Radiotherapy for Laryngeal Cancer

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Evidence Based Recommendation?

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Laryngeal cancer: United Kingdom National Multidisciplinary guidelines

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outline

• Epidemiology and Staging
• Role of radiation treatment (RT) in early laryngeal SCC
• Evidence for radiation –based laryngeal preservation
• Role of RT in advanced laryngeal SCC
• Radiotherapy Pathway–waiting times, treatment interruptions
• IMRT- “gold standard” in UK (basics, target volume delineation, treatment planning, treatment delivery)
• Radiation related toxicities
• Future directions
Laryngeal SCC: Epidemiology

- **Worldwide**: 157,000 cases in 2012
- **UK**: in 2013, 2300 pts (6/d)
  - <1% of all new cancers
  - 82% men, 18% women (M:F; 4.5:1)
  - 1% of all cancers in men, 0.3% in women
  - 60% in > 65y

**Incidence and mortality trends**

- 6% **reduction** in cases since 1970s (15% decrease in men)
- Marked **decrease** in aged-standardised mortality over the last decade (25 & 16% in men and women respectively)

25% HPV Positive (types 16 and 18)
Larynx: Basic anatomy

- Voice
- Breathing
- Swallowing

Anatomical structures:
- Vallecula
- Hyoid
- Epiglottis
- Preepiglottic fat
- Arytenoid
- Thyroid cartilage
- Cricoid
- Ventricle
- Esophagus
- Trachea
- Tongue
- Supraglottis
- Glottis
- Subglottis
- Vocal cord
- Larynx

<1%
# Laryngeal cancer: Staging

<table>
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<tr>
<th></th>
<th>T1 &lt; 2cm</th>
<th>T2 2-4 cm</th>
<th>T3 &gt;4cm</th>
<th>T4a + Invasion</th>
<th>T4b +Invasion</th>
<th>M1</th>
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<tbody>
<tr>
<td>N0</td>
<td>I</td>
<td>II</td>
<td>III</td>
<td>IV A</td>
<td>IV B</td>
<td>IV C</td>
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<tr>
<td>N1 &lt;3cm SIPSI</td>
<td>III</td>
<td>III</td>
<td>III</td>
<td>IV A</td>
<td>IV B</td>
<td>IV C</td>
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<tr>
<td>N2 3-6cm BIL</td>
<td>IV A</td>
<td>IV A</td>
<td>IV A</td>
<td>IV A</td>
<td>IV B</td>
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<td>N3 &gt;6cm</td>
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<th>M1</th>
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<tr>
<td>N0</td>
<td>EARLY</td>
<td>LOCALLY ADVANCED</td>
<td>METASTATIC</td>
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<td>N1 &lt;3cm SIPSI</td>
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Treatment modalities for laryngeal scc

- Surgery
- Radiotherapy
- Chemotherapy
- Targeted therapies

- Single Modality for early stage or combined in advanced stage
- Induction, Concurrent with RT (organ preservation or postoperative) or palliative
Management of Early (T1-T2a) Glottic scc

Low Tumour Volume  
Low incidence of metastatic neck disease

Extremely good chances of cure!

- Radiotherapy  
- Transoral Laser Microsurgery  
- Open partial surgery

Similar OS and LC  
HOWEVER NO COMPARISON IN RCT

How do we then decide??

Cochrane ENT Group, 2012
CAREFUL PATIENT SELECTION
Is complete oncologic resection feasible through transoral approach?
Will patient tolerate aspiration if occurs?
Will surgery alone be adequate?

Patient Factors
- Pretreatment condition
- Priorities

Disease factor
- Staging
- Prognosis

Treatment factor
- Morbidity
- Options
Radiotherapy for early glottic scc

- Megavoltage photons from a linear accelerator
- Energy 4-6MV
Radiotherapy for early glottic scc

**Position:** Supine neutral position, cervical spine straight

**Volume:** centered at the level of vocal cord
- 4x4 cm (T1), 6X6 cm (T2) to cover supra or sub-glottic extension

- **What do we cover?**
  - Sup : top of thyroid cartilage
  - inf : bottom of cricoid/include 1\textsuperscript{st} tracheal ring
  - ant : 1cm skin flash
  - post : anterior edge of vertebral body

  **Bolus the anterior commissure**

**Technique:** Parallel opposed lateral wedged fields or ant oblique wedged (obese or stockily built patients)

Elective treatment of the neck not recommended
Radiotherapy for early glottic SCC

Dose/Fractionation

Hypofractionated RT schedules (fraction size $>2$ Gy) equivalent outcomes to longer schedules without increased toxicity

- 50 – 52 Gy in 16 # over three weeks
- 53-55 Gy in 20 # over four weeks

Or conventional 65 Gy in 30 # over 6 weeks

_Dose $< 2$ Gy/# not recommended as compromises outcome_

_Yamazaki et al, (2006):_ prospective study on hypofractionated vs standard for T1 Glottic: 5y OS 92% VS 73% (P=.004)
Any role for more sophisticated RT?

**WHY?**

- Long term **local control** (90% and 75% for T1 and T2 respectively)
- **Mortality** is unrelated to their cancer
- H&N cancer pts receiving RT are at higher risk of Carotid artery stenosis and stroke
  - **5.6 times higher** *(Chang et al, j Vasc Surrg, 2009;50(2):280-5)*
  - **75%** relative increase in risk of fatal stroke *(Swisher-McClure et al, Head and Neck, 2014;36(5):611-6)*

**Controversial:** increased conformity increases the risk of marginal misses through contouring errors and organ motion
**Design:**
- All pts with T1/T2 laryngeal scc treated with definitive RT (1989-2011): 330 pts total
- 48 pt treated with IMRT (2006-2011)
- 6.3% Tis, 66.7% T1, 13% T2
- Median dose 65.25 Gy
- 2.25 Gy
- Dosimetric data (including dose to L & R carotid arteries)

**Results:**
- 3y LC 91% for T1, 80% for T2
- 3y laryngectomy free survival was 87% and 74% for T1, & T2.
- No significant difference in LC between IMRT and 3DCRT
- No data relating dose to CVM
- IMPACT of IMRT: unproven
- Hypothesis: breast cancer study showed linear increase of 7.4% in the rate of CAE for each additional gray of mean heart dose.
Management of Early (T1-T2) supraglottic SCC

- Radiotherapy
- TLM
- Transoral Robotic surgery
- Supraglottic Laryngectomy in selected cases

All valid therapeutic options

Similar OS and LC, HOWEVER NO RANDOMISED DATA!

RICH LYMPHATIC SUPPLY

→ SIGNIFICANTLY HIGHER RISK OF NODAL DISEASE COMPARED TO EARLY GLOTTIC SCC
→ ELECTIVE TREATMENT OF AT LEAST BILATERAL LEVEL II AND III (either with RT or selective neck dissection) is recommended
Radiotherapy for early glottic/supraglottic SCC

Side Effects

Acute

• Progression of hoarseness
• Fatigue
• Mucositis
• Thick, sticky secretions
• Odynophagia
• Skin reactions

Resolution of toxicity 4 to 6 weeks post completion

Long Term

• Very rare significant late effects for early glottic
• Xerostomia

Radiation Vasculopathy in H&N pts treated with RT
Management of locally advanced disease

Organ preservation with CRT >30y of clinical trial experience

Preserve function QoL

staging, PS, Comorbidities, preexisting function

Laryngectomy: physiological and psychosocial implications

Current standard: CRT, however careful selection of patients is paramount!!

Evidence?
• VALCSG Study: IC+RT vs S → RT
  Similar 2y OS: 68% vs 64%

LARYNGEAL PRESERVATION 64%

More local recurrences but fewer DM in the ICT arm
**Design:** RCT

- CRT vs IC+RT vs RT
- Laryngeal preservation at 3 y superior in CRT (88 vs 75 vs 70% respectively)

<table>
<thead>
<tr>
<th></th>
<th>induction</th>
<th>CRT</th>
<th>RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Larynx Preservation</td>
<td>72 %</td>
<td>84 %</td>
<td>67 %</td>
</tr>
<tr>
<td>Laryngectomy free survival</td>
<td>43 %</td>
<td>45 %</td>
<td>38 %</td>
</tr>
<tr>
<td>OS</td>
<td>55 %</td>
<td>54 %</td>
<td>56 %</td>
</tr>
<tr>
<td>PFS</td>
<td>38 %</td>
<td>36 %</td>
<td>27 %</td>
</tr>
<tr>
<td>G3-4 during RT</td>
<td>38 pt</td>
<td>73 pt</td>
<td>42 pt</td>
</tr>
</tbody>
</table>
CONFIRMED BENEFIT OF CRT

CONCURRENT CRT ‘STANDARD OF CARE’ FOR NON SURGICAL MANAGEMENT OF ADVANCED LARYNGEAL CANCER
Radiotherapy for advanced laryngeal cancer: indications

CONCURRENT CHEMORADIOThERAPY:

Cisplatin
100mg/m2 d1, 22, 43 of RT
IMRT 65Gy/30#/6w

RADIOTHERAPY ALONE:

Altered fractionation regimens (accelerated and hyperfractionated):
improve LC compared to conventional, BUT don’t improve outcomes when combined or compared with CRT

- T2b - T3 glottic scc
- Most patients with T3 supraglottic scc
- T4: unless tumour invasion through cartilage or into soft tissues of the neck

where comorbidity precludes concurrent chemotherapy, cetuximab or surgery

Accelerated RT with hypoxia modification (nimorazole or carbogen/nicotinamide):
NIMRAD STUDY recruiting in UK
EVIDENCE FOR DOSE ESCALATION?

• **Accelerated RT (AFX):** shortening overall treatment time to avoid tumour cell repopulation

• **Hypofractionated RT:** Larger dose per fraction to increase tumour cell kill

• **Hyperfractionated RT (HFX):** same duration as standard radiation therapy with radiation divided into smaller doses and treatments are given more than once a day.
EVIDENCE FOR DOSE ESCALATION

RTOG 9003, PHASE III RCT
HFX, AFC-C, AFX-S VS SFX

Endpoint: LRC
- SFX: 70Gy/35#
- HFX: 81.6Gy/68#/2 daily/7w
- AFX-S: 67.2Gy/42#/6w with a 2 w rest after 38.4Gy
- AFX-C: 72G/42#/6w

ONLY HRT IMPROVED 5y OS
WORST TOXICITY IN AFX-C ARM


ARTDECO Phase III
Multicentre RCT
Dose escalation vs standard dose IMRT

65Gy/30# (2.167Gy), 54Gy/30# (1.8Gy) vs
67.2Gy/28# (2.4Gy)
56Gy/28# (2.0Gy)

Status: F-U
Radiotherapy for advanced laryngeal cancer: indications

**POST OPERATIVE RADIOThERAPY:**

- 60Gy/30#/6w

**CASES AT HIGH RISK OF LOCOREGIONAL FAILURE AND DISTANT METASTASIS**

- T3, T4 DISEASE
- LVI
- PNI
- Close Margins
- multiple N+

**POSTOPERATIVE CHEMO- RADIOTHERAPY :**

- Positive Margins, ECS

**RTOG 9501**, Cooper et al, 2004

- 459 pt with high risk SCC:
  - S → RT VS S → CRT
  - 2Y LC 72% VS 82%
  - NO DIFFERENCE IN OS
  - WORSE TOXICITY IN CRT

**EORTC22931**, Bernier et al, 2004
Radiotherapy for Advanced Laryngeal Cancer

• Technique: IMRT ...........

• Definitions: a focused type of 3D Conformal Therapy or high precision conformal radiotherapy. IMRT uses multiple beams, each with a nonuniform intensity profile to create dose distributions that can exquisitely conform to convex and concave structures alike.

“If you can’t explain it to a 6 year old, you don’t understand it yourself”

Albert Einstein
Well...
IMRT the basics...

- Can create radiation beams of different strengths
- Can shape RT beams more precisely: different doses of RT to different parts of treatment area so that dose to normal tissues is kept as low as possible

Requirements:
- More accurate definition of tumour and OARS → Structures not specified are not considered in the planning process and may absorb high dose
- Leakage and scattered radiation, more absorbed radiation outside PTV
- QA Process

Types:
- IMRT with static fields
- Dynamic IMRT
- Rotational therapy (IMAT or Tomotherapy)

Image Guidance-value in H&N patients
- Weight loss → decision to replan
- Tumour response
During the course of RT

Response

Replanning scan: initial plan vs replan

Radiotherapy Pathway

EACH STEP IS IMPORTANT!

Patient Positioning and Immobilization

Volumetric data acquisition

image transfer to the TPS

Plan Evaluation and QA

Target volume delineation/Inverse planning

Preparation: SALT, Dietetic review, Dental Assessment

Patient weekly review-toxicity assessment

Treatment/treatment verification as per departmental policy

Megavoltage portal imaging, planning KV, cone beam CT
Target Volume Delineation: What to include?

Definitive RT/CRT

**Step 1. Gross Tumour Volume** for primary (GTVp) and involved nodes (GTVn) on each CT slice

**Step 2:** GTV +1cm
Ensure contouring whole organ and GTV+Margin is well covered.
- **Include bilateral parapharyngeal spaces & retrostyloid nodes if II+**
- **CTVp +CTVn merged to form CTV1**

**Step 3:**
**CTV2:** nodal levels at risk of microscopic spread
(EORTC, GORTEC, RTOG / PARSPORT)

**Important considerations:**
- For Supraglottis extend sup border 2cm above CTV.
- Include the whole level of involved node
- If ECS, SMC included at that level.

**OARs:** SC, SC(PRV), Brainstem, Mandible, Parotids, Oral Cavity
Target Volume Delineation: What to include?

Postoperative RT/CRT

- Whole surgical bed
- Include tracheostomy site

**Dose:** CTV 60Gy: surgical bed and neck dissection sites

**OARs:** SC, SC(PRV), Brainstem, Mandible, Parotids, Oral Cavity
## CTV2- Nodal Irradiation

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>T2B/T3 GLOTTIC, N0</td>
<td>At least II,III,IV Bilaterally</td>
</tr>
<tr>
<td>T3 SUPRAGLOTTIC, N0</td>
<td>At least II,III,IV Bilaterally</td>
</tr>
<tr>
<td>T2B/T3 GLOTTIC N+</td>
<td>II-V Ipsilateral, II-IV Contralateral and ipsilateral Ib if II involved</td>
</tr>
<tr>
<td>T3 SUPRAGLOTTIC N+</td>
<td>II-V Ipsilateral, II-IV Contralateral and ipsilateral Ib if II involved</td>
</tr>
<tr>
<td>T4, N0</td>
<td>Bilateral II,III,IV,V&amp;VI</td>
</tr>
<tr>
<td>T4, N+</td>
<td>Bilateral II,III,IV,V&amp;VI</td>
</tr>
</tbody>
</table>

*Jones et al, The Journal of Laryngology & Otology, 2016, 130, s75-s820*
Dose/fractionation

Definitive / concurrent CRT

CTV1 → HIGH DOSE VOLUME
65 Gy, 30 fractions over 6 weeks
(RADIOBIOLOGICAL EQUIVALENT TO 70 Gy/35#

CTV2 → LOW DOSE VOLUME
54 Gy, 30 fractions over 5 weeks
(PARSPORT/COSTAR REGIMENS)

Altered fractionation not used outside clinical trials

Postoperative RT/ concurrent CRT

60 Gy/30#/6 weeks (ONE CTV)
66 Gy/30#/6 weeks CTV1 if macroscopic disease
60 Gy/30#/6 weeks CTV2 to the surgical bed
Treatment interruptions-prolongation of treatment: does it matter?

**A National Audit of Radiotherapy in Head and Neck Cancer**

N. D. James*, G. Robertson†, C. J. Squire‡, H. Forbes§, K. Jones§, B. Cottier§ on behalf of the RCR Clinical Oncology Audit Sub-committee

*Cancer Research UK Institute for Cancer Studies, Edgbaston, Birmingham; †Beatson Oncology Centre, Glasgow; ‡The Royal College of Radiologists, London; §National Cancer Services Analysis Team, Clatterbridge Centre for Oncology, Bebington, U.K.

**INTERRUPTIONS:**
- **1 day** interruption → 0.7-1.4% reduction in LC
- **7 day** interruption → 14-20%

MAJORITY WERE PREDICTABLE → *Departmental policies advised*
Treatment interruptions

3.1 Category 1

Patients with the tumour types for which there is evidence that prolongation of treatment affects outcome, and who are being treated radically with curative intent. The data reviewed\(^9\) show very strong evidence that prolongation of overall treatment time affects treatment outcome or local tumour control (cure rates) in patients with the tumours listed below.

Any audit of this category of patient – departmental or national – should show that there was no prolongation of overall treatment time in excess of two days for at least 95% of the group.

3.1.1 External beam radiotherapy

Patients with the following tumours should not have their radical radiotherapy prolonged:

- Squamous cell carcinoma of the head and neck region\(^9,35,37,38,90\) (grade B recommendation on level 2\(^*\) evidence)
Side effects

**Acute**
- Mucositis
- Fatigue
- Odynophagia
- Xerostomia
- Dysphagia

**Long term**
- Xerostomia
- Dysphagia
- Necrosis
- Tube dependance

Toxicities managed in an MDT fashion (SALT, Dietetics, CNS)

Smoking cessation Clinics Recommended in the UK
PLANNED NECK DISSECTIONS? PET NECK STUDY

- PET CT surveillance in chemoradiotherapy complete responders obviates the need for neck dissection in patients with negative post treatment PET – CT scan.
Key Messages

• Radiotherapy is a reasonable treatment option for T1a/T2a glottic and T1-2 supraglottic carcinomas.

• Most patients with T2B-T3Glottic and T3 Supraglottic cancers are suitable for non-surgical larynx preservation management.

• Concurrent chemoradiation should be regarded as standard of care for non-surgical management of stage III/IV laryngeal cancer.

• T4 disease: larynx preservation should be considered unless invasion through cartilage or into soft tissues of the neck.
Key Messages

• Patients with N2/N3 neck disease with CR after negative post treatment PET CT do not require planned neck dissection
• Postoperative (chemo)radiation is recommended in the presence of advanced disease or adverse histological features.
• Role of IMRT is being investigated in the treatment of early glottic cancer (reduce dose to carotid arteries → reduce cerebrovascular events)
• IMRT: Standard of care for H&N cases treated with RT in the UK
• Altered fractionation may have a role and is investigated in clinical trials (+ with hypoxia modification)
Careful selection of cases is paramount!

“I still have my larynx, but I can’t breathe or eat properly…”
Thank you