# Management of Early carcinoma larynx and hypopharynx

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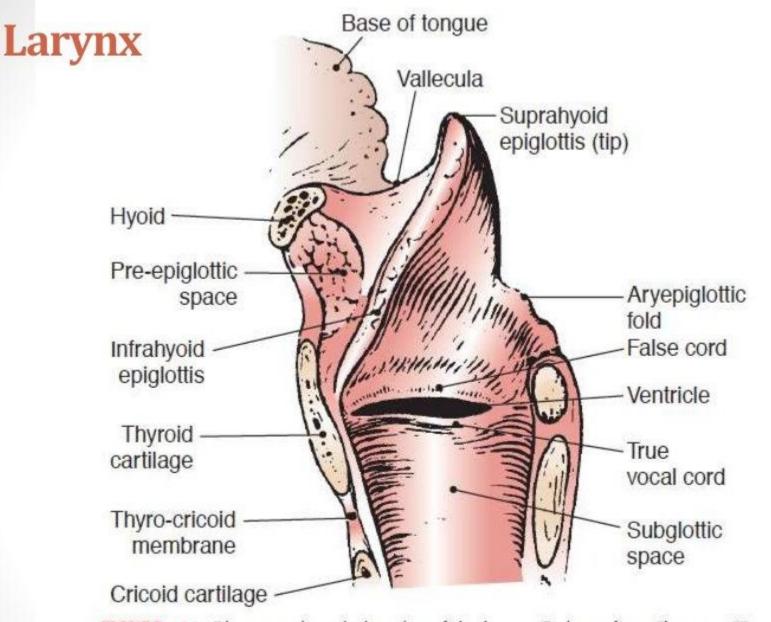


FIGURE 47.1. Diagrammatic sagittal section of the larynx. (Redrawn from Clemente CD. Anatomy: a regional atlas of the human body. Philadelphia: Lea & Febiger, 1975. Copyright Urban & Schwarzenberg, Munich, Germany, 1975.)

### Larynx

- It is the most common head and neck cancer
- At diagnosis :
  - 51% cases remain localized
  - 29% regional spread
  - 15% distant metastases
- Glottic : Supraglottic carcinoma = 3:1
- Glottic most common site is anterior portion of the cord
- Subglottic rare

### **CLINICAL PRESENTATION**

**Glottic** 

Early: hoarseness (true vocal cords)

Advanced: Sore throat, ear pain, pain localized to the thyroid cartilage and airway obstruction

Supraglottic –

Early: Pain on swallowing, sore throat, lump in the throat, Otalgia (Arnold's nerve : auricular branch of vagus)

Advanced: Halitosis, dysphagia and aspiration

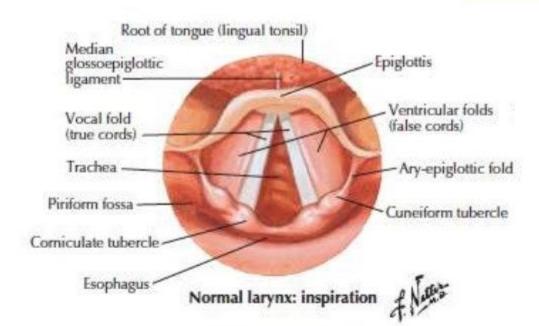
Subglottis

Airway obstruction

Hoarseness of voice

## Diagnostic Workup

- General
  - History
    - Smoking
    - Alcohol
    - Weight loss
    - Odynophagia/dysphagia
  - Physical examination
    - Laryngeal crepitus
    - Cervical lymph nodes
  - Indirect laryngoscopy
  - Direct laryngoscopy
  - Biopsy under GA
  - Blood investigations including CBC, KFT, LFT
  - Baseline TSH





## **Diagnostic Workup**

- Nutrition, speech and swallowing evaluation/therapy, and baseline audiogram as clinically indicated
- Dental evaluation
- Multidisciplinary consultation as clinically indicated
- Radiographic
  - Chest X-ray
  - X-ray Soft tissue neck
  - CECT (before biopsy) method of choice
  - MRI (selected cases) motion artifact
  - Pulmonary reserve in supraglottic cancers (ABG, PFT, CXR, walking two flights to assess tolerance to pulmonary stress)

- TO (No evidence of primary tumor) removed in 8<sup>th</sup> edition
- Supraglottis:

T category	T criteria		
Tx	Primary tumor cannot be assessed		
Tis	Carcinoma in situ		
T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility		
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx		
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage		
T4a	Moderately advanced local disease		
T4b	Very advanced local disease		

### Supraglottis:

T category	T criteria
T4a	Moderately advanced local disease  Tumor invades through the outer cortex of the thyroid cartilage and /or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

M category	M criteria
M0	No distant metastasis
M1	Distant Metastasis

### Glottis :

T category	T criteria	
Tx	Primary tumor cannot be assessed	
Tis	Carcinoma in situ	
T1a	Tumor limited to one vocal cord	
T1b	Tumor involves both vocal cords	
T2	Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility	
T3	Tumor limited to the larynx with vocal cord fixation and/or invasion of paraglottic space, and/or inner cortex of the thyroid cartilage	
T4a	Moderately advanced local disease  Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, cricoid cartilage, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)	
T4b	Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures	

### Subglottis :

T category	T criteria	
Tx	Primary tumor cannot be assessed	
Tis	Carcinoma in situ	
T1	Tumor limited to the subglottis	
T2	Tumor extends to vocal cord(s) with normal or impaired mobility	
Т3	Tumor limited to larynx with vocal cord fixation and/or invasion of paraglottic space and/or inner cortex of thyroid cartilage	
T4a	Moderately advanced local disease  Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)	
T4b	Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures	

## Lymphatic Spread

- Supraglottic carcinoma: level II-V nodes
  - incidence of clinically positive nodes 55% at the time of diagnosis; 16% are bilateral

#### Glottic :

- Incidence zero for T1 lesions
- Incidence <2% for T2 lesions</li>
- Incidence 20% to 30% for T3 and T4 lesions
- Supraglottic spread : level II nodes
- Anterior commissure and anterior subglottic invasion : pretracheal lymph node (level VI)
- Subglottic: 10% incidence; drain to pretracheal (Delphian), paratracheal, and inferior jugular nodes

# **Regional Lymph Nodes**

N category	Clinical N criteria (cN)	Pathological N criteria (pN)
Nx	Regional lymph nodes cannot be assessed	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE (-)	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE (-)
N2a	Metastasis in a single ipsilateral lymph node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE (-)	Metastasis in a single ipsilateral lymph node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE (-)  OR  Metastasis in a single ipsilateral or contralateral node, 3 cm or smaller in greatest dimension and ENE (+)

N category	Clinical N criteria (cN)	Pathological N criteria (pN)
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension and ENE (-)	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension and ENE (-)
N2c		Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension and ENE (-)
N3a		Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE (-)
N3b	Metastasis in any lymph node(s) with clinically overt ENE (+)	Metastasis in any lymph node(s) with clinically overt ENE (+) OR Metastasis in single ipsilateral node, larger than 3 cm in greatest dimension and ENE (+)

A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L)

AJCC Cancer Staging Manual, 8<sup>th</sup> ed.

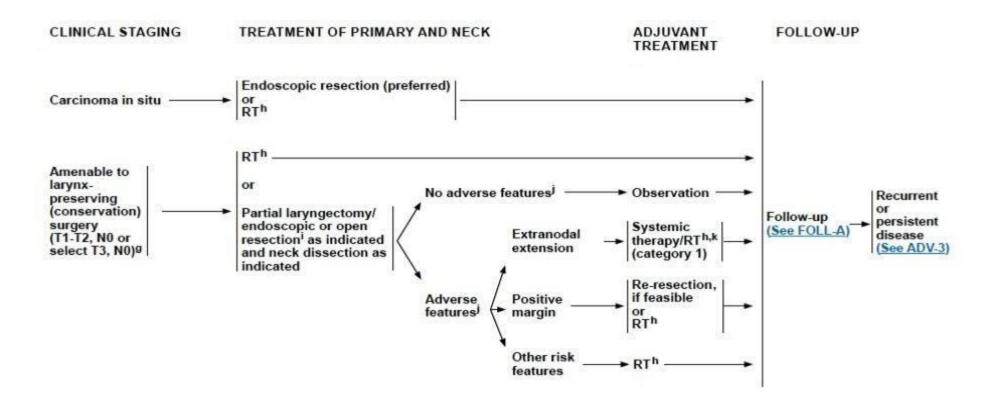
# **AJCC Prognostic Stage Grouping**

T	N	M	Stage	
Tis	N0	M0	0	
T1	N0	M0	1	
T2	N0	M0	II	
T3	NO	MO	III	
T1, T2, T3	N1	MO	III	
T4a	N0, N1	MO	IVA	
T1, T2, T3, T4a	N2	MO	IVA	
Any T	N3	MO	IVB	
T4b	Any N	M0	IVB	
Any T	Any N	M1	IVC	

### Treatment of Laryngeal Carcinoma

- Choice of treatment depends upon :
  - Local control rate (primary goal)
  - Voice preservation (secondary goal)
  - Fitness for surgery
  - Reliability of follow-up

## **NCCN**



CIS → ENDOSCOPIC RESECTION/RT

STAGE I/II→ RT(PREFERRED)/ SURGERY (PARTIAL LARYNGECTOMY)

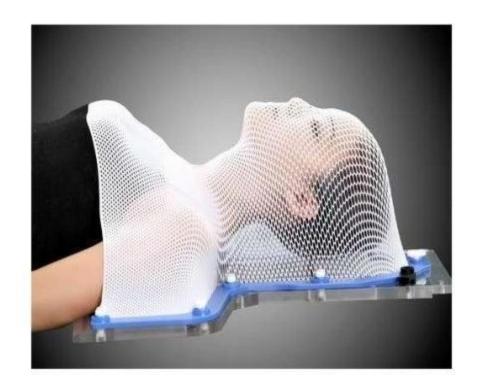
### **Vocal Cord Carcinoma**

- Carcinoma in situ: Endoscopic resection (CO<sub>2</sub> laser) > RT
- Early group: T1 and T2 lesions
  - High chances of cure with larynx preservation
  - Radical Radiotherapy preferred (better quality of the voice)
  - Cordectomy or Partial laryngectomy ± selective neck dissection (recommended for early verrucous carcinoma of the glottis)
  - 5 year survival rates 80-95%
  - Local recurrence : T1 (10-20%) and T2 (25-30%)

Surgery	Indication	Parts removed	
Cordectomy	Small lesion or early T1a lesion of middle 1/3 <sup>rd</sup> of vocal cord	Involved vocal cord	
Vertical partial laryngectomy	<ul> <li>Lesion of mobile cord extending to anterior commissure, i/l vocal process and anteriosuperior portion of arytenoid.</li> <li>Subglottic extension &lt; 5 mm.</li> <li>Fixed VC lesion not crossing the midline.</li> <li>Not involving more than anterior third of opposite cord.</li> </ul>	<ul> <li>Removes adjacent thyroid cartilage.</li> <li>Removal one TVC and up to 1/3 or 5mm of other TVC</li> </ul>	
Supracricoid partial laryngectomy (SCL)	<ul> <li>Selected T2 and T3 glottis disease</li> <li>Involving b/l post commissure only</li> <li>Lesion on mobile cord extending to ant. commissure</li> <li>Cord fixation in an otherwise T2 lesion</li> </ul>	Both true and false cords + entire thyroid cartilage     May remove the arytenoids	
Total Laryngectomy	<ul> <li>Lesions with transglottic or extensive         (&gt;1cm) subglottic extension</li> <li>Salvage for RT failure</li> </ul>	Total laryngectomy     + removal of     varying amount     of pharyngeal     wall	

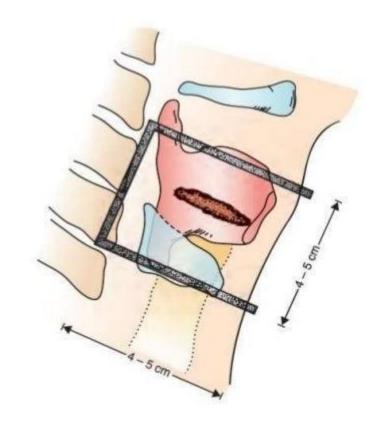
## Mould and scan

- Supine position with hands by side
- Head immobilized in neutral neck position
- Head and neck thermoplastic cast (S- frame)
- Use appropriate head rest
- Scan limit Base of skull to sterno-clavicular joint
- Slice thickness → 2mm-3mm



# 2D planning

- Treated with parallel opposed lateral wedged fields
- 15 degree wedge with heel anteriorly
- Field borders:
- T1 lesions → from the thyroid notch superiorly to the inferior border of the cricoid and fall off anteriorly
- Posterior border → 1-1.5 cm posterior to back edge of thyroid cartilage
- For T2 tumors, the field is extended depending on the anatomic distribution of the tumor.
- Field size :
- 4 × 4 cm to 5 × 5 cm (plus an additional 1.0 cm of "flash" anteriorly) and is occasionally 6 × 6 cm for a large T2 lesion



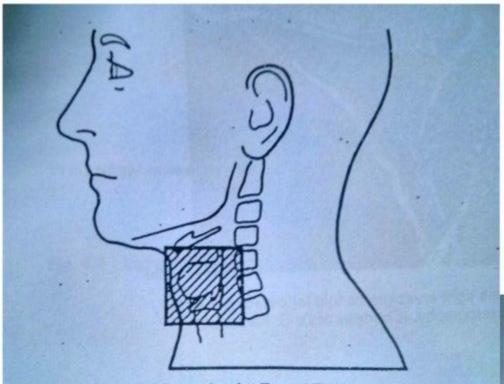


Fig. 4.4 Field margins for T<sub>1</sub> and T<sub>2</sub> glottic carcinoma.

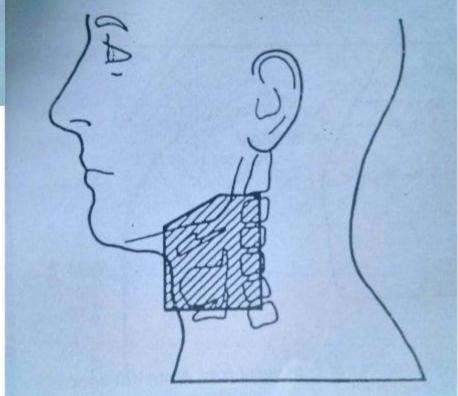


Fig. 4.5 Field margins for supra-glottic carcinoma

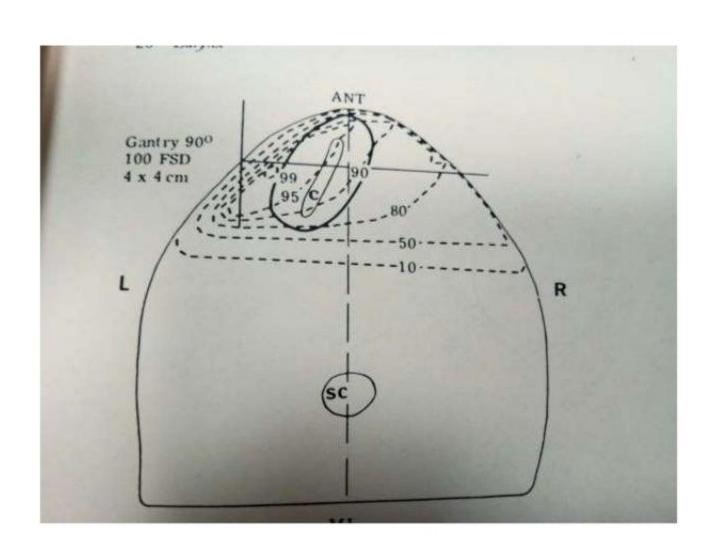
### Glottic larynx traditional field design.

# Lateral portal showing a field used to treat a T1 glottic carcinoma



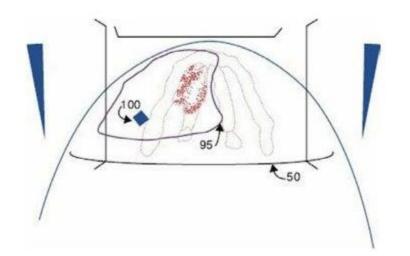
- Wedges can be removed to add hotspot in anterior region with an anterior bolus.
- For anteriorly placed tumours without involvement of the posterior vocal cord, posterior border can be moved anteriorly by 0.5 cm after a dose sufficient for subclinical disease (approximately 50 Gy for standard fractionation) is achieved.
  - To reduce arytenoid edema

# Single Lateral field technique for very early glottic carcinoma



# Technique for early glottis carcinoma: **3 field** technique

- ~90 95% dose is delivered through opposed lateral wedged fields weighted to the side of the lesion
- Remaining dose is delivered by an anterior field shifted 0.5 cm toward the side of the lesion
- In such cases, dose is usually specified at the 95% normalized isodose line.



Normalized isodose distribution for three-field technique for treatment of a tumor involving the anterior two-thirds of one true vocal cord. The dose is specified at the 95% isodose line.



### Dose and Schedules

#### T1 Glottic Cancer

- Conventional Fractionation: 66 Gy in 33# @ 2 Gy/#
- Hypofractionation<sup>1</sup>: 2.25Gy/#;
  - 63 Gy/28 fr/5.6 wk
  - 56.25Gy for Cis
- Smaller daily fractions should not be used as studies have suggested that they are associated with reduced local control rates.<sup>2,3</sup>

- Yamazaki et al. IJROBP 2006
- 2. Mendenhall et al, Cancer 2004
- Mendenhall et al, IJROBP 1988

### Dose and Schedules

#### T2 Glottic Cancer

#### Conventional Fractionation

70 Gy/ 35#/7 weeks @ 2 Gy/#

If level II-III nodes included 54 Gy to larger field with smaller field covering larynx only upto 70 Gy

### Hypofractionation 65.25Gy/29# @2.25Gy/#

### Hyperfractionated

79.2 Gy/ 66 #/6.5 weeks @ 1.2Gy/# bid)

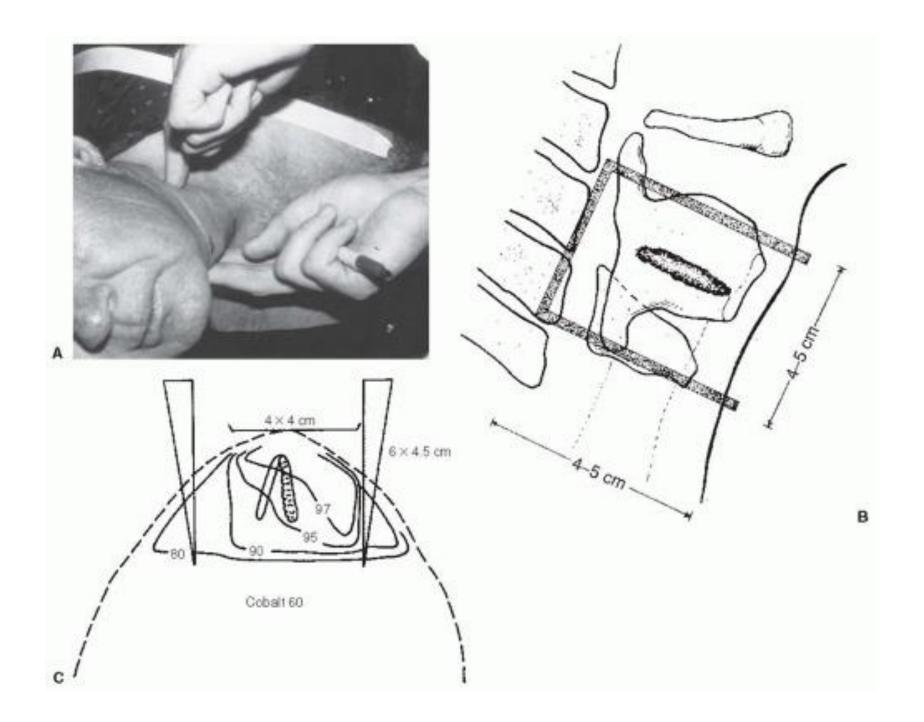
- May provide better sidease control
- No prospective evidence-based data
- 1. Garden et al, *IJROBP* 2003
- Yamazaki et al, IJROBP 2006
- 3. RTOG 95-12, *IJROBP* 2014

# Decubitus technique for early glottic carcinoma

- Patient treated in lateral decubitus "chicken wing" position with arm flexed at elbow and tucked under thorax
- The field is set up by physician at treatment machine each day according to palpable anatomic landmarks, and new lines drawn on the patient each day



The lateral decubitus is chosen because identification of posterior border of thyroid cartilage is easier than when patient is supine and the maximum lateral thickness of the patient is reduced



### **IMRT for Early Glottic Cancer**

Pros-

Potential normal tissue sparing:-

Carotid arteries-

Potential reduction in the incidence of CVA

Cons-

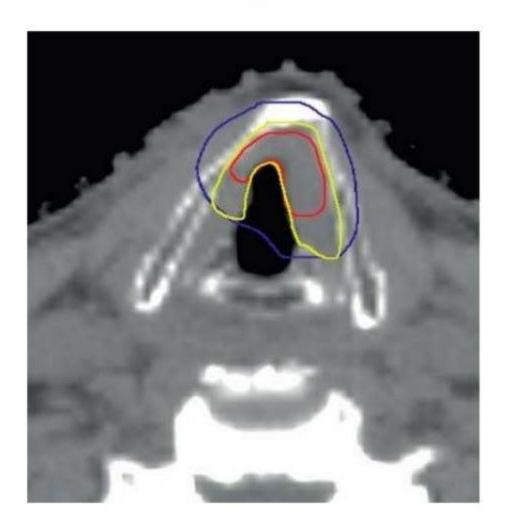
Results with IMRT uncertain –

Good results with conventional planning-

Severe complications rare - Target miss with IMRT

# Conformal Planning#

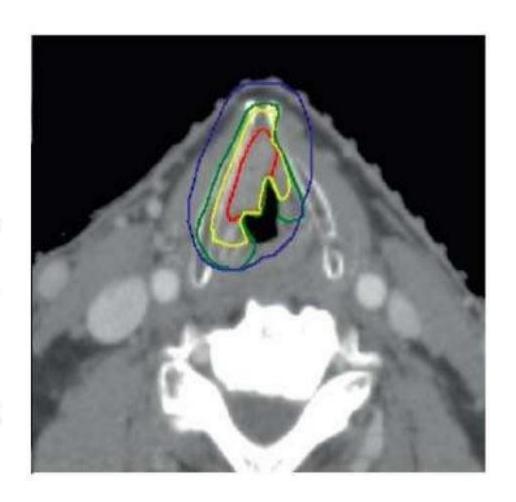
- ➤ T1
- GTV- P = All gross primary disease
- CTV-P1 = GTV-P + 5 mm in all directions.
- CTV-P1 include the paraglottic space, the anterior commissure for anterior vocal cord tumour, the anterior part of the contralateral vocal cord for tumour extending to the anterior commissure, and the vocal process of the arytenoid cartilage for tumour extending to the posterior vocal cord, but excludes the thyroid cartilage and the air cavity



**#→** GREGOIRE GUIDELINES

#### ➤ T2

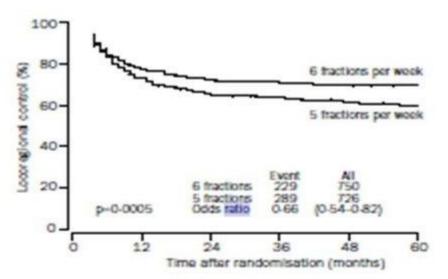
- CTV-P1 = GTV-P + 5 mm in all directions.
- CTV-P2 = GTV-P + 10 mm in all directions.
- CTV-P2 includes the paraglottic space, the anterior commissure, the anterior part of the contralateral vocal cord for tumour extending to the anterior commissure, and the vocal process of the arytenoid cartilage for tumour extending to the posterior vocal cord
- may include the thyroid cartilage in relation to the GTV-P, but excludes the cricoid cartilage



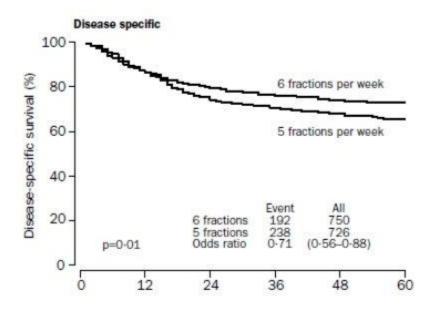


# DAHANCA 6 & 7 (2003): Five vs Six fractions a week in Head and Neck Cancer

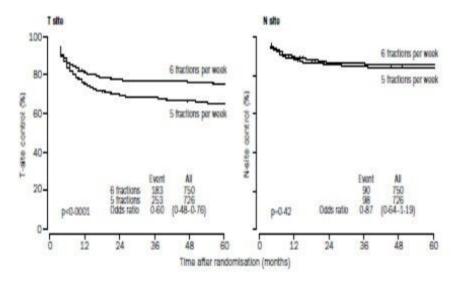
- To assess if shortening the OTT by pure acceleration (6#/wk) improves the tumour response compared to standard fractionation
- 1476 patients of glottic (690), supraglottic (218) and other sites (568) with 29%, 25%, 21% and 25% Stage I, II, III and IV disease.
- Comprising two subprotocols:
   DAHANCA 6, which included all glottic carcinomas, and DAHANCA 7, which included the rest.
- Primary end point: LRC
- Secondary end points:
  - Local T site and regional N site control
  - Voice preservation
  - Disease-specific survival
  - Overall survival
  - Treatment morbidity



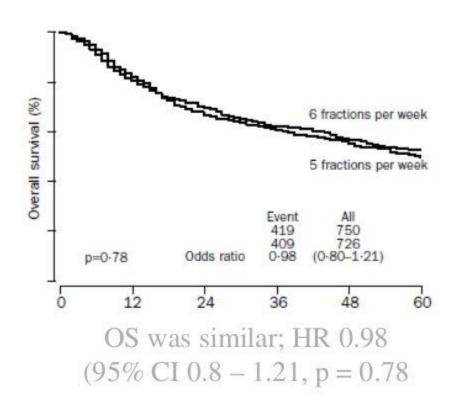
5-year **LRC**: 70% vs 60% for 6# vs 5#, p=0.0005



Disease-specific Survival: 73 vs 66% for 6# vs 5#, p = 0.01



Primary tumour control: 76 vs 64% for 6# vs 5#, p=0.0001





# Yamazaki et al (2006): Randomized trial in T<sub>1</sub>N<sub>0</sub>M<sub>0</sub> glottic Carcinoma

ARM	Tumor <2/3 of glottis (minimal disease)	Tumor >2/3 of glottis (> minimal disease)
A1 (n=31)	60 Gy/30#/6 wks	
A2 (n=57)		66 Gy/33#/6.5 wks
B1 (n=31)	56.25 Gy/25#/5 wks	
B2 (n=61)		63 Gy/28#/5.6 wks
N = 180		

#### Results

- The 5-year local control rate for the entire group was 86%
  - 76% for Arm A vs 92% for Arm B (p = 0.004)
- Treatment toxicity was not significantly different between the two arms.

### Conclusion

- The 2.25-Gy/fraction scheme with a shorter overall treatment time is superior to 2 Gy/fraction for local control of Stage T1 glottic carcinoma.
- No difference was found between the two arms in terms of OS (87% for Arm A, 88% for Arm B) or cause specific survival (98% for Arm A and 100% for Arm B).



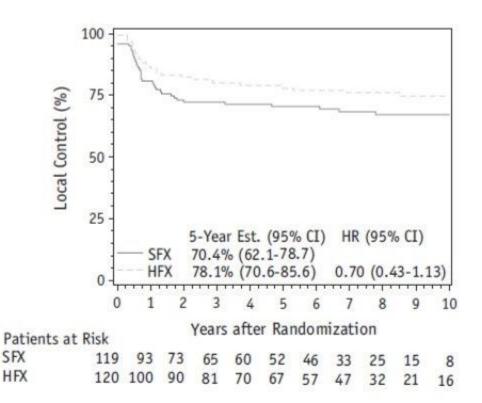
### RTOG 95-12 (Trotti, 2014): Randomized trial in T2 Glottic Carcinoma

- 250 patients, randomized into
  - Standard Fractionation Arm (SFX)
     70Gy / 35# (2Gy/#, once daily, 5 days/wk, 7 wks)
  - Hyperfractionation Arm (HFX)
     79.2Gy / 66# (1.2Gy/#, twice a day, 5 days/wk, 6.5 weeks)

### Results

- Similar Grade 1 and 2 acute toxicities in both arms
- Higher acute grade 3 toxicity with HFX than with SFX (33.3% vs 22.7%; p=0.084), but no difference in late grade 3 toxicity at 5 years (8.5% in both arms).
- Primary end point: Local control at 5 years was 70% vs 78%, p = 0.14.
- Locoregional control was 67% vs 73% (HR 0.77, p = 0.26).

	Once a day RT (n=119)	Twice a day RT (n=120)	
Local control	70%	78%	P=.14; HR=0.70
Local-regional control	67%	73%	P = .26, HR = 0.77
Disease-free survival	40%	49%	P = .13; HR = 0.79
Overall survival	63%	72%	P = .29; HR = 0.82



5 year local control

#### Conclusion

 The 5-year local control was modestly higher with HFX compared to SFX for T2 glottic carcinoma, but the difference was not statistically significant.

Trotti et al. Int J Radiat Oncol Biol Phys. 2014;89(5):958-63.

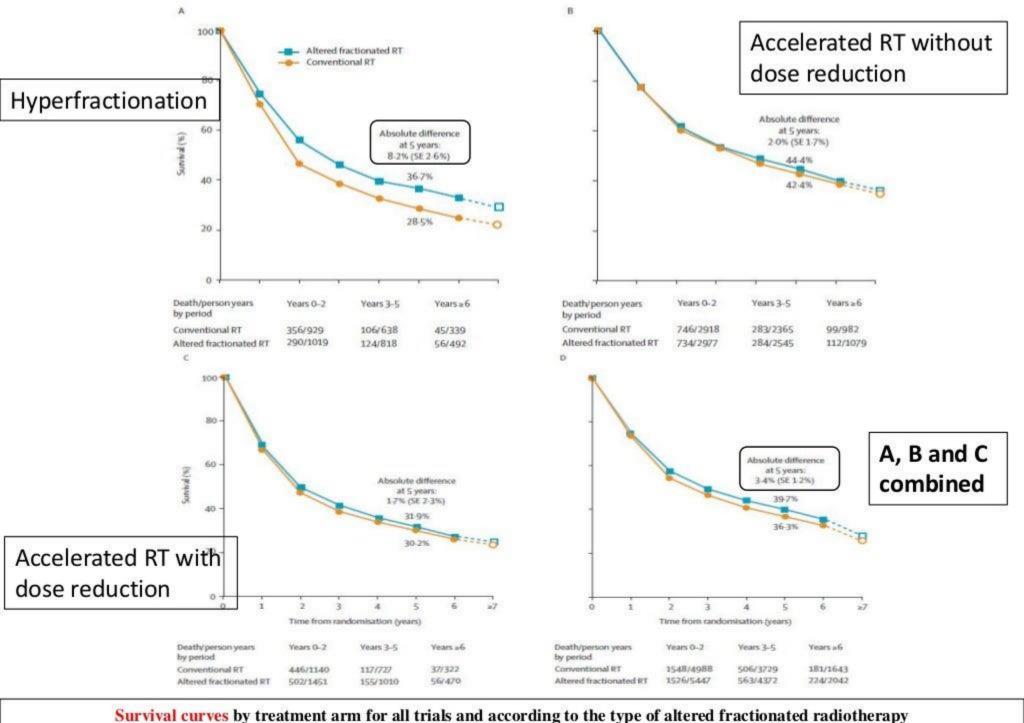
#### P

# MARCH Meta-analysis (2006): Hyperfractionated or accelerated radiotherapy

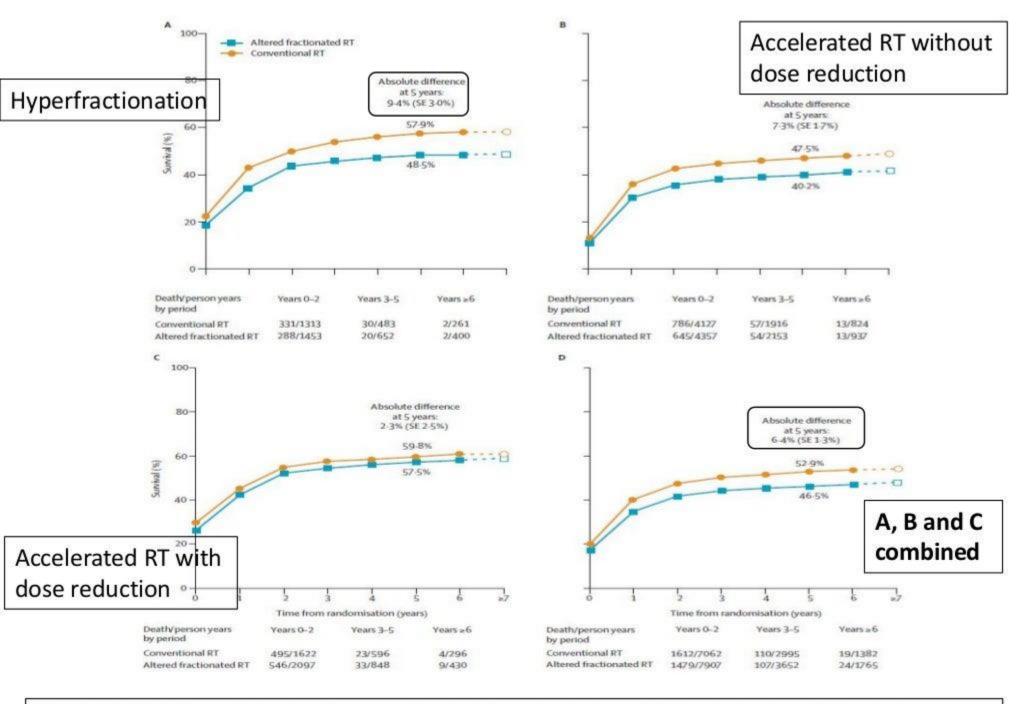
- 15 Randomized Trials of Varied Fractionation with 6515 patients (1970-1998)
- Mostly Oropharynx (44%) and Larynx (34%) patients
- Follow up from 4 to 10 years, median 6 years
- 74% stage III & IV disease

	Overall	Hyper- fractionation	Accelerated fractionation, same total dose	Accelerated fractionation, total dose reduced
OS Benefit	3.4%	8.2%	2%	1.7%
LRC Benefit	6.4%	9.4%	7.3%	2.3%

- Overall, 8% reduction in risk of death
- Survival benefit at 2 years -3.3%, at 5 yrs -3.4%



(A) Hyperfractionation. (B) Accelerated fractionation without total dose reduction. (C) Accelerated fractionation with total dose reduction. (D) All three groups together. The slopes of the broken lines from year 6 to year +7 are based on the overall death rates in the seventh and subsequent years



Locoregional control curve by treatment arm according to the type of radiotherapy(A) Hyperfractionation. (B) Accelerated fractionation without total dose reduction. (C) Accelerated fractionation with total dose reduction. (D) All three groups together.

# Altered Fractionation: Summary

- In early Glottic Carcinoma, reducing the overall treatment time (OTT) provides good disease control and hypofractionated RT can be considered for this purpose. (Yamazaki, DAHANCA 6&7)
- In locally advanced disease, conventional fractionation is still the norm though there is benefit from reduction in OTT by acceleration or hypofractionation (MARCH meta-analysis).
- Hyperfractionation is a valid option, but its adoption in a resource strained setting is difficult. (RTOG 90-03, MARCH)

Radiotherapy for early supraglottic cancer

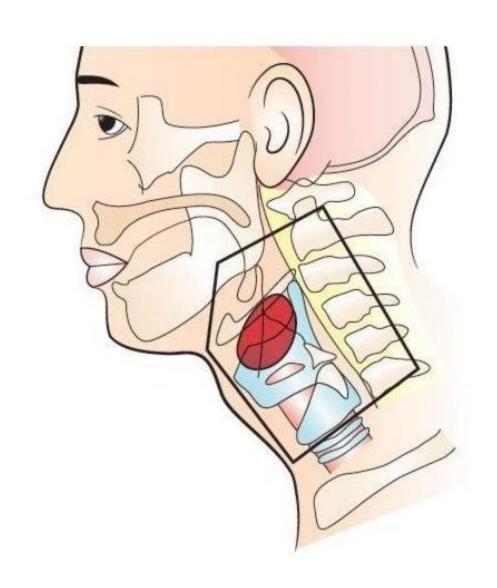
## General Principles

- 20-50% of T1-T2 Supraglottic cancer have +L.N so objective is to cover both the primary and clinical/subclinical disease in the Levels II and III cervical nodal beds.
- Shrinking field technique with off cord ± GTV boost (2 or 3 phases)
- For extensive supraglottic disease 3 Field technique used
  - 2 lateral field + matched LAN field to cover the low anterior nodes (i.e. levels I - IV)
- Gross nodal disease in the post neck to be bossted with 6–9 MeV electrons after off cord done at 45Gy.

# 2D planning

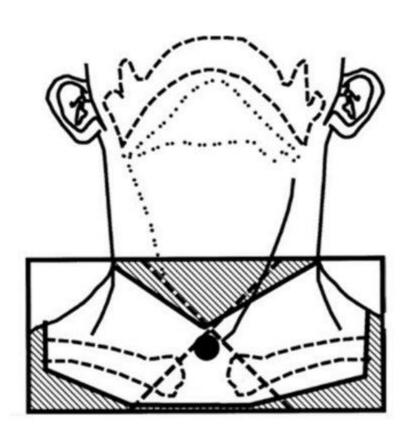
- The primary lesion and both sides of the neck are treated with opposed lateral portals.
- 15 degree wedges are used to compensate for the contour of the neck
- The lower neck nodes are irradiated through a separate anterior portal
- Field borders:
- Superior → superior to mandibular angle
- Inferior → bottom of cricoid cartilage
- If Subglottic extension is present, shoulders should be pulled down as much as possible.
- Anterior → 0.5–1 cm skin fall-off to neck and one-third of mandible
- Posterior 

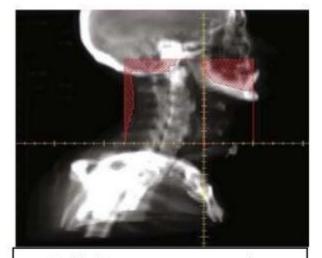
   Usually spinous processes



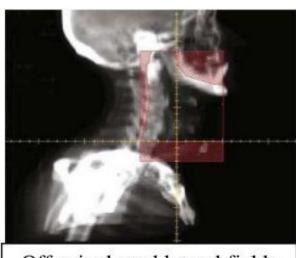
#### Low anterior neck field

- **Superiorly**: Match with the inferior borders lateral field
- Laterally: at junction of medial 2/3<sup>rd</sup> and lateral 1/3<sup>rd</sup> of clavicle
- Inferiorly: 1cm below clavicle

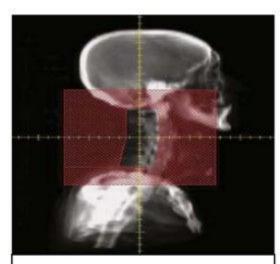




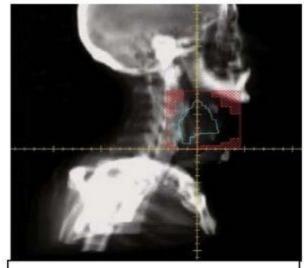
Initial treatment portals: Lateral opposed fields



Off spinal cord lateral fields



Post. neck boosted with matched electron-beam

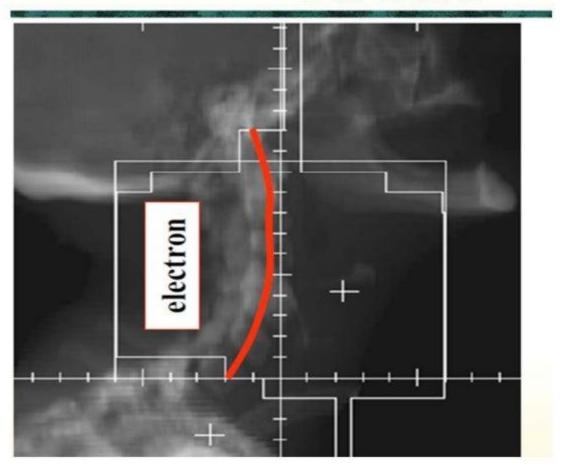


Final boost fields to the tumor with a margin.



SCF field matched to the upper neck (lateral) fields

## Off Cord



# **Final Boost**

# Dose and Schedules

#### **Standard fractionation:**

- 70 Gy in 35 fractions over 7 weeks to gross disease
- 50 Gy to subclinical disease.

#### **Altered fractionation:**

- **Hyper fractionated:**76.8 Gy/1.2Gy/#
- Concomitant boost :72 Gy/42 fractions/6weeks
  - 54 Gy/30#/6weeks @ 1.8 Gy/#/day to larger field
  - 1.5 Gy/#/day boost field given 6hrs later for the last 12 treatment days



Radiologically enlarged retropharyngeal nodes (%)  Clinical presentation  N- N+			1 :	Pathologic nodal metastasis (%)									
	Let N-	vel I N+	Lev N-	el II	Leve N-	el III	Lev	el IV	Lev N-	rel V			
Larynx		23.1		***	1	3*10.11	41	5,430.00	11	11,1		-1,	
Supraglottic larynx Glottic larynx	0	4	6	2 9	18 21	70 42	18 29	48 71	9	17 24	2 7	10	

## Role Of IMRT In Laryngeal Cancer

- IMRT is not recommended for T1–2, N0 glottic cancers, but may be considered for more advanced lesions
- The most common indications for IMRT for laryngeal cancers would be patients with a node-positive T3-T4 cancer, where the retropharyngeal nodes would be electively irradiated.
- Extensive subglottic invasion, where achieving an difficult to achieve adequate inferior margin with conventional lateral portals.
- Advantages:
  - Dose to the contralateral parotid gland can be reduced
  - Can circumvent a difficult low match between the lateral fields and the LAN field in a patient with a short neck and large shoulders.
- · Carotid sparing IMRT only in selected cases

#### Fractionation schedule in IMRT

#### Simultaneous integrated boost (SIB)

- in 35#: GTV = 70Gy/35#, CTV1 = 63Gy @ 1.8Gy/#, CTV2 = 56 Gy @ 1.6Gy/#.
- In 33#: GTV = 70Gy/33# @ 2.12Gy/#, CTV1 = 59.4 Gy @ 1.8Gy/#, CTV2 = 54Gy at 1.64Gy/#.

#### **Sequential** (2 or 3 phase planning)

• Initial lower-dose phase (weeks 1–5) followed by high dose boost volume phase (weeks 6 and 7) using 2-3 separate dose plans.

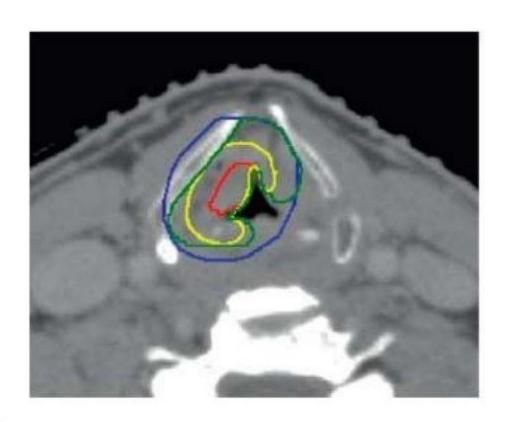
#### **Concomitant Boost schedule.**

 Delivers dose to subclinical targets once daily for 6 weeks, and a separate boost plan as second daily treatment during last 12 treatment days.

# Conformal Planning#

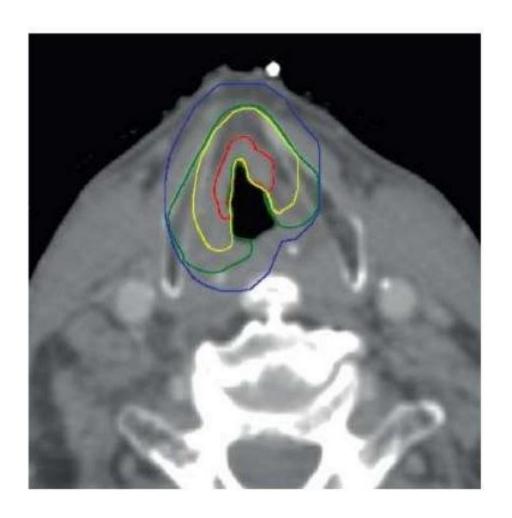
#### ➤ T1

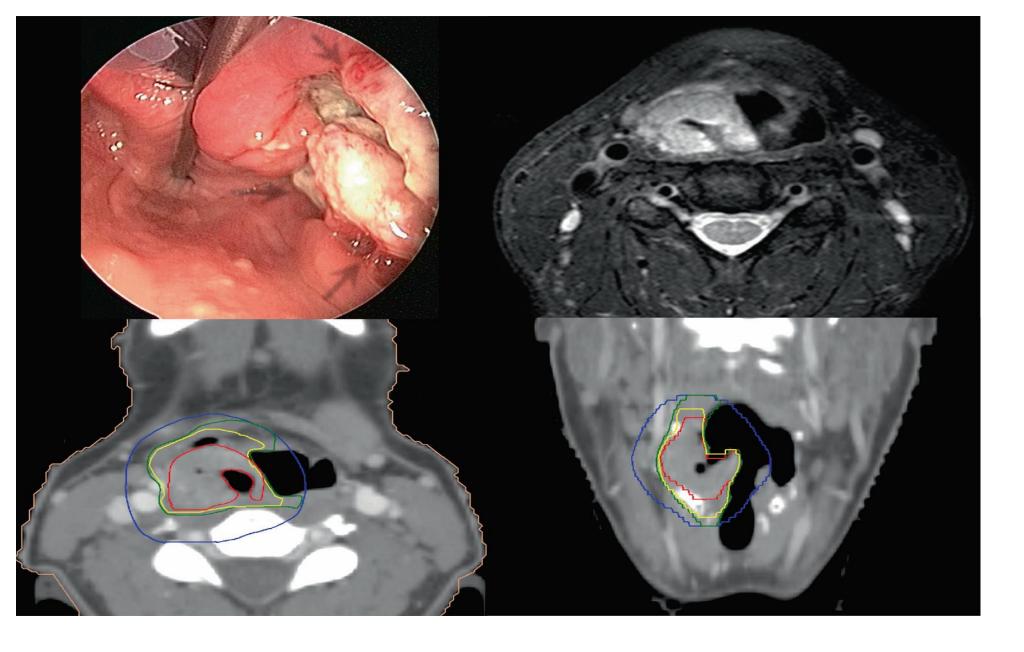
- GTV- P = All gross primary disease
- CTV-P1 (yellow) = GTV-P + 5 mm in all directions.
- CTV-P2(green) = GTV-P + 10 mm in all directions.
- CTV-P2 includes the pre-epiglottic space and the para-laryngeal space.
- Excludes the thyroid cartilage and the air cavity.
- Ventricle → CTV-P2 extend into the glottic area.
- Aryepiglottic fold and supra-hyoid epiglottis → CTV-P2 extend into the vallecula.
- Inter-arytenoid mucosa → it is recommended that the posterior pharyngeal wall is excluded from the CTV-P2



**#→** GREGOIRE GUIDELINES

- > T2
- CTV-P1 = GTV-P + 5 mm margin in all directions.
- CTV-P2 = GTV-P + 10 mm margin in all directions.
- CTV-P2 includes the pre-epiglottic space, the para-laryngeal space, thyroid cartilage
- Excludes strap muscles and the air cavities
- Ventricle → CTV-P2 extend into the glottic area.
- Aryepiglottic fold and supra-hyoid epiglottis >
   CTV-P2 extend into the vallecula.
- inter-arytenoid mucosa > it is recommended that the posterior pharyngeal wall is excluded from the CTV-P2





Endoscopic view (upper left), diagnostic axial contrast enhanced CT (upper right; arrows to delineate the tumour), and planning CT on axial (lower left) and coronal (lower right) reconstructions of a T4a (UICC 8th edition) SCC of the supraglottic larynx. The tumour originates from the infra-hyoid epiglottis and extends to both false cords caudally, and the anterior third of both ary-epiglottis folds cranially. The left true vocal cord is not infiltrated, while it is likely that the right true vocal cord is. On diagnostic CT-scan, the tumour invades the pre-epiglottic space and extends outside of the laryngeal structures. On the endoscopic view, the letters "A", "R", "L" and "P" indicate the anterior, right, left and posterior orientations, respectively. Arrows depict the tumour extension. The GTV-P is delineated in red. A 10-mm isotropic expansion is delineated in blue. The CTV-P2 is delineated in green after edition for air cavities, the cricoid cartilage and the anterior skin. The CTV-P1 is delineated in yellow

#### Doses and schedule

- Standard fractionation:
- 70 Gy in 35 fractions over 7 weeks to gross disease
- 50 Gy to subclinical disease
- Altered fractionation:
- Hyper fractionated:76.8 Gy with 1.2Gy/#
- Concomitant boost :72 Gy/42 fractions for 6weeks
  - 54 Gy/30#/6weeks at 1.8 Gy/#/day to larger field
  - 1.5 Gy/#/day boost field given 6hrs later for the last 12 treatment days

#### 3D Conformal RT: Delineation

- Gross tumor volumes (GTV) includes all known primary and cervical lymph node tumor extension based on clinical, endoscopic and imaging findings.
- Clinical target volume (CTV) –
- HRCTV: GTV is expanded to include a margin for microscopic extension forming high dose CTV
- IRCTV: optional. Includes area adjacent to GTV at high risk of having occult submicroscopic spread
- LRCTV: nodal regions at low risk for occult submicroscopic spread included in a low-risk CTV.

 Planning target volume (PTV): CTV is expanded with 3-7 mm margin to account for organ motion & setup error

### **Determination of CTV**

Based on incidence and location of metastatic node from larynx primary

Radiologically enlarged retropharyngeal nodes (%)  Clinical presentation N- N+	Radiolo	gically	anounon	or metasta	inc diseas		logic noda			eck nodes	i i	
	Lev N-	vel I N+	Lev N-	el II N+	Lev	el III N+	Lev N-	el IV	Lev N-	rel V		
Larynx Supraglottic larynx Glottic larynx	0	4	6	2 9	18 21	70 42	18 29	48 71	9	17 24	2 7	16

# Surgery for Supraglottic Carcinoma

Surgery	Indication	Parts removed
Supraglottic (horizontal partial) laryngectomy (SGL)	<ul> <li>Voice         preservation         surgery for early         supraglottic         lesion.</li> </ul>	<ul> <li>Removes epiglottis, AE folds, false cords, upper 1/3-1/2 of thyroid cartilage.</li> <li>Hyoid bone may be removed if epiglottic space involvement.</li> </ul>
Extended Supraglottic Laryngectomy (Extended SGL)	Supraglottic lesion     with     < 1 cm base of     tongue invasion	Same as SGL with removal of Ipsilateral BOT up to circumvallate papillae

#### **SURGERY**

Advantages: 1. Treatment in single sitting

- 2. Minimal absence from employment
- 3. Certainty of removal of specimen & ability to assess margin surgically
- 4. Allows further laryngeal surgery or radiotherapy in case of recurrence

#### Disadvantages:

- oAffect voice quality
- o Access sometimes difficult
- o Requires general anaesthesia & may need repeated operations for which patient may not be fit

#### SUB-GLOTTIC CARCINOMA

It should be understood that sub-glottic SCC represents less than 5% of the laryngeal SCC.

T1 tumour: CTV-P1 = GTV-P with a concentrically isotropic margin of 5 mm. CTV-P1 should always be delineated within CTV-P2.

CTV-P2 = GTV-P with a concentrically isotropic margin of 10 mm in all directions. The thyroid cartilage and the air cavity of the larynx are excluded. As the sub-glottic mucosa lies over

the cricoid cartilage, a margin extending e.g. 2 mm into the cricoid cartilage is adequate.

## Follow up

- Every 4 to 8 weeks for 2 years
- Every 3 months for third year
- Every 6 months for fourth and fifth year
- Annually for life
- Work up at each follow up :
  - History/physical examination
  - endoscopy or indirect mirror exam
  - Imaging of the neck (whenever patients develop new signs or symptoms suggestive of recurrence)
  - Imaging of the thorax recommended annually
  - TSH every 6–12 month if neck irradiated
  - Speech, swallow, dental, and hearing evaluations and rehabilitation as indicated
  - Smoking cessation counseling

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# **Treatment Sequelae**

- Edema of the larynx
- Mild sore throat
- Associated dry mouth
- Loss of taste
- Sensation of a lump in the throat

 Voice begins to improve approximately 3 weeks after completion of treatment, usually reaching a plateau in 2 to 3 months

#### Recurrence

- Most recurrences appear within 18 months, but late recurrences may appear after 5 years
- An increase in edema, particularly if associated with hoarseness or pain, suggests recurrence, even if there is no obvious tumor
- PET Scan may be useful to distinguish recurrent tumor from necrosis

# Management of Hypopharyngeal Cancers

#### INTRODUCTION

Hypopharyngeal cancers arise from the mucosa of one of the three anatomical subsites of the hypopharynx

.It is characterised by advanced disease at presentation mainly because the hypopharynx is a silent area, allows tumours to grow for a substantial period of time before symptoms occur.

Hypopharyngeal cancers are relatively rare neoplasms with unfavourable prognosis among all cancers.

Aggressive behaviour represented by strong tendency for submucosal spread

- Early occurrence of nodal metastatic involvement.
- Direct invasion of adjacent structures in the neck and high incidence of distant metastases.
- O 30% of patients have local disease at the time of diagnosis.
- 70% have local regional disease.
- 10% present with distant metastases.

# Hypopharynx

Pyriform sinus

65 - 75 % cases

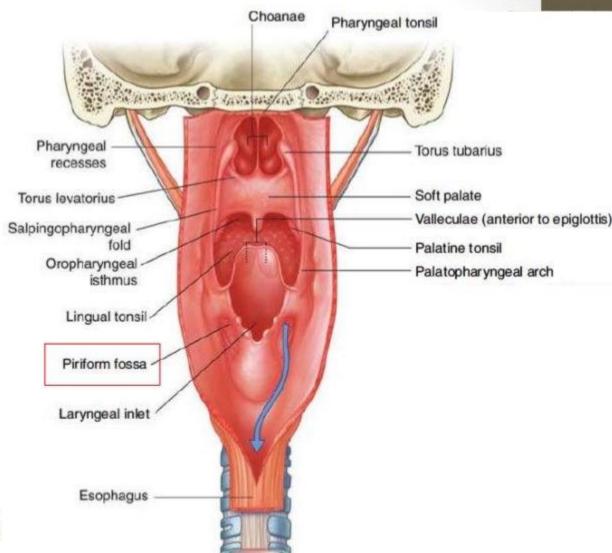
Post cricoid region

5- 15 %

Post pharyngeal wall

10% - 20%

HPV positive in 20-25 %



#### **Clinical Presentation**

- Neck mass
- Change in Voice Quality
  - "hot potato" voice may be due to the involvement of the base of tongue.
- Persistent Sore throat
- Unilateral Otalgia (Arnold's nerve : auricular branch of vagus)
- Weight Loss
- Dysphagia
- Aspiration
- Plummer Vinson Syndrome :
  - iron-deficiency anemia
  - hypopharyngeal webs
  - weight loss
  - dysphagia

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# Diagnostic Workup

- General
  - History
    - smoking
    - alcohol
    - weight loss
  - Physical Examination
    - laryngeal crepitus (post cricoid extension)
    - Cervical lymph nodes
  - Indirect Laryngoscopy
  - Pan-endoscopy (direct laryngoscopy, bronchoscopy and oesophagoscopy)
  - Biopsy with frozen section under GA
  - Blood Investigations including CBC, KFT, TFT

# **Diagnostic Workup**

- Nutrition, speech & swallowing evaluation and audiogram as clinically indicated
- Dental evaluation
- Multidisciplinary consultation as clinically indicated
- Radiographic
  - Chest X-ray
  - X-ray Soft tissue neck
  - HRCT or MRI vocal cord fixation
  - Barium swallow
  - Chest CT (with or without contrast) as clinically indicated: recommended for advanced nodal disease to screen for distant metastases, and for select patients who smoke to screen for lung cancer

# **AJCC TNM Staging**

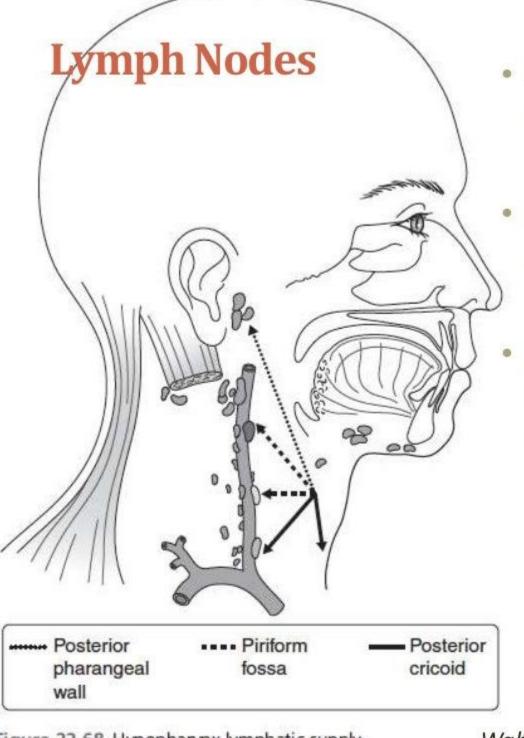
TO (No evidence of primary tumor) removed in 8<sup>th</sup> edition

T category	T criteria
Tx	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor limited to one subsite of hypopharynx and/or 2 cm or less in greatest dimension
T2	Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest dimension without fixation of hemilarynx
Т3	Tumor more than 4 cm in greatest dimension or with fixation of hemilarynx or extension to esophagus
T4a	Moderately advanced local disease
T4b	Very advanced local disease

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T category	T criteria
T4a	Moderately advanced local disease Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, or central compartment soft tissue (Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat)
T4b	Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

M category	M criteria
M0	No distant metastasis
M1	Distant Metastasis



 Pyriform sinus : Level II and III

Post cricoid region : Levels
 III, IV and level VI

 Post pharyngeal wall : Retropharyngeal nodes and deep cervical lymph nodes

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# **Regional Lymph Nodes**

N category	Clinical N criteria (cN)	Pathological N criteria (pN)
Nx	Regional lymph nodes cannot be assessed	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE (-)	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE (-)
N2a	Metastasis in a single ipsilateral lymph node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE (-)	Metastasis in a single ipsilateral lymph node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE (-)  OR  Metastasis in a single ipsilateral or contralateral node, 3 cm or smaller in greatest dimension and ENE (+)

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N category	Clinical N criteria (cN)	Pathological N criteria (pN)
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension and ENE (-)	
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension and ENE (-)	lymph nodes, none more than 6 cm in
N3a		Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE (-)
N3b	Metastasis in any lymph node(s) with clinically overt ENE (+)	Metastasis in any lymph node(s) with clinically overt ENE (+) OR Metastasis in single ipsilateral node, larger than 3 cm in greatest dimension and ENE (+)

A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L)

AJCC Cancer Staging Manual, 8<sup>th</sup> ed.

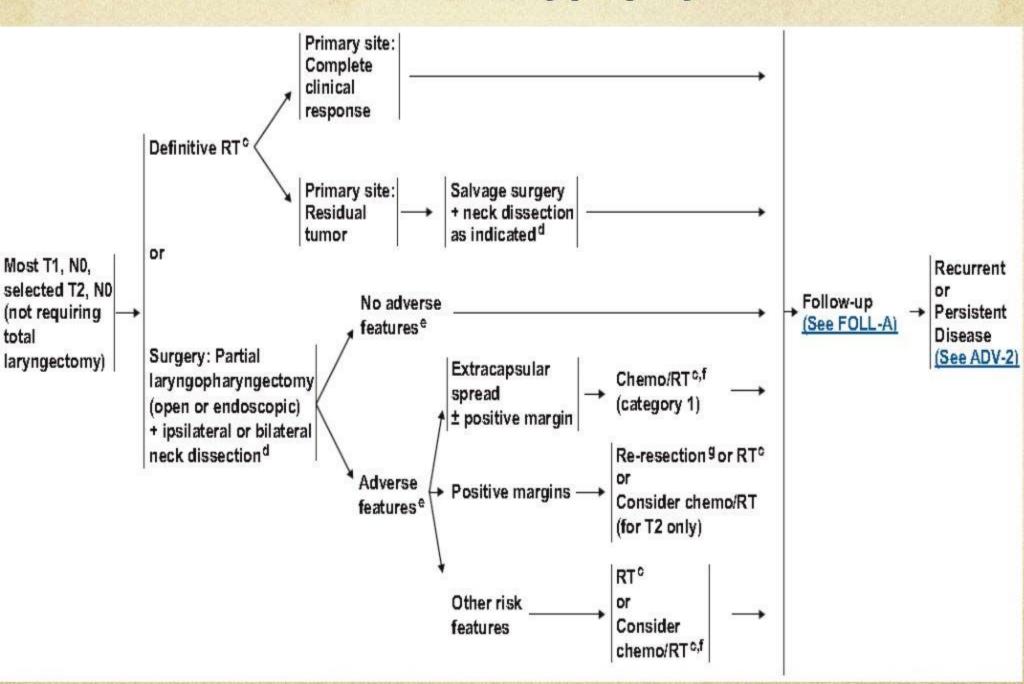
# **AJCC Prognostic Stage Groups**

T	N	M	Stage	
Tis	N0	M0	0	
T1	N0	M0	1	
T2	N0	MO	П	
T3	N0	MO	III	
T1, T2, T3	N1	MO	III	
T4a	N0, N1	MO	IVA	
T1, T2, T3, T4a	N2	MO	IVA	
Any T	N3	MO	IVB	
T4b	Any N	M0	IVB	
Any T	Any N	M1	IVC	

## **Field Cancerization**

- Carcinogens induce dysplastic changes throughout the mucosa
  of the upper aerodigestive tract, leading to an increased risk
  for field cancerization that enhances the likelihood of
  synchronous or metachronous secondary primary tumors
- Approximately 7% of patients with hypopharynx cancer will manifest a second primary tumor at initial diagnosis
- Between 10% to 20% will develop a secondary primary tumor over time

# **NCCN Guidelines Hypophyarnx**



#### NCCN Guidelines Version 2.2017 Cancer of the Hypopharynx

NCCN Guidelines Index Table of Contents Discussion

#### PRINCIPLES OF RADIATION THERAPY<sup>1,2</sup>

#### DEFINITIVE:

#### RT Alone

- PTV
- High risk: Primary tumor and involved lymph nodes (this includes possible local subclinical infiltration at the primary site and at the high-risk level lymph node(s))
  - Fractionation:
  - 66 Gy (2.2 Gy/fraction) to 70 Gy (2.0 Gy/fraction); daily Monday-Friday in 6-7 weeks3
  - 66-70 Gy (2.0 Gy/fraction; 6 fractions/wk accelerated)
  - 69.96 Gy (2.12 Gy/fraction) daily Monday-Friday in 6-7 weeks4
  - Concomitant boost accelerated RT: 72 Gv/6 weeks
  - (1.8 Gy/fraction, large field; 1.5 Gy boost as second daily fraction during last 12 treatment days)
  - Hyperfractionation: 81.6 Gy/7 weeks
    - (1.2 Gy/fraction, twice daily)
- Low to intermediate risk: Sites of suspected subclinical spread
  - 44-50 Gy (2.0 Gy/fraction) to 54-63 Gy (1.6-1.8 Gy/fraction)<sup>5</sup>

#### CONCURRENT CHEMORADIATION: 6,7

- PTV
- High risk: typically 70 Gy (2.0 Gy/fraction)
- Low to intermediate risk: 44-50 Gy (2.0 Gy/fraction) to 54-63 Gy (1.6-1.8 Gy/fraction)<sup>5</sup>

Either IMRT or 3-D conformal RT is recommended.

# Treatment of Hypopharyngeal Carcinoma

#### TABLE 19.6 General Treatment Recommendations for Hypopharyngeal Cancer

T1NO, T2NO not requiring laryngectomy Radiation alone or

Larynx-preserving surgery (open or endoscopic) with neck dissection ± postoperative radiation

T2N0 bulky and/or requiring laryngectomy Radiation alone (consider concurrent chemotherapy) or

Laryngopharyngectomy ± postoperative radiation

Resectable stage III and IV with functional Concurrent chemoradiation ± selective neck dissection or

laryngopharynx Induction chemotherapy followed by (chemo)radiation if response or surgery if no response or

Laryngopharyngectomy +postoperative (chemo)radiation

Stage III and IV with dysfunctional Laryngopharyngectomy with postoperative (chemo)radiation (preferred) or

laryngopharynx<sup>a</sup> Induction chemotherapy followed by (chemo)radiation if response or surgery if no response or

Concurrent chemoradiation ± selective neck dissection

Unresectable, nonmetastatic disease Concurrent chemoradiation ± selective neck dissection or

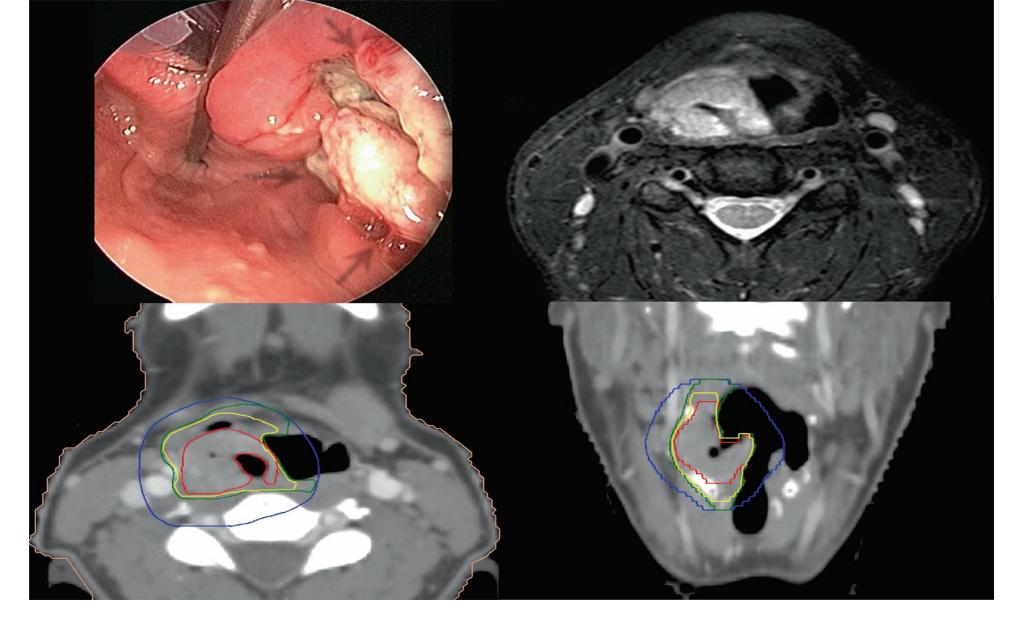
Induction chemotherapy followed by (chemo)radiation

Patients with bulky, destructive tumors that destroy cartilage, bone and deep soft tissue and/or severely compromise the airway are often best served with immediate surgery.

# Definitive RT in Pyriform fossa

#### T1 and T2 lesions with N0:

- Curative RT
- Upper margin : angle of mouth
- Lower margin: lower border of cricoid cartilage
- Posterior border: in front of spinal cord
- Boost volume includes primary tumor volume and grossly involved lymph nodes
- Parallel opposed lateral portals is used
- Patient is treated in supine position with neck straight



Endoscopic view (upper left), diagnostic axial T2 MRI (upper right), and planning CT on axial (lower left) and coronal (lower right) reconstructions of a T3 (UICC 8th edition; max diameter of 46 mm) SCC of the right piriform sinus. On the endoscopic view, the signs "\*" and "#" identify the right arytenoid and the posterior hypopharyngeal wall, respectively; the letters "A", "R", "L" and "P" indicate the anterior, right, left and posterior orientations, respectively. The arrows depict the tumour extension. The GTV-P is delineated in red. A 10-mm isotropic expansion of the GTV-P is delineated in blue. The CTV-P2 is delineated in green after edition for air cavities, the thyroid gland, vertebral bodies, the longus colli and longus capitis muscles, the hyoid bone and the sub-mandibular gland. The CTV-P1 is delineated in yellow

# **Definitive RT in Post Cricoid Region**

T1 and T2 lesion : Radical RT

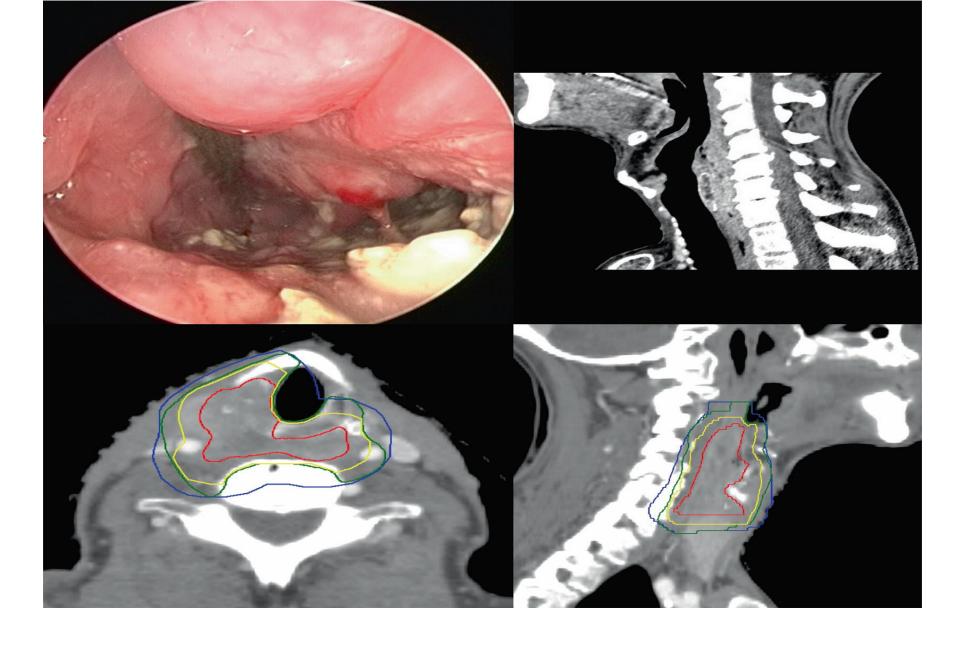
T3 and T4 lesion : CT-RT

 Target volume includes primary disease including inferior spread into the cervical esophagus and adjacent lymphatics

Patient is treated in supine position with neck straight

# Definitive RT in Posterior Pharyngeal Wall

- Target volume includes whole hypopharynx, bilateral deep cervical LNs and retropharyngeal space with 2 cm margins
- Patient is treated in supine position with neck straight



Endoscopic view (upper left), diagnostic sagittal CT (upper right), and planning CT on axial (lower left) and sagittal (lower right) reconstructions of a T4b (UICC 8th edition; infiltration of the pre-vertebral fascia; max diameter of 56 mm) SCC of the posterior wall of the hypopharynx extending from the level of the tip of the epiglottis to the pharyngo-oesophageal junction. On the sagittal diagnostic CT, the arrows depict the upper and caudal boundaries of the tumour. On the endoscopic view, the signs "#" and "T" identify the inter-arytenoid area and the tumour, respectively; the letters "A", "R", "L" and "P" indicate the anterior, right, left and posterior orientations, respectively. The GTV-P is delineated in red. A 10-mm isotropic expansion of the GTV-P is delineated in blue. In the cranio-caudal direction, a 15 mm cranio-caudal mucosal expansion has been used. The CTV-P2 is delineated in green after edition for air cavities, the left thyro-hyoid and sterno-thyroid muscles, the right sub-cutaneous tissues and part of the vertebral bodies. The CTV-P1 is delineated in yellow

## Doses and schedule

**Definitive: RT Alone** 

#### Standard Fractionation

- Gross disease : 66 to 70 Gy in 6-7 weeks at 2.2 2.0 Gy/#/day
- Subclinical disease: 44-50 Gy at 2 Gy/#/day to 54-63 Gy at 1.6-1.8 Gy/#

#### **Concomitant Boost**

- Total dose: 72.0 Gy/42 # over 6 weeks as 54 Gy in 30 # (1.8 Gy/#/day) to a relatively large field including subclinical disease
- -A second daily fraction at least 6h later 18.0 Gy/12# (1.5 Gy/#) to a small "boos field" for gross disease

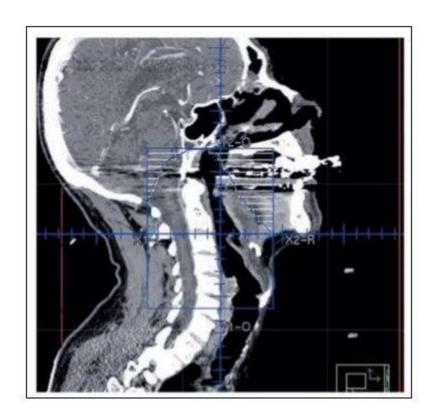
#### Hyperfractionation

- 81.6 Gy in 7 weeks at 1.2 Gy b.i.d.

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Disease site	CTV44
T 1/2 N0 pyriform fossa (confined to lateral wall)	Ipsilateral II–IV
T 1/2 N0 post cricoid /posterior pharyngeal wall	Bilateral II-IV. Include bilateral RP nodes if posterior pharyngeal wall involved
T3/4 N0 pyriform fossa	Bilateral level II-IV
T3/4 N0 postcricoid/posterior pharyngeal wall	Bilateral levels II-IV. Include bilateral RP nodes if posterior pharyngeal wall involved. Include level VI nodes if tumour extends into cervical oesophagus
Pyriform fossa N+	Bilateral level II-IV. Level Ib and V nodes on the side of any lymphadenopathy. Bilateral RP nodes if N2b/3 or if posterior pharyngeal wall involved
Postcricoid/posterior pharyngeal wall N+	Bilateral level II-IV, RP nodes. Level lb and V nodes on the side of any lymphadenopathy. Level VI nodes if tumour extends into the cervical oesophagus

# RT Techniques in Hypopharynx



# RT Techniques in Hypopharynx

- To allow for submucosal spread, the GTV is enlarged by 10 mm axially and 15mm longitudinally to form the CTV70
- The CTV70 is edited to take account of natural barriers to tumour progression and to include all sites of primary disease at presentation.
- For example
  - A pyriform fossa cancer invading the tongue base at diagnosis may respond to induction chemotherapy to leave residual tumour in the pyriform fossa alone
  - The tongue base should be included in the CTV70
- CTV is further edited to include sites of high risk nodal disease
- For N disease the CTV70 includes level II–IV nodes adjacent to the primary GTV, any involved nodes at other levels and any nodes in between

# RT Techniques in Hypopharynx

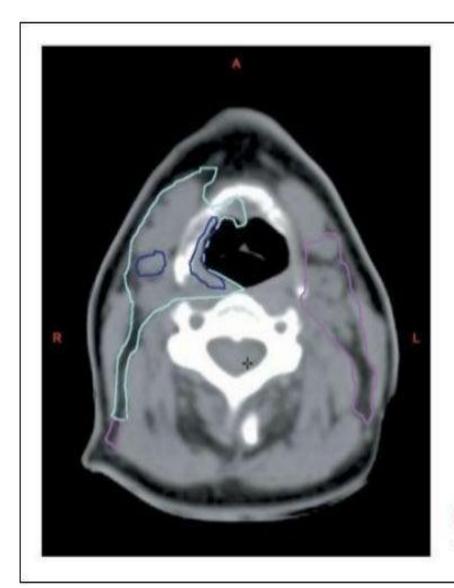
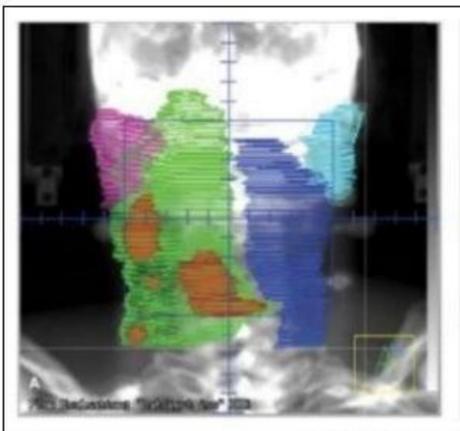
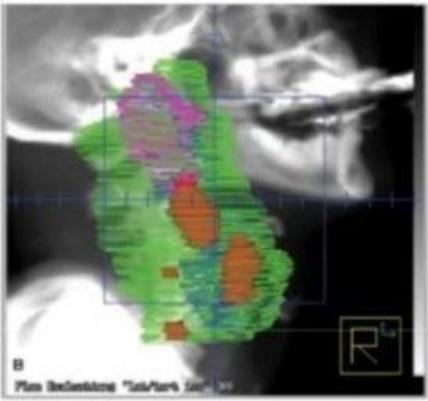
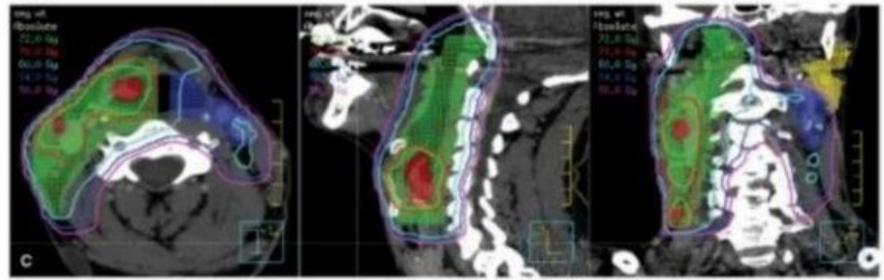


Figure 12.4 GTV, CTV70 and CTV44 for a T1N1 right pyriform fossa tumour.







## Doses and schedule

#### **Concurrent Chemoradiation**

- High Risk: 70 Gy at 2.0 Gy/#/day
- Intermediate to Low Risk: 44-50 Gy at 2 Gy/#/day to 54-63 Gy at 1.6-1.8 Gy/#

**Post op RT :** Preferred interval between resection and postoperative RT is ≤6 weeks

- High Risk: 60–66 Gy (2.0 Gy/# per day) in 6–6.5 weeks
- Intermediate to Low Risk: 44-50 Gy at 2 Gy/#/day to 54-63 Gy at 1.6-1.8 Gy/#

# Follow up

- Every 4 to 6 weeks for first 6 months
- Recommendations:
- Every 1 to 3 months for first year
- Every 2 to 4 months for second year
- Every 4 to 6 months for third to fifth year
- Every 6 to 12 months thereafter

# **Treatment Sequelae**

- Xerostomia
- Mucositis
- Radiation dermatitis
- Loss of taste
- Dysphagia
- Laryngeal edema
- Sensation of a lump in the throat

### Recurrence

- PET Scan is useful to distinguish recurrent tumor from necrosis
- Confirmed by Biopsy and restaged
- Most patients with recurrent disease are not good candidates for aggressive surgery or salvage radiation therapy and are best served with systemic chemotherapy or supportive care approaches

# Post-Treatment Follow-Up

 Follow-up is important because early detection of recurrence results in salvage that may include cure with voice preservation.

• The majority of recurrences will occur within the first 2 years and nearly all within 3 years (Fu et al. 2000; Forastiere et al. 2003, 2013).

 Patients are followed 1-2 monthly for the 1<sup>st</sup> year, 2-4 monthly for the 2<sup>nd</sup> year, 3-6 monthly for years 3-5 and annually thereafter.

# Work-Up at each follow up

- History/physical examination
- endoscopy or indirect mirror exam.
- Imaging of the neck (whenever patients develop new signs or symptoms suggestive of recurrence)
- Imaging of the thorax recommended annually.
- TSH every 6–12 month if neck irradiated.
- Speech, swallow, dental, and hearing evaluations and rehabilitation as indicated.
- Smoking cessation counselling.

### **Acute Effects**

- During RT or within 90 days of start of RT
- Hoarseness
- Sore throat
- Dysphagia
- Odynophagia
- Mucositis
- Skin pigmentation in radiation field

#### Late reactions

- Develop/persist more than 90 days after start of RT
  - Laryngeal oedema
  - Glottic stenosis
  - Xerostomia
  - Swallowing dysfunction
  - Pharyngeal stricture
  - Weight Loss
  - hypothyroidism

# TAKE HOME MESSAGE

Early stage larynx or hypopharynx treatment of choice is radiotherapy.

Radiotherapy is an effective means of larynx preservation without compromising survivals.•

Addition of chemotherapy provides better results for larynx preservation than RT alone (concurrent > NACT).

However the impact on survival is still unclear. specifically for early glottic cancers,

Hypofractionated RT can provide better outcomes in early glottic cancer.

# **Thank You**