WHY QUANTEC?

Convegno
Fisica e Radioterapia

NUOVE FRONTIERE
TRA HIGH TECH
E
POST GENOMICA

Perugia, 2 Luglio 2010

Convento di S. Francesco del Monte
Monteripido

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- Most dose-volume predictors from Emami *et al* (1991) 28 organs
- 9 authors - 7 MD's, 2 PhD's
- NTCP analysis (Burman *et al*, 1991)

- 2007, AAPM/ASTRO, ca 60 participants
- Steering Committee - 3 MD, 5 PhDs
- 2010, IJROBP vol 73, n6, 2010

  QUANTEC:**Qu**antitative **A**nalysis of **N**ormal **T**issue **E**ffects in **C**linic
- excluded: eye lens/eye/retina, TM joint /mandible, thyroid, skin, rib cage, cauda equina, brachial plexus, femoral head, colon
- new: penile bulb

QUANTEC group was formed from a loose network of researchers with a longstanding interest in dose–volume modeling. The Steering Committee defined three aims for QUANTEC.

(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

Table 1. Dose-volume relationships *ca.* 1990 and 2009+

ca. 1990	2009+
Treatment usually with parallel opposing fields or ''box'' techniques—three-dimensional conformal radiation therapy gaining ground clinically in some centers	Widespread use of conformal techniques, including intensity-modulated radiation therapy, often resulting in highly nonuniform dose distribution in organs at risk with large volumes receiving low doses
Radiation therapy typically delivered as single modality— spectrum of toxicities relatively well-characterized	Many curative cases receiving combined modality therapy—many regimens are very toxic leading to problems with compliance
Conventional fractionation dominates—clinical trials of hyperfractionation and accelerated fractionation	Conventional fractionation dominates—clinical trials of hypofractionation in progress
Authors search for a ''safe'' dose–volume constraint	Increasing appreciation of the risk-benefit tradeoff in an individual patient—a monotonic increase in toxicity risk with increasing dose/increasing volume
Early interest in normal tissue complication probability modeling—Lyman model most widely used	Change from ''more models'' to ''more data''—Lyman model still widely used, but new modeling strategies are being pursued
Analysis often based on groups of patients	Analysis of individual patient level data
Lack of consistency in contouring organs at risk among investigators	Lack of consistency in contouring organs at risk among investigators
Models often applied with parameters from the literature—no adjustment for patient or treatment characteristics	Statistical estimation of model parameters—often with adjustment for significant patient or treatment characteristics
Toxicity underscored and underreported in most studies	Toxicity underscored and underreported in most studies—despite attempts to define dictionaries for toxicity reporting such as Common Terminology Criteria for Adverse Events
A lack of quantitative, evidence-based dose–volume constraints—Emami *et al.* develops a ground-breaking set of consensus constraints for partial organ irradiation	A lack of quantitative, evidence-based dose-volume constraints—the QUANTEC group initiates a series of systematic literature reviews

Exposure	**Outcome**
Dosimetric data	Clinical data

- NTCP/predictors: clinical and dosimetric input data
  - most clinical studies for low grade toxicity/low incidence
  - organs have several endpoints
    - Lung: radiation pneumonitis, fibrosis, functional measures
    - Brainstem: necrosis, neuropathy, radiological changes
  - complications different degrees of severity (lung: gr 1 cough, gr 5 death)
  - classifications: different toxicity grading systems

- **RTOG / EORTC** Late Morbidity Scoring Criteria and Acute Radiation Morbidity Scoring Criteria (1995)
- **LENT / SOMA** systems for assessment and recording of late radiotherapy related morbidity (1995)
- **CTC** : Common Toxicity Criteria for early/acute morbidity (2000)
- **WHO**: World Health Organization classification

”Many patients who receive complex multimodality treatment have multiple coincident or sequential events (or both) that are not fully reflected in established summary presentations.”

TAME: development of a new method for summarising advers events of cancer treatment by the Radiation Therapy Oncology Group

Andy Trotti, Thomas F Pajak, Clement K Gwede, Rebecca Paulus, Jay Cooper, Arlene Forastiere, John A Ridge, Deborah Watkins-Bruner,

Adam S Garden, K Kian Ang, Wally Curran

http://oncology.thelancet.com **Vol 8 July 2007**

Short-term (acute) Toxicity (T)

Adverse long-term (late) effects (A)

Mortality risk (M) generated by a treatment programme

End results (E) assigns treatments to risk classes for each risk domain

QUANTEC recommendations, H&N region

	Absorbed dose recommendations	EQD2/BED/NTCP recommendations	Prob.curve
Brain	Yes	Predictors for 5 and 10% are given in BED and EQD2. α/β=3Gy	Incidence as function of BED
Optic nerve/ Chiasm	Yes	-	-
Brainstem	Yes	Total dose vs fraction dose curves for EQD2 using α/β=3.3, 2.5, 2.1Gy	-
Spinal cord	Yes	EQD2 α/β=3Gy	Probability as function of EQD2
Cochlea	Yes	-	-
Salivary gland	Yes	-	(tox severity vs mean dose ; TD50(50% function loss) vs follow up months)
Larynx/Pharynx	Yes	-	Probability as function 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 α/β=3Gy	NTCP α/β=3Gy
Esophagus	Yes	-	Tox rate as function of V20-70
Liver	Yes	EQD2 α/β=2Gy	NTCP α/β=2Gy
Stomach / Small bowel	Yes	-	-
Kidney	Yes	-	Incidence as function of Equivalent total dose (TBI, 6 fx, 10 cGy/min dose rate)

QUANTEC recommendations, pelvic region

	Absorbed dose recommendations	EQD2/BED/NTCP recommendations	Prob.curve
Bladder	Yes	-	Incidence as function of mean dose and EQD2 α/β=6Gy
Rectum	Yes	”Conventional” fx NTCP α/β=3Gy	Volume % as function of EQD2 α/β=3Gy grade 2 rectal tox
Penile bulb	Yes	-	Incidence as function of median/mean dose /D60-70

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)†	Endpoint	Dose (Gy), or dose/volume parameters†	Rate (%)	Notes on dose/volume parameters
Brain	Whole organ	3D-CRT	Symptomatic necrosis	Dmax <60	<3	Data at 72 and 90 Gy, extrapolated from BED models
	Whole organ	3D-CRT	Symptomatic necrosis	Dmax = 72	5	
	Whole organ	3D-CRT	Symptomatic necrosis	Dmax = 90	10	
	Whole organ	SRS (single fraction)	Symptomatic necrosis	V12 <5–10 cc	<20	Rapid rise when V12 > 5–10 cc
Heart	Pericardium	3D-CRT	Pericarditis	Mean dose <26	<15	Based on single study
	Pericardium	3D-CRT	Pericarditis	V30 <46%	<15	
	Whole organ	3D-CRT	Long-term cardiac mortality	V25 <10%	<1	Overly safe risk estimate based on model predictions
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	

Ogni constraint e' associato a un'incidenza di tossicita'.
La scelta del constraint e' una scelta di rate di tossicita', lasciata alla responsabilita' dell'utente.

Still left to do:

QUANTEC: VISION PAPER

IMPROVING NORMAL TISSUE COMPLICATION PROBABILITY MODELS: THE NEED TO ADOPT A "DATA-POOLING" CULTURE

Clinical studies of the dependence of normal tissue response on dose-volume factors are often confusingly inconsistent, as the QUANTEC reviews demonstrate. A key opportunity to accelerate progress is to begin storing high-quality datasets in repositories. Using available technology, multiple repositories could be conveniently queried, without divulging protected health information, to identify relevant sources of data for further analysis. After obtaining institutional approvals, data could then be pooled, greatly enhancing the capability to construct predictive models that are more widely applicable and better powered to accurately identify key predictive factors (whether dosimetric, image-based, clinical, socioeconomic, or biological). Data pooling has already been carried out effectively in a few normal tissue complication probability studies and should become a common strategy.

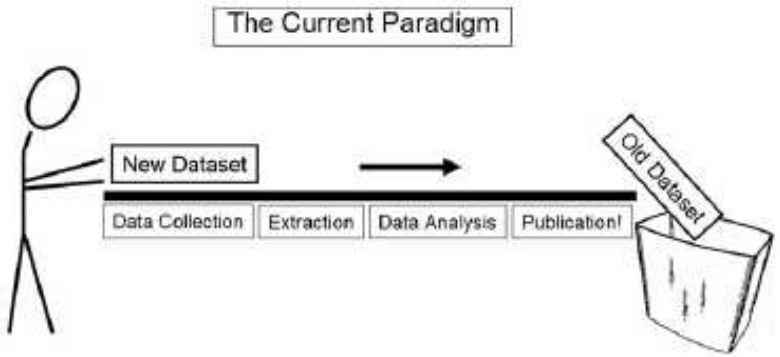


Fig. 2. "The current (data-loss) paradigm." Data are effectively lost to the wider scientific community after publication. Capturing key datasets in query-able data repositories would accelerate the discovery of causative factors and increase the accuracy of parameter estimates.

If the radiation oncology world were to adopt a data reuse policy, progress toward improved NTCP models (and other types of treatment effect comparisons) would accelerate, new factors relevant to outcomes would be identified, and the road block to consensus would be surmountable. It is only by making published datasets available for ongoing combined analyses that we can hope to produce powerful and validated models of quantitative normal tissue effects in the clinic.

Still left to do:

Table 1. Normal tissue end points and tolerance parameters

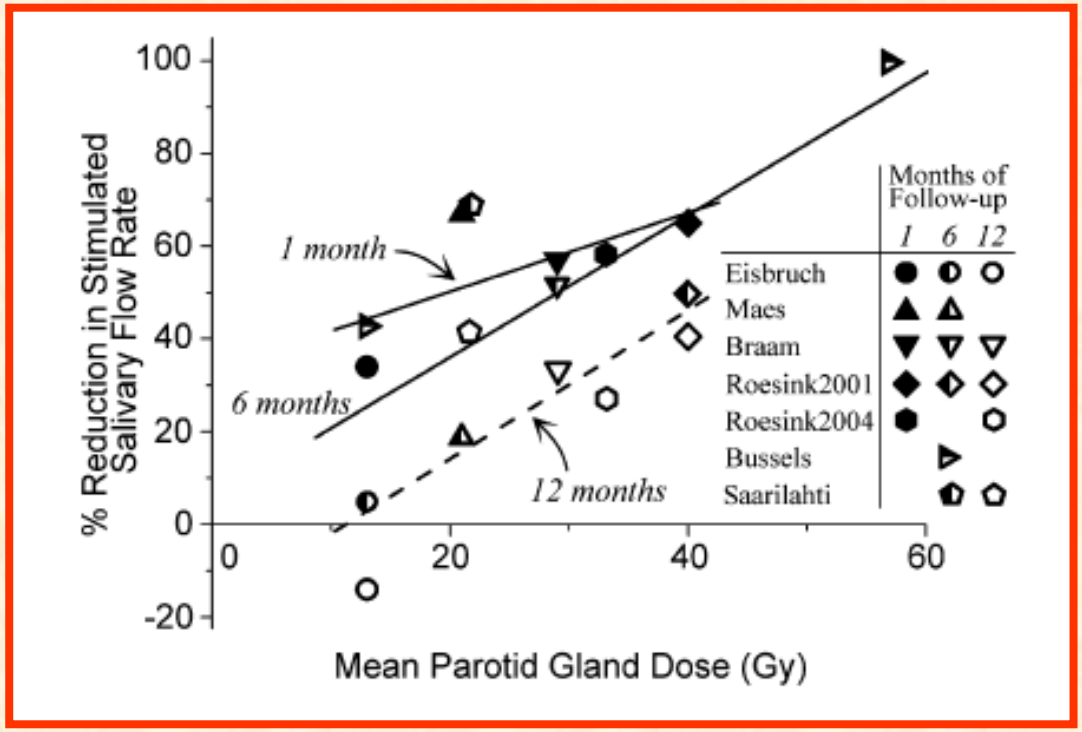
Organ	Fit parameters				End point
	V_{ref}	n	m	TD_{50}	
Bladder	Whole organ	0.5	0.11	80	Symptomatic bladder contracture and volume loss
Brachial plexus	Whole organ	0.03	0.12	75	Clinically apparent nerve damage
Brain	Whole organ	0.25	0.15	60	Necrosis/infarction
Brain stem	Whole organ	0.16	0.14	65	Necrosis/infarction
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
Femoral head and neck	Whole organ	0.25	0.12	65	Necrosis
Heart	Whole organ	0.35	0.10	48	Pericarditis
Kidney	Whole organ	0.70	0.10	28	Clinical nephritis
Larynx	Whole organ	0.11	0.075	80	Cartilage necrosis
Larynx	Whole organ	0.08	0.17	70	Laryngeal edema
Lens	Whole organ	0.30	0.27	18	Cataract requiring intervention
Liver	Whole organ	0.32	0.15	40	Liver failure
Lung	Whole organ	0.87	0.18	24.5	Pneumonitis

Parotid glands – xerostomia

Clinical criteria: **mean dose** **≤ 25Gy**

Available data: **mean dose threshold** **24 – 26 Gy**
(suppression of salivary flow)
mean dose (no thereshold) **35 – 45 Gy**
(decreased salivary flow)

LKB model	***TD50***	***m***	n
Emami (1991) No 3D - retrosp.	46 Gy	0.18	0.7
Eisbruch (1999) 88 pts – prosp.	28.4 Gy (25 – 34.7)	0.18 (0.10 – 0.33)	1 (fixed)
Roesink (2001) 180 pts – prosp. 95% CI	39 Gy (34 - 44)	0.45 (0.33 - 0.65)	1 (fixed)



- Outcome data (reducation in salivary flow) and sampling time
- @ 1month: almost independent of mean dose
- shift to right: higher mean dose with longer follow-up

Parotid glands - summary

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)†	Endpoint	Dose (Gy), or dose/volume parameters†	Rate (%)	Notes on dose/volume parameters
Parotid	Bilateral whole parotid glands	3D-CRT	Long term parotid salivary function reduced to <25% of pre-RT level	Mean dose <25	<20	For combined parotid glands¶
	Unilateral whole parotid gland	3D-CRT	Long term parotid salivary function reduced to <25% of pre-RT level	Mean dose <20	<20	For single parotid gland. At least one parotid gland spared to <20 Gy¶

(*Continued*)

Recommendations:

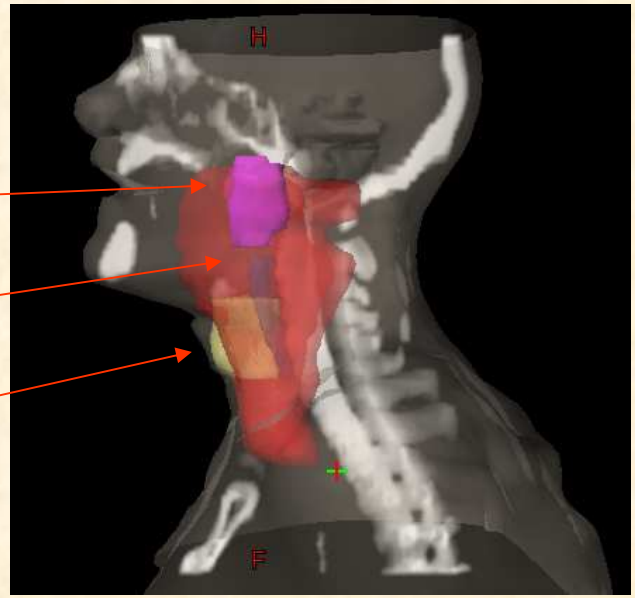
- to reduce severe xerostomia:

  Mean dose to one parotid gland < 20 Gy

  Mean dose to both parotid glands < 25 Gy
- ? Mean dose to submandibular gland < 35 Gy
- ? Thereshold value, < 10 Gy ?

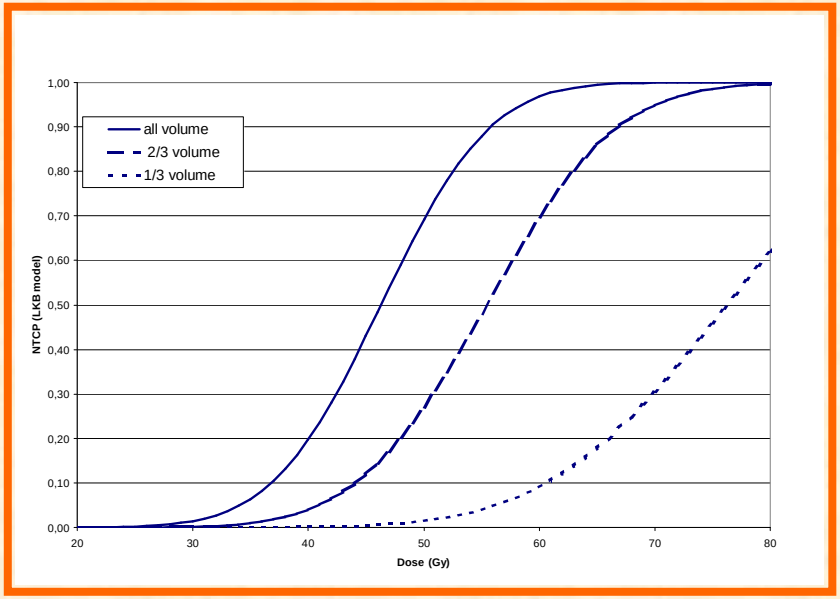
Larynx and Pharynx irradiation

- RT advantage: larynx preservation, implying speech and swallowing retention
- RT damage: laryngeal edema/fibrosis, leading in the long term to problems in speech and swallowing retention
- Larynx (and pharynx): often partially included in the target

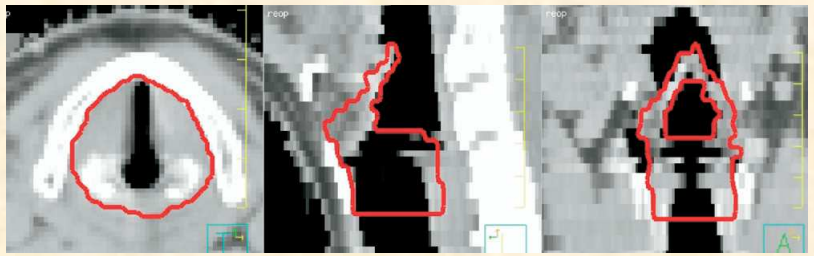


LOGEUD	*TD50*	*k*	
Rancati (2009)	46.0 ± 1.8	9.95 ± 3.46	

LKB	*TD50*	***m***	*n*
Rancati (2009)	46.3 ± 1.8	0.16 ± 0.05	0.45 ± 0.028



Rancati et al *IJROBP 2009*



Laryngeal edema:

•Large volume effect

suggested EUD<30-35 Gy (n=0.45)

V50≤27 Gy; mean dose ≤44 Gy

Larynx is parallel for edema

Disphagia

- Supraglottic larynx and constrictor muscles
- Feng et al, 2006 (ASTRO): evidence of a quantitatively assessed dose-volume effect for disphagia & aspiration (36 pts)
- Aspiration: mean dose, V50-V65 to PC, and supraglottic larynx correlated.
- Most predictive: V65(PC)<50%

Pharynx irradiation:dysphagia

Table 3. Organs at risk and dose–volume relationship above which swallowing dysfunction increases significantly

Investigator/patients (*n*)	Critical organs	Dose–volume data: Mean dose (Gy)	Median dose (Gy)	V_{50}	V_{60}	V_{65}	Endpoint	Evaluation method
Eisbruch *et al.* (13),	Larynx	60		50%	—	—	Aspiration	VF
Feng *et al.* (14)/36 patients	PC	66		80%	70%	50%	Aspiration	
IMRT + chemotherapy	PC			85%	70%	60%	Stricture	
Caglar (19)/96 patients	Larynx	48*		21%			Aspiration and stricture	VF
IMRT + chemotherapy	IC	54		51%				
Doornaert *et al.* (18)/81 patients	Pharyngeal mucosa and	45					QOL	RTOG/EORTC
RT + chemotherapy	constrictors							C30 and H/N 35
O'Meara *et al.* (20)/148 patients	Pharyngoesophageal inlet		50				Grade 3 plus pharyngoesophageal	RTOG late
2D-RT plus chemotherapy							dysfunction	Toxicity
Levandag *et al.* (15)/81 patients	Superior and middle	55					Grade >3 EORTC	RTOG
3D-CRT/IMRT plus	constrictors						PSS–HN MDADI	QOL
brachytherapy + chemotherapy								QOL
Dornfeld *et al.* (7)/27 patients	Aryepiglottic fold	50					Diet score	QOL
IMRT + chemotherapy	False cord						HN QOL	Clinical assessment
	Lateral pharyngeal						Weight loss	
	Wall near false cord						PEG tube	
Jensen *et al.* (16)/25 patients	Larynx/upper esophageal	60					Aspiration	EORTC QOL
3D-CRT	sphincter						QOL	FEES
RT alone								

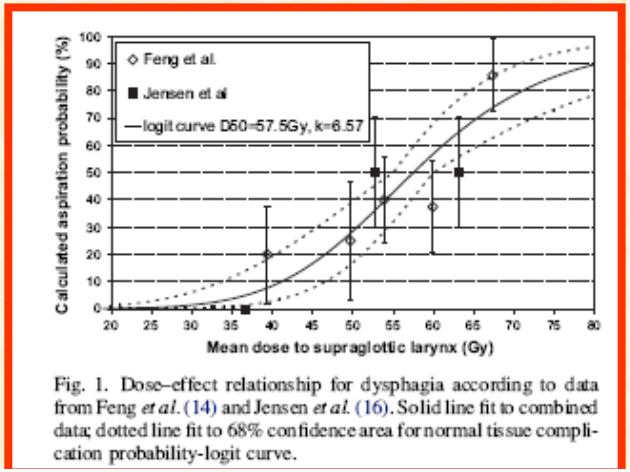
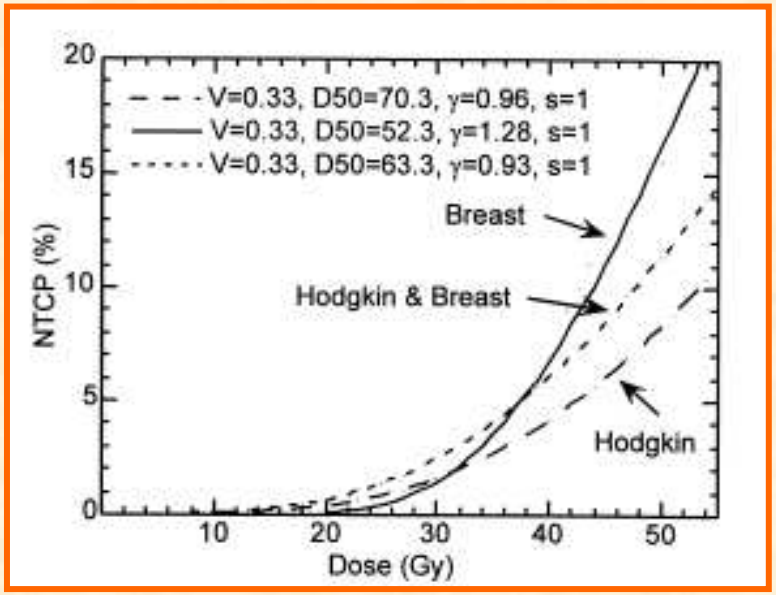


Fig. 1. Dose–effect relationship for dysphagia according to data from Feng *et al.* (14) and Jensen *et al.* (16). Solid line fit to combined data; dotted line fit to 68% confidence area for normal tissue complication probability-logit curve.

- Mean dose < 50 Gy < 20% incid.
- Recommendations: minimize volume of the constrictors >60 Gy & reducing volumes receiving > 50 Gy

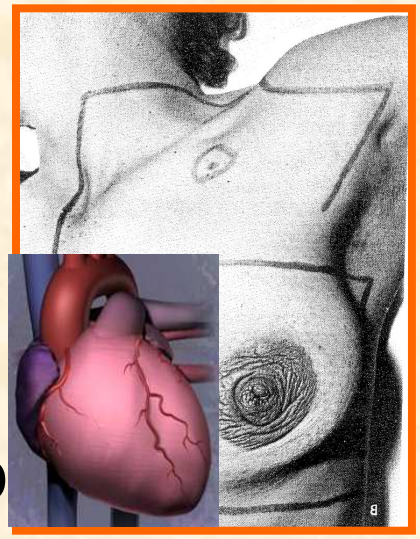


Hodgkin's data and breast data:

1) different parts of heart irradiated (almost complementary)

2) breast dose-response curve: steeper-safer (think of LDA location in tangential fields irradiation)

Eriksson F, *et al. Radiother Oncol* 2000;55:153–162.



by courtesy of C.Taylor,Oxford

Cardiac mortality modeling problems:

• Clinical data: low number of events (registers are needed)

• Long-term complications

• Dosimetrical data (retrospective studies; lack of 3D information)

•**VERY GOOD NEWS**: next results from **EBCTCG05,** and **RACE** (case - control study: UK, SE, DK) (www.race.ki.se)

Lung irradiation – large consensus but

- many endpoints and many diagnosis (breast, lung, mediastinum, Hodgkin's…)
- different dose distribution patterns; some only ipsilateral, some more central

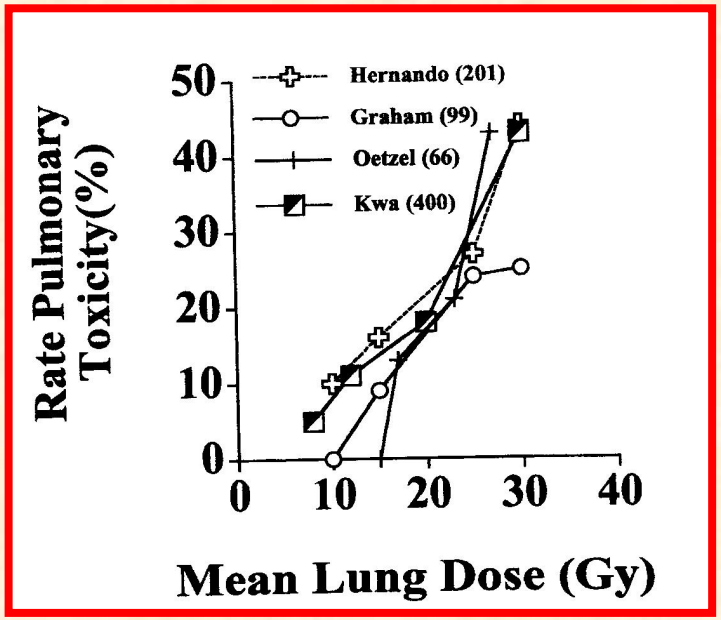
- early radiation effects
  Radiation Pneumonitis; 1-8 months after RT
  symptoms: from fever, dispnoea, cough to death from respiratory failure
- late effects : fibrosis, from 6 months onwards

- data from many treatments: most studies and results for acute effects
- irradiated lung: strong volume dependence
- lung apex less sensitive than the rest of the organ: on mice (*Travis et al 1995)*, on pts (*Seppenwoolde et al 2004, York et al 2005*)

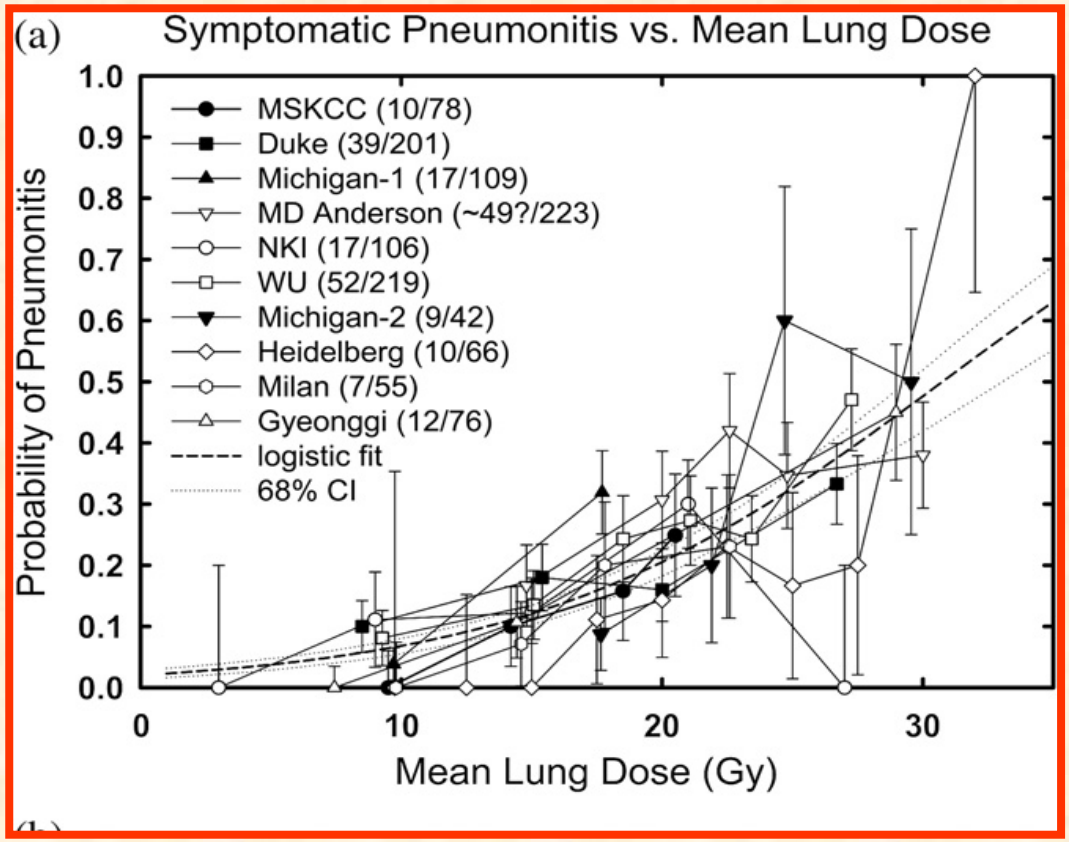
- dose calculations in low density tissue (algorithms do not take in account electron transfer – local dose in lung tissue overestimated by 10 – 20%., EPL overestimates dose at the lung boarder, see *De Jaeger et al 2003*)

review paper**:** *Seppenwolde et al, Sem Rad Onc,11,3:247, 2001*

Marks *et al*, ***IJROBP vol 76, n3, S70-S76, 2010***



More data on MLD:
(Hernando *et al* IJROBP 2001)



MLD trend confirmed in recent reviews.

Predictors (lung and the rest): in the first place they describe a numerical association between cuts and incidence rate. Very practical; a phenomenological explanation requires more than that.

NTCP, parameter values for RP

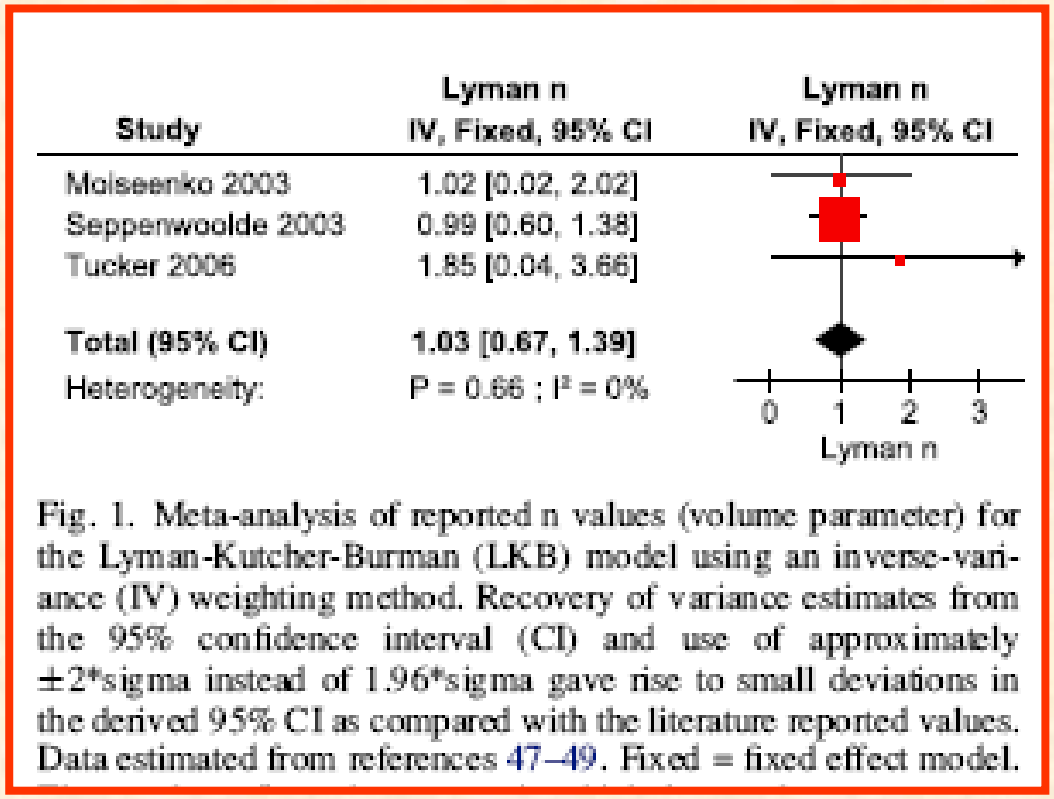


Fig. 1. Meta-analysis of reported n values (volume parameter) for the Lyman-Kutcher-Burman (LKB) model using an inverse-variance (IV) weighting method. Recovery of variance estimates from the 95% confidence interval (CI) and use of approximately ±2*sigma instead of 1.96*sigma gave rise to small deviations in the derived 95% CI as compared with the literature reported values. Data estimated from references 47–49. Fixed = fixed effect model.

- RP-MLD: logistic fit

  TD_{50}=30.8 (28.7,33.9) Gy

  γ_{50}=0.97 (0.83,1.12)

- Probit response function (LKB, n=1)

  TD_{50}=31.4 (29,34.7) Gy

  m=0.45 (0.39,0.51)

Lung, summary

Organ	Volume segmented	Irradiation type (partial organ unless otherwise stated)†	Endpoint	Dose (Gy), or dose/volume parameters†	Rate (%)	Notes on dose/volume parameters
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	

Recommendations:

- for NSCLC, for RP $\leq$ 20% : V_{20} $\leq$ 30-35%
  MLD $\leq$ 20-23 Gy
- to avoid bronchial stricture: central airways < 80 Gy
- for mesothelioma (RT following pneumonectomy)
  V_5<60%
  $V_{20}\leq$ 4-10 %
  MLD $\leq$ 8 Gy

Conclusions – NTCP modelling and various predictors

- Dosimetric data (organ movements, organ definition, inclusion of set-up errors, dose calculations, summed treatment plans, **treatment DVH…**)
- Fractionation patterns and corrections (missing: dose matrix, α/β)
- Clinical data (endpoint definition, relevant clinical endpoint, pretreatment status, risk factors, concomitant treatments)
- Models (formalism, inclusion of carcinogenesis effects, of low dose hypersensitivity). Uncertainties in parameters
- Main hypothesis: Exposure – Outcome

  Organ irradiation – organ complication (dose distribution in the organ - DVH/dose matrix) organ? / system? (see ICRU 50)

Conclusions – NTCP modelling and various predictors

- Concomitant treatments - modelling (input data + formalism) required
- Modelling: Table
- Predictors (lung and the rest): in the first place they describe a numerical association between cuts and incidence rate. Very practical; a phenomenological explanation requires more than that.
- Data pooling / Decision Support Systems (e.g.nomograms)