Role of Induction [Neoadjuvant Chemotherapy] in Oropharyngeal Cancer

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Head and Neck Cancer Regions

- Cancers of the epithelial lining
- Cancers of the glands
- Cancers of the musculoskeletal structures
- Cancers of the skin

Changing Biology

- Smoking related cancers are declining
- HPV epidemic is here
Decline of smoking

- 1950s: Case-control Studies, Ernst Wynder
- 1964: Surgeon General’s Report
- 1998: Master Settlement
- Ban in public spaces

Head Neck Cancer

Sturgis, 2007
From 1984 to 2004

- HPV-ve cancer fell 50%
- HPV+ve cancer rose 225%

Chaturvedi, JCO, 2011

- HPV+ve and HPV-ve
  OPH are widely different diseases
As Biology of Cancer changes, we need to change our treatment paradigms to best manage the disease.

In the foreseeable future, we will have a rising incidence of OPC and the majority of these will be HPV +.

Based upon a superior outcome of HPV + OPC, we need to design treatment paradigms to maintain or improve these outcomes while minimizing long term toxicity. [Think ALL + HD]

Induction therapy may be one option to maximize outcomes and minimizing toxicity.

Induction therapy can be incorporated under a few scenarios:

- IC → Surgery → Adjuvant XRT ± CT
- IC → Concurrent CRT
- IC → Primary Surgery → obs
- IC → CRT → Surgery for residual
- IC → Salvage Surgery [in recurrence post XRT]
Key studies

### Year | No |
--- | --- |
2011 | 26 |
2012 | 46 |
2013 | 51 |
2014 | 90 |
2015 | 78 |
2016 | 67 |

RTOG 90-03, 2000
EORTC, 1996
MACH, 2000
RTOG 9501, 2004
EORTC 22931, 2004
DeCIDE, Paradigm 2013, 2014

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**Induction Chemotherapy Plus Radiation Compared with Surgery Plus Radiation in Patients With Advanced Laryngeal Cancer**

**Abstract**

Background. We performed a prospective, randomized study in patients with previously untreated advanced (Stage III or IV) laryngeal squamous carcinoma to compare the results of induction chemotherapy followed by definitive radiation therapy with those of conventional laryngectomy and postoperative radiation.

Methods. Three hundred thirty-two patients were randomly assigned to receive either three cycles of chemotherapy (cisplatin and fluorouracil) and radiation therapy or surgery and radiation therapy. The clinical tumor response was assessed after two cycles of chemotherapy, and patients with a response received a third cycle followed by definitive radiation therapy (6600 to 7800 cGy). Patients in whom there was no tumor response or who had locally recurrent cancers after chemotherapy and radiation therapy underwent salvage laryngectomy.

Results. After two cycles of chemotherapy, the clinical tumor response was complete in 31 percent of the patients and partial in 54 percent. After a median follow-up of 33 months, the estimated 2-year survival was 68 percent (95 percent confidence interval, 60 to 76 percent) for both treatment groups (P = 0.084). Patterns of recurrence differed significantly between the two groups, with more local recurrences (P = 0.0005) and fewer distant metastases (P = 0.018) in the chemotherapy group than in the surgery group. A total of 59 patients in the chemotherapy group (36 percent) required total laryngectomy. The larynx was preserved in 64 percent of the patients overall and 64 percent of the patients who were alive and free of disease.

Conclusions. These preliminary results suggest a new role for chemotherapy in patients with advanced laryngeal cancer and indicate that a treatment strategy involving induction chemotherapy and definitive radiation therapy can be effective in preserving the larynx in a high percentage of patients, without compromising overall survival.

Figure 1. Overall Survival and Progression-free Survival. Panel A shows the Kaplan-Meier estimates of overall survival among the 501 patients in the intention-to-treat population who were randomly assigned to induction chemotherapy with TPF or PF. The hazard ratio for death in the TPF group as compared with the PF group was 0.70 (95% CI, 0.54 to 0.90; P=0.006 by the log-rank test). Median survival in the TPF group was 71 months (95% CI, 49 to not reached), as compared with 30 months (95% CI, 21 to 52) in the PF group. Panel B shows the Kaplan-Meier estimates of progression-free survival among the 501 patients in the intention-to-treat population. The hazard ratio for disease progression in the TPF group as compared with the PF group was 0.71 (95% CI, 0.56 to 0.90; P=0.004 by the log-rank test). Median progression-free survival in the TPF group was 36 months (95% CI, 18 to not reached) and 13 months in the PF group (95% CI, 11 to 20). The points on the curves show when data for patients were censored. PF denotes cisplatin and fluorouracil, and TPF docetaxel plus cisplatin and fluorouracil.
Phase III Randomized Trial of Induction Chemotherapy in Patients with N2 or N3 Locally Advanced Head and Neck Cancer

Fig 3. Survival by treatment arm and corresponding P-values. (A) Chemotherapy was the only treatment arm. (B) Chemotherapy followed by concurrent chemoradiation. (C) Concurrent chemoradiation followed by chemotherapy. (D) Concurrent chemoradiation followed by chemotherapy. (E) Concurrent chemoradiation followed by chemotherapy. (F) Concurrent chemoradiation followed by chemotherapy. (G) Concurrent chemoradiation followed by chemotherapy. (H) Concurrent chemoradiation followed by chemotherapy. (I) Concurrent chemoradiation followed by chemotherapy. (J) Concurrent chemoradiation followed by chemotherapy. (K) Concurrent chemoradiation followed by chemotherapy. (L) Concurrent chemoradiation followed by chemotherapy.
• Induction Chemotherapy [IC] is not the standard of care for HPV+ OPC.
• IC does show a survival benefit in N2c and N3 OPC in subset analysis.
• It is recommended in the NCCN Guidelines as category III evidence.
• I use IC in this subgroup as a badge to definitive therapy [surgery or CRT].
• In large centers with experience in delivering TPF as outpatient induction therapy can be successfully delivered to nearly 100% of eligible patients.

• RR [CR & PR] with TPF IC approach 80%
• Only 4% of patients progress on IC. They have a poor prognosis irrespective of definitive therapy.
• With GCSF support the grade 3 and 4 toxicity of TPF is <8%. It is primarily myelosuppression and mucositis.
• There is a hint however that IC may not allow patients to receive full does RT.
• There is no difference in post op complication rate in patients who receive TPF.
Trend Toward De-Escalation

- Based on good prognosis of HPV patients
- What patients are suitable for de-escalation?
- What are the strategies currently being explored?

Impact of HPV on Prognosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Trial</th>
<th>Treatment Details</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fakhry, 2008</td>
<td>RTOG 2399</td>
<td>IC x2 followed by CRT</td>
<td>2-yr OS 95% vs 62%</td>
</tr>
<tr>
<td>Rischin, 2010</td>
<td>TROG 02.02</td>
<td>CRT (Cis vs Cis-Tirapazamine)</td>
<td>2-yr OS 91% vs 74%</td>
</tr>
<tr>
<td>Ang, 2010</td>
<td>RTOG 0129</td>
<td>CRT (AFX vs SFX)</td>
<td>3-yr OS 82% vs 57%</td>
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<tr>
<td>Rosenthal, 2015</td>
<td>IMCL-9815</td>
<td>XRT vs XRT+Erbitux</td>
<td>3-yr OS 88 and 72% vs 42 and 34% for cetux-RT and RT</td>
</tr>
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</table>
Impact of HPV on Prognosis

- Failure pattern – more DM
- Can occur beyond 2-yr period
- Survival is better after failure
- 2\textsuperscript{nd} primary cancers are less likely

Why De-Escalation?

- Acute and long-term morbidity of chemoradiation is significant
A predictive model for swallowing dysfunction after curative radiotherapy in head and neck cancer

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***Department of Otolaryngology/Head and Neck Surgery, University Medical Center, Amsterdam, The Netherlands

Results: After univariate and multivariate logistic regression analyses, the following factors turned out to be independent prognostic factors for SWALL12months: T3–T4, bilateral neck irradiation, weight loss prior to radiation, oropharyngeal and nasopharyngeal tumours, accelerated radiotherapy and concomitant chemoradiation. By summation of the regression coefficients derived from the multivariate model, the Total Dysphagia Risk Score (TDRS) could be calculated. In the logistic regression model, the TDRS was significantly associated with SWALL12months (p < 0.001). Subsequently, we defined three risk groups based on the TDRS. The rate of SWALL12months was 5%, 24% and 40% in case of low-, intermediate- and high-risk patients, respectively. These observed percentages were within the 95% confidence intervals of the predicted values. The TDRS risk group classification was also significantly associated with acute dysphagia (p < 0.001 at all time points) and with late swallowing dysfunction at 12, 18 and 24 months (p < 0.001 at all time points).
Huang, et al, 2015

5-yr OS in 573 HPV-OPC treated by RT/CRT

HPV status by p16

RPA I (T1-3N0-2b), II (T1-3N2c), III (T4, N3)
82, 76, 54% 5-yr OS

Development and validation of a staging system for HPV-related oropharyngeal cancer by the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S): a multicentre cohort study

AHR-New stage classification

<table>
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<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
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<tr>
<td>N0</td>
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<td>N1</td>
<td>I</td>
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<td>II</td>
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<td>N2a</td>
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<td>I</td>
<td>II</td>
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<tr>
<td>N2b</td>
<td>I</td>
<td>I</td>
<td>II</td>
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<tr>
<td>N2c</td>
<td>II</td>
<td>II</td>
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<tr>
<td>N3</td>
<td>III</td>
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1907 patients from 7 centers. RT/CRT.
5-yr OS 85, 75, and 53%
### De-Escalation Trials

<table>
<thead>
<tr>
<th>Table 4. De-escalation Trials in HPV-Positive GLOSCC</th>
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<tr>
<td><strong>Inclusion Criteria</strong></td>
</tr>
<tr>
<td>Cerami et al, phase 2</td>
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<tr>
<td>NCT01009585</td>
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<tr>
<td>RT0G 106, phase 3</td>
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<tr>
<td>NCT01009585</td>
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<td>ECOC 331, phase 2</td>
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<td>NCT01009585</td>
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<tr>
<td>Quarterback trial, phase 3</td>
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<td>ADEPT, phase 3</td>
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<td>NCT01009585</td>
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<tr>
<td>TROG 12.01, phase 3</td>
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<td>NCT01009585</td>
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<tr>
<td>De-escalate, phase 3</td>
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<td>NCT01009585</td>
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**Median FU 33 mo**

**No LRF**

**52 are alive**

**1 died of DM**

**1 unrelated**

**2-yr OS and DSS**

**96 and 98%**
Comprehensive genomic characterization of head and neck squamous cell carcinomas

The Cancer Genome Atlas

The Cancer Genome Atlas profiled 279 head and neck squamous cell carcinomas (HNSCCs) to provide a comprehensive landscape of somatic genomic alterations. Here we show that human papillomavirus-associated tumours are dominated by helicase domain mutations of the oncoprotein P16, novel alterations involving loss of TRAF3, and amplification of the cell cycle gene p27. Smoking-related HNSCCs demonstrate near universal loss-of-function PI3K mutations and CDKN2A inactivation with frequent copy number alterations including amplification of 3p26-28 and 11q13/22. A subgroup of oral cavity tumours with favourable clinical outcomes displayed infrequent copy number alterations in conjunction with activating mutations of HRAS or PIK3CA coupled with inactivating mutations of CASP8, NF1 and PI3K. Other distinct subgroups contained loss-of-function alterations of the chromatin modifier NSD1, WNT pathway genes, AURKA and FADD, and activation of oxidative stress factor NFE2L2, mainly in laryngeal tumours. Therapeutic candidate alterations were identified in most HNSCCs.
MULTIDISCIPLINARY TEAM

The management of patients with head and neck cancers is complex. All patients need access to the full range of support services and specialists with expertise in the management of patients with head and neck cancer for optimal treatment and follow-up.

- Head and neck surgery
- Radiation oncology
- Medical oncology
- Plastic and reconstructive surgery
- Specialized nursing care
- Dental hygiene
- Respiratory therapy
- Speech and swallowing therapy
- Physical therapy
- Speech and language therapy
- Nutrition support
- Pathology (including cytopathology)
- Diagnostic radiology
- Adjunctive services
- Neurosurgery
- Ophthalmology
- Psychiatry
- Social work
- Audiology
- Palliative care

SUPPORT SERVICES

Follow-up should be performed by a physician and other health care professionals with expertise in the management and prevention of treatment sequelae. It should include a comprehensive head and neck exam. The management of head and neck cancer patients may involve the following:

- General medical care
- Pain and symptom management
- Physical support
- Enteral feeding
- Oral supplements
- Dental care for RT effects
- Anorexia management
- Smoking and alcohol cessation
- Speech and swallowing therapy
- Audiology
- Tracheotomy care
- Wound management
- Depression assessment and management
- Social work and case management
- Pain management
- Palliative care

Note: All recommendations are category 2A unless otherwise indicated.


Thank you for attending. Furhan Yunus, MD, Ochsner Medical Center, Gayle & Tom Benson Cancer Center, Chairman, Hematology & Medical Oncology, Malignant Heme Transplant.