Head and Neck Cancer
*(Neo) Adjuvant therapy*

Sanjoy Chatterjee
Tata Medical Center: Kolkata
Oral Cavity
Oral Cavity Cancers treated with Surgery first: higher chance of cure...

Early Closure of a Randomized Trial: Surgery and Postoperative Radiotherapy Versus Radiotherapy in the Management of Intra-oral Tumours

result, but, after 35 patients had been entered, the trial was closed prematurely with a marked difference in overall survival in favour of the combination arm ($P = 0.0006$).

At this analysis, carried out 23 months after trial closure, the survival difference between the two arms remains statistically significant for all causes of mortality ($P = 0.001$; relative death rate = 0.24; 95% CI 0.10–0.59).
Are Oral Cavity Cancers clinico-pathologically similar to other HNSCA?

• Anatomical Barriers

• Patterns of Nodal Spread

• Most reports/trials included patients with non nasopharyngeal head and neck sites together...
Why need adjuvant therapy after major surgery?

- Stage III/IV a/b cancers have a 30-40% 5 year survival

- A more than 15% risk of recurrence has traditionally been used to recommend adjuvant therapy

Selecting patients?  
Risk factors for recurrence

**Primary**
- positive or close (<5mm) resection margin
- pT3/T4 tumours
- oral cavity site
- perineural invasion
- lymphovascular space invasion
- Depth of invasion
- subglottic extension

**Nodal**
- Extra capsular extension
- 2 or more nodes or 2 or more nodal stations involved
- Node more than 3cm in size

Huang et al Int J Radiat Oncol Biol Phys 1992;23:737-742
Risk stratification of patients

HIGH RISK PATIENTS:
- Extracapsular extension of nodal disease
- ≥ 2 of the following risk factors
  - oral cavity site
  - microscopically positive mucosal margins
  - nerve invasion
- ≥ 2 involved neck nodes
- > 1 positive nodal group
- node size >3 cm
- >6 week interval between surgery and radiat

MODERATE RISK PATIENTS: One risk factor (excluding extracapsular extension)

Study Design and Population
Registered (8/91 - 8/97): 288 Patients

- LR (n=31): No PoRT
- IR (n=31): 57.6 Gy/6.5 W
- HR (n=151): Randomize

Ineligible for PoRT (n=30)
Elected to receive PoRT closer to hometown or declined randomization (n=45)

63 Gy/5 wk (n=76)
63 Gy/7 wk (n=75)

Ang KK et al Int J Radiat Oncol Biol Phys 2001;51(3):571-8
Selecting patients for intervention

MD Anderson Studies

- oral cavity, oropharynx, hypopharynx, p T3 to T4 in 61%
- 58% had N2 to N3 neck disease.
- 86% III/IV disease

Ang KK et al Int J Radiat Oncol Biol Phys 2001;51(3):571-8

• local–regional control rate of 83%. = LOW RISK, not for RT
Does RT help in the adjuvant setting?

**Huang et al**
*Int J Radiat Oncol Biol Phys* 1992

1982-88, 441 cases
125 ECS or positive margins 71 Surgery, 54 PORT.

LC@ 3 years S vs PORT:
- ECS: 31% vs 6% (P =0.03)
- positive margins, 41% vs 49% (P =0.04), respectively; and
- ECS and positive margins: 0% and 68% (P =0.001), respectively.
- multivariate analysis of local control
- use of PORT (P =0.0001)
- macroscopic
- extracapsular extension (P =0.0001)
- margin status (P =0.09) significantly impacted local control. DFS@ 3 years was 25vs 45%

**Lundahl et al / Kao et al**

95 patients with node-positive squamous cell carcinoma who were treated with S +/- PORT

- 56 matched pairs of patients were identified
- recurrence in the dissected neck (RR=5.82; P =0.0002)
- death from any cause higher for Surgery only group (RR=1.67; P =0.0182)

Which patients may NOT benefit from RT?

RT proven to reduce risk:
- Extra capsular extension
- Node positivity
- Positive or close (<5mm) resection margin
- Advanced T stage

What about other risk factors?
- pT1-T2 N0 tumours?
- Perineural invasion
- Lymphovascular space invasion
- Depth of invasion
- Subglottic extension
- Oral Cavity site
TREATMENT RESULTS OF POSTOPERATIVE RADIOTHERAPY ON SQUAMOUS CELL CARCINOMA OF THE ORAL CAVITY: COEXISTENCE OF MULTIPLE MINOR RISK FACTORS RESULTS IN HIGHER RECURRENCE RATES

Kang-Hsing Fan, M.D., Hung-Ming Wang, M.D., Chung-Jan Kang, M.D.,
Li-Yu Lee, M.D., Shiang-Fu Huang, M.D., Chien-Yu Lin, M.D., Eric Yen-Chao Chen, M.D., I-How Chen, M.D., Chun-Ta Liao, M.D., and
Joseph Tung-Chieh Chang, M.D., M.H.A.

Fig. 1. Recurrence-free survival of patients with intermediate squamous cell carcinoma of the oral cavity with different numbers of significant variables in univariate analysis (p < 0.01 in multivariate analysis).
## Current TMC clinical protocol: early oral cavity cancers

- Any margin close or positive: Adjuvant chemoradiation
- The remaining patients undergo risk stratification based on the following risk factors:

The DFS figures are based on a revised analysis on 110 patients who had clear margins and all other risk factors known.

### Risk Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>0-2 risk factors positive: No adjuvant treatment</th>
<th>3-6 risk factors positive: Adjuvant Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Tongue Primary</td>
<td>Actuarial 3 year Disease-free survival 95%</td>
<td>Actuarial 3 year disease free survival 64%</td>
</tr>
<tr>
<td>pT2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVI+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PNI+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor thickness &gt;=5mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poorly differentiated tumor</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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*ESTRO 2016*
ICRO JIPMER Aug 2017

TMC Audit: T1/2 N0 (n=120)

- Median FU 23 months
- 38% received RT, as per MDT
- Thirteen patients had recurrence (local 8; nodal 4, distant 3, including overlapping failures).
- **All locoregional failures were within the radiotherapy volumes.**
- The 2 year and 3 year disease-free-survival (DFS) was 89% and 82% respectively.

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>N (%)</th>
<th>3 Year DFS</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tongue Primary ( vs others)</td>
<td>66 (55%)</td>
<td>76.0 ( vs 91.7%)</td>
<td>0.1</td>
</tr>
<tr>
<td>pT2 ( vs pT1 )</td>
<td>67 (56.3%)</td>
<td>72.5 ( vs 95.6%)</td>
<td>0.039</td>
</tr>
<tr>
<td>LVI ( VS Absent)</td>
<td>10 (8.3%)</td>
<td>58.3 ( vs 83.6%)</td>
<td>0.024</td>
</tr>
<tr>
<td>PNI ( v absent )</td>
<td>38 (31.7%)</td>
<td>75.0 ( vs 85.6%)</td>
<td>0.013</td>
</tr>
<tr>
<td>Depth of invasion &gt;= 5 mm( vs &lt; 5 mm)</td>
<td>72 (61%)</td>
<td>73.8 ( vs 97.5%)</td>
<td>0.017</td>
</tr>
<tr>
<td>Poorly diff cancer ( vs Mod or well diff )</td>
<td>10 (8.3%)</td>
<td>88.9 ( vs 81.2%)</td>
<td>0.956</td>
</tr>
<tr>
<td>Close or +ve margins ( vs clear margins)</td>
<td>7 (5.8%)</td>
<td>83.3 ( vs 80.9%)</td>
<td>0.854</td>
</tr>
</tbody>
</table>

ESTRO 2016
DOES ADJUVANT RADIATION THERAPY IMPROVE OUTCOMES IN pT1-3N0 ORAL CAVITY CANCER WITH TUMOR-FREE MARGINS AND PERINEURAL INVASION?

CHUN-TA LIAO, M.D.,* JOSEPH TUNG-CHEH CHANG, M.D., M.H.A.,† HUNG-MING WANG, M.D.,‡ SHU-HANG NG, M.D.,§ CHUEN HSUEH, M.D.,¶ LI-YU LEE, M.D.,¶ CHIH-HUNG LIN, M.D.,¶ I-HOW CHEN, M.D.,§ SHIANG-FU HUANG, M.D.,§ ANN-JOY CHENG, PH.D.,** LAI-CHEE SEE, PH.D.,†† AND Tzu-Chen Yen, M.D., PH.D.‡‡

Oral Cavity: 461 cases

Kaplan-Meier analysis of the 5-year local control rate in patients with perineural invasion compared with those without.

Fig. 3. Kaplan-Meier analysis of the 5-year local control rate with and without postoperative adjuvant radiotherapy (RT).
RT details: Dose

Median dose of at least 60Gy
Even lower risk patients for RT have higher relapse if <57.6Gy
For ECS and positive margins higher dose may benefit

RT cannot compensate for suboptimal margins/surgery

RT: Overall time from Surgery

Egyptian studies: Hypothesis generating (Better LC in higher risk adjuvant patients)
MD Anderson:
Higher risk arm – Conv RT versus Altered Frac
• Trend to better LC and DFS for Altered Frac
• Delay of starting RT >6weeks =poorer outcome

Overall time from Surgery to Rt completion>100days= poorer outcome

Ang KK et al Int J Radiat Oncol Biol Phys 2001;51(3):571-8
Rosenthal et al Head Neck 2002;24:115-126
• Use generous margins to prevent marginal failure
• Address contralateral neck when lymphatics could communicate with contralateral side
Altered fractionation

Adjuvant studies:
• Trend to LC benefit

Increased acute toxicity

Opinion:
• To compensate for overall treatment time, if needed
• Benefit may be in higher risk patients, compared to RT only
• Extra acute toxicity
• Logistically difficult

Suwinski R et al Radiother Oncol 2008;87 (2):155–63
Chemotherapy Alone prior to RT

Table 1. Actuarial Local Failure, Disease Free Survival and Overall Survival at 4 Years from Intergroup 0034 [17]

<table>
<thead>
<tr>
<th></th>
<th>RT</th>
<th>Chemo/RT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local failure</td>
<td>29%</td>
<td>26%</td>
<td>n.s.</td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>38%</td>
<td>46%</td>
<td>n.s.</td>
</tr>
<tr>
<td>Overall survival</td>
<td>44%</td>
<td>46%</td>
<td>n.s.</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>30%</td>
<td>20%</td>
<td>p=0.02</td>
</tr>
</tbody>
</table>

Current Cancer Therapy Reviews, 2005, Vol. 1, No. 1
Adjuvant in ALL
(mainly non oral) HNSCCA
Concurrent Chemotherapy

- 3 Cisplatinum based studies

Table 4. Results for Phase III Randomized Chemoradiation vs. Radiation Alone Trials

<table>
<thead>
<tr>
<th></th>
<th>#pt</th>
<th>F/U</th>
<th>LRC</th>
<th>DFS</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 9501 [26]</td>
<td>459</td>
<td>46 month median</td>
<td>81% vs 70%</td>
<td>33% vs 25%</td>
<td>45% vs 38%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p = 0.01</td>
<td>p = 0.04</td>
<td>P = 0.19</td>
</tr>
<tr>
<td>EORTC 22931 [27]</td>
<td>334</td>
<td>60 month median</td>
<td>82% vs 69%</td>
<td>47% vs 36%</td>
<td>53% vs 40%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p = 0.007</td>
<td>p = 0.04</td>
<td>p = 0.02</td>
</tr>
<tr>
<td>Bachaud (1996) [25]</td>
<td>83</td>
<td>5 year minimum</td>
<td>70% vs 55%</td>
<td>45% vs 23%</td>
<td>36% vs 13%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p = 0.05</td>
<td>p &lt; 0.02</td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>

Numbers are actuarial at 5 years, and in the case of the RTOG are estimated based on the published actuarial curves. The RTOG trial showed an improvement in locoregional control (the primary endpoint) and DFS, at the expense of increased acute morbidity. The EORTC study and the French study both showed improved local control, DFS, and survival with chemotherapy. None of the studies demonstrated any difference in distant failure or late morbidity [25-27].

- Carboplatin concurrently may not produce similar results as cisplatin
Combined Analyses: Justifying Toxicity to Benefit

Eligibility

Outcomes

Bernier et al, Head & Neck 2005
ICRO JIPMER Aug 2017

Benefits of CTRT may not be sustained

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Overall survival by cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assigned treatment</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td></td>
</tr>
<tr>
<td>Death from any cause*</td>
<td>RT</td>
</tr>
<tr>
<td></td>
<td>RT + CT</td>
</tr>
<tr>
<td>Death from study cancer</td>
<td>RT</td>
</tr>
<tr>
<td></td>
<td>RT + CT</td>
</tr>
<tr>
<td>Death not from study cancer</td>
<td>RT</td>
</tr>
<tr>
<td></td>
<td>RT + CT</td>
</tr>
<tr>
<td>Patients who had involved margin(s) and/or extracapsular extension</td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td>RT</td>
</tr>
<tr>
<td></td>
<td>RT + CT</td>
</tr>
<tr>
<td>Death from study cancer</td>
<td>RT</td>
</tr>
<tr>
<td></td>
<td>RT + CT</td>
</tr>
<tr>
<td>Death not from study cancer</td>
<td>RT</td>
</tr>
<tr>
<td></td>
<td>RT + CT</td>
</tr>
</tbody>
</table>
## Summary recommendations

<table>
<thead>
<tr>
<th>Type of intervention</th>
<th>Level 1 evidence (strong)</th>
<th>Level 2 evidence</th>
<th>Level 3 evidence (weak)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTRT (cisplatin +RT)</td>
<td>Positive margins, ECS, fit for CTRT (age &lt;70)</td>
<td>T3.T4 disease; Node positive without ECS irrespective of nodal stations</td>
<td>Close margins</td>
</tr>
<tr>
<td>RT</td>
<td>Positive margins, ECS, and NOT fit for CTRT</td>
<td>LVI, Depth of invasion</td>
<td></td>
</tr>
</tbody>
</table>
Will AJCC 8 affect treatment?

Prognostic factors may NOT be predictive of RT response
Neo- Adjuvant
Neo Adjuvant Taxanes

TAX 323
TPF induction chemotherapy for 4 cycles followed by RT better than PF followed by RT-improved local control and improved overall survival
TAX 324
TPF induction 3 cycles followed by CXRT vs PF plus CXRT

Improved OS (HR 0.7, p=0.006) and Local control (p=0.04)
Original article

Induction chemotherapy followed by concurrent radio-chemotherapy versus concurrent radio-chemotherapy alone as treatment of locally advanced squamous cell carcinoma of the head and neck (HNSCC): A meta-analysis of randomized trials

Wilfried Budach a, Edwin Bölke a, Kai Kammers b, Peter Arne Gerber d, Klaus Orth c, Stephan Gripp a, Christiane Matuschek a,*

aMedical Faculty, Department of Radiation Oncology, Heinrich Heine University, Dusseldorf, Germany; bDepartment of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA; cMedical Faculty, Department of General, Visceral, and Thoracic Surgery, Asklepios Harz Hospitals, Goslar; and dMedical Faculty, Department of Dermatology, Heinrich Heine University, Dusseldorf, Germany
<table>
<thead>
<tr>
<th>Characteristics, treatment compared number of patients and risk of bias.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial characteristics</strong></td>
</tr>
<tr>
<td>Cohen [19]</td>
</tr>
<tr>
<td>Takacsi-Nagy [18]</td>
</tr>
<tr>
<td>Hitt [15]</td>
</tr>
<tr>
<td>Haddad [14]</td>
</tr>
<tr>
<td>Gh i [20]</td>
</tr>
</tbody>
</table>
TPF-CTRT versus CTRT

**TPF→RT-CHX vs. RT-CHX in locally advanced head and neck cancer**

Meta-analysis of randomized controlled trials: PFS

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>HR</th>
<th>95% CI +</th>
<th>95% CI -</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacagnella et al.(^{16})</td>
<td>101</td>
<td>0.718</td>
<td>0.424</td>
<td>1.137</td>
<td>0.187</td>
</tr>
<tr>
<td>Cohen et al.(^{39})</td>
<td>273</td>
<td>0.840</td>
<td>0.550</td>
<td>1.268</td>
<td>0.099</td>
</tr>
<tr>
<td>Naddeo et al.(^{14})</td>
<td>145</td>
<td>1.070</td>
<td>0.590</td>
<td>1.529</td>
<td>0.629</td>
</tr>
<tr>
<td>Hirsh et al.(^{15})</td>
<td>283</td>
<td>0.912</td>
<td>0.692</td>
<td>1.201</td>
<td>0.313</td>
</tr>
<tr>
<td>Talácsí-Nagy et al.(^{18})</td>
<td>60</td>
<td>1.315</td>
<td>0.653</td>
<td>2.607</td>
<td>0.506</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>862</td>
<td>0.948</td>
<td>0.751</td>
<td>1.198</td>
<td>0.319</td>
</tr>
</tbody>
</table>

**Fig. 2.** Meta-analysis of randomized trials. Hazard ratios of induction CHX and concomitant RT-CHX versus RT-CHX alone are given for PFS.
Conclusion

• In general NACT does not seem to add a sustained survival benefit in comparison with cisplatin and CTRT

• Can be judiciously used in select patients depending on clinical stage, logistics and PS
Neoadjuvant Chemotherapy has no role in the routine management of oral cancers.
Early Closure of a Randomized Trial: Surgery and Postoperative Radiotherapy Versus Radiotherapy in the Management of Intra-oral Tumours

result, but, after 35 patients had been entered, the trial was closed prematurely with a marked difference in overall survival in favour of the combination arm \( P = 0.0006 \).

At this analysis, carried out 23 months after trial closure, the survival difference between the two arms remains statistically significant for all causes of mortality \( P = 0.001 \); relative death rate = 0.24; 95% CI 0.10–0.59).
NEOADJUVANT CHEMOTHERAPY FOR SQUAMOUS CELL CARCINOMA OF THE ORAL TONGUE IN YOUNG ADULTS: A CASE SERIES

*Head Neck 27: 748–756, 2005*

- Site matched control
- Stage was lower in NACT group (Mainly Taxane based)
- Hypothesis generation: Intense Taxane based NACT can improve outcomes for matched groups?
Randomized Phase III Trial of Induction Chemotherapy With Docetaxel, Cisplatin, and Fluorouracil Followed by Surgery Versus Up-Front Surgery in Locally Advanced Resectable Oral Squamous Cell Carcinoma

- Post hoc analysis N2 disease ?? Better with TPF?
Induction chemotherapy prior to surgery with or without postoperative radiotherapy for oral cavity cancer patients: Systematic review and meta-analysis

European Journal of Cancer (2015) 51, 2596–2603

Fig. 4. Forest plot of comparison: Chemotherapy × Control (no chemotherapy). Outcome: overall survival.

Fig. 6. Forest plot of comparison: Chemotherapy × Control (no chemotherapy). Outcome: disease-free survival for cN2 patients.
Induction chemotherapy in technically unresectable locally advanced oral cavity cancers: Does it make a difference?

Indian Journal of Cancer | January-March 2013 | Volume 50 | Issue 1
Total Surgery= 29/84; 11 responders to chemo

Total Surgery= 13/39; 5 responders to chemo
post NACT ($P = 0.0001$). **CONCLUSION:** Induction chemotherapy was effective in converting technically unresectable oral cavity cancers to operable disease in approximately 40% of patients and was associated with significantly improved overall survival in comparison to nonsurgical treatment.
Total Surgery = 29/84; 11 responders to chemo

Total Surgery = 13/39; 5 responders to chemo
Neoadjuvant chemotherapy followed by surgery in very locally advanced technically unresectable oral cavity cancers

Results: 721 patients with stage IV oral-cavity cancer received NACT. 310 patients (43%) had sufficient reduction in tumour size and underwent surgical resection. Of the remaining patients, 167 received chemoradiation, 3 radical radiation and 241 palliative treatment alone. The locoregional control rate at 24 months was 20.6% for the overall cohort, 32% in patients undergoing surgery and 15% in patients undergoing non surgical treatment ($p = 0.0001$). The median estimated OS in patients undergoing surgery was 19.6 months (95% CI, 9.59–25.21 months) and 8.16 months (95%, CI 7.57–8.76) in patients treated with non surgical treatment ($p = 0.0001$).
Unblinded assessor; Retrospective study...

We used clinical and radiological response to decide respectability. We also categorised the response according to the RECIST criteria. On reviewing the data, we found that nearly 30% of patients with stable disease according to RECIST could undergo successful resection. After review of the scans, it was seen that several patients had a decrement more than 10% which was sufficient the volume of the tumour [30]. This reaffirms our belief that the decision to operate should be made on both clinical and radiological grounds.
Regression post chemo is not concentric and centripetal...

Pre- and post-neoadjuvant chemotherapy positron emission tomography-computed tomography scan showing Neoadjuvant chemotherapy in oral cancers: Selecting the right patients
Tata Medical Center Data (Aug 2011-Sept 2015)

• 8 patients with unresectable Oral Cavity tumours received NACT (2 oral tongue)

• Median age 52yrs

• 6 Stage IVA, 2 IVB

• 2 or more cycles: 6 patients, 6 TPF, 1 Pacli-Carbo
• 2 patients were admitted (10 days each with sepsis)
Further to NACT

- 6 received radical treatment
- Only 1 had surgery +RT, 4 CTRT, 1 RT alone
  (NACT to CTRT delay 33days)
- >1 cycles of chemo- 6 patients
Survival

• 1 patient disease free - The one who had Surgery
• OS - median 6m
Neoadjuvant Chemotherapy has no role in the routine management of oral cancers.
Thank You