La relazione dose - volume: il documento QUANTEC

La relazione dose - volume: OLTRE QUANTEC

Rancati Tiziana

Programma Prostata, Fondazione IRCCS-Istituto Nazionale dei Tumori

Dose-volume relationship: the beginning

Int J Radiat Oncol Biol Phys. 1991 May 15;21(1):109-22.

TOLERANCE OF NORMAL TISSUE TO THERAPEUTIC IRRADIATION

B. Emami, M.D.,[1] J. Lyman, Ph.D.,[5] A. Brown, M.D.,[4] L. Coia, M.D.,[3] M. Goitein, Ph.D.,[4]
J. E. Munzenrider, M.D.,[4] B. Shank, M.D.,[2] L. J. Solin, M.D.[3] and M. Wesson, M.D.[2]

- Unfortunately, current knowledge on tolerance of normal tissue organs to irradiation is less than adequate.
- With the increasing use of 3-D treatment planning and dose delivery, this issue, particularly volumetric information, will become even more critical.
- In this manuscript we present the updated information on tolerance of normal tissues, based on available data, with a special emphasis on partial volume effects.
- Due to a lack of precise and comprehensive data base, opinions and experience of the clinicians from four universities involved in the contract have also been contributory.

Emami et al., 1991: 9 authors - 7 MDs, 2 PhDs, 28 organs

Organ	TD 5/5 Volume			TD 50/5 Volume			Selected endpoint
	1/3	2/3	3/3	1/3	2/3	3/3	
Kidney I	5000	3000*	2300	—	4000*	2800	Clinical nephritis
Kidney II							
Bladder	N/A	8000	6500	N/A	8500	8000	Symptomatic bladder contracture and volume loss
Bone:							
Femoral Head I and II	—	—	5200	—	—	6500	Necrosis
T-M joint mandible	6500	6000	6000	7700	7200	7200	Marked limitation of joint function
Rib cage	5000	—	—	6500	—	—	Pathologic fracture
Skin	10 cm² / —	30 cm² / —	100 cm² / 5000	10 cm² / —	30 cm² / —	100 cm² / 6500	Telangiectasia
	7000	6000	5500	—	—	7000	Necrosis Ulceration
Brain	6000	5000	4500	7500	6500	6000	Necrosis Infarction
Brain stem	6000	5300	5000	—	—	6500	Necrosis Infarction
Optic nerve I & II	No partial volume		5000	—	—	6500	Blindness
Chiasma	No partial volume		5000	No partial volume		6500	Blindness

Int J Radiat Oncol Biol Phys. 1991 May 15;21(1):123-35.

FITTING OF NORMAL TISSUE TOLERANCE DATA TO AN ANALYTIC FUNCTION

C. BURMAN, PH.D.,[1] G. J. KUTCHER, PH.D.,[1] B. EMAMI, M.D.[2] AND M. GOITEIN, PH.D.[3]

Table 1. Normal tissue end points and tolerance parameters

	Fit parameters				
Organ	V_{ref}	n	m	TD_{50}	End point
Bladder	Whole organ	0.5	0.11	80	Symptomatic bladder contracture and volume loss
Brachial plexus	Whole organ	0.03	0.12	75	Clinically apparent nerve damage
Brain	Whole organ	0.25	0.15	60	Necrosis/infarction
Brain stem	Whole organ	0.16	0.14	65	Necrosis/infarction
Cauda equina	Whole organ	0.03	0.12	75	Clinically apparent nerve damage
Colon	Whole organ	0.17	0.11	55	Obstruction/perforation/ulceration/fistula
Ear (middle/ external	Whole organ	0.01	0.15	40	Acute serous otitis
Ear (middle/ external	Whole organ	0.01	0.095	65	Chronic serous otitis
Esophagus	Whole organ	0.06	0.11	68	Clinical stricture/perforation

QUANTEC: the idea

In 2006 both AAPM and ASTRO recognized:

- Need for a systematic overhaul of our understanding of normal tissue tolerances
- For use in clinical treatment planning and optimization

QUANTEC

QUantitative Analysis of Normal Tissue Effects in the Clinic

QUANTEC: history

- 2006 Steering Committee:
  Deasy, Bentzen, Yorke, Ten-Haken, Constine (3 MDs, 5 PhDs)
- 2007 1st QUANTEC meeting in Madison
  Initial review of tolerances involving pl physicians (≈60 participants from North A
- 2007-2009 Preparation of Papers:
  Reviews and meta analysis of li complications in 16 organs (~58 authors)
- March 2010 Publication:
  Special Issue of Red Journal (IJROBP articles on future directions

QUANTEC: main goals

(1) To provide a *critical overview of the current state of knowledge* on quantitative dose–response and dose–volume relationships for clinically relevant normal-tissue endpoints

(2) To produce *practical guidance* allowing the clinician to reasonably (though not necessarily precisely) categorize toxicity risk based on dose–volume parameters or model results

(3) To identify *future research avenues* that would help improve risk estimation or mitigation of early and late side effects of radiation therapy

QUANTEC vs Emami

- METHOD:

  experts' opinion vs review of published studies

- CONSIDERED ORGANS :

  excluded: eye lens/eye/retina, TM joint /mandible, thyroid, skin, rib cage, cauda equina, brachial plexus, femoral head, colon

  new: penile bulb

- CONSIDERED ENDPOINTS:

  severe endpoints vs mild/moderate endpoints

- OUTPUT TABLES:

  very high consistency vs flexibility

- NTCP MODELS:

  comprehensive set of parameters vs limited energy in encouraging use of models

Organ-Specific Papers

1. **Brain**
2. **Optic Nerve/Chiasm**
3. **Brain Stem**
4. **Spinal Cord**
5. **Ear**
6. **Parotid**
7. **Larynx/Pharynx**
8. **Lung**
9. **Heart**
10. **Esophagus**
11. **Liver**
12. **Stomach/Small Bowel**
13. **Kidney**
14. **Bladder**
15. **Rectum**
16. **Penile Bulb**

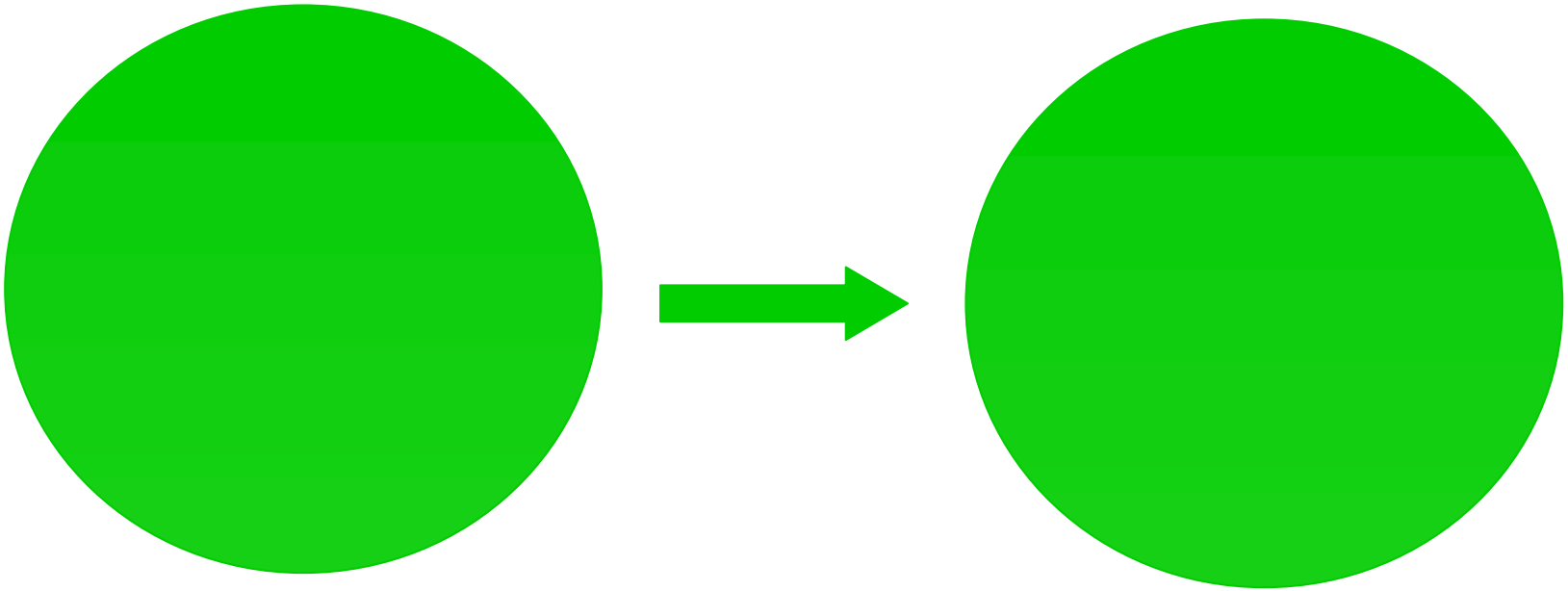
Vision Papers

True Dose
Imaging
Biomarkers
Data Sharing
Lessons of QUANTEC

Each with 10 sections

1. **Clinical Significance**- Describes the clinical situations where the organ is irradiated, and the incidence/significance of organ injury.
2. **Endpoints**- Describes the different endpoints often considered when assessing injury, the impact of endpoint-selection on the reported injury rates, the challenges/utilities of different endpoints, and the time course of organ injury.
3. **Challenges Defining Volumes**- Describes how the organ is typically defined (or segmented) on treatment planning images. Includes a discussion of uncertainties/challenges in organ definition (e.g. changes in organ volume/shape during therapy), and the associated impact on DVH's and dose/volume/outcome analyses.
4. **Review of Dose/Volume Data**- A comprehensive summary of reported 3D dose/volume data for clinically-relevant outcomes.
5. **Factors Affecting Risk**- Other clinical factors affecting the risk of injury are noted (e.g. age, combined modality therapy, dose fractionation).
6. **Mathematical/Biological Models**- Models that have been used to relate 3D dose/volume data to clinical outcomes are summarized, along with associated model parameters, limitations and uncertainties.
7. **Special Situations**- Most of the data discussed relates to conventional fractionation. This section describes situations were the presented data/models may not apply (e.g. hypo-fractionation).
8. **Recommended Dose/Volume Limits**- The available information is condensed into meaningful dose/volume limits, with associated risk rates, to apply clinically.
9. **Future Toxicity Studies**- Describes areas in need of future study.
10. **Toxicity Scoring**- Recommendations on how to score organ injury.

Why is it difficult to develop models for radio-induced toxicity?



Why is it difficult to develop models for radio-induced toxicity?

1. Very large and **high quality databases** are mandatory:

   - ✓ to evaluate a low-incidence event
     (3-10% rectal bleeding, 2-5% rectal incontinence)

   - ✓ to discriminate the role of radiation dose
     (which is a strong, probably the strongest predictor)

   - ✓ to validate models and potentially allow their predictive use in the clinic

2. **Prospective evaluation** of toxicity is highly desirable to reduce biases in the analysis of morbidities

3. To avoid biases in the subjective evaluation of toxicity, **objective measurements** (patient-assessed questionnaires, instrumental measurements) should be used

4. Different components of toxicity are present: **acute reactions** (early warning that the patient is unusually sensitive to radiation?), which are usually transient, and **late reactions**, which usually occur in deep visceral organs, are seldom transient and may progress to more severe tissue dysfunction

5. Need to obtain a **"baseline" score** before treatment, because the organ function may already show mild to moderate deviations from normality

6. Need to follow up on patients for a **long time** with the risks of:

   - ✓ Having a *drift in toxicity recording* within a study in the long period from its start to its end

   - ✓ Increasing the *confounding effect of aging* and advent of comorbidities which are not RT related

7. Need to have **different models for different endpoints**

8. Need to **reduce a continuous scale of symptoms** to a graded/dichotomized endpoint for modelling purposes

9. Need to choose which **aspect of toxicity is relevant to the patient's Quality of Life** (severe peak toxicity? persistent mild toxicity? toxicity involving social impairment?)

Table 1. QUANTEC Summary: Approximate Dose/Volume/Outcome Data for Several Organs Following Conventional Fractionation (Unless Otherwise Noted)* (*Continued*)

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)†	Endpoint	Dose (Gy), or dose/volume parameters†	Rate (%)	Notes on dose/volume parameters
	Bilateral whole parotid glands	3D-CRT	Long term parotid salivary function reduced to <25% of pre-RT level	Mean dose <39	<50	For combined parotid glands (per Fig. 3 in paper) ¶
Pharynx	Pharyngeal constrictors	Whole organ	Symptomatic dysphagia and aspiration	Mean dose <50	<20	Based on Section B4 in paper
Larynx	Whole organ	3D-CRT	Vocal dysfunction	Dmax <66	<20	With chemotherapy, based on single study (see Section A4.2 in paper)
	Whole organ	3D-CRT	Aspiration	Mean dose <50	<30	With chemotherapy, based on single study (see Fig. 1 in paper)
	Whole organ	3D-CRT	Edema	Mean dose <44	<20	Without chemotherapy, based on single study in patients without larynx cancer**
	Whole organ	3D-CRT	Edema	V50 <27%	<20	
Lung	Whole organ	3D-CRT	Symptomatic pneumonitis	V20 ≤ 30%	<20	For combined lung. Gradual dose response
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 7	5	Excludes purposeful whole lung irradiation
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 13	10	
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 20	20	
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 24	30	
	Whole organ	3D-CRT	Symptomatic pneumonitis	Mean dose = 27	40	
Esophagus	Whole organ	3D-CRT	Grade ≥3 acute esophagitis	Mean dose <34	5–20	Based on RTOG and several studies
	Whole organ	3D-CRT	Grade ≥2 acute esophagitis	V35 <50%	<30	A variety of alternate threshold doses have been implicated. Appears to be a dose/volume response
	Whole organ	3D-CRT	Grade ≥2 acute esophagitis	V50 <40%	<30	
	Whole organ	3D-CRT	Grade ≥2 acute esophagitis	V70 <20%	<30	

Table 1. QUANTEC Summary: Approximate Dose/Volume/Outcome Data for Several Organs Following Conventional Fractionation (Unless Otherwise Noted)* (*Continued*)

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)†	Endpoint	Dose (Gy), or dose/volume parameters†	Rate (%)	Notes on dose/volume parameters
Rectum	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity, Grade ≥ 3 late rectal toxicity	V50 <50%	<15 <10	Prostate cancer treatment
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity, Grade ≥ 3 late rectal toxicity	V60 <35%	<15 <10	
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity, Grade ≥ 3 late rectal toxicity	V65 <25%	<15 <10	
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity, Grade ≥ 3 late rectal toxicity	V70 <20%	<15 <10	
	Whole organ	3D-CRT	Grade ≥ 2 late rectal toxicity, Grade ≥ 3 late rectal toxicity	V75 <15%	<15 <10	
Bladder	Whole organ	3D-CRT	Grade ≥ 3 late RTOG	Dmax <65	<6	Bladder cancer treatment. Variations in bladder size/shape/location during RT hamper ability to generate accurate data
	Whole organ	3D-CRT	Grade ≥3 late RTOG	V65 ≤50 % V70 ≤35 % V75 ≤25 % V80 ≤15 %		Prostate cancer treatment Based on current RTOG 0415 recommendation
Penile bulb	Whole organ	3D-CRT	Severe erectile dysfunction	Mean dose to 95% of gland <50	<35	
	Whole organ	3D-CRT	Severe erectile dysfunction	D90‖ <50	<35	
	Whole organ	3D-CRT	Severe erectile dysfunction	D60-70 <70	<55	

QUANTEC recommendations, H&N region

	dose recomm	EQD2/BED/NTCP recommendations	Prob.curve
Brain	-	Predictors for 5 and 10% are given in BED and EQD2. a/b=3Gy	Incidence as func of BED
Optic nerve/ Chiasm	Yes	-	-
Brainstem	Yes	Total dose vs fraction dose curves for EQD2 using a/b=3.3, 2.5, 2.1Gy	-
Spinal cord	Yes	EQD2 a/b=3Gy	Probability as funct of EQD2
Cochlea	Yes	-	-
Salivary gland	Yes	-	tox severity vs mean dose TD50(func loss) vs f-up mos)
Larynx/Pharynx	Yes	-	Probability as func of mean dose

QUANTEC recommendations, thorax region

	Absorbed dose recommendations	EQD2/BED/NTCP recommendations	Prob.curve
Lung	Yes	-	Probability as function of mean dose and Vx
Heart	Yes	NTCP a/b=3Gy	NTCP a/b=3Gy
Esophagus	Yes	-	Tox rate as function of V20-70Gy
Liver	Yes	EQD2 a/b=2Gy	NTCP a/b=2Gy
Stomach / Small bowel	Yes	-	-
Kidney	Yes	-	Incidence as function of Equivalent total dose

QUANTEC recommendations, pelvic region

	Absorbed dose recommendations	EQD2/BED/NTCP recommendations	Prob.curve
Bladder	Yes	-	Incidence as function of mean dose and EQD2 a/b=6Gy
Rectum	Yes		NTCP curve
Penile bulb	Yes	-	Incidence as function of median/mean dose /D60-70

QUANTEC IS:

- Updating our clinical understanding of normal tissue tolerances
- Providing clinical guidelines where possible, with appropriate caveats
- Defining areas of our ignorance
- Recommend studies to remedy this
- Investigating future directions:
    - Reporting standards
    - Clinically relevant but specific endpoint definitions
    - Inter-institutional data synthesis (atlases or pooling)

BEYOND QUANTEC:

- Development of NTCP models with inclusion of clinical risk factors
- Longitudinal definitions of toxicity endpoints
- Use of imaging to define and score toxicity endpoints

NTCP models with inclusion of clinical risk factors

Lyman model + DVHs reduced to EUD + clinical risk factor

4 parameter model

n,m derived from the whole set

$D_{50,\text{clinical factor}}$ and $D_{50,\text{no clinical factor}}$ derived in separate datasets

$D_{50,\text{clinical factor}} / D_{50,\text{no clinical factor}}$ = dose modifying factor

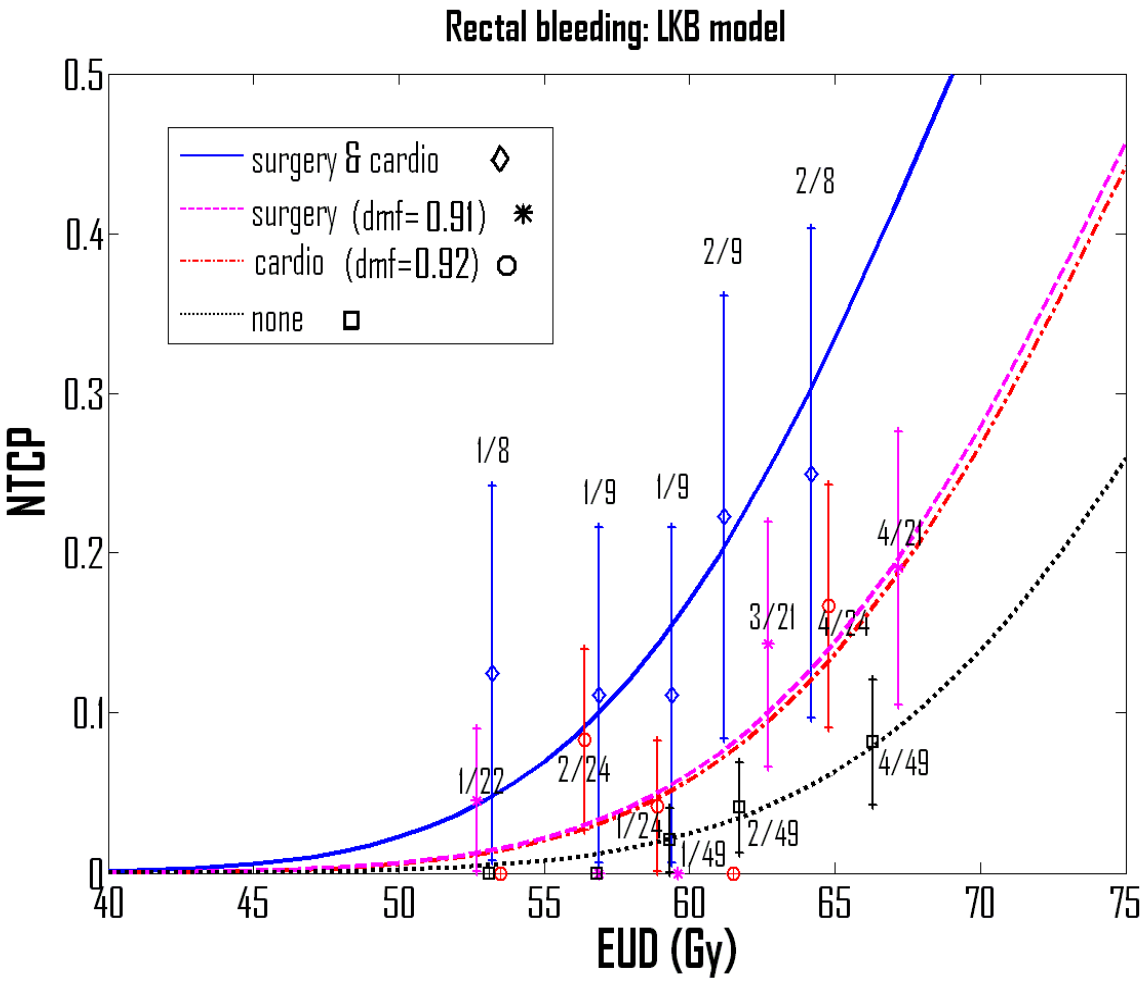
CLINICAL INVESTIGATION

RECTAL BLEEDING, FECAL INCONTINENCE, AND HIGH STOOL FREQUENCY AFTER CONFORMAL RADIOTHERAPY FOR PROSTATE CANCER: NORMAL TISSUE COMPLICATION PROBABILITY MODELING

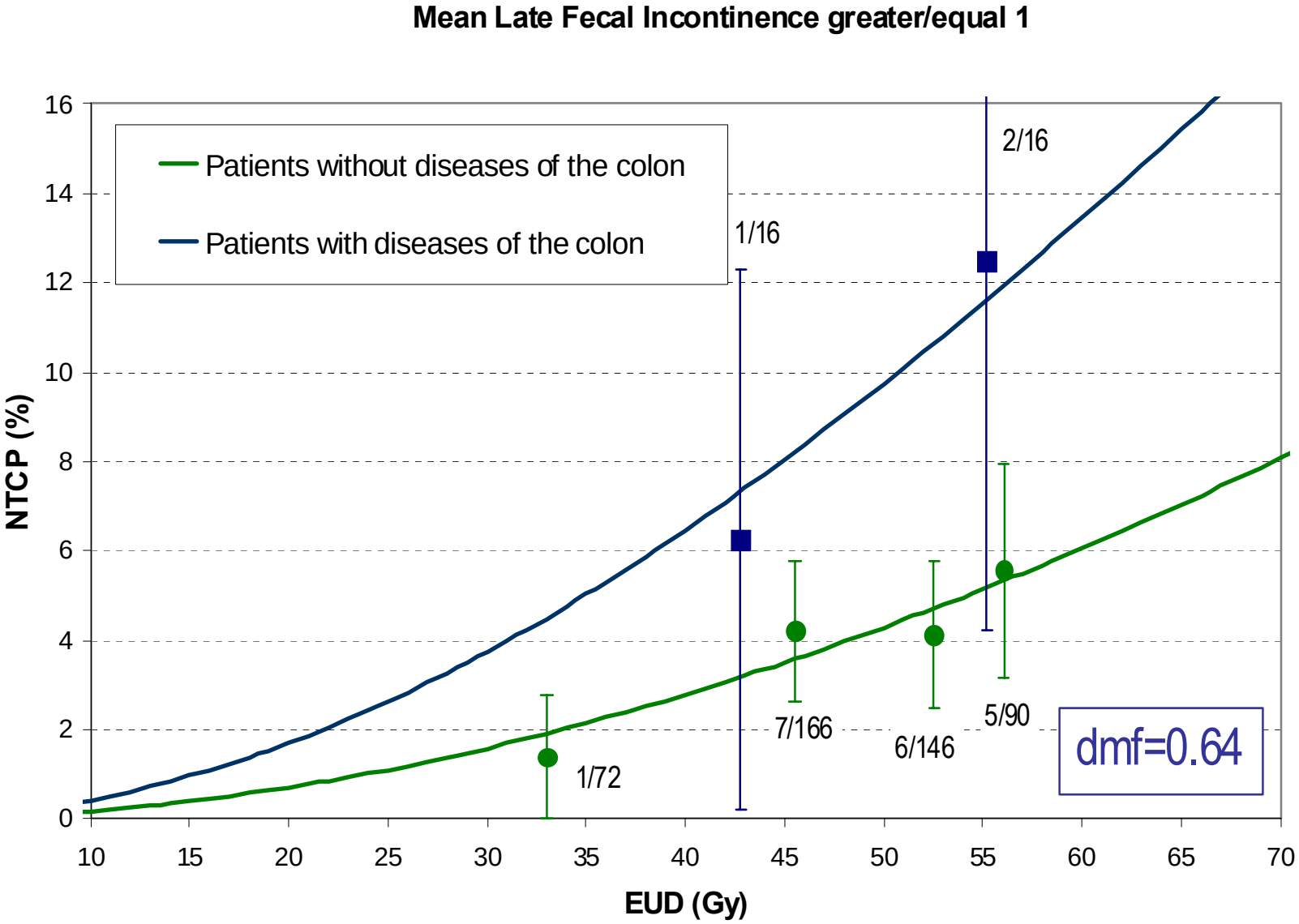
STEPHANIE T. H. PEETERS, M.D.,* MISCHA S. HOOGEMAN, PH.D.,† WILMA D. HEEMSBERGEN, M.SC.,* AUGUSTINUS A. M. HART, M.SC.,* PETER C. M. KOPER, M.D., PH.D.,‡ AND JOOS V. LEBESQUE, M.D., PH.D.*

IJROBP 2006

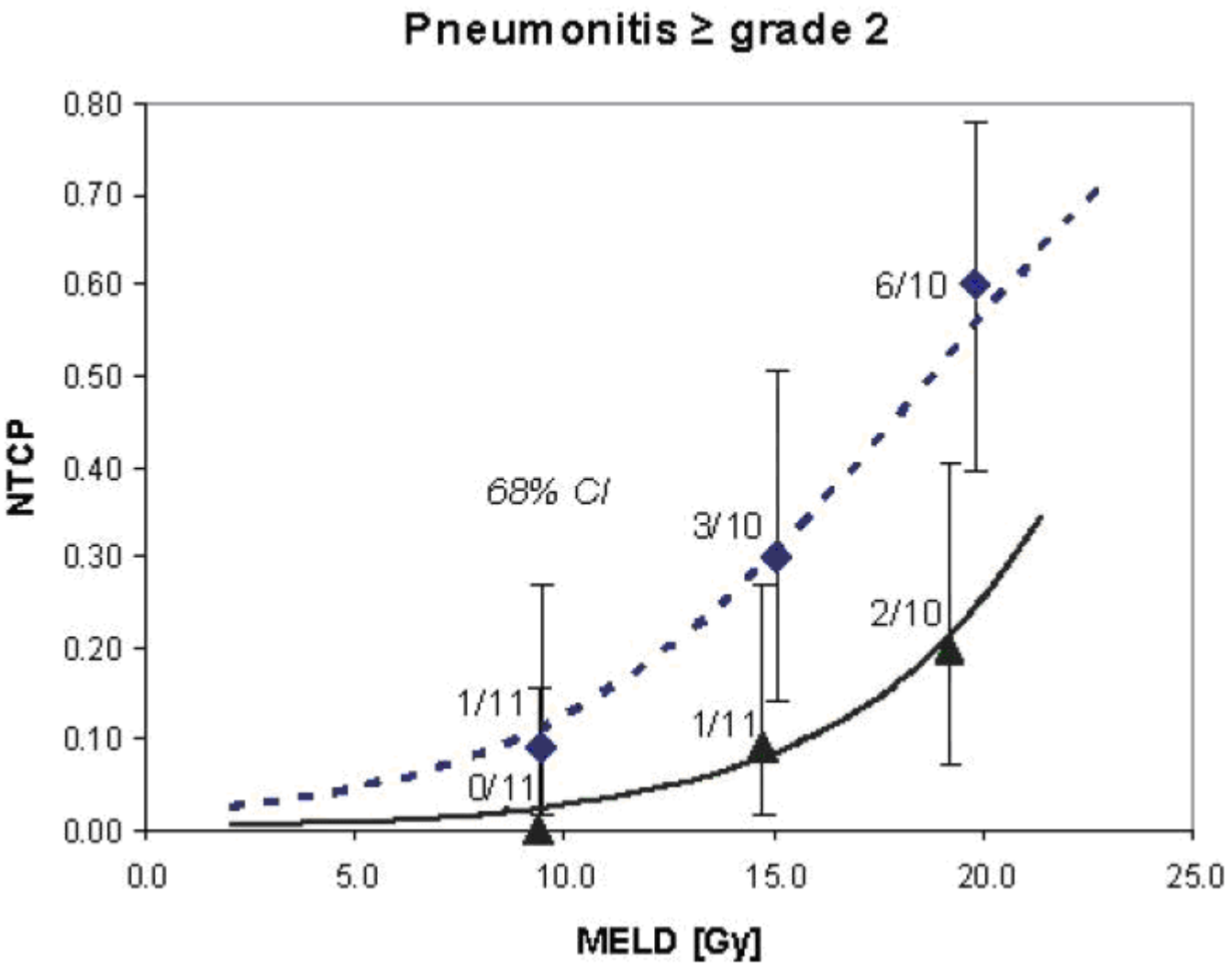
Rectal bleeding (anorectal wall)	79.0 (74.0; 86.5)	0.15 (0.12; 0.20)	0.18 (0.09; 0.33)



updated results of the Dutch prostate dose escalation trial
(courtesy of G. Defraene and J. Lebesque, accepted IJROBP)

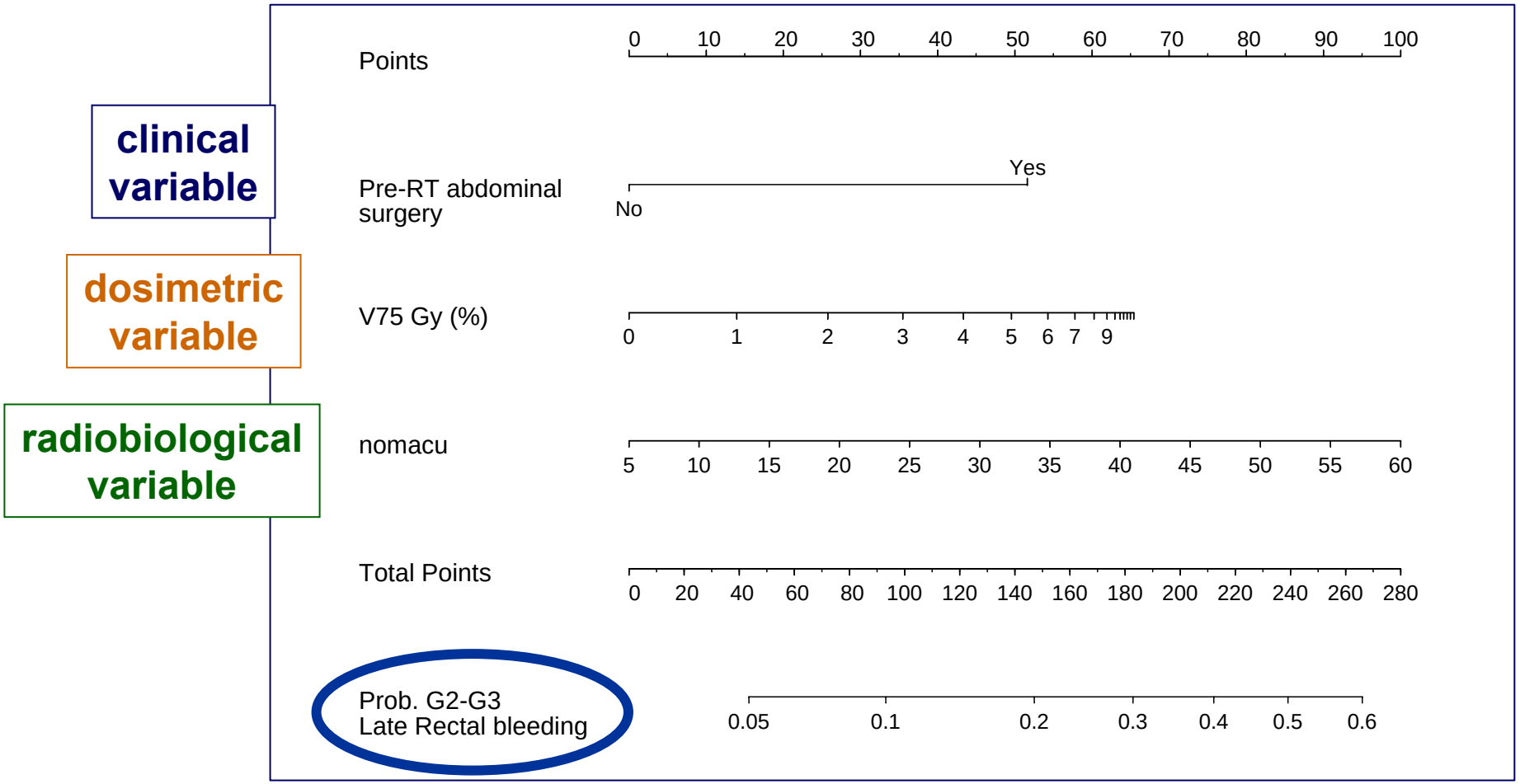


results from the AIROPROS 0102 prospectice multicenter trial (Rancati et al, RO submitted)

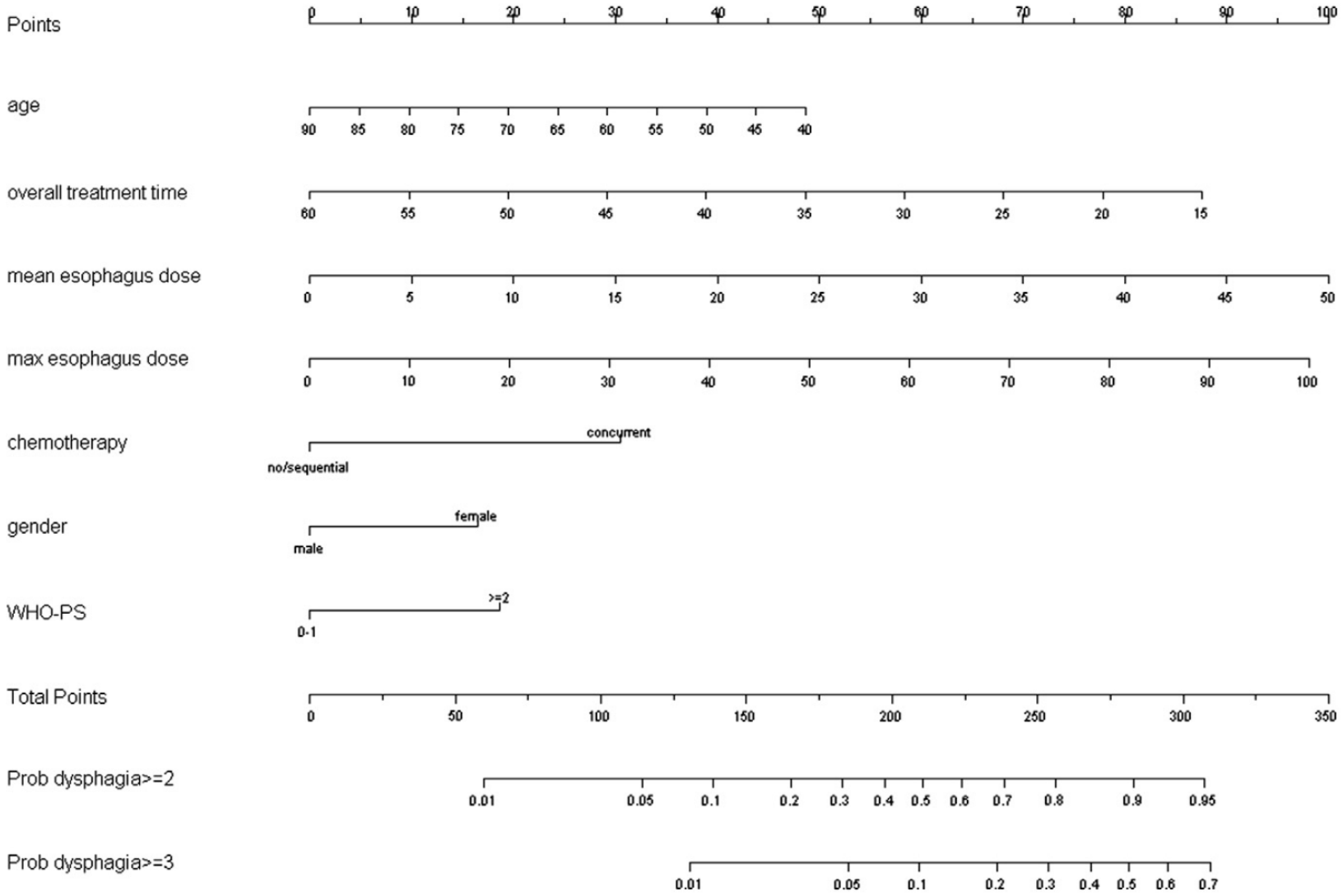


Applet, presented at ESTRO 2011

Development of nomograms



R. Valdagni et al, accepted IJROBP 2011



Dehing-Oberije et al, RO 2010

Longitudinal definitions of toxicity endpoints

Which toxicity is relevant to the patient's Quality of Life (severe peak toxicity? persistent mild toxicity? toxicity involving social impairment?)

AIROPROS 0102 trial: analysis of different definitions of late fecal incontinence

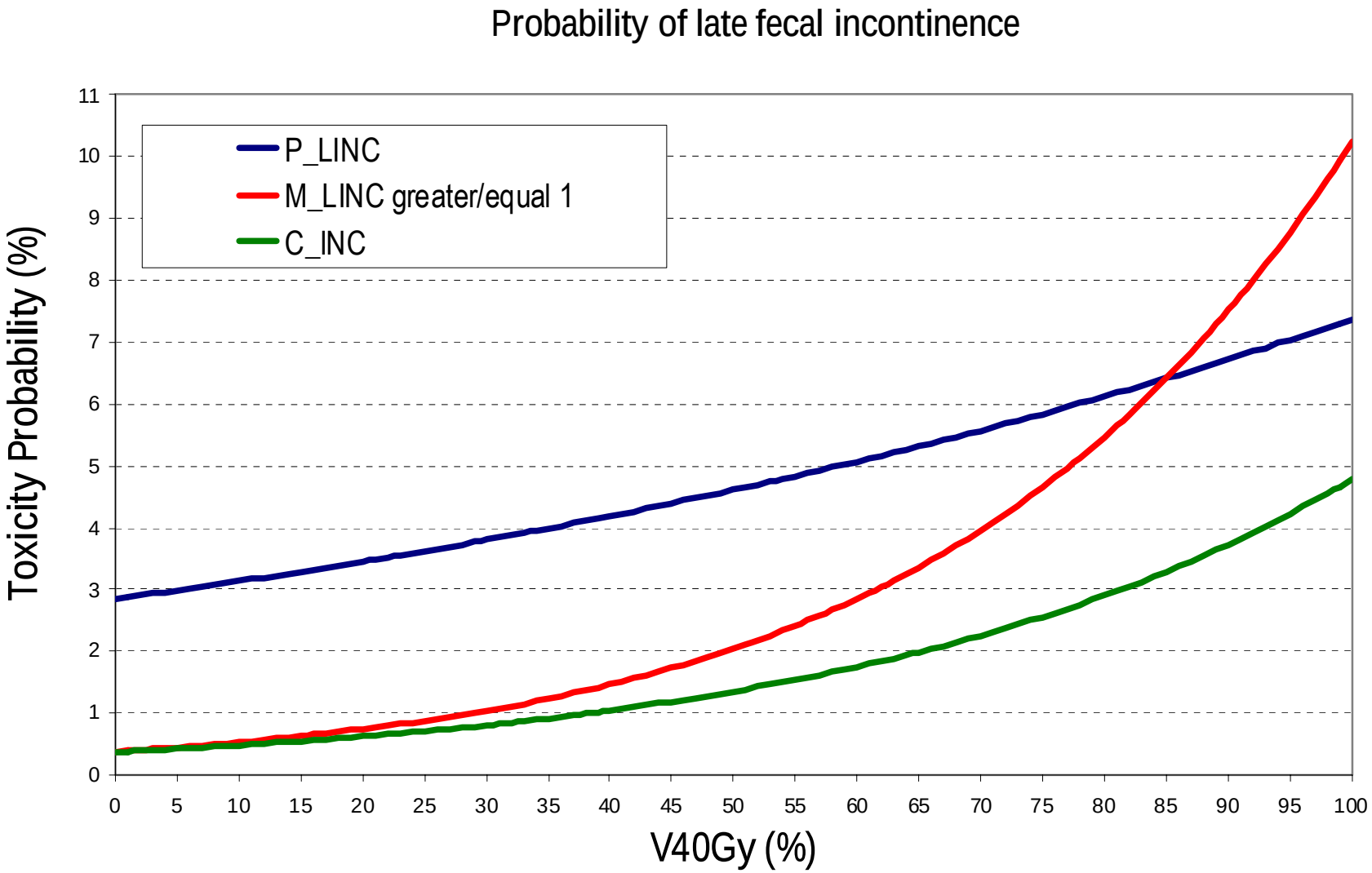
Obviously different toxicity rates were obtained:

37/550 (6.7%) Sever Peak_INC

22/550 (4.0%) Mean_INC ≥1

17/550 (3.1%) Severe Chronic_INC

A different dose-volume relationship was also obtained:



Logistic MVA results

Variable	P	OR
C_INC (V40Gy continuous)		
Previous diseases of the colon	0.009	7.1
Use of anti-hypertensives	0.009	0.15
V40Gy (continuous)	0.12	1.027
Previous abdominal surgery	0.037	4.7
Haemorrhoids	0.2	2.2
?G3 acute Incontinence	0.014	10.2
M_INC?1 (V40Gy continuous)		
Previous diseases of the colon	0.041	4.2
Use of anti-hypertensives	0.022	0.28
V40Gy (continuous)	0.021	1.035
Previous abdominal surgery	0.17	2.5
P_INC (V40Gy continuous)		
?G2 acute Incontinence	0.0008	6
V40Gy (continuous)	0.29	1.01

Use of imaging to define and score toxicity endpoints: the rationale

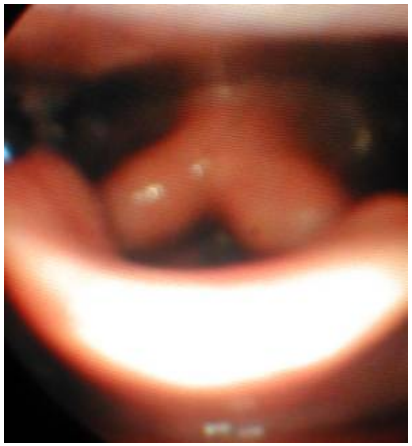
- Local damage of radiotherapy may induce changes of imaging parameters…that can be visualized/measured
- Early reactions may evolve in late modifications (local, regional, whole-organ) …that can be visualized/measured
- Early assessment of local changes/abnormalities may predict late/chronic effects (possibility to adapt the treatment to avoid them, potential for fast assessment of supportive therapies and/or changes of therapeutic options……)
- Finding pre-treatment dosimetric/clinical predictors of early imaging changes

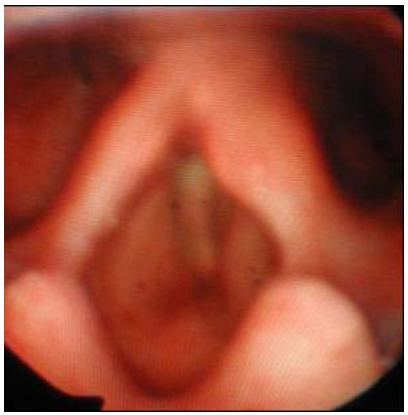
Image-based quantitative score of toxicity

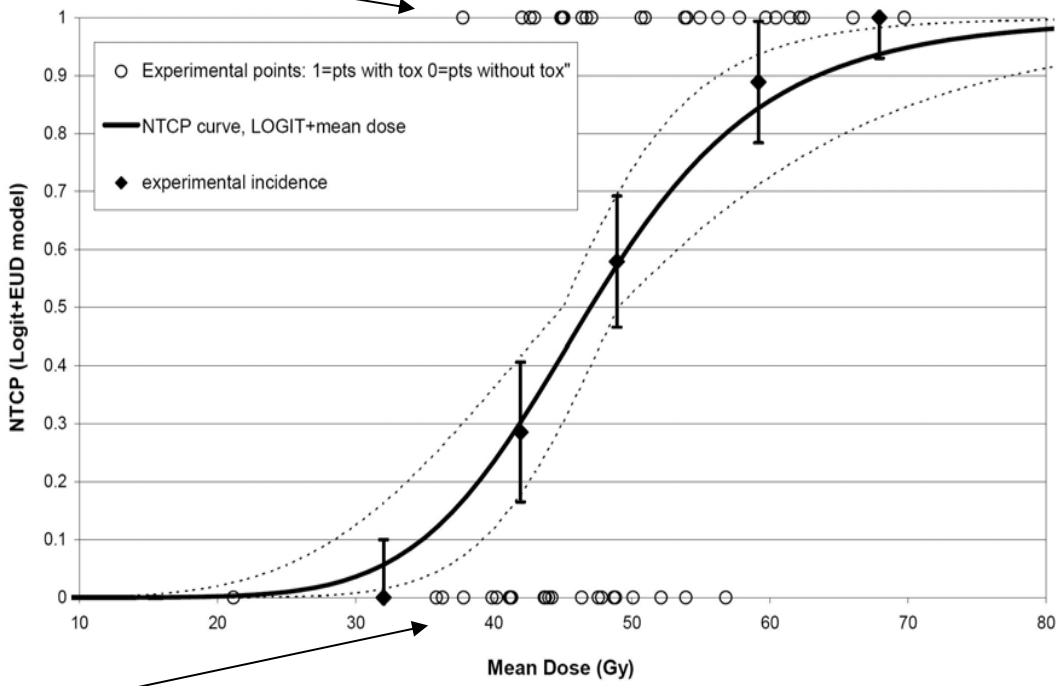
- Changes may be assessed based on “subjective” scores (imaging appearance)….defined by well assessed criteria
- Changes may be quantitatively measured directly or after image processing (density, volume, different MRI Intensity signal, FDG-PET SUV, perfusion/diffusion coefficients, MRI spectroscopy….)

Image-based assessment of toxicity: an example of “subjective” assessment

Videofluoroscopy assessment of larynx edema



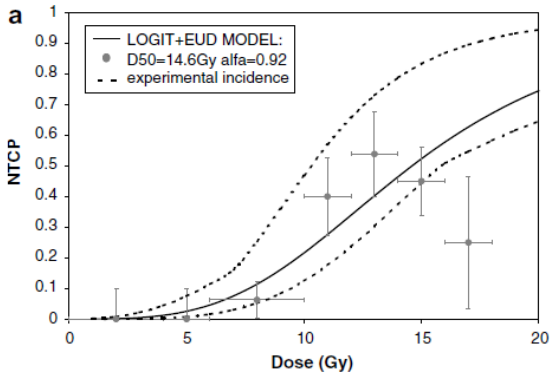




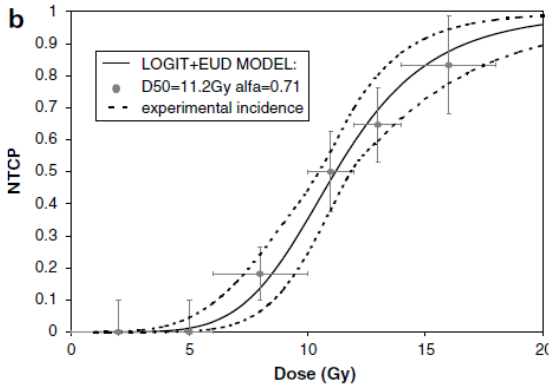
Rancati et al. IJROBP 2010

Objective Image-based assessment of toxicity: few relevant examples

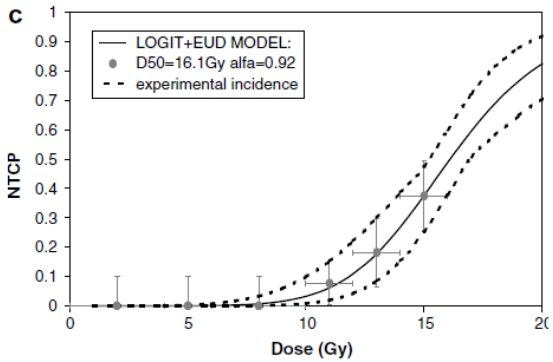
Anatomical imaging: density variation in lungs after RT for breast cancer and grade 1-2 pneumonitis



Clinical assessment



Density changes assessment (X-Rays)

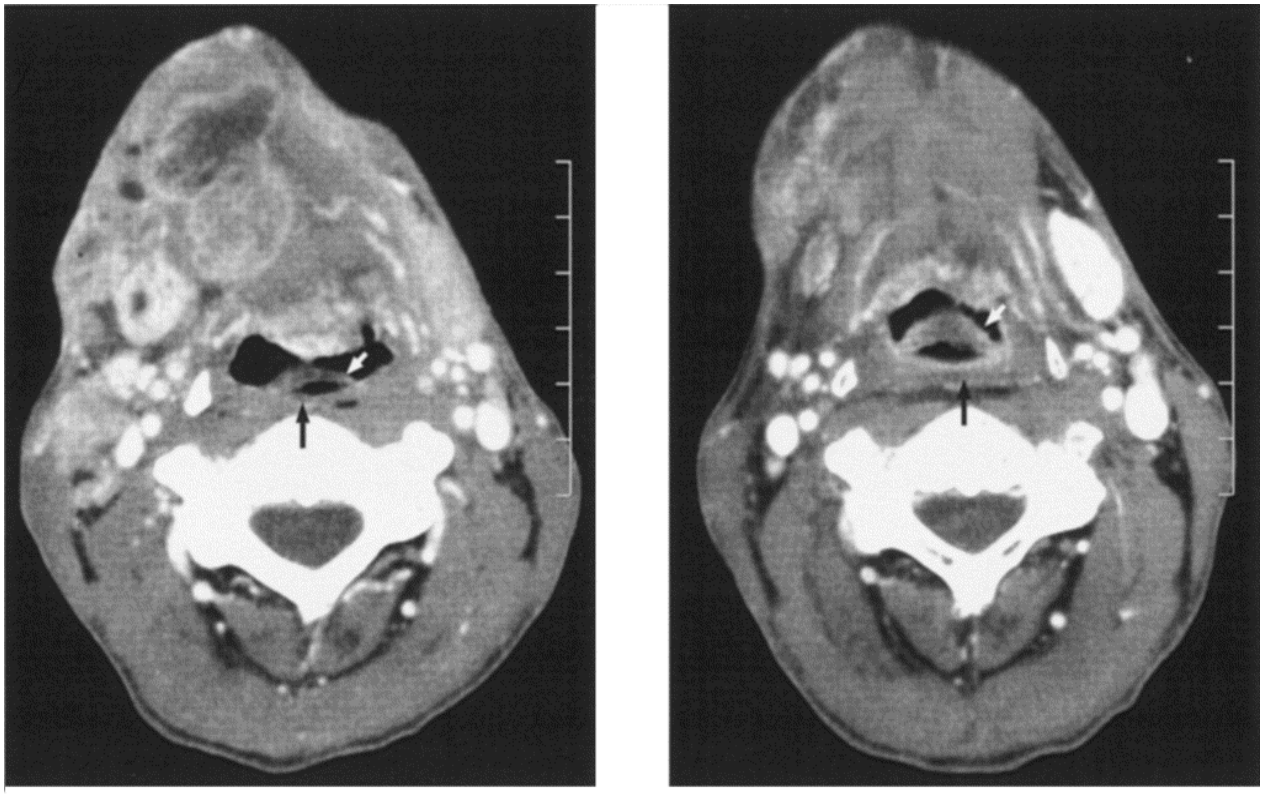


Density changes assessment (CT)

Rancati et al. R&O 2007

Objective Image-based assessment of toxicity: few relevant examples

Anatomical imaging: CT-based damage to constrictors, volume variations



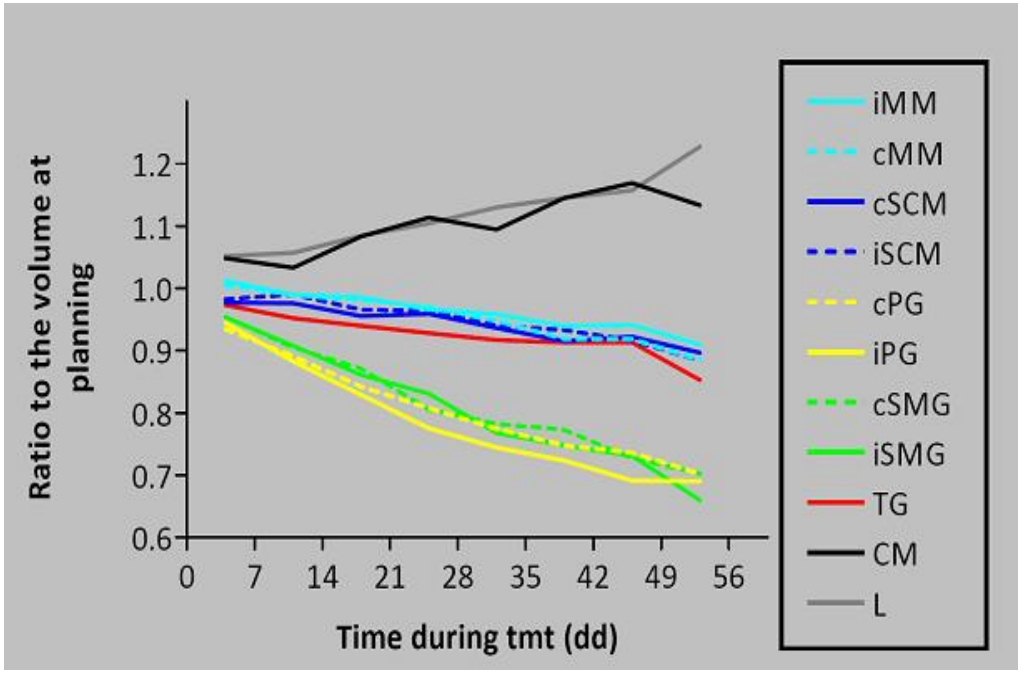
Eisbruch et al. IJROBP 2003

IGRT: Opportunities for imaging-based scoring

- Widely available IGRT in RT centers means a large amount of available (mainly CT) imaging information describing how anatomical changes occur during RT….for the first time in the history of RT (!)
- Despite the limits of actually available in-room imaging, a lot of “biological” information is inside these images
- Quantitative assessment of organ deformation can be used as a potentially powerful tool for scoring and predicting toxicity

Volume changes during RT imaged by IGRT to assess (tumor and) normal tissue effects

Volume variation of parotids and other organs during IMRT for HN cancer



PG: parotid glands
SMG: submandibular glands
TG: thyroid gland
CM: constrictor muscles
SCM:sternocleidomastoid muscles
MM: masticatory muscles
L: larynx
i=ipsi, c=contro

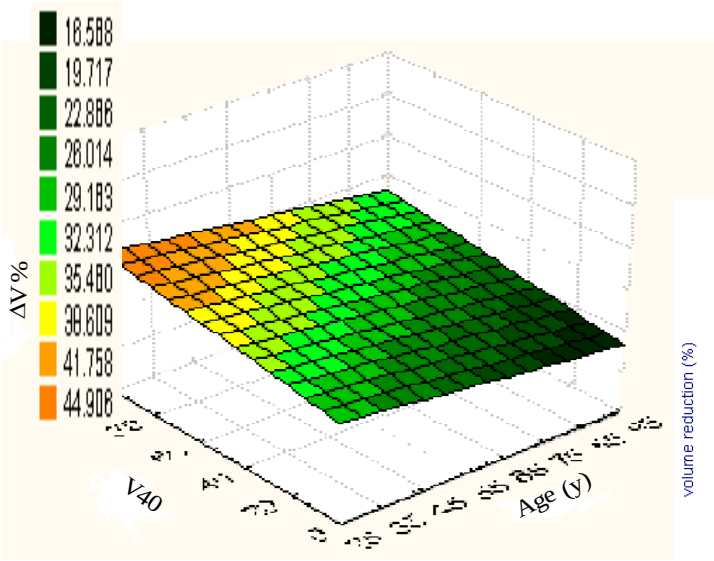
Ricchetti et al. IJROBP 2011

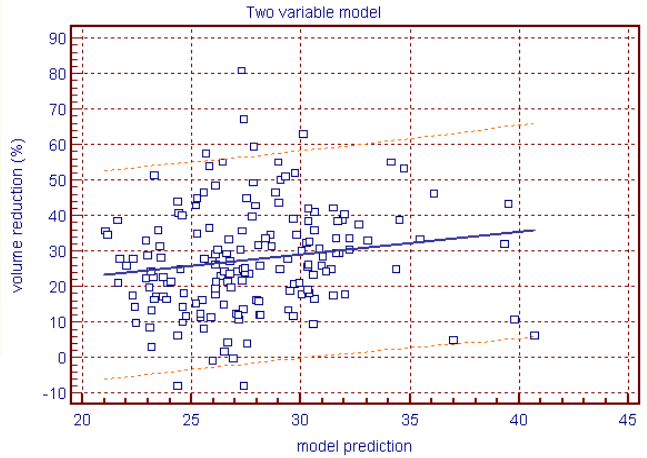
Predictors of parotid shrinkage during RT

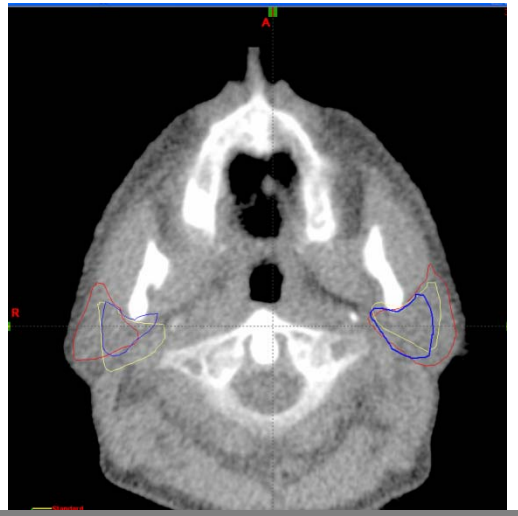
- % Parotid volume reduction depends on V40/Dmean, Age (and weight loss during RT)
- Data from 4 institute (87 patients)

Bi-linear model of parotid shrinkage

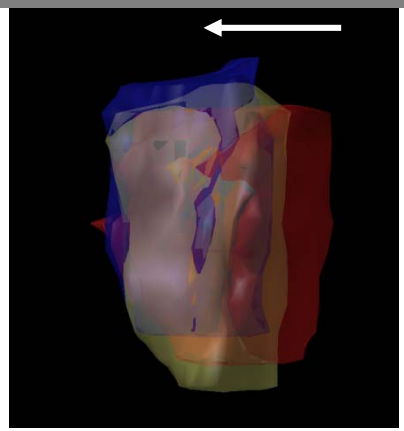
$\Delta V(\%) = 34.34 + 0.192\ V40 - 0.2203\ Age$







Red: day 1; Yellow: day 15; Blue: day 30



Broggi et al. R&O 2010

Quantifying deformation during (and after) RT as a measure (or a predictor) of toxicity

- Shrinkage of organs (i.e: parotids), reduction of muscle mass
- Edema effects
- Changes in ventilatory capacity (i.e.:lungs)
- Changes of elastic properties (i.e.: bladder, rectum)
- Changes in mobility, (i.e: rectum)
- Fibrosis

What next ?....

Early assessment of anomalous organ deformation

as a tool to correct/adapt the treatment to reduce toxicities !!

If the risk detected by Imaging during the early phase of RT is > X%:

- Adaptation of the treatment through replanning (if possible)
- Changing therapeutic approach
- Supportive cares
- Intensified follow-up schedule

Challenges and research direction

- Imaging findings are now much more available than in the past
- This may constitute an integration of clinical assessment of toxicity, not a substitute (!)
- There is a need of dose-volume effect models including image-based quantitative scores
- Some studies are showing the intriguing potentials of early imaging-assessed modifications in Adaptive RT and, more in general, in treatment personalization
- The challenge is to cope with complexity and specificity vs the need to keep synthetic scores, recognizing priorities and use common language

$\Rightarrow$ keping the patient as the central focus !!!

Radiobiology: the appliance of science (A. Nahum, expert opinion, 2007)

“.. With the relentless onward march of technology, we now have many "degrees of freedom" at our disposal when it comes to carrying out EBRT.

But how are radiation oncologists to choose between the alternatives? And having made this choice, how do they decide what dose to prescribe to the tumour?

The answer to both of these questions lies in enlisting the aid of radiobiology - the study of the effects of ionizing radiation on living matter.

At times, I feel that we as a profession are too much in love with technology, forever waiting for our next high-tech fix, rather than making the maximum use of the incredible tools we already have.”

But isn't it all too difficult to express the aim of radiotherapy in mathematical terms?

The aim of any radiotherapy treatment administered with curative intent can be stated thus:
"Maximize local tumour control for an agreed (acceptable) complication risk."

For today's sophisticated, 3D radiotherapy treatment-planning systems this is eminently achievable, provided the functions for tumour control probability (TCP) and normal-tissue complication probability (NTCP) are embedded in the treatment-planning software.

How will we make rational use of the new information in PET/MRI of the tumor, presence of hypoxia, molecular biology, individual radiosensitivity, genetic predisposition of the patient to higher complication risk, poor vasculature and so on?

Only by using a TCP model containing explicit parameters such as radiosensitivity coefficients α and β, along with an NTCP model that includes the tolerance dose for accepted complication rate.

One can then choose patient-specific values as and when such information becomes available.

For too long the speciality of radiotherapy has been something of a "black art", based on rules of thumb.
With radiobiological guidance, it is now time to move radiotherapy to being a *science*.
The knowledge and the tools are there.

Overview

Cinical Oncology 2009

Escalation and Intensification of Radiotherapy for Stage III Non-small Cell Lung Cancer: Opportunities for Treatment Improvement

J. D. Fenwick*†, A. E. Nahum*, Z. I. Malik‡, C. V. Eswar‡, M. Q. Hatton§, V. M. Laurence||, J. F. Lester¶, D. B. Landau**

- Modelling of how radiotherapy tumour control and complication rates vary with dose, fractionation, schedule duration, irradiated volume and use of chemotherapy for stage III NSCLC

- use the modelling to study the effectiveness of different NSCLC dose-escalation approaches being developed in the UK

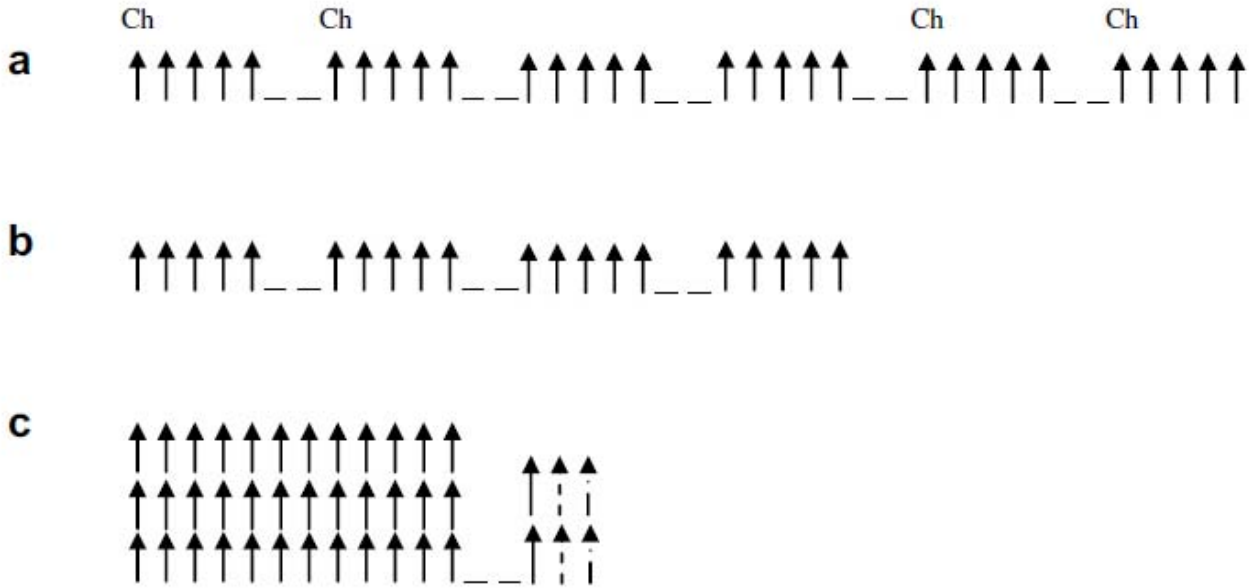


Fig. 6 — Escalated, intensified schedules. (a) 'IDEAL' concurrent chemoirradiation schedule delivering equal radiotherapy fractions 5 days/week over 6 weeks. (b) 'IDART' radiotherapy schedule delivering equal radiotherapy fractions 5 days/week over 4 weeks. (c) 'CHART-ED' radiotherapy schedule delivering CHART (3 × 1.5 Gy fractions/day given ≥ 6 h apart, for 12 days) followed by a 2 day break, followed by 1, 2 or 3 additional days of 2 × 1.8 Gy given ≥ 8 h apart.

Data for pneumonitis, lung fibrosis, early and late oesophagitis, cord and cardiac complications, and local progression-free survival at 30 months

Use of the linear-quadratic incomplete repair model to account for dose and fractionation effects, making linear corrections for differences in schedule duration, and characterising volume effects using parallel- and series-type concepts

Table 6 — Doses that may be deliverable using the different escalated schedules, together with associated modelled tumour control probabilities. Baseline schedule data are also tabulated

Schedule	IDEAL (6 week)	IDART (4 week)	CHART-ED (2.5 week)
Dose-limiting toxicities	Pneumonitis/lung fibrosis Higher dose-level complications	Pneumonitis/lung fibrosis Higher dose-level complications Acute oesophagitis?	Acute oesophagitis Lung fibrosis?
Range of doses that may be deliverable*	64—75 Gy	55—66 Gy†	57.6, 61.2, 64.8 Gy‡
Modelled tcp (30 month progression-free survival) for a 150 cm^3 tumour	44—76%§	31—67%	31, 40, 50%‡
Baseline schedule	60—64 Gy/30—32 fractions over 40—44 days	55 Gy/20 fractions in 26 days	54 Gy/36 fractions in 12 days
Baseline schedule tcp	17—20% no concurrent chemotherapy 30—35% + concurrent chemotherapy	31% no concurrent chemotherapy 44% + concurrent chemotherapy	21% no concurrent chemotherapy

Un ringraziamento particolare a:

Claudio Birattari

Giovanna Gagliardi
Mauro Cattaneo

Claudio Fiorino

Riccardo Valdagni
A tutti clinici e fisici dell'AIROPROS 0102

… e a tutti voi per la paziente attenzione
a questa lunghissima presentazione