

# Chemo-Radiation Therapy : Organ Conservation and Future strategies

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# Radiation Therapy for:

- Conservation in locally advanced cancers
- Conservation in early cancers
- Improving outcomes in the near future...

# Locally Advanced Cancers

Is there is an alternative to:



Total Laryngectomy is morbid...



## Modern surgical techniques have shown promising outcomes

- Single Centre
- Operator dependant
- Not tested in prospective RCT with standard comparators
- Not all studies have reported longer QOL
- Studies await longer follow up

# The alternative must be equal or better than Laryngectomy

## *Outcome*

Locoregional control

Disease free survival

Overall survival

## *Function*

(Is organ preservation possible?)

## *Cosmesis*

# Radiation for conservation: VA till now..

- VA study: IC ( 2+1 Cis-5FU) followed by RT after **chemo selection** versus total laryngectomy and post-operative RT.
- Non-partial responders received surgery after 2 IC
- 322 pts Pts with stage III and IV larynx cancer
- 2/3<sup>rd</sup> had supraglottic tumours
- 64% in IC arm had conserved larynx
- 30 patients received laryngectomy pre RT and 29 as salvage
- Decreased distant metastases with IC, more LR, similar OS



# VA study: When was salvage laryngectomy required?

- Glottic vs. Supraglottic carcinoma (43% vs. 31%)
- Fixed vs. mobile vocal cords (41% vs. 29%)
- Gross cartilage involvement vs. no cartilage involvement (41% vs 35%)
- stage IV versus III cancers (44% vs 29%)
- T<sub>4</sub> vs other T (56% vs 29%)

# EORTC 24891- Hypopharynx

- T<sub>2</sub> -T<sub>4</sub> , No-N<sub>2</sub> PFS, AEF
- Trial schema similar to VA (IC+RT vs S+RT)/ Salvage
- Dose of definitive RT standard 70GY (50Gy +20Gy)
- 58% of IC arm completed patients had conserved larynx at 5yrs
- DFS same (25 vs 27%) at 5 yrs; OS better for IC at 3yrs but similar at 5yrs and 10yrs (13.8 vs 13.1%)
- Fewer distant metastases with IC
- IC response related to T stage (T<sub>4</sub>-0%, T<sub>3</sub>-48%, T<sub>2</sub> 84%)

## RTOG 91 11: Laryngeal Cancers (No hypopharyngeal cancers)

- T<sub>2</sub>-T<sub>4</sub>(low volume and not going to more than 1cm in BOT)
- RT vs IC-RT vs CTRT
- Larynx Preservation at 10yrs (67.5% vs 63.8% vs 81%)
- DFS similar at 10yrs
- LC better (Larynx Preservation) with CTRT and lesser distant metastases with IC-RT

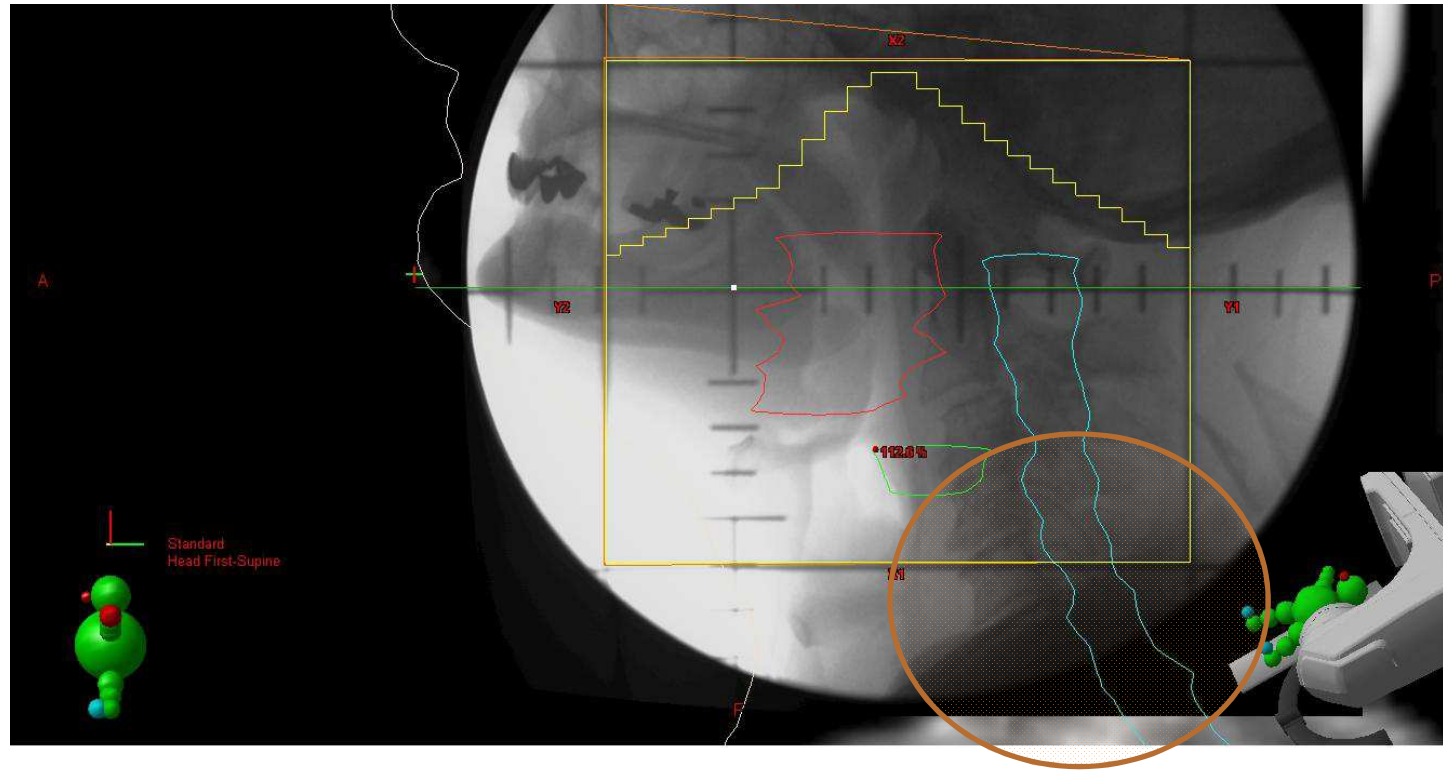
# RTOG 91 11

- Established CTRT as the new standard for Laryngeal Sq CA
- Increased toxicity compared to RT
- CTRT- Trend towards poorer OS (extra non larynx cancer related death)
- Differentiated between larynx preservation and Laryngectomy free survival rates (Speech/swallowing)
- No difference in Laryngectomy free survival between IC-RT vs CTRT although both were better than M

# EORTC 24954

- Clubbing Larynx and Hypopharynx together
- T2-4, No-2, who would otherwise need Laryngectomy
- 2 Cis/5FU IC + RT (70Gy) versus 4 Cis/5FU + RT as split course 3 phases 20Gy/10fr
- At 6.5yrs F/U- no difference in functional Larynx preservation
- Less acute toxicity in alternating arm (Dose related)

# Challenges with RT to the Larynx



# Image Guided radiotherapy

- What image guidance do we have now?

Isocentre check:

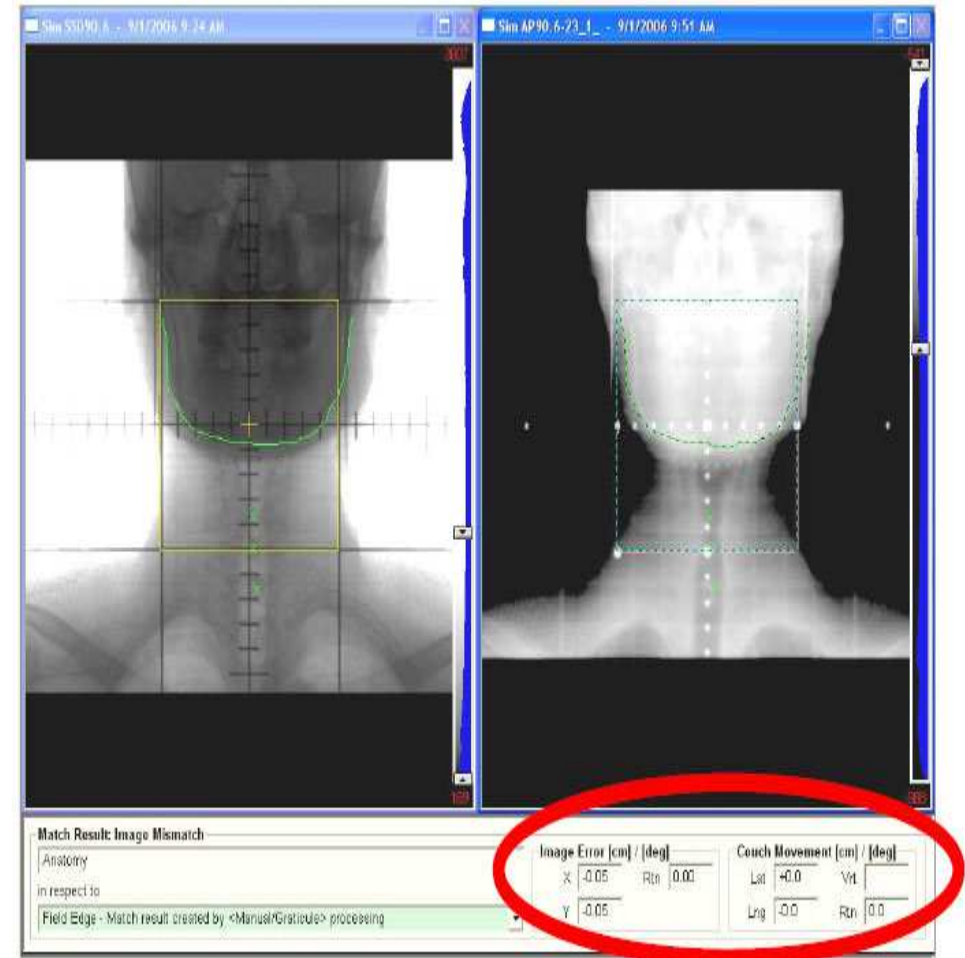
Good for 2D / 3D RT planning

2D images

Sup-Inf/ Lateral movements-

Matching on treatment

2 D images (Portal Images) to Pre treatment (Digitally reconstructed radiographs)



# Intensifying Induction chemotherapy: GORTEC 2000 01

- TPF versus PF as IC followed by RT  
(otherwise schema similar to the VA study)
- Larynx and Hypopharynx (n=223)
- But Functional preservation of Larynx was primary endpoint
  
- CR rates higher with TPF- 80% vs 50.2%
- 3yr Larynx preservation 70.3 vs 57.5%
- Functional preservation at 5 yrs 36 vs 28%



# Smaller Studies

- GETTEC group: S+RT vs IC +RT
- Larynx Only
- Worse DFS and OS in IC group: ? IC detrimental
- Small Study (n=68) – underpowered to conclude as above
  
- TAX 324 subgroup- n=123 (TPF vs PF and Carbo RT)
- TPF improved PFS and larynx-function survival compared to PF.
- lower risk of death with TPF: median survival 71m vs 27m (non significant)
- Trial not designed for Larynx conservation (Early Larynx Cancers also)

# TPF followed by CTRT

## TREMPLIN

- Phase 2 (n=153/116)

- 3 IC cycles (TPF):

Pts with response <50% had surgery,

>50% were randomized to RT + P vs. RT  
+Cetuximab

No difference in functional larynx preservation

P-RT more toxic and more B-RT salvage possible

?? Is there a trend that salvage is difficult post  
TOF and CTRT?

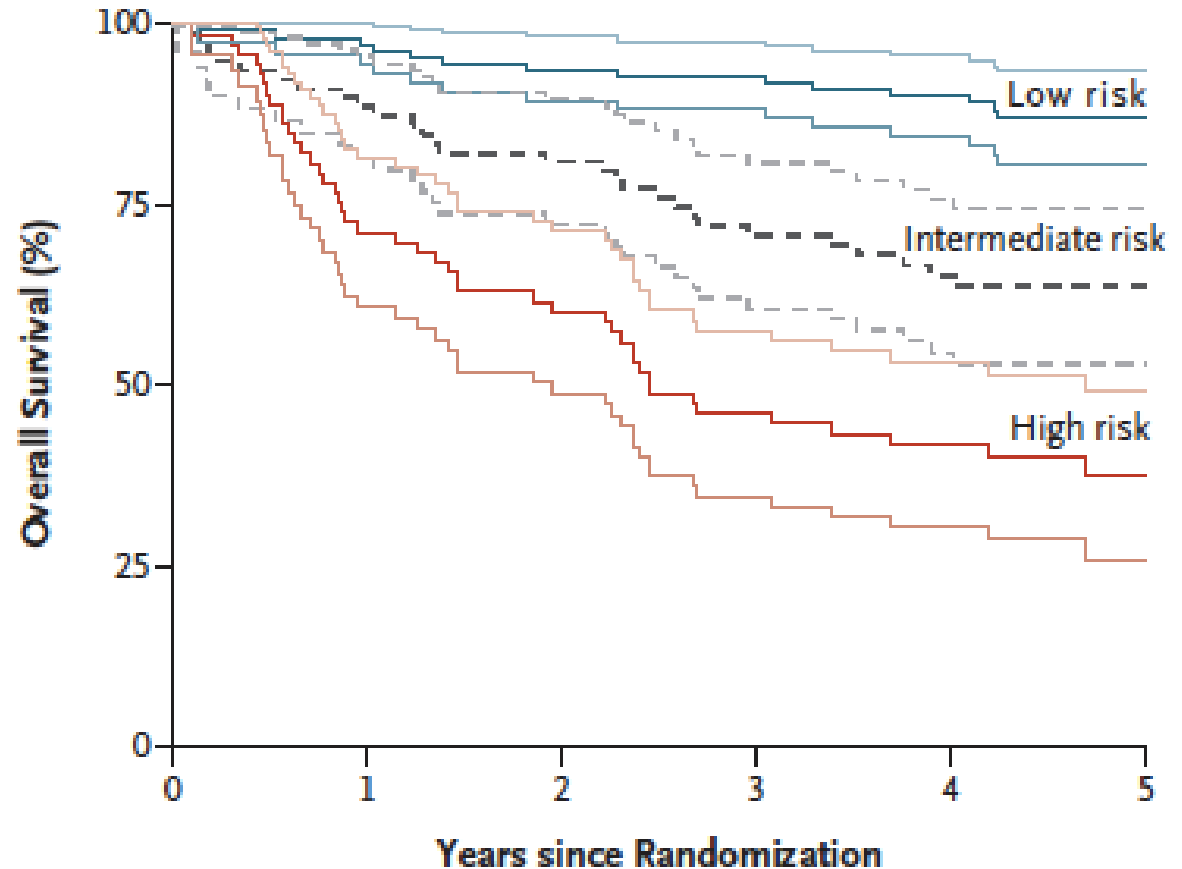
# Molecular Markers

- HPV not beneficial for Laryngeal/Hypopharyngeal cancers
- ERCC<sub>1</sub>
- Investigational

# Oropharynx

# RTOG 0129 OPC subgroup

- 433 (of 721 patients)- 60%)OPC
- 266 of these patients had Smoking status documented



# Biomarkers

- Smoking (Tobacco)
- HPV status

# Which group of patients do we deal with?

## Demographics

- Majority locally advanced
- Majority HPV negative

## Outcome of 100 CTRT patients

SITE	NUMBER (FREQUENCY)
OROPHARYNX	52 (43.3 %)
HYPOPHARYNX	20 (16.7 %)
LARYNX	48 (40 %)
<b>TOTAL</b>	<b>120 (100%)</b>

STAGE	NUMBER (FREQUENCY)
III	63 (52.5 %)
IVA	54 (45 %)
IV B	3 (2.5 %)
<b>TOTAL</b>	<b>120 (100%)</b>

SITE	OS %	DFS %
OROPHARYNX	82.7	80.8
HYPOPHARYNX	85	95
LARYNX	81.3	89.6
<b>OVERALL</b>	<b>82.5</b>	<b>86.7</b>

TMC data unpublished

# Strategies for escalation

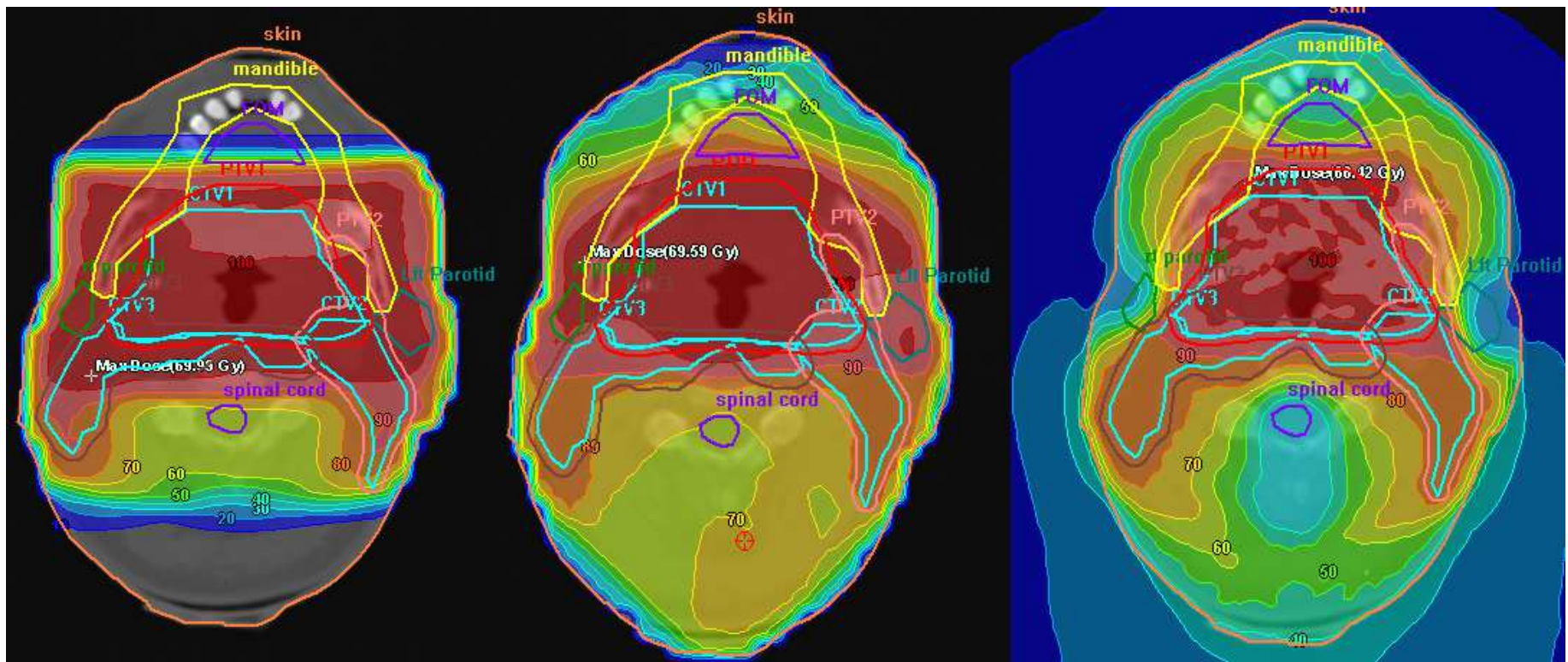
- Will our patients accept escalation?
- Adding more chemotherapy? Will this help?
- Accelerating and Hypofractionating
- Brachytherapy Boost (? Unlikely to work in Laryngeal cancers)



# The Future: Some Research and Development concepts.....

# Radiobiological Comparison of the different plans: TCP

## 2phase vs. single phase vs. Tomotherapy



# Escalating Radiation Dose

- Is there a need
- What do Indian patients feel?

# Study Methodology

## Inclusion criteria: (all of)

- Informed consent obtained
- Stage III/IV head and neck cancer patients - to be treated by CTRT
- Squamous cell carcinoma
- Non salivary gland primary

## • Exclusion Criteria: (any of)

- Previous radiotherapy
- Has had surgery first for the tumour
- Salivary gland tumour
- Is unable to read English, Bengali or Hindi.
- Patient is in such an emotional state that the treating oncologist feels taking part in the study will be detrimental to patient's psychological health

# What is the benefit that persuaded choosing CTRT versus RT?

Difference in cure %	Before Trt (1)		Completion of CTRT (2)		3 months post CTRT (3)		p-value		
	CTR	RT (%)	CTR	RT (%)	CTR	RT (%)	1-2	1-3	2-3
60% vs 60%	0	100	0	100	0	100	NS	NS	NS
65% vs 60%	83.3	16.7	30	70	46.6	53.4	S	S	S
70% vs 60%	96.6	3.4	76.6	23.4	76.6	23.4	S	S	NS
75% vs 60%	96.6	3.4	93.3	6.7	90	10	NS	NS	NS

# What is the benefit that persuaded choosing CTRT versus RT?

Difference in cure %	Before Trt (1)		Completion of CTRT (2)		3 months post CTRT (3)		p-value		
	CTR	RT	CTR	RT	CTR	RT	1-2	1-3	2-3
95% vs 95%	0	100	0	100	0	100	NS	NS	NS
95% vs 90%	<b>86.6</b>	13.4	57.8	42.2	50	<b>50</b>	S	S	NS
95% vs 85%	<b>96.6</b>	3.4	76.6	23.4	<b>76.6</b>	23.4	S	S	NS
95% vs 80%	100	0	93.3	6.7	96.6	3.4	NS	NS	NS

## How important a factor was Nasogastric Tube placement to choose CTRT versus RT?



- Q3 Will you accept for CTRT a 25% chance of short term feeding tube dependence v/s <5% chance of short term feeding tube dependence with RT alone?

	Before Trt (1)		Completion of RT(2)		3 months post RT (3)		p-value		
	Yes (%)	No	Yes (%)	No	Yes (%)	No	1-2	1-3	2-3
NG tube placement	80	20	40	60	46.4	53.6	S	S	NS

QN	Question	Response	T1	T2	T3
2	What are your fears about NG tube feeding	No problems	60	6.6	70
		Afraid of tube and does not want CTRT	3.3	60	30
		Does not want Ryle's tube	16.6	6.6	
		Has to eat by any means	3.3		
		Afraid of Ryles tube but will endure it	16.6	26.6	

- **Conclusion**

- **Survival advantage 5-10%: 20-36% patients regret deciding on CTRT**

- **Survival advantage 5% (Baseline RT survival 60%): 50% regretted choosing CTRT at T2 BUT significant % reverted back to choosing CTRT at T3.**

*(This group may choose dose escalation studies if such strategies provide a 10% extra benefit compared to RT)*



# Strategies for dose escalation

- SIB IMRT
- Accelerating and Hypofractionating
- Brachytherapy Boost (? Unlikely to work in Laryngeal cancers)

## Fractionation: SIB IMRT vs Conventional

	PTV 1	PTV 2
Dose level 1	63.0Gy 28# (2.25Gy) BED <sub>10Gy</sub> 66.6, BED <sub>3Gy</sub> 110.3 Log cell kill 10.12	51.8Gy 28# (1.85Gy) N/A
Conventional 70Gy 35#	70Gy 35# (2Gy) BED <sub>10Gy</sub> 74.1, BED <sub>3Gy</sub> 116.67 Log cell kill 10.26	50Gy 25# (2Gy) N/A

Fowler 2008: Work in progress

Slide: Courtesy Dr C Nutting



# Dose escalation Hypopharynx and Larynx trial results

28 fractions	Cohort 1 63Gy N=29 %- (95% CI)	Cohort 2 67.2Gy N=31 %- (95% CI)
Loco-regional disease free survival	65% (48-82)	83% (68-98)
Disease specific survival	73% (58-88)	85% (71-99)
Laryngectomy free survival	84% (71-97)	92% (82-102)
Overall survival	71% (54-88)	75% (59-91)

Guerrero Urbano et al Radiotherapy and Oncology 85 (2007) 36–41  
Miah et al has also updated this





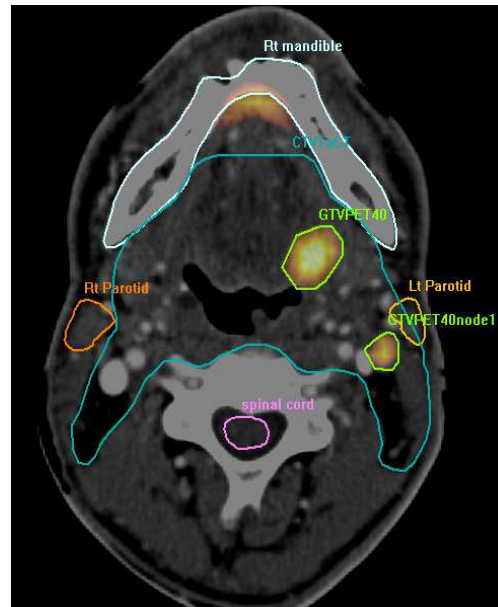
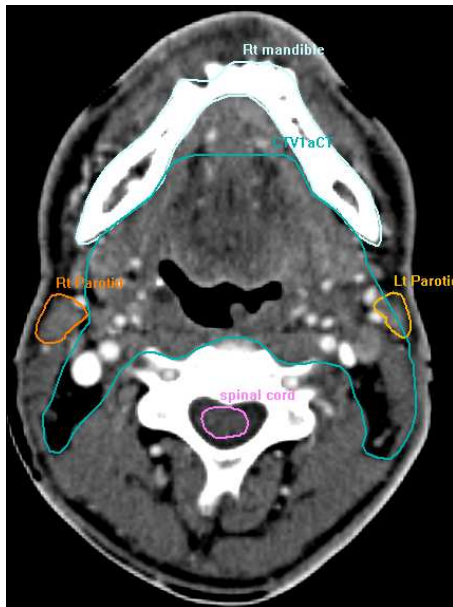
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## VorigrERN

### Vortigern:

Variation of radiotherapy target volume definition, dose to organs at risk (OAR) and clinical target volumes using anatomic (CT) vs. combined anatomic and molecular imaging (PET-CT): Intensity Modulated Radiotherapy delivered using a Tomotherapy Hi Art machine



9<sup>th</sup> October 2009

- **Inclusion criteria**
- Patients with tumours of oropharynx with involved or uninvolved neck nodes and who are being treated with IMRT will be included in the study.

- **Objective**

Primary Objectives

1. To determine whether there is change in the tumour volumes used for radiotherapy planning from PET-CT images compared to CT images of head and neck cancers.
2. To estimate whether there is a difference in mean radiation dose received by organs at risk (parotid glands, larynx and spinal cord) when using PET-CT images rather than CT images to plan tomotherapy treatment.

Secondary Objective

To develop tools for dose escalation within tumour, tumour sub-regions and nodal areas according to quantitative images of CT and PET tracer distribution..

Clin Oncol (R Coll Radiol). 2012 Dec;24(10):e173-9. doi: 10.1016/j.clon.2012.09.004. Epub 2012 Oct 15.

**Variation in radiotherapy target volume definition, dose to organs at risk and clinical target volumes using anatomic (computed tomography) versus combined anatomic and molecular imaging (positron emission tomography/computed tomography): intensity-modulated radiotherapy delivered using a tomotherapy Hi Art machine: final results of the VortigERN study.**

Chatterjee S<sup>1</sup>, Frew J, Mott J, McCallum H, Stevenson P, Maxwell R, Wilsdon J, Kelly CG.

**Feasibility of PET-CT based hypofractionated accelerated dose escalation in oropharyngeal cancers: Final dosimetric results of the VORTIGERN study. (Secondary endpoint of UK NCRI portfolio: MREC No: 08/H0907/127, UKCRN ID 7341)**

Sanjoy  
Chatterjee,  
Charles Kelly\*,  
Moses Arun Singh,  
Chandan



**Trial Protocol**

***Intensifying radiation treatment in advanced/ poor prognosis larvngeal,  
hypopharyngeal (LH) and oropharyngeal cancers (OPC) using PET –CT  
based dose escalation strategies. ( INTELHOPE)***

# Studies of RT Dose escalation



Trial Protocol

Arm of Treatment	N	Overall Time (weeks)	d	a/b	BED	Kappa	D-28	BED loss	Total effective BED
Int CTV1	30	6	2.1	10	76.23	0.9	14	12.6	63.63
BTV	30	6	2.45	10	91.51	0.9	14	12.6	78.90
Std CTV1	30	6	2.2	10	80.52	0.9	14	12.6	67.92
CTV2	30	6	1.8	10	63.72	0.9	14	12.6	51.12

Radiobiology of doses used in other International studies:

Intensifying radiation treatment in advanced/ poor prognosis laryngeal, hypopharyngeal (LH) and oropharyngeal cancers (OPC) using PET-CT based dose escalation strategies. (INTELHOPE)

Study name	N	Overall Time (weeks)	d	a/b	BED	Kappa	D-28	BED loss	Total effective BED
DAHANCA (7)	34	5.5	2	10	81.6	0.9	10	9	72.60
ART DECO(3)	28	5.5	2.4	10	83.328	0.9	10	9	74.32
RTOG (8)	30	6	2.4	10	89.28	0.9	14	12.6	76.68
ARTFORCE (9)	35	6	2.2	10	93.94	0.9	14	12.6	81.34
Leclerc et al (10)	30	6	2.5	10	93.95	0.9	14	12.6	81.15
<u>Proposed study</u>	30	6	2.45	10	91.51	0.9	14	12.6	78.90

# Escalating Radiation Dose

- Will OUR patients accept dose escalation?

Yes

- Can we escalate dose?

Yes

- Is it safe?

Await results



Thank You

