The International Federation of Head and Neck Oncologic Societies

Current Concepts in Head and Neck Surgery and Oncology 2018

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Advances in Radiotherapy

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Role of radiotherapy in HNC

- 75% HNC patients benefit from RT
  - Post-operative
  - Definitive
  - Palliative

Barton MB et al Radiother Oncol, 2014

Progress over 30 years

- Improved locoregional control & overall survival probability
  - LRC 27% to 80% over 30 years[1]
- Reduction in long term adverse effects[2]
- Superior QoL & patient reported outcomes[3]
- Transition from primary surgery to function preserving RT (pharyngolaryngeal disease)[4]

[1]*Overgaard J JAMA, 2014*
[2]*Langendijk JA et al JCO, 2008*
[3]*O'Sullivan B et al Clin Oncol, 2012*
[4]*Gregoire V et al JCO, 2015*

Advances

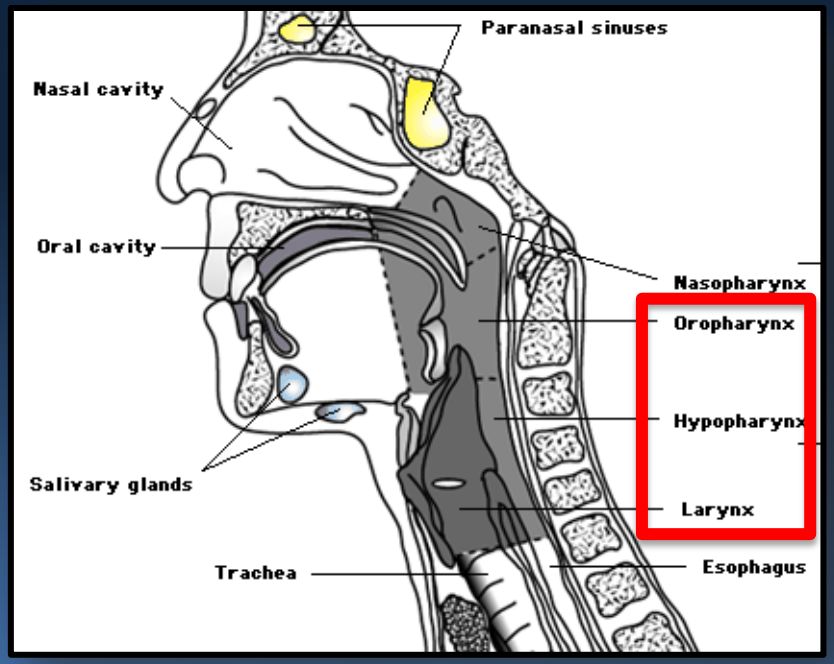
- Treatment intensification
- Treatment-related morbidity
- Radiotherapy delivery & image guidance
- Post-therapy assessment
- Biologic insights & de-escalation strategies
- Radiotherapy quality assurance
- Contouring consensus guidelines

Future advances

- Molecular imaging to identify tumour sub-volumes that may be targeted through dose escalation or targeted agent (dose painting)
- Adaption tracking of tumour or patient changes during treatment (MRI-Linac)
- Improved dose distribution (protons and heavy particle therapy)
- Concomitant immunotherapy

Role of radiotherapy in HNC

- Post-operative
- Definitive
- Palliative



TREATMENT INTENSIFICATION

Meta-analysis conventional vs altered fractionation (MARCH)

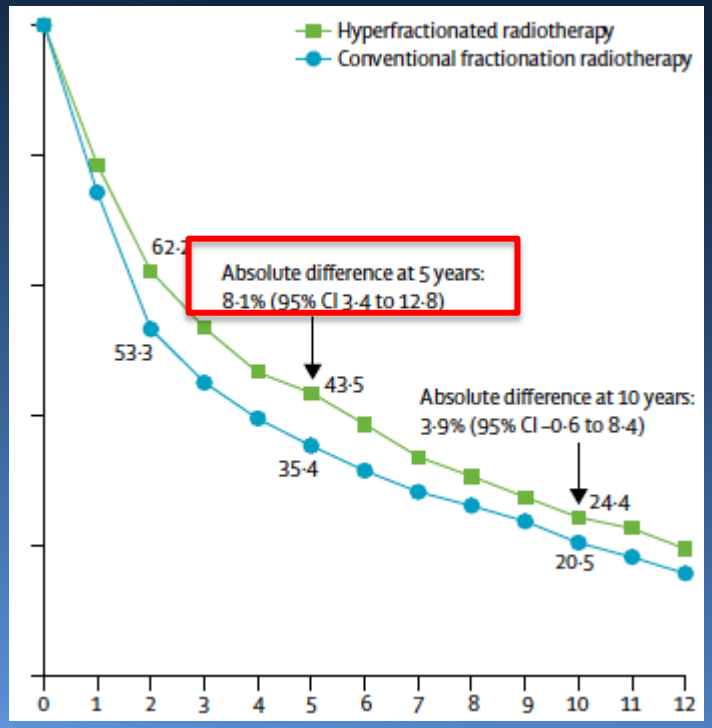
- 15 randomised trials comparing conventional RT vs altered fractionation RT (6515 pts)

- Significant benefit in favour of altered fractionation at 5 years
  - Absolute survival benefit of 3.4%
  - Absolute locoregional control benefit of 6.4%

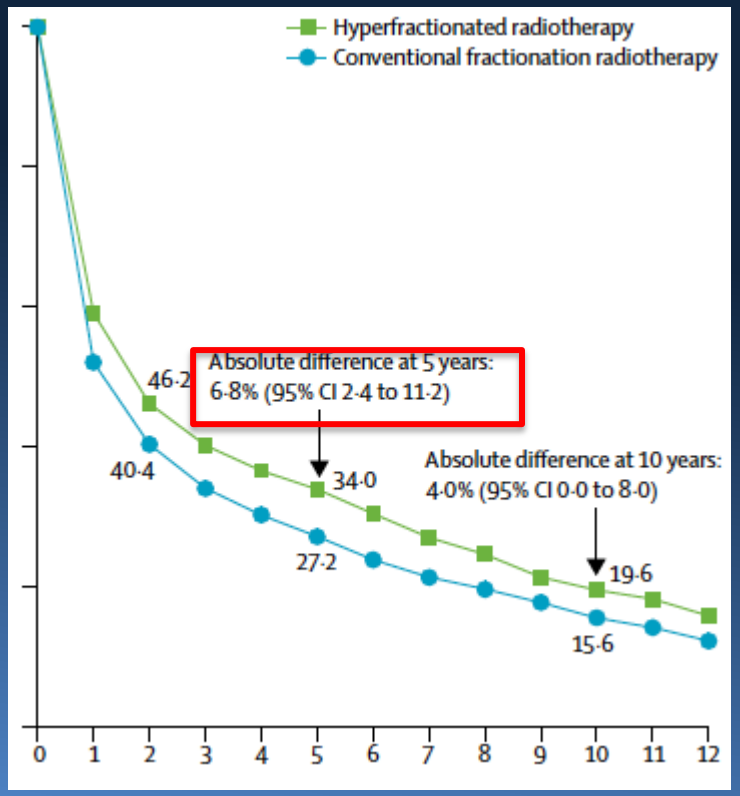
Bourhis J et al Lancet, 2006

Conventional RT vs Hyperfractionation

Overall Survival



Progression Free Survival



MARCH; updated meta-analysis
Lacas B et al Lancet Oncol, 2017

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

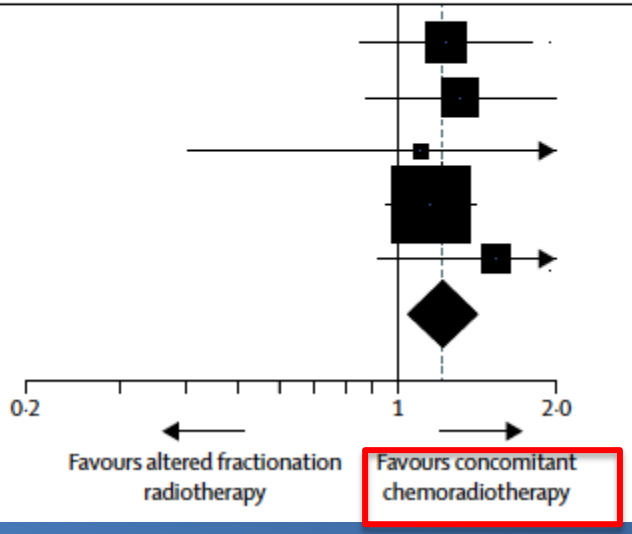
Pignon & Bourhis Lancet, 2000

Altered fractionation vs chemo-RT

	Events (n)/patients (N)		Observed minus expected	Variance	HR (95% CI)
	Altered fractionation radiotherapy	Concomitant chemoradiotherapy			
INRC-HN-9[43]	58/66	55/70	5·9	27·9	1·24 (0·85–1·79)
ORO 9301[55]	50/65	42/64	6·2	22·7	1·32 (0·87–1·98)
EORTC 22962[45]	7/13	9/15	0·4	3·8	1·11 (0·40–3·03)
GORTEC 9902[36]	207/281	196/279	14·7	100·2	1·16 (0·95–1·41)
TMH 1114[37]	34/68	26/65	6·3	14·7	1·54 (0·92–2·56)
Total	**356/493**	**328/493**	**33·6**	**169·4**	**1·22 (1·05–1·42)**

χ^2 test for hetergeneity: p=0·87, I^2=0%

Treatment effect: p=0·0098

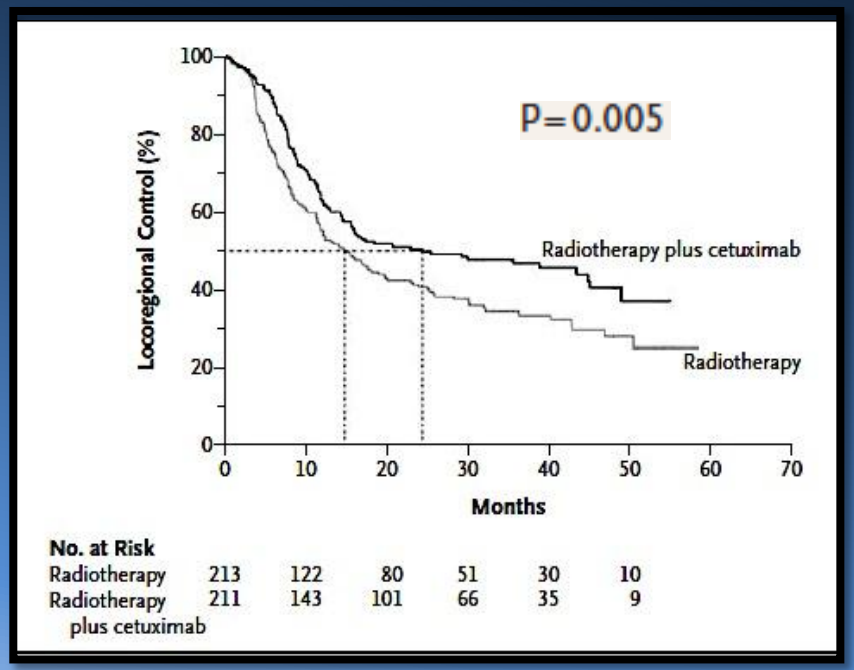


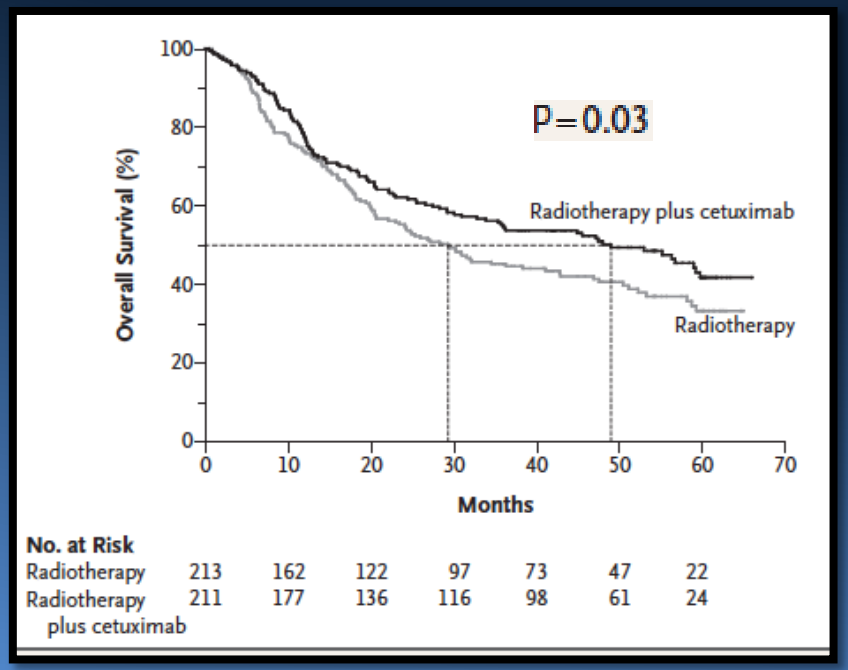
MARCH; updated meta-analysis
Lacas B et al Lancet Oncol, 2017

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radiotherapy plus Cetuximab for Squamous-Cell Carcinoma of the Head and Neck





Bonner et al J NEJM, 2006

Treatment Intensification

Efficacy Outcome	RT	CETUX-RT	p-value
LRC median (mo)	14.9	24.4	0.005
PFS median (mo)	12.4	17.1	0.006
OS median (mo)	29.3	49.0	0.03

Bonner et al J NEJM, 2006

Treatment Intensification

No increase in in-field toxicity

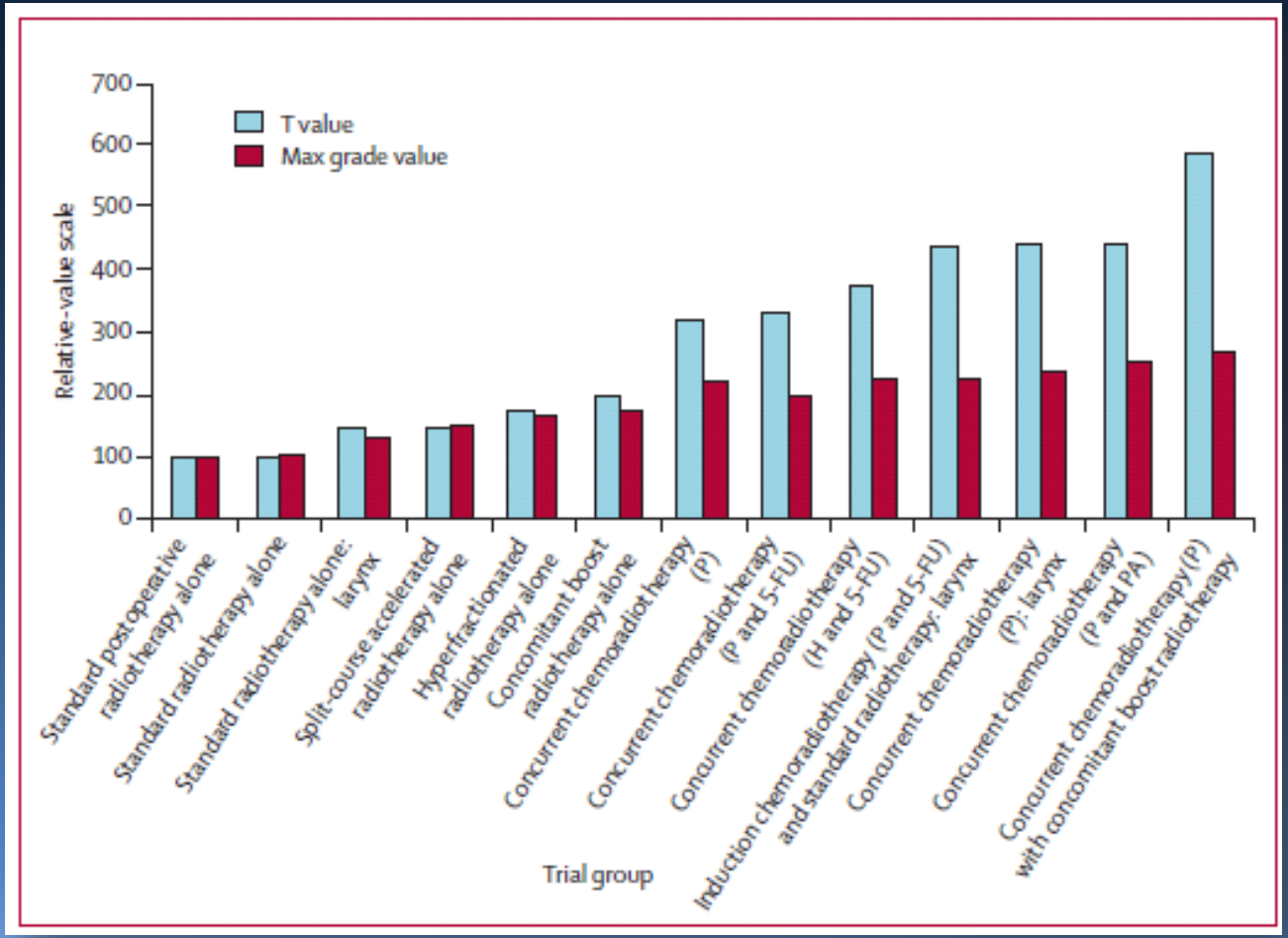
	Radiotherapy (N=212)			Radiotherapy plus cetuximab (N=208)		
	All grades	Grade 3/4	Grade 4	All grades	Grade 3/4	Grade 4
Skin reaction*	200 (94·3%)	45 (21·2%)	3 (1·4%)	204 (98·1%)	73 (35·1%)‖	4 (1·9%)
Mucositis/stomatitis†	199 (93·9%)	110 (51·9%)	9 (4·2%)	194 (93·3%)	116 (55·8%)	13 (6·3%)
Dysphagia	134 (63·2%)	63 (29·7%)	3 (1·4%)	136 (65·4%)	54 (26·0%)	1 (0·5%)
Xerostomia‡	150 (70·8%)	6 (2·8%)	0 (0%)	150 (72·1%)	10 (4·8%)	0 (0%)
Acneiform rash§	21 (9·9%)	3 (1·4%)	0 (0%)	174 (83·7%)‖	35(16·8%)‖	1 (0·5%)
Infusion reaction¶	4 (1·9%)	0 (0%)	0 (0%)	32 (15·4%)‖	6 (2·9%)‖	2 (1·0%)

Table 2: Most common adverse events

Bonner et al J NEJM, 2006

TREATMENT-RELATED ADVERSE EFFECTS

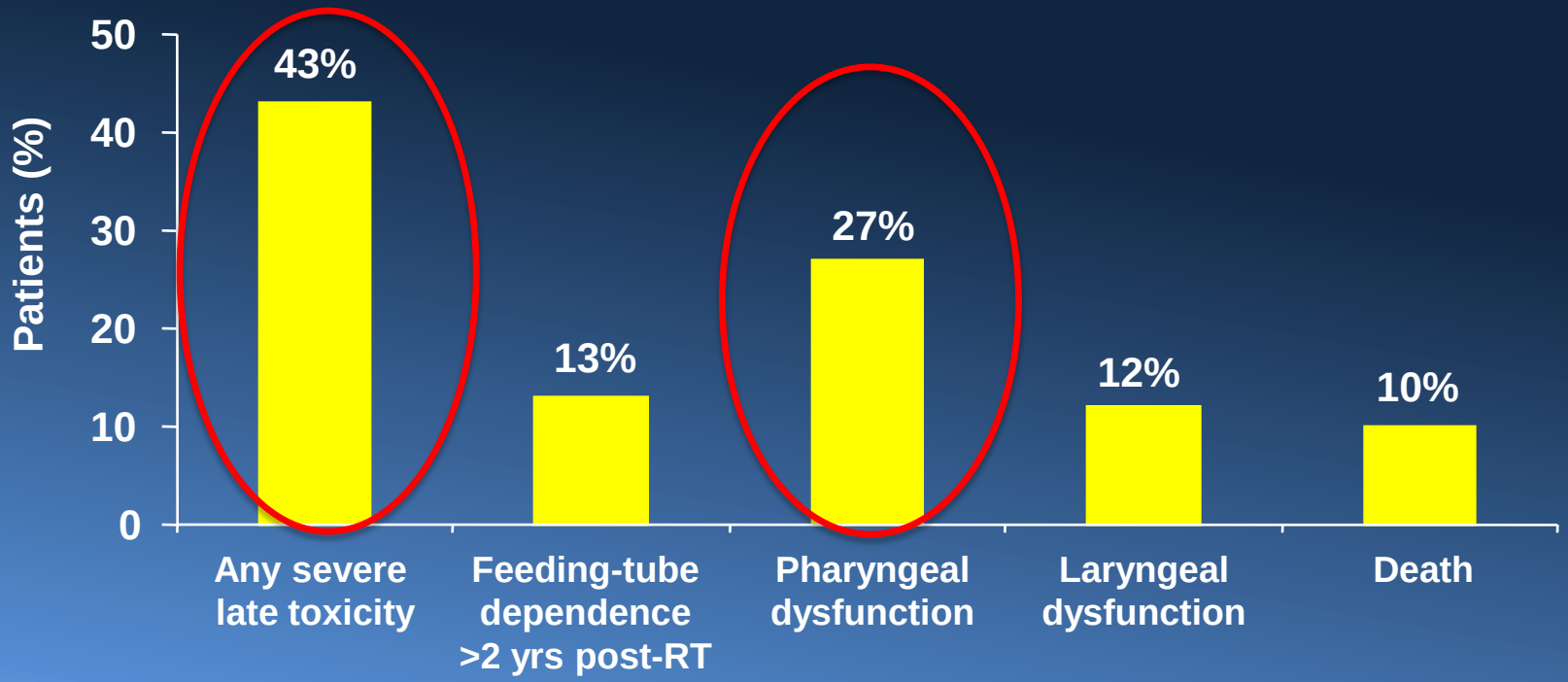
Treatment related adverse effects



Trotti A et al Lancet Oncol, 2007

Treatment related adverse effects

Analysis of 230 patients receiving CRT in 3 studies
(RTOG 91-11, 97-03, 99-14)



Machtay M et al J Clin Oncol, 2008

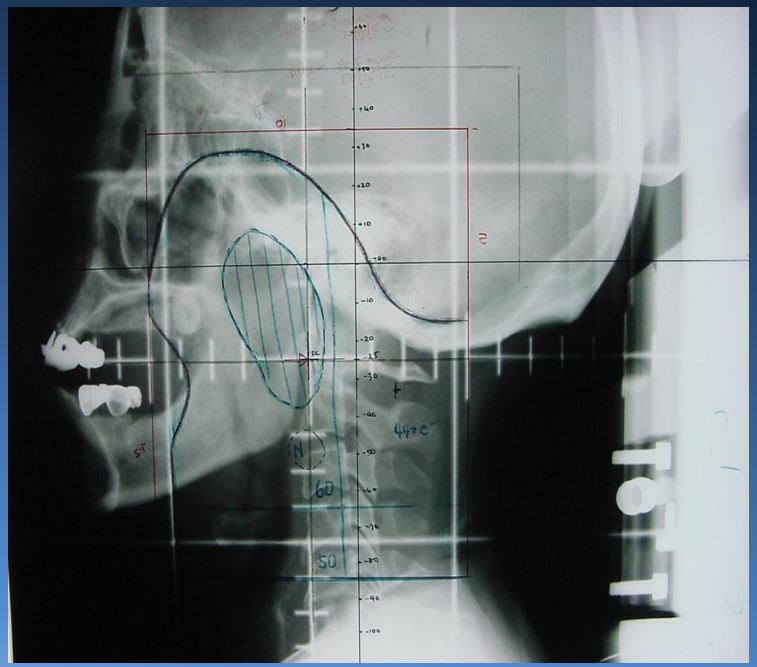
Treatment related adverse effects

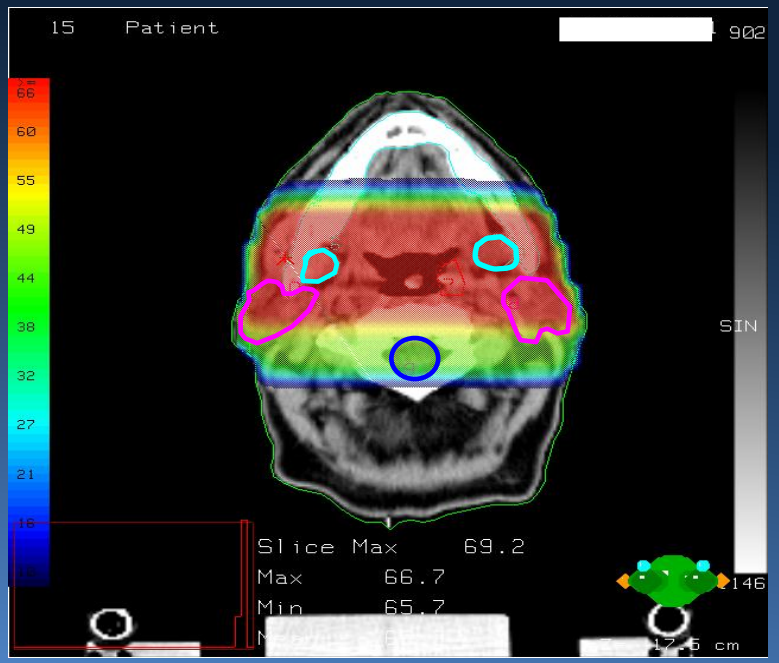
T4N2M0 Nasopharyngeal carcinoma (2008)
Concurrent chemotherapy + IMRT (70Gy)

RADIOTHERAPY DELIVERY & IMAGE GUIDANCE

Radiotherapy delivery

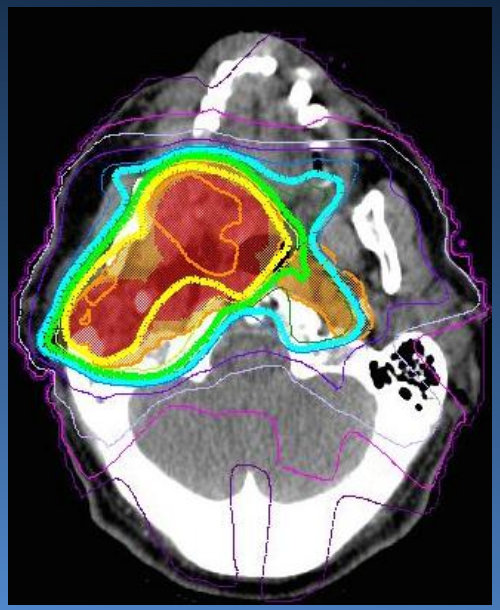
- 2 Dimensional



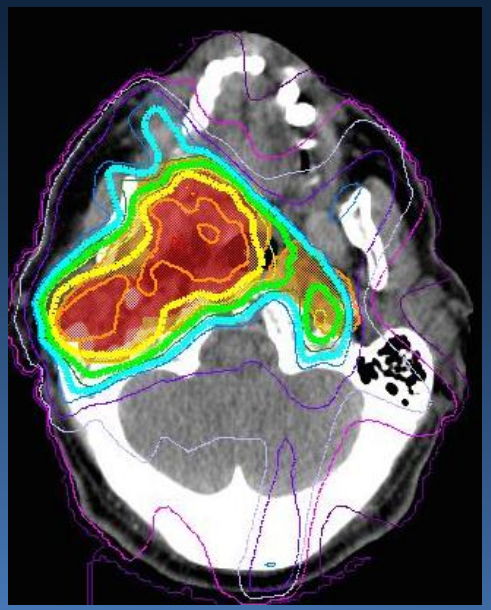


Radiotherapy delivery

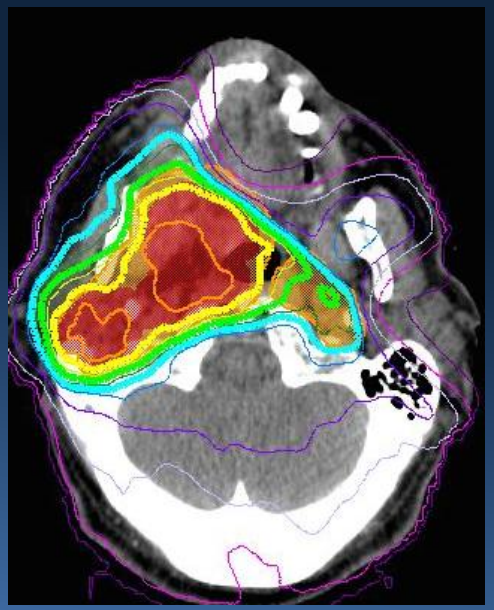
3D CT



IMRT



Dynamic IMRT



Dose Volume Histogram

Oral Cavity

VMAT

IMRT

3D CT

ROI Statistics

Line Type	ROI	Trial or Record	Min.	Max.	Mean	Std. Dev.
◇ ——	Oral Cavity	3DCRT 70	11.53	73.57	51.05	20.47
◆ -----	Oral Cavity	IMRT	5.42	74.30	42.50	21.06
◇ ——	Oral Cavity	Trial_1 VMAT	4.66	71.83	34.61	24.48

PARSPORT Trial Design

Head and neck cancer patients
at risk of radiation induced xerostomia
(oropharynx/hypopharynx)

Randomisation 1:1

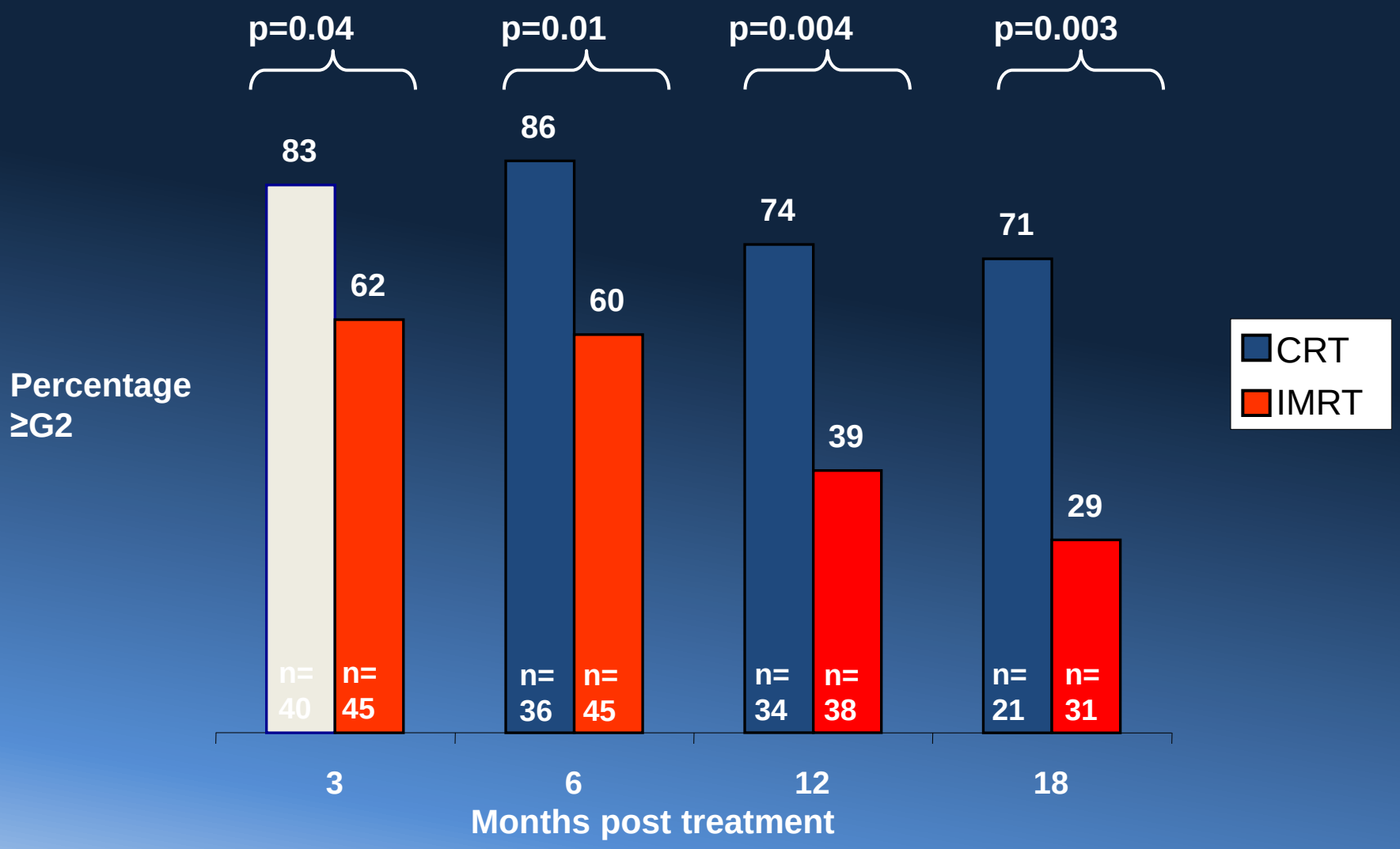
Conventional radiotherapy (CRT)

Parotid-sparing IMRT
(Contralateral Parotid Mean dose <24Gy)

65Gy/30 fractions in 6 weeks - radical and post-operative R1/R2
60Gy/30 fractions in 6 weeks - post-operative R0

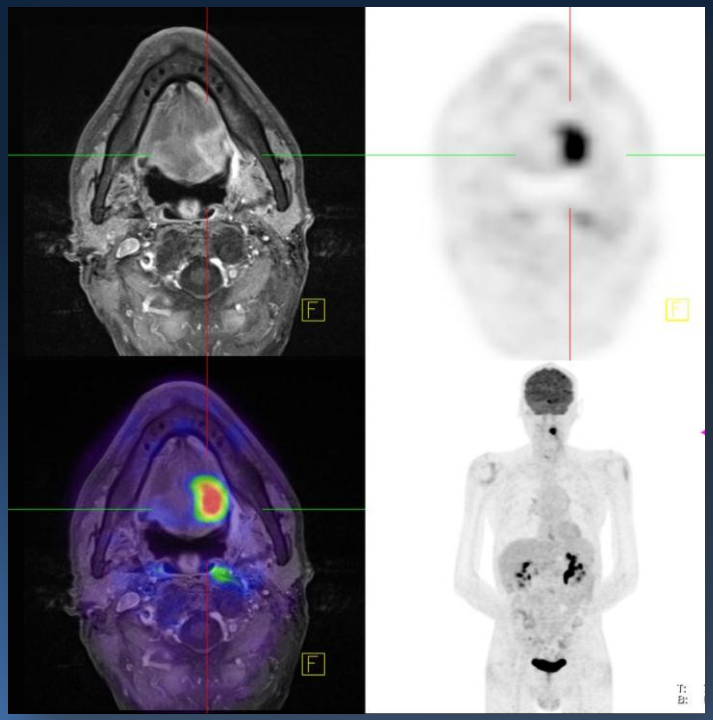
Nutting CM et al Lancet Oncol, 2011

LENT SOMA Subjective Xerostomia rates



Nutting CM et al Lancet Oncol, 2011

Improved tumour delineation

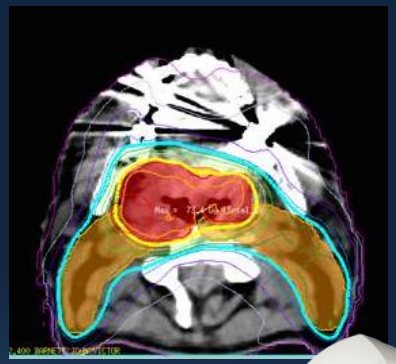


Molecular imaging (FDG PET) - structural imaging (CT/MRI)

Image guided radiotherapy

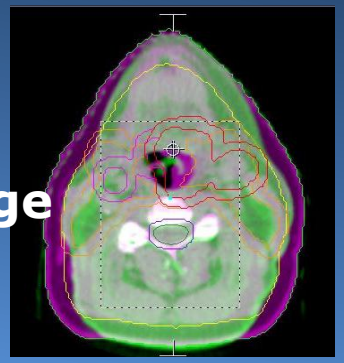
Cone beam CT (CBCT)

- Efficient in-room 3D treatment verification
- Assess and account for translation and rotation
- Ability to match to predefined region and correct around a point of interest
- Monitoring of anatomical change during treatment
- Use for adaptive radiotherapy



Volumetric Modulate
Arc Therapy Delivery

Linac with CBCT



Week 5 CBCT image

POST-THERAPY ASSESSMENT

PET in the post-therapy assessment of residual nodes

Negative Predictive Value
12-16 week restaging PET
95-97%

Yao et al IJROBP 2005
Porceddu SV et al HN 2005

Brisbane PET Protocol Study
Post-therapy PET guided management of the neck

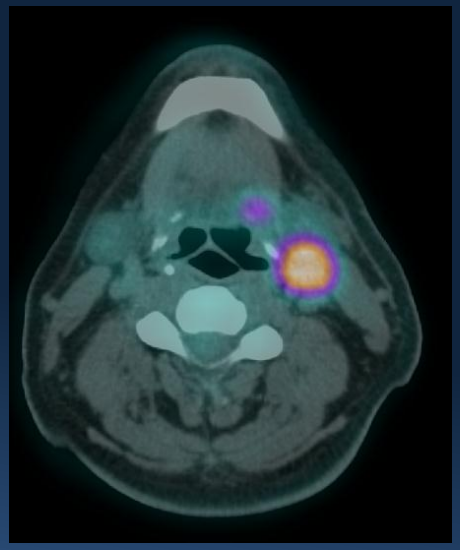
- regardless of the presence of *residual nodal* abnormality

2 year total nodal failures 3.5%

- median residual node 1.5cm (1.0-4.0cm)

Safe to observe neck if residual nodal abnormality is PET negative

Porceddu SV et al Head Neck 2011



Pre-treatment PET

12 week post-therapy PET

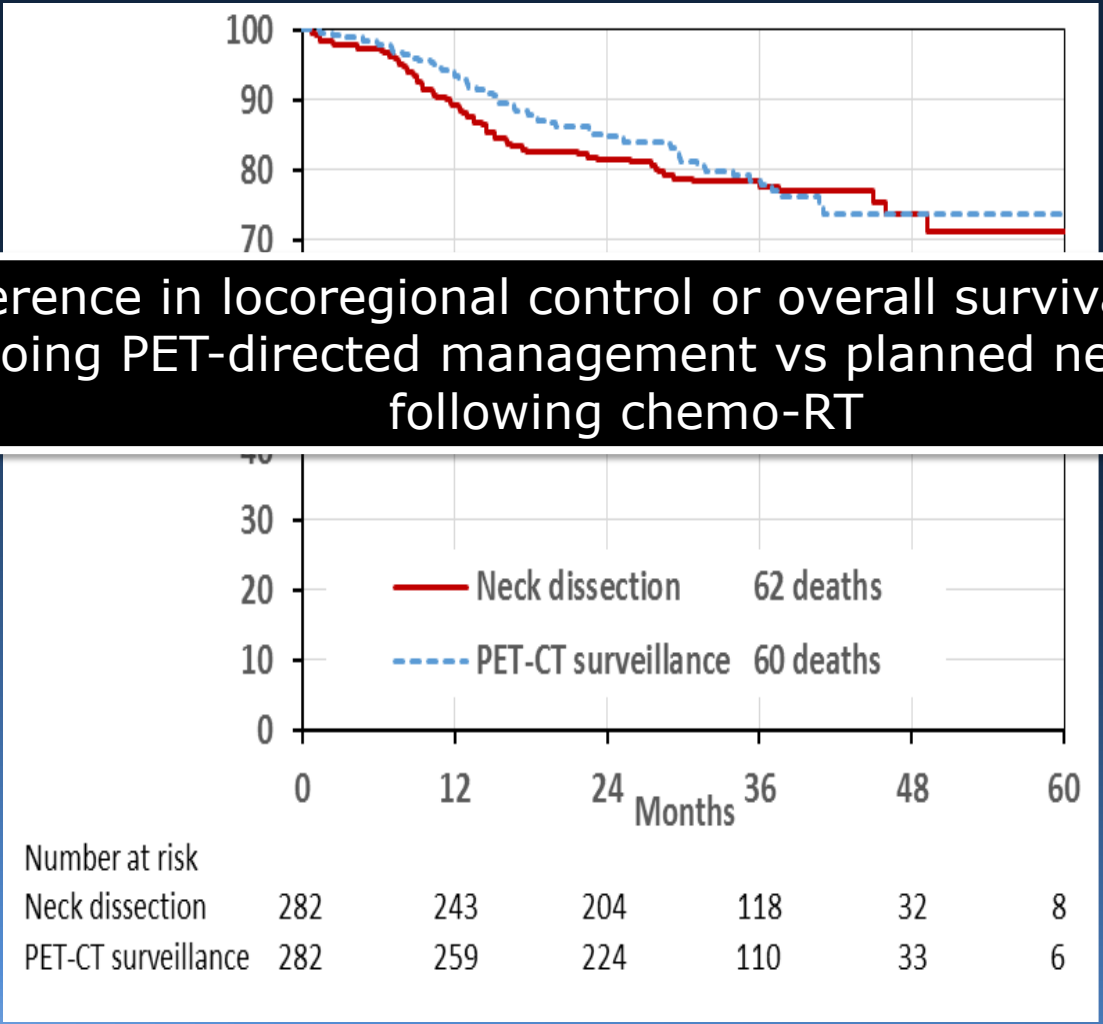
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PET-CT Surveillance versus Neck Dissection in Advanced Head and Neck Cancer

Hisham Mehanna, Ph.D., Wai-Lup Wong, F.R.C.R.,
Christopher C. McConkey, Ph.D., Joy K. Rahman, M.Sc.,
Max Robinson, Ph.D., Andrew G.J. Hartley, F.R.C.R., Christopher Nutting, Ph.D.,
Ned Powell, Ph.D., Hoda Al-Booz, F.R.C.R., Martin Robinson, F.R.C.R.,
Elizabeth Junor, F.R.C.R., Mohammed Rizwanullah, F.R.C.R.,
Sandra V. von Zeidler, Ph.D., Hulya Wieshmann, F.R.C.R., Claire Hulme, Ph.D.,
Alison F. Smith, M.Sc., Peter Hall, Ph.D., Janet Dunn, Ph.D.,
for the PET-NECK Trial Management Group*

Overall survival



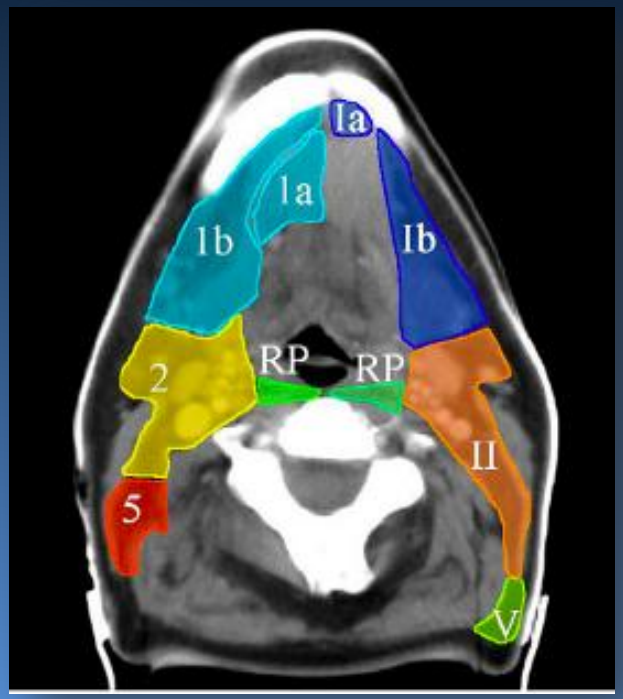
No difference in locoregional control or overall survival in patients undergoing PET-directed management vs planned neck dissection following chemo-RT

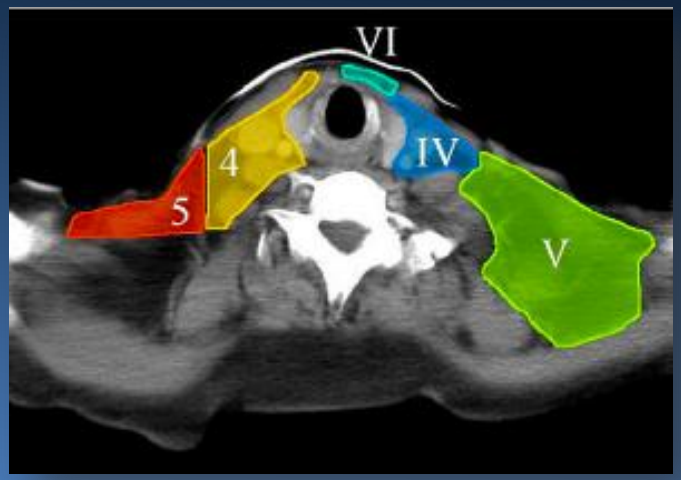
Mehanna H et al NEJM, 2016

CONTOURING CONSENSUS GUIDELINES

Delineation of the neck node levels for head and neck tumors: A 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines ☆

Vincent Grégoire [a,*], Kian Ang [b], Wilfried Budach [c], Cai Grau [d], Marc Hamoir [e], Johannes A. Langendijk [f], Anne Lee [g], Quynh-Thu Le [h,i], Philippe Maingon [j], Chris Nutting [k], Brian O'Sullivan [l], Sandro V. Porceddu [m], Benoit Lengele [n]

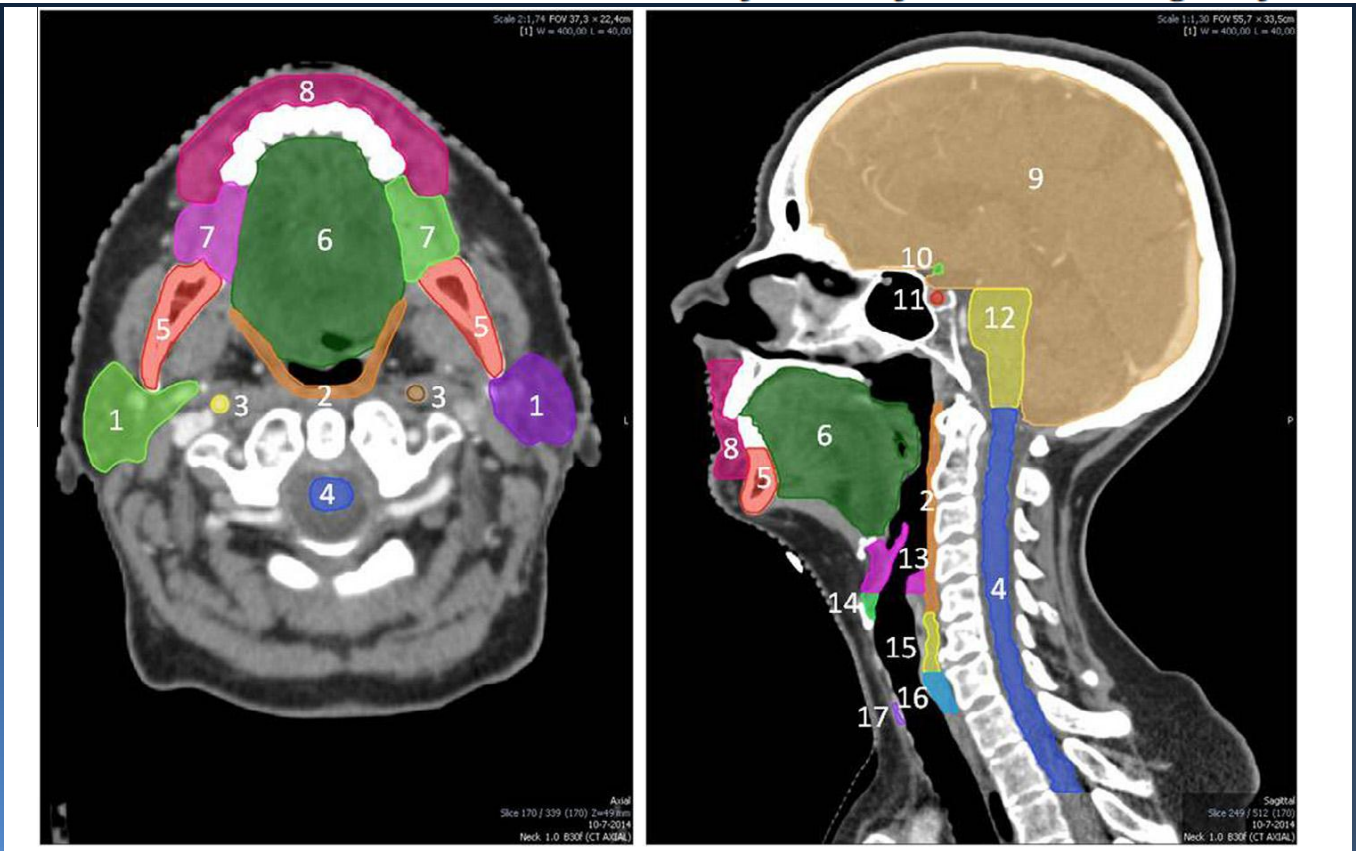




Gregoire V et al Radiother Oncol, 2014

CT-based delineation of organs at risk in the head and neck region: DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG consensus guidelines

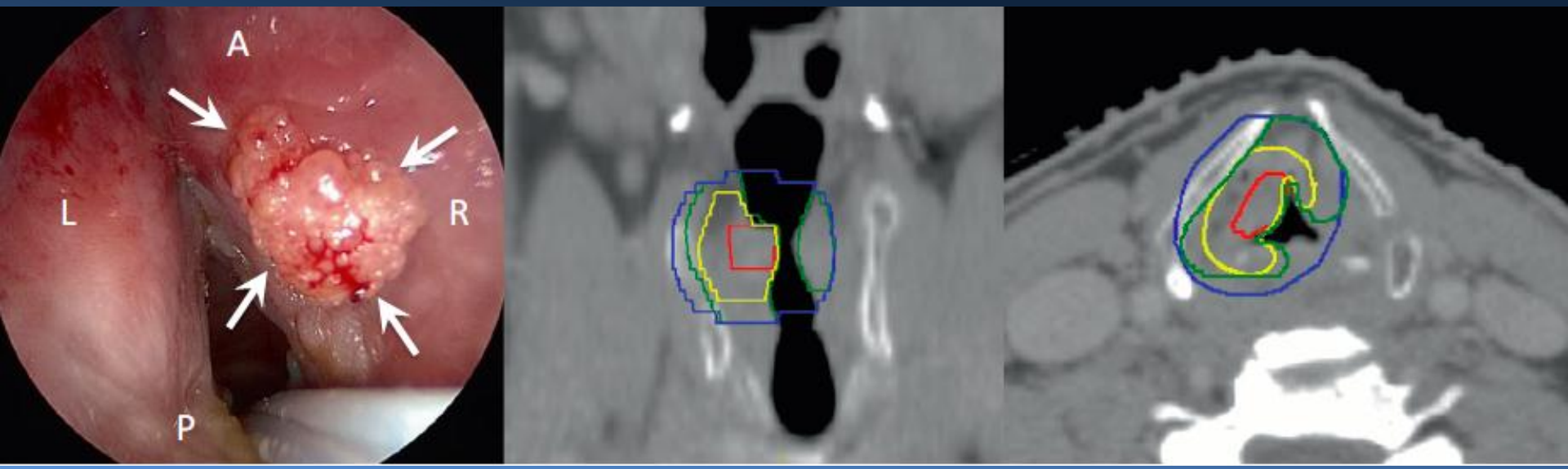
Charlotte L. Brouwer [a,*,1], Roel J.H.M. Steenbakkers [a,1], Jean Bourhis [b], Wilfried Budach [c], Cai Grau [d], Vincent Grégoire [e], Marcel van Herk [f], Anne Lee [g], Philippe Maingon [h], Chris Nutting [i], Brian O'Sullivan [j], Sandro V. Porceddu [k], David I. Rosenthal [l], Nanna M. Sijtsema [a], Johannes A. Langendijk [a]



Brouwer CL et al Radiother Oncol, 2015

Delineation of the primary tumour Clinical Target Volumes (CTV-P) in laryngeal, hypopharyngeal, oropharyngeal and oral cavity squamous cell carcinoma: AIRO, CACA, DAHANCA, EORTC, GEORCC, GORTEC, HKNPCSG, HNCIG, IAG-KHT, LPRHHT, NCIC CTG, NCRI, NRG Oncology, PHNS, SBRT, SOMERA, SRO, SSHNO, TROG consensus guidelines

Vincent Grégoire [a,*], Mererid Evans [b], Quynh-Thu Le [c], Jean Bourhis [d], Volker Budach [e], Amy Chen [f], Abraham Eisbruch [g], Mei Feng [h], Jordi Giralt [i], Tejpal Gupta [j], Marc Hamoir [k], Juliana K. Helito [l], Chaosu Hu [m], Keith Hunter [n], Jorgen Johansen [o], Johannes Kaanders [p], Sarbani Ghosh Laskar [j], Anne Lee [q], Philippe Maingon [r], Antti Mäkitie [s], Francesco Micciche' [t], Piero Nicolai [u], Brian O'Sullivan [v], Adela Poitevin [w], Sandro Porceddu [x], Krzysztof Składowski [y], Silke Tribius [z], John Waldron [v], Joseph Wee [aa], Min Yao [ab], Sue S. Yom [ac], Frank Zimmermann [ad], Cai Grau [ae]



Gregoire V et al Radiother Oncol, 2018

BIOLOGIC INSIGHTS & DE-ESCALATION STRATEGIES

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.

Radiation Therapy Oncology Group 0129

STRATIFY

Tumor Site
1. Larynx
2. Non-Larynx

Nodal Stage
1. N0
2. N1 or N
3. N2c or

Zubrod P S
1. 0
2. 1

RAND[illegible]ZE

Arm 1:
Standard Fractionation
70 Gy/35 Fx/7 weeks
plus cisplatin 100 mg/m^2 on days 1, 22, 43

No difference in OS or PFS

Arm 2:
Accelerated Fractionation by Concomitant Boost
72 Gy/42 Fx/6 weeks
plus cisplatin 100 mg/m^2 on days 1, 22

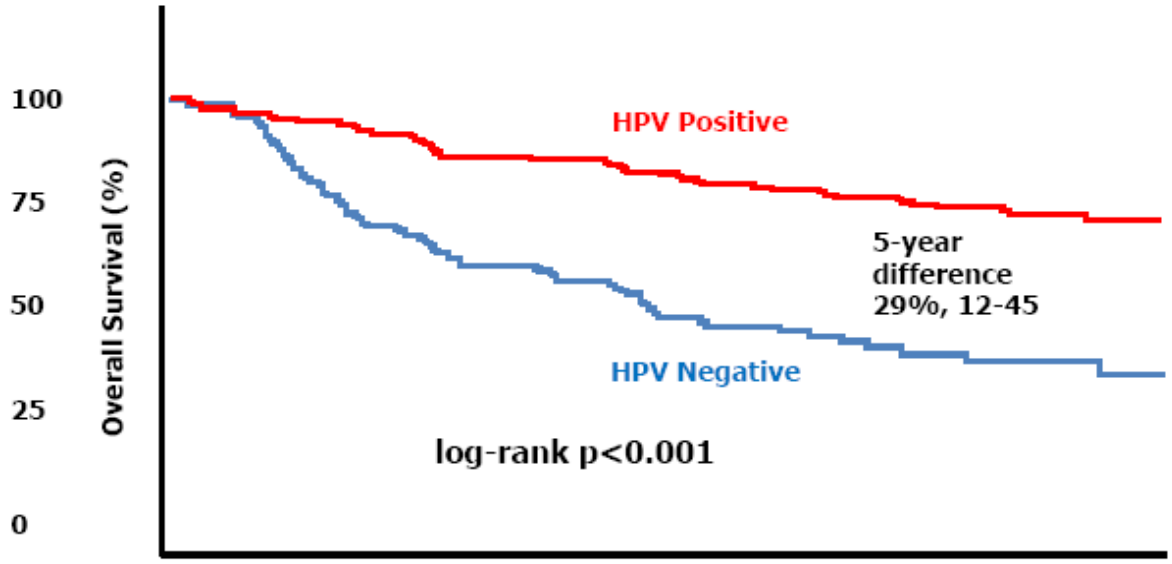
- Oropharyngeal 433

Gillison M. ASCO 2009, Orlando, abstract # 6003

RTOG 0129

RTOG
Radiation Therapy Oncology Group

Survival outcomes by HPV status

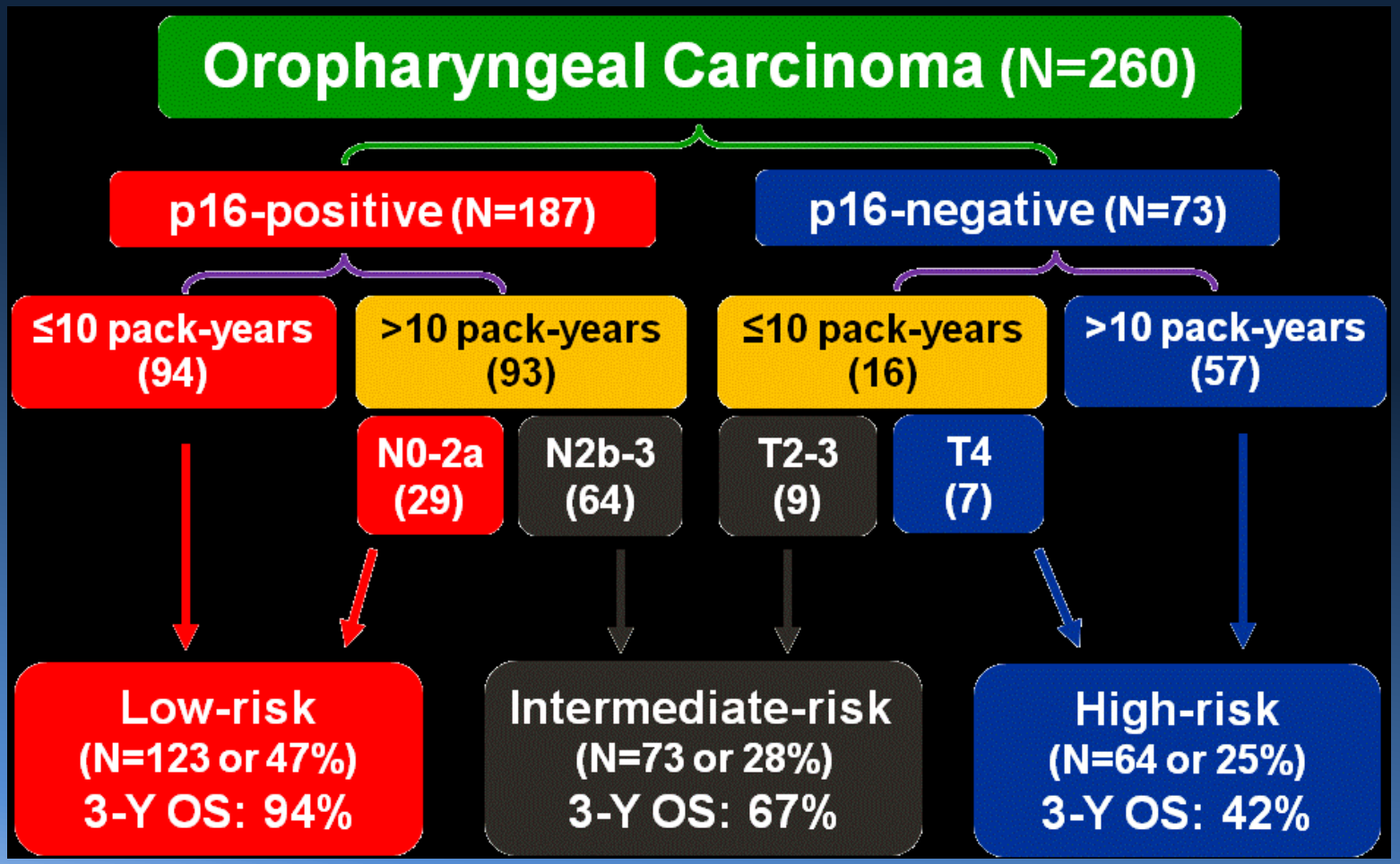


Patients at risk

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

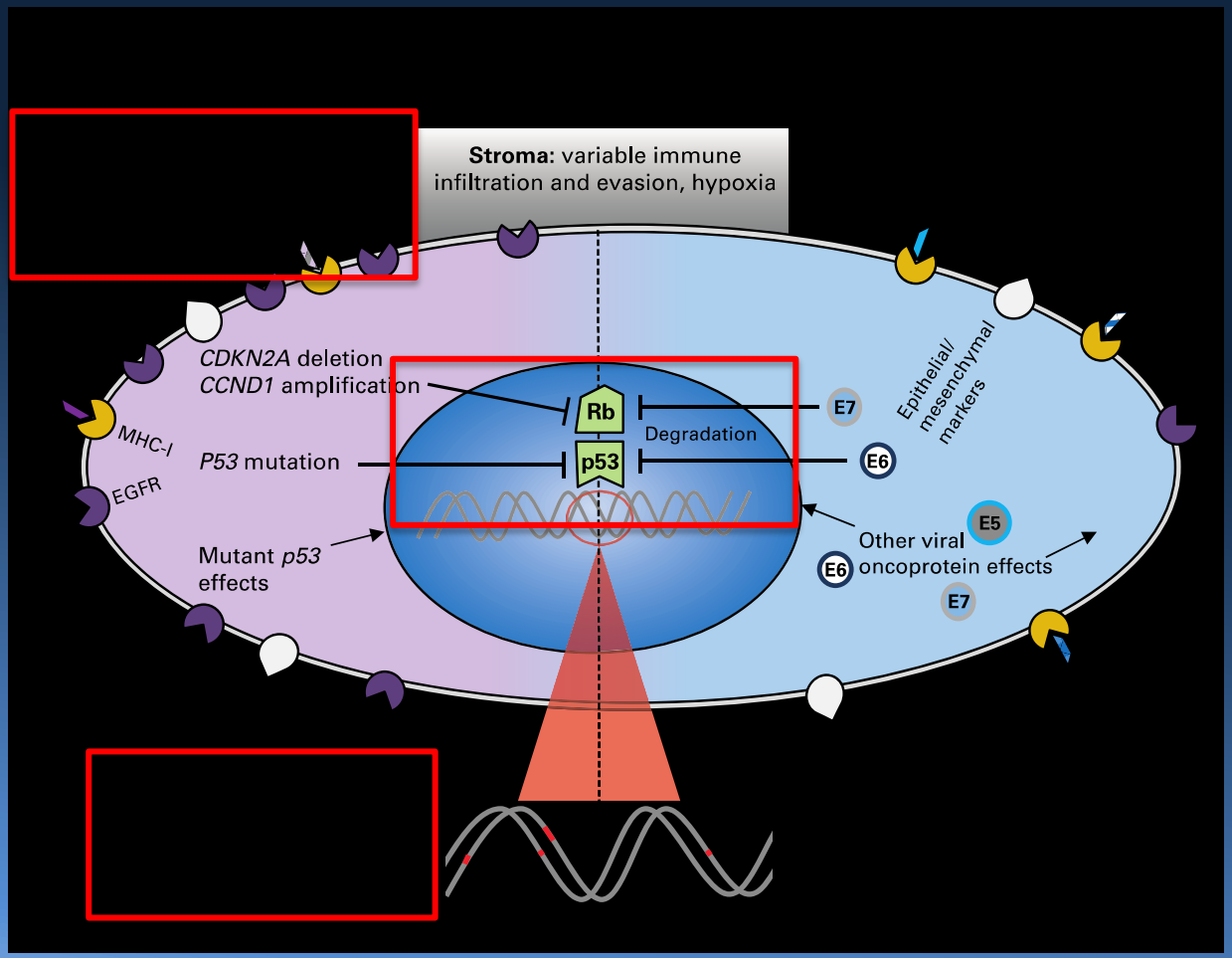
Gillison M. ASCO 2009, Orlando, abstract # 6003

RTOG 0129



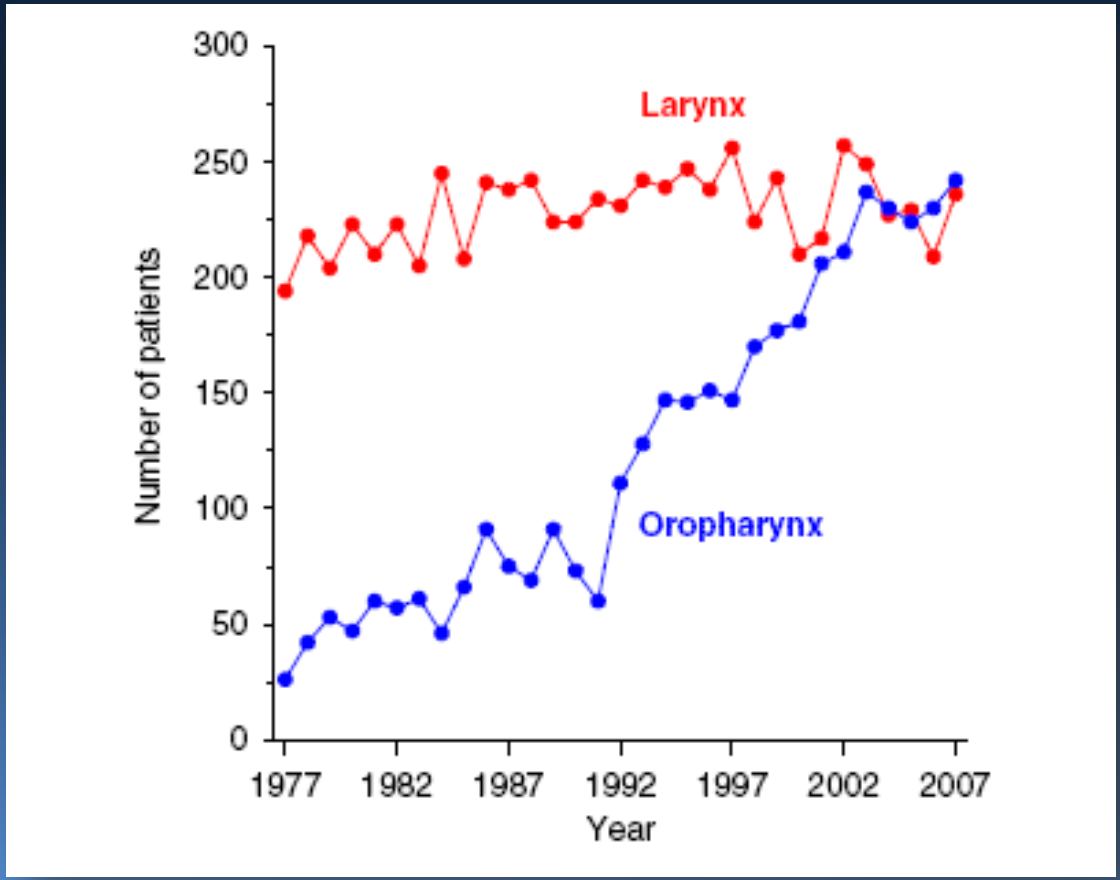
KK Ang et al NEJM, 2010

Biologic differences OPC based on HPV status



Adapted from Dillon & Harrington JCO, 2015

Rising incidence of HPV+ OPC



Larsen P Radiother Oncol, 2010

De-escalation strategies

- Substitute biologic agent for cytotoxic chemotherapy
- Omit or reduce chemotherapy
-
-
  dose
- Surgical excision and stratify further treatment based on pathologic findings

Pending de-escalation studies

RADIOTHERAPY QUALITY ASSURANCE

VOLUME 28 · NUMBER 18 · JUNE 20 2010

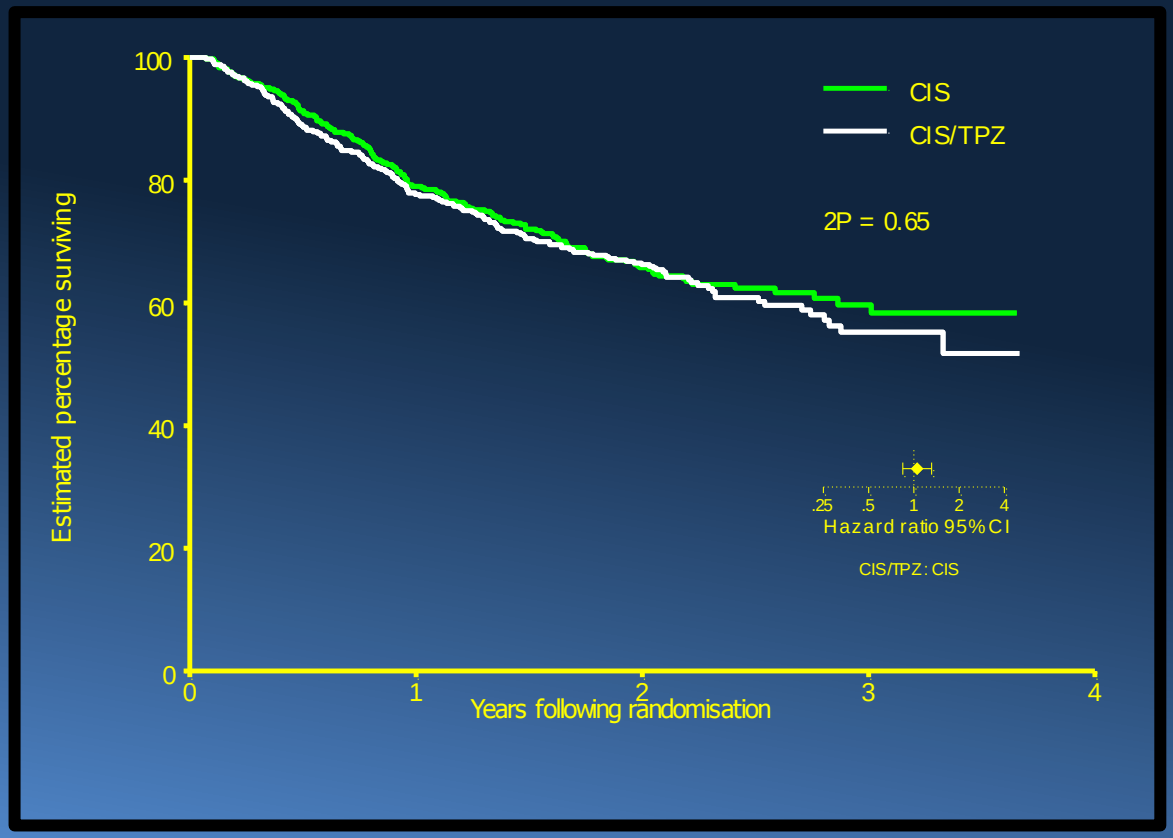
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Tirapazamine, Cisplatin, and Radiation Versus Cisplatin and Radiation for Advanced Squamous Cell Carcinoma of the Head and Neck (TROG 02.02, HeadSTART): A Phase III Trial of the Trans-Tasman Radiation Oncology Group

Danny Rischin, Lester J. Peters, Brian O'Sullivan, Jordi Giralt, Richard Fisher, Kally Yuen, Andy Trotti, Jacques Bernier, Jean Bourhis, Jolie Ringash, Michael Henke, and Lizbeth Kenny

Overall Survival TROG 02.02



Rischin D et al J Clinic Oncol, 2010

VOLUME 28 · NUMBER 18 · JUNE 20 2010

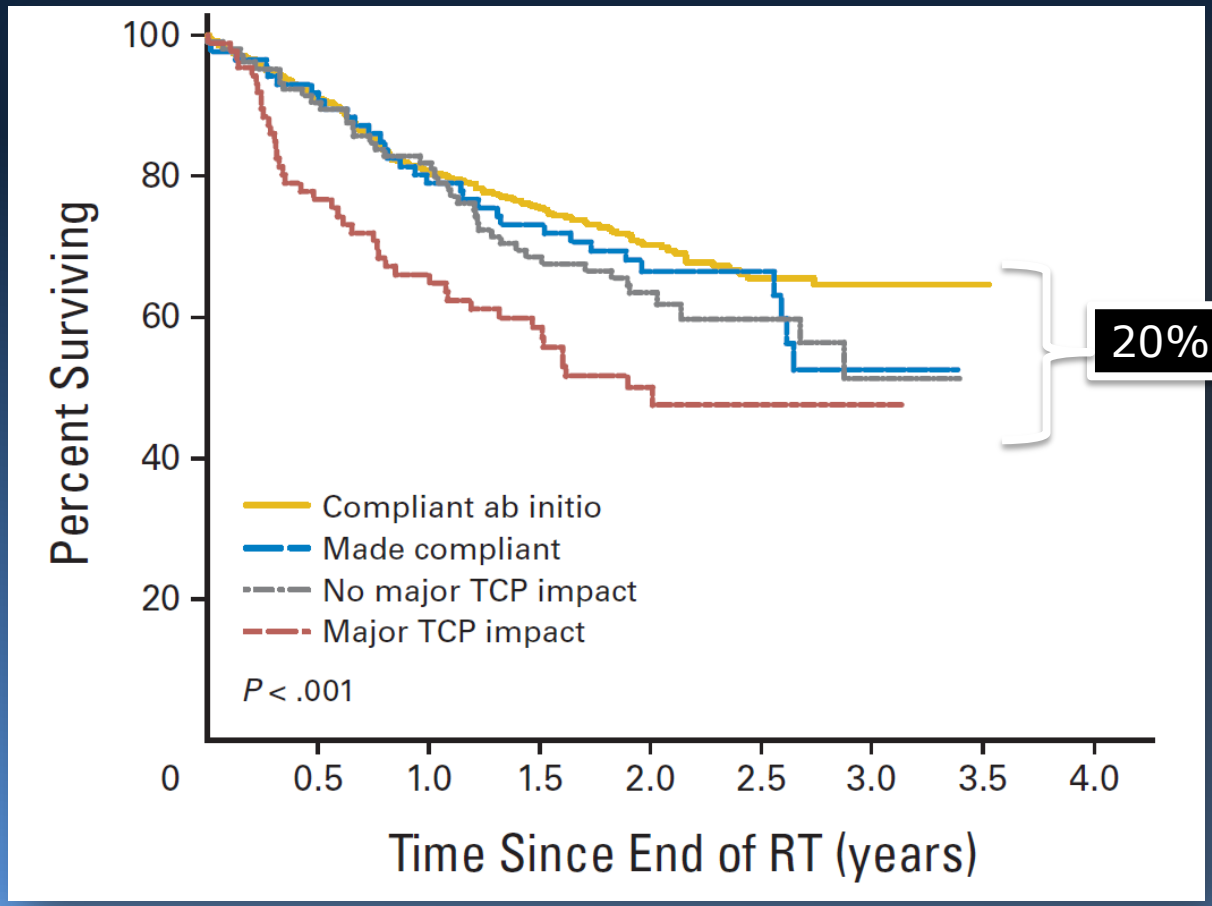
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Critical Impact of Radiotherapy Protocol Compliance and Quality in the Treatment of Advanced Head and Neck Cancer: Results From TROG 02.02

Lester J. Peters, Brian O'Sullivan, Jordi Giralt, Thomas J. Fitzgerald, Andy Trotti, Jacques Bernier, Jean Bourhis, Kally Yuen, Richard Fisher, and Danny Rischin

Survival based on RT Quality



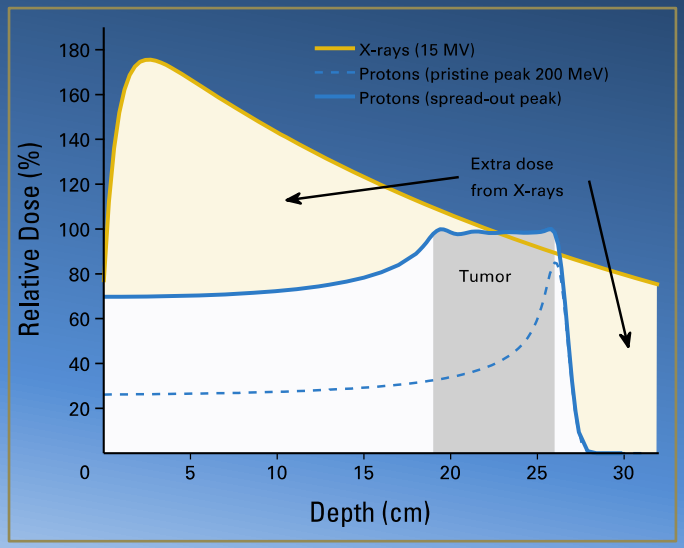
Peters LJ et al JCO, 2010

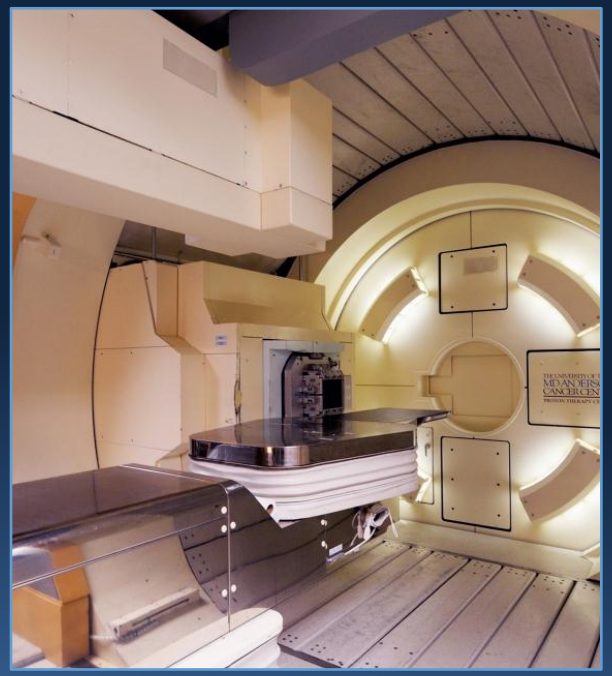
HEAVY PARTICLE RADIATION THERAPY

PROTON THERAPY

Proton Therapy Unit

- Heavy-particle radiation therapy
- Differing physical properties to photons





Clinical implications

- Less integral dose
- Negligible dose beyond the Bragg Peak

Re-treatment following previous RT
Salivary gland tumours

ChemoRT/checkpoint inhibitor trials

	Eligible	Drug	Arm 1	Arm 2	Endpoint
JAVELIN 100 (Pfizer)	Locally advanced head and neck cancer	Avelumab	Avelumab + Cisplatin chemoradiation	Placebo + Cisplatin chemoradiation	PFS
KEYNOTE 412 (Merck)	Locally advanced head and neck cancer	Pembrolizumab	Pembrolizumab + Cisplatin chemoradiation	Placebo + Cisplatin chemoradiation	EFS
NCT03349710 (Bristol-MyersSquibb)	Locally advanced head and neck cancer	Nivolumab	Nivolumab + Cetuximab/Cisplatin + radiation	Placebo + Cetuximab/Cisplatin + radiation	EFS
NCT03452137 (Roche)	Locally advanced head and neck cancer	Atezolizumab	Standard definitive local therapy (multi-modality) followed by adjuvant atezolizumab	Standard definitive local therapy (multi-modality) followed by placebo	EFS

Concluding remarks

- Substantial improvement in locoregional control, modest improvement in survival & an overall reduction in toxicity with radiotherapy due to
  - role of concomitant chemotherapy
  - improved technologies & techniques (IMRT)
  - improved quality assurance of planning & delivery
  - image guidecancer
  - universally accepted contouring guidelines