The place of radiation therapy in head and neck cancer

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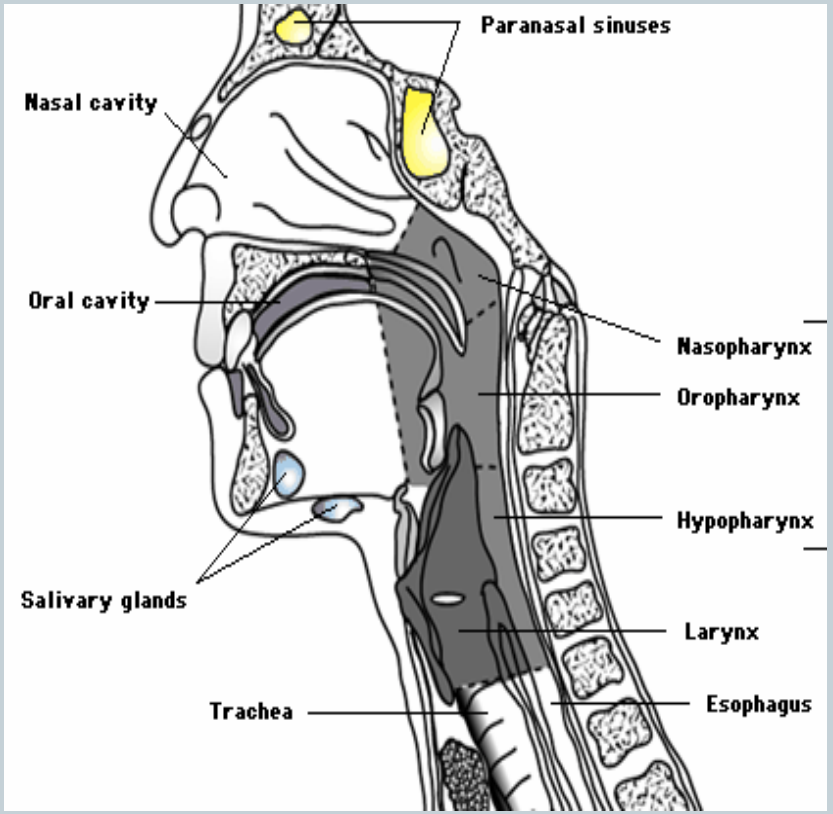
Disclaimer

Head and Neck Cancer

- 3% of all cancers
- 5% of cancer-related deaths
- Commonly mucosal SCC
- Smoking related
- Increasing incidence of HPV-related HNC



Chemoradiotherapy

- Overview of radiotherapy principles
- Role of chemo-radiotherapy in HNC
- Discuss clinical scenario

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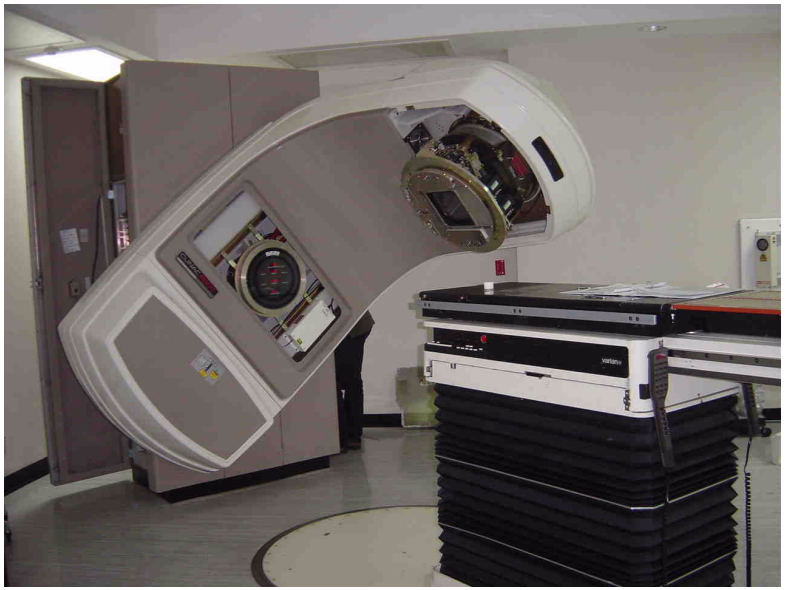
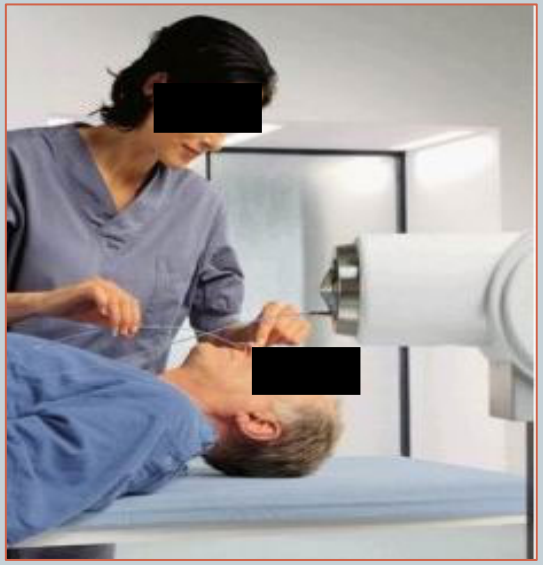
Radiotherapy Types

- External Beam
  - Linear Accelerator
    - Photons
    - Electrons



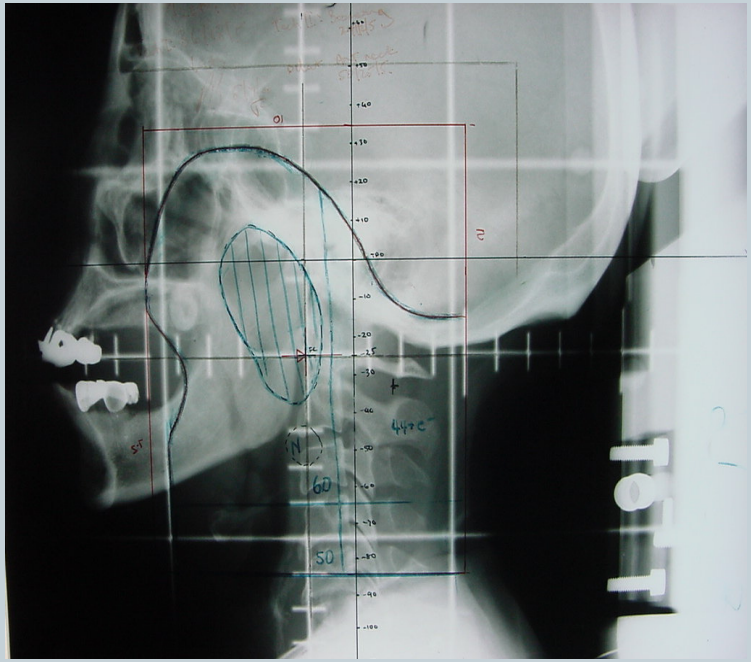
Radiotherapy Types

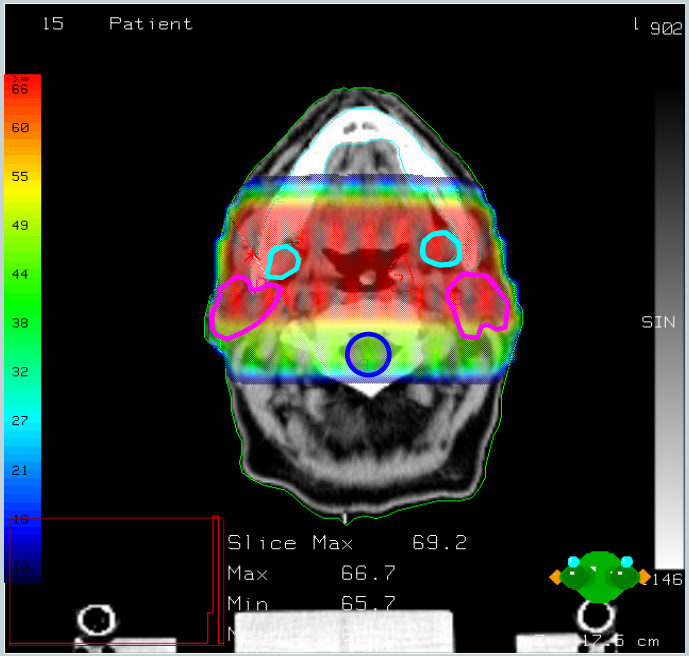
- Brachytherapy
  - Seeds
  - Needles
  - Wire
  - Plaques



Radiotherapy delivery

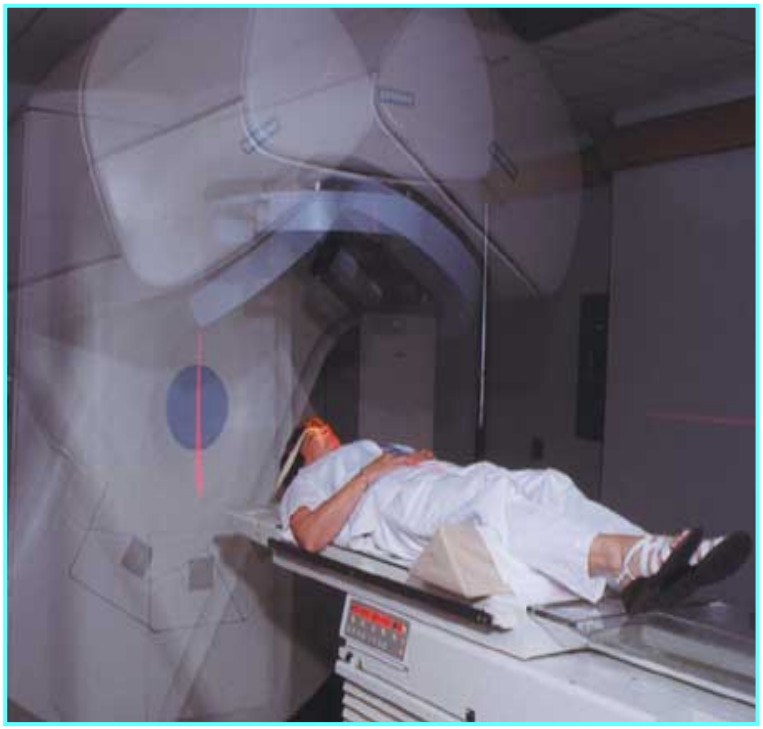
- 2 Dimensional

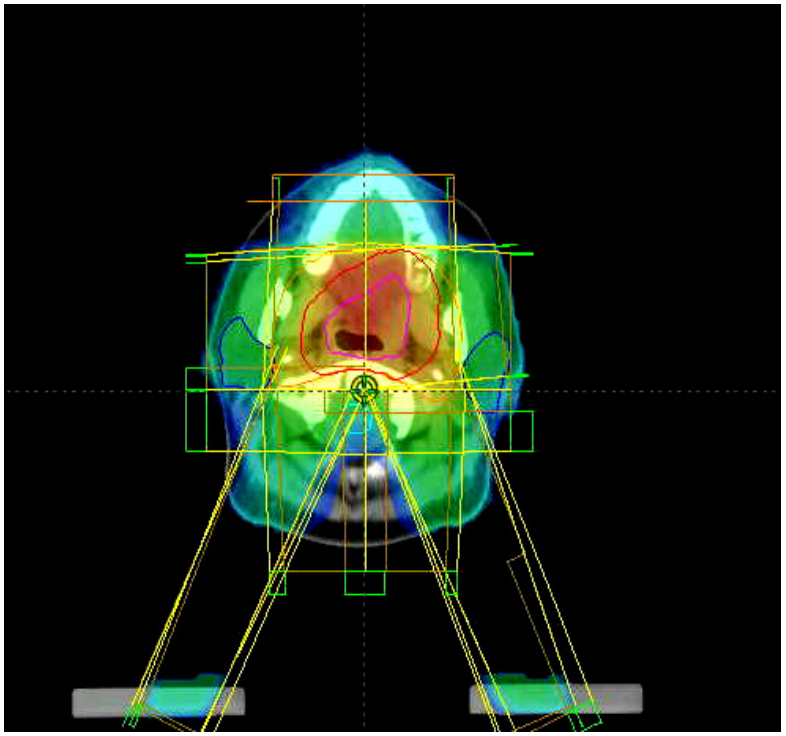




Radiotherapy delivery

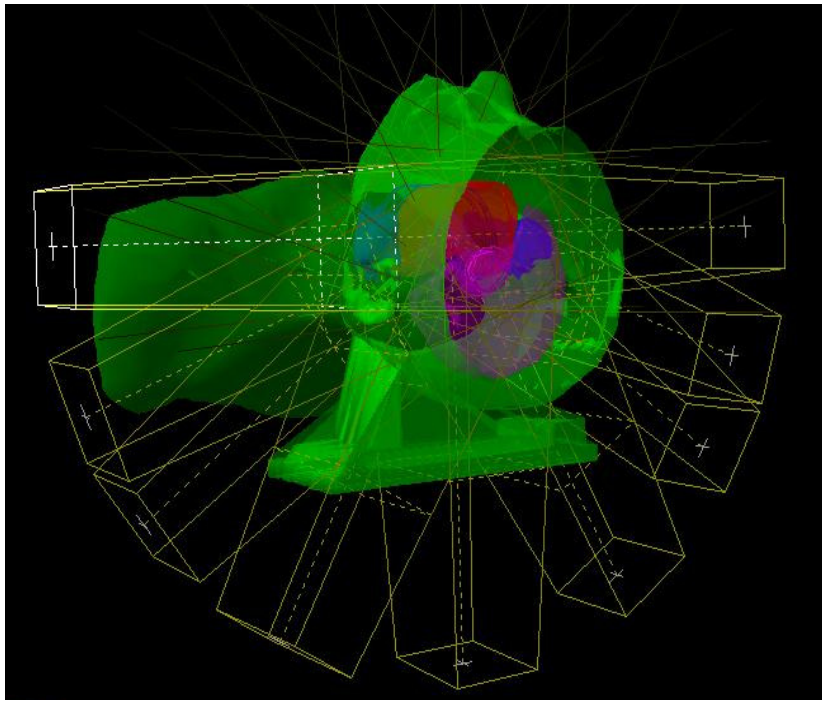
- 3 Dimensional

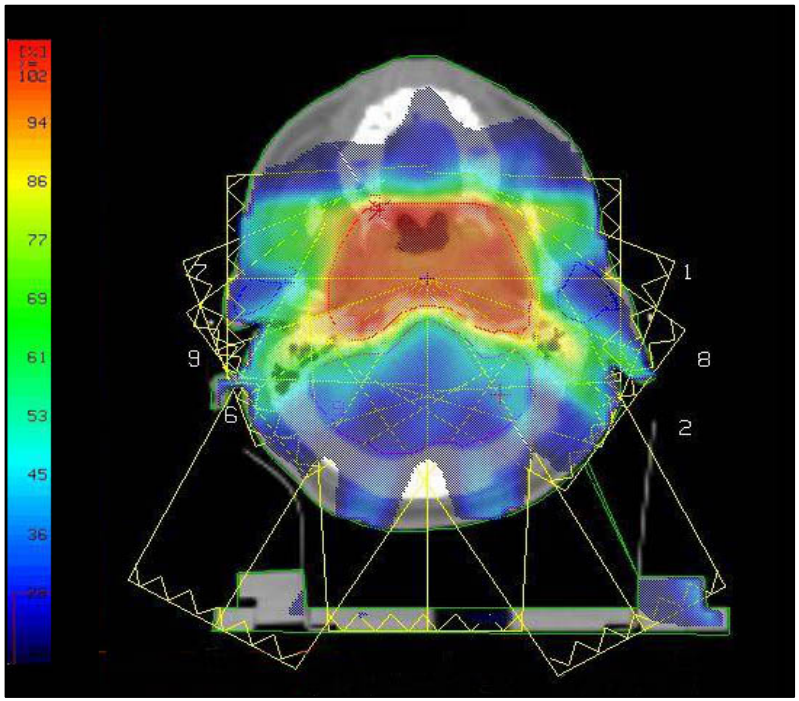




Radiotherapy delivery

- Intensity Modulated Radiotherapy (IMRT)





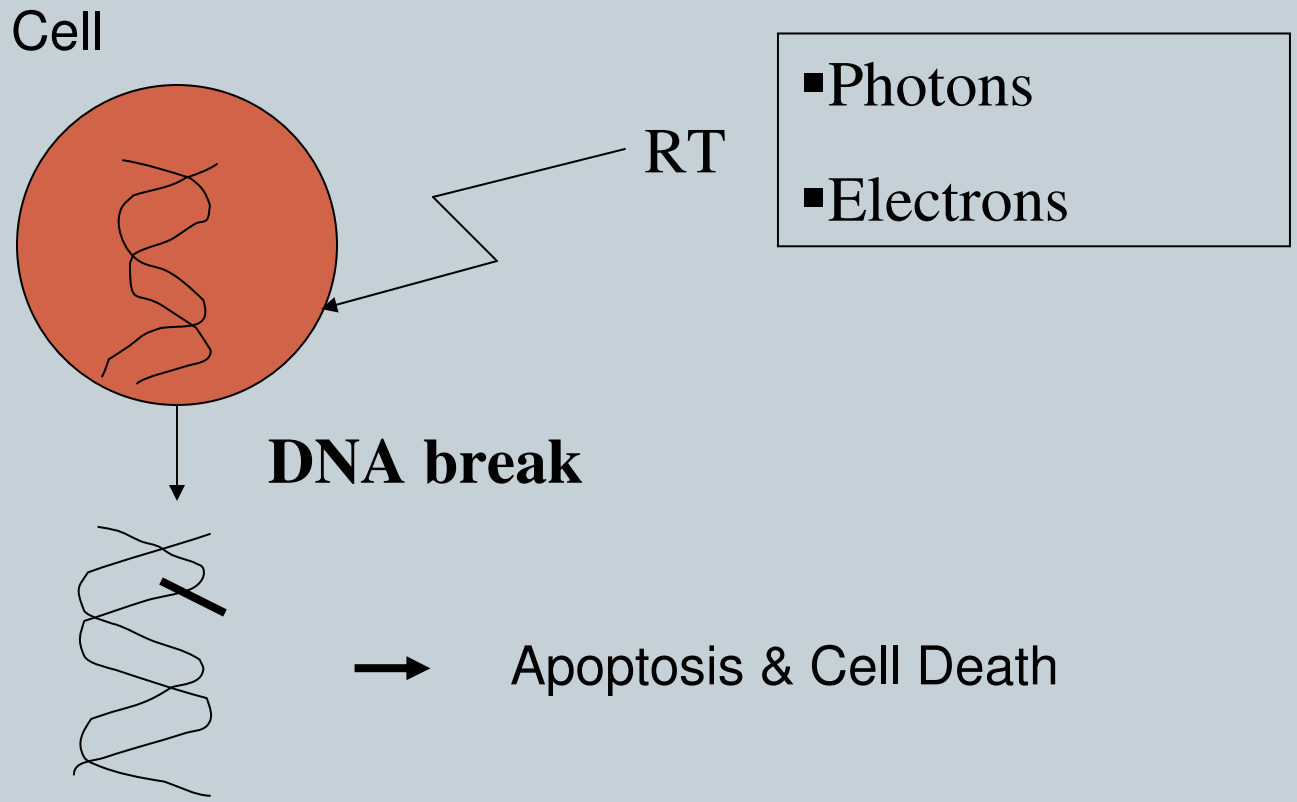
Radiotherapy Dose/fractionation

- Conventional Fractionation
  - 1.8-2.0 Gy per day 5/week
- Altered Fractionation
  - Hyperfractionation <1.8-2.0y/day
  - Hypofractionation >1.8-2.0Gy/day
  - Accelerated <7 weeks (definitive Tx)
    <6 weeks (post-op Tx)

Radiotherapy Doses

- Elective Nodal Bed 50Gy/25#
- Surgical Bed 54Gy/27#
- Resected Disease (R0) 60Gy/30#
- Resected Disease (R1) 66Gy/33#
- Definitive Disease 70Gy/35#

Radiobiology



Acute Toxicity

- Lethargy
- Loss of facial hair
- Otitis externa and media
- Skin reaction
- Salivary changes

- Mucositis
- Taste changes
- Odema
- Dysphagia
- Odynophagia

Late effects (>30days)

- Fatigue
- Hair loss
- Hearing impairment
- Skin atrophy & hypopigmentation
- Xerostomia
- Trismus

- Mucosal atrophy and telangectasia
- Altered taste
- Lymphodema
- Dysphagia
- Subcutaneous fibrosis and atrophy

Late effects (>30days): less Common

- Osteoradionecrosis
- Brachial plexopathy
- Myelopathy
- Thyroid Dysfunction
- Second cancer

Chemoradiotherapy in HNC

- Overview of radiotherapy principles
- Role of chemo-radiotherapy in HNC
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Role of Radiotherapy in HNC

- Post-operative RT (PORT)
- Definitive (organ preservation)
- No defined role as neoadjuvant (pre-op)

Indications for PORT in HNC

M- Margins +/≤ 5 mm*
U- Undifferentiated (salivary gland)
L- Lymph nodes ≥2, ≥3cm
T- T3, T4
I- Immunosuppressed
P- Perineural infiltration
L- LVSI
I- Invasion >4mm depth (oral cavity)
E - Extracapsular nodal extension*
R- Recurrence

*Post-op chemo-RT

Treatment intensification; rule of thumb

- T + N = 1 — Single modality treatment
  Surgery or conventional RT
- T + N = 2 — Altered fractionated RT
- T+ N > 3# — Chemo-RT or surgery/PORT

Consider Altered fractionation RT alone
T3N0 tonsil superficial &
T2N1 Oropharyngeal p16+

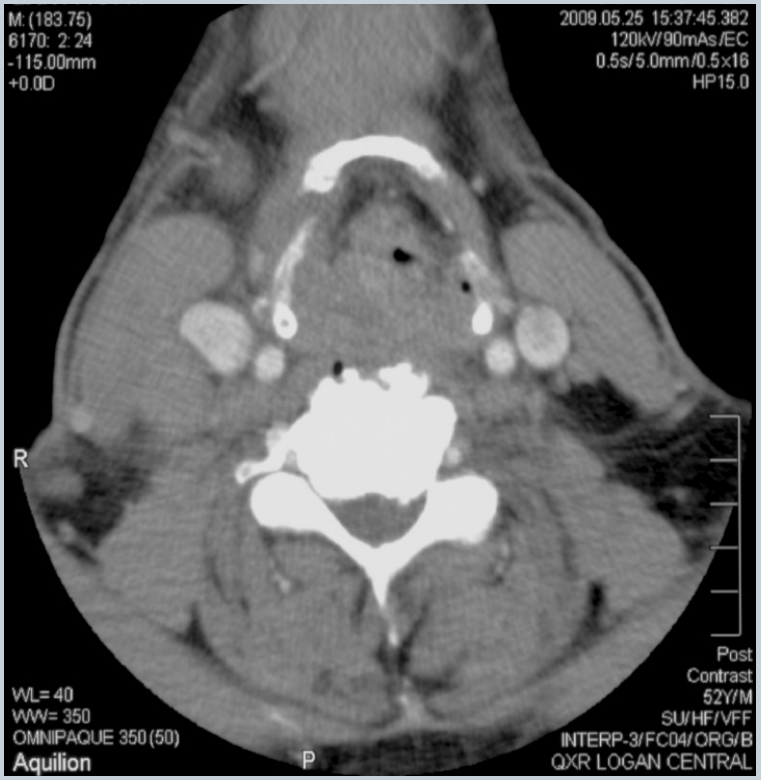
Principles in management of LAHNSCC

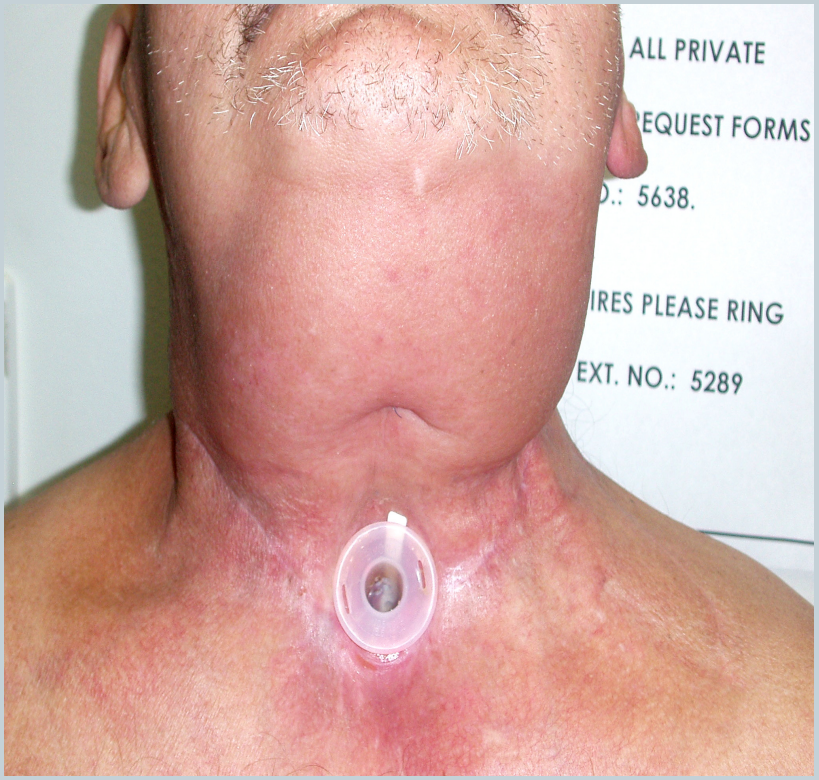
- Functional outcome
  - Is it worth preserving?
  - What is the functional deficit
- Can I obtain clear macroscopic margins
- Aim to use the least number of modalities to obtain the required clinical outcome
- Biological profile of tumour (eg p16 status)

Where surgery is favoured

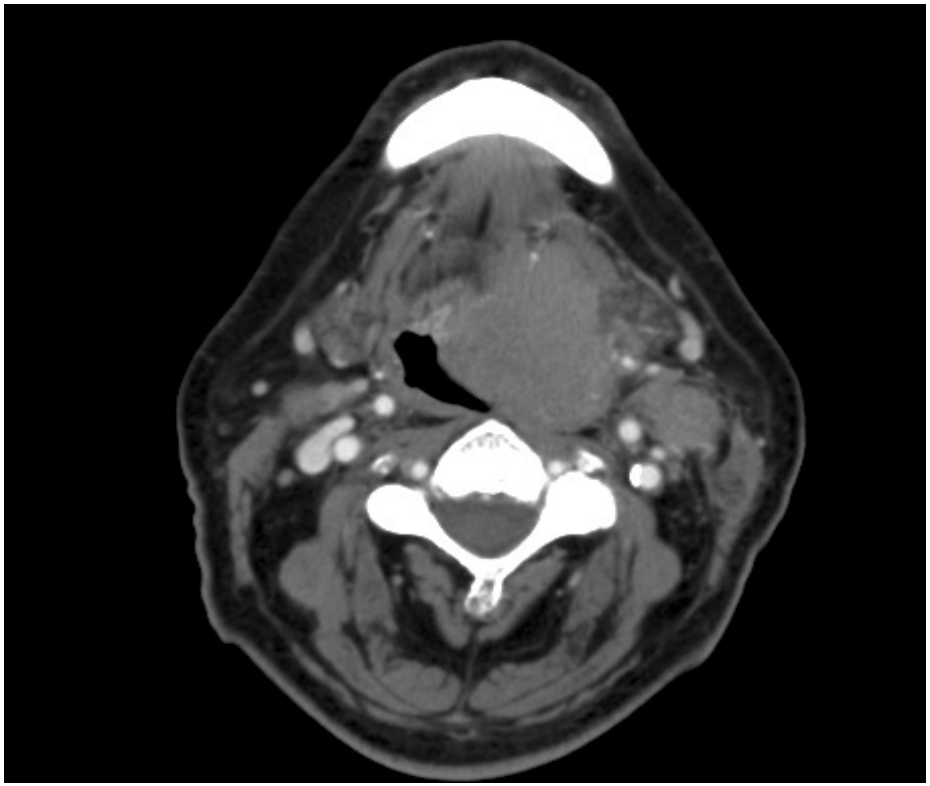
- Patient preference
- Previous head and neck XRT
- Site; oral cavity & hypopharynx
- Early cancer where risk of nodal disease is low (<10%); Superficial (≤ 5mm) oropharynx T1 lesion, T1-2 glottic SCC
- Very advanced disease; obstructive airway symptoms, bilateral vocal cord palsies, destroyed larnygeal cartilage & mandible/bone invasion

Laryngectomy



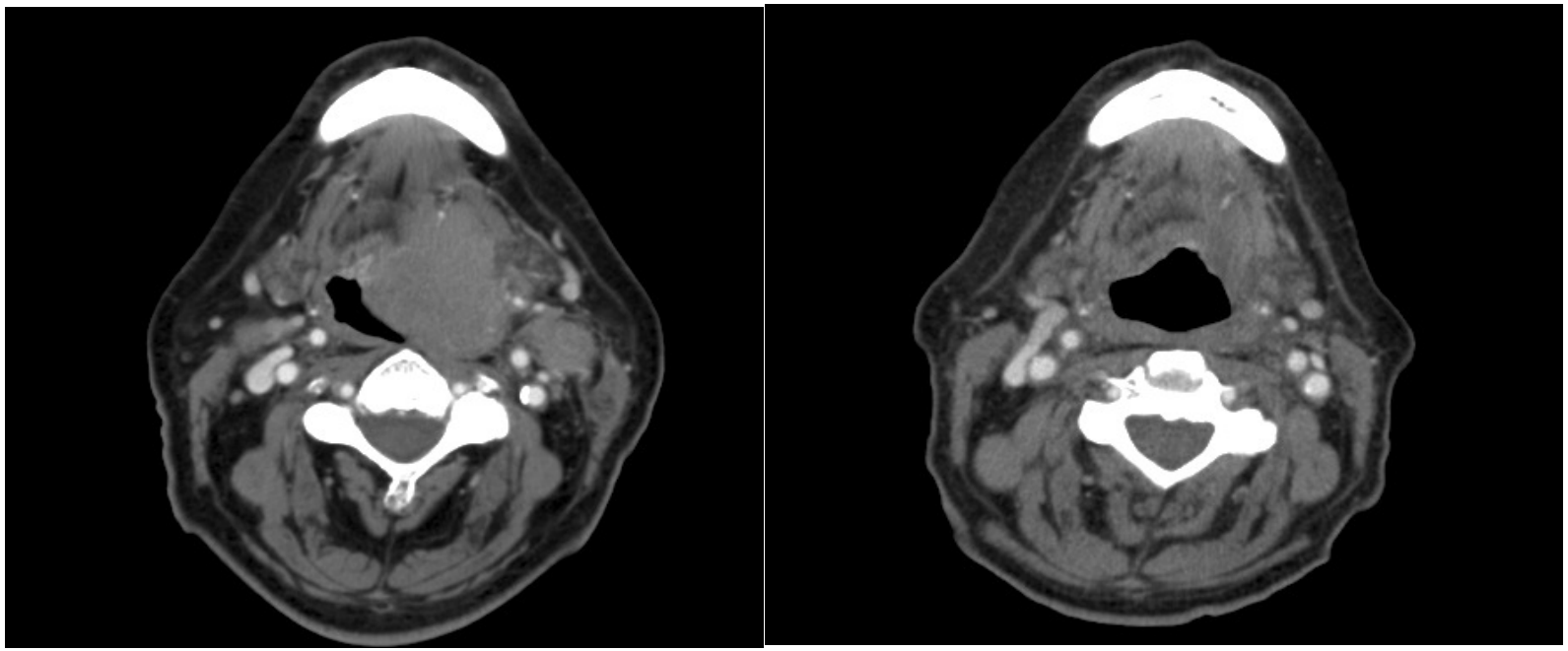


Role of Radiotherapy in HNC



Tongue Base SCC

Role of Radiotherapy in HNC



70Gy over 7 weeks
Cisplatin (100mg/m^2) weeks 1, 4, 7

Chemoradiotherapy

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Discuss the role of chemo-radiotherapy in the management of a T2N2b tonsil SCC (p16+)

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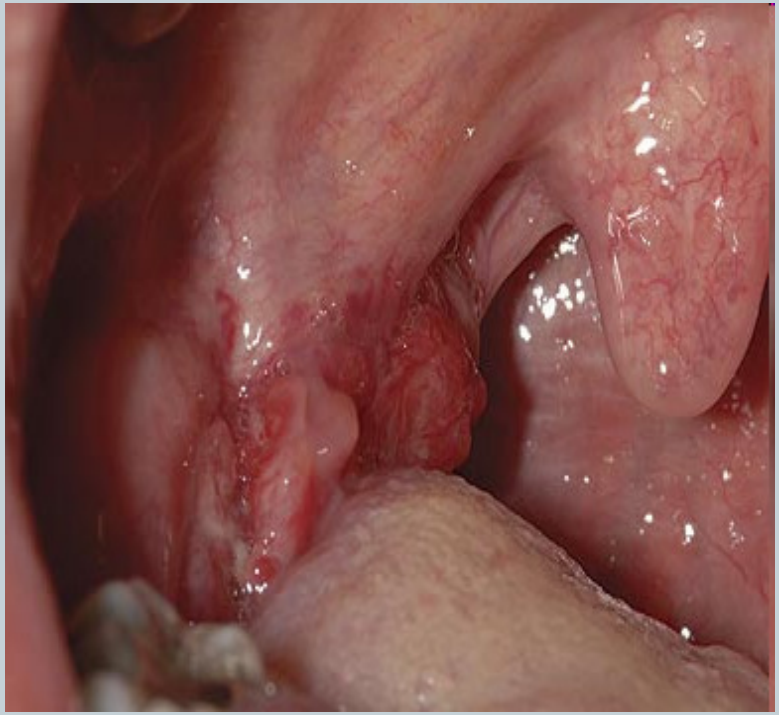
"There are, in fact, two things, science and opinion; the former begets knowledge, the latter ignorance."

Hippocrates 2000 yrs ago

Discuss the role of chemo-radiotherapy in the management of a T2N2b tonsil SCC (p16+)



Management of a T2N2b tonsil SCC (p16+)

- 2 major roles for CT-RT in this clinical scenario either PORT or as definitive therapy
- Minimal role for chemo-RT as pre-operative therapy and no established role for adjuvant chemotherapy

Management of a T2N2b tonsil SCC (p16+)

- No randomised evidence comparing surgery/post-operative(chemo)RT vs definitive chemo-RT
- Decision of which modality to use is based on functional outcomes and perceived curative rates.

Management of a T2N2b tonsil SCC (p16+)

Post-operative Chemo-RT

- In LAHNSCC the outcomes with surgery alone or RT alone are poor 30-40% 5 yr survival
- Surgery and PORT improves this to 40-70% 5 yr survival
- 2 randomised trials in high-risk patients have shown a benefit of post-op chemo-RT vs PORT

Management of a T2N2b tonsil SCC (p16+)

<u>Definitive Chemo-RT</u>

- The standard of care for organ-preservation curative management of LAHNSCC is *concurrent chemotherapy and RT* consisting of high-dose cisplatin (100mg/m^2/iv) weeks 1,4 & 7 and RT (70Gy/35#/7 weeks)

RTOG 91-11 (Forestiere NEJM 2003)

Pignon et al Meta-analysis 2000

Management Current chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer; RTOG 91-11

- 547 pts randomised

	2 year intact larynx
• induction cispl/5FU→ RT	75%
cispl* & RT	88%
RT alone	70%

- Overall survival no different

- Cisplatin iv 100mg/m² weeks 1,4 & 7*

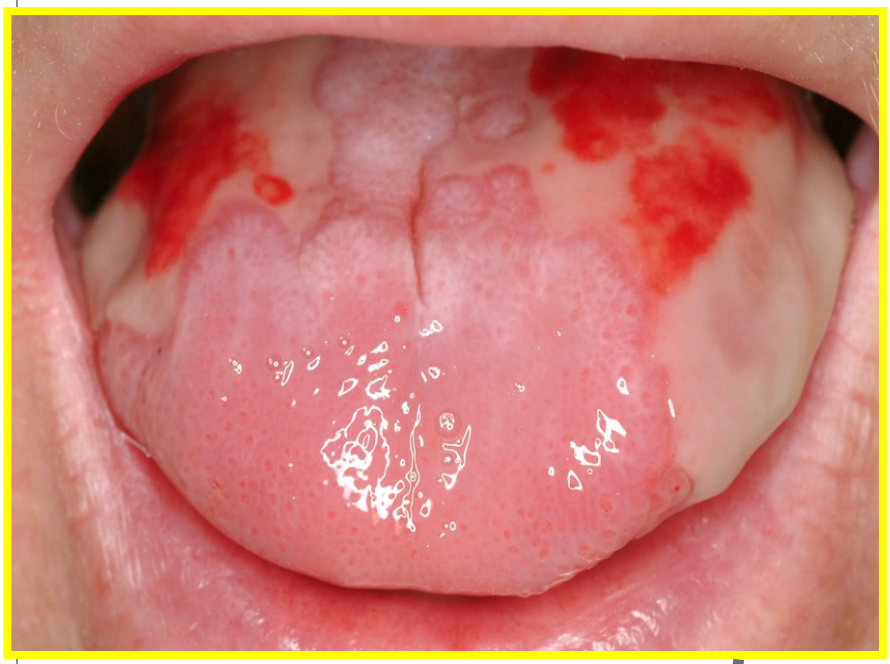
Forestiere et al NEJM 2003

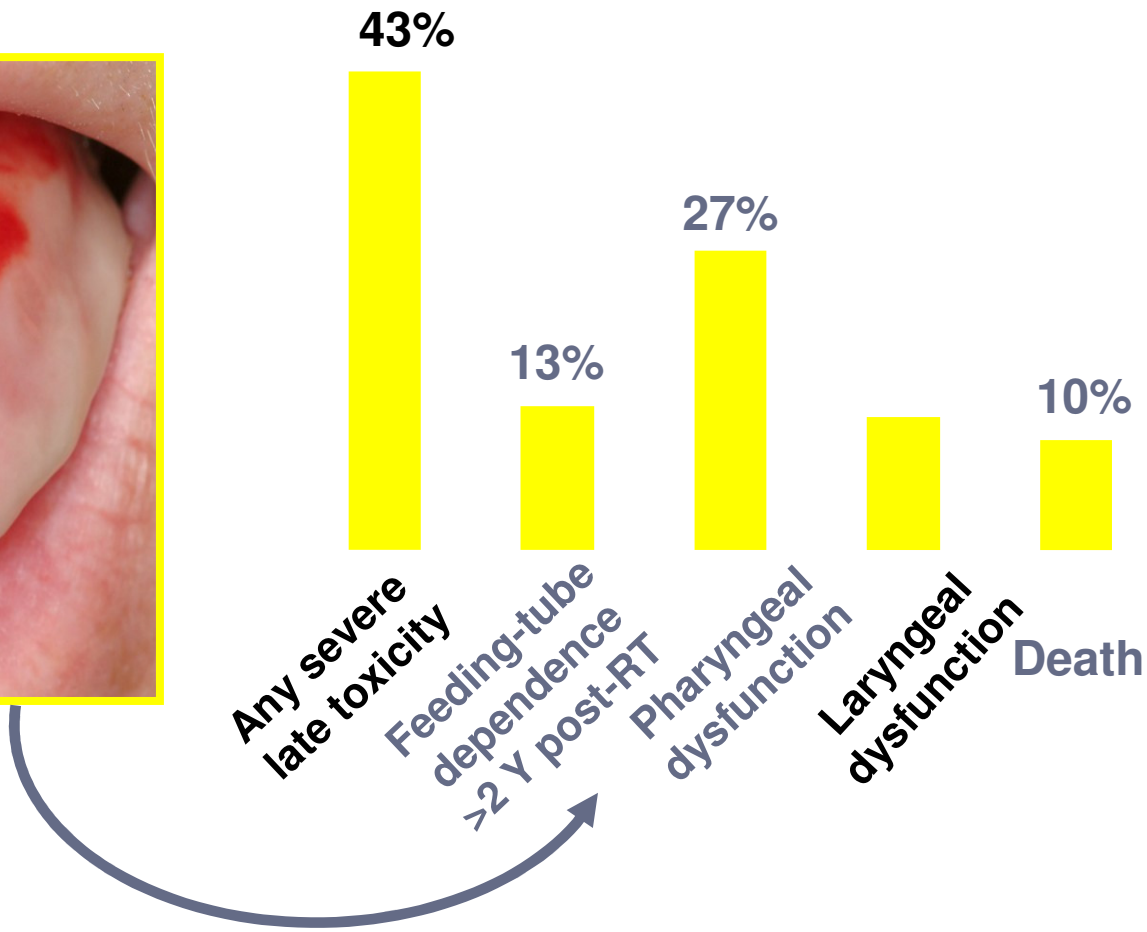
Management of a T2N2b tonsil SCC (p16+)

<u>Definitive Chemo-RT</u>

- Limited functional outcome data with these studies
- Concurrent chemo-RT increases morbidity (Machtay JCO 08)

Impact of Toxicity on Function





Machtay (Ang), J Clin Oncol 26:3582, 2008

Management of a T2N2b tonsil SCC (p16+)

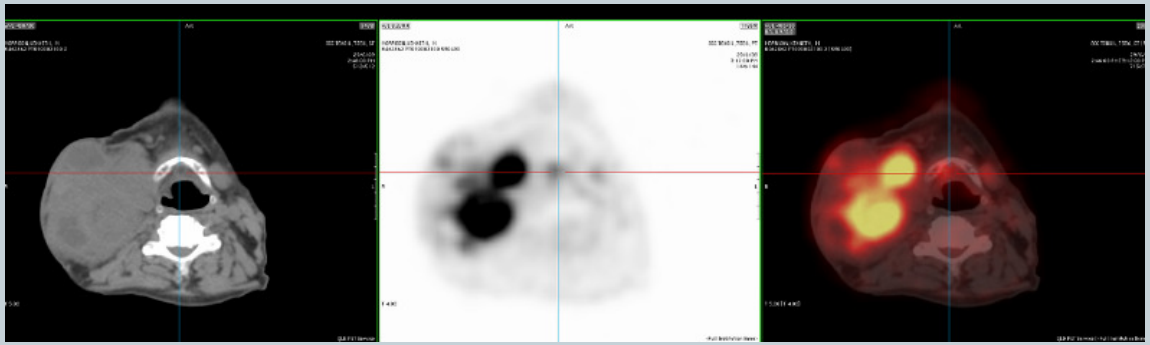
Induction Chemotherapy

- This remains controversial!
- Theoretical benefit of reducing the tumour burden prior to definitive treatment and addressing subclinical distant mets
- Theoretical disadvantage is the increase in overall treatment time and patients may end up too sick to receive the definitive treatment

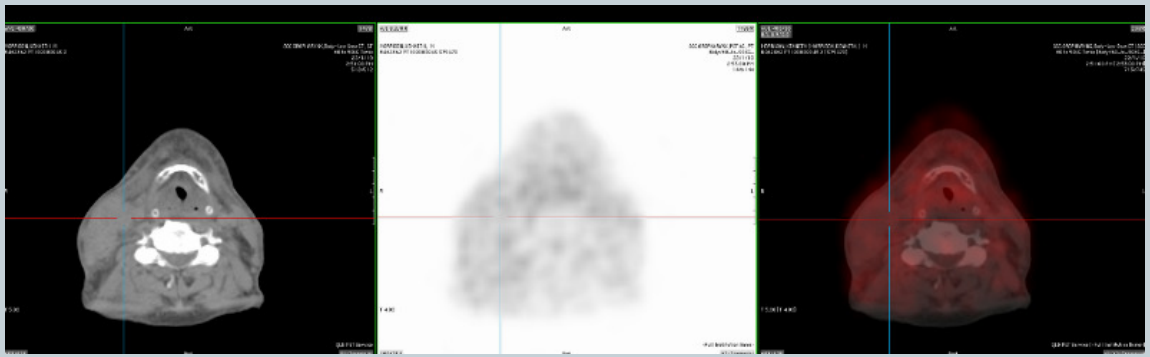
Induction chemotherapy

T1N3 BOT SCC p16+, >10pack yrs

Pre-treatment



Post-treatment



Disease free at 20 months

Management of a T2N2b tonsil SCC (p16+)

Induction Chemotherapy

- 2 recent randomised trials comparing induction T (docetaxel) , P (cisplatin), F (5 Fluorouracil) with PF induction chemotherapy followed by definitive RT (Vermorken and Posner NEJM 2007)
- Both studies demonstrated superior disease free and overall survival with induction TPF compared with induction PF
- Neither study used standard definitive concurrent chemoRT
- Increased toxicity lowered the compliance with treatment

Management of a T2N2b tonsil SCC (p16+)

Patients ineligible for high dose cisplatin

- Altered fractionated RT alone (Bouhris Lancet 2006)
- Cetuximab (systemic) and RT* (Bonner NEJM 2006)
- Weekly low dose cisplatin (30mg/m^2) (No quality data)
- Concurrent carboplatin/5FU given weeks 1,4 and 7

Cetuximab in HNC

- Cetuximab is an anti-epidermal growth factor inhibitor, EGF is over-expressed in 90% of HNSCC
- Superior outcomes with cetuximab/RT compared with RT alone (LRC and OS)
- No increased “in-field” toxicity
- Acneiform Rash (outcomes better with rash)
- Australia - available on PBS only for Cisplatin-ineligible patients

Human Papilloma Virus

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

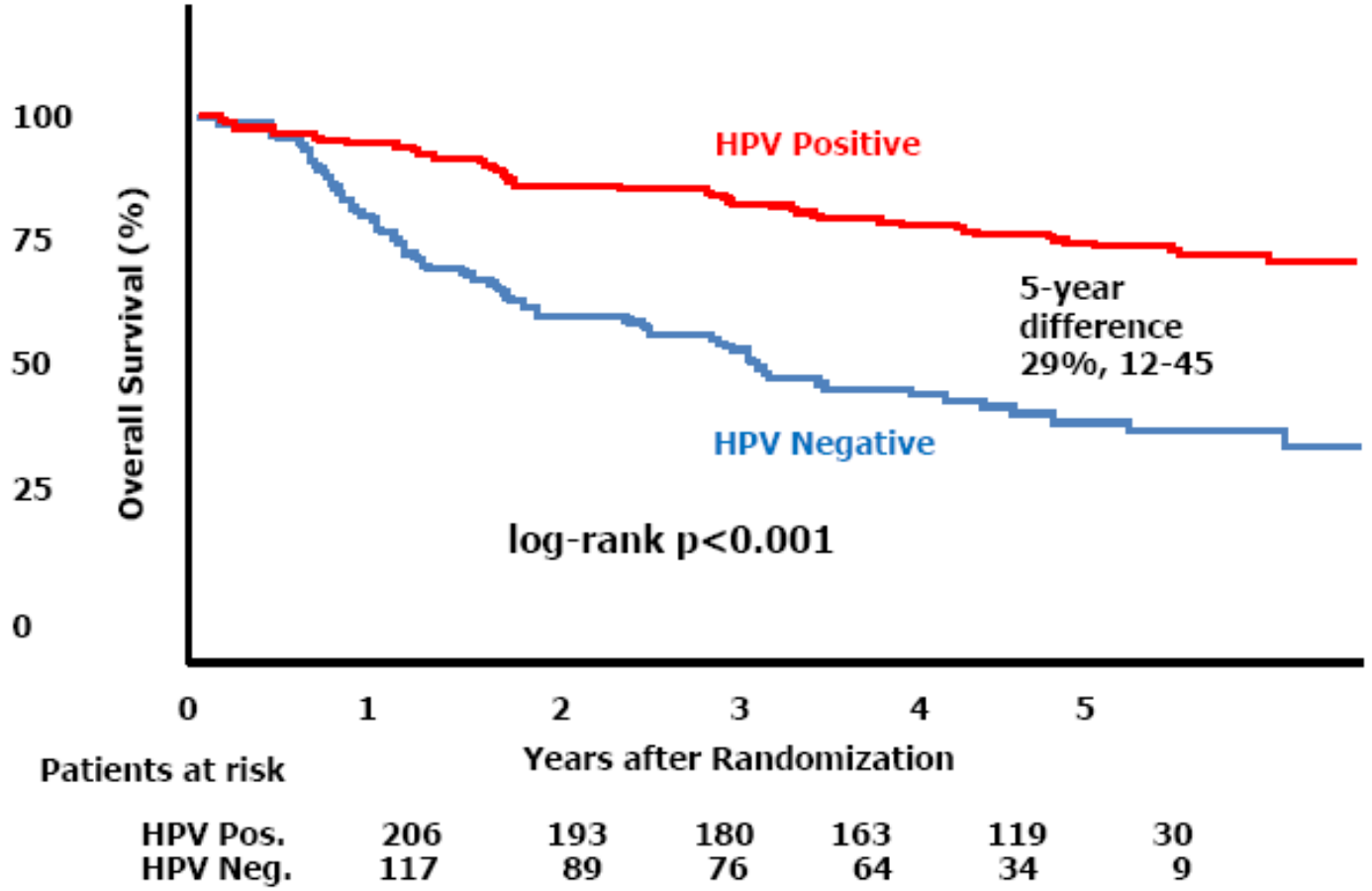
Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer

K. Kian Ang, M.D., Ph.D., Jonathan Harris, M.S., Richard Wheeler, M.D., Randal Weber, M.D., David I. Rosenthal, M.D., Phuc Felix Nguyen-Tân, M.D., William H. Westra, M.D., Christine H. Chung, M.D., Richard C. Jordan, D.D.S., Ph.D., Charles Lu, M.D., Harold Kim, M.D., Rita Axelrod, M.D., C. Craig Silverman, M.D., Kevin P. Redmond, M.D., and Maura L. Gillison, M.D., Ph.D.

N ENGL J MED 363;1 NEJM.ORG JULY 1, 2010

RTOG
Radiation Therapy Oncology Group

Survival outcomes by HPV status



Patients at risk

HPV Pos.	206	193	180	163	119	30
HPV Neg.	117	89	76	64	34	9

Gillison M. ASCO 2009, Orlando, abstract # 6003

HPV-related oropharyngeal SCC

- p16+ patients have favourable outcomes with either surgery/PORT or chemo-RT (Ang KK NEJM 2010)
  - Low risk (p16+, non-smoker), chemoRT 82% 3yr survival

Management of a T2N2b tonsil SCC (p16+)

Recommendation

- Favour chemo-RT due to high cure rate >80% (p16+)
- Pre-therapy staging PET
- High-dose cisplatin wks 1,4,& 7 (cetux if ineligible for cisplatin) with IMRT (70GY)
- If patient achieves a complete response at the primary site and neck based on the 12 week re-staging PET no further treatment required

Chemoradiotherapy in HNC

- Chemo-radiotherapy can be used as post-operative treatment or definitive (curative) treatment
- No randomised studies comparing definitive surgery/PORT vs chemo-radiotherapy
- Decision made on perceived functional outcome and potential cure rate
- Concurrent Chemo-radiotherapy is the standard of care for LAHNC when surgery is not used

Chemoradiotherapy in HNC

- Induction chemotherapy followed by chemo-RT remains controversial
- Cetuximab is considered the alternative drug combined with RT when patients ineligible to cisplatin
- p16 (HPV) oropharyngeal SCC has excellent outcomes with RT

Randomised trials chemo-RT vs RT mucosal H&N SCC

Study	Pts	Risk Feature	Treatment	Outcome (CT-RT)
Bachaud 1996	88	**ECE**	Cisplat 50mg 65-74Gy	**5yr LRC Sig (59%)** **5yr DFS Sig (70%)** **5yr OS Sig (36%)**
RTOG NEJM 2004	459	**ECE + margins ≥ 2 nodes**	Cisplat 100mg/m^2 wks 1,4,7 60-66Gy	**2yr LRC NS (82%)** **2yr DFS Sig (54%)** **2yr OS NS (63%)**
EORTC NEJM 2004	334	**T3-4, N2-3 ECE, PNI**	Cisplatin 100mg/m^2 wks 1,4,7 66Gy	**5yr LRC Sig (79%)** **5yr PFS Sig (47%)** **5yr OS Sig (53%)**

Post-op chemo-RT superior to RT alone in high risk patients

Altered fractionation meta-analysis

- 15 Randomised trials comparing conventional RT vs Altered fractionation RT (6515 pts)
- Significant benefit in favour of Altered Fractionation at 5 years
  - Absolute survival benefit of 3.4%
  - Absolute loco-regional control benefit of 6.4%

Bourhis J et al Lancet 2006

Meta-analysis chemo-RT vs RT
Phase III HNSCC Trials from 1965

Therapy Modality	Absolute benefit at 5 years*	Risk Reduction*	*P*
All (N=17,493)	4.1 %	10 %	< 0.0001
Adjuvant	2.3 %	2 %	NS
Neoadjuvant	2.2 %	5 %	NS
Concurrent	6.9 %	19 %	< 0.0001

*Relative to Conventional Local-Regional Therapy

Pignon & Bourhis, Lancet, 2000

Role of induction chemotherapy

- Early larynx preservation studies
  - VA study NEJM 1991
  - EORTC JNCI 1996
- Induction chemotherapy (Cisplatin/5FU)
  - Responders had definitive RT
  - Non-responders had surgery/PORT
- Larynx preservation rate 66% at 2 years
- No difference in survival

Role of induction chemotherapy

- 2 recent NEJM publications
  - Posner et al 2007*
  - Vermorken et al 2007
- Compared induction cisplatin/5FU (PF) to docetaxel (T) & PF followed by RT
- One study had current chemotherapy (carboplatin) & RT*