Tossicità tardiva in radioterapia: ipofrazionamento versus frazionamento convenzionale

L'esperienza clinica nel polmone

Cristina Mantovani

Hypofractionation: radiobiological rationale and clinical implications

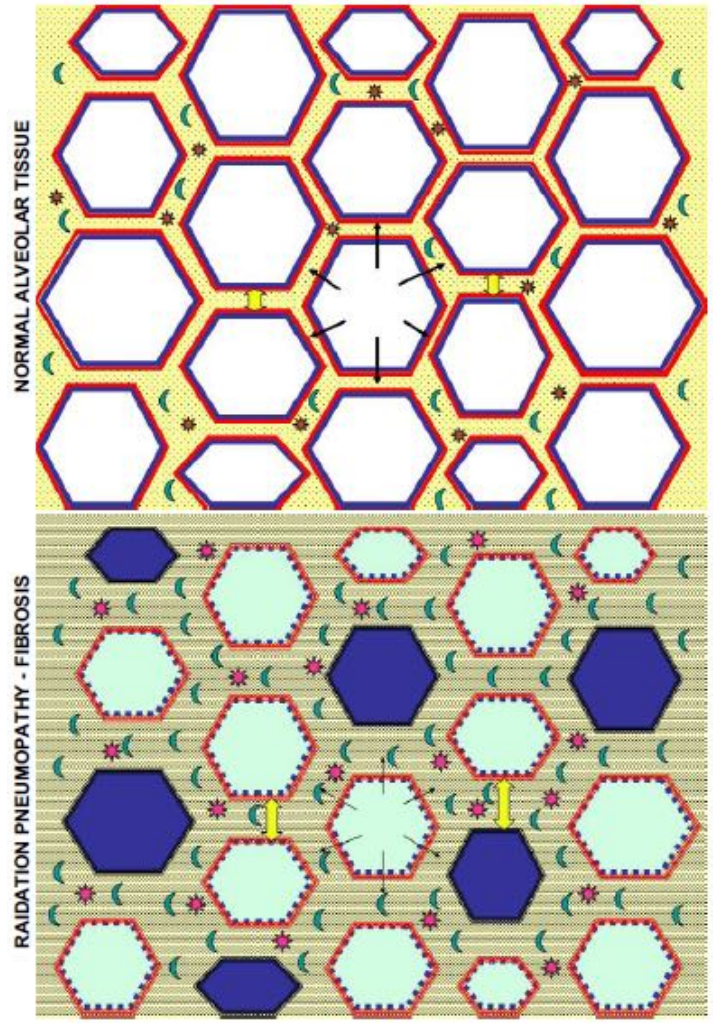
- **Higher dose per fraction**
  Potential dose escalation with a higher BED: theoretical advantage on local tumor control

- **Reduced overall treatment time**
  Reduce tumor cell repopulation
  Improved patient convenience and reduced cost (reduce demand on RT resources)

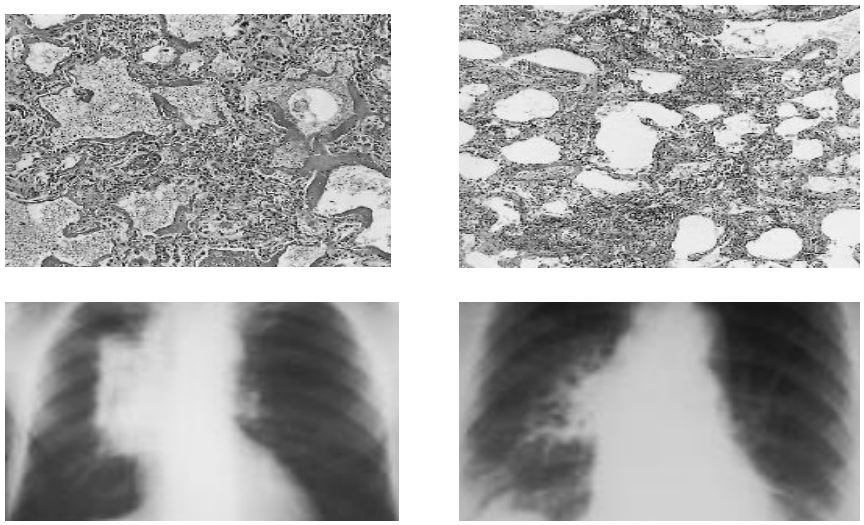
- **Concerns of a disproportionate increase in late normal tissue toxicity**
  (α/β ratio of tumor and lung of 10 Gy and 3 Gy respectively)

  - Dose per fraction higher than 2.2 Gy???
  - 10-20 fractions?
  - How does the radiobiology change with fraction size and type of delivery (IMRT, VMAT….)?

Radiation pneumonitis and fibrosis: mechanisms underlying its pathogenesis



Schematic representation of radiation pneumopathy



Pneumonitis **Fibrosis**

- Radiation pneumonitis an early inflammatory reaction involving alveolar cell depletion and inflammatory cell accumulation in the interstitial space that occurs within 12 weeks after RT.
- Radiation fibrosis, a late effect, that consists mainly of fibroblast proliferation, collagen accumulation, and destruction of the normal lung architecture

Esophageal radiation toxicity

- No comprehensive dose-volume based analyses have been published; no large body of data on LET

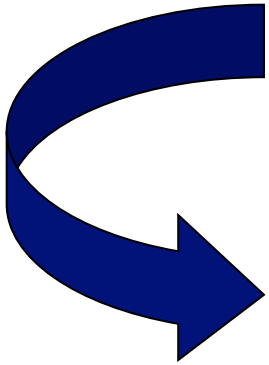
- A few reports have been published of serious esophageal toxicity from hypo-RT

- A 34 Gy mean dose recommendation was adopted in the RTOG 0617 phase III trial

- V75Gy and maxAET significant predictors of LET (Belderbos, ESTRO 2012)

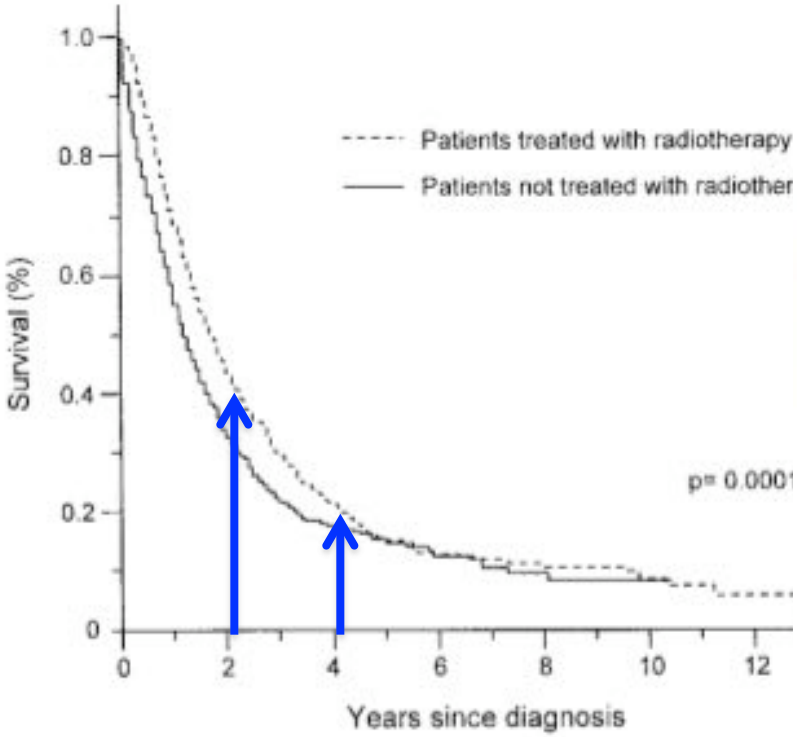
Hypofractionation: rationale

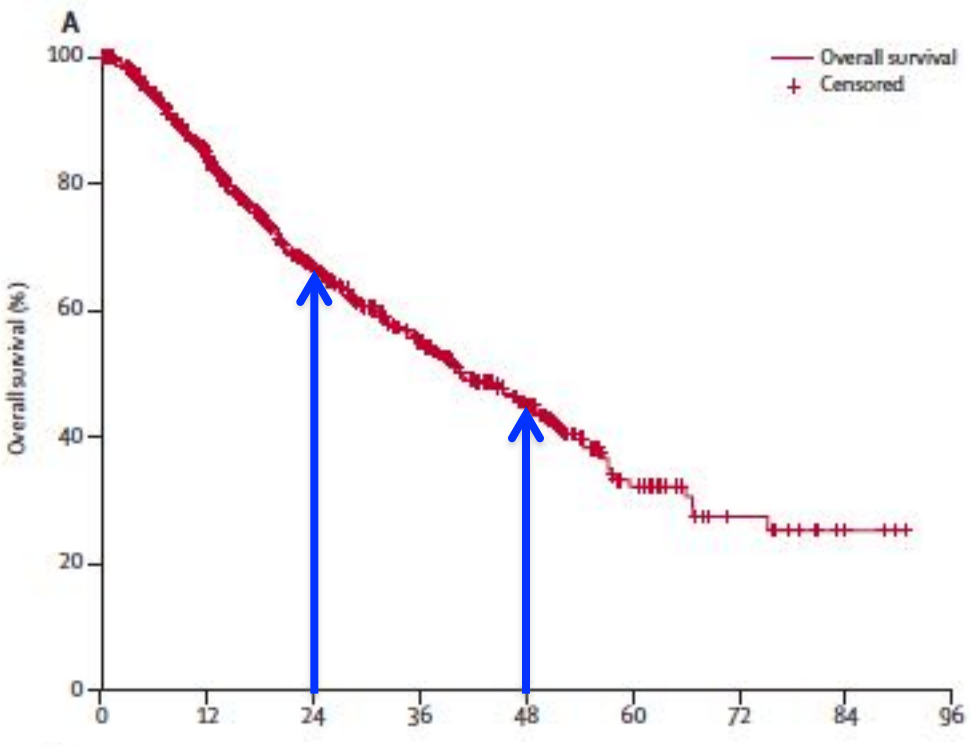
….Times have changed….. Technology has improved. ….The Biology of radiation response is better understood…..



SBRT in Early Stage NSCLC

Comparison between historical RT series and SBRT





Senthi et al, Lancet Oncol 2012

Severe Pulmonary Toxicity

	No Pts	Dose	Grade 3+ Toxicity
Uematsu	66	30-76 Gy 5-15 fx	0%
Nakagawa	22	15-24 Gy 1 fx	0%
Nagata	40	40-48 Gy 4 fx	0%
Wulf	61	26-37.4 Gy 1-3 fx	3%
Hara	23	20-30 Gy 1 fx	4%
Hof	10	19-26 Gy 1 fx	0%
Onimaru	57	48-60 Gy 8 fx	2%
Whyte	23	15 Gy 1 fx	0%
Blomgren	17	30 Gy 2-3 fx	6%
Ricardi	62	45 Gy/3fx or 26 Gy/1fx	3%

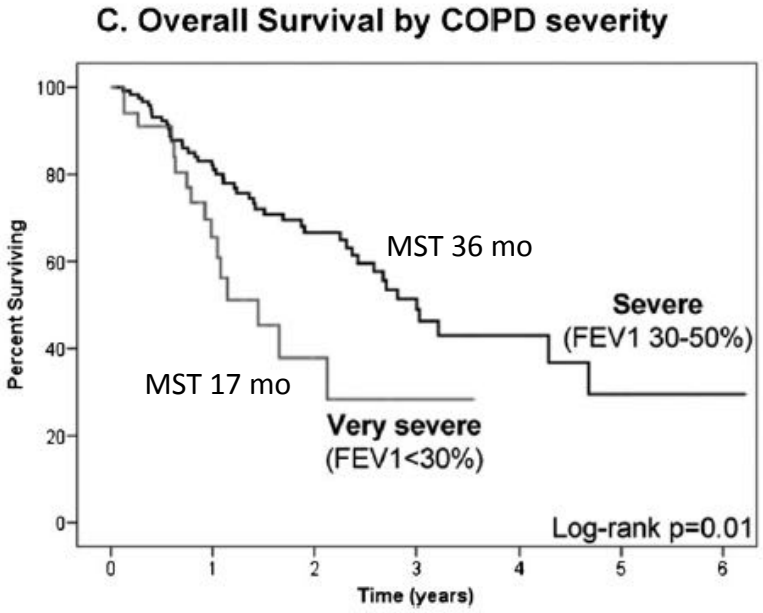
CLINICAL INVESTIGATION

CURATIVE TREATMENT OF STAGE I NON–SMALL-CELL LUNG CANCER IN PATIENTS WITH SEVERE COPD: STEREOTACTIC RADIOTHERAPY OUTCOMES AND SYSTEMATIC REVIEW

David Palma, M.D., M.Sc., F.R.C.P.C.,*† Frank Lagerwaard, M.D., Ph.D.,*
George Rodrigues, M.D., M.Sc., F.R.C.P.C.,† Cornelis Haasbeek, M.D., Ph.D.,*
and Suresh Senan, M.R.C.P., F.R.C.R., Ph.D.*

*VU University Medical Center, Amsterdam, Netherlands; †Division of Radiation Oncology, London Regional Cancer Program, London, Ontario, Canada

A single-institution cohort of 176 patients with COPD GOLD III-IV and Stage I NSCLC treated with SBRT



Thirty-day mortality and complications associated with treatment of stage I NSCLC in patients with poor ventilatory function

First author	30-day mortality	Complications
Surgery		
Magdeleinat (26)	8%*	>90% admitted to ICU >45% with complications (pneumonia, air leak, and arrhythmia most common)
Lau (19)	25% after open lobectomy* 7% for open segmentectomy or VATS procedure*	Median hospital stay 8–12 days <10% admitted to ICU
SBRT		
Henderson (27)	0%*	>69% with Grade 1 or 2 toxicity of some kind†
Stephans (28)	0%*	No Grade 3 or higher pneumonitis
Palma (current study)	0%	6 patients (3%) with Grade 3 toxicity

Is there an optimal fractionation schedule for maximizing the therapeutic ratio?

Type of Radiotherapy	Typical Dose per Fraction (Gy)	Characteristics
Conventionally fractionated radiotherapy	1.5 to 2.0	High cumulative doses, less apt to cause "late effects"
Hypofractionated radiotherapy	>2.0 to 8.0	Most commonly used for palliative treatment for patients near end of life, increasingly used for curative treatment in breast and prostate cancer therapy
Ablative radiotherapy	>8.0	Stops both cellular division and cellular function, overwhelms tumor repair, more likely to cause "late" effects

Can "adapted" hypofractionation be applied to

lung cancer patients with larger tumors?

Unresectable stage III NSCLC

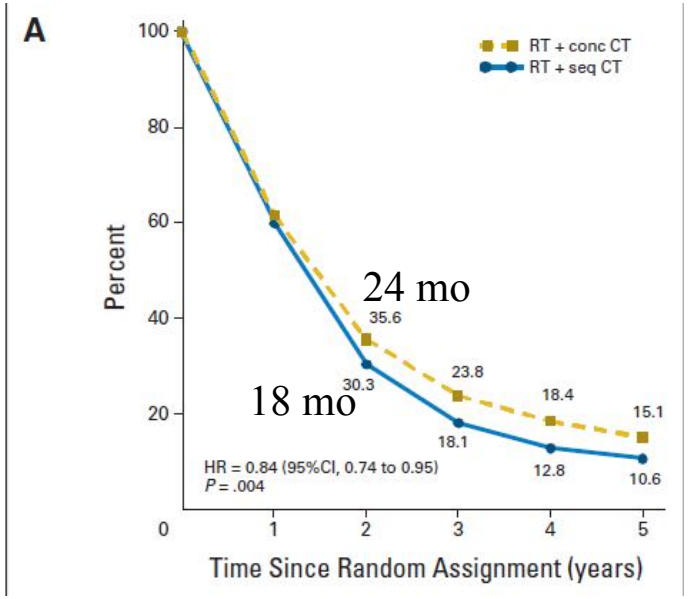
- At present, concurrent chemotherapy with radiotherapy to a dose of 60-66 Gy in 30-33 daily fractions is considered to be the standard treatment

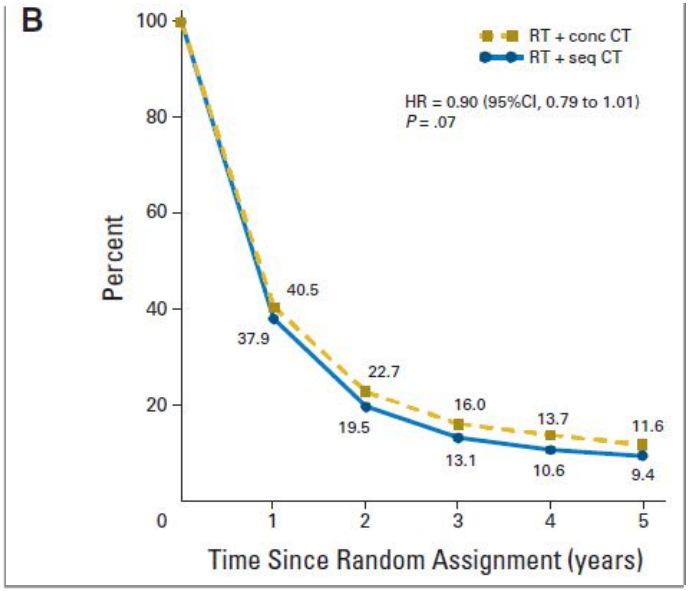
- Indirect evidence suggests that radiation dose-escalation may improve survival also in the context of chemo-radiation

Meta-Analysis of Concomitant Versus Sequential Radiochemotherapy in Locally Advanced Non–Small-Cell Lung Cancer

Anne Auperin, Cecile Le Péchoux, Estelle Rolland, Walter J. Curran, Kiyoyuki Furuse, Pierre Fournel, Jose Belderbos, Gerald Clamon, Hakki Cuneyt Ulutin, Rebecca Paulus, Takeharu Yamanaka, Marie-Cecile Bozonnat, Apollonia Uitterhoeve, Xiaofei Wang, Lesley Stewart, Rodrigo Arriagada, Sarah Burdett, and Jean-Pierre Pignon

- A significant overall survival benefit with a lower rate of locoregional progression in the concomitant approach
- Symptomatic RPs occur in 15%-40% of patients receiving concomitant CT-RT
- Increased acute G3-G4 esophageal toxicity (from 4% to 18%) in concomitant approach compared with sequential RT-CT
- No data regarding esophageal and pulmonary late toxicity





(A) Survival curves and (B) progression-free survival curves.

Unresectable stage III NSCLC

- At present, concurrent chemotherapy with radiotherapy to a dose of 60-66 Gy in 30-33 daily fractions is considered to be the standard treatment

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REVIEW

Lung Cancer Management, 2012

Radiation therapy in locally advanced non-small-cell lung cancer: an overview of dose/fractionation strategies to improve outcomes

Andrea Riccardo Filippi*[1], Cristina Mantovani[1] & Umberto Ricardi[1]

Innovative intensified schedules

- Hyperfractionated/Accelerated Radiotherapy
- Hypofractionated/accelerated radiotherapy
- INDividualised Accelerated Radiotherapy (INDAR)

RADIATION DOSE PRESCRIPTION FOR NON–SMALL-CELL LUNG CANCER ACCORDING TO NORMAL TISSUE DOSE CONSTRAINTS: AN *IN SILICO* CLINICAL TRIAL

ANGELA VAN BAARDWIJK, M.D.,* GEERT BOSMANS, M.SC.,* SØREN M. BENTZEN, PH.D., D.SC.,†
LIESBETH BOERSMA, M.D., PH.D.,* ANDRÉ DEKKER, M.SC., PH.D.,* RINUS WANDERS, M.D.,*
BRADLY G. WOUTERS, PH.D.,* PHILIPPE LAMBIN, M.D., PH.D.,* AND DIRK DE RUYSSCHER, M.D., PH.D.*

* Department of Radiation Oncology (MAASTRO), GROW Research Institute University Hospital Maastricht, Maastricht, The Netherlands; and † Department of Human Oncology, University of Wisconsin, Madison, WI

- A planning study estimating the TCPs and therapeutic index comparing an individualized MTD prescription for both conventional and accelerated fractionation schemes with a classic non escalated dose schedule

- 64 NSCLC pts; 5 treatment plans were compared (two used classic fractionation to a DFT 60 Gy or determined by the individualized MTD, the third an hypofractionated schedule of 2.75 Gy fractions, the fourth and the fifth used a hyper/accelerated scheme)

Variable	$QD_{classic}$ (60 Gy/2.0 Gy QD)	QD_{MTD} (MTD/2.0 Gy QD)	QDhypofr (MTD/2.75 Gy QD)	$BID_{classic}$ (61.2 Gy/1.8 Gy BID)	BID_{MTD} (MTD/1.8 Gy BID)
TTD (Gy)					
Mean ± SD	58.3 ± 3.6	66.6 ± 9.2	57.5 ± 8.7	58.4 ± 5.1	65.3 ± 11.3
Range	42.0–60.0	42.0–76.0	33.0–66.0	37.8–61.2	37.8–79.2
EQD_2 tumor (corrected for repopulation) (Gy)					
Mean ± SD	47.5 ± 2.3	52.0 ± 5.3	56.9 ± 6.9	56.9 ± 3.8	62.1 ± 8.5
Range	37.2–48.6	37.2–57.4	35.1–63.5	40.8–59.0	40.8–72.5
Normal tissue					
EQD_2 spinal cord (Gy)					
Mean ± SD	42.1 ± 10.8	47.1 ± 9.9	47.2 ± 9.7	44.7 ± 10.9	48.8 ± 9.5
Range	7.9–54.5	9.5–54.5	9.3–54.4	8.3–54.4	9.2–54.4
nMLD (Gy)					
Mean ± SD	12.0 ± 4.5	13.3 ± 4.5	11.5 ± 4.3	11.8 ± 4.5	13.0 ± 4.5
Range	2.7–20.0	3.2–20.0	2.7–20.0	2.8–19.9	3.0–19.9
Estimated TCP (%)					
Mean ± SD	4.5 ± 0.1	10.1 ± 0.7	19.1 ± 1.4	16.9 ± 0.7	30.9 ± 2.4
Range	0.6–5.1	0.6–17.0	0.4–31.5	1.3–20.3	1.3–56.9

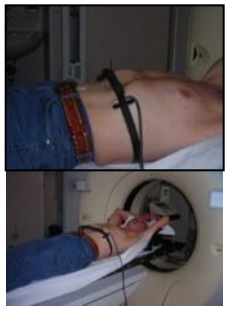
- Dose escalated and hypofractionated scheme resulted in an increase in the mean estimated TCP of 5.6% and 14.6% respectively, compared with classic fractionation. The escalated and accelerated scheme improved the TCP by 26.4%.

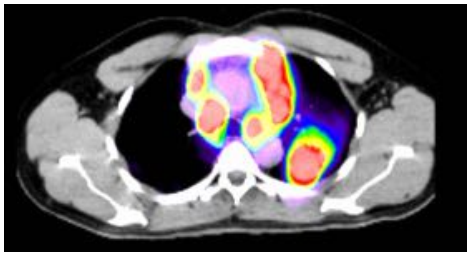
- A limited increase in the estimated risk of pneumonitis for the BID-MTD schedule (9.5%) compared with the QD classic scheme (8.3%) and the hypofractionated schedule (7.9%)

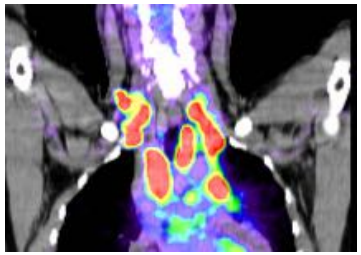
Int. J. Radiation Oncology Biol. Phys., Vol. 71, No. 4, pp. 1103–1110, 2008

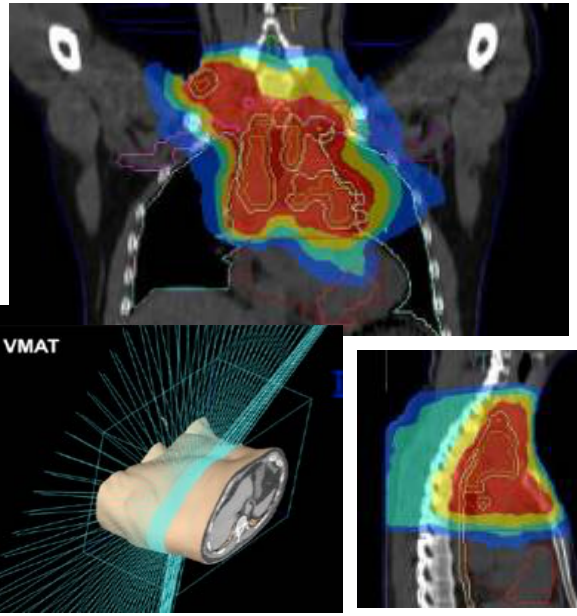
Hi-Tech Radiotherapy:
very steep dose gradient between tumor and healthy tissues

1. **Use of 4D-CT**: accounting for tumor motion during breathing
2. **CTV-Definition**: minimization based on functional Imaging (PET-CT) and shift to smaller volumes

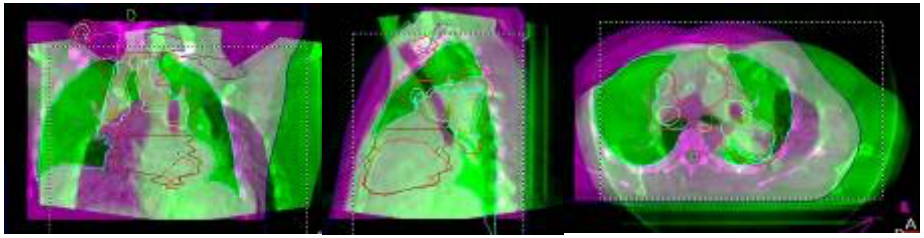




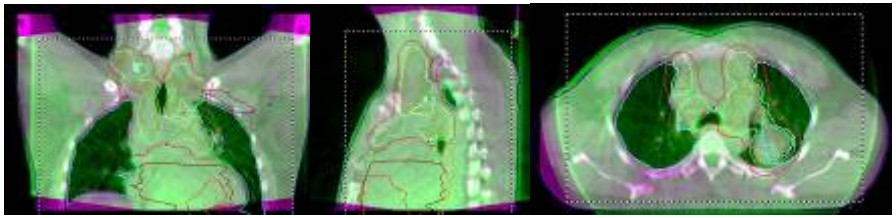




2. Treatment Planning as IMRT based on Monte-Carlo Dose calculation (dose-painting)



Suboptimal Positioning

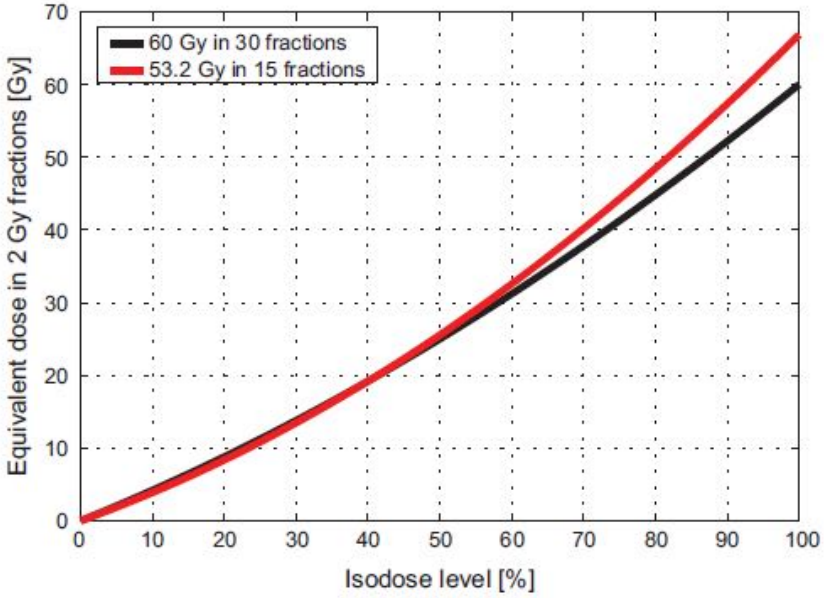


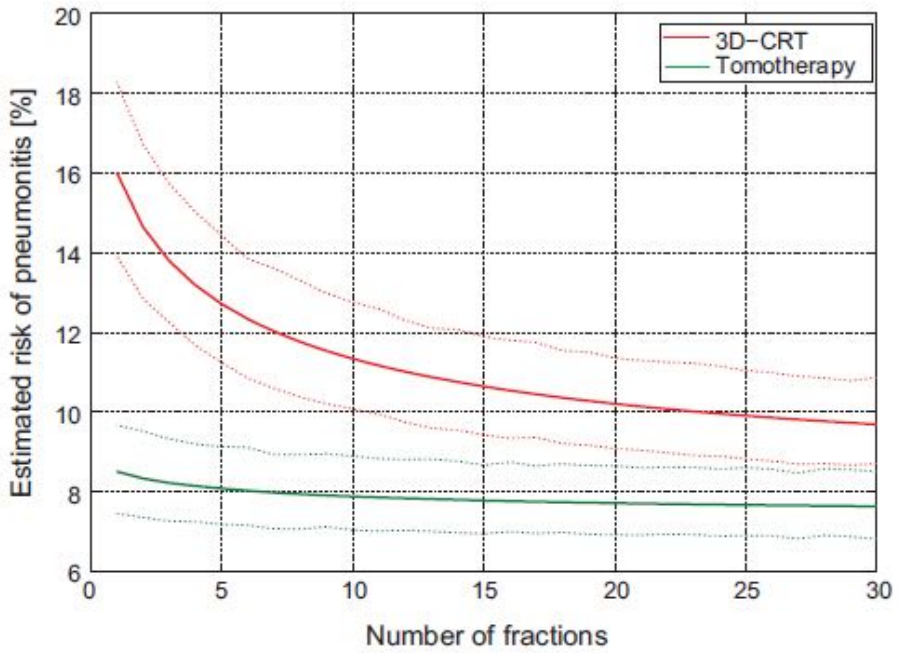
Optimal Positioning

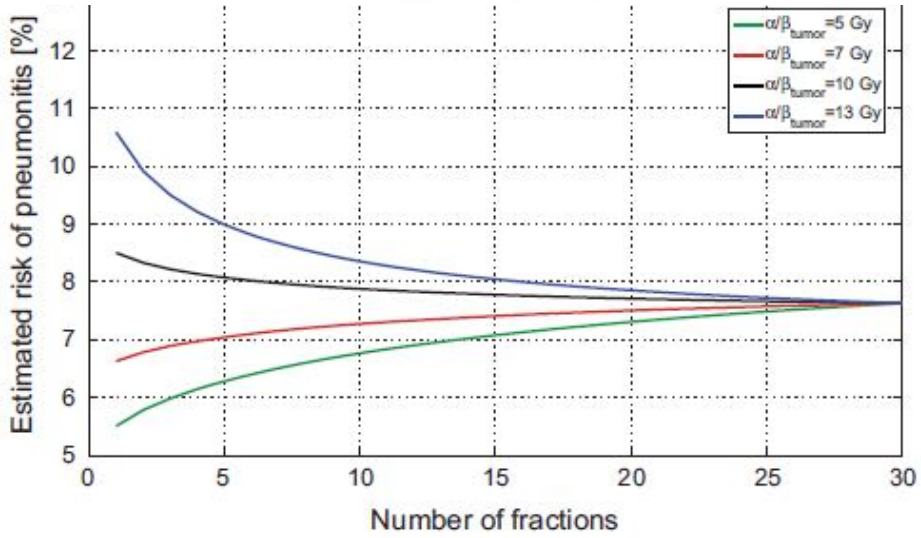
3. Image Guided Radiotherapy Treatment with Cone-Beam-CT at Linac for margins reduction

Hypofractionation does not increase radiation pneumonitis risk with modern conformal radiation delivery techniques

IVAN S. VOGELIUS[1,2], DAVID C. WESTERLY[1], GEORGE M. CANNON[1] & SØREN M. BENTZEN[1]







Systematic review

Radiotherapy and Oncology 99 (2011) 6–11

Dose escalation for non-small cell lung cancer: Analysis and modelling of published literature

Mike Partridge [a,*], Mónica Ramos [b], Angela Sardaro [b], Michael Brada [a]

[a] The Institute of Cancer Research; and [b] The Royal Marsden NHS Foundation Trust, Sutton, UK

- Review of published clinical data on NSCLC patients treated with radical RT (with standard RT, hyper and hypofractionated treatment schedule)
- Prescription dose was converted to biologically-equivalent dose (BED), with a correction for repopulation

- Clinical data show a clear tumor-dose response; best outcomes for hypofractionated schedules (overall treatment time < 6 weeks) in terms of 2-years DFS compared to short hyperfractionated schedules or prolonged conventionally fractionated treatments

- Not a clear correlation between tumor delivered dose and toxicity rates (pneumonitis/esophagitis) was observed.

Retrospective studies of hypofractionated RT in locally advanced NSCLC

Study	***N. pts***	PTV (median)	***Chemotherapy***	***RT schedule***	***Outcome***	Acute toxicity Grade 3-4	***Late toxicity Grade 3-4 tox.***
Zhu *et al.*	34	282 cc	*Induction* CT 34 *Consolidative* CT (31/34)	50Gy/20fr 65-68Gy/ 22-23f	Median OS 19 mo 1yLRPFS 69.6% 2yLRPFS 60.9%	Pneumonitis 1/34 Esophagitis 2/34	No G3-G4
Pembert *et.al*	47 (hypo) Vs 93 (CHART)	---	*Induction* CT 26 (hypo) vs 46 (CHART)	HypoRT (55Gy/20fr) vs CHART	Median PFS 20 *vs.* 11.m 2y OS 45% *vs.* 34%	Grade 2-3 Pneumonitis 20 vs 23 Grade 2-3 esophagitis 25 vs 31	No G4
Amini *et al.*	119 vs 90 vs. 91	---	*Induction* CT 23vs61vs27 *Consolidative* 14vs5vs5	45Gy/15fr vs. 60-63Gy vs >63Gy	Response(OS/PFS) NS	Grade ≥2 pneumonitis 14 vs 19 vs 20 Grade ≥2 esophagitis 12 vs 10 vs 9	---
Kepka *et al.*	173	111	*Induction* CT 118	56.7Gy/21f (2.7) 60.9Gy/21f (2.9)	2y OS 32% 2y LPFS 40%	Grade 3 esophagitis 7% Grade 3 pneumonitis 6%	2/9 pts (60.9 Gy) died of pulmonary toxicity.

Comparison of reported series of dose-escalated hypofractionated RT in inoperable NSCLC

Ref.	Stage III (n/tot)	Dose Gy	Fraction Gy	Selection	LPFS 1 yr	LPFS 2 yr	iLR
Bral	40/40	70.5	2,35	NA	66%	50%	18%
Bradley	83/179	71-90	2,15	V20	61%	50%	18%
Belderbos	42/88	60-94	2,25	rMLD	-	-	28%
Thirion	16/25	72	3	NA	72%	-	-

Some considerations:

- A mixed populations of inoperable patients
- Patients were classified according to DVH-predictors of lung toxicity, and, as such, higher doses were primarily given to smaller-volume disease
- Paucity of data regarding late toxicity profile

EUROPEAN JOURNAL OF CANCER 43 (2007) 114–121

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Randomised trial of sequential *versus* concurrent chemo-radiotherapy in patients with inoperable non-small cell lung cancer (EORTC 08972-22973)

Inoperable T1-4 N0-3 NSCLC

WHO 0-1

Weight loss <10%

FEV1 >1L

Diffusion capacity >60%

158 pts

Concurrent CT-RT

N=80

Daily low-dose cisplatin (6mg/m^2) concurrent with RT

Sequential CT-RT

N=78

2 cycles of GMC (1250 mg/m^2 d1,8)+Cisplatin (75mg/m^2 day 2) followed by RT

- Primary endpoint OS
- Secondary endpoints:DFS, LC, toxicities, QoL

RT (66 Gy in 24 fractions in 32 days)

EUROPEAN JOURNAL OF CANCER 43 (2007) 114–121

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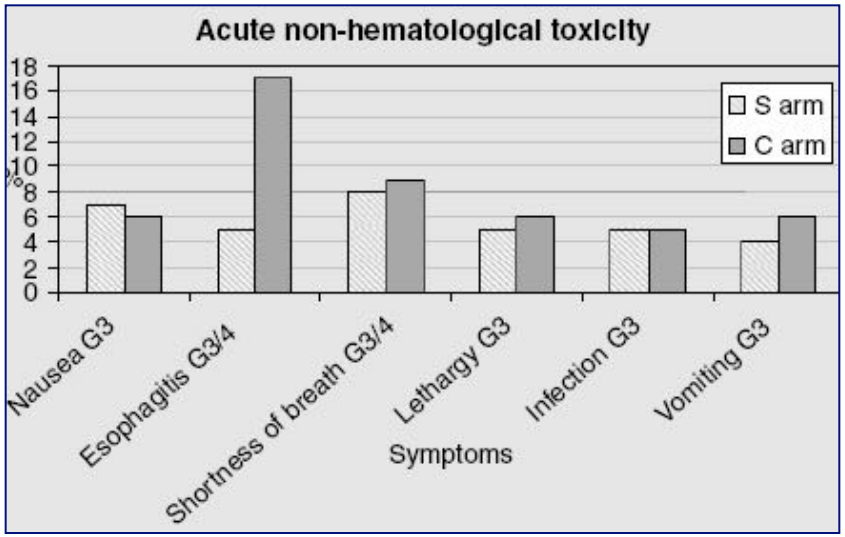

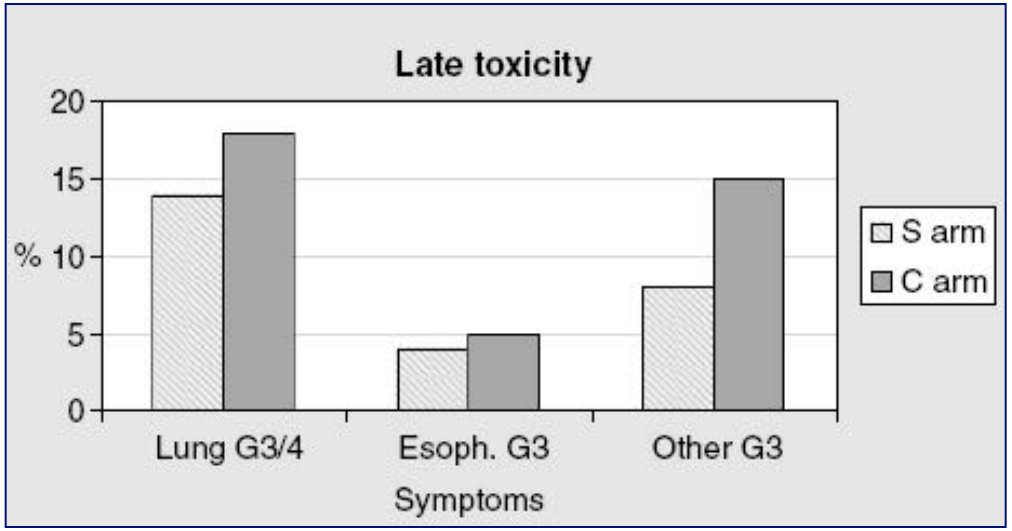

SOCCAR: Sequential or concurrent chemotherapy and hypofractionated accelerated radiotherapy in inoperable stage III NSCLC

- To address the feasibility, toxicity and efficacy of accelerated radical RT combined with either concurrent (con) or sequential (seq) CT
- 130 pts were randomised to 55Gy/20f over four weeks with four cycles of either conc (67) or seq (60) CDDP+vinorelbine.
Median follow up of 31 months

- Median survival 27.4 mo con vs 18.6 mo seq
- 2 year OS 54% con vs 42% seq.
- 3 year OS 38% con vs 27% seq

-SAE: 46% con vs 47% seq.
-CTC esophagitis G3: 6 (con) vs 1(seq). G4 esophagitis did not occur.

-Accelerated RT with concurrent CDDP-vinorelbine is feasible, safe and effective for patients with stage III NSCLC

Hypofractionated RT in lung cancer

- The use of Hypo-RT for locally advanced lung cancer is increasing due to technical advances that improve ability to target treatment and reduce toxicity

- Preliminary experiences with hypofractionated RT revealed a limited toxicity profile

- Hypofractionated-accelerated schedules, guided by response during radiotherapy and planned by using predictive factors of radiation induced lung injury, remains to be explored in phase II-III studies.