XXV CONGRESSO NAZIONALE
AIRO 2015
PALACONGRESSI - Rimini, 7-10 novembre

LEZIONE DI AGGIORNAMENTO:

Volumi clinici nella radioterapia dei tumori del distretto cervico-cefalico

Giuseppe Sanguineti

Oncologia Radioterapica
Istituto Tumori Regina Elena
Roma

IRE

DICHIARAZIONE

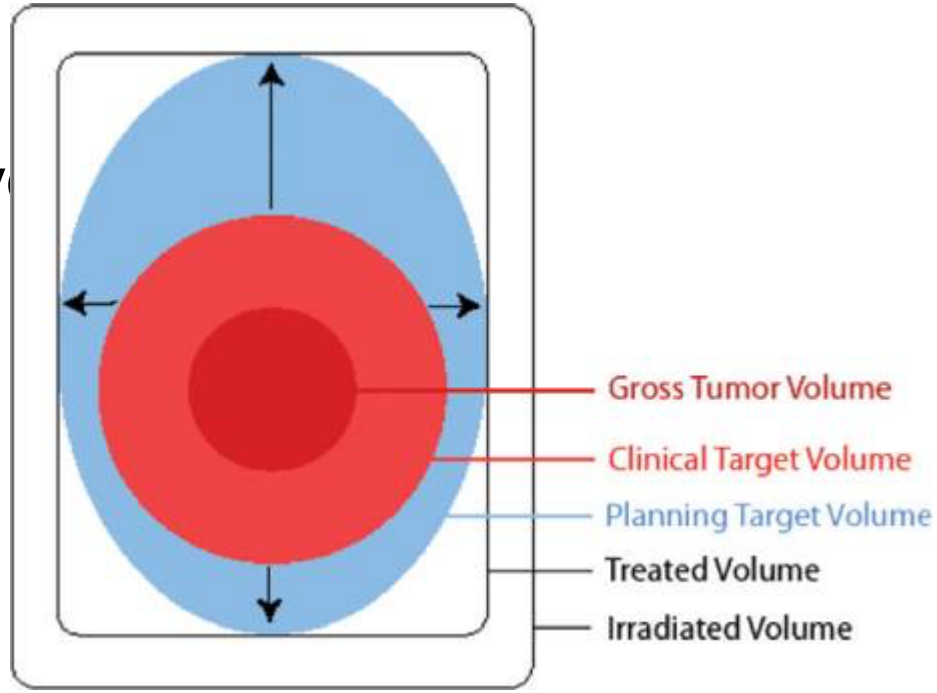
GIUSEPPE SANGUINETI

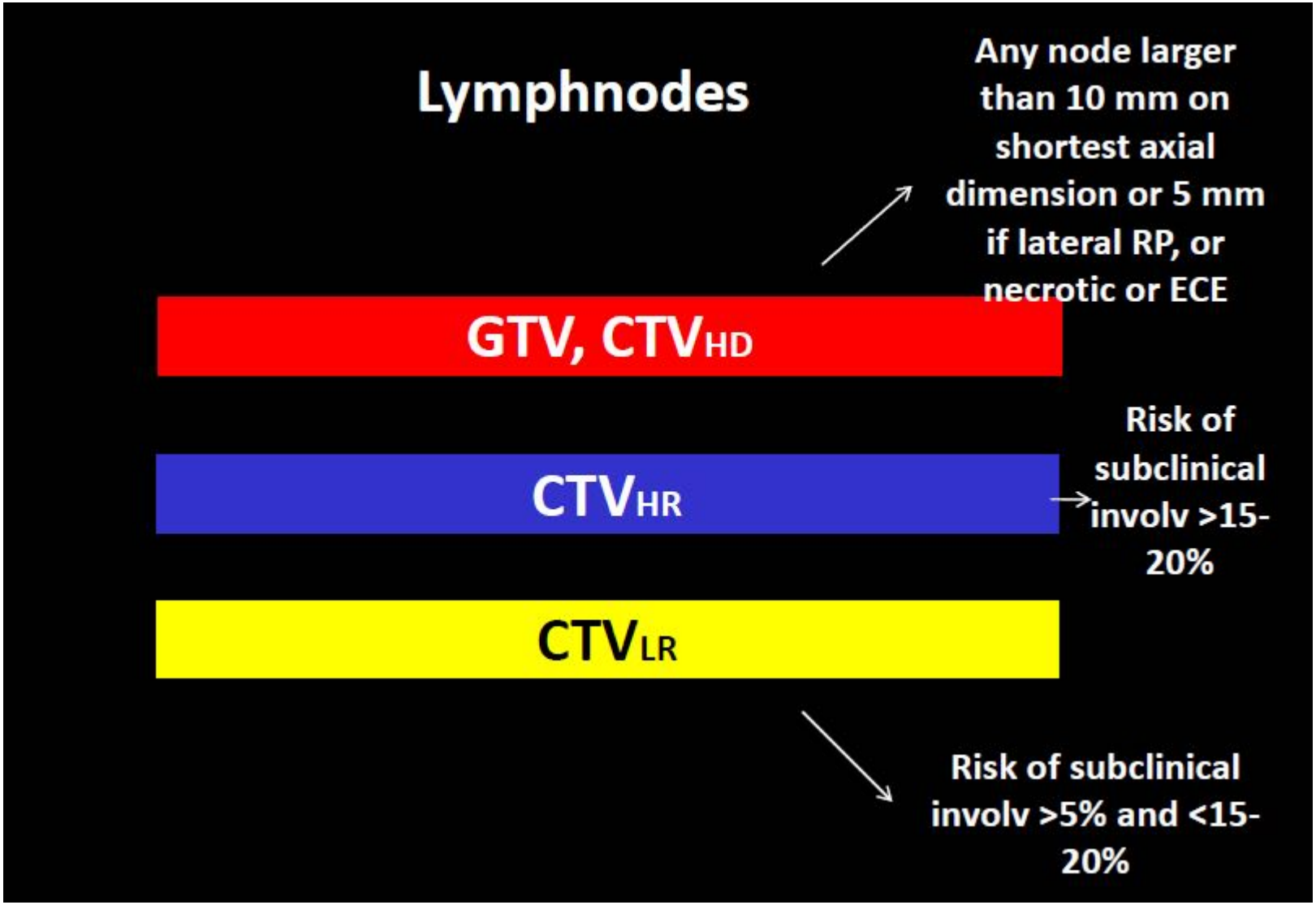
Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

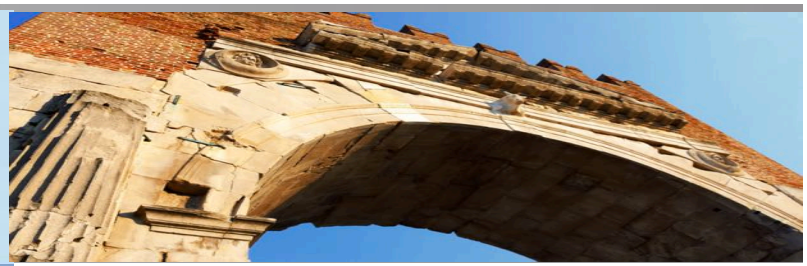
- Posizione di dipendente in aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Consulenza ad aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Partecipazione ad Advisory Board: **NIENTE DA DICHIARARE**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario: **NIENTE DA DICHIARARE**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **NIENTE DA DICHIARARE**
- Altro **NIENTE DA DICHIARARE**

Definitions

- GTV, CTV, PTV
- OAR, PRV
- Irradiated vs treated v







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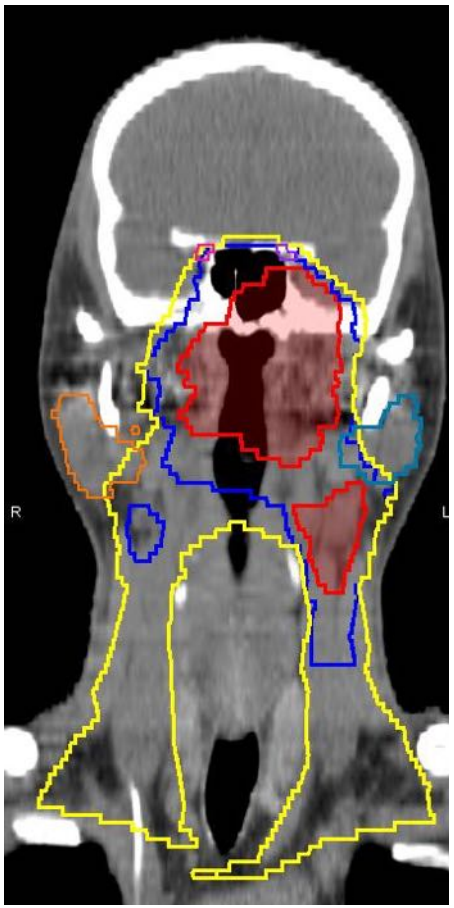


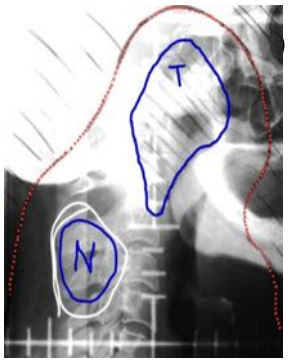
Gross Tumor Volume

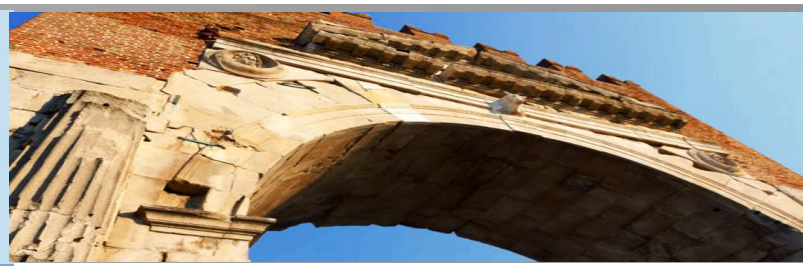
Clinical Target Volume

Planning Target Volume

Evolution of clinical volumes over time

- From 2D to 3D/IMRT, *from what to be spared* *b*





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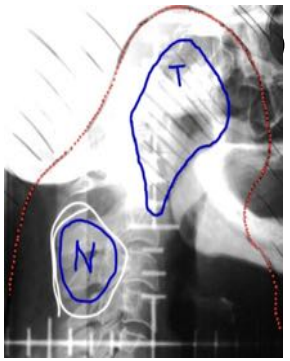
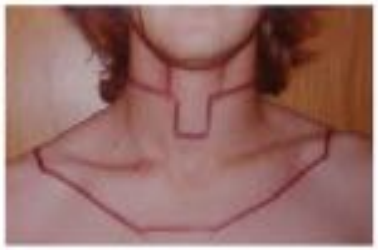


- Empirically evolved o



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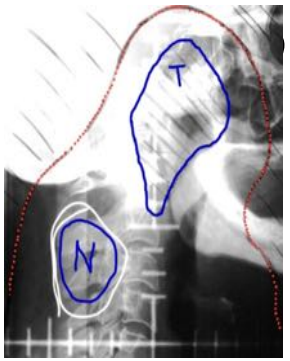

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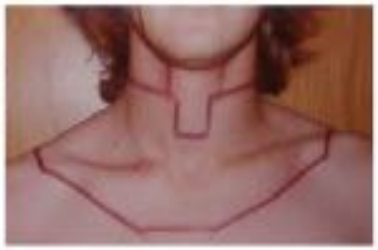
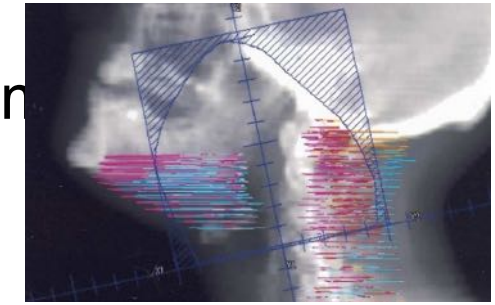
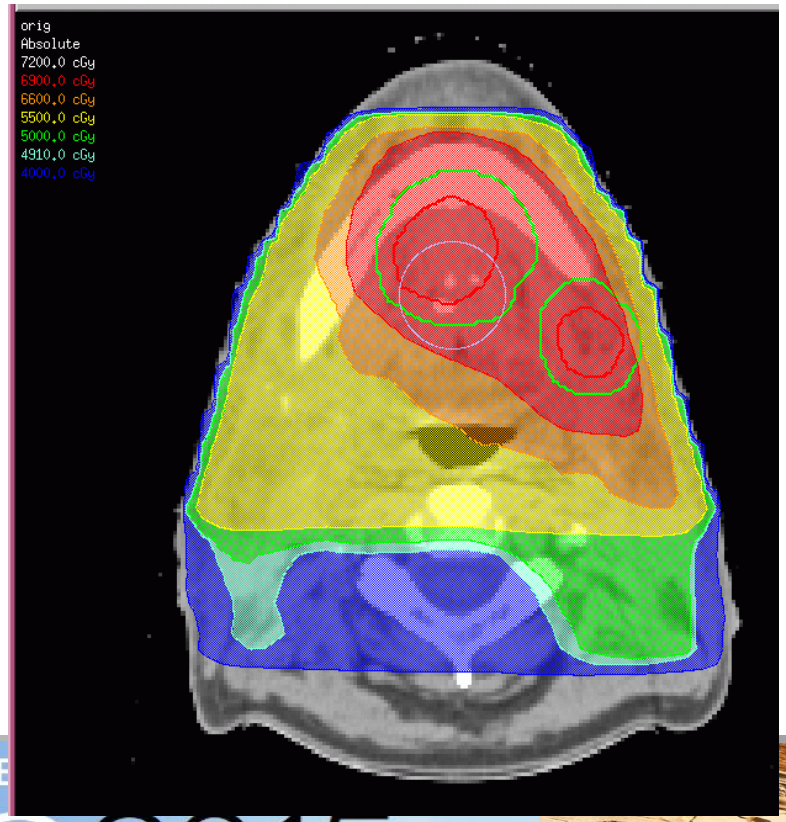


- lack of guidelines for several years, con w 'old' volumes



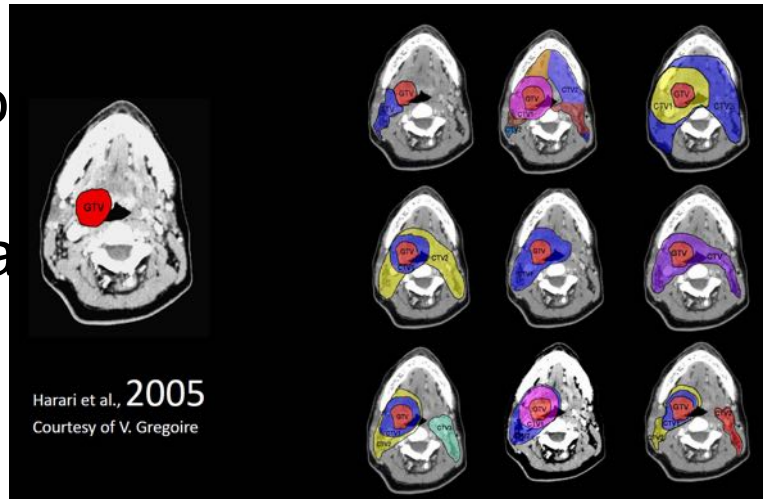
Evolution of clinical volumes over time

- The capability to cover large volumes considered a distinct advantage of RT over surgery



Prescribe tmt – Indication to/no

Contouring, how to cover – Atla



Merlotti *et al. Radiation Oncology* (2014) 9:264
DOI 10.1186/s13014-014-0264-9

RADIATION ONCOLOGY

REVIEW Open Access

Technical guidelines for head and neck cancer IMRT on behalf of the Italian association of radiation oncology - head and neck working group

Anna Merlotti[1†], Daniela Alterio[2†], Riccardo Vigna-Taglianti[3†], Alessandro Muraglia[4†], Luciana Lastrucci[5†], Roberto Manzo[6†], Giuseppina Gambaro[7†], Orietta Caspiani[8†], Francesco Miccichè[9†], Francesco Deodato[10†], Stefano Pergolizzi[11†], Pierfrancesco Franco[12†], Renzo Corvò[13†], Elvio G Russi[3*†] and Giuseppe Sanguineti[14†]

Pattern of failure studies

CLINICAL INVESTIGATION

PATTERNS OF LOCOREGIONAL FAILURE AFTER EXCLUSIVE IMRT FOR OROPHARYNGEAL CARCINOMA

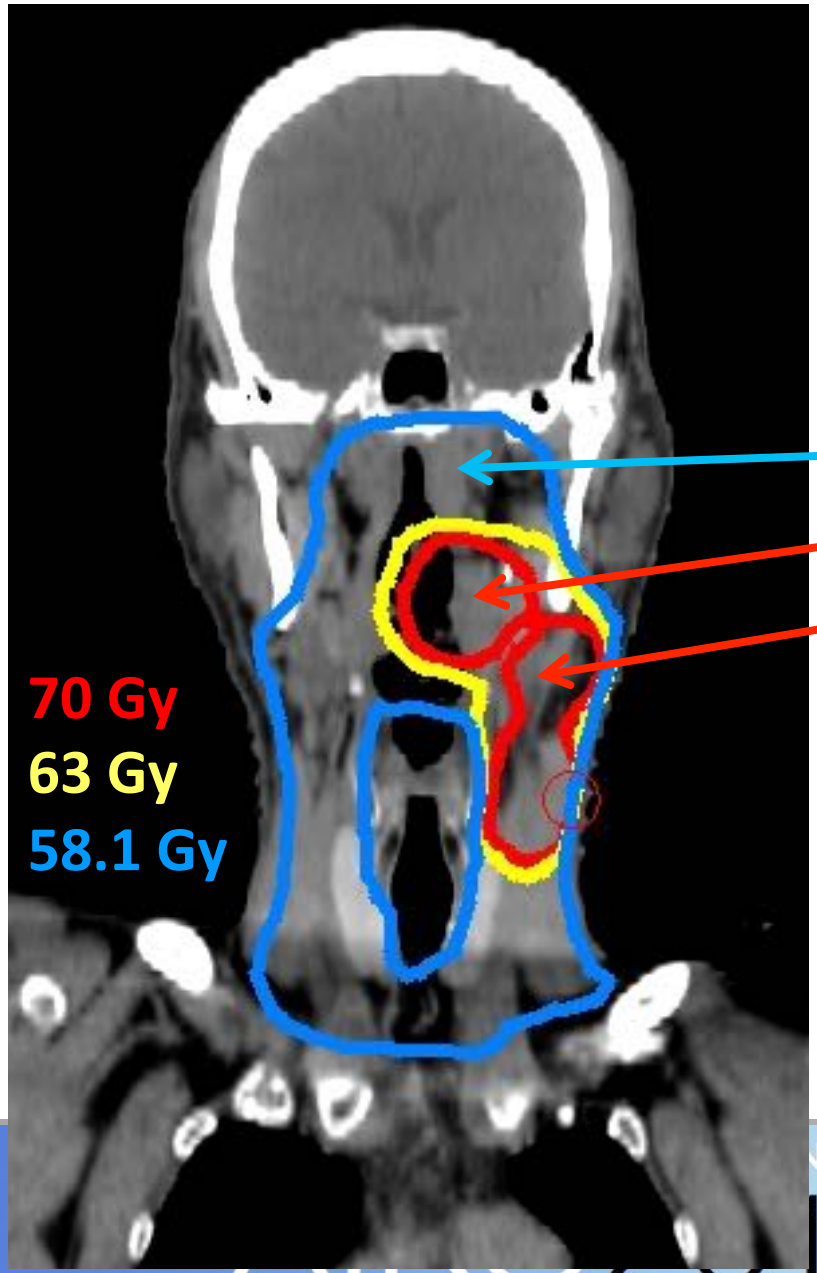
GIUSEPPE SANGUINETI, M.D.,* G. BRANDON GUNN, M.D.,* EUGENE J. ENDRES, C.M.D.,†
GREGORY CHALJUB, M.D.,‡ PRAVEENA CHERUVU, M.D.,* AND BRENT PARKER, PH.D.†

Departments of *Radiation Oncology, †Medical Physics, and ‡Neuroradiology, University of Texas Medical Branch, Galveston, TX

IJROBP 2008

- 50 pts (58% stage IV),
- minimum FU 1 yr (median 32.6 mths),
- IMRT alone (no surgery, no chemo)
- (no PET)

UTMB
The University of Texas Medical Branch



- 9 failures
- 8 pts
- 3-yr LC 93.8%-RC 85.1%

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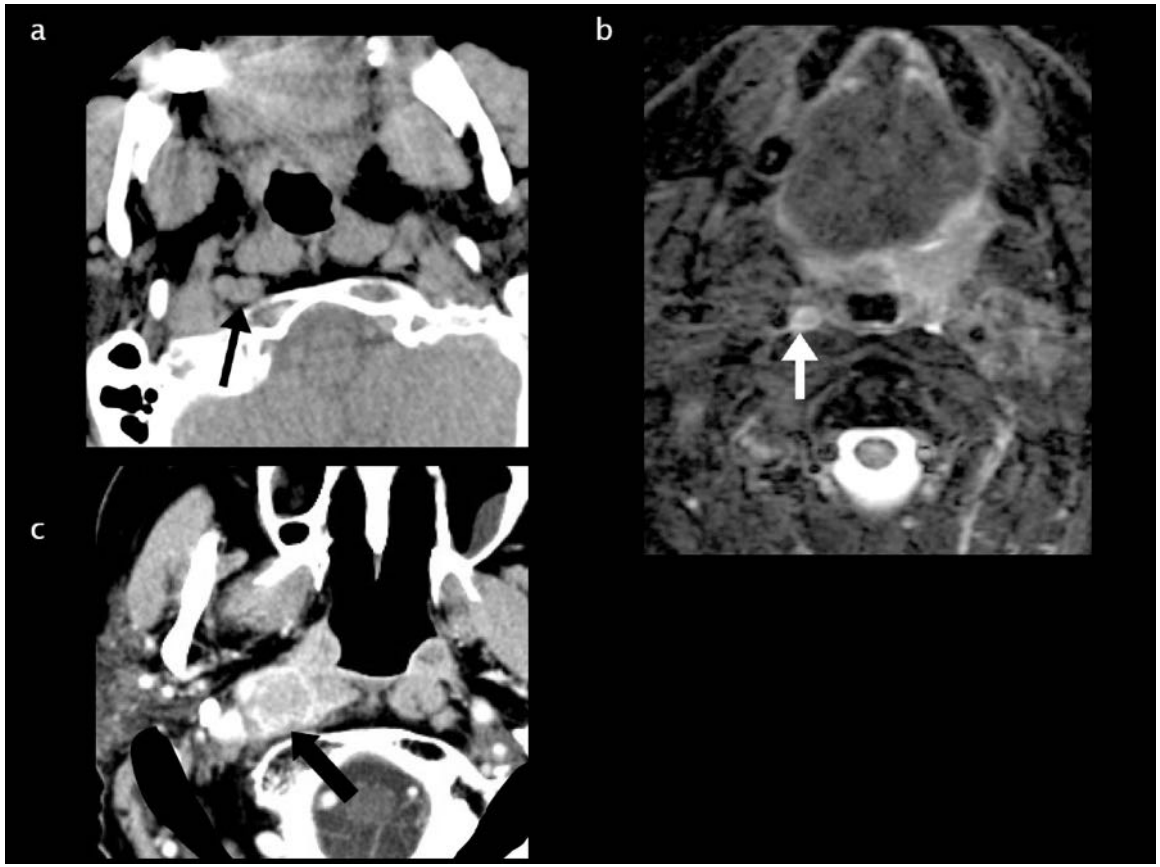
4 – all pre-existing nodes

3

2

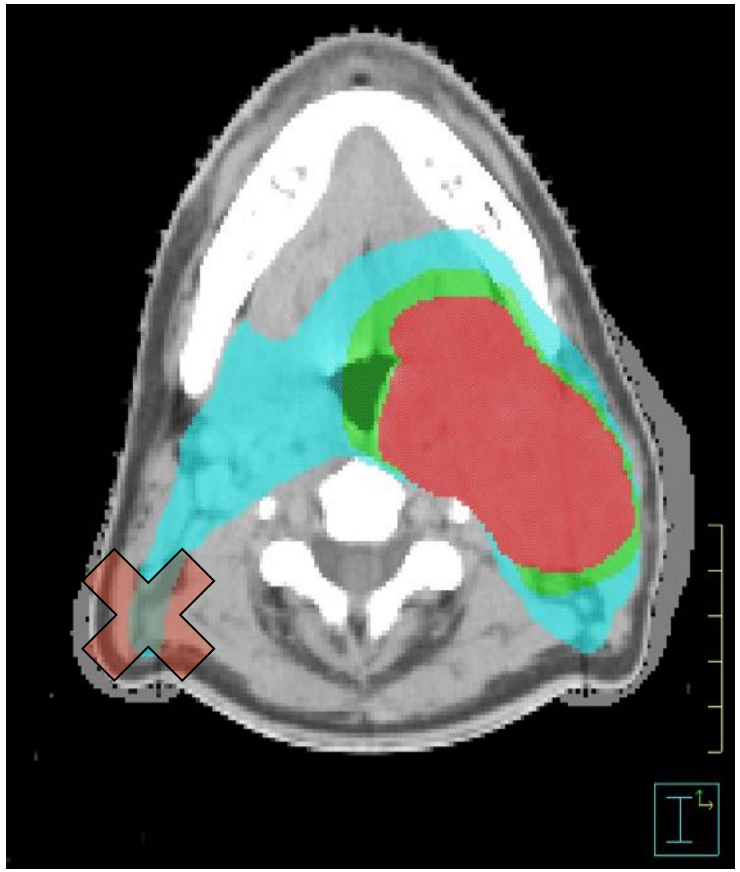
UTMB
The University of Texas Medical Branch

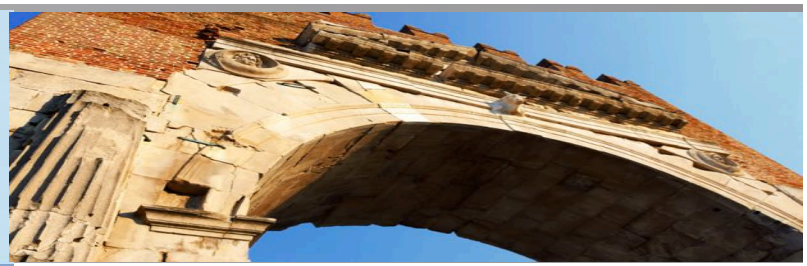
Pattern of failure studies



UTMB
The University of Texas Medical Branch

‘Omitting volumes’





(Recent) examples of omitted volumes

- Level V in OPC*
- Level IB in OPC
- RP cranial to C1 in OPC*
- Medial part of RP in OPC
- T site after TORS*
- Level IV in NPC
- All levels if pN0 (HNSCC)*
- …

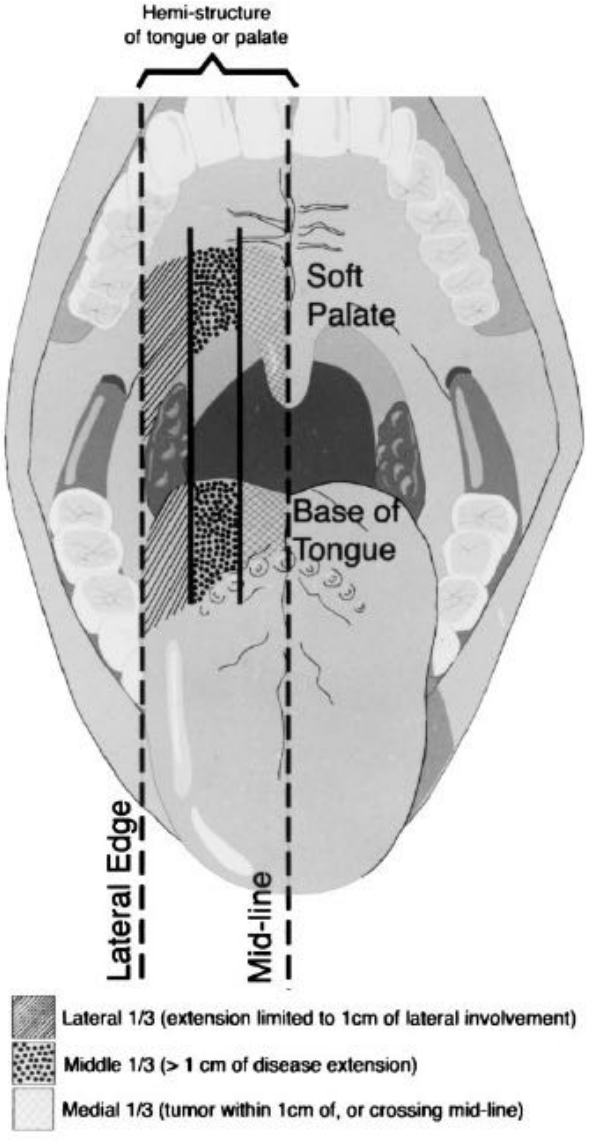
* ASTRO 2015

(Recent) examples of omitted volumes

- Level V in OPC*
- Level IB in OPC
- RP cranial to C1 in OPC*
- Medial part of RP in OPC
- T site after TORS*
- Level IV in NPC
- All levels if pN0 (HNSCC)*
- …

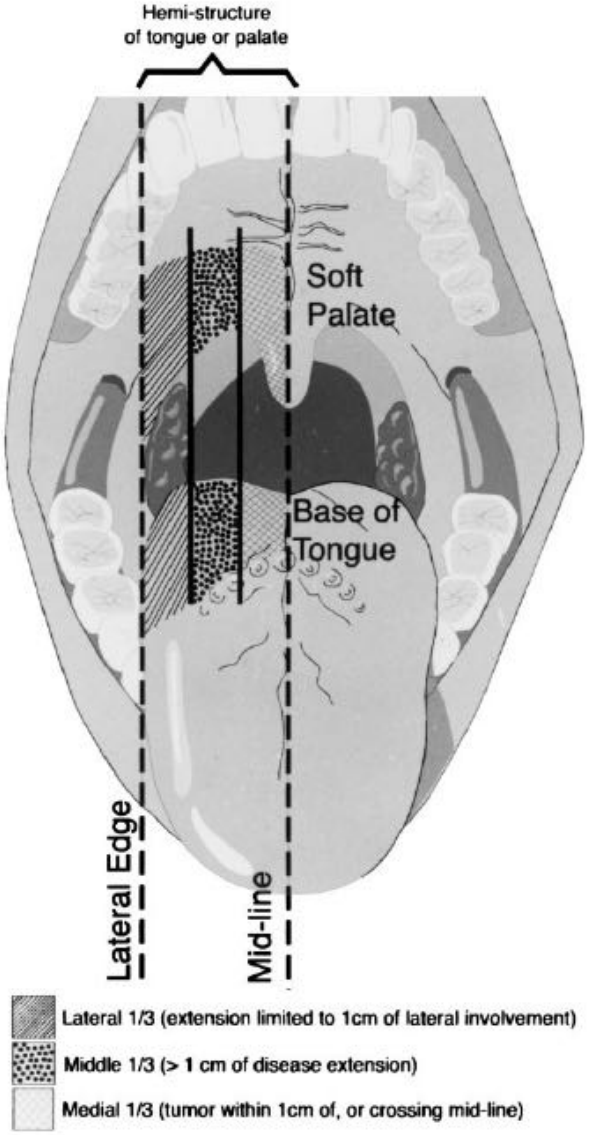
… to avoid incidental irradiation of embedded & surrounding OARs

Contralateral neck nodes



- ipsilateral tmt an option for pts with lateralized dis [within 1 cm] and w/o advanced neck dis [N0-1].
- in properly selected pts, controlateral neck recurrence <10% (VCC/PMH/ MDACC)

Contralateral neck nodes



- ipsilateral tmt an option for pts with lateralized dis [within 1 cm] and w/o advanced neck dis [N0-1].
- in properly selected pts, controlateral neck recurrence <10% (VCC/[illegible]H/ MDACC)

STANDARD OF CARE

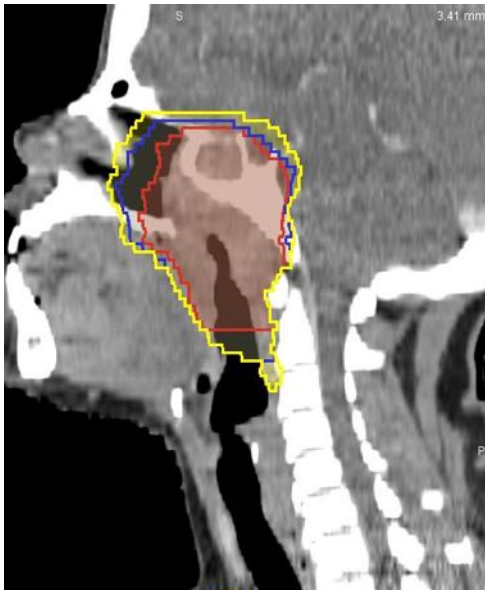
Pituitary fossa coverage in stage I-II

STANDARD OF CARE

No need to cover the pituitary fossa in T1

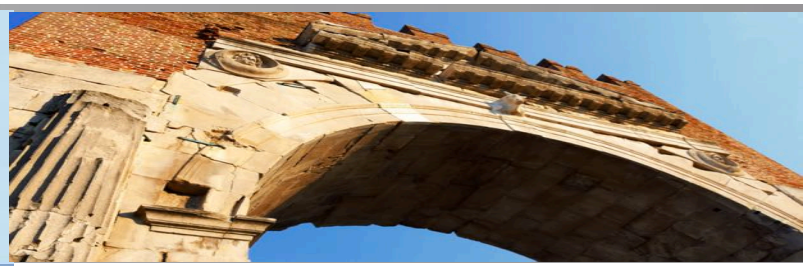
- 152 pts w/o erosion of base of skull and sphenoid sinus (CT), no extention to the nasal fossa or ethmoid sinus
- Random: w or without shielding of the pituitary fossa (sphenoid sinus)
- no difference in tumor control (p=0.39), but in neuroendocrine complications (p=0.006)

Sham et al, IJROBP 1994



RISKS/BIASES

Which is the clinically meaningful threshold to withhold treatment?



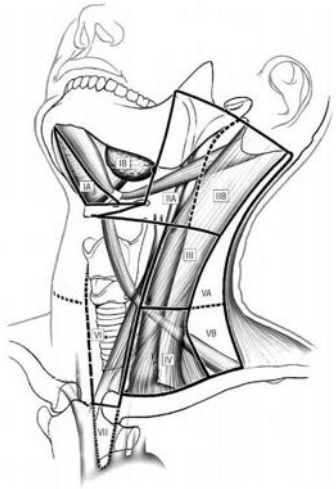
RISKS/BIASES

Which is the clinically meaningful threshold to withhold treatment?

0-4.9% — **Very Low Risk – no elective tmt**

5-14.9% — **Low Risk - elective tmt, 50sh Gy**

15+% — **High Risk – elective tmt, 60sh Gy**



RISKS/BIASES

Which is the clinically meaningful threshold to withhold treatment?

Inappropriate & inadequate baseline literature data

RISKS/BIASES

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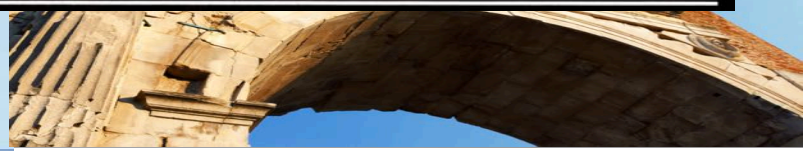
Million book, 1992

TABLE 6-2. Incidence of Lymph Node Metastasis by Site of Primary in Head and Neck Squamous Cell Carcinoma

Site	N+ at Presentation (%)	N0 Clinically N+ Pathologically (%)	N0 → N+ With No Neck Treatment (%)
Floor of mouth	30–59[42,49,58]	21–50[19,52,126]	20–35[5,21,91]
Gingiva	18–52[20,28,42,75]	12–19[19,20]	17[5,20]
Hard palate	13–24[24,33,75]	No data	22[5]
Buccal mucosa	9–31[42,58]	0/10[19]	16[5]
Oral tongue	34–65[42,49,56,58]	25–54[12,28,44,64,127]	38–52[44,56,91,130]
Nasopharynx	86–90[14,69,95]	No data	19–50*[55,96]
Anterior tonsillar pillar or retromolar trigone	39–56[7,59,68]	35[19]	10–15[126]
Soft palate or uvula	37–56[7,59,68]	No data	16–25[68]
Tonsillar fossa	58–76[14,49,59,62,69,95]	No data	22†[118]
Base of the tongue	50–83[59,95,103,109,126]	22–33[19,103]	No data
Pharyngeal walls	50–71[59,95,103,126]	46–66[19,103]	No data
Supraglottic larynx	31–64§[49,126]	16–26[19,103,112]	33[38,112]
Hypopharynx	52–78[28,94,103,126]	38–56[19,103]	No data



Real Q

Which the Risk of Subclinical Involvement of Each Nodal Level when Negative on Imaging?

RISKS/BIASES

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Inappropriate & inadequate baseline literature data

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Supraglottic larynx	31–64[49,126]	1[…]26[19,103,112]	33[38,112]
Hypopharynx	52–78[28,94,103,126]	38–56[19,103]	No data

Of very limited interest

Staging modality

Competing risks

Classic data of nodal involv for oropharyngeal SCC

Candela FC, Kothari K, Shah JP. Patterns of cervical node metastases from squamous carcinoma of the oropharynx and hypopharynx. *Head Neck* 1990;12:197–203.

Lindberg R. Distribution of cervical lymph node metastases from squamous cell carcinoma of the upper respiratory and digestive tracts. *Cancer* 1972;29:1446–1449.

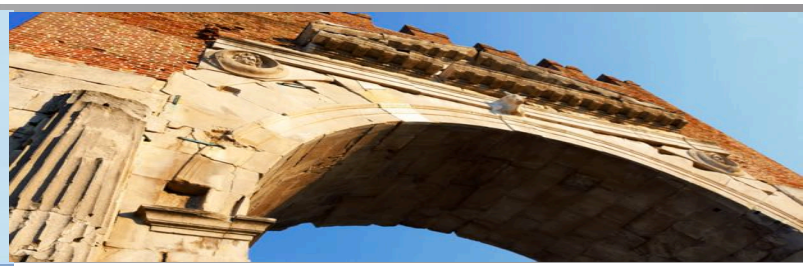
At pathology after surg

At presentation on palp

JHU data

Jan 1998 — 2000 — Dec 2010

1. `upfront` neck dissection (ND), i.e., before definitive RT±CHT
2. early clinical primary tumor stage (cT1 or cT2);
3. neck nodes clinically palpable or detectable on imaging at dx;
4. no previous/synchronous tumors;
5. no previous neck surgery or `neck violation`;
6. dissection of at least 3 contiguous neck nodal levels;
7. neck surgery at Johns Hopkins Institutions;
8. neck specimen processed by surgical levels;



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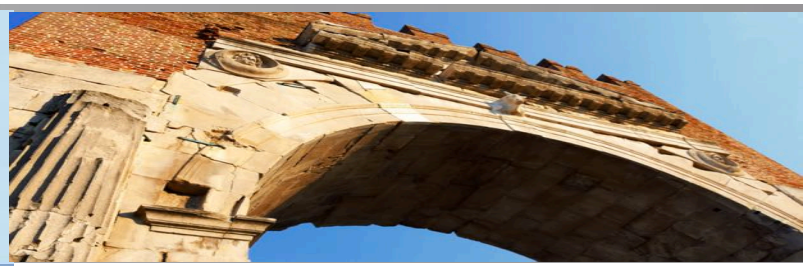
6. dissection of at least 3 contiguous neck nodal levels;
7. neck surgery at Johns Hopkins Institutions;
8. neck specimen processed by surgical levels;
9. *tumor positive for Human Papilloma Virus at in situ hybridization and/or for p16 at immunohistochemistry.*

JOHNS HOPKINS MEDICINE



From the pathology report, we extracted the prevalence rate of involvement of levels IB-V.

Then, for each nodal level we computed the negative predictive value (NPV) based on literature data of sensitivity/specificity for CT [Curtin et al, 1998]. SENS=0.88, SPEC=0.39

$$\mathrm{NPV} = \frac{(\text{specificity})(1-\text{prevalence})}{(\text{specificity})(1-\text{prevalence})+(1-\text{sensitivity})(\text{prevalence})}$$

Here we report 1-NPV or the risk that a level that does not contain any node larger than 10 mm harbors subclinical disease.

JOHNS HOPKINS
MEDICINE

Studies

108 pts (up to 2007)
regardless HPV

CLINICAL INVESTIGATION

DEFINING THE RISK OF INVOLVEMENT FOR EACH NECK NODAL LEVEL IN PATIENTS WITH EARLY T-STAGE NODE-POSITIVE OROPHARYNGEAL CARCINOMA

Giuseppe Sanguineti, M.D.,* Joseph Califano, M.D.,† Edward Stafford, M.D.,† Jana Fox, M.D.,* Wayne Koch, M.D.,† Ralph Tufano, M.D.,† Maria Pia Sormani, M.D.,‡ and Arlene Forastiere, M.D.†

Departments of *Radiation Oncology and Molecular Radiation Sciences, †Head and Neck Surgery, and †Oncology, Johns Hopkins University, Baltimore, MD; and ‡Biostatistics Unit, University of Genoa, Genoa, Italy

Int J Radiat Oncol Biol Phys, 2009

119 pts (up to 2007)
regardless HPV/incl exc bx

Level V Involvement in Patients With Early T-Stage, Node-Positive Oropharyngeal Carcinoma

Kavita M. Pattani, MD; Joseph Califano, MD; Giuseppe Sanguineti, MD

Laryngoscope, 2010

91 pts (up to 2010)
only HPV +

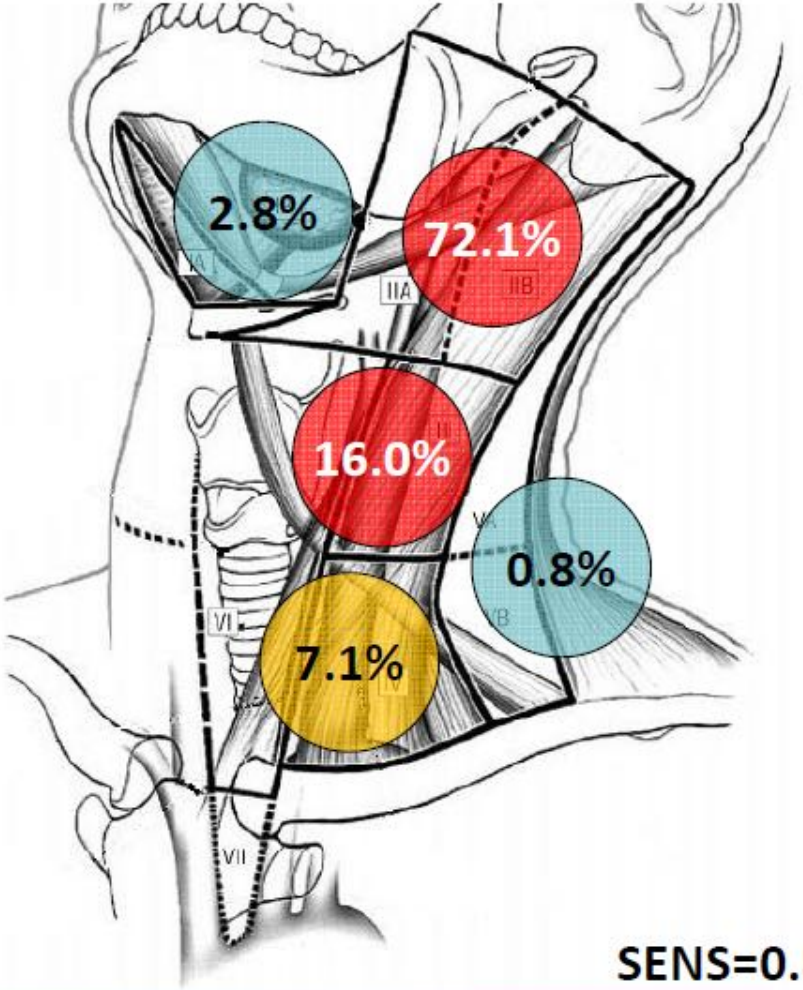
HPV-related oropharyngeal carcinoma with Overt Level II and/or III metastases at presentation: The risk of subclinical disease in ipsilateral levels IB, IV and V

GIUSEPPE SANGUINETI[1], SARA PAI[2], HAROLD AGBAHIWE[1], FRANCESCO RICCHETTI[1], WILLIAM WESTRA[3], MARIA PIA SORMANI[4], STEFANIA CLEMENTE[1] & JOSEPH CALIFANO[2]

Acta Oncologica, 2013

JOHNS HOPKINS MEDICINE

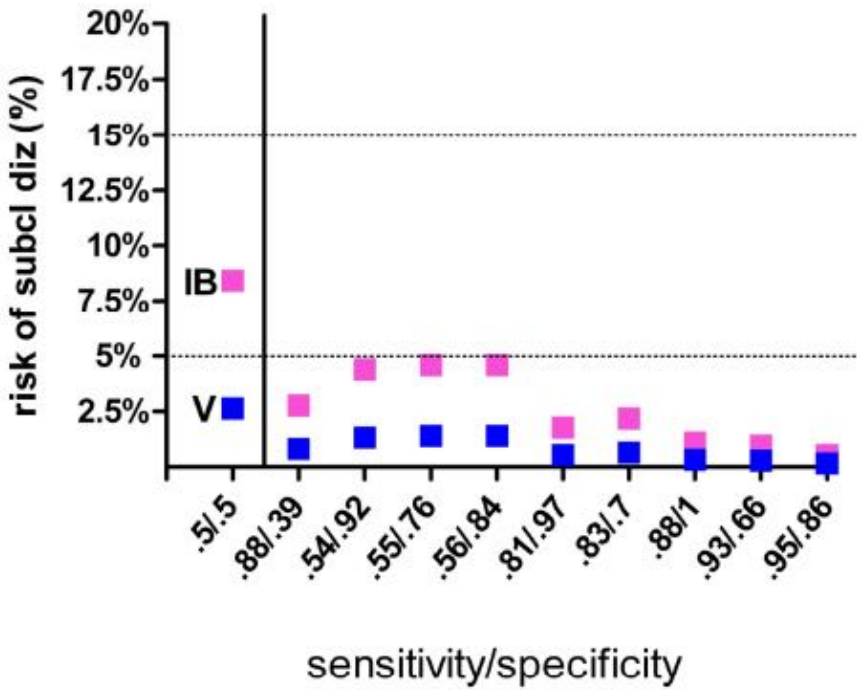
Risk of subclinical disease in each level when negative on CT



SENS=0.88, SPEC=0.39

ASTRO

Risk of subclinical disease in levels IB & V according to different values of sensitivity and specificity



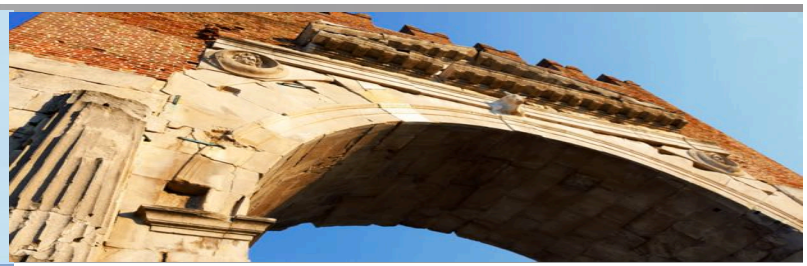
high risk

low risk

very low risk

ASTRO

JOHNS HOPKINS MEDICINE



91 pts, HPV pos

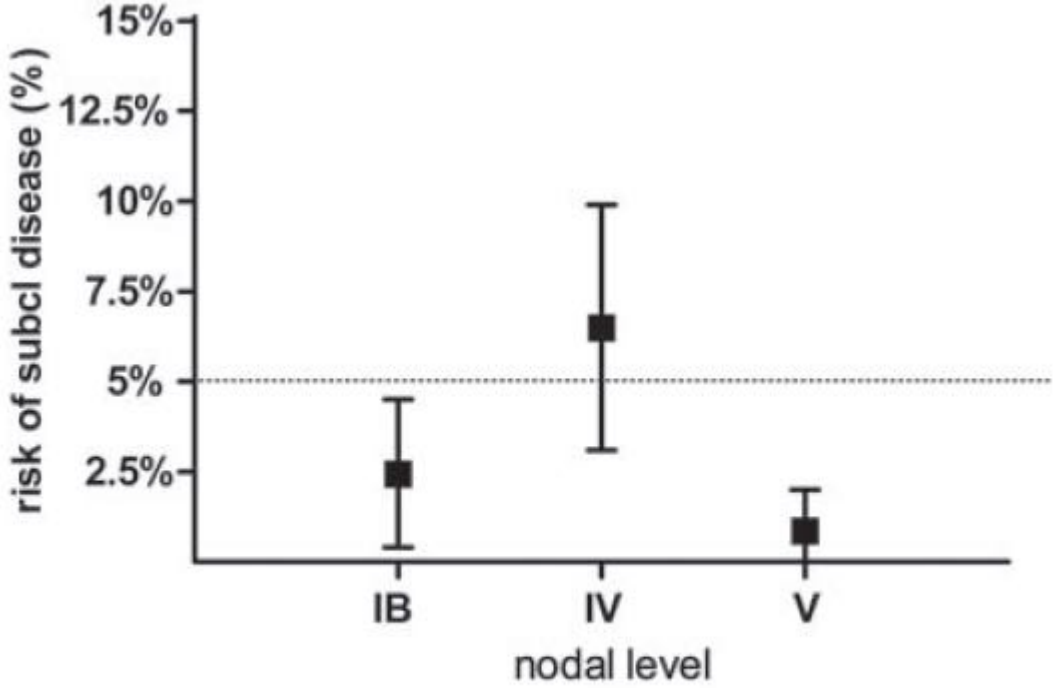


Figure 1. Estimated risk (mean and 95% CI) of subclinical involvement of levels IB, IV and V.

Sanguineti et al, Acta Oncologica 2013

91 pts, HPV pos

The only factor that showed an association with pathological involvement of level IB was the number of pathologically involved neck levels besides IB: none of the 47 patients with only one (other) level involved was found to harbor disease in ipsilateral level IB as opposed to 6/33 (18.2%) with two or more other levels involved (OR 22.4, 95% CI 2.5–2980, p = 0.0026).

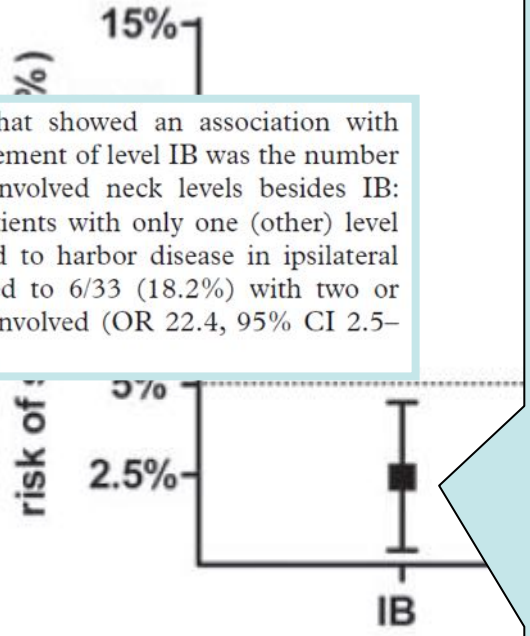


Figure 1. Estimated risk (mea
involvement of levels IB, IV and V.

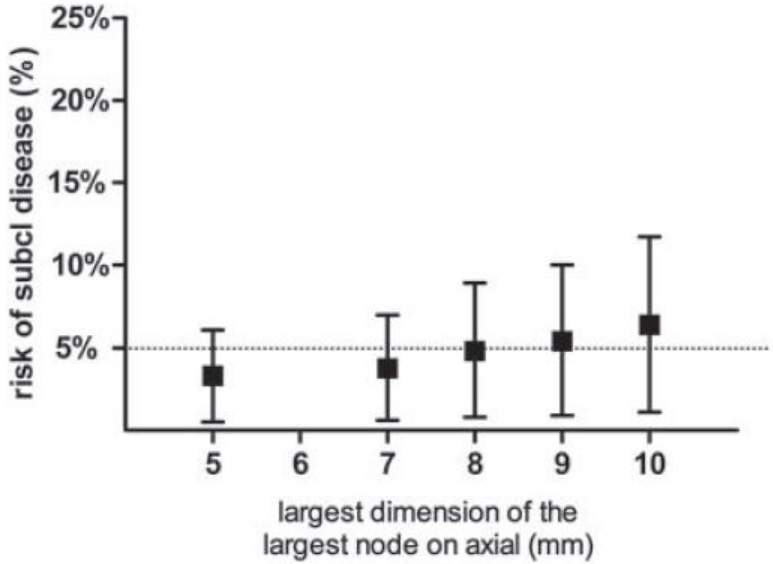


Figure 2. Estimated risk (mean and 95% CI) of subclinical involvement of level IB by the largest size of the largest node on axial slices when two or more ipsilateral levels besides IB are pathologically involved.

Sanguineti et al, Acta Oncologica 2013

91 pts, HPV pos

Both the number of pathologically involved levels beyond level IV (1 vs. >1, 4/57, 7.0% vs. 12/30, 40.0%, OR 8.8, 95% CI 2.5–30.9, p<0.001) and level III involvement (no vs. yes, 4/52, 7.7% vs. 12/35, 34.3%, OR 6.2, 95% CI 1.8–21.5, p = 0.004) predicted the presence of disease in level IV at univariate logistic regression. The two covariates were highly correlated (Spearman's rho = 0.79, p<0.001).

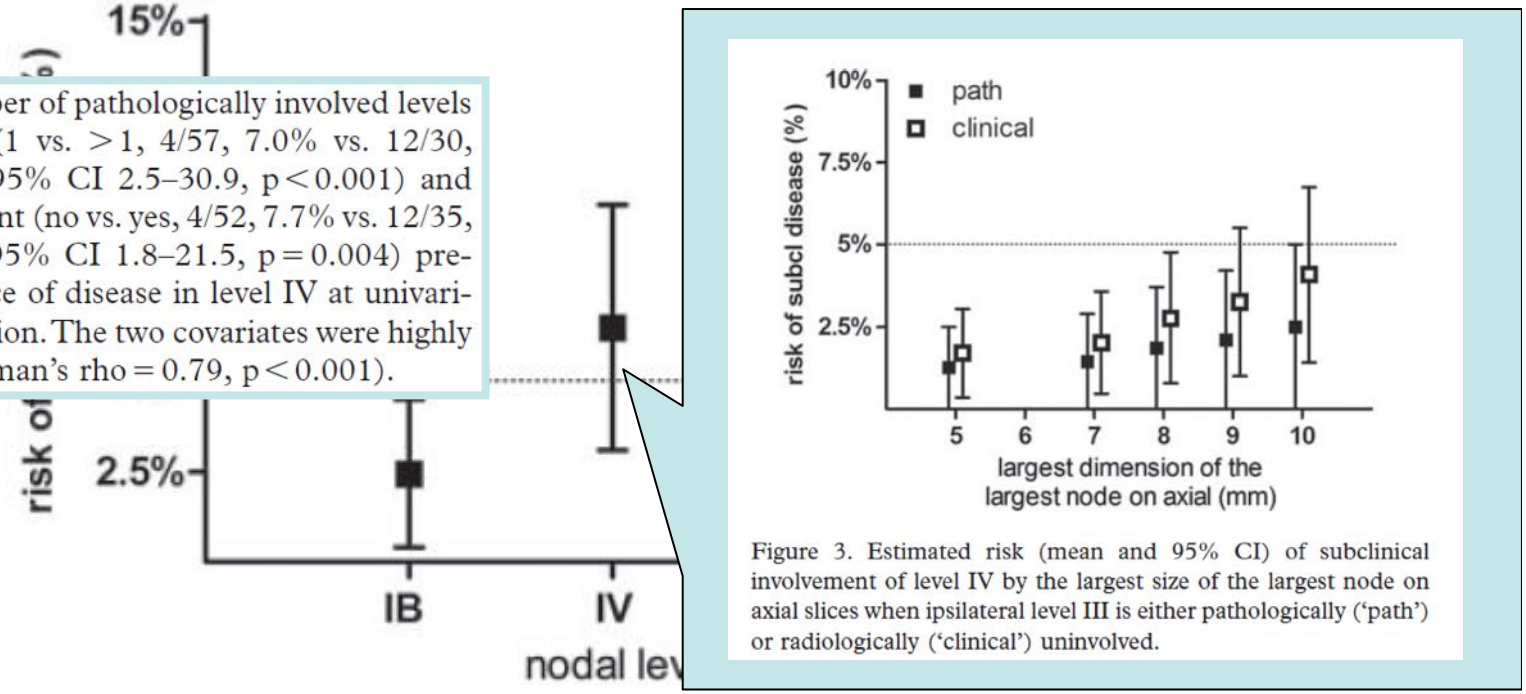


Figure 3. Estimated risk (mean and 95% CI) of subclinical involvement of level IV by the largest size of the largest node on axial slices when ipsilateral level III is either pathologically ('path') or radiologically ('clinical') uninvolved.

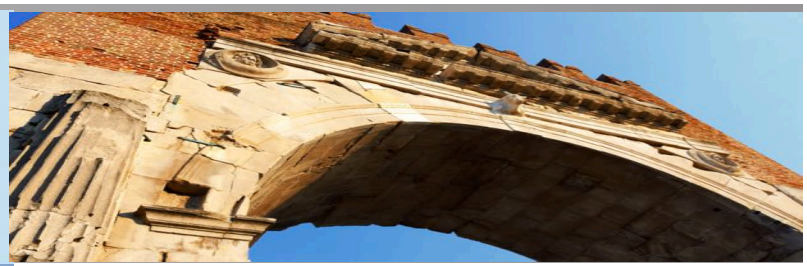
Figure 1. Estimated risk (mean and 95% CI) of subclinical involvement of levels IB, IV and V.

Sanguineti et al, Acta Oncologica 2013

HPV-OPC ipsilateral nodal levels

The present paper, that is the first one to focus on HPV positive patients only, provides the rationale for avoiding treatment of ipsilateral ‘ very low risk ’ (<5%) levels, that would include levels V and IB. The latter may qualify for elective irradiation only when two or more other levels are involved.
Level IV might also be spared when level III is negative on a ‘reliable ’ imaging study or when the negativity of level III is pathologically assessed.

Sanguineti et al, Acta Oncologica 2013



RP nodes in OPC

Eisbruch et al, IJROBP 2004, being addressed by MSKCC

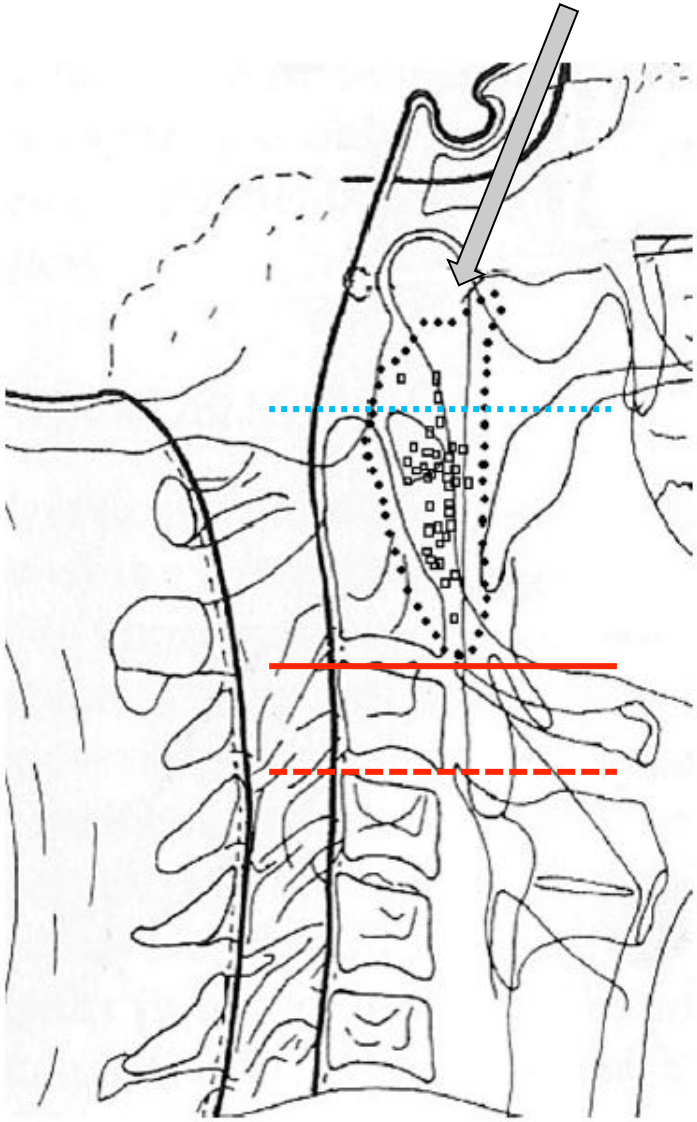


Fig. 1. In sagittal plane, center of all pathologic retropharyngeal nodes localized at C1 and C2 levels. Maximal extension of nodes was up to base of skull cranially and down to caudal border of C2.

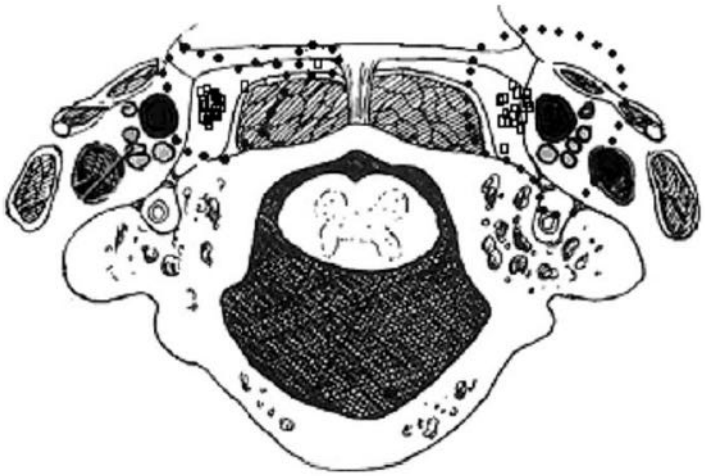


Fig. 2. In transverse plane, all but one center (of one retropharyngeal node in 1 patient) were located in space bordered laterally by internal carotid artery and medially by prevertebral muscles.

208 pts, CT-based, 16% invo

→ Subcl 5.5-

Bussels et al, IJROBP 2006

RP nodes in OPC

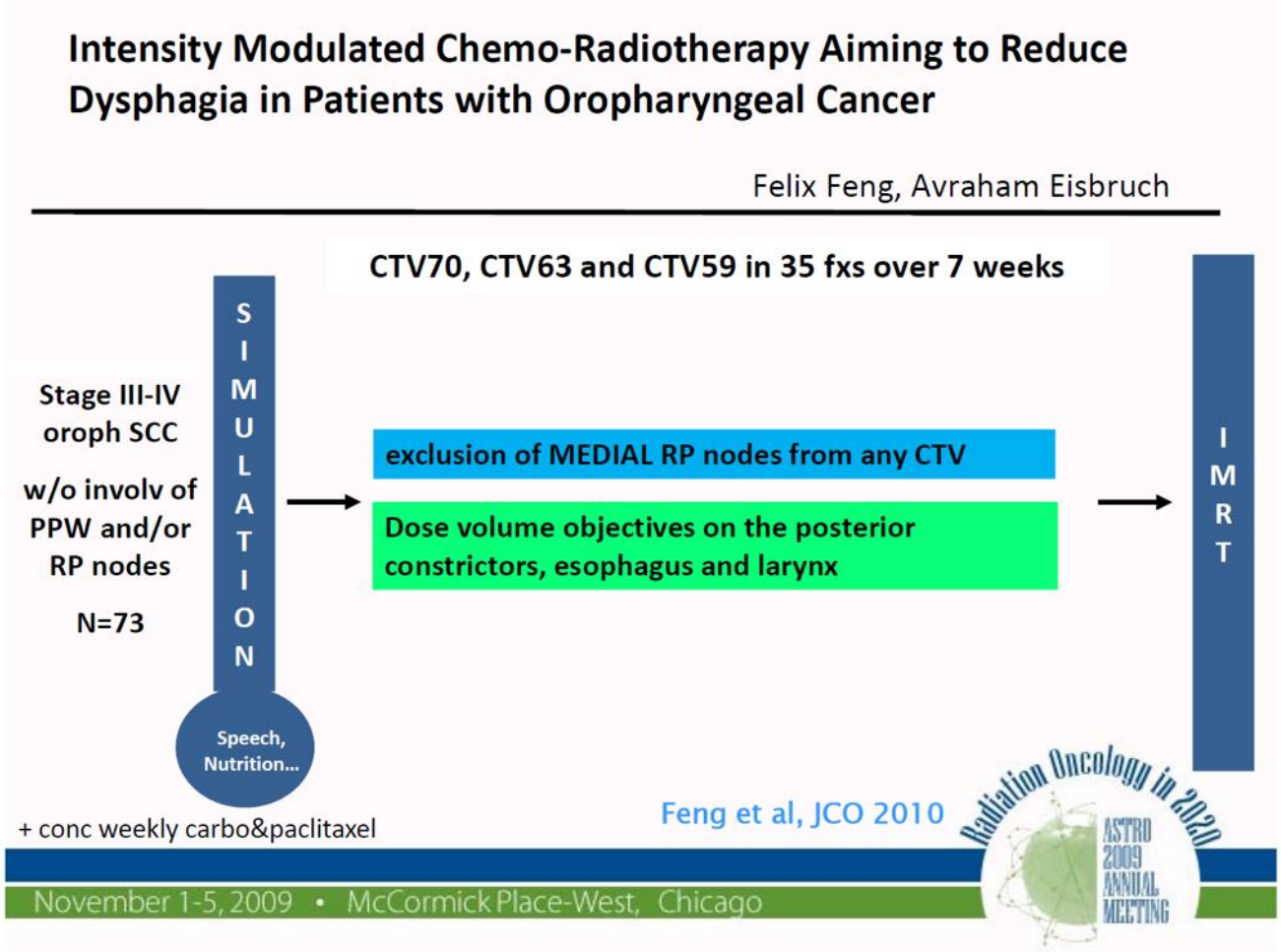
RPLN involvement was associated with T-stage, N-stage, T-location, N-level…

T site: T, 11%; BOT, 6%; SP, 12%, PW, 23% of patients;
N-level: lv IV, 26%; lv III, 9.4%; lvs IB-II, 7.2%, cN0, 7.2%

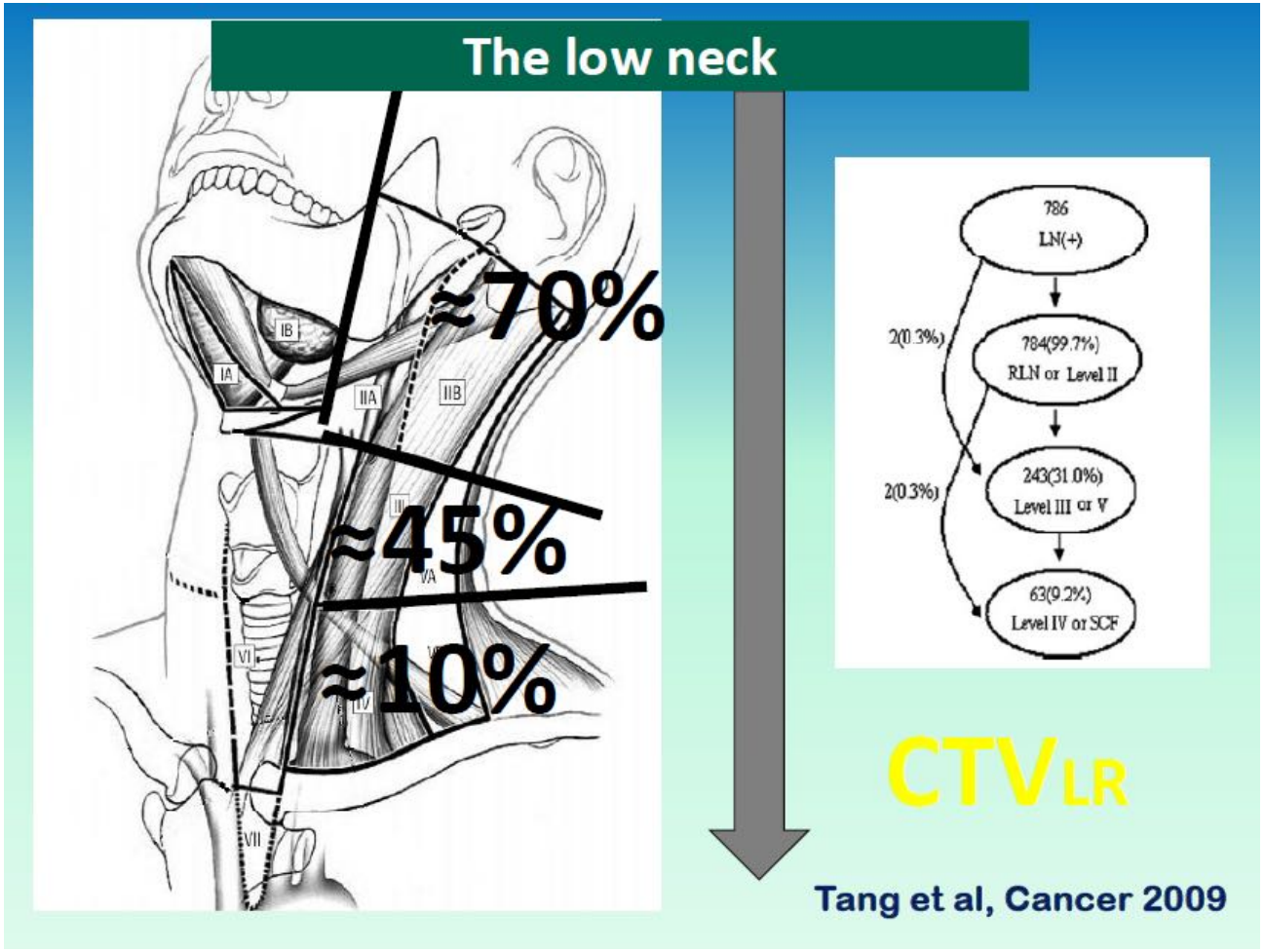
981 pts, CT-based, 10%

Gunn et al, cancer 2013

RP nodes in OPC



Level IV nodes in NPC



Omission of T site in OPC after TORS

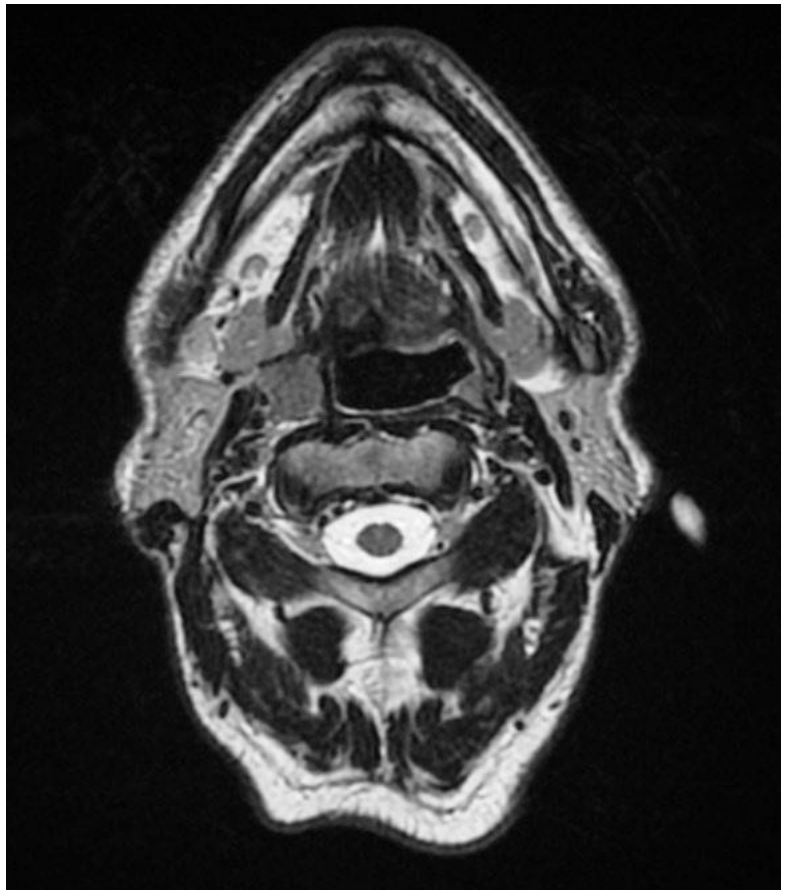
Indications to postop XRT

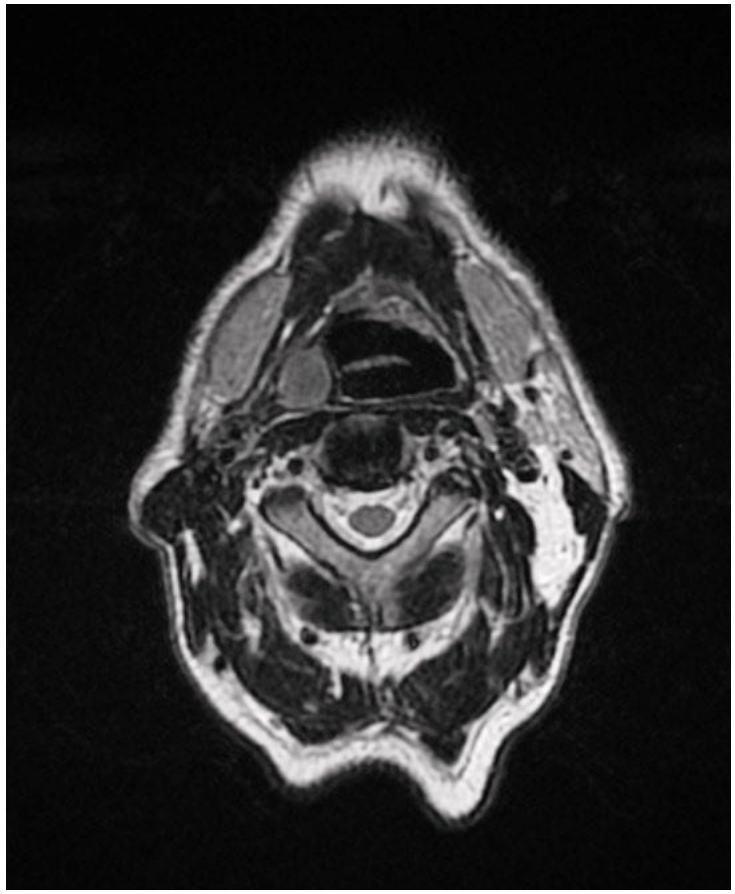
- Primary: T4 (T3)
  - Linfovascular invasion (LVSI)
  - Perineural invasion (PNI)
  - Positive margins (PRM)
  - Close (<3-5 mm) margins
  - Ca in situ at margin
  - Converted margins (tongue)
  - Primary site (tongue, oral cavity)
  - Multifocal dis
  - High grade

Lack of field cancerization in HPV-related diz

Rusthoven et al, IJROBP 2008

Omission of T site in OPC after TORS





Omission of pN0

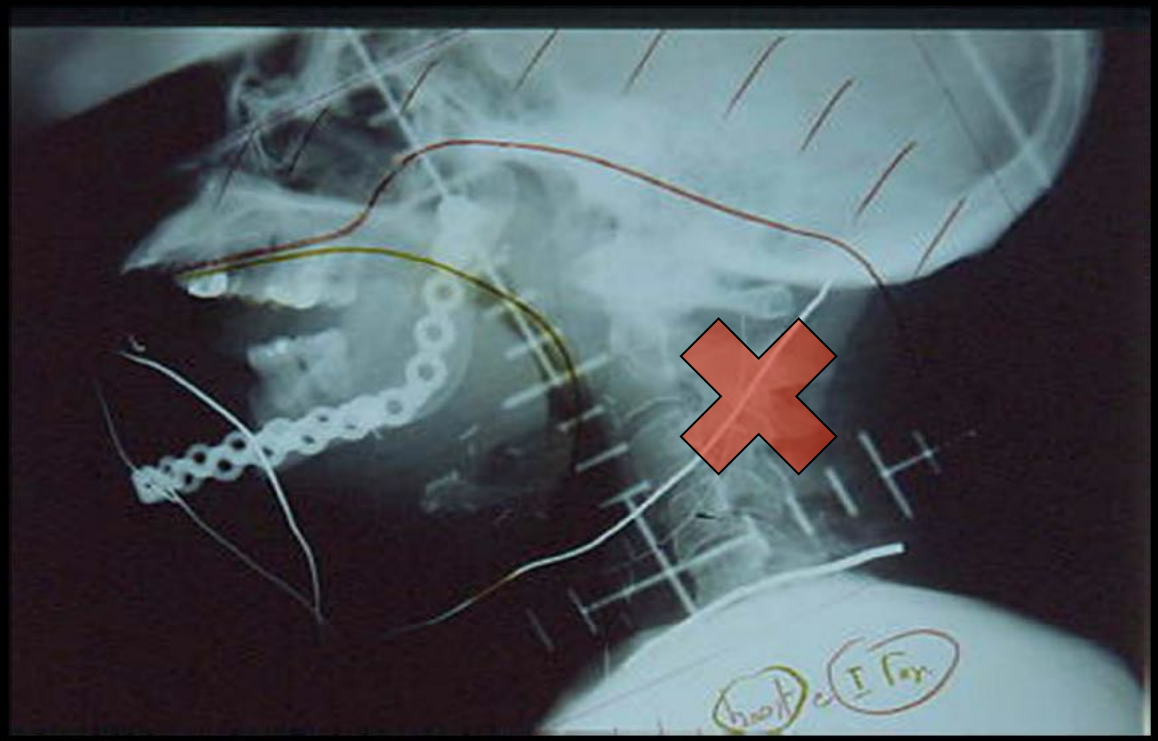
Primary Tumor Bed

Final dose *(using shrinking field technique)*: Minimum 58 Gy to resected regions. Boost to 62-66 Gy for high-risk factors *(Section 3.0)*.

Neck Lymph Nodal Bed

Final dose *(using shrinking field technique)*: Minimum 58 Gy to resected regions. Boost to 62-66 Gy for high-risk factors *(Section 3.0)*.

Contralateral and other unoperated lymph node regions *(Levels 1-5, and for pharyngeal cancers, the retropharyngeal lymph node region)*: 50 Gy minimum dose.



RTOG H-0024

Omission of pN0

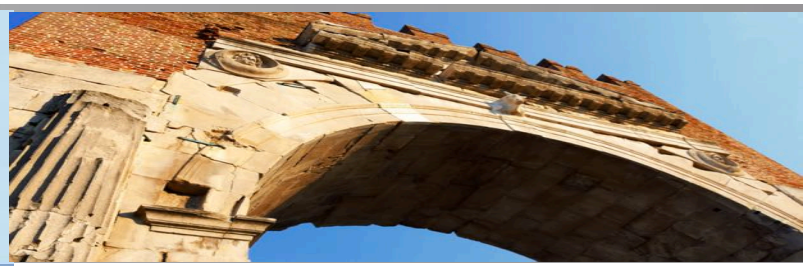
Indications to postop XRT

- Neck: elective of undissected N0
  pN>1 (node larger than 3 cm or multiple)
  pN1 if ND not adequate
  ECE
  atypical location (skip)

Omission of pN0

Risk of regional failure in the pN0 neck after

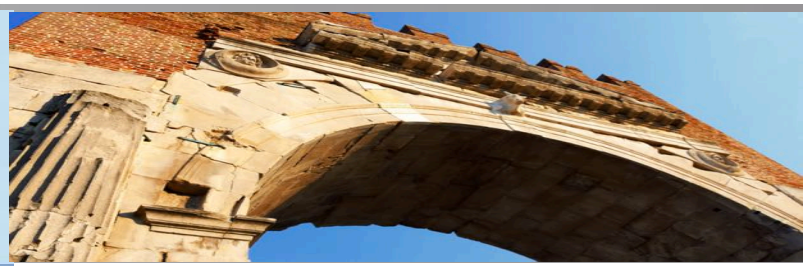
- RND <1%
- MRND <3%
- SND <5%



Omission of pN0

…BUT

- Lack of data on the pattern of failure
- Risk of seeding during surgery at other/T sites

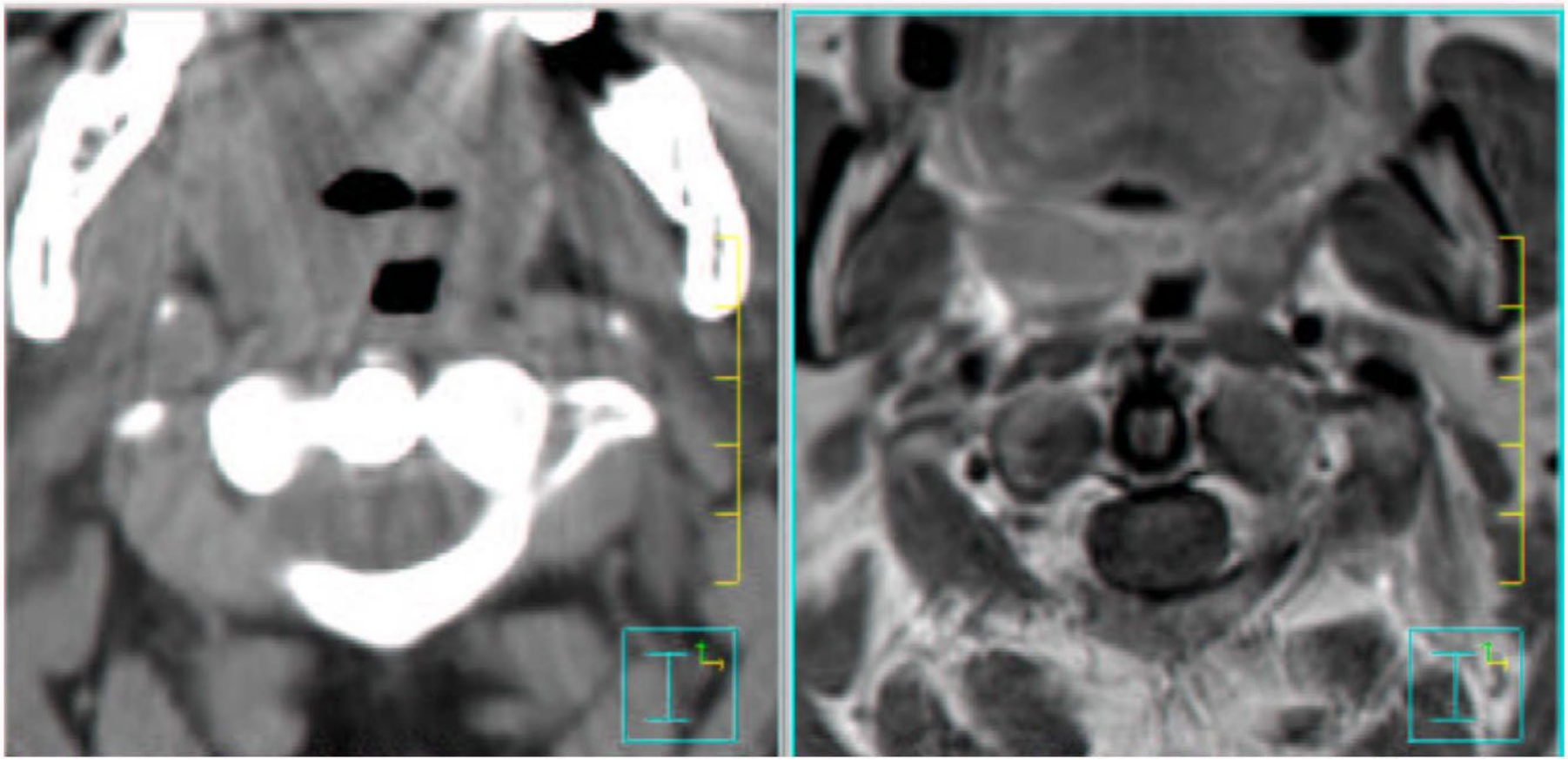


Omission of pN0

these findings. The areas at risk of recurrence are less predictable in patients with recurrent tumors who have had previous extensive surgery, similar to Patient 11. Thus, we currently do not enroll such patients on conformal and IMRT protocols, as the target volumes at risk are not easily defined. The isolated marginal recurrence in the high retro-

Dawson et al, IJROBP 2000

‘Shrink’ GTV volume



‘Shrink’ GTV volume

ADAPTIVE DOSE PAINTING BY NUMBERS FOR HEAD-AND-NECK CANCER

FRÉDERIC DUPREZ, M.D., WILFRIED DE NEVE, M.D., PH.D., WERNER DE GERSEM, IR., PH.D., MARC COGHE, LIC, AND INDIRA MADANI, M.D., PH.D.

Department of Radiotherapy, Ghent University Hospital, Ghent, Belgium

Int. J. Radiation Oncology Biol. Phys., Vol. 80, No. 4, pp. 1045–1055, 2011

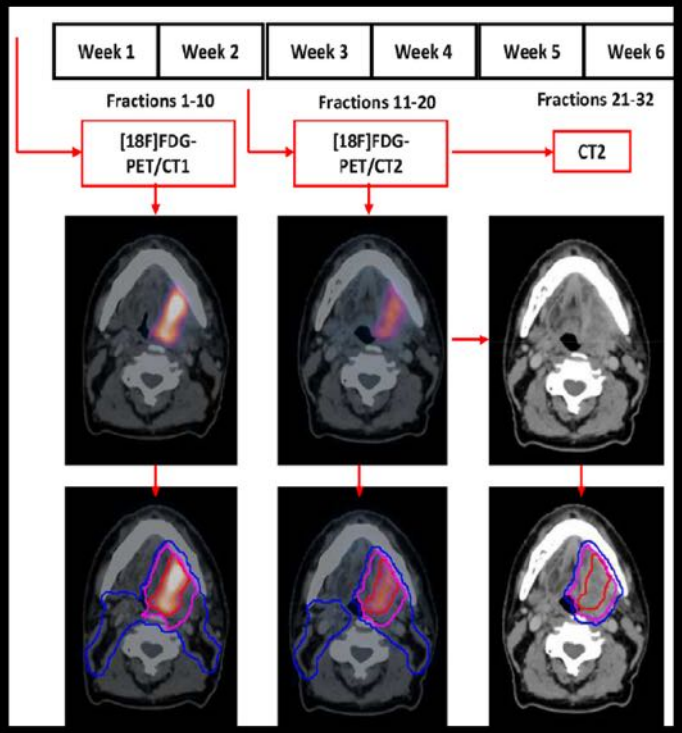


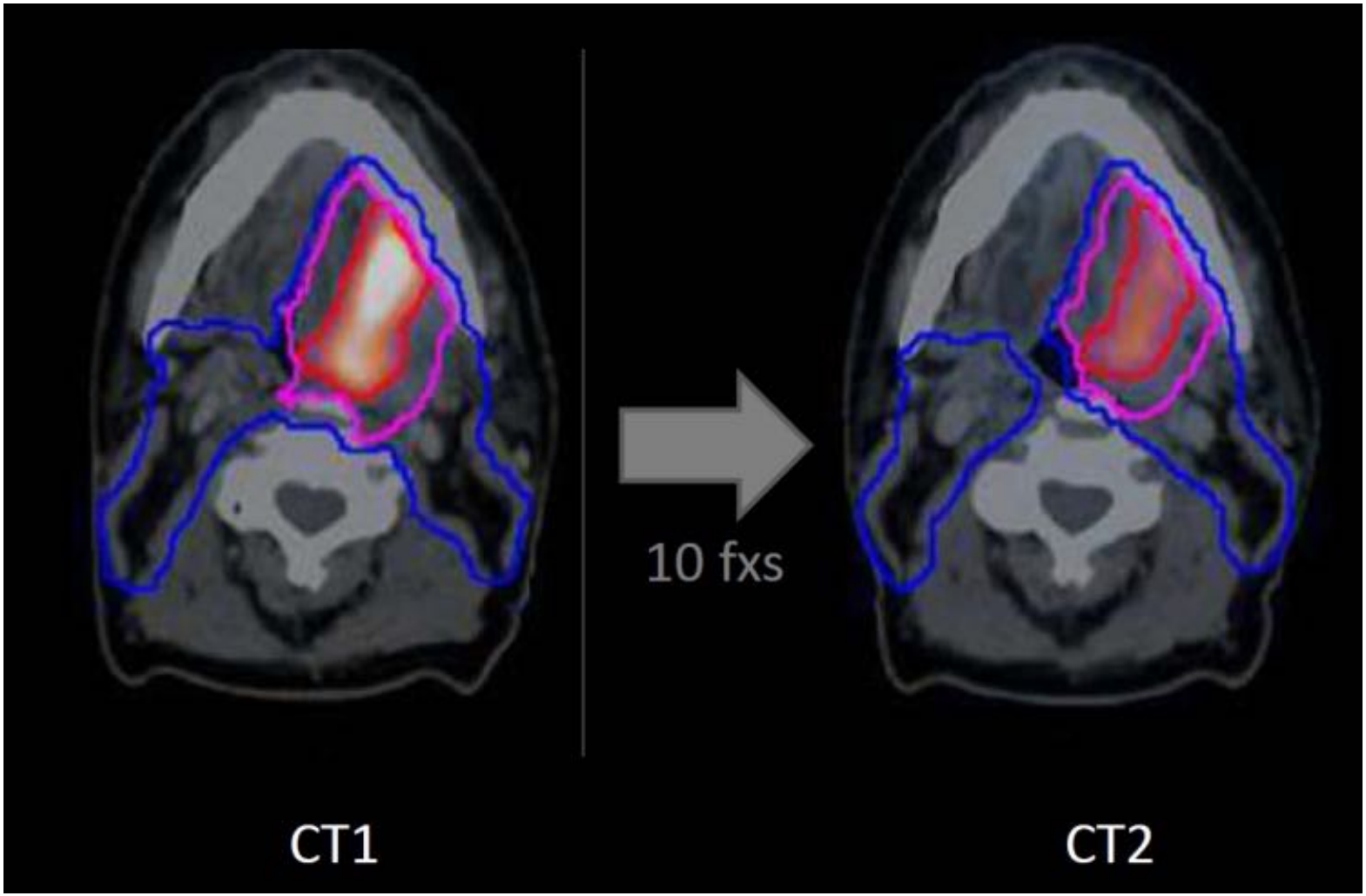
Table 1. Prescription dose levels to the targets

Target	Dose painting Median fraction dose (Gy), fractions 1–10	Dose painting Median fraction dose (Gy), fractions 11–20	No dose painting Median fraction dose (Gy), fractions 21–32	Whole treatment Median total dose (Gy), fractions 1–32	NID_{2Gy} (Gy)
Dose level I					
CTV_{high_dose}	2.5 dose range 2.16–3.0	3.0 dose range 2.5–3.5	2.16	80.9	91
Dose level II					
GTV	3.0 dose range 2.5–3.5	3.0 dose range 2.5–3.5	2.16	85.9	102
$PTV_{elective\_neck}$	2.16	2.16	—	43.2	50

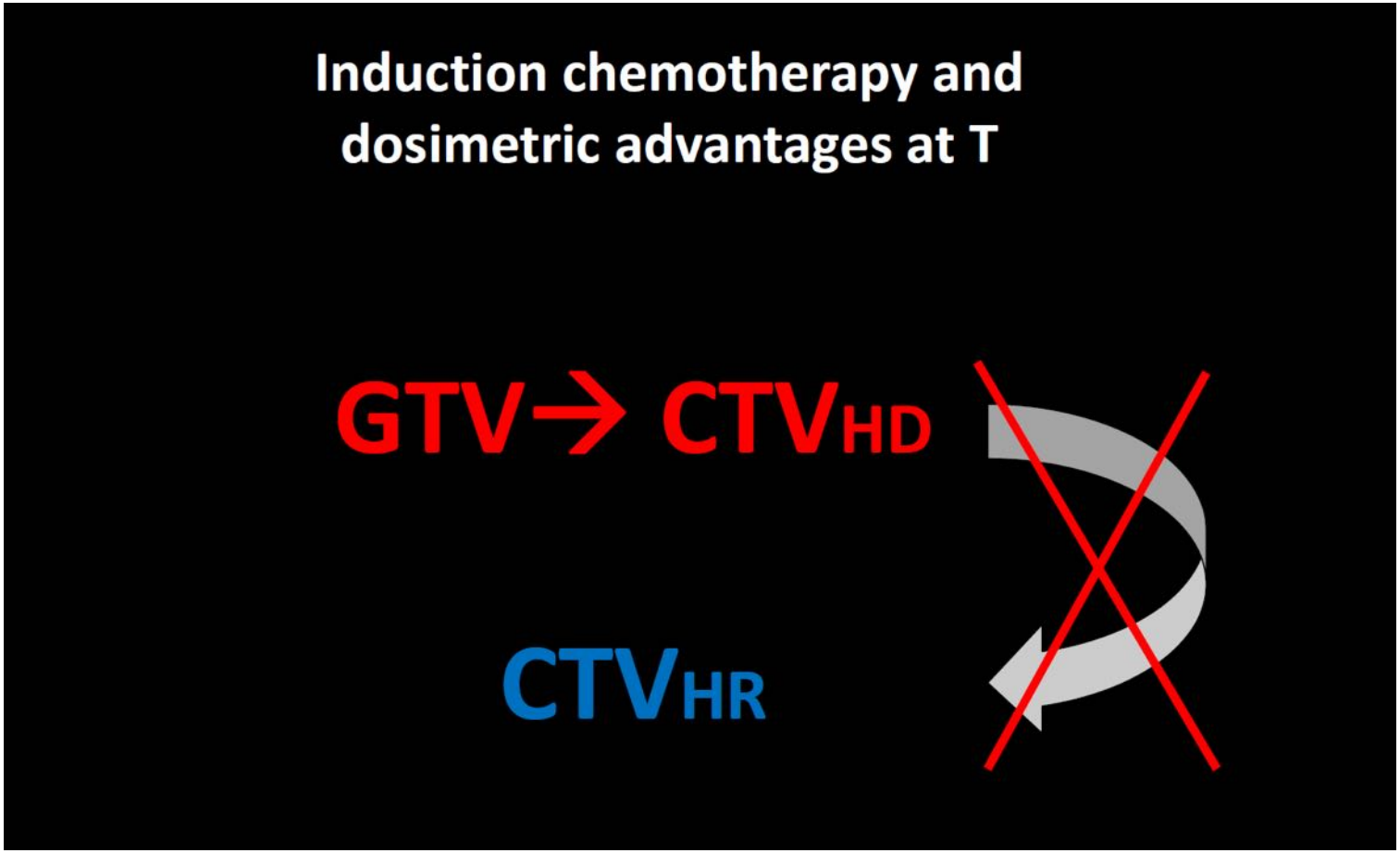
GTV
CTV high dose
PTV

‘Shrink’ GTV volume

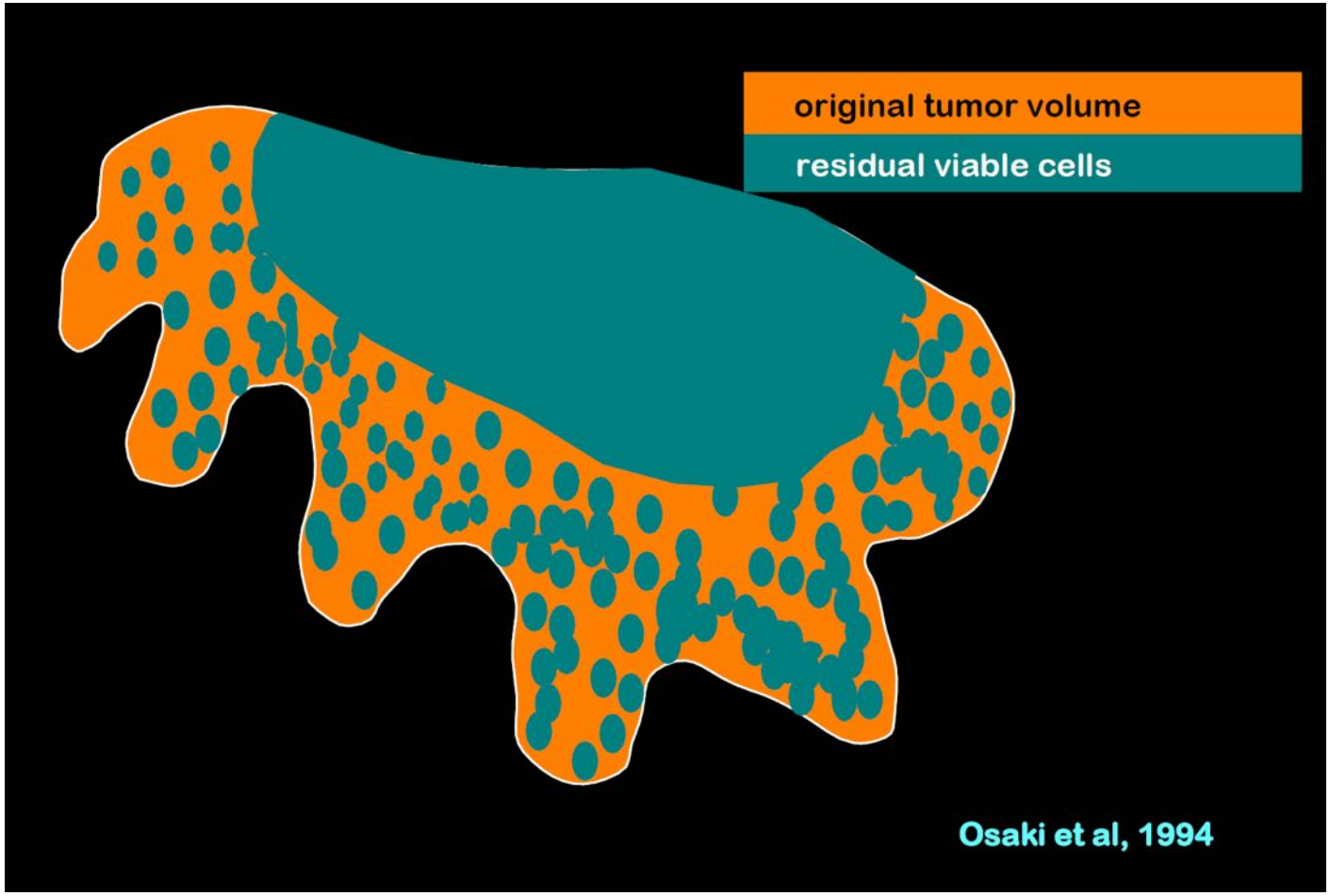
Duprez et al, IJROBP 2013



Induction chemotherapy



Induction chemotherapy

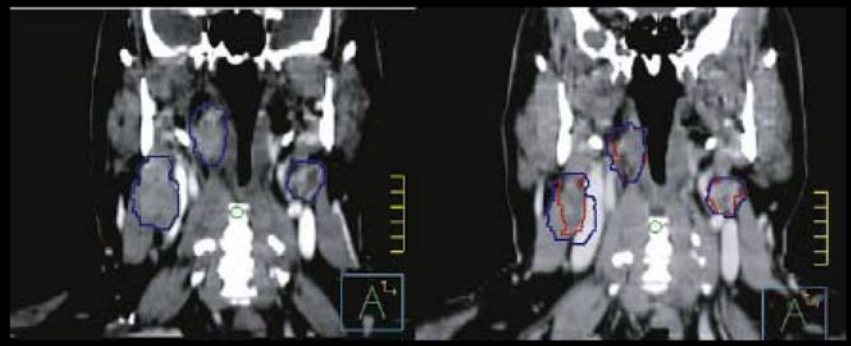


Induction chemotherapy

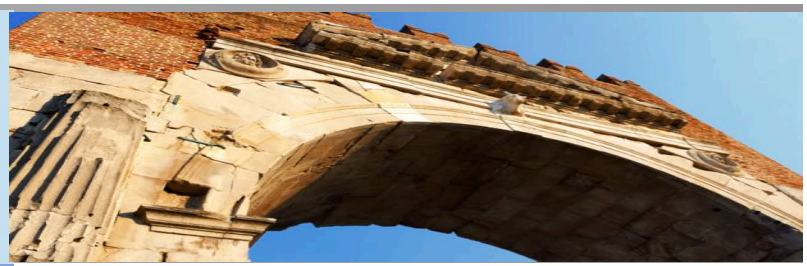
CLINICAL PRACTICE GUIDANCE FOR RADIOTHERAPY PLANNING AFTER INDUCTION CHEMOTHERAPY IN LOCOREGIONALLY ADVANCED HEAD-AND-NECK CANCER

Joseph K. Salama, M.D.,* Robert I. Haddad, M.D.,† Merril S. Kies, M.D.,‡ Paul M. Busse, M.D., Ph.D.,§ Lei Dong, Ph.D.,‡ David M. Brizel, M.D.,¶ Avraham Eisbruch, M.D.,‖ Roy B. Tishler, M.D., Ph.D.,† Andy M. Trotti, M.D.,# and Adam S. Garden, M.D.‡

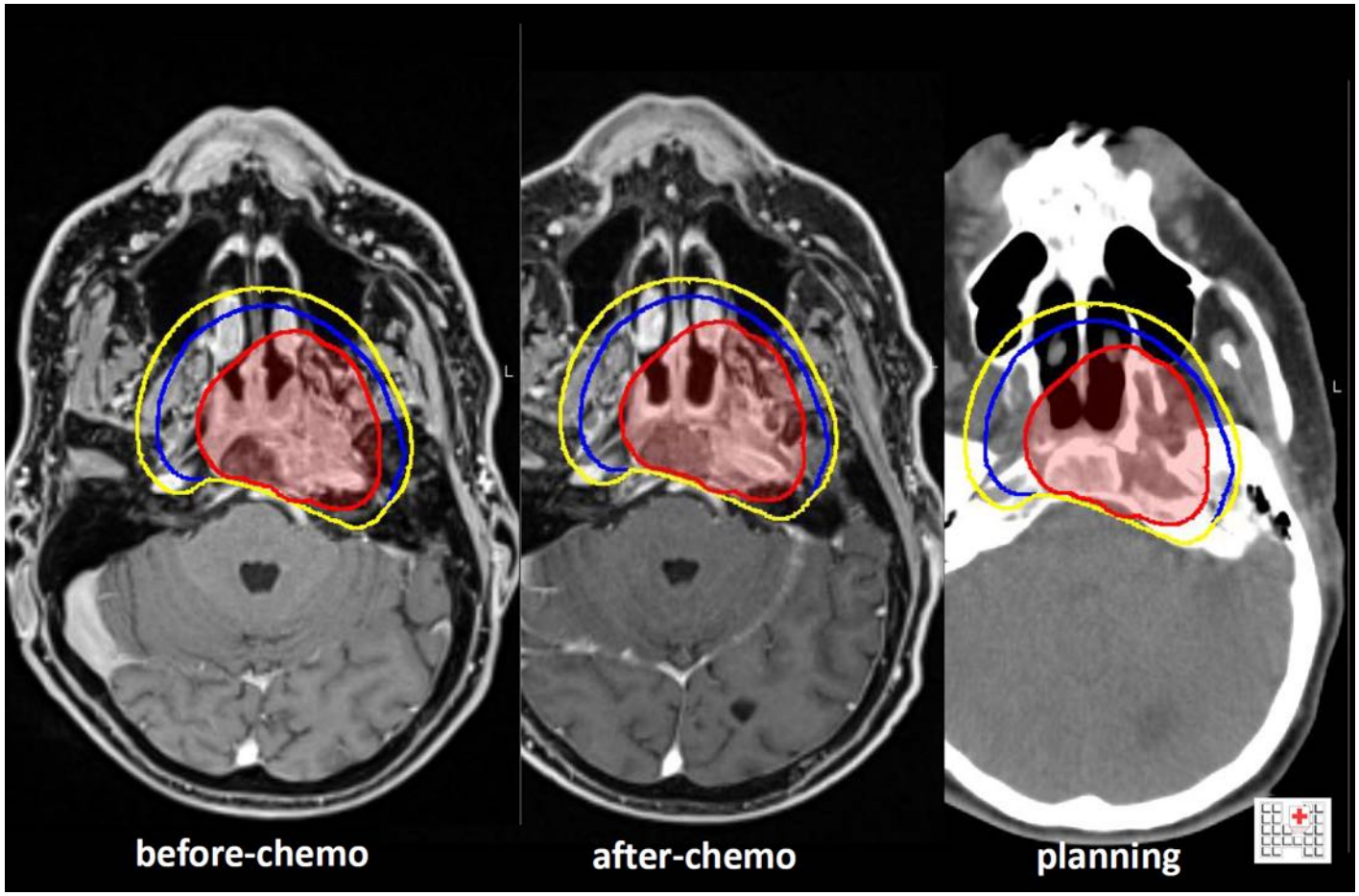
Results: Recommendations and guidelines emerged that emphasize up-front evaluation by all members of the head-and-neck management team, high-quality baseline and postinduction planning scans with the patient in the treatment position, the use of preinduction target volumes, and the use of full-dose RT, even in the face of a complete response.



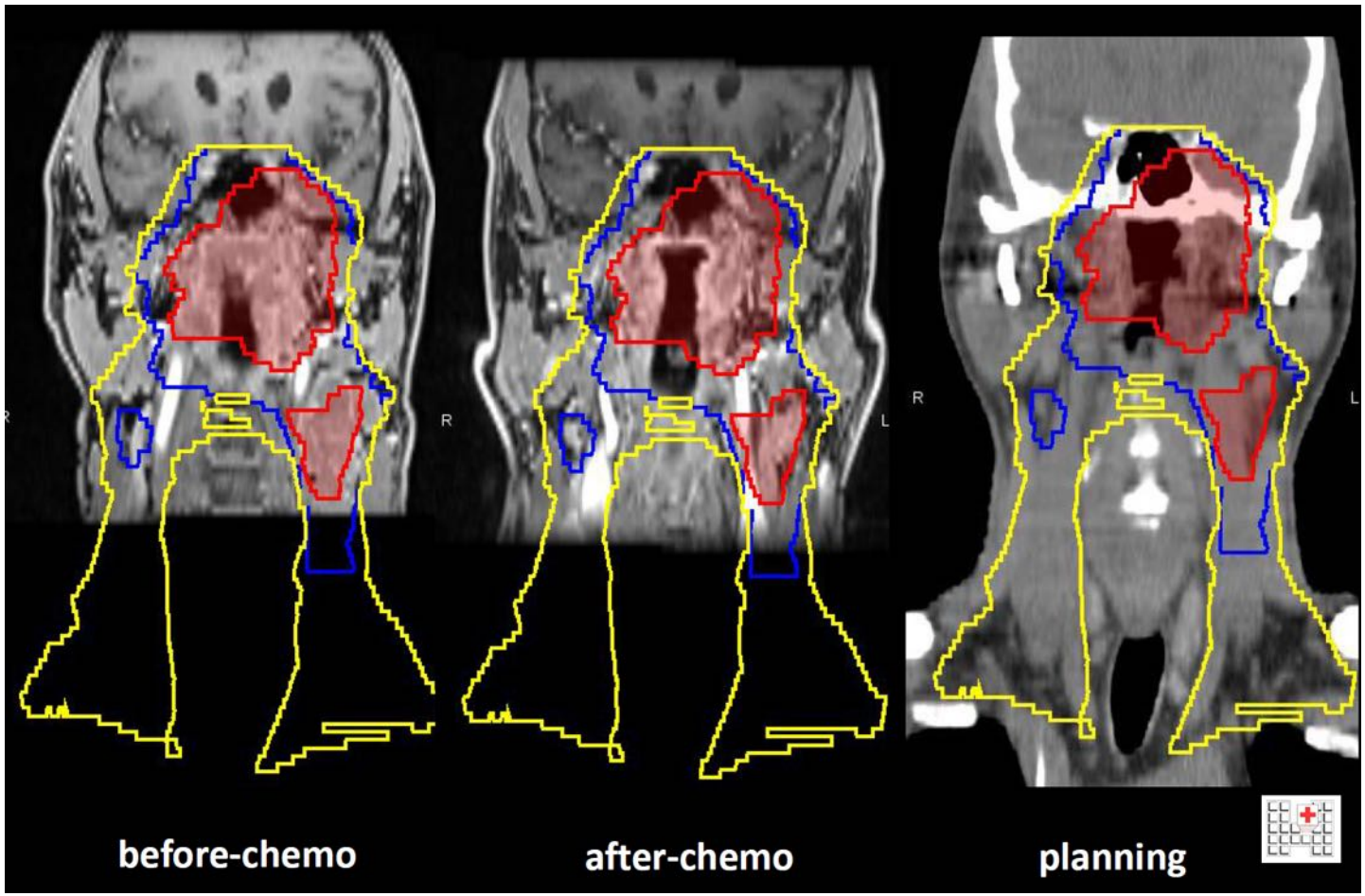
Int. J. Radiation Oncology Biol. Phys., Vol. 75, No. 3, pp. 725–733, 2009

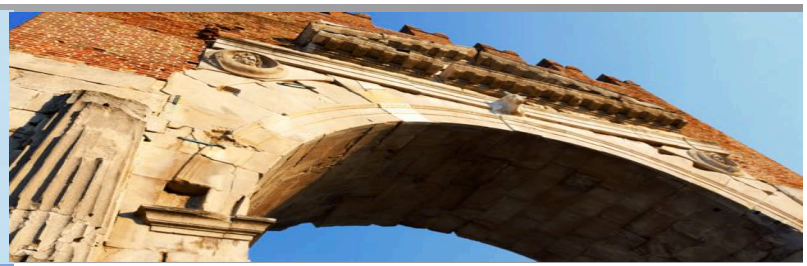


Induction chemotherapy

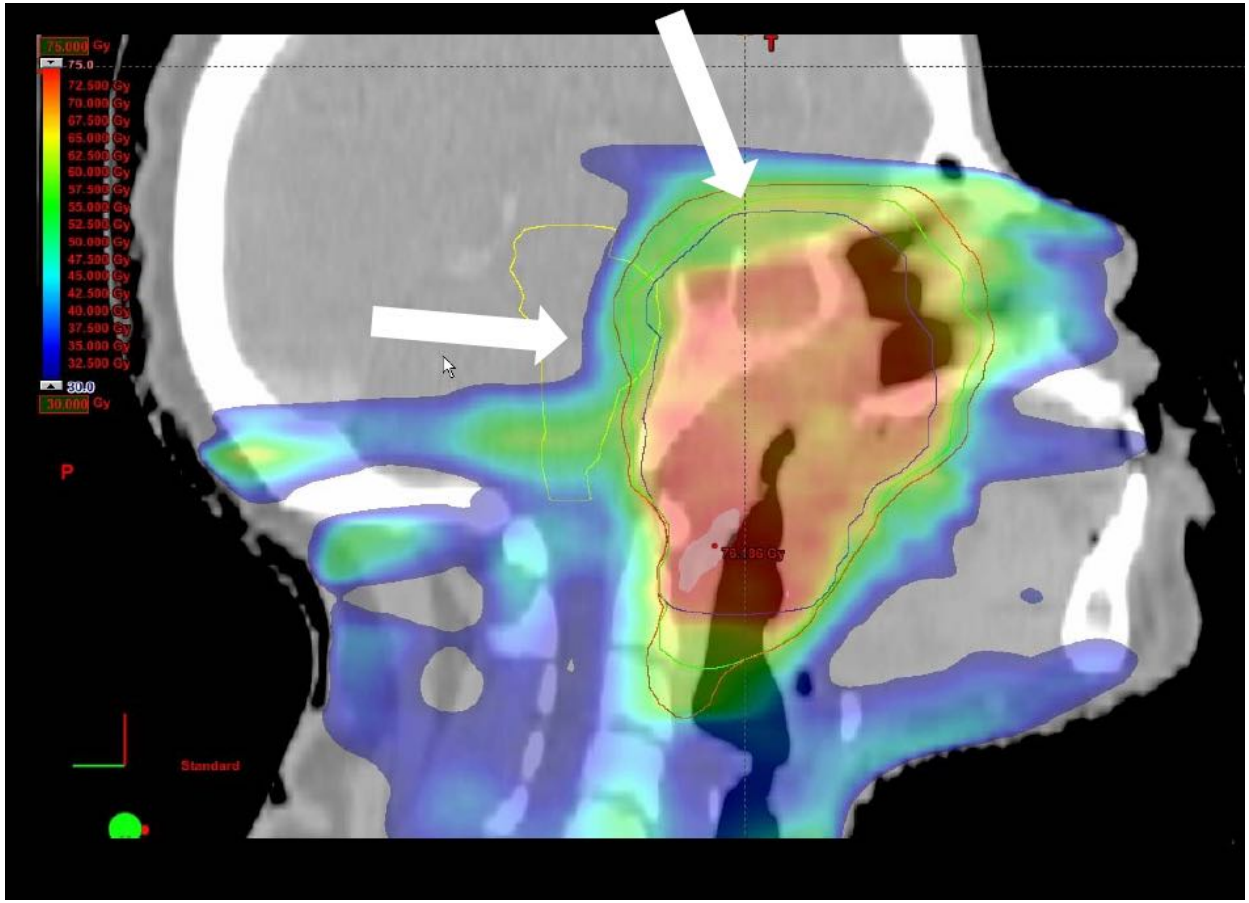


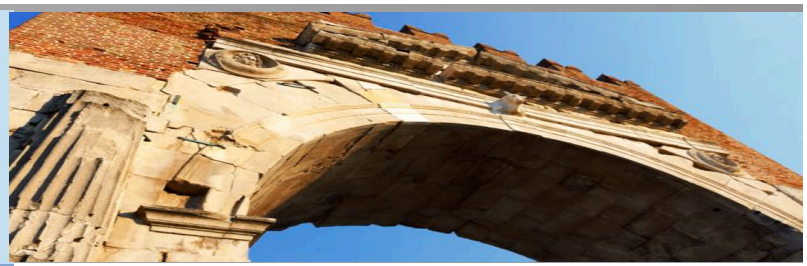
Induction chemotherapy





Induction chemotherapy





Response adapted volume deescalation

Materials/Methods: Patients (pts) with measurable locally advanced head and neck squamous cell cancer received 2 cycles of IC (cisplatin, paclitaxel, with or without cetuximab and/or everolimus). Patients with "good" response (GR), defined as ≥ 50% reduction in the sum of gross tumor diameters, received TFHX2 (paclitaxel, fluorouracil, hydroxyurea, and 1.5 Gy twice daily RT every other week) to 75 Gy with the planning target volume (PTV1) encompassing exclusively gross disease. Patients with < 50% response (NR) were treated with volumes encompassing PTV1 and the next nodal station at risk (PTV2) to 45 Gy, followed by a sequential boost to PTV1 to 75 Gy.

Melotek et al, ASTRO 2015
University of Chicago

Response adapted volume deescalation

Tumor Response is (the) strong(est) predictor of outcome

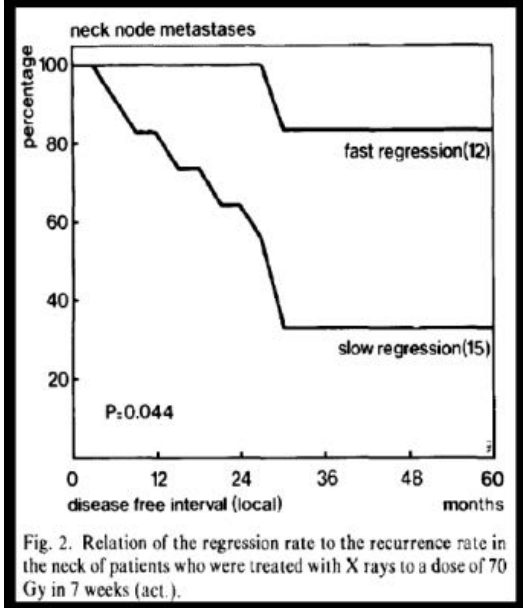


Fig. 2. Relation of the regression rate to the recurrence rate in the neck of patients who were treated with X rays to a dose of 70 Gy in 7 weeks (act.).

PROGNOSTIC VALUE OF THE REGRESSION RATE OF NECK NODE METASTASES DURING RADIOTHERAPY

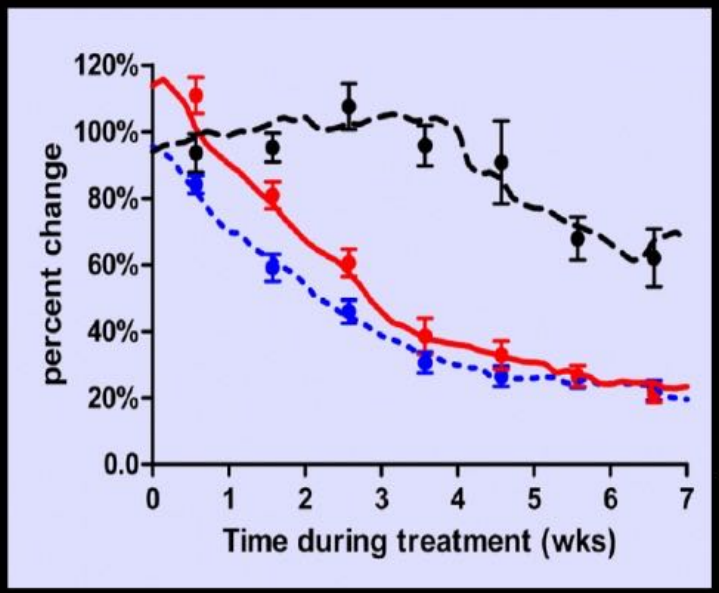
HARRY BARTELINK, M.D., PH.D.

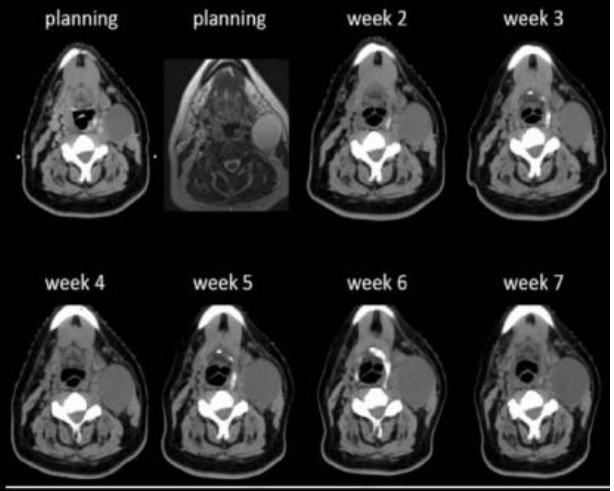
A prospective study was carried out in order to assess whether the regression rate can be applied as a parameter, which could be correlated with the probability of recurrence after radiation of neck node metastases. Measurements were made on neck node metastases during the radiation treatment period in 47 patients. Tumors with a slow regression rate were shown to have a high probability of recurrence. The results indicate that accurate measurements of the regression rate provide prognostic information, which is obtained early enough for the radiotherapist to consider additional treatment.

IJROBP, 1983

Response adapted volume deescalation

Volumetric change of nodes during IMRT





79 nodes in 50 pts, all HPV +ve

Sanguineti et al, H&N 2012

Evaluation of Volumetric/Functional changes during tmt

Tool		Tech	Endpoint	Biology
Physical Exam			Volume & Consistency	
Re-biopsy			Tumor cells	
Imaging	CT	Volumetric	Volume & Morphology	
		DCE	Perfusion & permeability	Hypoxia
	MRI	Volumetric	Volume & Morphology	
		DWI	Cell loss	Viable cells
		DCE	Perfusion & permeability	Hypoxia
	PET	FDG	Glucose Metabolism	Viable cells
		FLT	Proliferation	Viable cells
		F-miso	Hypoxia in viable cells	Hypoxia

Optimal parameters, reproducibility, standardization…

Response adapted volume deescalation

Acta Oncologica, 2013; 52: 1257–1271

informa
healthcare

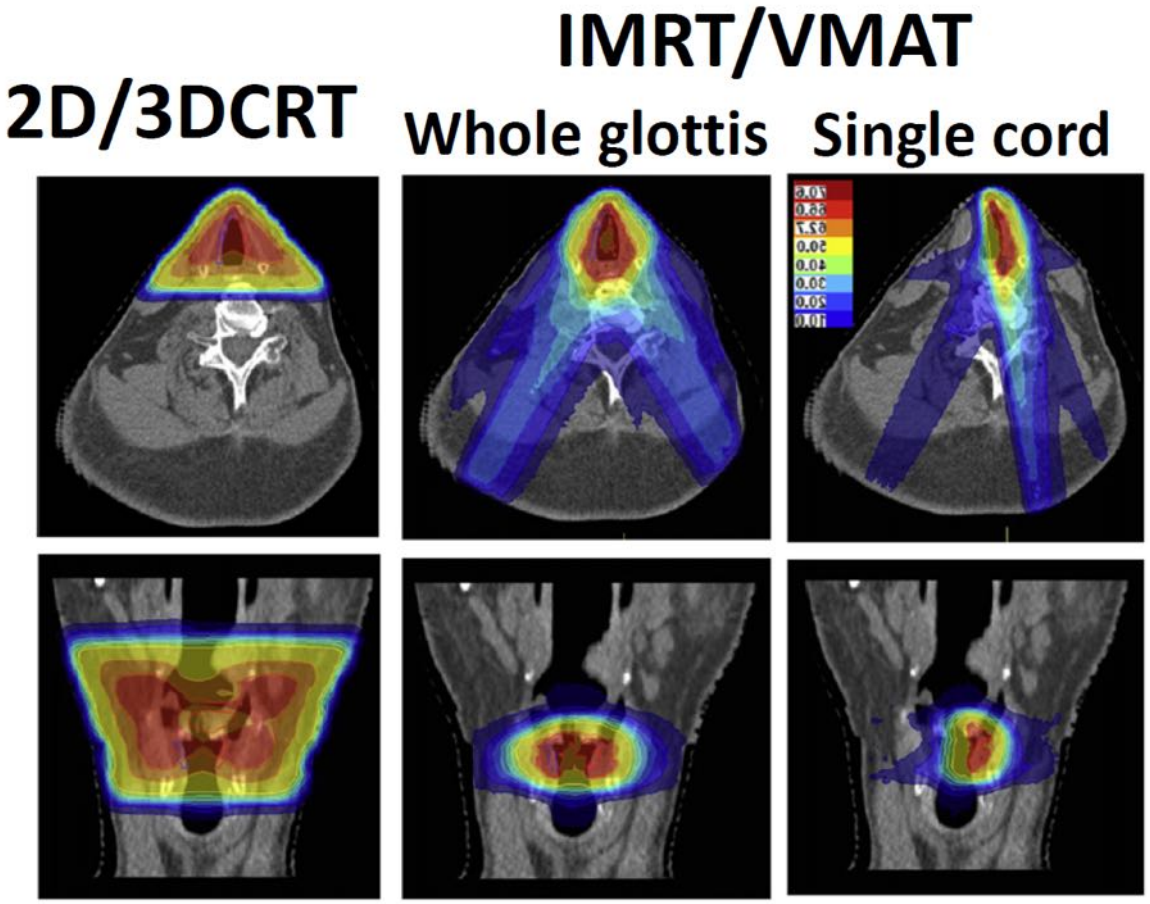
REVIEW ARTICLE

Molecular PET imaging for biology-guided adaptive radiotherapy of head and neck cancer

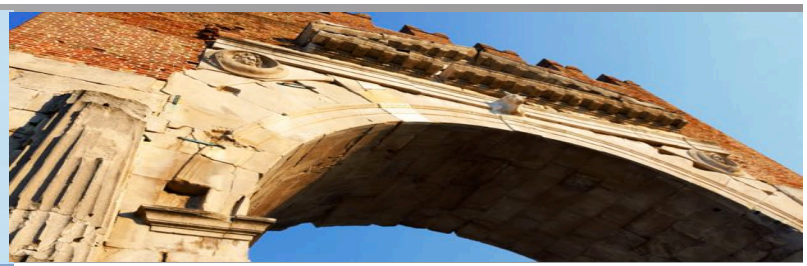
BIANCA A. W. HOEBEN[1], JOHAN BUSSINK[1], ESTHER G. C. TROOST[3], WIM J. G. OYEN[2] & JOHANNES H. A. M. KAANDERS[1]

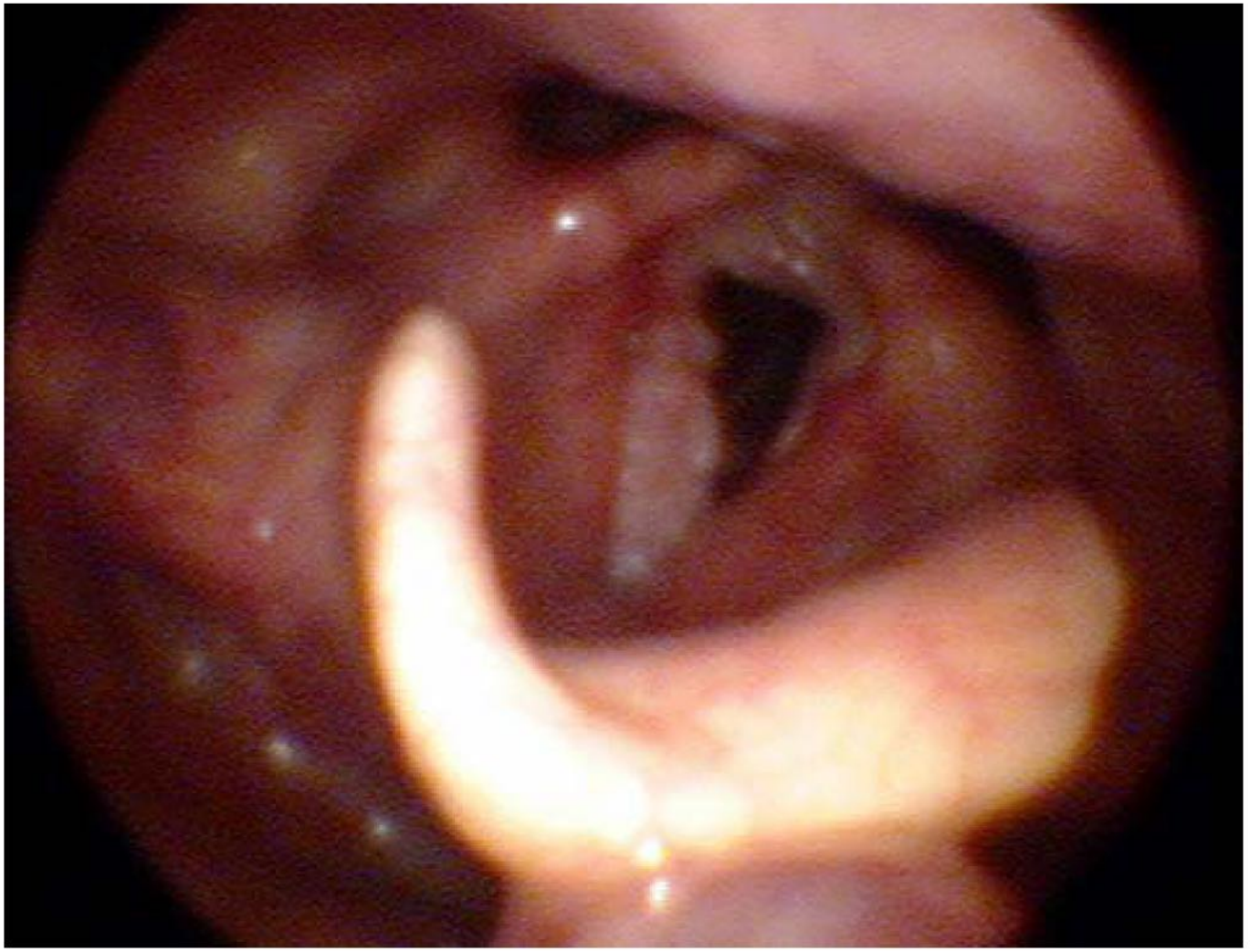
[1]*Department of Radiation Oncology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands,* [2]*Department of Nuclear Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands and* [3]*Maastro Clinic, GROW School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, The Netherlands*

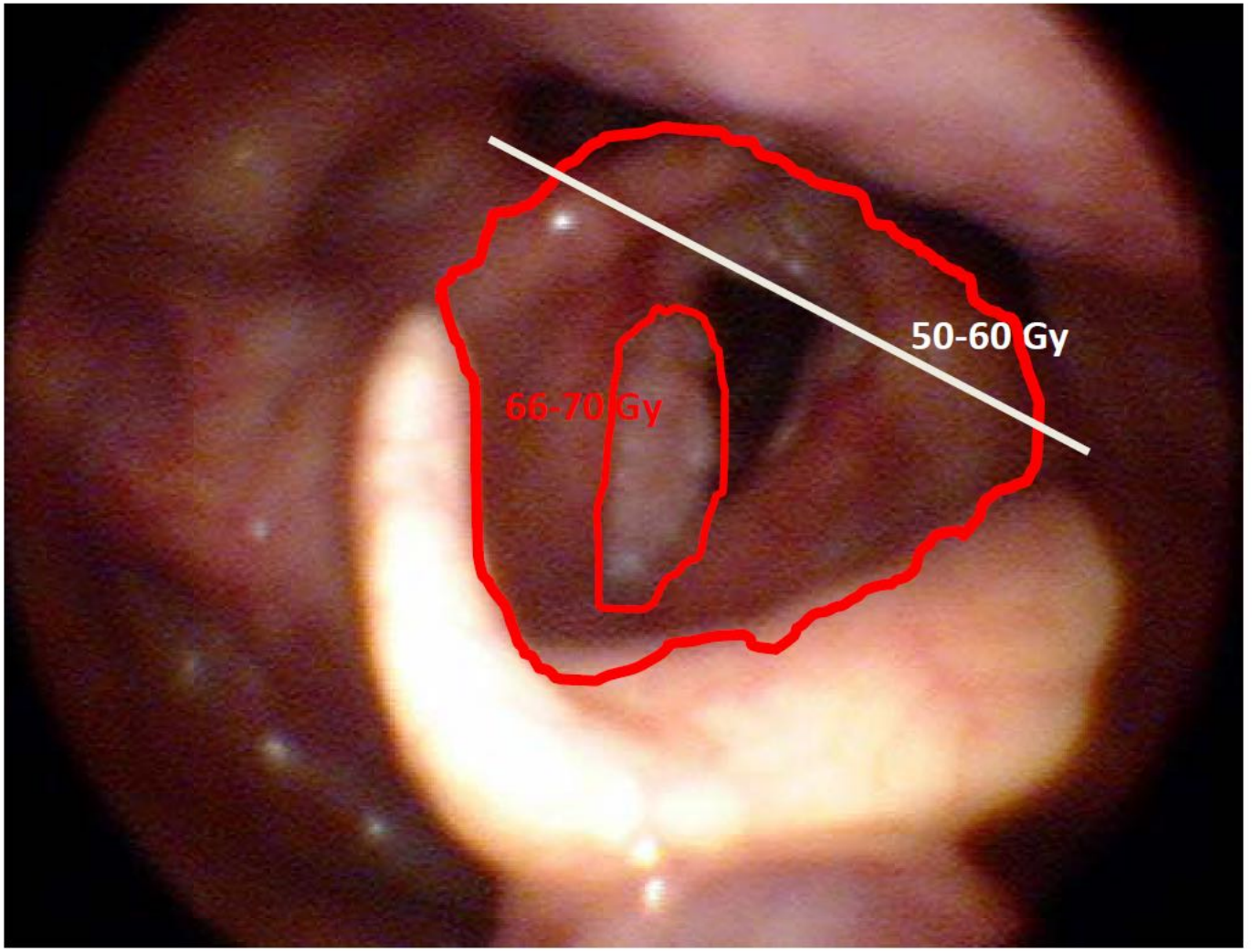
Whole larynx vs whole glottis vs TVC for T1N0 glottis



IRE






50-60 Gy
66-70 Gy

Whole larynx vs whole glottis vs TVC for T1N0 glottis

Clinical Investigation

Single Vocal Cord Irradiation: Image Guided Intensity Modulated Hypofractionated Radiation Therapy for T1a Glottic Cancer: Early Clinical Results

Abrahim Al-Mamgani, MD, PhD,* Stefan L.S. Kwa, PhD,* Lisa Tans, MD,* Michael Moring, RTT,* Dennie Fransen, RTT,* Robert Mehilal, MD,* Gerda M. Verduijn, MD,* Rob J. Baatenburg de Jong, MD, PhD,† Ben J.M. Heijmen, PhD,* and Peter C. Levendag, MD, PhD*

*Department of Radiation Oncology — Erasmus MC Cancer Institute, and †Department of Otolaryngology and Head and Neck Surgery — Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

Received Mar 4, 2015, and in revised form Jun 5, 2015. Accepted for publication Jun 8, 2015.

3.63 Gy x 16, D= 58.08 Gy, 5 fxs/wk 4DCT, IGRT Anisotropic margins (3 mm but sup/inf, 5 mm)

IMRT-VMAT	Sign shrinkage of treated volume over 3DCRT Same CTVs, Same or slightly ↑D, same or slightly ↓# fxs Tumor cell apoptosis
SBRT-SRS	Sign shrinkage of CTV over IMRT-VMAT Ablative D in few fxs Tumor cell and endotelial apoptosis

IMRT-VMAT

Sign shrinkage of treated volume over 3DCRT
Same CTVs,
Same or slightly ↑D, same or slightly ↓# fxs
Tumor cell apoptosis

Moderate HYPO

SBRT-SRS

Sign shrinkage of CTV over IMRT-VMAT
Ablative D in few fxs
Tumor cell and endotelial apoptosis

RISKS/BIASES
Which is the clinically meaningful threshold to withhold treatment?
Inappropriate & inadequate baseline literature data
Is it clinically driven?

RISKS/BIASES
Which is the clinically meaningful threshold to withhold treatment?
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Volume	Pros
Level IB	Spare incidental oral cavity
Level IV	Esoph, brachial plexus, thyroid gland
Level V	Posterior neck alopecia
RP	Constrictors
Larynx	Carotid arteries, allow SBRT

RISKS/BIASES
Which is the clinically meaningful threshold to withhold treatment?
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Volume	Pros
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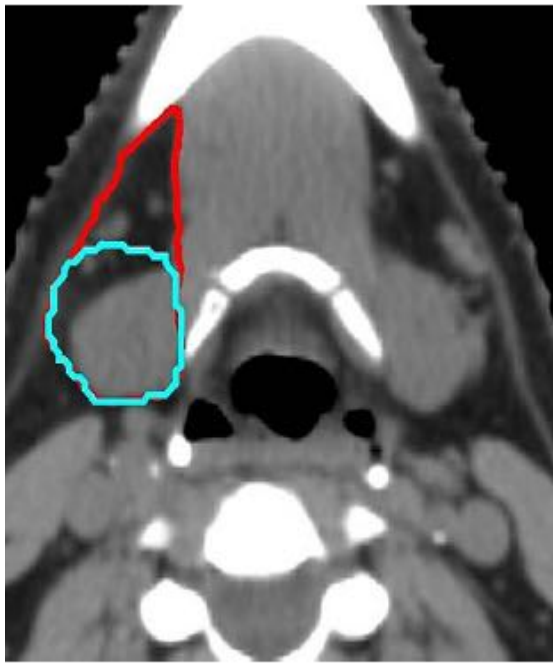
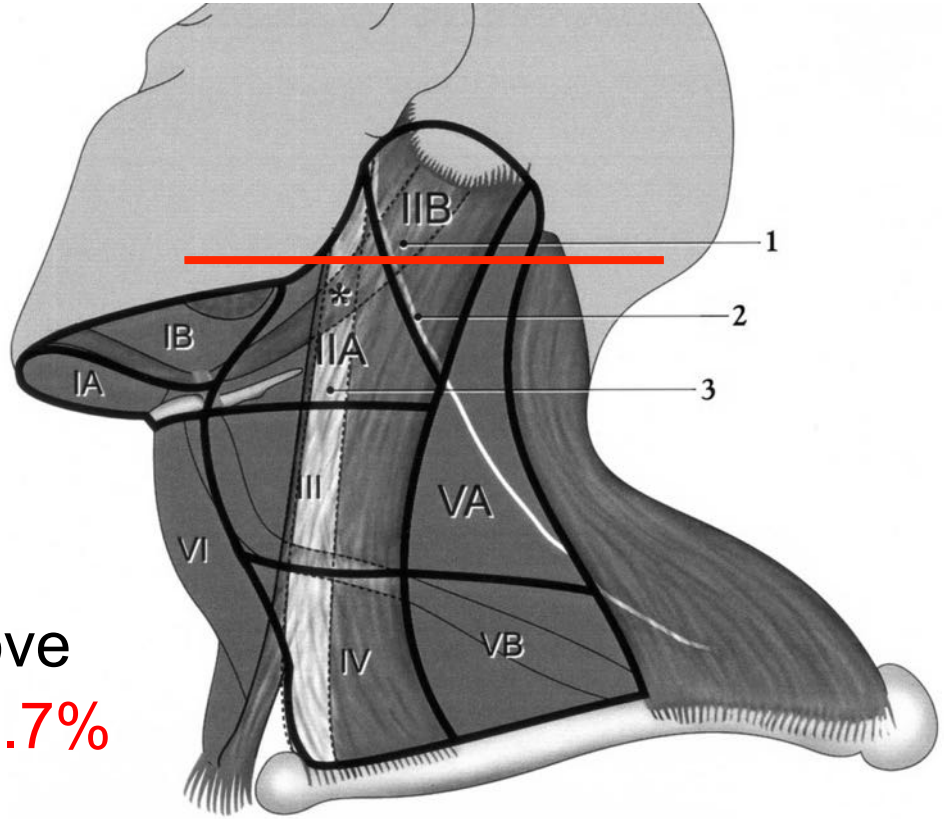


Sanguineti et al, IJROBP 2000

Contralateral neck nodes

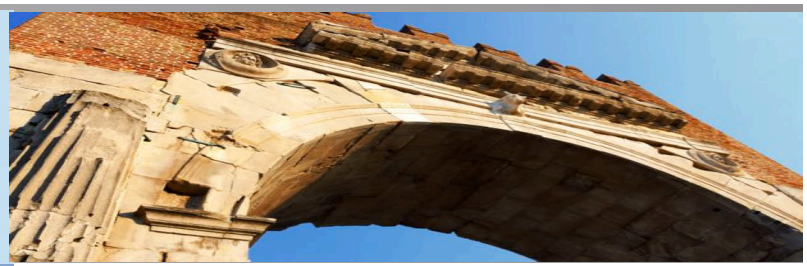
Uppermost level of contralateral clinically negative neck is the caudal edge of the lateral process of C1 OR the surgical landmark, the level on the planning CT in which the posterior belly of the digastric muscle crosses the jugular vein



133 pts, 0% failure rate above

95% CI 0-2.7%

Eisbruch et al, IJROBP 2004



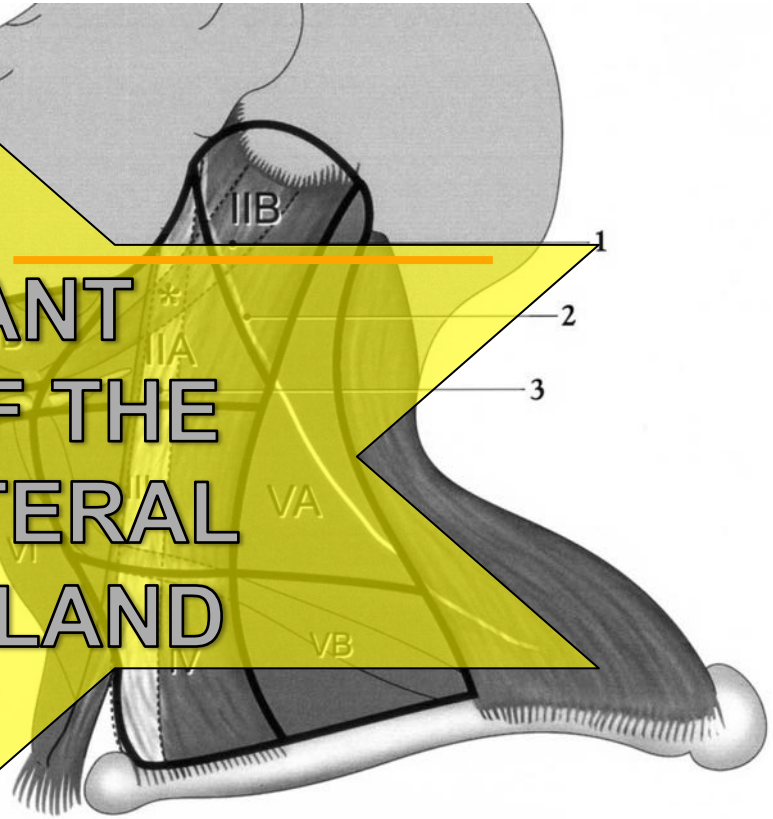
Contralateral neck nodes

Uppermost level of contralateral clinically negative neck is the caudal edge of the lateral process of C1 OR the surgical landmark, the level of the planning CT in which the posterior belly of the digastric muscle dissects above the jugular vein

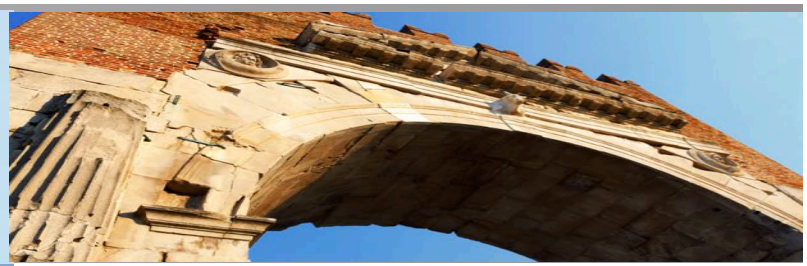
133 pts, 0% failures

95% CI 0-2.7%

SIGNIFICANT SPARING OF THE CONTRALATERAL PAROTID GLAND



Eisbruch et al, IJROBP 2004



RISKS/BIASES
Which is the clinically meaningful threshold to withhold treatment?
Inappropriate & inadequate baseline literature data
Is it clinically driven?
Complete spare vs underdosing

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Most studies actually do not achieve ‘complete’ spare but only underdosage to 25-40 Gy

Table 2–17. *Percentage of Eradication of Expected Occult Infestation in the Lymphatics of the Neck as Function of Dose**

Adenocarcinoma of the breast		Squamous cell carcinoma of the upper respiratory and digestive tracts	
3000–3500 rads (89 patients)	60–70%	3000–4000 rads (50 patients)	60–70%
4000 rads (121 patients)	80–90%		
5000 rads (273 patients)	>90%	5000 rads (356 patients)	>90%

* 1000 rads per week, 5 days a week
Adapted from Fletcher: *In* Biological and Clinical Basis of Radiosensitivity. Springfield, Illinois, Charles C Thomas Publisher, 1974, pp. 485–501.

Fletcher book 1978

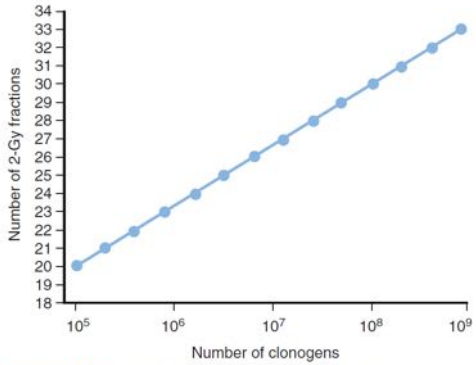


FIGURE 3-3. The theoretical relationship is depicted for the number of 2-Gy fractions and the number of clonogens, for which the goal is to achieve 90% local control. The relationship was modeled by assuming a surviving fraction of 0.5 after each fraction (SF_2). The tumor control probability (TCP) is equal to e^{-SN}, in which S is the surviving fraction after F fractions ($S = [SF_2]^F$), and N is the clonogen number. The straight line is the relationship if the dose were a continuous variable.

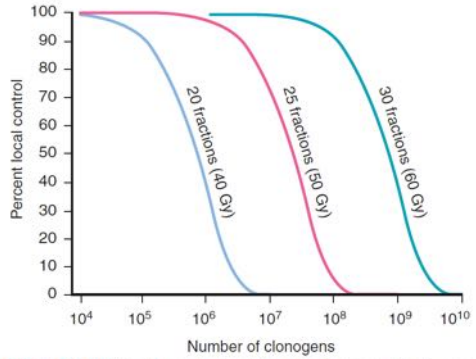
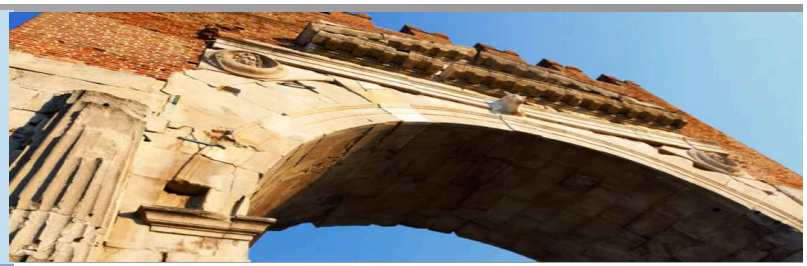
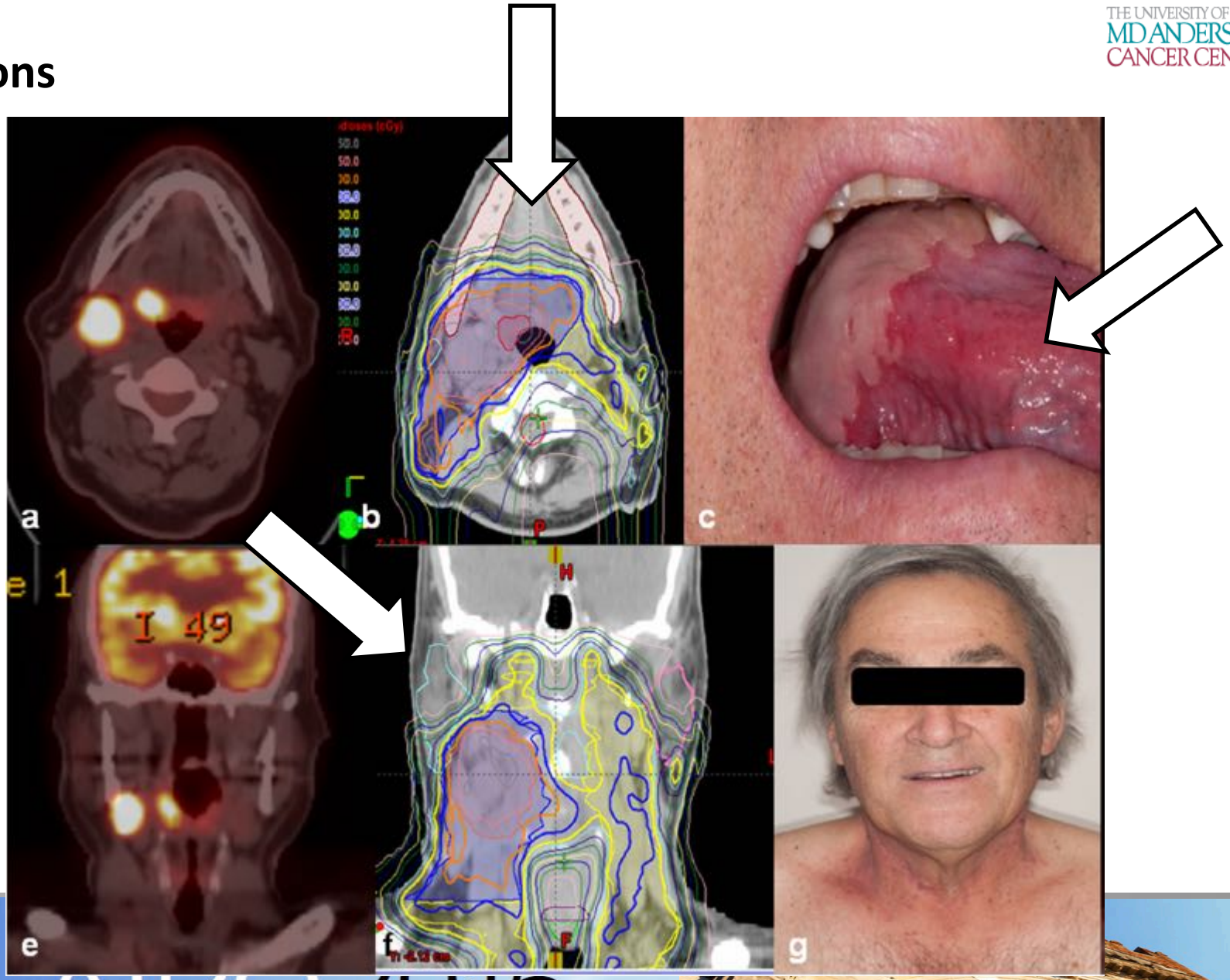


FIGURE 3-4. The theoretical relationship between local control and clonogen number is depicted for different total doses delivered at 2 Gy per fraction. The parameters are the same as in Figure 3-3.

Cox & Ang book 2010



Protons



Frank et al, IJROBP 2014

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Appropriate methodology for validation

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Should we perform non-inferiority studies of empirically developed volumes?

Should we investigate the supposed clinical benefit (on OAR) while controlling for tumor outcome?

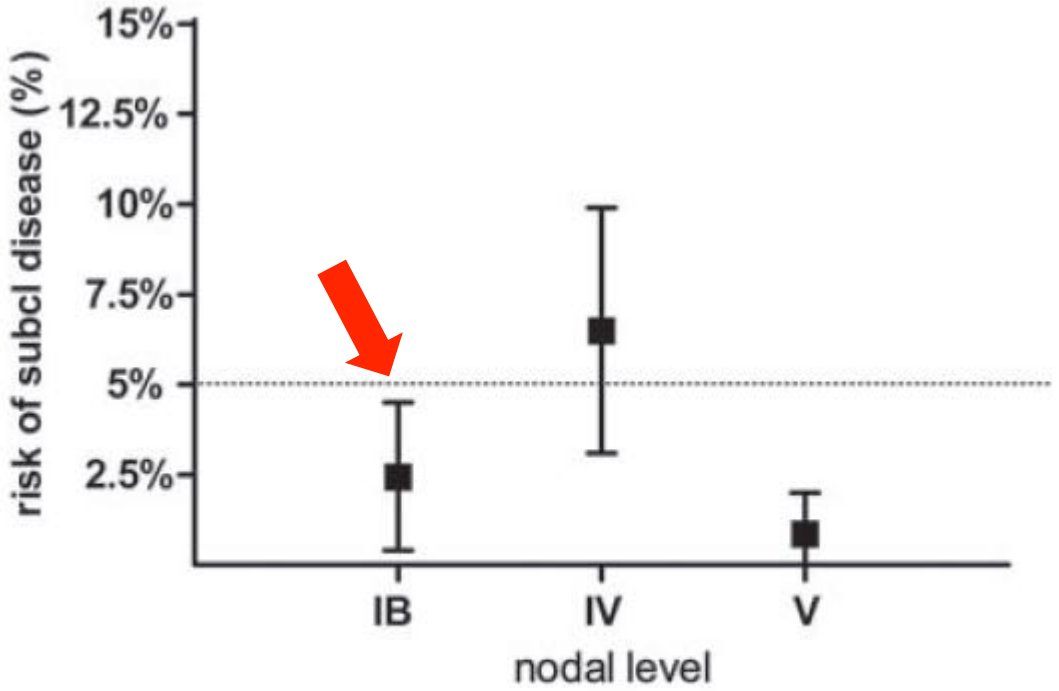

Figure 1. Estimated risk (mean and 95% CI) of subclinical involvement of levels IB, IV and V.

TREATMENT OF STAGE I NASOPHARYNGEAL CARCINOMA: ANALYSIS OF THE PATTERNS OF RELAPSE AND THE RESULTS OF WITHHOLDING ELECTIVE NECK IRRADIATION

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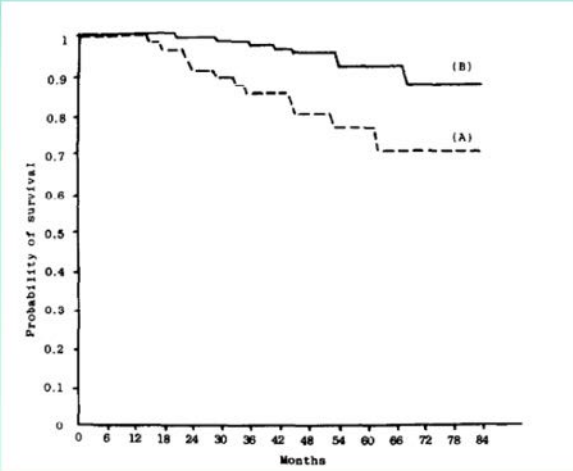
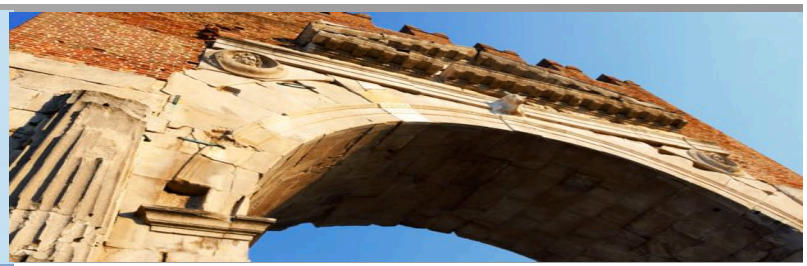
- outcome of 196 pts w stage I NPC not electively in the neck;
- 53 pts (27%) subsequently failed in the neck, mostly upper neck
- nodal salvage rate was 81%
- however, OS was lower for pts who failed compared to pts who did not fail in the neck due to a higher incidence of DM (20% vs 3%)



IJROBP, 1989



Conclusions

- Indications and contouring guidelines are now available in the literature;
- Challenging indications and volumes developed empirically over decades is reasonable, but should be clinically driven
- For OPC, it is reasonable to consider avoiding the uppermost part of the contralateral uninvolved level II, as well as contralat levels IB (and V)
- For NPC, nodal volume de-escalation should be cautiously done