Organ and functional preservation strategies in head and neck cancers

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Overall results - surgery/RT

- Surgical series – 40-60%
- Radiotherapy series – 15-40%

So, if we wish to preserve the organ by radiotherapy, clearly there is a need for survival figures to match the surgical series (stage for stage)!
What are the subsets in which we can think of organ preservation?

- Early Disease
- Locally advanced disease

- Surgery/RT
- Organ preservation
- Unresectable
- Resectable± Post op RT
### Background

<table>
<thead>
<tr>
<th></th>
<th>5 year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>Operable advanced</td>
<td>26-50%</td>
</tr>
<tr>
<td>Unresectable advanced</td>
<td>0-30%</td>
</tr>
</tbody>
</table>

Organ preservation

Bulky resectable/T4/Cartilage

Curative CRT/RT

Palliative
What is this so called resectable disease in Larynx?

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Tumor limited to the vocal cord(s)</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor extends to supraglottis, subglottis, with impaired vocal cord mobility</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor limited to larynx with vocal cord fixation, invades paraglottic space, minor thyroid cartilage erosion</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumor invades the thyroid cartilage, invades tissues beyond the larynx (e.g. trachea, deep muscle of tongue, strap muscles, thyroid, or esophagus)</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures</td>
</tr>
</tbody>
</table>
What subsets are amenable to Organ preservation?

Primary site

Mod volume

Early & Intermediate stage

Larynx

Hypo phx
Who decides the operability?

Surgical member of the Joint clinic team
Bottomline is...

- Surgery is the gold standard.
- No head on comparison.
- If you can operate (i.e. resectable disease) you should. BUT…
- In resectable disease – if you can save the organ – you should.

Non surgical organ preserving strategy – Radiotherapy
May need intensification (select group) to match surgical results
So, What are the OP strategies?

Addition of chemotherapy to RT
Alteration of fractionation
Integration of both

Chemotherapy in what form ...

Induction CT+RT
Concurrent CT+RT
Alternating CTRT
Adjuvant CT
3 issues one needs to consider...

- Locoregional control
- Metastatic spread (20%)
- Functional morbidity

CT will improve LRC

CT will ↓ distant failure

CT may substitute pr. site Sx= OP
**Induction chemotherapy**

- Wayne State protocol- **Cisplatin+FU**
- Aim – to replace primary surgery with CT
- Reasons- better drug delivery
  - naïve pts- better tolerance
  - high dose- ↓ micrometastasis
  - Down sizing before IMRT
  - Waiting times
- Demerits – prolongs treatment
  - Repopulation of resistant cells

Induction chemotherapy

- Rationale: downstages the tumor
- CR: 20-30; OR: 60-80%
- Organ preservation
- Act as a predictor for radiation response
- Act on distant micro metastasis

NACT trials
Induction CT
(Evidence – Veterans trial– NEJM 1991)

- N=332
- Stage III/IV glottis and supraglottis primary
  2-3 cycles CDDP+5FU

  
<table>
<thead>
<tr>
<th>Organ Preserv</th>
</tr>
</thead>
<tbody>
<tr>
<td>After trt</td>
</tr>
<tr>
<td>At 2 yrs</td>
</tr>
<tr>
<td>At 5 yrs</td>
</tr>
</tbody>
</table>

Surgery + Post op RT

NACT trials- resectable gp
Veterans Trial

- OS similar 35%

- *What it answered?* Identified the subset that will respond to radiation

- Pathological response – Best predictor

- *What it didn’t answer?* Was Radiotherapy equally good enough for organ preservation

*NACT trials - resectable gp*
Is RT good enough for OP? - RTOG 91-11, Forestierre et al

- Resectable Stage III/IV larynx ca.
- 3 arm trial-
- NACT versus CTRT versus RT
- N=547

<table>
<thead>
<tr>
<th></th>
<th>Organ preserv</th>
<th>LRC at 2yrs</th>
<th>DMF rate</th>
<th>OS at 5yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>NACT</td>
<td>75%</td>
<td>61%</td>
<td>91%</td>
<td>55%</td>
</tr>
<tr>
<td>RT</td>
<td>70%</td>
<td>56%</td>
<td>84%</td>
<td>54%</td>
</tr>
<tr>
<td>CTRT</td>
<td>88%</td>
<td>78%</td>
<td>92%</td>
<td>56%</td>
</tr>
</tbody>
</table>

NEJM, 2003
Concurrent CT-RT

Rationale

- Independent cell kill
- Radio potentiation
- Distant micro metastasis
- Cost and high toxicity!

Between 2000 to 2009

8% survival benefit at 5 years
88% Organ preservation rate at 2 years

MACH NC meta analysis and update
RTOG 91-11, 2003
Conclusions of RTOG 91-11

- OP best with CTRT
- Addition of CT decreases distant metastasis rate
- Induction chemotherapy took a back seat

Good CTRT candidates
T2
T3
Low volume T4

Poor CTRT candidates
Significant BOT inv.
Gross Cartilage inv.
Induction CT (platin + FU) – OP and 5% survival benefit
Why NACT → CTRT?

- NACT has pronounced effect on distant spread
- CTRT pronounced effect on LRC
- May complement each other

TPF protocol

- PF benefits but outcome < 50%
- Single agent Taxane activity seen
Table 2. Results of phase III trials comparing OS, progression-free survival (PFS) and organ preservation for TPF and PF in curable patients

<table>
<thead>
<tr>
<th>Study population</th>
<th>N</th>
<th>Primary end point</th>
<th>Regimen</th>
<th>Significant outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tax 321 inoperable [42]</td>
<td>358</td>
<td>PFS</td>
<td>PF/RT versus TPF/RT</td>
<td>TPF better, PFS and OS $P &lt; 0.01$</td>
</tr>
<tr>
<td>TAX 321 locally advanced [5, 45]</td>
<td>501</td>
<td>OS</td>
<td>PF/CRT versus TPF/CRT</td>
<td>TPF better, 5-year PFS and OS $P = 0.01$; LFS $P &lt; 0.03$</td>
</tr>
<tr>
<td>GORTEC 2000-01 resectable larynx/hypopharynx [9]</td>
<td>213</td>
<td>Larynx preservation (LP/FLFS)</td>
<td>PF/RT versus TPF/RT</td>
<td>TPF better, LP/FLFS $P &lt; 0.04$</td>
</tr>
</tbody>
</table>

RT, radiotherapy.

Toxic schedule

NEJM, 2007
Unresectable HN or OP

Unresectable TPF versus PF

OP TPF versus PF

NR versus 42 mo

40 versus 21 mo

Holds promise in Organ preservation subset

Q - Does Sequential CTRT (TPF → CTRT) offer advantage over concurrent CTRT?
Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial


N=145; Median follow up -49 months
Poor accrual
Similar survival
Organ preservation not discussed
Conc CTRT is as good!

Which strategy to choose between – RT or NACT or CTRT?

- Stage
- Age
- Performance status
- Co-morbidities
- Tracheostomy

Nutritional support required before, during and after radiation treatment.
No chemotherapy in elderly

**Physiology**

1. Fat replaces muscle | Fat soluble drugs overstay in the body
2. Liver | ↓ liver volume & blood flow
3. Kidney | Decline in renal function
4. Bone marrow | ↓ marrow reserve → myelosuppression
5. GI tract | Change in gastric motility and absorbability; Prone to diarrhoea and dehydration
Altered fractionation for OP

Articles

Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6&7 randomised controlled trial

Jens Overgaard, Hanne Sand Hansen, Lena Specht, Marie Overgaard, Cai Grau, Elo Andersen, Jens Bentzen, Lars Bastholt, Olfed Hansen, Jørgen Johansen, Lisbeth Andersen, Jan F Evensen, on behalf of the Danish Head and Neck Cancer Study Group

<table>
<thead>
<tr>
<th>Tumour site</th>
<th>Fractions per week</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Five</td>
<td>Six</td>
</tr>
<tr>
<td>Glottic</td>
<td>92/341</td>
<td>63/349</td>
</tr>
<tr>
<td>Supraglottic</td>
<td>48/101</td>
<td>39/117</td>
</tr>
<tr>
<td>Pharynx</td>
<td>103/222</td>
<td>86/213</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>40/62</td>
<td>41/71</td>
</tr>
<tr>
<td>T classification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1-2</td>
<td>154/494</td>
<td>103/512</td>
</tr>
<tr>
<td>T3-4</td>
<td>132/232</td>
<td>126/238</td>
</tr>
<tr>
<td>Nodal status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Node negative</td>
<td>164/504</td>
<td>125/542</td>
</tr>
<tr>
<td>Node positive</td>
<td>125/222</td>
<td>100/208</td>
</tr>
</tbody>
</table>

Graph showing survival curves for different T sites.
Organ preservation trials – realistic issues

Organ preservation ≠ Organ function

Multi disciplinary team

Patient Selection
Functions that impact QOL

- Deglutition
- Aspiration
- Speech
- Breathing
Why did patients continue to lose wt, complain of dysphagia and develop pneumonia?

- Late toxicity observed in form of cervical and pharyngeal fibrosis and laryngeal dysfunction
  - swallowing dysfunction
  - aspiration

- The range of dysfunction
  - pharyngeal retention of food: 90%
  - silent aspiration: 40%

- Aspiration per se is often unrecognized: dysphagia is the commoner presentation

- Patients subconsciously reduce intake and hence continue to lose weight!
Head and neck cancers

- Malnourished
- Elderly Co-morbidity
- Treatment sequelae
- Lower socioeconomic class
- Tobacco
- Summers
If not carefully selected, patient may die of intense treatment.

*Kumar et al Radiother Oncol, 2005*
Reasons for toxicity related deaths

- Aspiration
- Septicemia
- Dyselectrolytemia & dehydration

As you intensify treatment toxicity increases

Long term problems following radiotherapy

- Dryness of mouth
  - Speech
  - Taste
  - Dental caries
  - Swallowing

- Swallowing difficulties
  - Malnutrition
  - Aspiration
  - Pneumonia
  - Failure to thrive
  - Death

20% aspiration rate in hypopharyngeal cancers

Relevance of toxicity with OP strategies

- Enhanced radiosensitization - synergistic effect
- Increased apoptosis
- Excessive fibrosis and xerostomia
- Speech and swallowing dysfunction
Long-Term Results of RTOG 91-11: A Comparison of Three Nonsurgical Treatment Strategies to Preserve the Larynx in Patients With Locally Advanced Larynx Cancer


RT was not better than treatment with RT alone (HR, 1.26; 95% CI, 0.88 to 1.82; P = .35). No difference in late effects was detected, but deaths not attributed to larynx cancer or treatment were higher with concomitant chemotherapy (30.8% vs 20.8% with induction chemotherapy and 16.8% with RT alone).
Impact of Late Treatment-Related Toxicity on Quality of Life Among Patients With Head and Neck Cancer Treated With Radiotherapy

Johannes A. Langendijk, Patricia Doornaert, Irma M. Verdonck-de Leeuw, Charles R. Leemans,
Neil K. Aaronson, and Ben J. Slootman

Conclusion
Late radiation-induced toxicity, particularly RTOGswallowing and RTOGxerostomia, has a significant impact on the more general dimensions of HRQoL. These findings suggest that the development of new radiation-induced delivery techniques should not only focus on reduction of the dose to the salivary glands, but also on anatomic structures that are involved in swallowing.
Factors affecting

**Original Articles**

**Risk Factors for Severe Dysphagia after Concurrent Chemoradiotherapy for Head and Neck Cancers**

Keiichiro Koiwai, Naoto Shikama, Shigeru Sasaki, Atsunori Shinoda and Masumi Kadoya

Department of Radiology, Shinshu University School of Medicine, Matsumoto, Nagano, Japan

Received January 20, 2009; accepted March 15, 2009; published online April 20, 2009

**Conclusions:** Larger radiation portal field was associated with severe dysphagia induced by chemoradiotherapy. Jpn J Clin Oncol, 2009

Site, stage & treatment modality? do not impact the course of dysphagia

Nguyen NP, Anticancer research, 2009; 29: 3299-3304
What are the solutions?
Proper selection of patients & treatment strategy

Feasibility of organ-preservation strategies in head and neck cancer in developing countries

Trivedi NP, Kekatpure VD, Trivedi NN, Kuriakose MA, Shetkar G, Manjula BV
Department of Head and Neck Oncology, Mazumdar-Shaw Cancer Center, Narayana Hrudayalaya, Bangalore, India

- Results from developed world cannot be copied in the developing country
- An Indian survey of 100 head and neck physicians
- 40% cobalt unit
- 1/3 MDT and 1/3 adequate set up
- >2/3 need dose modification

Trivedi, IJC, 2012, vol 49; 15-20
Need for a multidisciplinary team

- Physics team
- Surgeons
- Dietician
- Oncologist
- Speech therapist
Role of exercise - before & after


**USE IT OR LOSE IT: EAT AND EXERCISE DURING RADIOTHERAPY OR CHEMORADIOTHERAPY FOR PHARYNGEAL CANCERS**

Katherine A. Hutcheson, PhD, Mihir K. Bhayani, MD, Beth M. Beadle, MD, PhD, Kathryn A. Gold, MD, Eileen H. Shinn, PhD, Stephen Y. Lai, MD, PhD, and Jan Lewin, PhD

Retel et al. *BMC Cancer* 2011, 11:475
http://www.biomedcentral.com/1471-2407/11/475

**RESEARCH ARTICLE** Open Access

A cost-effectiveness analysis of a preventive exercise program for patients with advanced head and neck cancer treated with concomitant chemo-radiotherapy
Intensity-Modulated Chemoradiotherapy Aiming to Reduce Dysphagia in Patients With Oropharyngeal Cancer: Clinical and Functional Results

Felix Y. Peng, Hyungjin M. Kim, Teresa H. Lyden, Marc J. Hazer, Francis P. Warden, Mary Peng, Jeffrey S. Mayer, Mark E. Prince, Thomas B. Carey, Gregory T. Wolf, Carol R. Bradford, Douglas B. Chepeha, and Abraham E. Eisbruch

Conclusion
Chemoradiotherapy with IMRT aiming to reduce dysphagia can be performed safely for OPC and has high locoregional tumor control rates. On average, long-term patient-reported, observer-rated, and objective measures of swallowing were only slightly worse than pretherapy measures, representing potential improvement compared with previous studies.
Summary

Successful treatment of dysphagia requires interdisciplinary collaboration, accurate diagnostic workup, effective therapeutic strategies, and consideration of unique patient characteristics.
Thank you