ADVANCED LARYNGEAL CANCER

Dimitrios Moraitis, MD
OUTLINE

• ANATOMY AND EMBRYOLOGY OF THE LARYNX
• PROGNOSIS OF LARYNGEAL TUMORS
• PATIENT EVALUATION
• TREATMENT OPTIONS
  • SURGERY
  • RADIOTHERAPY
  • CHEMOTHERAPY
  • CHEMO-RADIOTHERAPY
HNSCC

<table>
<thead>
<tr>
<th>Location</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tongue</td>
<td>6,900</td>
</tr>
<tr>
<td>Mouth</td>
<td>10,900</td>
</tr>
<tr>
<td>Pharynx</td>
<td>8,200</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>4,200</td>
</tr>
<tr>
<td>Larynx</td>
<td>10,100</td>
</tr>
<tr>
<td>Thyroid</td>
<td>18,400</td>
</tr>
</tbody>
</table>
LARYNGEAL CANCER

- Tongue: 1,700
- Mouth: 2,300
- Pharynx: 2,100
- Oral cavity: 1,700
- Larynx: 3,900
- Thyroid: 1,200
LARYNGEAL CANCER

- Localized: 46%
- Regional: 30%
- Distant: 24%
ADVANCED LARYNGEAL CANCER

• Extensive local, or loco-regional disease
  Cartilage/soft tissue invasion, voice or airway compromise

• Disseminated laryngeal CA

• Tumors that require treatment with more than one therapeutic modality

• Advanced laryngeal CA is stage III/IV disease
LARYNGEAL CANCER

- Supraglottic: 3%
- Glottic: 41%
- Subglottic: 56%
ANATOMY AND EMBRYOLOGY

• Complex anatomy and embryology
• Supraglottis is embryologically distinct from the glottis
• Anatomic barriers produce laryngeal compartments
  Quadrangular membrane and conus elasticus form supra and subglottic barriers respectively
• Growth and spread of cancer is determined by the site of origin of the primary tumor
ANATOMY AND EMBRYOLOGY

• Supraglottic structures arise from the buccopharyngeal anlage (arch III & IV)
• Glottic and subglottic structures from the tracheobrochial anlage (arch V & VI)
• The glottis seems to arise from paired lateral structures that fuse at the midline at the anterior commissure
TUMOR SITE AND CLINICAL BEHAVIOR

- Subtle symptoms in supraglottic CA often ignored
  Slowly growing well differentiated glottic CA
- Rich lymphatics and absence of barriers promote early bilateral spread of supraglottic CA
- High rate of occult and bilateral metastasis in supraglottic CA
  Rare LN metastasis in glottic CA
- 19% incidence of nodal metastasis in glottic tumors w subglottic extend, 33% in supraglottic and 52% in transglottic disease
PROGNOSTIC FEATURES

- Tumor differentiation
- Infiltrative pattern
  Cartilage invasion is associated with nodal metastasis and decreased survival
- Nodal status
  ECS is associated with worse prognosis
PATTERNS OF CERVICAL LYMPH NODE METASTASIS IN LARYNGEAL CA

STAGE DISTRIBUTION OF PATIENTS WITH LARYNGEAL CANCER
FIVE-YEAR DISEASE-FREE SURVIVAL IN LARYNGEAL CANCER BY SITE AND STAGE

![Bar chart showing disease-free survival rates by stage and site for laryngeal cancer. The chart compares supraglottic and glottic cancers across stages I-IV.]
PATIENT EVALUATION

ASSESS THE PATIENT

• General medical condition and comorbidities
• Physiologic age
• Life style (smoking, ETOH)
• Pulmonary function
• Symptoms (hoarsness, dysphagia, stridor)
• Geographic location
• Compliance and reliability

ASSESS THE TUMOR

• Staging the disease
• Assess metastatic or second primary tumors
• Physical exam
• Radiologic studies (CT, MRI, PET)
• Fiberoptic nasendoscopy
• Rigid endoscopy and biopsy
• Determine resectability and plan treatment
TREATMENT OF ADVANCED LARYNGEAL CA
IS IT A “TIGER” COUNTRY?
ADVANCED LARYNGEAL CANCER TREATMENT

- Single-modality treatment for early disease
- Multimodality treatment for advanced disease
- Surgery with radiotherapy post operatively
- Chemotherapy and radiation as part of laryngeal preservation strategies
TREATMENT PLANNING

• Physicians and patients should have realistic expectations of functional outcome
• Patient preference
  preservation of voice and swallowing
  avoidance of stoma
  cost, length of treatment and travel
  toxicity of therapy
• Physician preference
  expertise and experience
  institutional policies and protocols
  available resources
More than 15 surgical procedures for laryngeal CA

1873 T. Billroth performed the first total laryngectomy

1878 the first hemilaryngectomy

1939 Alonso reported a partial horizontal laryngectomy

1956 Leroux described a supraglottic laryngectomy

1965 Ogura described an extended supraglottic laryngectomy

Early 1980s supracricoid laryngectomies
WHAT TYPE OF SURGERY?

• Advanced disease traditionally treated with total laryngectomy
• Neck dissection
• In selected patients endoscopic laser resection or partial laryngectomies such as supraglottic, supracricoid or subtotal
• Functional expectations should not compromise oncologic outcomes
• Patient preference/reliability, tumor characteristics and surgeon expertise determine the surgical option
OTHER TREATMENT MODALITIES

• Radiotherapy alone
• Induction chemotherapy followed by radiotherapy
• Concurrent chemo-radiotherapy
RADIATION

- 1895 Roentgen discovered the x-rays
- 1903 Schepegrell first used XRT to treat laryngeal CA
- 1933 Coutard defined dosimetry and radiobiology
ALTERED FRACTIONATION

• RT historically played a major role in the management of HNSCC
• Advanced T3,4 lesions treated with conventional RT only may have poorer prognosis
• Altered fractionation refers to delivery of multiple fractions/day without increasing the overall treatment time
• To address tumor repopulation and increase tumor kill without increasing long-term toxicity
• Acute toxicity may be increased
ALTERED FRACTIONATION

- Hyperfractionation (↑total dose & number fractions ↓ dose/fraction)
- Accelerated fractionation (unchanged total dose & number fractions ↓ overall treatment time)
- Split course accelerated fractionation schedule
- Accelerated fractionation with concomitant boost (boost dose as a second daily fraction for the last 12 days of a 6 wk therapy)
<table>
<thead>
<tr>
<th>STUDY</th>
<th>PTS</th>
<th>STAGE</th>
<th>F/U</th>
<th>TREATMENT</th>
<th>SURVIVAL</th>
<th>LP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christie</td>
<td>114</td>
<td>T3NO G G</td>
<td>5 yr</td>
<td>RT with salvage surg</td>
<td>54% local control XRT</td>
<td>66%</td>
</tr>
<tr>
<td>1994</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>68% w salvage surg 80%</td>
<td></td>
</tr>
<tr>
<td>Gainesville</td>
<td>75</td>
<td>T3 G G</td>
<td>5 yr</td>
<td>hyperfractionation</td>
<td>80% local control</td>
<td>66%</td>
</tr>
<tr>
<td>1996</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>with salvage surgery</td>
<td></td>
</tr>
<tr>
<td>CHART</td>
<td>918</td>
<td>all sites</td>
<td>5 yr</td>
<td>continuous hyperfractionated accelerated vs conventional RT</td>
<td>same survival</td>
<td></td>
</tr>
<tr>
<td>1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>But ↑DFS w ↑ stage</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7% better local control</td>
<td></td>
</tr>
<tr>
<td>DAHANCA</td>
<td>1476</td>
<td>T3,4(32%)</td>
<td>G(47%)</td>
<td></td>
<td>better control and</td>
<td>80%</td>
</tr>
<tr>
<td>2003</td>
<td></td>
<td>SG(16%)</td>
<td></td>
<td>accelerated 6 vs 5 fractions RT/wk</td>
<td>DFS (73 vs 66%)</td>
<td>vs.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>same survival</td>
<td>68%</td>
</tr>
</tbody>
</table>
RTOG 9003 TRIAL

- Randomized trial locally advanced HNSCC from all sites. 15% were stage III/IV supraglottic CA
- Standard fractionation was compared to hyperfractionation, accelerated fractionation with split and accelerated with boost
- Pts with hyperfractionation and accelerated fractionation with boost had better local-regional control than conventional fractionation
- Trend toward better DFS
  - No difference in overall survival

Int J Radiat Oncol Biol Phys, 2000; 48(1):7-16
# RTOG 9003 TRIAL

<table>
<thead>
<tr>
<th>2-year endpoints</th>
<th>STANDARD FRACTIONATION (N=268)</th>
<th>HYPER FRACTIONATION (N=263)</th>
<th>ACCELERATED FRACTIONATION WITH SPLIT (N=274)</th>
<th>ACCELERATED FRACTIONATION WITH BOOST (N=268)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOCO-REGIONAL</td>
<td>46%</td>
<td><strong>54.4%</strong></td>
<td>47.5%</td>
<td><strong>54.5%</strong></td>
</tr>
<tr>
<td>DISEASE-FREE SURVIVAL</td>
<td>31.7%</td>
<td><strong>37.6%</strong></td>
<td>33.2%</td>
<td><strong>39.3%</strong></td>
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<tr>
<td>OVERALL SURVIVAL</td>
<td>46.1%</td>
<td>54.5%</td>
<td>46.2%</td>
<td>50.9%</td>
</tr>
</tbody>
</table>

Int J Radiat Oncol Biol Phys, 2000; 48(1):7-16
COMPLICATIONS AFTER RT

- Compared to standard fractionation all three altered fractionation schemes had significantly worse acute side effects (about 50% patients)
- Accelerated fractionation with concomitant boost had also worse late effects (28-37% patients)

At 6-24 mo there was no difference in the late effects

Int J Radiat Oncol Biol Phys, 2000; 48(1):7-16
COMPLICATIONS AFTER RT

• Increased rate of acute radiation-related morbidity in accelerated fractionation protocols.
  53% confluent mucositis vs 33% in conventional treatment. Mucositis persists (3 months).

• Late radiation-related morbidity effects persisting in 20% at 5 yr follow-up.

CHEMOTHERAPY

- At least 10 nonrandomized trials of chemotherapy based protocols
- Most are small series of mixed primaries
- Although the concepts of larynx and function preservation were not clear roughly one-third to one-half of the patients seem to retain their larynx
• Combining CT with RT may improve locoregional and distant failure rates after RT of advanced malignancies
• Sublethaly damaged cells between RT fractions can be repaired and cause recurrence of disease
• Chemotherapy agents (cisplatin) can inhibit lethal damage repair of cancer cells and augment RT damage
• Cytoreduction of hypoxic tumor cells with CT might improve tumor oxygenation and radiosensitivity
• Antimetabolites or taxanes can address the issue of tumor cell repopulation
CONTRAINDICATIONS TO LARYNGEAL PRESERVATION

- Tumor characteristics
  (extensive cartilage and soft tissue extend, subglottic extension, obstructing lesions)
- Patient factors (preference or unreliability)
- Previous treatments (radiotherapy)
## NONRANDOMIZED CHEMOTHERAPY PROTOCOLS

<table>
<thead>
<tr>
<th>STUDY</th>
<th>PTS</th>
<th>SITE</th>
<th>STAGE</th>
<th>F/U (mo)</th>
<th>ORGAN PRESERVATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karp, 1991</td>
<td>35</td>
<td>L(14) H(21)</td>
<td>T2-T4</td>
<td>84</td>
<td>L:77%H:33%, at 2 yr</td>
</tr>
<tr>
<td>Pfister, 1991</td>
<td>40</td>
<td>L(13)H(9)O(18)</td>
<td>II-IV</td>
<td>49</td>
<td>L:68%</td>
</tr>
<tr>
<td>Nicolaou, 1991</td>
<td>28</td>
<td>L</td>
<td>III-IV</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Price, 1992</td>
<td>73</td>
<td>L</td>
<td>III-IV</td>
<td>12</td>
<td>L:18%, at 10 yr</td>
</tr>
<tr>
<td>Giglio, 1993</td>
<td>50</td>
<td>L</td>
<td>III-IV</td>
<td>12</td>
<td>L:78%</td>
</tr>
<tr>
<td>Demard, 1993</td>
<td>88</td>
<td>L(33) H(55)</td>
<td>T2-T4</td>
<td>28</td>
<td>L:22%, at 5 yr</td>
</tr>
<tr>
<td>Shirinian, 1994</td>
<td>63</td>
<td>L(25) H(29) O(9)</td>
<td>T2-T4</td>
<td>54</td>
<td>L:44%H:28%, O:22%</td>
</tr>
<tr>
<td>Kraus, 1994</td>
<td>25</td>
<td>H</td>
<td>II-IV</td>
<td>41</td>
<td>L:32%</td>
</tr>
<tr>
<td>De Andres, 1995</td>
<td>20</td>
<td>L</td>
<td>III</td>
<td>36</td>
<td>L:57%</td>
</tr>
<tr>
<td>Zelefski, 1997</td>
<td>26</td>
<td>H</td>
<td>II-IV</td>
<td></td>
<td>52% at 5 yr</td>
</tr>
<tr>
<td>STUDY</td>
<td>PTS</td>
<td>SITE</td>
<td>STAGE</td>
<td>TREATMENT</td>
<td>F/U (mo)</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----</td>
<td>------------</td>
<td>---------</td>
<td>--------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>VACSP 1991</td>
<td>332</td>
<td>SG(63%) G(37%)</td>
<td>T3(65%)</td>
<td>Induction CT+RT (&gt;50% resp) vs surg+RT</td>
<td>96</td>
</tr>
<tr>
<td>EORTC 1996</td>
<td>194</td>
<td>SG(21%) HP(79%)</td>
<td>T3 (75%) T4 (3%)</td>
<td>Induction CRT (complete resp) vs surg+RT</td>
<td>51</td>
</tr>
<tr>
<td>GETTEC 1998</td>
<td>68</td>
<td>SG(31%) G(41%) TG(28%)</td>
<td>T3N0</td>
<td>Induction CRT (&gt;80% resp) vs surg+RT</td>
<td>96</td>
</tr>
<tr>
<td>INT R91-11 2001</td>
<td>547</td>
<td>SG(69%) G(31%)</td>
<td>T3(70%), N0-1(27%)</td>
<td>3 arms: concurrent CRT, induction CRT, RT alone</td>
<td>24</td>
</tr>
</tbody>
</table>
*INDUCTION CHEMOTHERAPY: cisplatin and 5-FU

SCHEMA FOR THE VA TRIAL

INDUCTION CHEMOTHERAPY
- 2 cycles

SURGERY

RESPONDERS
- ADDITIONAL CHEMO CYCLE

NON-RESPONDERS
- RT

Surgery

RT

RESIDUAL DISEASE
- COMPLETE RESPONSE

FOLLOW UP

332 patients randomized
SCHEMA FOR INTERGROUP R91-11

ARM 1: cisplatin 100mg/m² day 1+5-FU 1000 mg/m² day, days 1-5
ARM 2: cisplatin 100mg/m² days 1, 22 and 43
RADIOTHERAPY, all arms: Total 70 Gy, 2 Gy/fraction
CONCOMITANT OR SEQUENTIAL CHEMOTHERAPY?
INT R91-11 CONCLUSIONS

- All therapeutic schemes resulted in similar 2-yr survival rates
- Concomitant CT/RT: improved the 2-yr laryngectomy-free survival and progression to laryngectomy compared to RT improved progression to laryngectomy compared to sequential treatment
META-ANALYSIS OF CHEMOTHERAPY ON H&N CA

- Meta-analysis of 63 trials (10741 patients) of locoregional treatment with or without chemotherapy
- Absolute survival benefit of 4% at 2 and 5 years in favor of chemotherapy
- Chemotherapy given concomitantly to RT gave significant benefits but heterogeneity of the results prohibits any firm conclusions

Lancet, 2000;355: 949-55
META-ANALYSIS OF CHEMOTHERAPY ON LARYNGEAL CA

- Three trials (600 patients) with median F/U 5.7 years
- Chemotherapy reduced survival at 5 yrs by 6% from 45% to 39%
- Significant heterogeneity between the three trials
- Higher locoregional recurrence in the chemotherapy arms (25% vs 12%) but less metastasis (14% vs 19%)
- Reduction of disease-free survival at 5 yrs in the chemotherapy arm (34% vs 40%)
- Alive patients at 5 yrs 45% in the surgical arm and 39% in the chemotherapy arm.
- 23% alive with larynx. 16% alive without larynx

Lancet, 2000;355: 949-55
# INCIDENCE OF DEATHS DUE TO CHEMOTHERAPY TOXICITY

<table>
<thead>
<tr>
<th>STUDY</th>
<th>PTS</th>
<th>DEATHS</th>
<th>DRUG COMBINATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEYVRAZ</td>
<td>89</td>
<td>5 (6%)</td>
<td>Cisplatin, 5-FU, vindesine</td>
</tr>
<tr>
<td>LEFEBRE</td>
<td>57</td>
<td>1 (2%)</td>
<td>Cisplatin, 5-FU</td>
</tr>
<tr>
<td>URBA</td>
<td>38</td>
<td>2 (5%)</td>
<td>MGBG, Cisplatin, 5-FU</td>
</tr>
<tr>
<td>H&amp;N CONTRACTS</td>
<td>301</td>
<td>6 (2%)</td>
<td>Cisplatin, bleomycin</td>
</tr>
<tr>
<td>VACSP</td>
<td>166</td>
<td>1 (0.6%)</td>
<td>Cisplatin, 5-FU</td>
</tr>
<tr>
<td>TOTAL</td>
<td>651</td>
<td>15 (3%)</td>
<td>Cisplatin, 5-FU</td>
</tr>
</tbody>
</table>
SURGERY AFTER CHEMOTHERAPY

- Salvage surgery for residual/recurrent disease
  Most commonly total laryngectomy
- Possible delay in diagnosis that could affect survival
- Increased incidence of complications and wound healing problems
- Increased incidence of pharyngocutaneous fistulas
- In 12 reports the incidence of fistula varies from 9-35%
- Protection of the anastomosis with flaps might be necessary
SALVAGE SURGERY FOR UNSUCCESSFUL LARYNX PRESERVATION

- Most authors report complications after radiotherapy only or chemotherapy only
- Incidence of complications after high dose RT varies from 35-74%
- Complication rate after chemoradiation is in the range of 46-100%
- After induction CT without RT the complication rate varies between 46-56%
SALVAGE SURGERY FOR UNSUCCESSFUL LARYNX PRESERVATION

- 31 pts underwent salvage laryngectomy. 14 had laryngeal primary tumor
- Better local control (86%) and 2 yr DSS (56%) in laryngeal primaries
- 2 yr survival for failures after induction CT 30% vs. 46% for failures after CRT
- Pharyngocutaneous fistula in 39% resulting in prolonged hospitalization

SALVAGE SURGERY FOR UNSUCCESSFUL LARYNX PRESERVATION

61% major wound complications after salvage surgery. Mean time to resolution of fistulae and flap necrosis was 7.7 months

SALVAGE SURGERY FOR UNSUCCESSFUL LARYNX PRESERVATION

- 5 yr locoregional control was 75%
- As the number of laryngectomies decreases the number of fistulae increases.

In the recent DAHANCA study the annual risk of fistula rate increased from 12% to 30% over a 10-year period. High T stage and non-glottic tumors were significant factors for fistula formation.

Head and Neck 2003; 25:711-6
ANNUAL NUMBER OF LARYNGECTOMIES AND FISTULAE OVER THE 10 YR DAHANCA STUDY
AT WHAT PRICE IS VOICE PRESERVED?

• Toxicities
  Mainly acute side effects such as mucositis or leukopenia
• 50% carboplatin treated patients required gastrostomy feeding in recent study
• Chronic effects not consistently reported
• Swallowing might be impaired
HOW CRITICAL IS VOICE PRESERVATION?

- A good functional outcome seems to have limited impact on QOL
- Speech function might be negatively affected after chemoradiation
- Speech rehabilitation seems to have a positive effect after TL
VOICE AND SWALLOWING AFTER FUNCTION PRESERVING TREATMENT

• Radiotherapy can adversely affect swallowing
• Hypopharyngeal stenosis can occur due to fibrosis after RT
• RT resulting in xerostomia impairs mastication and initiation of swallowing reflex
• Aspiration rates vary between studies
• Treatment related decline in QOL during CRT improves after 6 months
FUNCTIONAL OUTCOMES FOLLOWING TREATMENT FOR ADVANCED LARYNGEAL CA

- Pts with preserved larynx had better speech intelligibility and communication profiles
- CT+RT and the surgery+RT group had the same swallowing difficulties
- Most TL patients after rehabilitation used TE speech (31%) or electrolarynx (55%)
- Only 8% remained non-vocal

HOW CRITICAL IS VOICE PRESERVATION?

- Patients on the chemotherapy arm of the VA study had improved QOL scores.
- Freedom from pain, better emotional well being and lower levels of depression rather than preservation of speech function were the reasons for the improved QOL scores.
  

- Patients after laryngectomy with tracheoesophageal speech and patients treated with radiotherapy had similar QOL and small differences in perceptual speech evaluation.

  Laryngoscope 1998;108:1566-73
FUNCTIONAL OUTCOMES FOLLOWING LARYNX PRESERVATION

- 33% patients had perceptually normal voice or mild dysphonia and 40% moderate dysphonia
- Vocal parameters of roughness (87%) or breathiness (78%) were the most frequent abnormalities
- Stasis was observed in the hypopharynx in 86% patients
- All these abnormalities were mild to moderate and allowed intelligible communication and efficient swallowing in most patients

Arch Otolaryngol Head Neck Surg 2003;129:733-8
MANAGEMENT OF THE NECK IN LARYNGEAL CANCER

• Radiotherapy alone
• Neck dissection and postoperative radiotherapy
• Chemoradiotherapy with planned neck dissection or observation and salvage ND
<table>
<thead>
<tr>
<th>STUDY</th>
<th>PTS</th>
<th>STAGE</th>
<th>cCR</th>
<th>cPR</th>
<th>NECK FAILURE</th>
<th>SURVIVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>VASLG 1992</td>
<td>92</td>
<td>N2,3</td>
<td>39%</td>
<td></td>
<td>28% cCR &amp; 68% pCR required salvage surgery</td>
<td>cCR associated w better survival 67% vs 33%</td>
</tr>
<tr>
<td>Armstrong J 1993</td>
<td>54</td>
<td>N1,2 (L 41%)</td>
<td>44%</td>
<td></td>
<td>higher neck failure in pCR compared to cCR after CT (20% vs. 6%)</td>
<td>43% CT+RT 53% CT+ND at 3 yrs</td>
</tr>
<tr>
<td>Stenson KM 2000</td>
<td>69</td>
<td>N2,3</td>
<td>43%</td>
<td>49%</td>
<td>26% complications</td>
<td></td>
</tr>
<tr>
<td>Wanebo H 2001</td>
<td>38</td>
<td>N1-3</td>
<td></td>
<td></td>
<td>residual disease after CRT in 22%</td>
<td>68%</td>
</tr>
<tr>
<td>McHam SA 2003</td>
<td>109</td>
<td>N2,3 (L 17%)</td>
<td>57%</td>
<td>46%</td>
<td>no neck failures in cPR 25% cCR had micro disease</td>
<td></td>
</tr>
</tbody>
</table>
## COMPLICATIONS POST RT/CRT NECK DISSECTION

<table>
<thead>
<tr>
<th>STUDY</th>
<th>PTS</th>
<th>PREVIOUS TREATMENT</th>
<th>TYPE OF DISSECTION</th>
<th>COMPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGuirt 1979</td>
<td>176</td>
<td>RT</td>
<td>RND</td>
<td>50%</td>
</tr>
<tr>
<td>Bland 1981</td>
<td>133</td>
<td>none</td>
<td>RND</td>
<td>38%</td>
</tr>
<tr>
<td>Mendenhall 1986</td>
<td>143</td>
<td>RT</td>
<td>MRND, SND</td>
<td>38%</td>
</tr>
<tr>
<td>Lavertu 1998</td>
<td>15</td>
<td>CRT</td>
<td>MRND</td>
<td>33%</td>
</tr>
<tr>
<td>Davidson 1999</td>
<td>34</td>
<td>CRT, RT</td>
<td>MRND, SND</td>
<td>37%</td>
</tr>
<tr>
<td>Stenson 2000</td>
<td>69</td>
<td>CRT</td>
<td>SND, MRND</td>
<td>26%</td>
</tr>
</tbody>
</table>
FOLLOW UP AFTER TREATMENT

• Tumor response and recurrence are difficult to evaluate
• Delay in diagnosis impacts on survival
• Recurrences are often submucosal and difficult to detect on direct laryngoscopy
FOLLOW UP AFTER TREATMENT

- Posttreatment changes, especially edema, fibrosis and necrosis can lead to interpretation errors on laryngoscopy and CT/MRI
- Postirradiation biopsies are frequently equivocal
- Surgeons are reluctant to obtain multiple biopsies in previously irradiated field in fear of aggravating radionecrosis
- Desirable to have a non-invasive diagnostic modality to differentiate recurrence from posttreatment changes
FOLLOW UP AFTER TREATMENT

- FDG-PET scan. Is it better than CT/MRI?
- When is the optimal time to order a FDG-PET scan?
- Can FDG-PET scan differentiate reliably recurrent/residual tumor from RT changes?
PET SCAN FOR RECURRENT HNSCC

• 143 pts and 35% laryngeal primaries. Average time between completion of CT and PET was 6.9 months
• PET seems more accurate at detecting disease at regional and distant sites
• Positive PET interpretation by nuclear medicine physician and higher SUV were strong prognostic determinants
• Increase in one unit SUV increased the patients relative risk for relapse and death by 11% and 14% respectively

J Clin Oncol 2002;20:4199-208
## PET Scan for Recurrent HNSCC

<table>
<thead>
<tr>
<th>PET</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
</tr>
</thead>
<tbody>
<tr>
<td>local</td>
<td>97</td>
<td>79</td>
</tr>
<tr>
<td>regional</td>
<td>92</td>
<td>95</td>
</tr>
<tr>
<td>distant</td>
<td>94</td>
<td>96</td>
</tr>
<tr>
<td>overall</td>
<td>96</td>
<td>72</td>
</tr>
<tr>
<td>physical examination</td>
<td>60</td>
<td>76</td>
</tr>
</tbody>
</table>
PET SCAN FOR PERSISTENT DISEASE AT THE PRIMARY SITE

- FDG-PET scan most useful to detect residual disease after larynx preservation treatment
- Timing of scan very important
- The optimal time seems to be somewhere between 1 and 4 months

High false negative rate (up to 18%) reported at 1mo post-treatment scanning
Conversely at 4 mo scanning the false negative rate was reported as low as 0%

Cancer 1994;74:1355-9
PET SCAN IDENTIFIES PERSISTENT DISEASE IN THE NECK

<table>
<thead>
<tr>
<th></th>
<th>SENSITIVITY (%)</th>
<th>SPECIFICITY (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET</td>
<td>67</td>
<td>100</td>
</tr>
<tr>
<td>CT/MRI</td>
<td>67</td>
<td>25</td>
</tr>
<tr>
<td>CLINICAL ASSESSMENT</td>
<td>58</td>
<td>75</td>
</tr>
</tbody>
</table>

NEW DIRECTIONS

• Intraarterial chemotherapy
  (attempt to decrease acute side effects. Good local control vs distant failures)
• Concurrent chemoradiation with paclitaxel-based regimens
• Biologic profile of tumor and patient that will help guide therapy
• Toxicity antagonists
• Targeted therapy
  EGFR inhibitors: monoclonal antibodies, tyrosine kinase-specific inhibitors, ligand-toxin conjugates and antisense approaches
### Table 1. Monoclonal antibodies under clinical investigation for the treatment of head and neck squamous cell carcinoma.

<table>
<thead>
<tr>
<th>Monoclonal antibody</th>
<th>Manufacturer</th>
<th>Concurrent therapy</th>
<th>Current trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>C225/IMC-225</td>
<td>Imclone Systems, Somerville, NJ</td>
<td>Radiation Therapy</td>
<td>Phase III¹⁶⁰</td>
</tr>
<tr>
<td>Cetuximab™</td>
<td>Imclone Systems, Somerville, NJ</td>
<td>Chemotherapy</td>
<td>Phase III¹⁶¹,¹⁶²</td>
</tr>
<tr>
<td>IMC-225</td>
<td>Imclone Systems, Somerville, NJ</td>
<td>Chemotherapy</td>
<td>Phase III¹⁶³</td>
</tr>
<tr>
<td>Erbitux™</td>
<td>Abgenix, Freemont, CA</td>
<td>Human</td>
<td>Phase I/II</td>
</tr>
<tr>
<td>ABX-EGF</td>
<td>Abgenix, Freemont, CA</td>
<td>None</td>
<td>Phase I⁶⁴</td>
</tr>
<tr>
<td>EMD 72000</td>
<td>Merck, Darmstadt, Germany</td>
<td>Radiation Therapy</td>
<td>Phase I⁶⁵</td>
</tr>
<tr>
<td>hR3</td>
<td>Center of Molecular Immunology, Havana, Cuba</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### NEW DIRECTIONS

<table>
<thead>
<tr>
<th>Tyrosine kinase inhibitors</th>
<th>Manufacturer</th>
<th>Type of inhibitor</th>
<th>Current trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>SU5416</td>
<td>Pharmacia, Peapack, NJ</td>
<td>None</td>
<td>Phase III&lt;sup&gt;66&lt;/sup&gt;</td>
</tr>
<tr>
<td>ZD1839</td>
<td>AstraZeneca, Pharmaceuticals, LP, Wilmington, DE</td>
<td>Reversible</td>
<td>Phase II/III&lt;sup&gt;67,68&lt;/sup&gt;</td>
</tr>
<tr>
<td>E1888&lt;sup&gt;™&lt;/sup&gt;</td>
<td>Iressa&lt;sup&gt;™&lt;/sup&gt;, Pharmaceuticals East, Hanover, NJ</td>
<td>Reversible</td>
<td>Phase I&lt;sup&gt;69&lt;/sup&gt;</td>
</tr>
<tr>
<td>OSI-774</td>
<td>OSI, Pharmaceuticals, Uniondale, NY</td>
<td>Reversible</td>
<td>Phase II/III&lt;sup&gt;68,70&lt;/sup&gt;</td>
</tr>
<tr>
<td>CI-1033</td>
<td>Pfizer, Pharmaceuticals, Groton, CT</td>
<td>Irreversible</td>
<td>Phase I&lt;sup&gt;71,72&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
CONCLUSIONS

Treatment of advanced laryngeal CA should be individualized

Patient and tumor factors should be carefully studied

Molecular data predicting tumor response to chemoradiation are needed for optimal treatment planning

Preservation of function should also preserve quality of life and guarantee a sound oncologic outcome