 trial

Jochen H Lorch, Olga Goloubeva, Robert I Haddad, Kevin Cullen, Nicholas Sarlis, Roy Tishler, Ming Tan, John Fasciano, Daniel E Sammartino, Marshall R Posner, for the TAX 324 Study Group*

Questions:
Is survival benefit sustained at longer follow-up?

Any sub-sites that benefit particularly - or not?

Tracheotomy and gastric feeding tube at longer follow-up?

Feb 2011, Lancet Oncology
TAX 324 5-year follow-up: Overall Survival

Sustained survival advantage at 5 years for TPF versus PF
Median OS - 71 vs 35 months (HR 0.74, \( p=0.0129 \))
Sustained improvement in patients with laryngeal and hypopharyngeal primary tumors with a 50% reduction of the risk of progression or death compared with PF (20.86 months, CI 12.42-58.65 versus 10.09 months, CI 7.72-13.60).

Feb 2011, Lancet Oncology
TAX324 5-year follow-up: OS Oropharynx

Improvement in OS for pts on TPF with Oroph tumors at 5 years (p=0.045)
### TAX324 5-year follow-up: Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>TPF (255)</th>
<th>PF (NR246)</th>
<th>Hazard Ratio</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Survival (Mo) at 3y</strong></td>
<td>71</td>
<td>30</td>
<td><strong>.70 (.54-.90)</strong></td>
<td><strong>.006</strong></td>
</tr>
<tr>
<td></td>
<td>71</td>
<td>35</td>
<td><strong>.74 (.58-.94)</strong></td>
<td><strong>.014</strong></td>
</tr>
<tr>
<td><strong>Oropharynx at 3y</strong></td>
<td>NR</td>
<td>NR</td>
<td><strong>.70 (.47-1.03)</strong></td>
<td><strong>.07</strong></td>
</tr>
<tr>
<td></td>
<td>NR</td>
<td>65</td>
<td><strong>.69 (.58-.94)</strong></td>
<td><strong>.045</strong></td>
</tr>
<tr>
<td><strong>Hypopharynx at 3y</strong></td>
<td>32</td>
<td>20</td>
<td><strong>.67 (.37-1.20)</strong></td>
<td><strong>.18</strong></td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>20</td>
<td><strong>.74 (.42-1.3)</strong></td>
<td><strong>.29</strong></td>
</tr>
<tr>
<td><strong>Larynx at 3y</strong></td>
<td>59</td>
<td>25</td>
<td><strong>.58 (.32-1.04)</strong></td>
<td><strong>.07</strong></td>
</tr>
<tr>
<td></td>
<td>58</td>
<td>25</td>
<td><strong>.72 (.41-1.24)</strong></td>
<td><strong>.29</strong></td>
</tr>
<tr>
<td><strong>Oral Cavity at 3y</strong></td>
<td>37</td>
<td>14</td>
<td><strong>.87 (.47-1.6)</strong></td>
<td><strong>.66</strong></td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>14</td>
<td><strong>.89 (.5-1.59)</strong></td>
<td><strong>.70</strong></td>
</tr>
</tbody>
</table>
TAX324 5-year follow-up:

No significant difference in long-term toxicities

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>TPF N (%)</th>
<th>PF N (%)</th>
<th>Fisher’s exact test, two sided</th>
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</thead>
<tbody>
<tr>
<td>Enteral feeding tube</td>
<td>3/91 (3%)</td>
<td>8/63 (13%)</td>
<td>P=0.14</td>
</tr>
<tr>
<td></td>
<td>n/a 40*</td>
<td>n/a 30 *</td>
<td></td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>6/86 (7%)</td>
<td>8/63 (12%)</td>
<td>P=0.60</td>
</tr>
<tr>
<td></td>
<td>n/a 39 *</td>
<td>n/a 30 *</td>
<td></td>
</tr>
</tbody>
</table>

No statistically significant difference in tracheostomy and enteral feeding tube dependence.
* no information could be obtained
Tax 323, 324 results….

- TPF is superior to PF as induction in LAHNC
- TPF improve survival, loco-regional control
- TPF induction reduces risk of death by 30%
- No additional toxicity with Docetaxel to PF
Pitfalls...

- Three drugs (TPF) vs two drugs (PF)
- Not compared with chemo-radiation
- Weekly carboplatin is not the standard (TAX 324)
- Significant drop outs and treatment delays
Phase III Study Comparing Cisplatin Plus Fluorouracil to Paclitaxel, Cisplatin, and Fluorouracil Induction Chemotherapy Followed by Chemoradiotherapy in Locally Advanced Head and Neck Cancer

Ricardo Hitt, Antonio López-Pousa, Javier Martínez-Trufero, Vicente Escrig, Joan Carles, Alfredo Rizo, Dolores Isla, M. Eugenia Vega, Juan L. Martí, Francisco Lobo, Pedro Pastor, Vicente Valentí, Joaquín Belón, Miguel A. Sánchez, Carlos Chaib, Cinta Pallarés, Antonio Antón, Andrés Cervantes, Luis Paz-Ares, and Hernán Cortés-Funes
Hitt et al. Ph III, JCO 2005

Stage III/IV SCCHN

PCF x 3 Q 3 wk

CF x 3 Q 3 wk

Radiation + CDDP 100mg/m2 D1,22,43

PCF – 189 pts, CF – 193 pts
Median f/u 23.2 mths

No direct Comparison to CTRT
### Hitt et al 2005, JCO 2005

<table>
<thead>
<tr>
<th>End point</th>
<th>PCF</th>
<th>CF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>43 mths</td>
<td>37 mths (p=.03)</td>
</tr>
<tr>
<td>2yr OS</td>
<td>66.5%</td>
<td>53.6%</td>
</tr>
<tr>
<td>Median TTF</td>
<td>20 mths</td>
<td>12 mths (p=0.003)</td>
</tr>
<tr>
<td>TTF</td>
<td>57%</td>
<td>66%</td>
</tr>
</tbody>
</table>

**TPF is superior to PF**
Randomized Trial of Induction Chemotherapy With Cisplatin and 5-Fluorouracil With or Without Docetaxel for Larynx Preservation

Yoann Pointreau, Pascal Garaud, Sophie Chapet, Christian Sire, Claude Tuchais, Jacques Tortochaux, Sandrine Faivre, Stephane Guerrif, Marc Alfonsi, Gilles Calais

213 patients randomized

Median follow-up 36months

Primary end point-Larynx preservation rate

J Natl Cancer Inst 2009
Randomized Trial of Induction Chemotherapy With Cisplatin and 5-Fluorouracil With or Without Docetaxel for Larynx Preservation

Yoann Pointreau, Pascal Garaud, Sophie Chapet, Christian Sire, Claude Tuchais, Jacques Tortoachaux, Sandrine Faivre, Stephane Guerrif, Marc Alfonsi, Gilles Calais

Operable stage III/IV Larynx, Hypopharynx

R

TPF x 3 Q 3 wk

PF x 3 Q 3 wk

Radiation ± chemotherapy P,Fu,Carbo

Follow

Non-responders Sx+RT

Calais G et al
Larynx preservation is better with TPF

<table>
<thead>
<tr>
<th></th>
<th>TPF Arm</th>
<th>PF Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rx as per Protocol</td>
<td>90%</td>
<td>80%</td>
</tr>
<tr>
<td>ORR</td>
<td>80%</td>
<td>59%, p=0.002</td>
</tr>
<tr>
<td>3yr Lnx Preservation</td>
<td>70%</td>
<td>57%, p=0.03</td>
</tr>
<tr>
<td>DFS</td>
<td>58%</td>
<td>44%, p=ns</td>
</tr>
<tr>
<td>OS</td>
<td>60%</td>
<td>60%</td>
</tr>
</tbody>
</table>

Better larynx preservation rate with TPF as compared to PF
Better tolerance with TPF
No improvement in OS

*Calais G et al*
Tax 323, 324, Hitt et al, Calais G et al…

- TPF is superior to PF as induction
- Better Larynx preservation is possible
- No direct comparison to CT+RT
Neo Adj vs Conc CT
Phase II RCT  Paccagnella A et al, *Proc ASCO 2006*

Conc CRT vs TPF => Conc CRT in LAHNC

Locally advanced SCCHN: unresectable Stage III/IVA

3 x TPF q3w
- **T** Taxotere 75 mg/m² D1
- **P** Cisplatin 80 mg/m² D1
- **F** 5-FU 800 mg/m² D1–4

R

2 x PF wk 1&6
- **P** Cisplatin 20 mg/m² D1–4
- **F** 5-FU 800 mg/m² D1–4

Same CRT

Daily radiotherapy
Paccagnella A et al, Phase II RCT
*Proc ASCO 2006*

Conc CRT vs TPF => Conc CRT in LAHNC

- N=96
- Radiological CR at the end of CRT
  - 20% vs 64% in sequential arm
- Comparable toxicity
  - Weight loss, mucositis, skin reactions, dysphagia

*Phase II and small no. of patients (96) => Ph III study ongoing*
Hitt R, Proc ASCO 2009
Final Results of Phase III Trial
Induction Chemo TPF vs PF followed by CRT vs CRT

Unresectable SCCHN

R

TPF x 3 Q 3 wk

PF x 3 Q 3 wk

CRT

CRT alone

TPF – 155 pts, PF – 156 pts, CRT alone - 128
## Final Results of Phase III Trial

**Hitt R, Proc ASCO 2009**

<table>
<thead>
<tr>
<th></th>
<th>IC/CRT</th>
<th>CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median TTF</strong></td>
<td>12.5 mths</td>
<td>4.9 mths</td>
</tr>
<tr>
<td><strong>LRC</strong></td>
<td>61%</td>
<td>44%</td>
</tr>
<tr>
<td><strong>Gr ¾ AEs</strong></td>
<td>83%</td>
<td>69%</td>
</tr>
<tr>
<td><strong>Neutropenia</strong></td>
<td>10%</td>
<td>1%</td>
</tr>
</tbody>
</table>

*Long follow up needed*
MACH-NC an update of 93 Randomized Trials
(MACH-NC 2000 10,741 pts, 64 trials)

Inclusion of trials 1994-2000, 17,346 pts!

24 new RCTs for concurrent chemo-rad (5744 pts)

Pignon et al 2009 Rad & Onc
Concurrent CT-RT
- OS benefit of 6.5% at 5 yrs (p<0.0001)
- EFS benefit of 6.2% at 5 yrs (p<0.0001)
- No diff in mono vs poly chemotherapy
- Significantly higher with Cisplatin than others
- Decreased effect of chemo with age (p=0.003)

NACT
- OS benefit 2.4% at 5 yrs

Pignon et al 2009 Rad & Onc
Induction vs Concurrent

Concurrent CT RT
- Better Survival 6.5% vs 2.4%
- Significant better OS, EFS, LRC
- Similar benefits in distant failure

MACH-NC, Pignon et al 2009 Rad & Onc
On going trials....

*Induction vs CT RT.*
Recent Trials

**Docetaxel Based Chemo Plus or Minus Induction Chemo to Decrease Events in H N Ca [DeCIDE]**

N2, N3 HNC  
Arm A – Induction +CRT  
Arm B – CRT alone

Induction – 2cycles TPF q 21days  
CRT – five -14 day cycles of T, F & HU with twice daily radiation (days 1-5)
Docetaxel Based Chemotherapy Plus or Minus Induction Chemotherapy to Decrease Events in Head and Neck Cancer [DeCIDE]

ASCO 2012 (Oral Abst.Session)

Phase III, open label
N2, N3 HNC
KPS>70%
N=280 pts (b/w 2004-09)
55% oropharynx
2yrs min. f/u

Arm A – CRT alone
5days D (25mg/m2), F(600mg/m2), H(500mg BID)
RT 150cGy BID followed by 9days break

Arm B – IC + CRT
Induction – 2cycles TPF (D1-D5) q 21days
Results:

• 87% pts in Arm B received CRT after IC
• <75% in both arms received target 5-Fu dose
• Grade 3/4 leucopenia significantly higher in IC arm

3yr outcome

<table>
<thead>
<tr>
<th></th>
<th>IC (%)</th>
<th>CRT (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>75</td>
<td>73</td>
<td>0.70</td>
</tr>
<tr>
<td>RFS</td>
<td>67</td>
<td>59</td>
<td>0.18</td>
</tr>
<tr>
<td>Cumulative DF Incidence</td>
<td>10</td>
<td>19</td>
<td>0.02</td>
</tr>
<tr>
<td>Cumulative LRF Incidence</td>
<td>9</td>
<td>12</td>
<td>0.55</td>
</tr>
</tbody>
</table>
Conclusions:

• Higher survival rates in both arms

• Reduced distant failure rates didn’t translate into better OS??

Pitfalls

• No HPV prognostication

• Poor accrual (planned for 400pts)

• Control arm did well

• Limited follow-up
Combination Chemo & Radiotherapy in stage III/IV Head and Neck Ca
PARADIGM TRIAL

Arm A
3 cycles of TPF q 21days
If pCR at primary, cCR at node => RT+ wkly carbo
Else : weekly T + RT

Arm B
RT + CDDP week 1 & 4
**Combination Chemotherapy and Radiotherapy**

**Stage III/IV Head & Neck Cancer**

(Paradigm Trial)

---

**Arm A (n=70)**

- IC - 3 cycles of TPF q 21 days
- If pCR at primary, cCR at node - RT (once daily) + weekly carboplatin
- Else - wkly T + RT (Accelerated Boost)

**Arm B (n=75)**

Accelerated Boost RT + CDDP week 1 & 4

---

**Lahnc**

145 pts enrolled (300 planned)

Accrual closed in 2008

Median f/u 49 mths

---

145 pts enrolled (300 planned)

Accrual closed in 2008

Median f/u 49 mths
Results:

<table>
<thead>
<tr>
<th></th>
<th>Arm A</th>
<th>Arm B</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>3yr OS</td>
<td>73%</td>
<td>78%</td>
<td>0.7</td>
</tr>
<tr>
<td>3yr PFS</td>
<td>67%</td>
<td>73%</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Conclusions:

No survival difference
Paccagnella A et al. Proc ASCO 2011
Phase III RCT

Study Design

420 patients
LAHNC
Oral cavity, orphx, hypophx
Unresectable, non-metastatic stage III/IV

Arm A
A1 CRT alone
A2 Cetuximab/RT

Arm B
3cycles TPF
B1 CRT
B2 Cetuximab/RT
Summary

Neo-adj. vs Conc Chemo
Randomized Clinical Trials

**On going trials- induc?**
- DeCIDE Trial / PARADIGM Trial
  - Paccagnella et al RCT

**Conc CTRT is superior**
- MACH-NC Update, Radiother Oncol ‘09
- TAX 324 update 2011, Lancet Oncology
  - TAX 323, 324 NEJM, Annals of Oncolgy
  - Hitt et al, JCO ’05/ GORTEC 2000-01, JCO ‘06
- RTOG 91-11, Forastiere A, NEJM ‘03
- MACH-NC, Pignon J, Lancet ‘00

**TPF > PF**
- VA Study, NEJM ’91 / Lefebvre (EORTC Study), JNCI ‘96
Summary

✓ Conc Chemo RT is still standard of care

✓ Induction CT followed by CRT:
  ✓ Promising, under active investg

✓ Multidisciplinary approach considering
  Age, PS, tolerability, QOL

✓ LRC, OS end points
Neo adjuvant chemo...

- **Positives**
  - Taxanes
  - Helps us to select pts
  - Larynx preservation
  - Made easy RT / Surg
  - Reduce mets

- **Issues**
  - Tolerance (May be T + P only)
  - Discontinuation of Rx
  - Prolonged Rx time
Selection of patients…

Single-cycle induction chemotherapy selects pts with advanced laryngeal ca for combined chemoRT: a new treatment paradigm.

Probably…

<table>
<thead>
<tr>
<th>Induction</th>
<th>Concurrent</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Vol disease</td>
<td>Low Vol disease</td>
</tr>
<tr>
<td>T 3, T4</td>
<td>T2 N0</td>
</tr>
<tr>
<td>N 2B, C,</td>
<td>T3 N0</td>
</tr>
<tr>
<td>N 3</td>
<td>T1,2 N1</td>
</tr>
</tbody>
</table>

When decision of surgery or radiotherapy is difficult
LAHNC... Take Home!

- Concentrated CT+RT is standard
- Induction CT is promising
  - Large vol disease
  - Young, Good PS
  - Hypo pharynx, Oropharynx
  - Larynx preservation
Thank you

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