Laryngeal Conservation

Sarah Rodriguez, MD
Faculty Advisor: Shawn Newlands, MD, PhD
The University of Texas Medical Branch
Department of Otolaryngology
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Advanced stage glottic cancer traditionally has been treated with surgery, most often total laryngectomy, and post-operative radiation therapy (PORT).

Several randomized trials have demonstrated the feasibility of organ preservation in patients with advanced laryngeal and hypopharyngeal cancer.
Landmark Studies

The Department of Veterans Affairs Laryngeal Cancer Study Group (1991)

The European Organization for Research and Treatment of Cancer (1996)

Goal:

to investigate whether induction chemotherapy and definitive XRT with laryngectomy reserved for salvage for patients with stage 3 or 4 laryngeal cancer represented a better initial treatment approach than total laryngectomy and post-operative XRT
VA study Design

Two arms (322 patients divided between groups):

- **Experimental arm**
  - Patients received two cycles of chemotherapy consisting of cisplatin and fluorouracil; those found not to have at least a partial response at the primary site went on to laryngectomy; the remainder received a third round of chemotherapy and the vast majority of these patients went on to definitive XRT

- **Control arm**
  - Patients received total laryngectomy and standard post-operative radiation therapy (PORT)
The larynx was preserved in 107 patients (64%) of those assigned to induction chemotherapy

- 59 underwent total laryngectomy: 30 prior to XRT and 29 after radiation (persistent disease present on planned endoscopy 12 weeks after XRT)
- Late salvage surgery required in 11 additional patients (80% of these occurred in the year after treatment)
- Salvage laryngectomy required more often in those with glottic vs supraglottic CA (43 vs 31%); fixed vs mobile VCs (41 vs 29%); gross cartilage involvement vs no cartilage involvement (41 vs 35%)--but all this not statistically significant
- Significantly, salvage surgery was required in 44 % of pts with stage IV cancers as compared with 29% of pts with stage 3 cancer AND 56% of patients with T4 cancers as compared with 29% of patients with smaller primaries
Other VA study Findings

- The estimated two year survival was 68% for the induction chemotherapy group and the surgery group.
- No significant differences in survival between treatments when pts grouped according to tumor stage or site.
- Survival rates similar for chemotherapy responders and non-responders.
- Patients in the induction chemotherapy arm had a higher rate of local failure but a decreased rate of distant metastases.
EORTC Study

Goal:

To compare the results of treating patients with T2-T4, N0-N2b squamous cell carcinoma of the pyriform sinus or aryepiglottic fold with either induction chemotherapy followed by radiation or standard surgical therapy and PORT.
EORTC Patients

- 94 patients randomized to the immediate surgery arm
- 100 patients randomized to the induction chemotherapy (cisplatin and fluorouracil) and XRT arm
- Patients in the induction chemo arm had to have a complete response in order to proceed to XRT
EORTC Results

Survival:

- Disease-free survival at 3 and 5 years essentially the same for the chemotherapy and immediate surgery arms: 43 and 25% for chemo arm and 32 and 27% for surgery arm.

- At three years the overall survival rates appeared to favor the chemotherapy arm; the survival rates at 5 years were similar between groups but this estimate based on small number of patients at risk.
EORTC Results, Laryngeal Preservation

For the entire group of 100 patients randomized to induction chemotherapy, the rate of being alive and having a functional larynx at 3 and 5 years was 28 and 17% respectively.

The 3 and 5 year rate of retaining a functional larynx in the patients who completed treatment in the induction chemotherapy arm were 64% and 58% respectively.
EORTC Observations and Conclusions

The authors conclude that attempted larynx preservation with induction chemotherapy is acceptably safe with hypopharyngeal cancer.

Fewer distant mets and increased time to distant mets in the chemotherapy arm.

Chemotherapy complete responders were more frequent among those with T2 disease (82%) than those with T3 (48%) or T4 (0%) disease.
Summary of VA and EORTC studies

Both trials suggest that organ preservation is possible in patients with advanced stage laryngeal or hypopharyngeal cancer;
The role of chemotherapy not elucidated; rates of organ preservation in the VA trial similar to published rates of organ preservation after radiation alone
Distant metastases appear to be decreased with chemotherapy
Suggest that head and neck squamous cell carcinoma is sensitive to cisplatin and fluorouracil
RTOG 91-11

Goal:
To investigate three radiation-based therapies in the treatment of stage 3 and stage 4 laryngeal cancer:
- Induction cisplatin and fluorouracil followed by XRT (identical to VA experimental arm protocol)
- Concurrent chemoradiation with cisplatin
- Standard radiotherapy
Patients

Eligible patients had stage 3 or 4 laryngeal cancer. T1 primary tumors were ineligible as well as T4 tumors that penetrated through cartilage or more than 1 cm into the base of tongue.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cisplatin plus Fluorouracil Followed by Radiation (N=173)</th>
<th>Radiotherapy with Concurrent Cisplatin (N=172)</th>
<th>Radiotherapy Alone (N=173)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
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</tr>
<tr>
<td>&lt;60 yr — no. (%)</td>
<td>91 (53)</td>
<td>83 (48)</td>
<td>89 (51)</td>
</tr>
<tr>
<td>≥60 yr — no. (%)</td>
<td>82 (47)</td>
<td>89 (52)</td>
<td>84 (49)</td>
</tr>
<tr>
<td>Median — yr</td>
<td>59</td>
<td>60</td>
<td>59</td>
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<tr>
<td>Range — yr</td>
<td>36–78</td>
<td>26–78</td>
<td>31–79</td>
</tr>
<tr>
<td><strong>Sex — no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>131 (76)</td>
<td>137 (80)</td>
<td>133 (77)</td>
</tr>
<tr>
<td>Female</td>
<td>42 (24)</td>
<td>35 (20)</td>
<td>40 (23)</td>
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<tr>
<td><strong>Karnofsky performance score</strong> — no. (%)</td>
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<tr>
<td>100</td>
<td>35 (20)</td>
<td>32 (19)</td>
<td>26 (15)</td>
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<tr>
<td>90</td>
<td>88 (51)</td>
<td>106 (62)</td>
<td>93 (54)</td>
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<tr>
<td>80</td>
<td>38 (22)</td>
<td>27 (16)</td>
<td>41 (24)</td>
</tr>
<tr>
<td>70</td>
<td>10 (6)</td>
<td>6 (3)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>60</td>
<td>2 (1)</td>
<td>1 (1)</td>
<td>3 (2)</td>
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<tr>
<td><strong>Site of tumor — no. (%)</strong></td>
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<tr>
<td>Supraglottis</td>
<td>118 (68)</td>
<td>114 (66)</td>
<td>124 (72)</td>
</tr>
<tr>
<td>Glottis</td>
<td>55 (32)</td>
<td>58 (34)</td>
<td>49 (28)</td>
</tr>
<tr>
<td><strong>American Joint Commission on Cancer stage — no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>111 (64)</td>
<td>115 (67)</td>
<td>111 (64)</td>
</tr>
<tr>
<td>IV</td>
<td>62 (36)</td>
<td>57 (33)</td>
<td>62 (36)</td>
</tr>
<tr>
<td><strong>Tumor–node–metastasis stage — no. (%)</strong></td>
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<td></td>
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<tr>
<td>T stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>19 (11)</td>
<td>21 (12)</td>
<td>20 (12)</td>
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<tr>
<td>T3 with fixed cord involvement</td>
<td>82 (47)</td>
<td>82 (48)</td>
<td>76 (44)</td>
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<tr>
<td>T3 without cord fixation</td>
<td>54 (31)</td>
<td>52 (30)</td>
<td>61 (35)</td>
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<tr>
<td>T4</td>
<td>18 (10)</td>
<td>17 (10)</td>
<td>16 (9)</td>
</tr>
<tr>
<td>N stage</td>
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<tr>
<td>N0</td>
<td>87 (50)</td>
<td>86 (50)</td>
<td>87 (50)</td>
</tr>
<tr>
<td>N1</td>
<td>38 (22)</td>
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<td>32 (18)</td>
</tr>
<tr>
<td>N2A</td>
<td>2 (1)</td>
<td>7 (4)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>N2B</td>
<td>17 (10)</td>
<td>13 (8)</td>
<td>13 (8)</td>
</tr>
<tr>
<td>N2C</td>
<td>26 (15)</td>
<td>23 (13)</td>
<td>36 (21)</td>
</tr>
<tr>
<td>N3</td>
<td>3 (2)</td>
<td>4 (2)</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

* Because of rounding, not all percentages total 100.
† T denotes tumor, and N node. The designation T4 was limited to low-volume disease that did not extend into the tongue base by more than 1 cm or penetrate through cartilage.
RTOG 91-11 Results

The rate of laryngeal preservation at a median follow-up of 3.8 years was significantly higher among patients receiving radiotherapy with concurrent cisplatin (84%) than among those receiving induction chemotherapy followed by XRT (72%) or those receiving radiotherapy alone (67%)

Chemotherapy suppressed distant metastases

Two and five year survival did not differ among treatment groups

Patients who were treated with concurrent chemoradation had significantly fewer local failures than either induction chemotherapy + XRT or radiotherapy alone

Two and five year disease free survival estimates

- Arm one: 52 and 38%
- Arm two: 61 and 36%
- Arm three: 44 and 27%
Areas of Interest

- Timing of combined chemoradiotherapy
- Other chemotherapeutic agents
- New biologic agents
  - EGFR monoclonal antibodies
  - Targeting hypoxic cells
- Altered radiation fractionation schedules
  - Hyperfractionation: lower doses per fraction, more fractions per day; increased dose of radiation; same duration of therapy; reduces late toxicity
  - Accelerated fractionation: same dose over a shorter period of time; increases acute toxicity; decrease tumor repopulation
Quality of Life and Functional Outcomes

If both surgery + PORT and chemoradiation yield good local control and essentially equivalent survival rates, what is the comparative quality of life for the patient?

What kinds of functional outcomes can be expected after aggressive organ preservation protocols?
A 1998 follow-up to the VA study identified 25 surviving patients from the surgery + PORT group and 21 patients from the induction chemo + XRT group. Patients were administered the University of Michigan Head and Neck Quality of Life (HNQOL) instrument, the Medical Outcomes Short-Form 36 (SF-36), and the Beck Depression Inventory (BDI).

- Chemo/XRT patients had significantly better quality of life scores on the SF-36 mental health domain and also had better HNQOL pain scores.
- Patients with intact larynges had significantly better HNQOL emotion scores.
- More patients in the surgery (28%) were depressed than in the chemo/XRT group (15%).
Other Quality of Life Studies

Lee-Preston

- 36 patients surveyed 3-12 months after treatment with radiotherapy only (24) total laryngectomy + PORT or salvage laryngectomy after XRT (12)
- Functional Assessment of Cancer Therapy (FACT) with head and neck subscale, Nottingham Health Profile and the Hospital Anxiety and Depression Scale
- Combined therapy patients had lower FACT head and neck scores (poorer QOL) with identified problems of dry mouth, swallowing, breathing and communication
- The two treatment groups showed no difference in anxiety but there was a trend towards greater depression in the combined therapy group
- Results of the NHP show that scores were worse for those in the combined therapy group in all domains except pain. The differences were statistically significant in the emotional reaction and social isolation subscales.
Other Quality of Life Studies

Hanna

- EORTCQOL administered to 42 patients treated either with concurrent chemorad or surgery and PORT for stage 3 or 4 laryngeal cancer
- No statistically significant differences in overall QOL scores
- Subscale analysis revealed a trend for pts in the surgery group to experience greater difficulties with social functioning relative to the chemorad group
- Surgery pts reported significantly greater sensory disturbances, use of painkillers, and coughing
- Chemorad pts reported significantly greater problems with dry mouth
VA Study: patients who retained their larynx fared significantly better from the standpoint of speech communication.

- At two years post-treatment, patients who retained their larynx had regained their pre-treatment level of functioning for two of the three measures tested (intelligibility and reading rate) and exceeded pretreatment performance on the third (a communication profile used to assess general communication status).
- Laryngectomy patients had a decrease in all three measures despite all options of speech rehabilitation and therapy.

RTOG

- No difference in treatment groups
- The reporting of moderate or worse speech impairment was reported as 6, 11, and 13% at one year and 3, 6 and 8 percent at two years
RTOG

- At one year, 23% of those assigned to concurrent chemorad could swallow only soft foods or liquids and 3% could not swallow at all.
- At one year only 9% of the induction chem/rad group was limited to soft foods or liquids and there were no patients that could not swallow at all. This was similar to the radiotherapy-only arm.
- All three groups were similar at two years with 14-16% of patients reporting difficulty swallowing.
Functional Outcomes/Swallowing

Gillespie recently reported a survey of pts 12 months or more out from treatment of stage 3 or 4 SCCA of the oropharynx, larynx or hypopharynx. 19 patients were in the larynx/hypopharynx category. 11 of these were treated with surgery + PORT; 8 were treated with concurrent chemoXRT

MD Anderson Dysphagia Inventory was used

- Global subscale: pts perception of degree of swallowing impairment
- Emotional subscale: upset or embarassment by dysphagias
- Functional subscale: ease of food preparation and eating in public
- Physical subscale: effect of dysphagia on dietary consistency, aspiration, weight maintenance

No difference between in scores between treatment type

All pts in study had scores 25-50% worse than the general population
Carrara de Angelis reports speech and swallow evaluations of 19 patients who underwent concurrent chemoradiation with paclitaxel and cisplatin for laryngeal or hypopharyngeal SCCA.

Analysis took place 2-9 mos post-treatment:
- 11 pts with tracheostomy and 14 pts with feeding tube at some point in treatment
- At time of analysis, 6 still had tracheostomy and 6 were still using a feeding tube

Results:
- 40% of patients with moderate dysphonia, 27% severe dysphonia
More Carrara de Angelis Results

DYSPHAGIA SEVERITY

1. Severe (feeding tube): unable to tolerate any oral contrast safely
2. Moderate to severe (not permitted oral intake): maximum assistance or use of strategies with partial oral contrast only (tolerates at least 1 consistency safely with total use of strategies)
3. Moderate (modified diet and/or independence): total assistance, supervision, or strategies, 2 or more diet consistencies restricted
4. Mild to moderate (modified diet and/or independence): intermittent supervision or cueing, 1 or 2 consistencies restricted
5. Mild (modified diet and/or independence): distant supervision, may need 1 diet consistency restricted
6. Within functional limits or modified independence (normal diet): patient may have mild delayed swallowing reflex, stasis spontaneously cleared, and there is no penetration or aspiration
7. Normal (normal diet): normal in all situations and the patient does not need strategies or extra time

*See the “Methods” section for an explanation of the dysphagia severity scores and Table 2 for an explanation of the penetration/aspiration scale scores.

Table 2. Laryngeal Penetration and Aspiration*

<table>
<thead>
<tr>
<th>Score</th>
<th>Contrast Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No penetration or aspiration</td>
</tr>
<tr>
<td>2</td>
<td>Penetration, no contact to the vocal folds, without residue</td>
</tr>
<tr>
<td>3</td>
<td>Penetration, contact to the vocal folds, with residue</td>
</tr>
<tr>
<td>4</td>
<td>Aspiration, passes vocal folds, without subglottic residue</td>
</tr>
<tr>
<td>5</td>
<td>Aspiration, passes vocal folds, with subglottic residue</td>
</tr>
<tr>
<td>6</td>
<td>Passes vocal folds with subglottic residue and absent response (silent aspiration)</td>
</tr>
</tbody>
</table>

*Adapted from Rosenbek et al.*
Staton

- Identified 45 patients available for follow-up 6 months after treatment with intra-arterial cisplatin and concurrent XRT for stage 3 or 4 laryngeal cancer
- Sixteen patients required a tracheostomy and/or gastrostomy (tracheostomy 13, gastrostomy 13, both 10)
- The only variable found to impact subsequent tracheostomy and feeding tube requirement was vocal cord fixation. T4 status and massive cartilage invasion both trended toward an association with laryngeal dysfunction
Conclusions: Quality of Life and Functional Outcome

- Existing studies are small groups measured on different instruments.
- Data on quality of life seem to favor chemoradiation for organ preservation.
- If rates of disease control are equal, more weight should be given to individual patient factors in determining treatment.
- What is the comparative quality of life in those that require surgical salvage?
- More data is required on how many patients require long-term tracheostomy or gastrostomy after chemoradiation and how these specific issues impact QOL.
- More data is required on swallowing function post-treatment to determine normal time course of improvement and impact on QOL.
Surgical Complications After Attempted Organ Preservation

Danish Study
- 472 patients treated with post-irradiation salvage laryngectomies
- 89 fistulae lasting more than two weeks = rate of 19%
- The number of laryngectomies performed per year declined and the fistulae rate increased; risk of fistula in 1987 12% vs risk of fistula in 1997 of 30%

RTOG
- No significant difference in the rate of systemic complications
- Fistulae developed in 25, 30 and 15% of patients in arms 1, 2 and 3 respectively

Lavertu
- Compared complications of a group of patients treated for stage 3 or 4 head and neck SCCA with either XRT or concurrent chemo/XRT
- 30 salvage procedures were done with total laryngectomy being part of the salvage procedure in 14
- Major complications included carotid artery rupture, fistula, and GI bleed (one of each in the radiotherapy-only group) AND sepsis, stroke and pharyngeal stenosis (one each in the chemo/rad group)
- Minor complications were not numerous and did not differ between groups
- Author concludes that major and minor complications did not differ between groups and that morbidity rates for salvage surgery after aggressive organ preservation protocols was acceptable
Conclusions

- More patients with advanced disease can enjoy organ preservation.
- Work is ongoing to define the ideal protocols for organ preservation.
- More work needs to be done to define which patients are acceptable for aggressive organ preservation and what quality of life and functional outcomes they can expect.
- Role of the surgeon is changing.
- Medical oncologist should come to tumor board.