



To salvage or not to salvage...

Professor Hisham Mehanna

Chair of Head and Neck Surgery

Director, Institute of Head & Neck Studies & Education

Use of primary chemoradiotherapy has increased considerably.

- National cancer database 1985 - 2001 in US
- CRT increased from 15 to 30% head and neck patients

Chen, *Laryngoscope*, 2007

Hence the emergence of salvage surgery after CRT failure

Currently what is the 3 year survival rate of recurrent OPC treated surgically?

- 10%
- 20%
- 35%
- 50%
- 65%

InHANSE Recurrence and Complex Case clinic

- Dedicated head and neck recurrence service
- Multi-disciplinary: surgeon, medical oncologist, radiation oncologist, palliative care physician, SLT, counsellor .
- Cutting edge treatments:
 - Reconstruction - 3D bone reconstruction and pre-plating
 - TOLS
 - Cyberknife and tomotherapy
 - Phase 1 and 2 clinical trials of new agents
 - Best supportive care and psychological support

Hypotheses

Salvage surgery has a high complication rate

Salvage surgery after chemoradiotherapy failure is feasible and effective.

Appropriate and adequate patient selection improves outcomes

Interventions can be undertaken to improve outcomes and decrease complications of surgery post CRT.

Complications of salvage surgery post-CRT

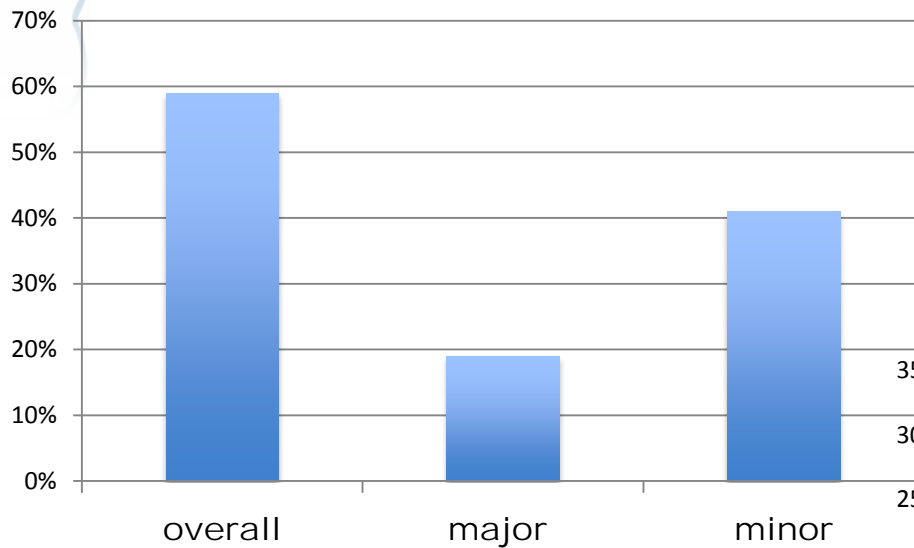


Complications of laryngeal salvage

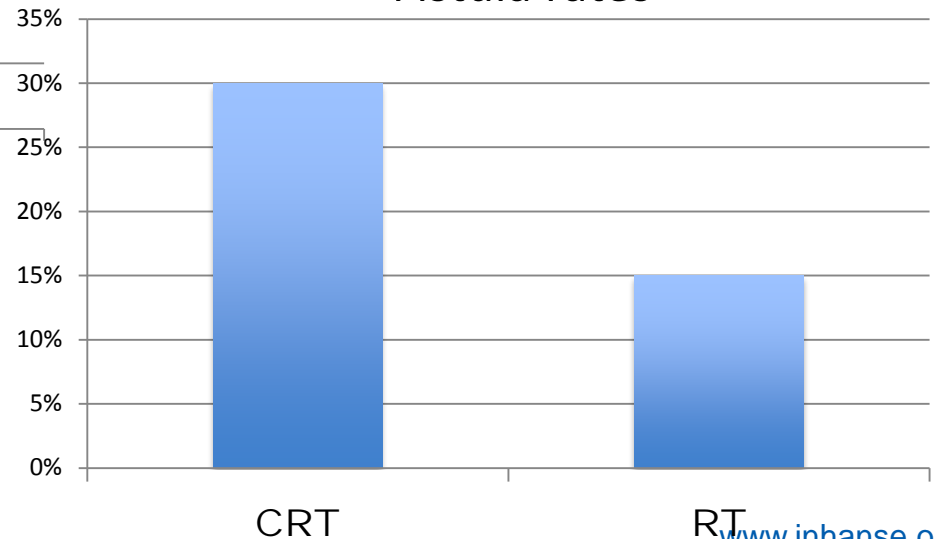
RTOG 91-11: complication rates of salvage laryngectomy

Weber, *Arch Otolaryng HNS*,

2008



Fistula rates



Complications of oropharyngeal salvage

MD Anderson

- Overall complications: 48%
- 71% >80% speech intelligibility
- 68% tolerate some oral intake, 87% de-cannulated

Zafaereo, Cancer, 2009

Vasso Rici: 21% fistula rate

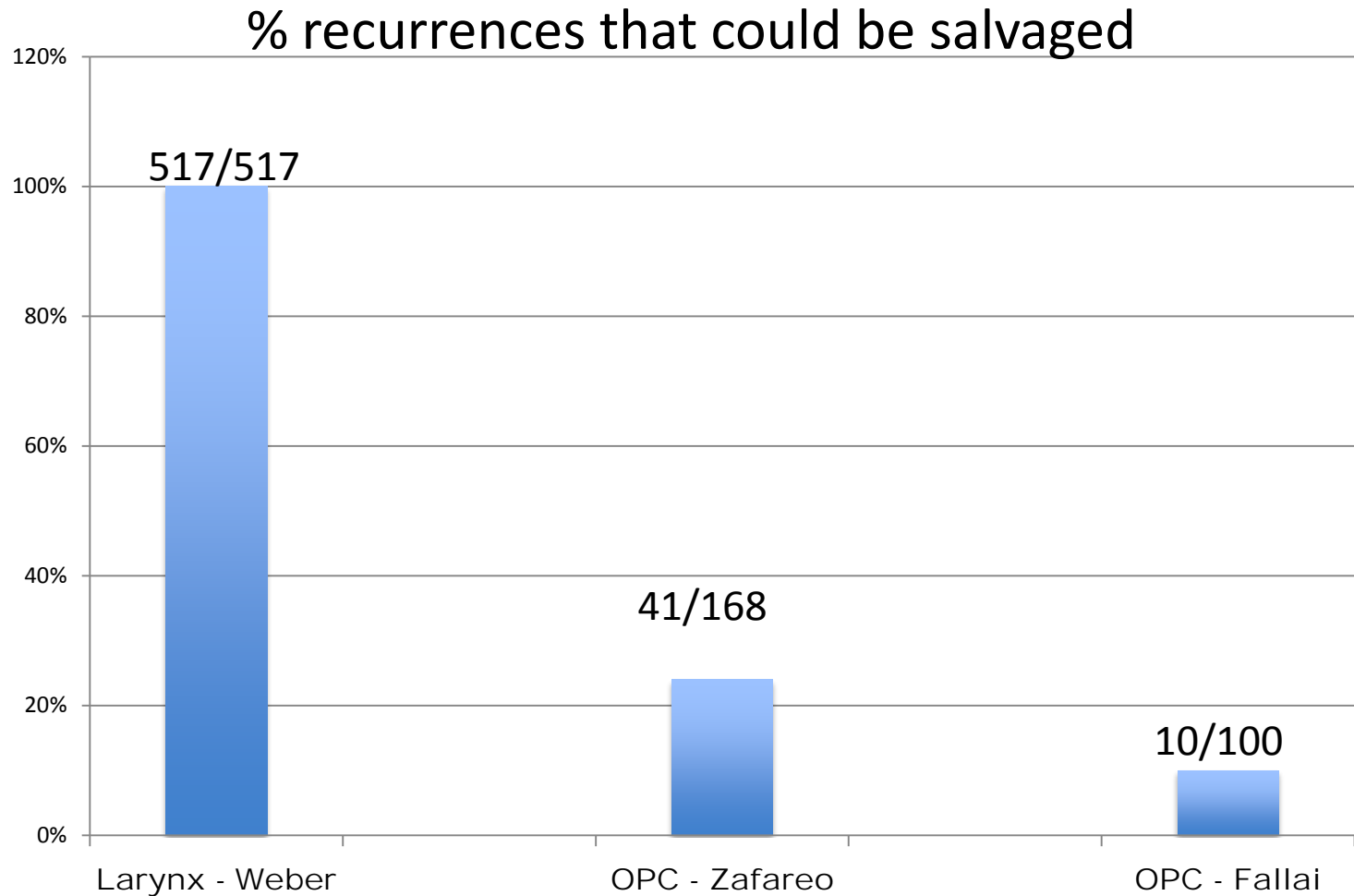
Complications of laryngeal and oropharyngeal salvage

Significant

Is salvage surgery feasible & effective?



Is salvage feasible?



Weber, *Arch Otolaryng HNS*, 2008; Zafaereo, *Cancer*, 2009; Fallai, *Tumori*, 2006

Is laryngeal salvage effective?

RTOG 91-11

- LRC 2 years 74%.
- OS 2 years 71%

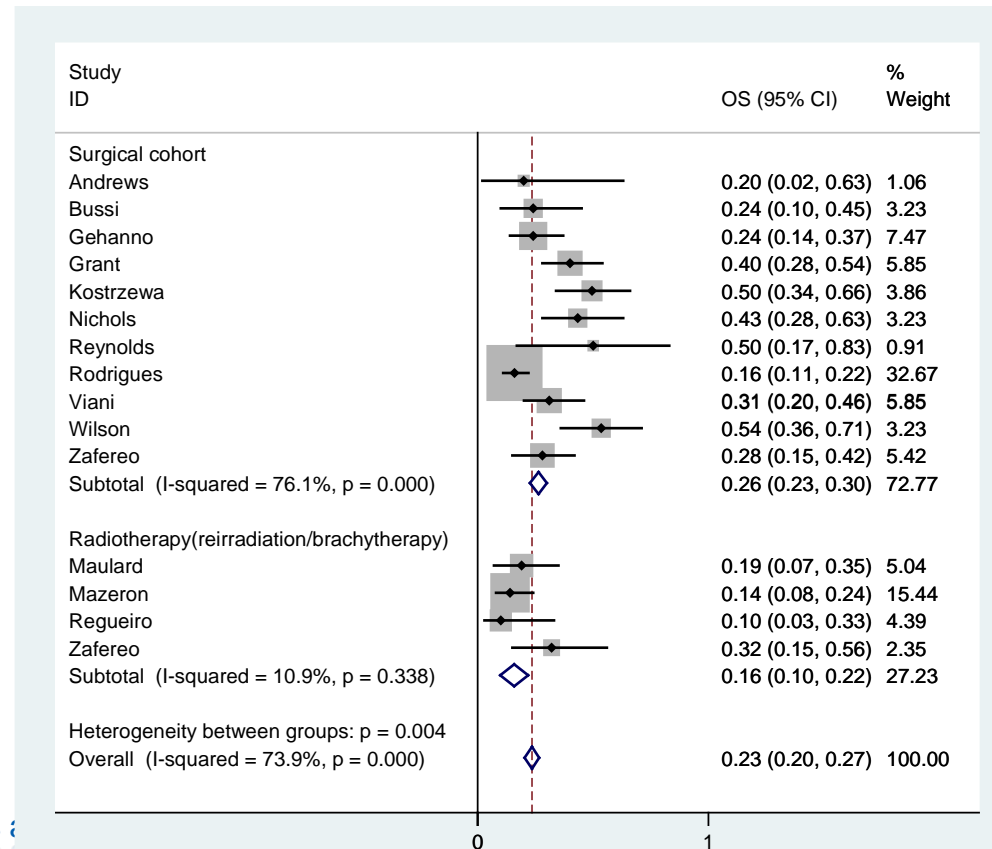
Weber, *Arch Otolaryng HNS*, 2008

Outcomes of OPC salvage

Meta-analysis; 1,015 patients

- Pooled 3 year OS = 26%
- Pooled 5 year OS = 23%

Jayaram, Mehanna, Head Neck, in print



Is salvage feasible and effective?

Yes,
but oropharyngeal much more difficult and
less successful

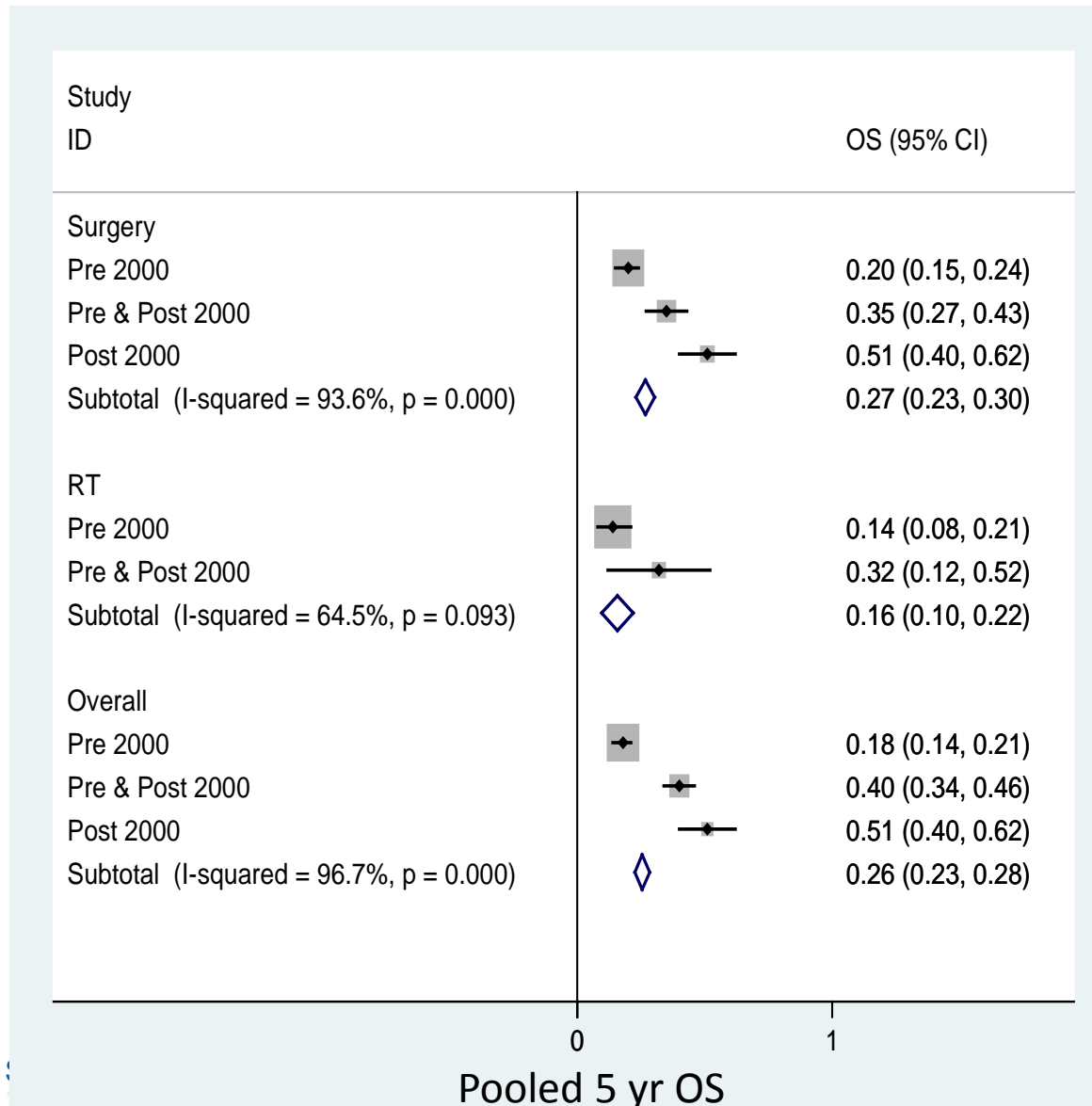
Evidence for improved outcomes

Monalisa after one week in USA



Before

Improving outcomes

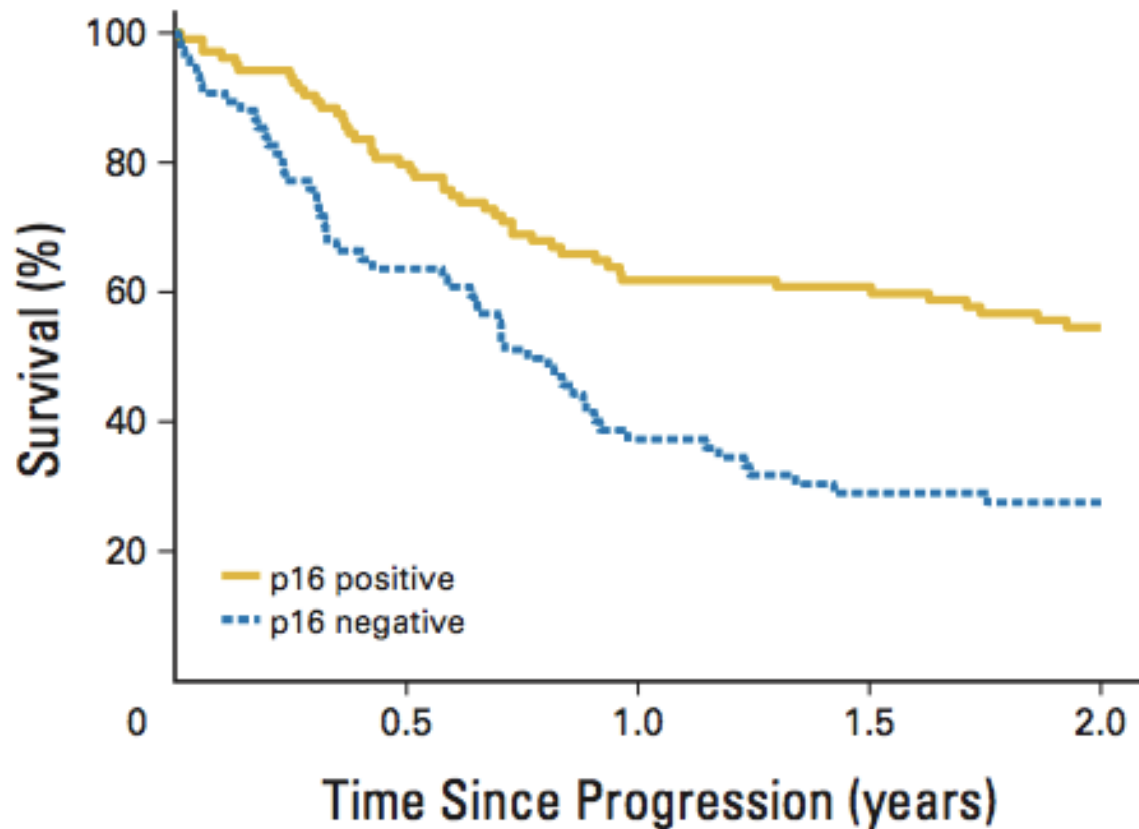


Jayaram, Mehanna,
Head Neck, in print

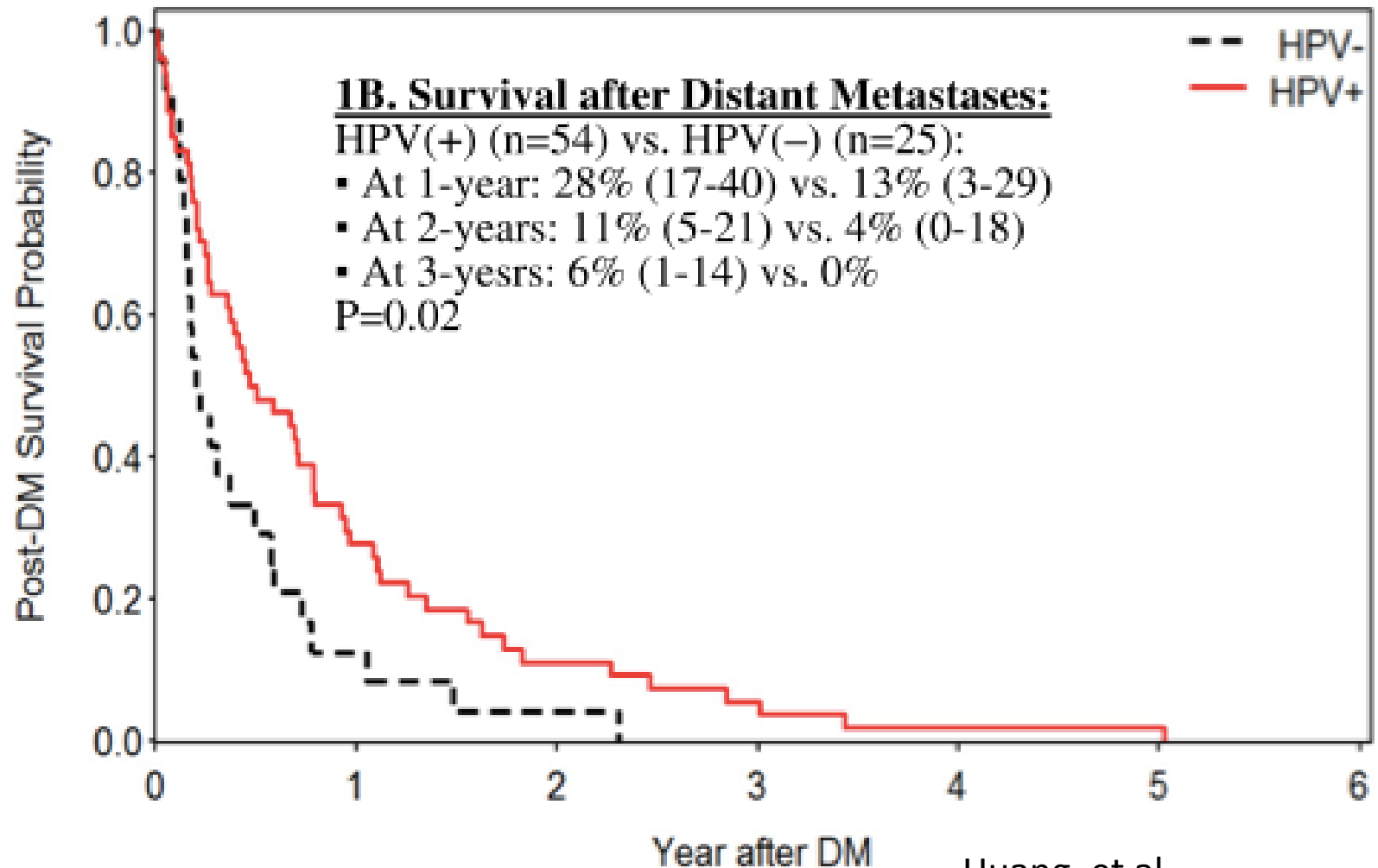
Why ?

HPV recurrence

2-year OS recurrence HPV+ 54.6% v HPV-ve 27.6%

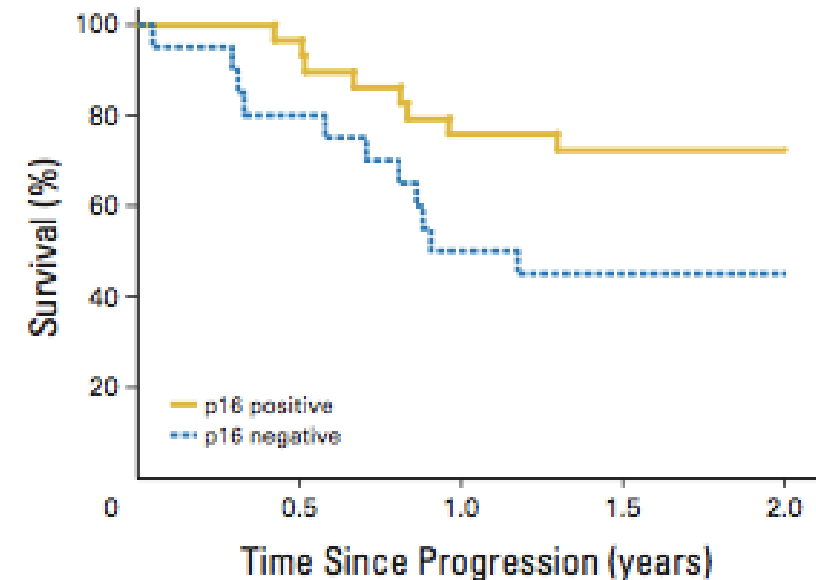


Distant metastasis and HPV



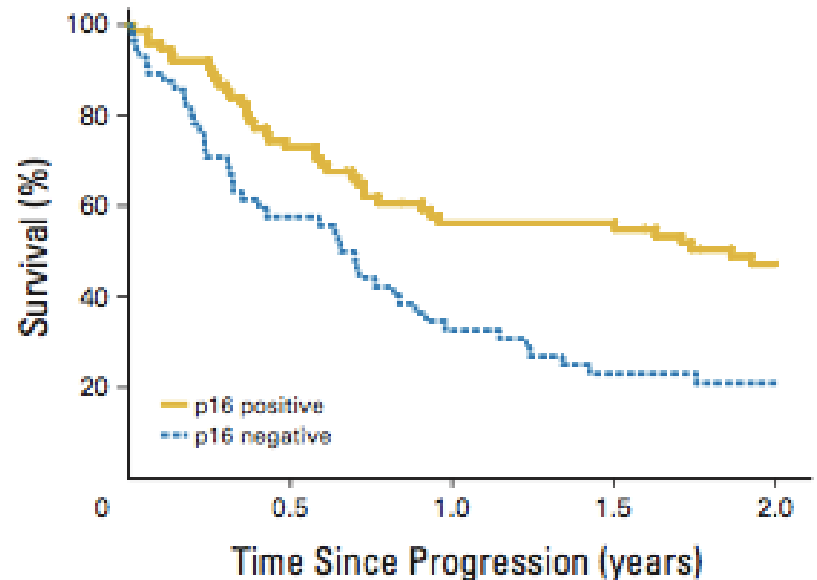
Huang et al,
Oral Oncology,
2012

Effect of surgical treatment and HPV status on outcomes of recurrence



Surgically salvaged

D



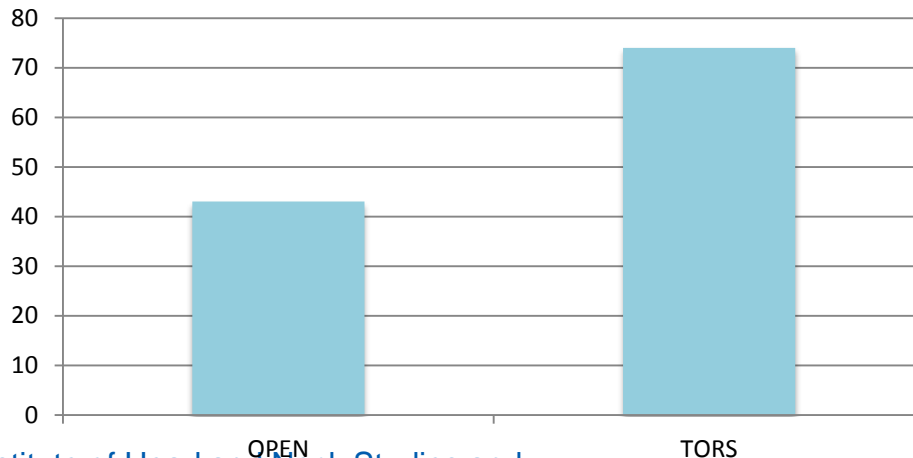
No Surgical salvage

Fakhry et al , JCO, 2015

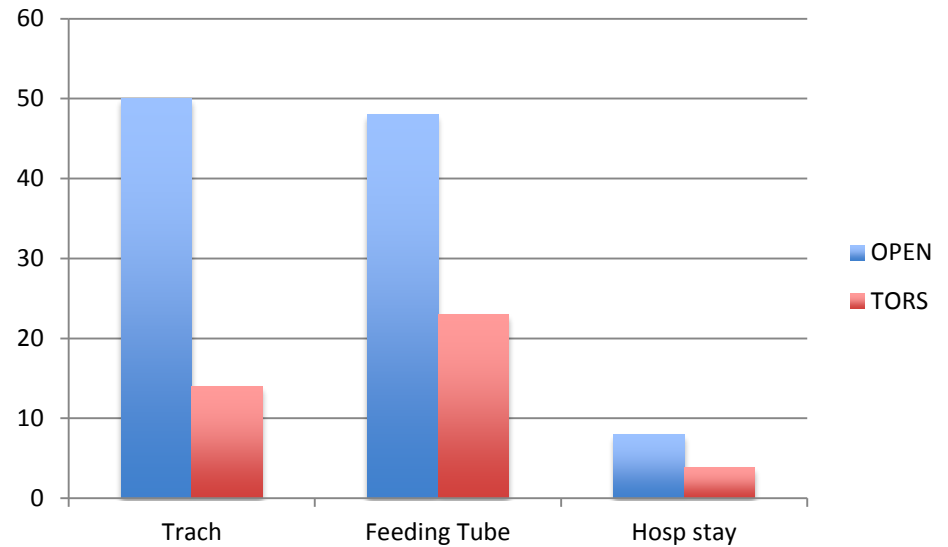
Better surgical techniques

64 open vs 64 TORS
multi-centre case-controlled
recurrent OPC

2yr Recurrence Free Survival



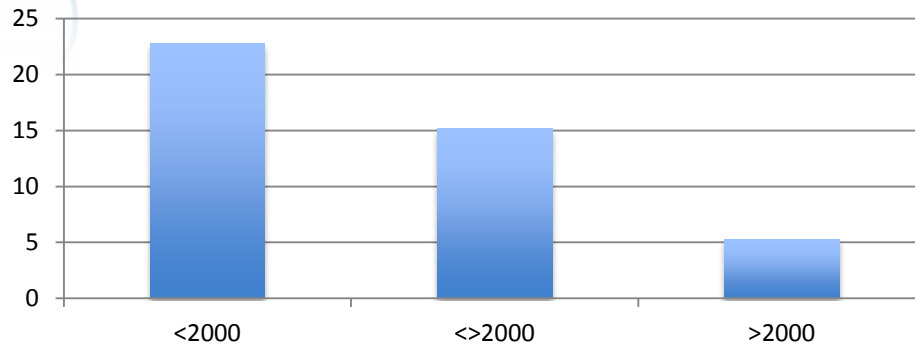
Complications



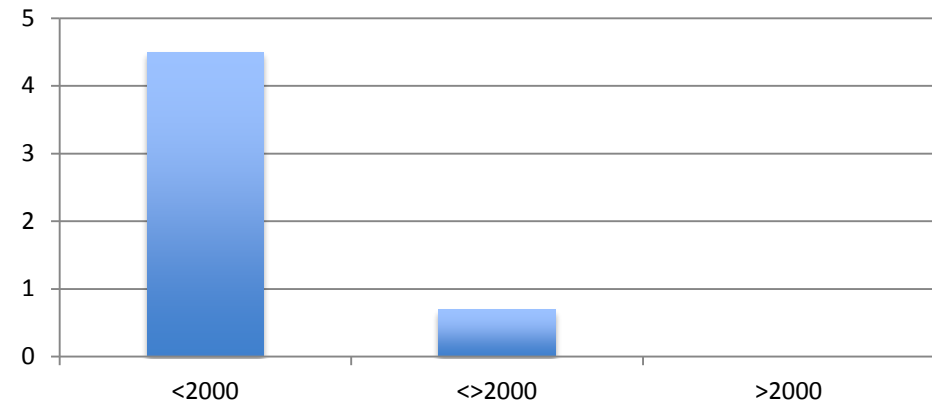
White, JAMA Oto;HNS, 2013

Better surgical outcomes and post-operative care

complications following salvage surgery OPC



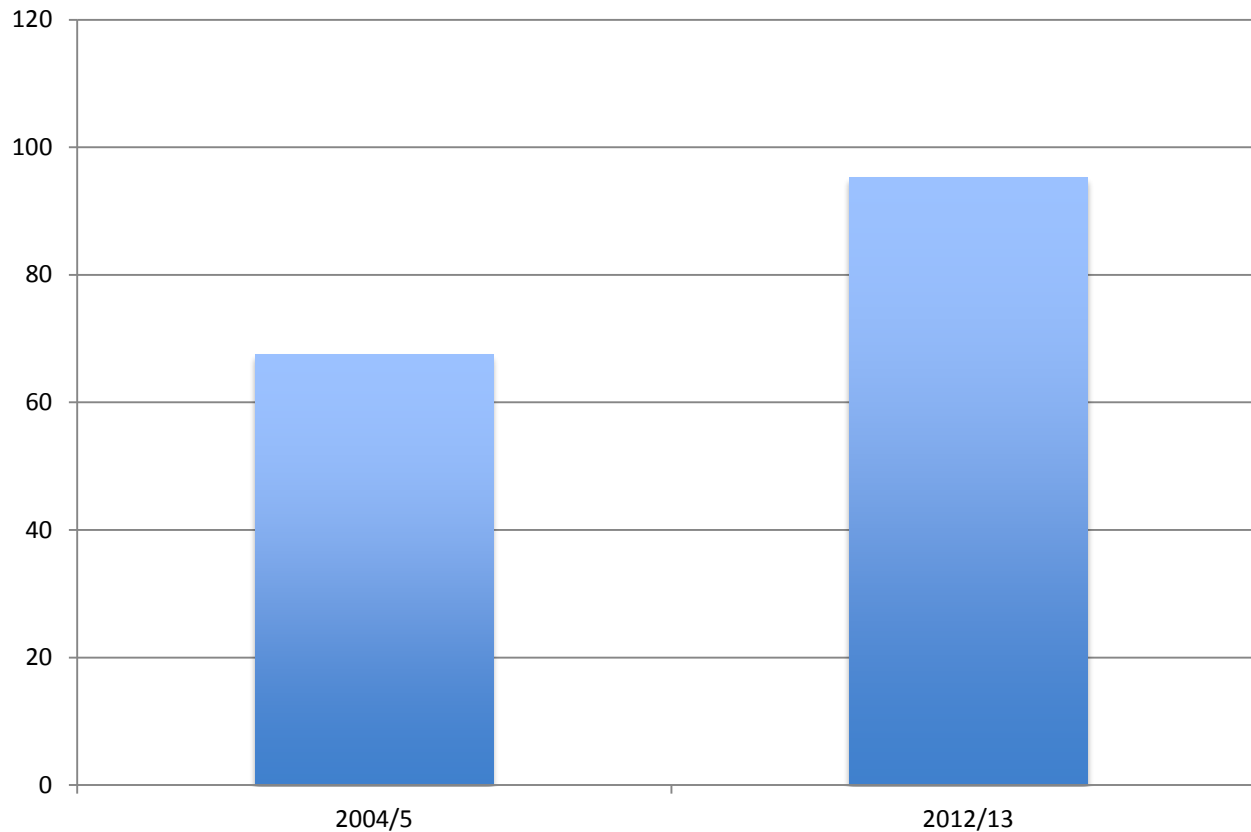
mortality following salvage surgery OPC



Jayaram, Paleri, Mehanna, Head Neck, in print

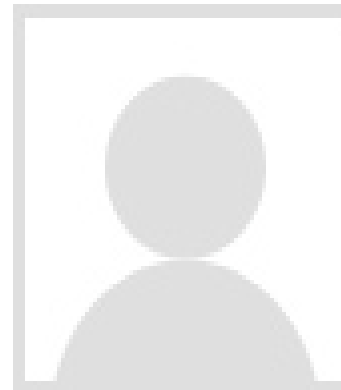
Better selection and decision making

% of patients discussed at MDT



Future

Birmingham Recurrence and Complex Case Clinic

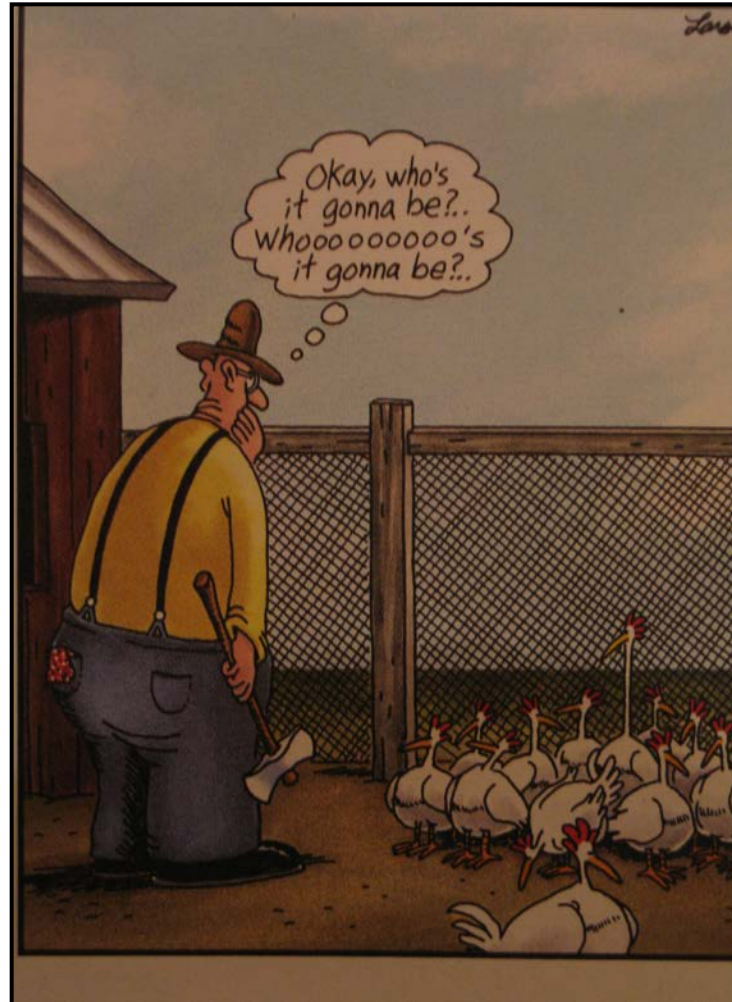


Evidence of improved outcomes in salvage surgery?

Yes

Better patient selection
Better techniques
Less complications
Better post-operative care

Patient selection...



Predictors of good outcome

Tumour factors

- Second primary tumours

2008

Weber, *Arch Otolaryng HNS*,

- Small localised tumour
 - Small T stage and overall stage

Kim, *Laryngoscope*. 2007; Agra et al, *Laryngoscope*. 2000, Zafaero, *Cancer*. 2009

- No neck disease on recurrence

Zafaero, *Cancer*. 2009

- Recurrence >12 months
 - Patients recurring <6months have persistent disease → worse prognosis

Agra et al, *Laryngoscope*. 2000; Zafaero, *Cancer*. 2009

- No extracapsular spread

Zafaero, *Cancer*. 2009

Predictors of good outcome

Patient factors

- Non-smoker or stopped smoking

Kim, *Laryngoscope*. 2007, Agra et al, *Laryngoscope*. 2000

- Good general health (ECOG state 0-1) and minimal co-morbidities

Paleri, *Oral Oncol*. 2007

- Good psychological state
Psychooncology, 2000

De Leeuw,

- Good family support – married

Agada, *J Laryngol Otol*. 2009

- Religious / spiritual

Predictors of good outcome

Treatment factors

- No previous RT or chemo
Paleri, *Oral Oncol.* 2007, Zafereo, *Cancer* , 2009
- No toxicity from previous treatment
Puthawala. *Int J Radiat Oncol Biol Phys* 2001
- Resectable with no gross tumour and no surgical margins
Zafereo, *Cancer* , 2009
- No vital structures involved - the carotid arteries, brachial plexus and pre-vertebral muscles.
Freeman, *Curr Opin Otolaryngol Head Neck Surg.* 2005

Ideal patient profile

- rT1-T2 N0-N1 second primary, no ECS
- >12 months after treatment
- ECOG 0-1, minimal morbidities
- Good psychological and social support
- Non smoker or stopped smoking
- No previous RT or CRT
- Fully involved in the decision making

Best methods to identify patients recurrence and metastases post CRT?



Best method for detection of recurrence

Clinical examination:

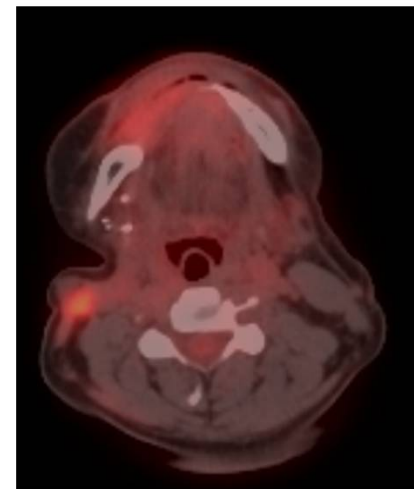
- Symptoms not specific.
- Indirect laryngoscopy: sens 87%, spec 14%.
- Exam under anaesthetic
 - 207 scopes in 131 patients.
 - 31% false negative biopsies with recurrence within 6mnth

Brouwer, *Eur Arch ORL*, 2006

CT/MRI

- CT/MR unable to differentiate reliably between cancer, oedema, interstitial radiation fibrosis and necrosis
- CT did not have value over clinical exam in 46 pts after RT

Ojiri, *Int J Radiat Oncol Biol Phys* 2002
- Follow up CT after initial post treatment CT detected 40% of recurrences earlier than clinical examination



A systematic review and meta-analysis of the role of positron emission tomography in the follow up of head and neck squamous cell carcinoma following radiotherapy or chemoradiotherapy

Isles, M.G.,* McConkey, C.[†] & Mehanna, H.M.*[†]

**Institute of Head and Neck Studies and Education, Department of Otorhinolaryngology Head Neck Surgery, University Hospital, Coventry, [†]Department of Otorhinolaryngology Head Neck Surgery, Heart of England Foundation Trust, Birmingham, and [‡]Warwick Medical School Clinical Trials Unit, University of Warwick, Coventry, UK*

Accepted for publication 8 February 2008

Clin. Otolaryngol. 2008, 33, 210–222

Detection of Recurrence – PET scan

	Sample size	Sens	Spec	PPV	NPV	Accuracy
Primary	453	91.8% (45 – 100)	80.8% (53 – 100)	76.4% (40 – 100)	93.6% (14 – 100)	84.9% (50 – 100)
Neck	70	93.4% (86 – 100)	80.8% (73 – 94)	63.7% (60 – 67)	97.5% (92 – 100)	82.1 (74 – 94)



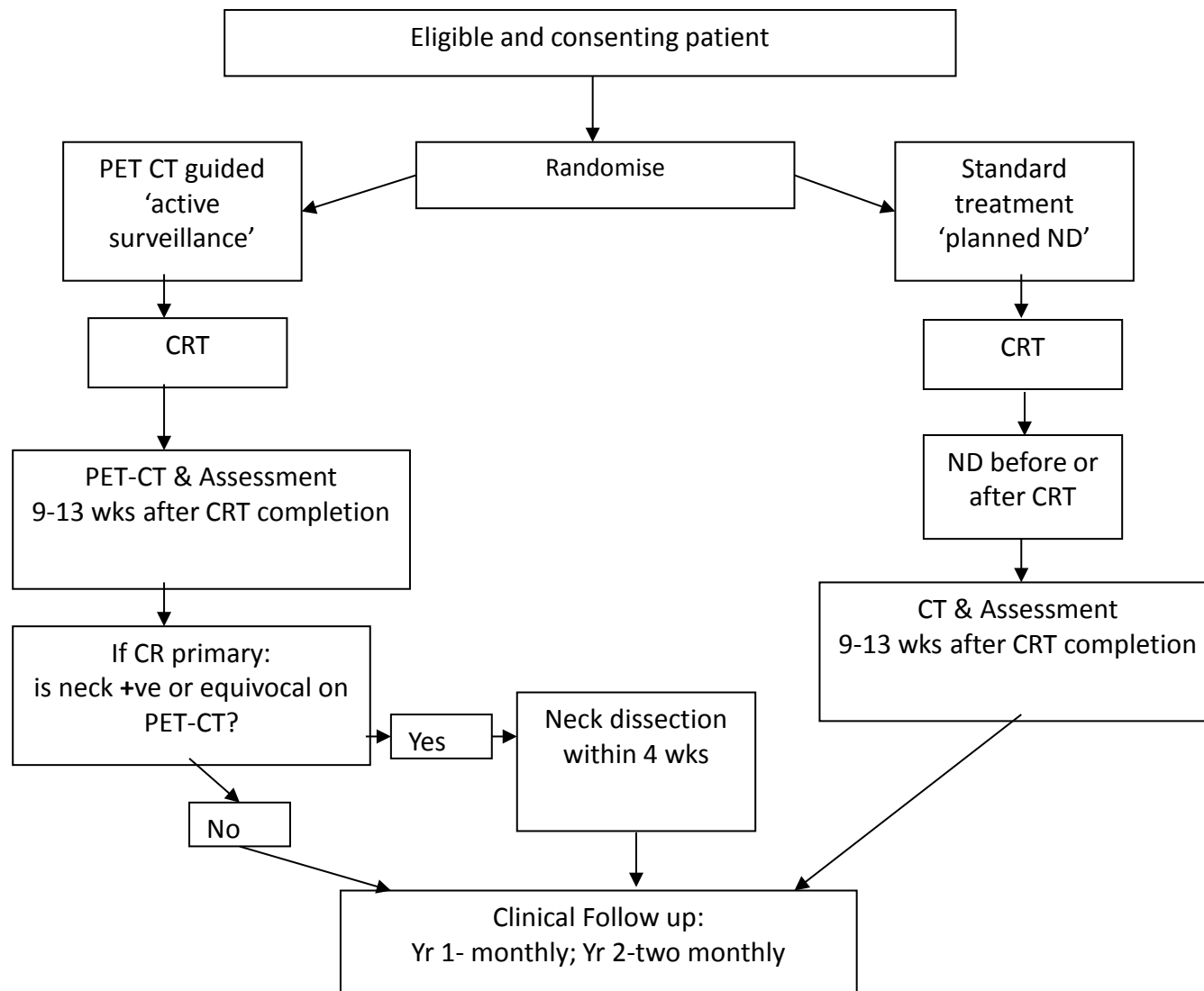
PET-NECK

A multi-centre randomised phase III trial comparing PET-CT guided watch and wait policy versus planned neck dissection for the management of locally advanced (N2/N3) nodal metastases in patients with head and neck squamous cancer

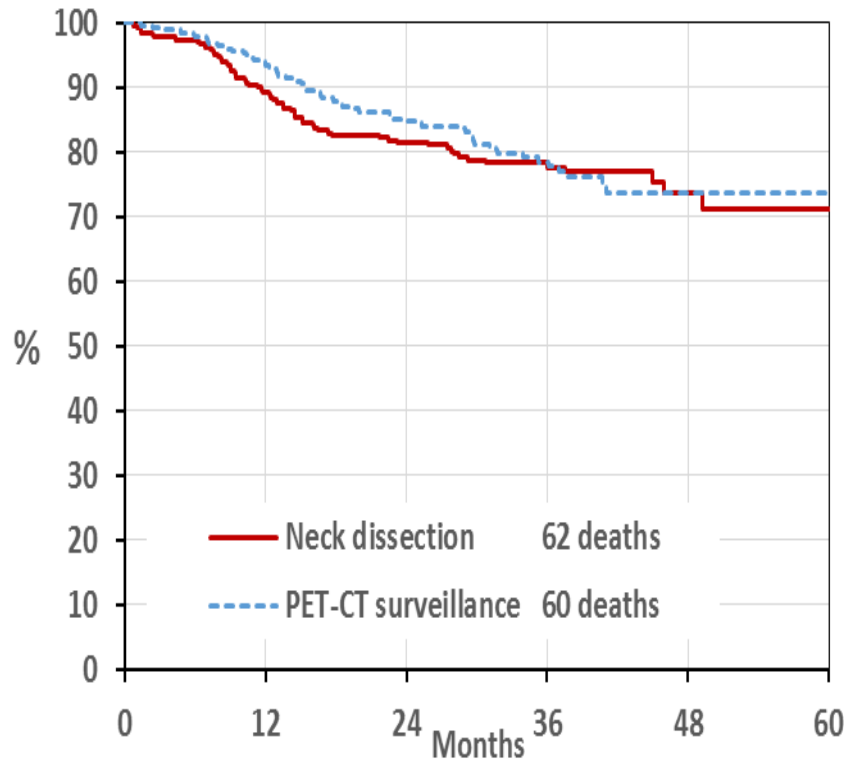
Chief investigator: Hisham Mehanna



PET Neck Trial schema



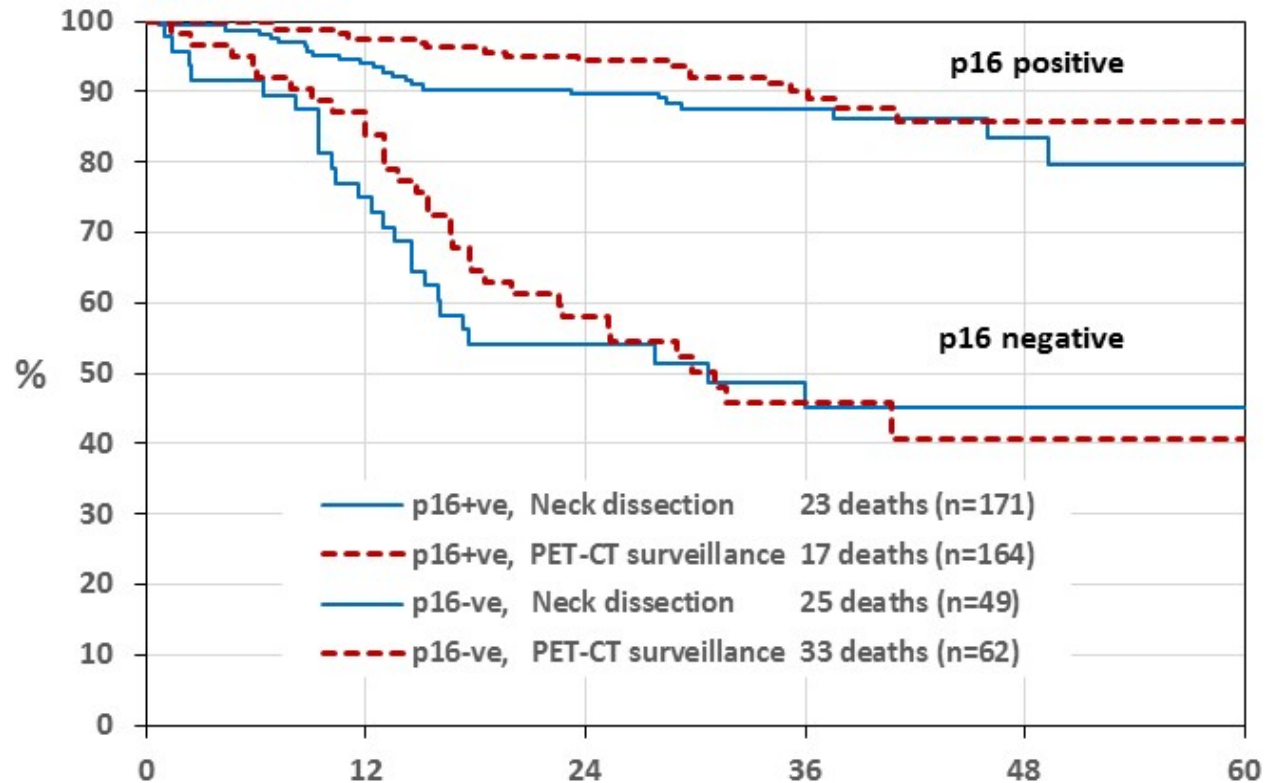
Results – Overall survival



- Control arm 2 year OS 81.5%, better than expected (75%)
- Treatment hazard ratio **0.92** in favour of surveillance
95% CI (0.65, 1.32)
- HR 0.92 rules out an unfavourable difference >4% in 2-year OS at the 5% one-sided alpha level

Number at risk						
Neck dissection	282	243	204	118	32	8
PET-CT surveillance	282	259	224	110	33	6

Overall survival by p16 status and treatment



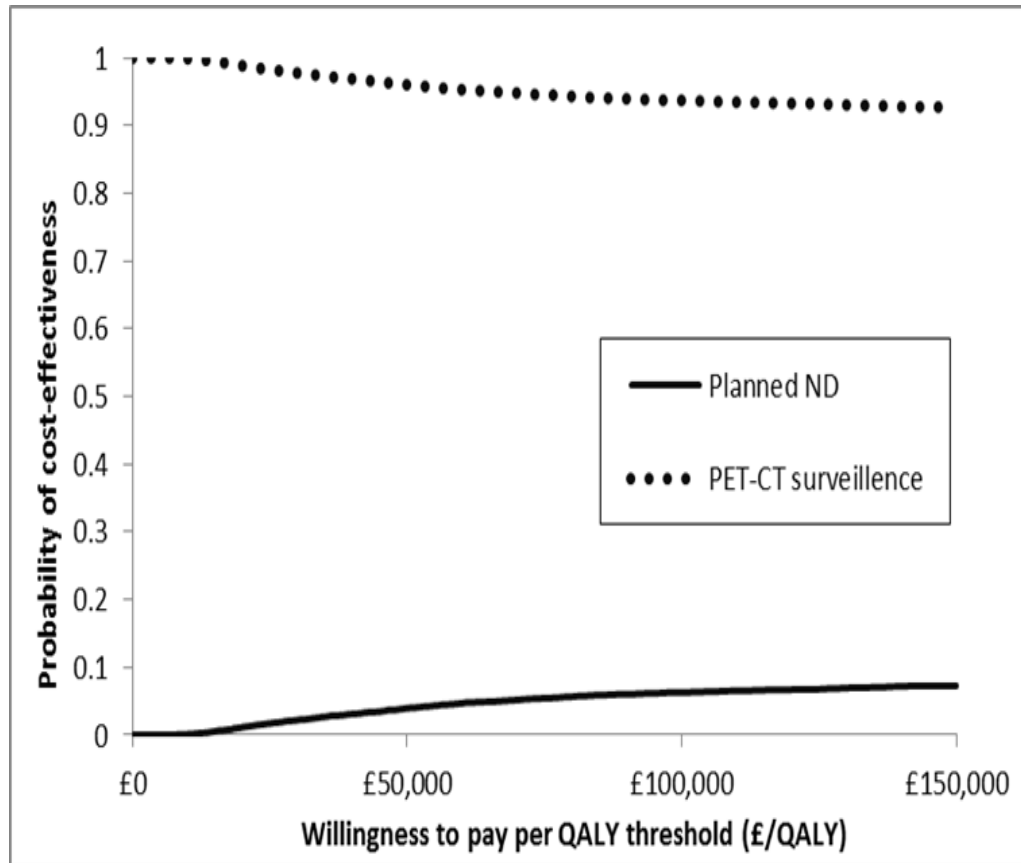
Two year overall survival:

P16 positive 92.1%, (95% CI 89.1 to 95.0)

P16 negative 56.3%, (95% CI 47.1 to 65.6)

Hazard ratio 5.9 (95% CI 3.9 to 8.8)

Results – Cost effectiveness



At a £20,000 per QALY threshold PET-CT guided management is associated with a **99% probability of being cost-effective** compared to planned ND.

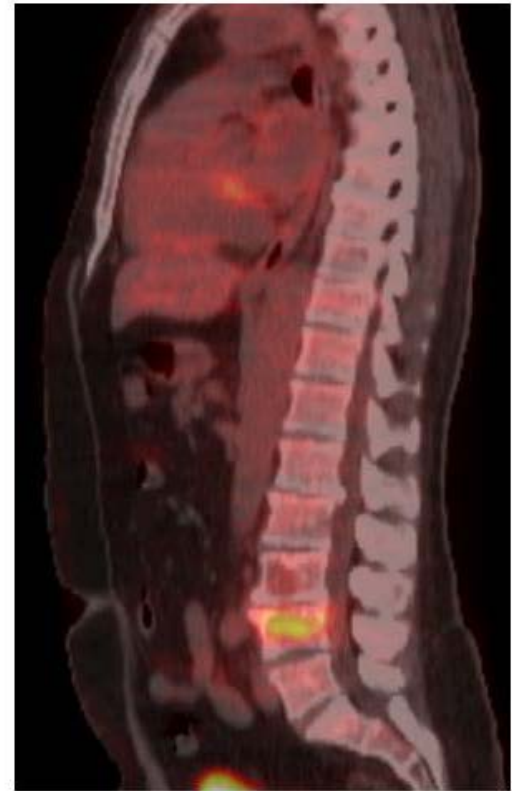
**Cost saving
per-person**

Secondary care
£1,415
(\$2,165)

Primary and
secondary care
£5,791
(\$8,963)

Detection of distant metastasis by PET CT

- RCT comparing PET CT vs Chest CT
- Distant metastasis in 21% of 92 HNC patients.
- FDG-PET higher sensitivity than CT (53% vs. 37%)
- Higher positive predictive value than CT (80% vs. 75%)



InHANSE RAC protocol for Assessment

Detailed History

Examination

PET CT

EUA and biopsy

- anaesthetic assessment

- research biopsies

Speech and language and dietetics assessment

Additional imaging for surgical/RT planning if necessary– CT/MR

InHANSE RAC Decision Making Protocol

1. What were the previous disease and treatments?
 including poor prognosis features and involved margins
 details of RT fields and doses – any geographic misses
 levels of neck dissection
 time since treatment
2. Is there any evidence of distant metastases?
3. Is there recurrence at the primary site?
 is it recurrence or a second primary tumour?
 what is extent/size of the primary recurrence?
4. Is there recurrence in the neck?
 what is extent/size of the neck recurrence?
 Is there evidence of soft tissue extension or nodal extra-
 capsular extension by physical examination and on imaging?

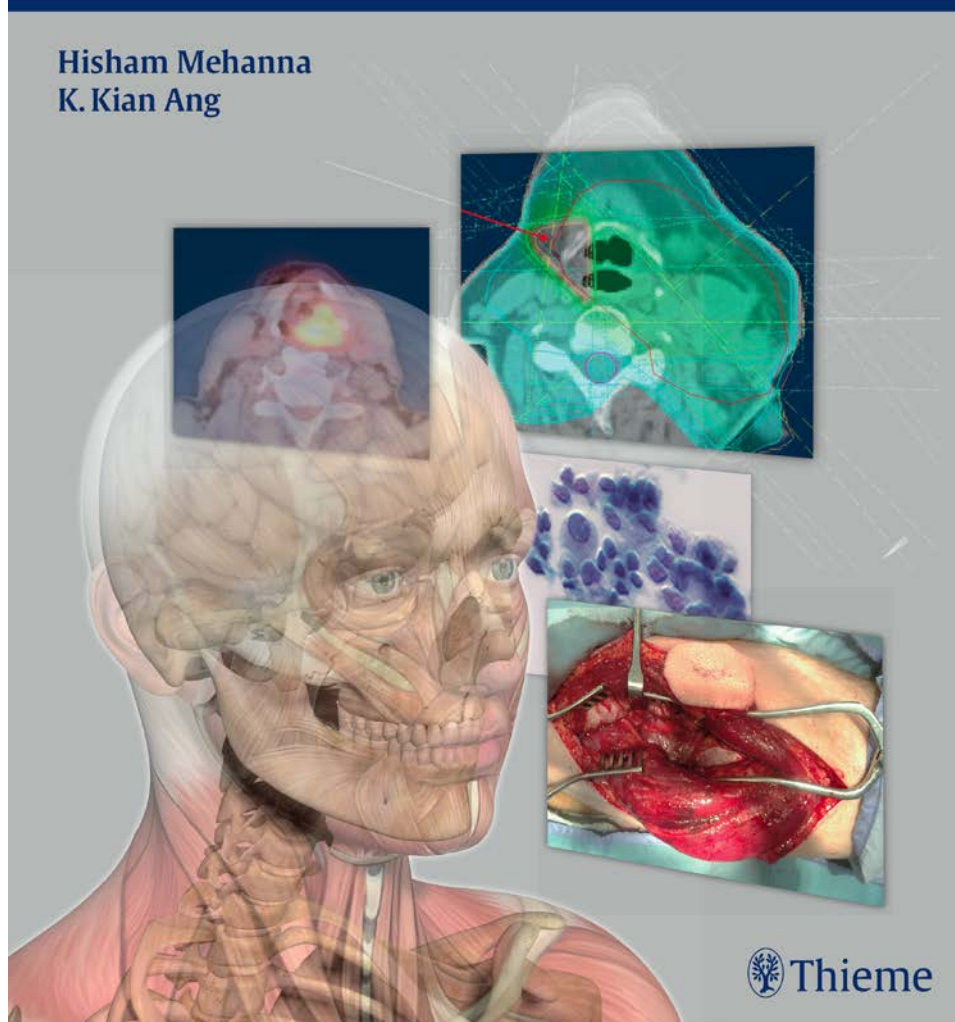
Assessment

5. Is there evidence of involvement of the carotid arteries, brachial plexus and pre-vertebral muscles?
6. Can the recurrence be excised surgically with no gross tumour left behind?
7. Are there complications and toxicity of previous treatment?
osteoradionecrosis
dysphagia
8. Is it possible to give more RT and /or chemotherapy?
9. What are the potential functional deficits of excision/treatment of the recurrence?
10. What is the state of the patient's reserve, psychological state, general health, and family / social support, and what are the patient's wishes?

Head and Neck Cancer Recurrence

Evidence-based, Multidisciplinary Management

Hisham Mehanna
K. Kian Ang



Reducing complications



"Nurse, get on the internet, go to SURGERY.COM, scroll down and click on the 'Are you totally lost?' icon."

Evidence-based techniques to reduce complications of salvage surgery

Selection of appropriate surgical options.

laryngectomy is not the only option:

laser CO2 – TORS – open partial procedures

Paleri, *Cancer*, 2011 ; Marioni, *Acta Oto*, 2006; Steiner, *Head Neck* , 2004

Decreasing morbidity of the surgery.

Decreasing fistula rates:

interposition flaps - Patel, *Otolaryngol Head Neck Surg*, 2009

flap closure of pharynx-Withrow, *Laryngoscope*, 2007

salivary bypass t-tubes -Murray DJ, *Head Neck*, 2007

secondary puncture-Emerick, *Otolaryngol Head Neck Surg*, 2009

Reducing strictures and improving wound healing:

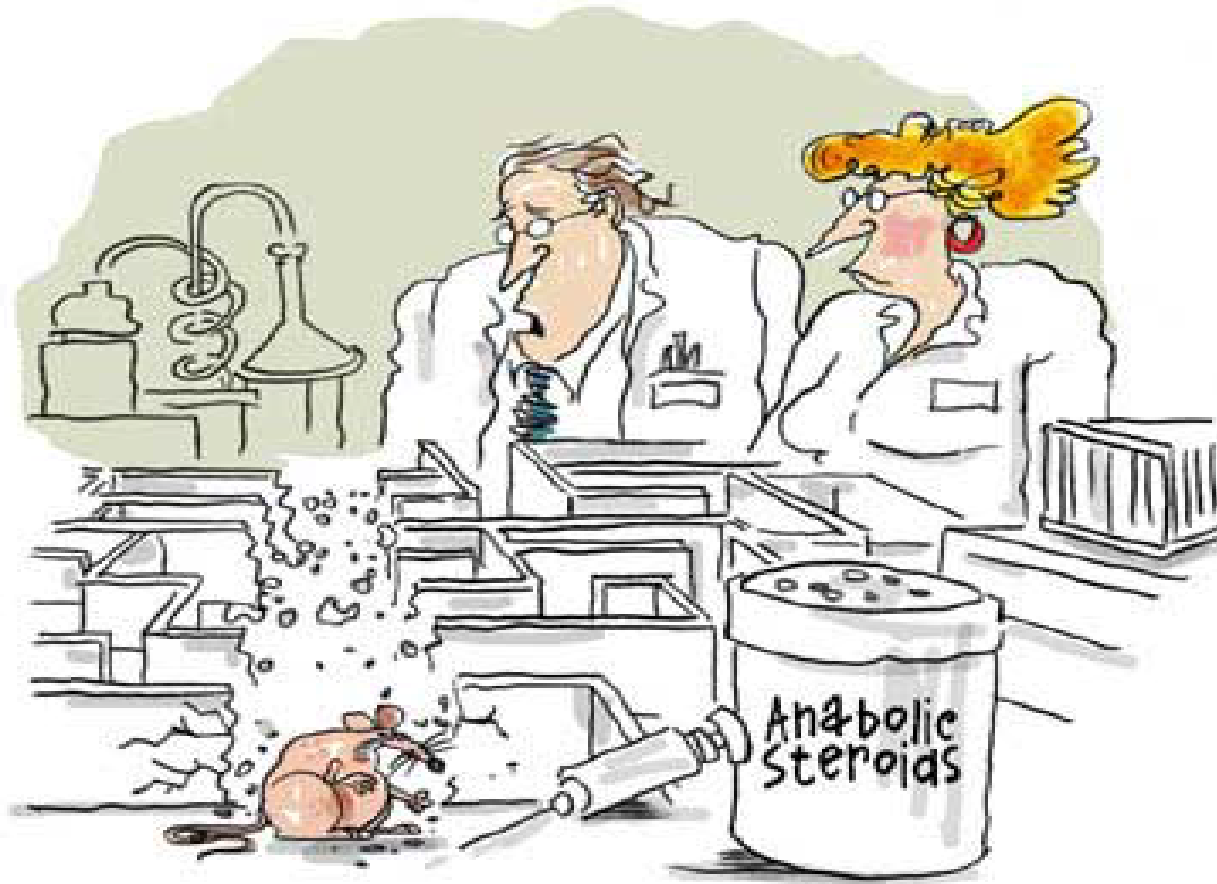
horizontal linear pharyngeal closure

separate stoma site -Emerick, *Otolaryngol Head Neck Surg*, 2009

Decreasing post-neck dissection morbidity:

selective neck dissection-Robbins, *Arch Otolaryngol Head Neck Surg*, 2005

Integrating research into multi-disciplinary clinical practice



"Maybe a smaller dose next time!"

InHANSE Recurrence and Complex Case clinic

- Dedicated head and neck recurrence service
- Multi-disciplinary: surgeon, medical oncologist, radiation oncologist, palliative care physician, SLT, counsellor .
- Cutting edge treatments:
 - Reconstruction - 3D bone reconstruction and pre-plating
 - TOLS
 - Cyberknife and tomotherapy
 - Phase 1 and 2 clinical trials of new agents
 - Best supportive care and psychological support

Integrating research into clinical practice

InHANSE Aim:

offer every HNC and complex patient coming to our service the opportunity to participate in a research trial.

Current trials activity at InHANSE

Phase III/IV

*Pet NECK**

*De-ESCALaTE HPV**

*ElaTION**

Co-STAR*

ARTDECO*

LIHNCS*

OroMouth HPV

HN5000

CRES

Quality of Life

*DeTEQT**

*QUIT**

*QuENCH**

Phase I/II & feasibility

ARCHIMEDES

Cyber-recurrence

PACiFIC

*ASPOD**

Diffusion Thyroid

TiTAN*

BAHA infection

*=RCT

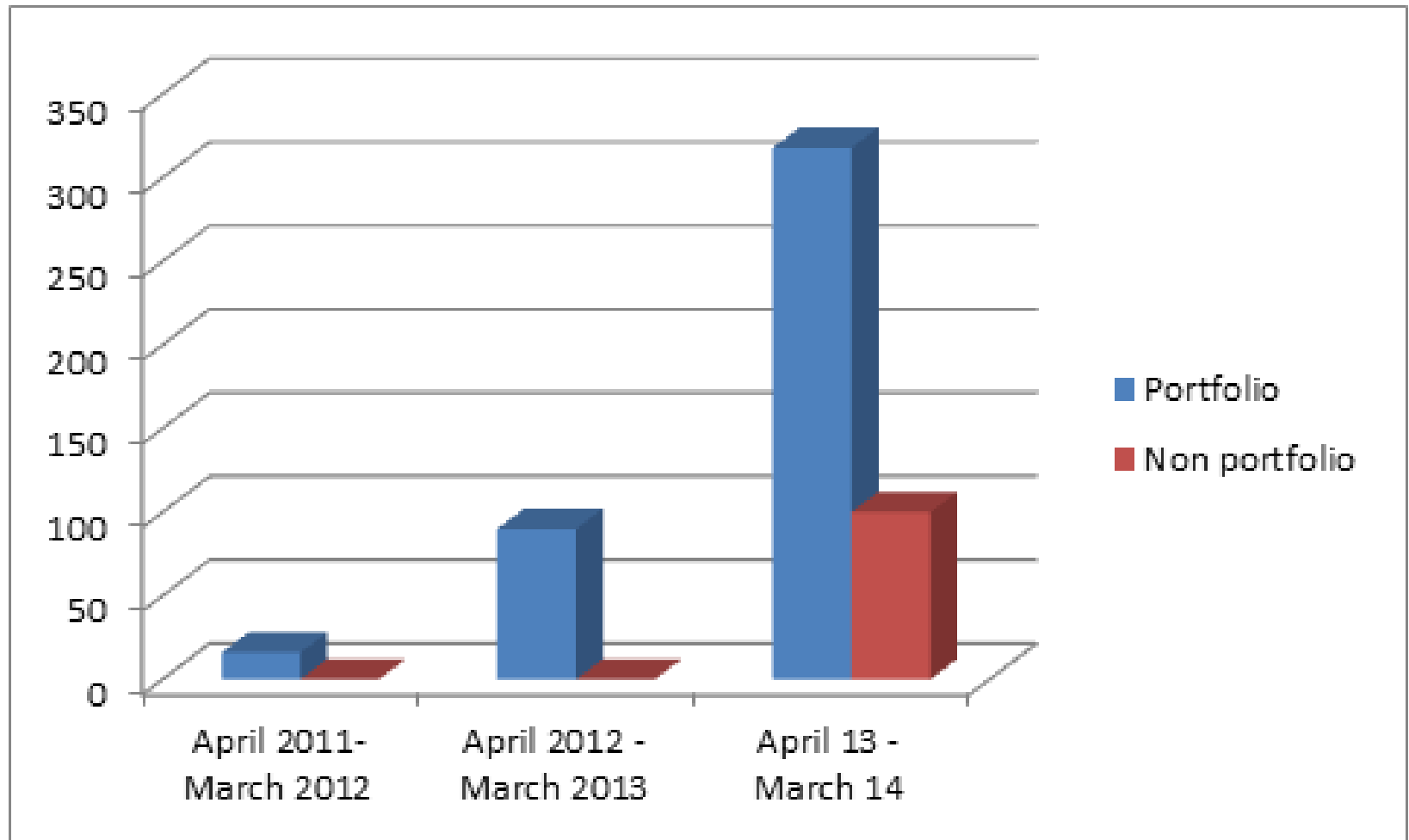
blue=led by InHANSE

Biomarker

Immugen

PrediCTR oropharynx

Recruitment in ENT Head Neck at UHB





Wee-1 inhibitor in addition to standard of care

Co-investigators

Hisham Mehanna, Birmingham
James Good, Birmingham
Kevin Harrington, RMH
Martin Forster, UCL
John Chester, Cardiff
Joe Sacco, Liverpool
Anthony Kong, Birmingham
Christina Yap, CRCTU
Rachel Watkins, InHANSE
Jo Parish, Birmingham

Future – CIRCA project

The NEW ENGLAND JOURNAL of MEDICINE

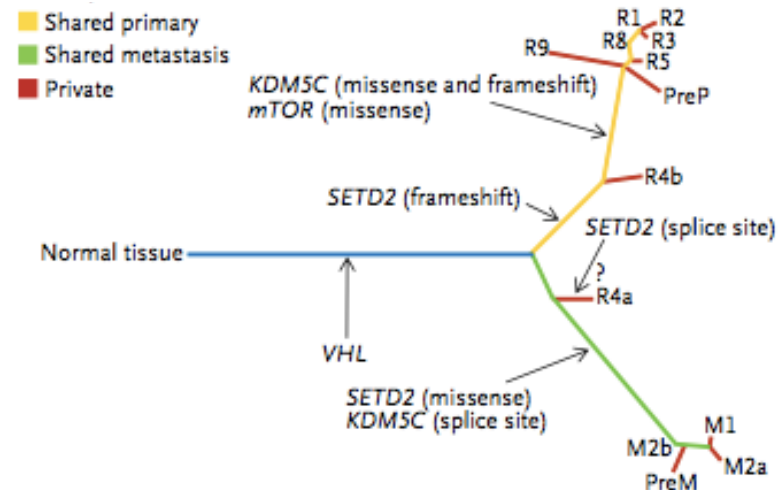
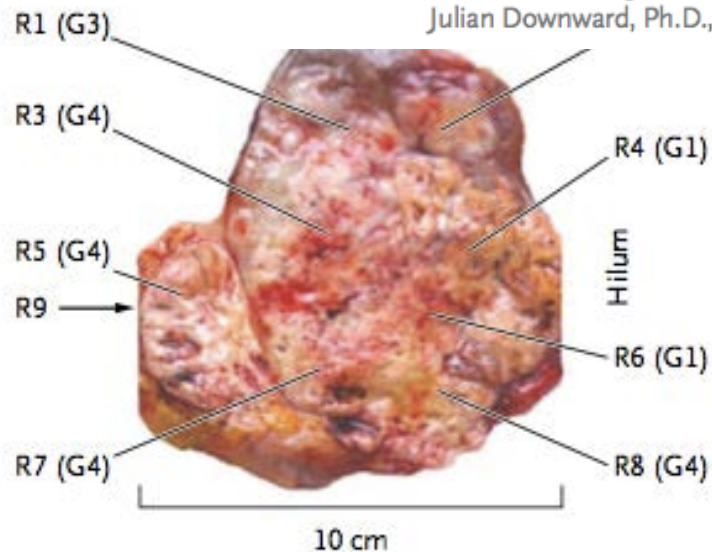
ESTABLISHED IN 1812

MARCH 8, 2012

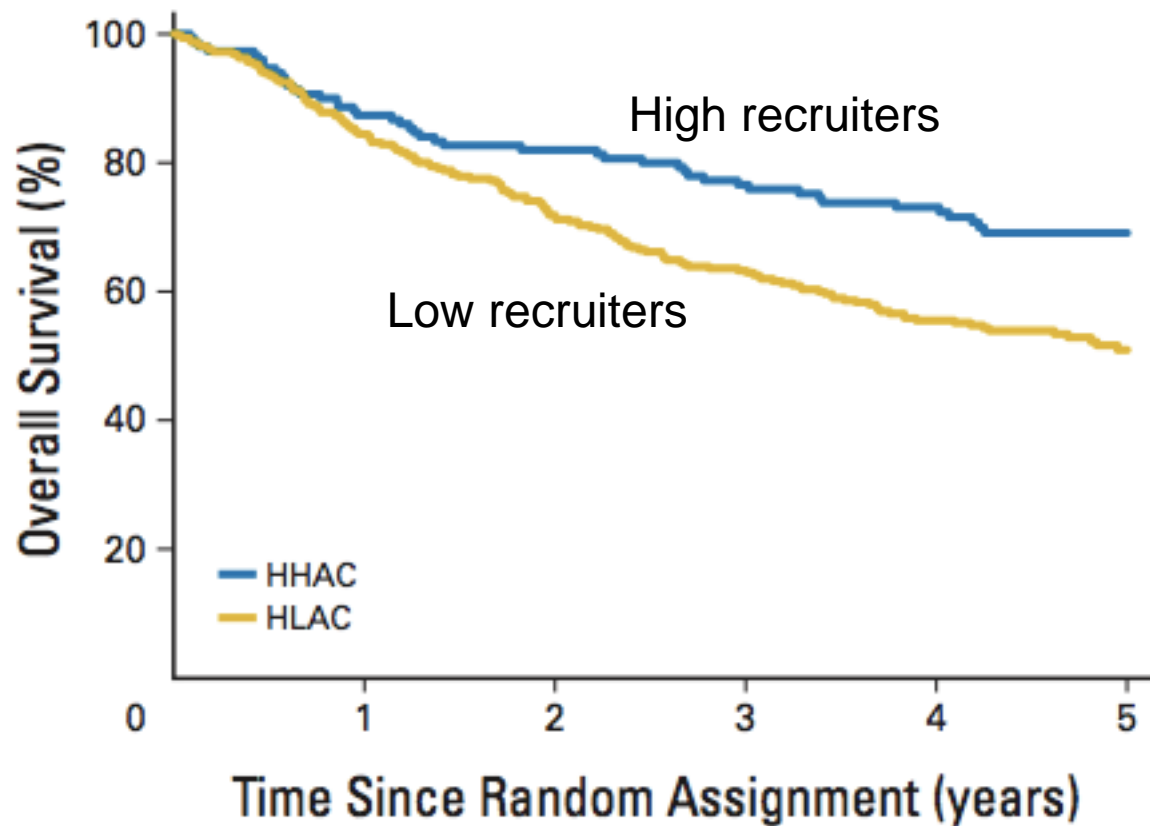
VOL. 366 NO. 10

Intratumor Heterogeneity and Branched Evolution Revealed by Multiregion Sequencing

Marco Gerlinger, M.D., Andrew J. Rowan, B.Sc., Stuart Horswell, M.Math., James Larkin, M.D., Ph.D., David Endesfelder, Dip.Math., Eva Gronroos, Ph.D., Pierre Martinez, Ph.D., Nicholas Matthews, B.Sc., Aengus Stewart, M.Sc., Patrick Tarpey, Ph.D., Ignacio Varela, Ph.D., Benjamin Phillimore, B.Sc., Sharmin Begum, M.Sc., Neil Q. McDonald, Ph.D., Adam Butler, B.Sc., David Jones, M.Sc., Keiran Raine, M.Sc., Calli Latimer, B.Sc., Claudio R. Santos, Ph.D., Mahrokh Nohadani, H.N.C., Aron C. Eklund, Ph.D., Bradley Spencer-Dene, Ph.D., Graham Clark, B.Sc., Lisa Pickering, M.D., Ph.D., Gordon Stamp, M.D., Martin Gore, M.D., Ph.D., Zoltan Szallasi, M.D., Julian Downward, Ph.D., P. Andrew Futreal, Ph.D., and Charles Swanton, M.D., Ph.D.



Volume of recruitment in head neck trials correlated with improved overall survival



Risk of death
at Low Recruiter
Centres
within same RCTs

91% higher
(HR 1.91,
95% CI, 1.37 to 2.65)

and

72% higher
(HR, 1.72;
95% CI, 1.23 to 2.40)
if adjust for
RT deviations

InHANSE team

Clinical trials

Anjola Awofisoye	Alison Edmonds
Michelle Faupel	Victoria Harrop
Gemma Jones	June Jones
Nyra Nyamayaro	Paul Nankivell
Linda Wagstaff	Neil Sharma
Lucy Winterbottom	Corinne Wragg

Translational

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 Max Robinson
 Vicki Smith
 Gosia Wiench
 Ciaran Woodman

Clinical UHB

Rasoul Amelkashipaz
 Steve Colley
 Andrew Hartley
 Chris Jennings
 Tim Martin
 Sat Parmar
 Paul Pracy
 Tedla

Paul Sanghera
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 Jayne Franklyn
 Julie Olliff
 John Watkinson
 O'Connell
 Adrian Warfield
 Zoe Neary
 Kate Reid
 Des McGuire

UHCW

Lydia Fresco
 Gary Walton
 Mark Wake
 Raj Sandhu
 Miro

Andrew Chan
HOEFT/City
 Ijaz Ahmed
 Huw Griffiths
 Janet

Sharan Jayan

Conclusions

Salvage of recurrences is feasible and effective.

Assess patient comprehensively - PET CT is most effective method of detection of recurrence.

‘Ideal’ profile for patient selection

Integrating research into multi-disciplinary clinical practice is an important aim.

Currently what is the 3 year survival rate of recurrent OPC treated surgically?

- 10%
- 20%
- 35%
- 50%
- 65%

For salvage surgery, make sure you assess and plan well...





Institute of Head and Neck Studies and Education

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Clinical trials and
effectiveness

Experimental and
translational medicine

Quality of life

