MRO.ART
INNOVATIVE TREATMENTS AND PATIENTS COMPLIANCE
31° RESIDENTIAL COURSE

Focus on Lung cancer innovation and compliance

Constraints and toxicity in innovative treatments

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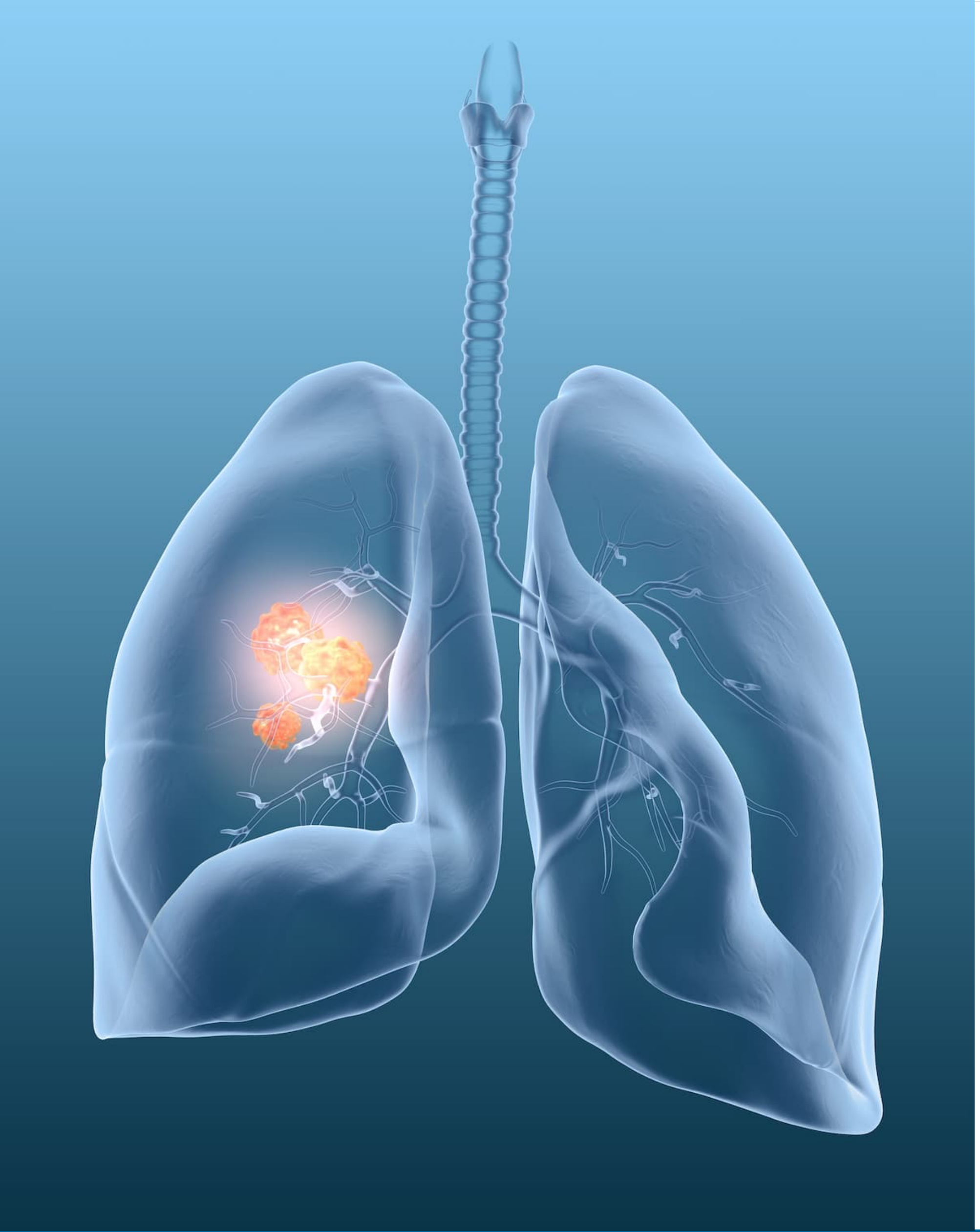


Lung cancer radiotherapy: assumptions

Early stage

- **SBRT** appropriate option
- Anatomical **site** has an impact on treatment outcomes

Locally advanced stage

- **Concomitant CRT** better than RT alone or sequential CRT
- Definitive CRT up to **60-70 Gy**
- **Immunotherapy**

Common issues

- **Motion** represents both a systematic and a random source of error and uncertainty in RT
- Frequent **comorbidities: patients selection**
- **Toxicity (≥ G3)** still burdens 10-30% of treatments
- Lung cancer accounts for **20.4% of cancer deaths**

Lung cancer constraints: a matter of dose?

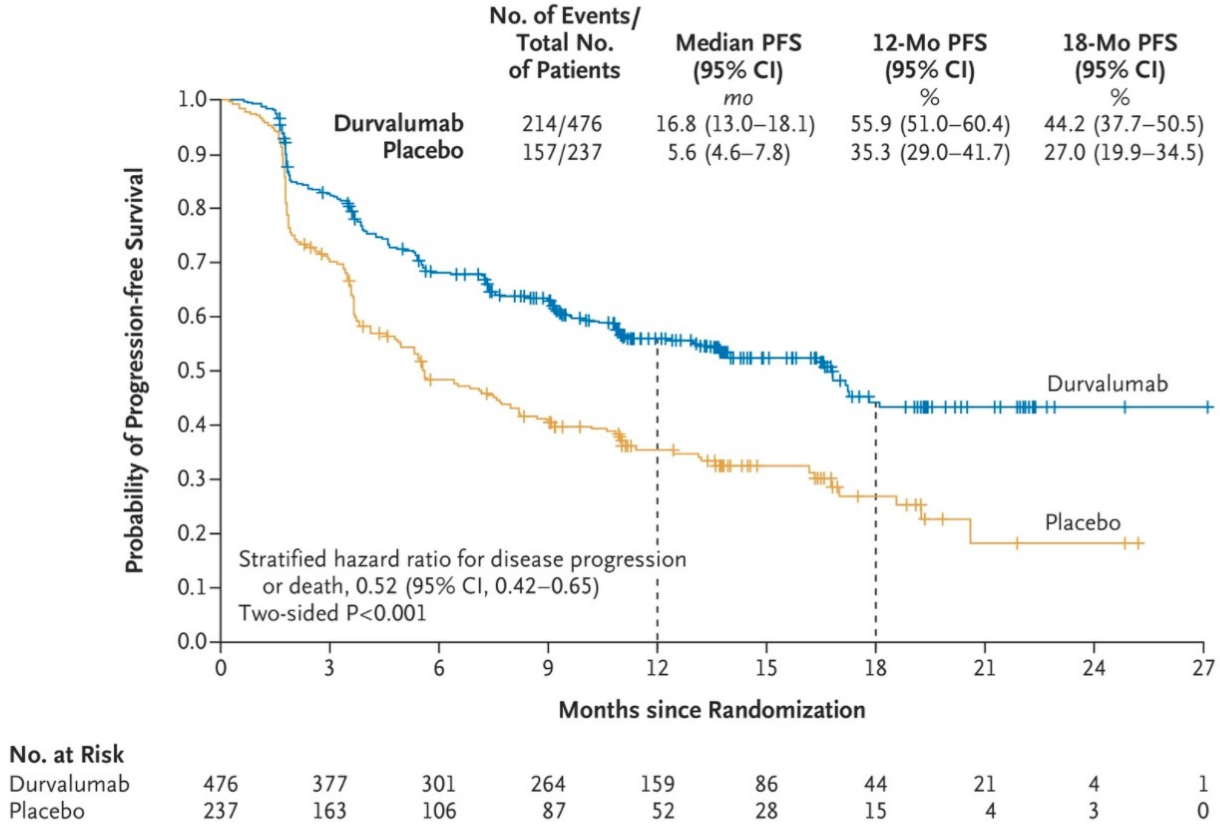
Early stage

Hypo FXSRT (2007) BED ≥ 100 Gy associated with better LC and OS

Locally advanced

RTOG 7301 (1980) 60 Gy as standard dose regimen
RTOG 0117 (2010) Dose limiting toxicity identified at 74 Gy
RTOG 0617 (2013) Dose escalation up to 74 Gy is detrimental for survival, same toxicity

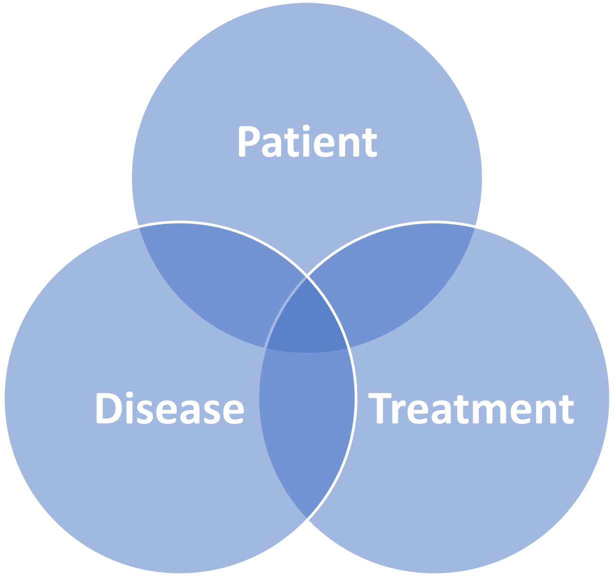
Lung cancer constraints: a matter of drugs?

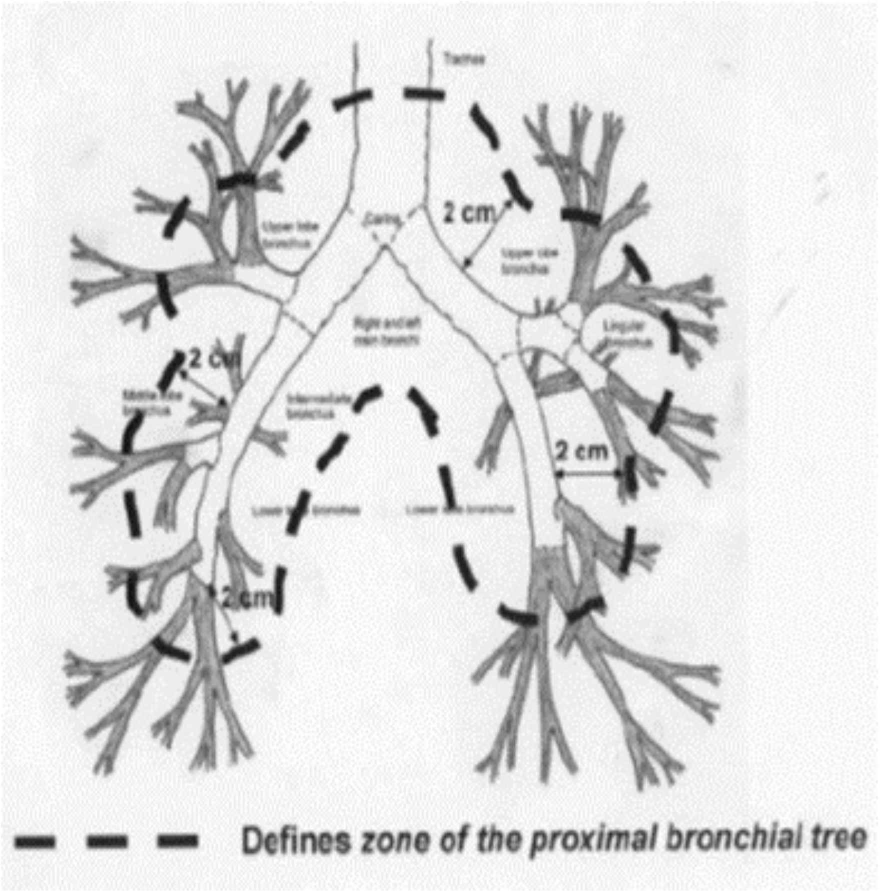


Antonia SJ et al. *N Engl J Med*. 2017;16.377(20):1919-1929

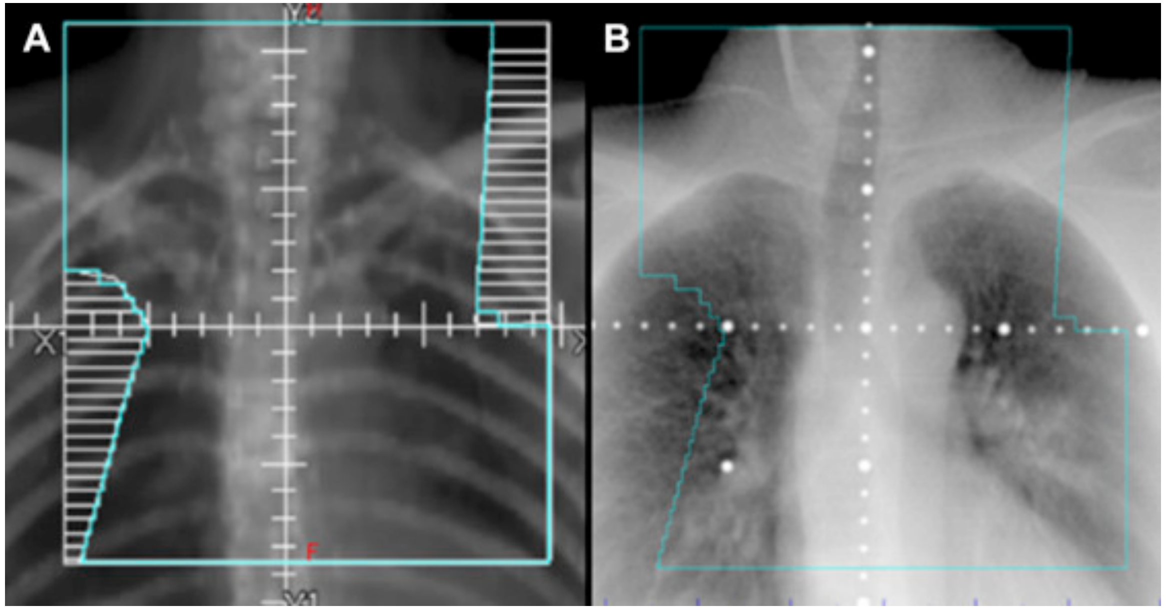
Lung cancer constraints: a matter of prescription?

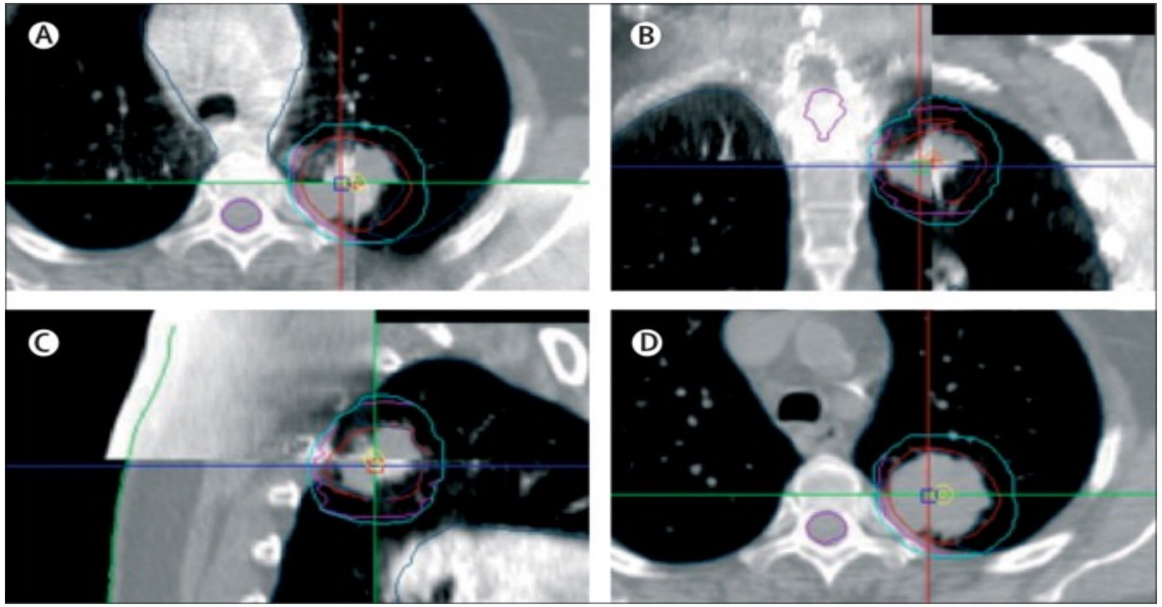
- Anatomy based prescription
- Risk adapted prescription
- Isotoxic prescription
- Isodose prescription





Lung cancer constraints: a matter of technology?





Lung cancer constraints: a matter of technology?

More **advanced technologies** (PET-CT planning, IMRT/VMAT, IGRT, motion management) have **better outcomes**

- **IMRT** associated with **60% reduction** of **high grade pneumonitis** (7.9%->3.5%) when compared to 3DCRT
- Appropriate **IGRT reduces toxicity** and is mandatory

Technique	RIP ≥ G2	Ref
2D	30-47%	Onishi 2003
3D	30-35%	Rehman 2014
IMRT	29-32%	Zhang 2019
VMAT	24-29%	Wu 2018
Protons	<5%	Chang 2017

Kasmann L et al, *Radiation Oncology* 2020
Brown S et al, *Br J Radiol* 2019

Tableau 3
Bénéfices dosimétriques et cliniques de la radiothérapie adaptative dans le cancer bronchique non à petites cellules.

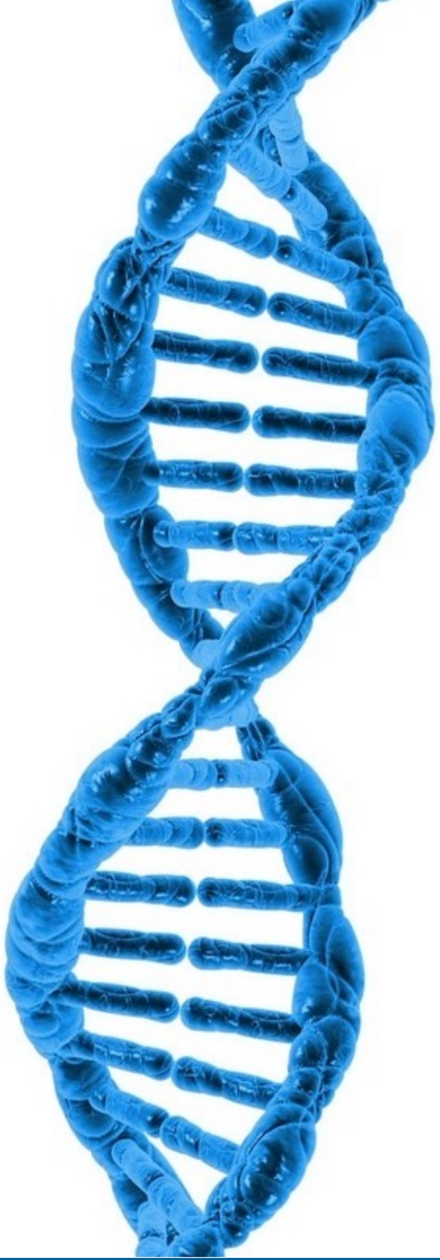
Auteur (année)	Nb pts	Techni-que RT	Dose/nb fx	Méthode RTA/nb plans de ttt	Imagerie pour RTA/fréquence	Bénéfices dosimétriques		Bénéfices cliniques	
						Volumes cibles	OAR	Contrôle et survie	Toxicité
Woodford et al. (2007) [45]	17	RCMI	60–64/30–32 fx	Replanification/-	MVCT/quotidienne	–	↓ dose aux poumons chez pts avec ↓ GTV ≥ 30 %	–	–
Feng et al. (2009) [48]	14	RC3D	46 Gy + boost/-	Replanification/2	TEP-scanner/à mi-ttt	Escalade de dose de 58 Gy	↓ NTCP de 0,4 à 3 %	–	–
Spoelstra et al. (2009) [49]	21	RC3D	≥ 46 Gy/-	Replanification/2	Scanner/à 15 fx	–	↓ PTV de 8 % chez 15 pts	–	–
Guckenberger et al. (2011) [50]	13	RC3D	66 Gy/33 fx	Replanification/2–3	Scanner/aux semaines 3 et 5	↑ TCP de 40 % par escalade de dose	–	–	–
Guckenberger (2011) [51]	13	RC3D	66 Gy/33 fx	Replanification/2–3	Scanner/aux semaines 3 et 5	Maintien de la couverture du GTV ↑ dose GTV de 66,8 à 73,6 Gy	↓ doses au poumon de 5 à 7,9 %	–	–
Weiss et al. (2013) [46]	10	RCMI	66 Gy/33 fx	Replanification/2–3	Scanner/aux semaines 2 et 4	Escalade de dose de 10,1 à 17,7 Gy ↑ TCP 23,4 %	–	–	–
Kataria et al. (2014) [52]	15	RCMI	44–46 Gy + 16–20 Gy/ 30–33 fx	Replanification/2	Scanner/à mi-ttt	↑ couverture du GTV	↓ PTV de 34,7 % ↓ doses : Poumon : 29,4 % Cœur : 35,2 % Moelle : 37,5 %	RC : 20 % RP : 80 % 2 décès liés à une progression à 11 mois	Oesophagite G2 : 30 % Pas de toxicité G ≥ 3
Tvilum v et al. (2015) [53]	52	RCMI	60–66 Gy/30–33 fx	Replanification/2	–/quotidienne	–	–	↑ CLR de 47 à 65 %	↓ pneumopathie sévère de 22 à 18 %
Dial et al. (2016) [54]	12	RCMI	63 Gy/35 fx	Replanification/-	–/mi-ttt, hebdomadaire et quotidienne	–	↓ doses aux poumons de 0,65 Gy, œsophage de 1,17 Gy, cœur de 0,37 à 0,99 Gy et moelle de 1,58 Gy	–	–
Kelsey et al. (2016) [55]	29	RC3D ou RCMI	60 Gy/30 fx	Replanification/2	TEP-scanner/à 25 fx	Escalade de dose chez 58 % pts	↓ doses aux poumons, œsophage et cœur	RC : 7 % RP : 83 % À 2 ans : PFS : 21 % OS : 32 %	Pas de toxicité de G ≥ 3 aiguë ou tardive excepté 1 IDM
Møller et al. (2016) [56]	63	RCMI	45–66 Gy/25–33 fx	Replanification/2	CBCT/quotidienne	↓ sous-dosage tumoral chez 75 % pts	↓ marges CTV-PTV ↓ Dmoy au poumon de 2 Gy	–	–
Kong et al. (2017) [57]	42	RC3D	–/30 fx	Replanification/2	TEP-scanner/à 40–50 Gy	Escalade de dose à 83 Gy	–	CLR à 2 ans : 62 % OS à 2 ans : 52 %	Toxicités G ≥ 3 : 28,6 % 4 décès
Ramella et al. (2017) [58]	50	RC3D	45–75 Gy/25–42 fx	Replanification/2	Scanner/hebdomadaire	–	–	CLR de 70 %	Toxicité G ≥ 3 : aiguë : 6 % chronique : 6 %
Xiao et al. (2017) [59]	17	RC3D ou RCMI	66 Gy/33 fx	Replanification/2	TEP-scanner/à 40 Gy	–	↓ doses aux poumons de 2,19 Gy, œsophage de 2,6 Gy, cœur de 3,92 Gy et moelle de 0,66 Gy	–	–
Zhong et al. (2017) [60]	7	RC3D ou RCMI	66 Gy/33 fx	Replanification/2	CBCT/hebdomadaire	Escalade de dose à 78,9–81,5 Gy	↓ doses aux poumons de 2,5 Gy	–	–

Briens A. et al. *Cancer Radiothérapie.* 2019;23:592–608

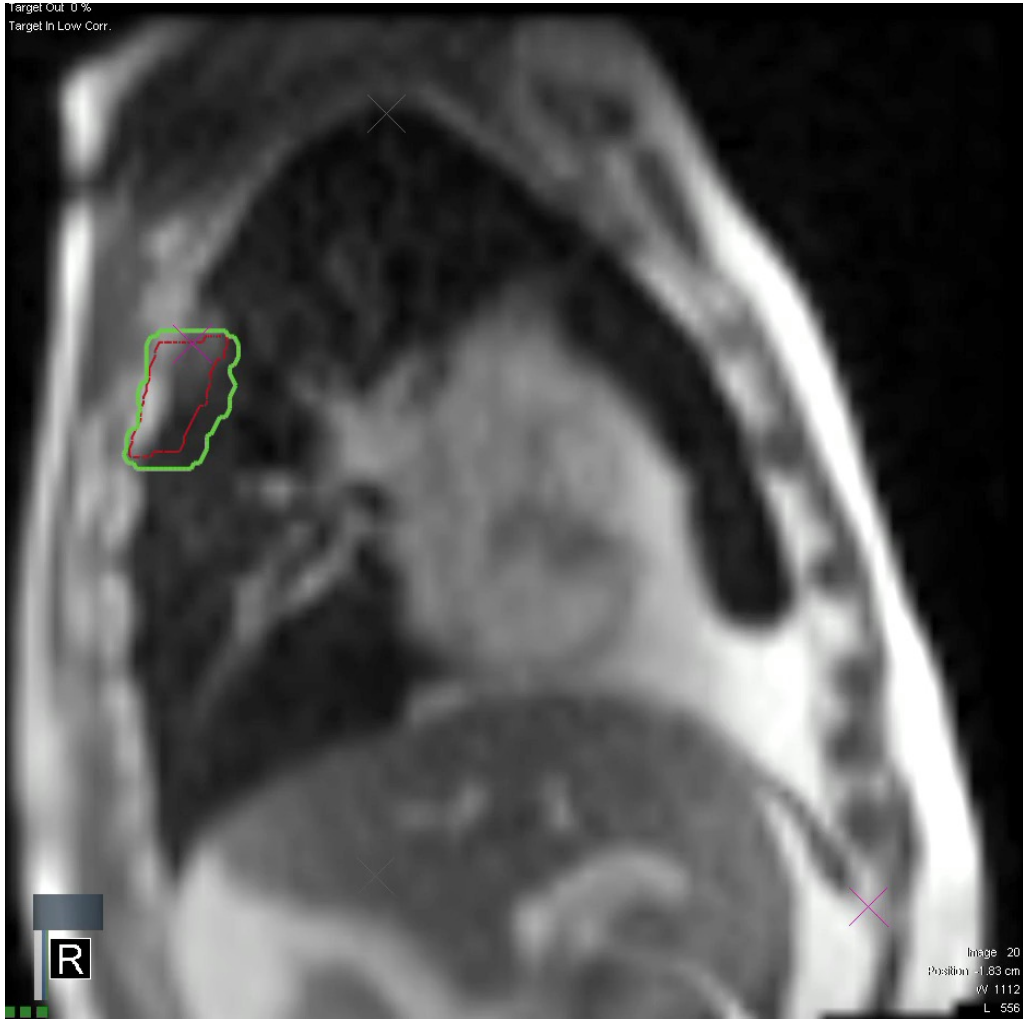
Lung cancer constraints: a matter of innovation?

MR-linac DNA

- **D**isruptive imaging
- **N**o extra dose
- **A**daptive online



- Higher risk for toxicity
- Central tumor location
- Significant tumor motion
- Pulmonary comorbidity



Lung
SBRT primary lesion

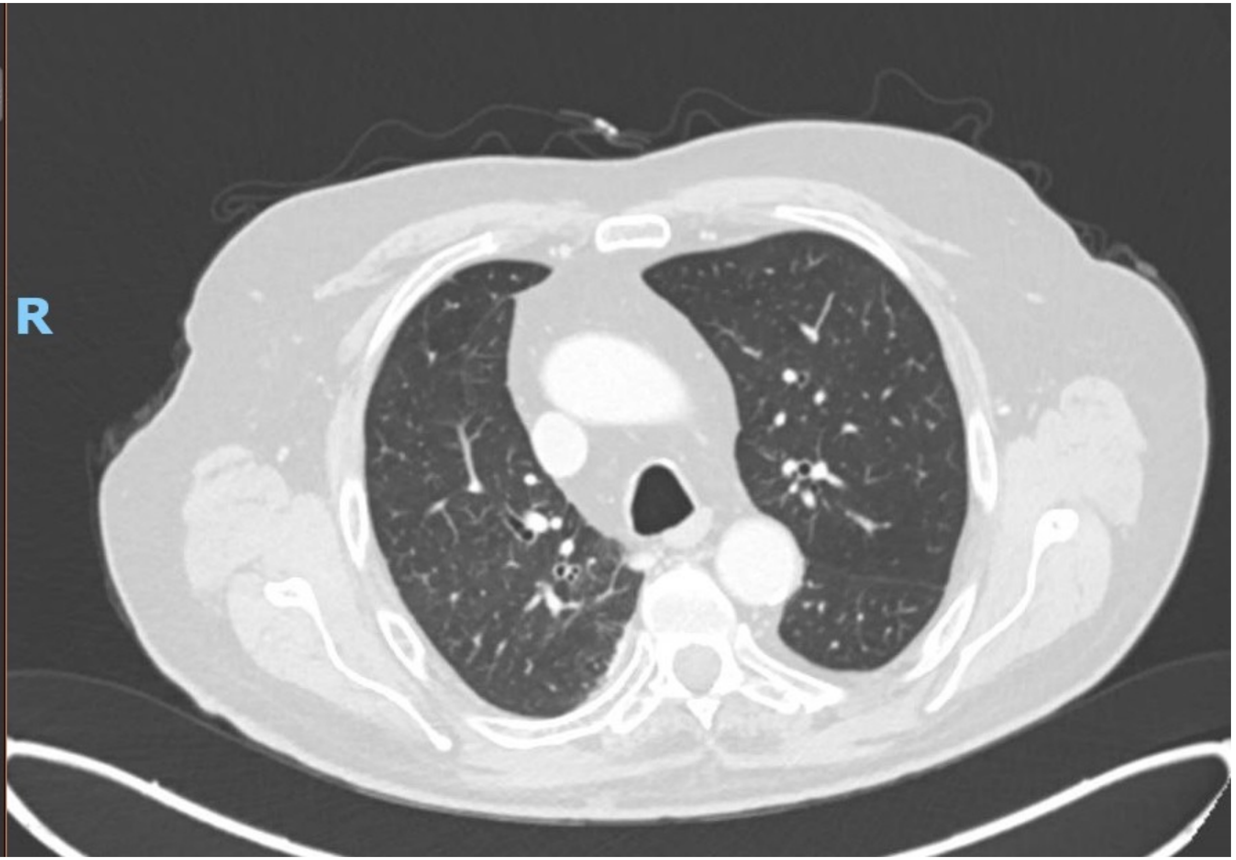
Inoperable primary lesion in 85 y.o. patient
50 Gy in 5 fractions (80% isodose)

Breathing phase: deep inspiration BH 4fps

ITV reduction in impaired parenchyma

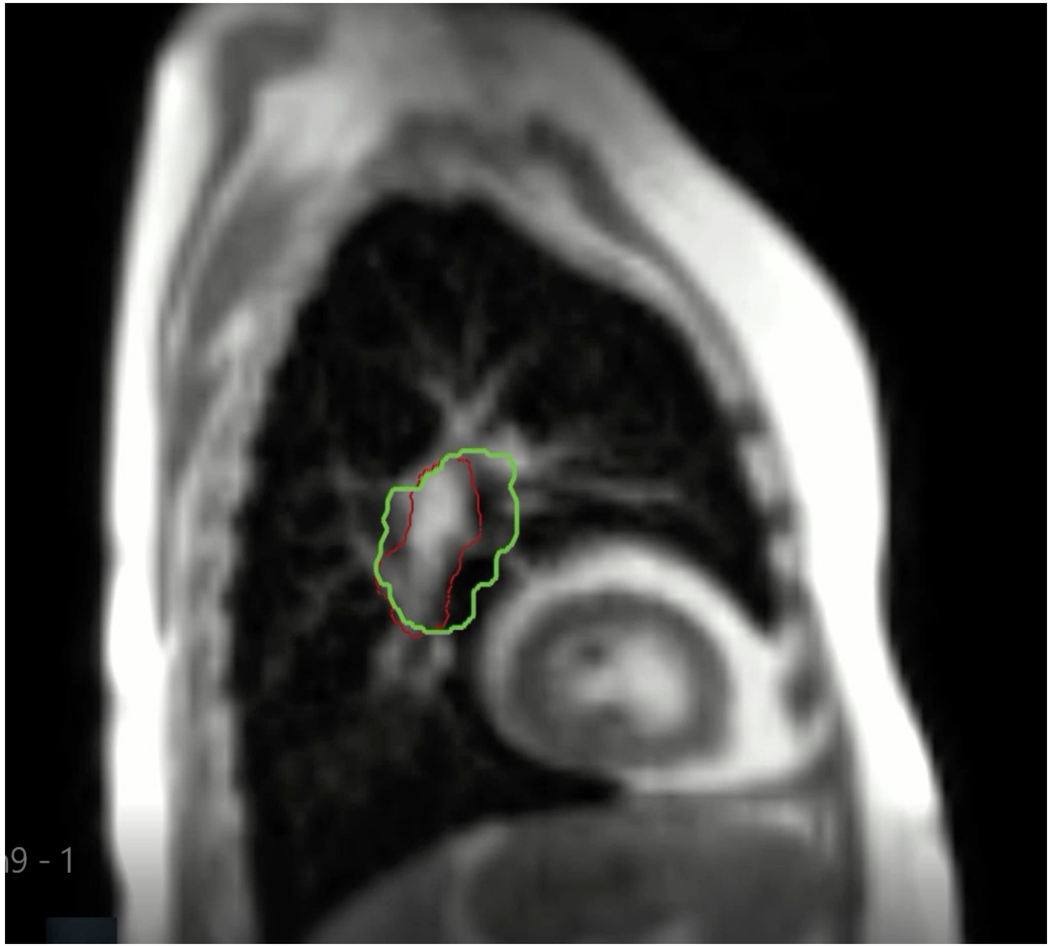
Feb 2017

Last FUP



early months FUP PET-CT negative

30 months FUP no signs of relapse/M



Lung
Radical treatment

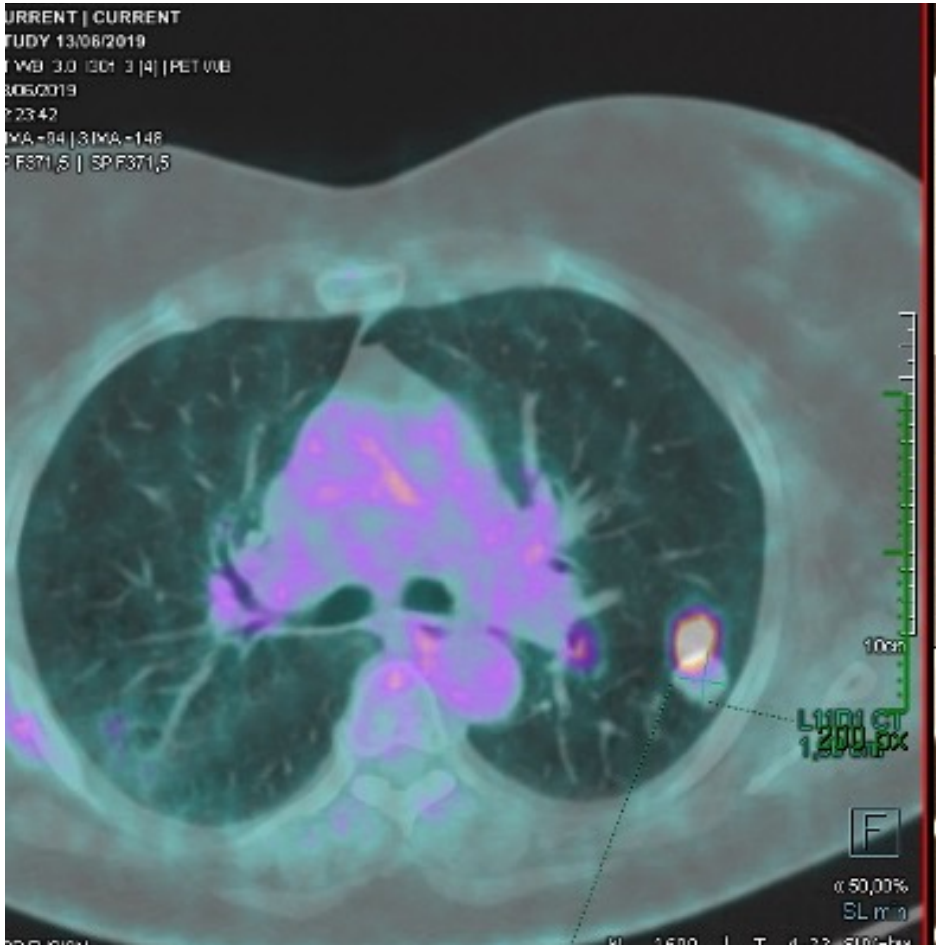
Small cell lung cancer - cT1cN2cM0 (IIIA)
in 59 y.o. patient
66 Gy in 33 fractions

Breathing phase: deep inspiration BH 8fps

RTOG 0617 : heart dose OS predictor
Metanalysis : V50 <25%

Speirs CK et al. J Thorac Oncol. 2017; 12:293-301

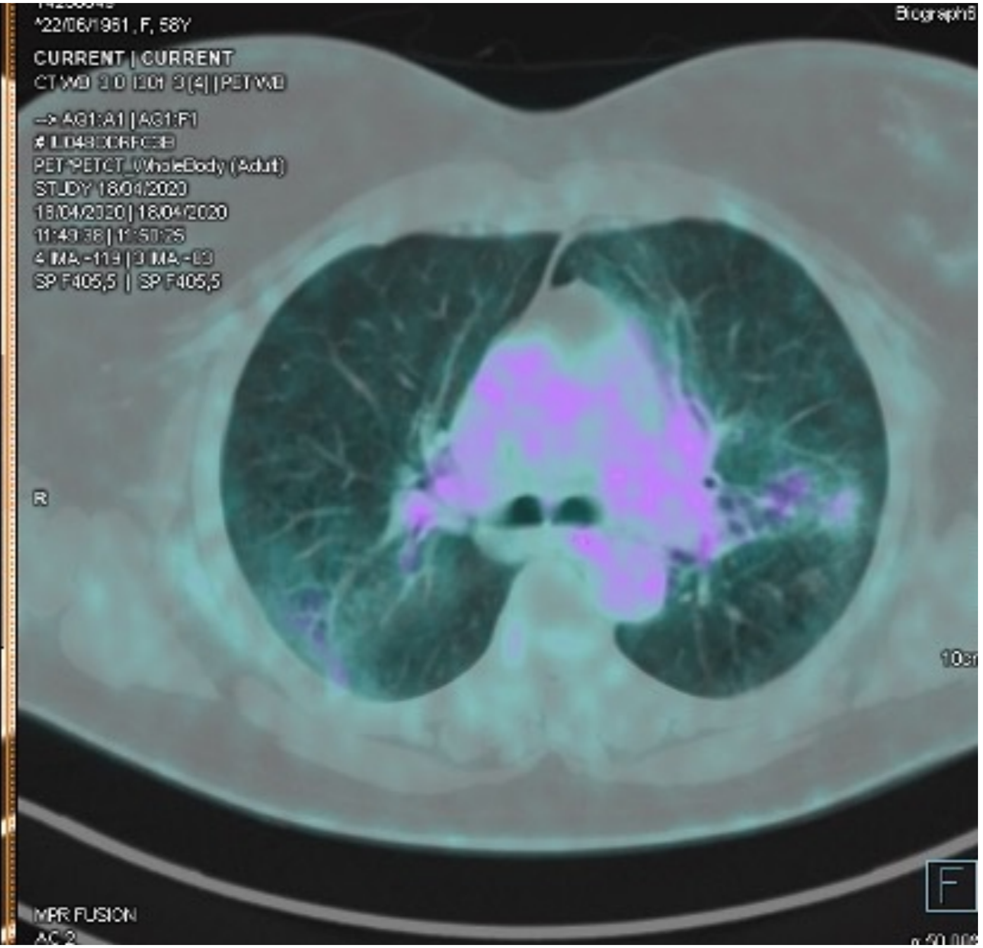
Jun 2019



4 months FUP PET-CT

7 months FUP

Apr 2020

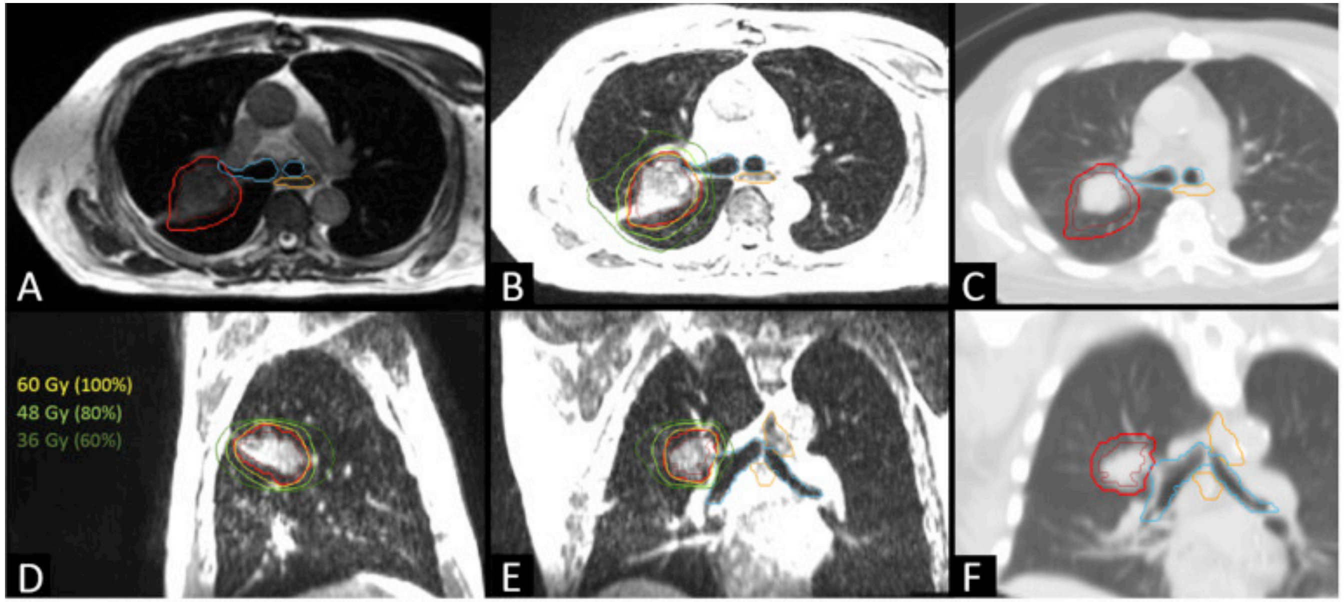


complete response

no signs of relapse/M

Innovative setting: adaptive MRgRT central lung tumors

25 pts
60 Gy in 8 fx (n=20) or
55 Gy in 5 fx (n=5)
Video-assisted, respiration-gated SMART



Toxicity profile

Reoptimized plan chosen in 92% of fractions (improved PTV coverage in 61% of fractions).
Reduction OAR planning constraint violations from 127 to 52 after reoptimization

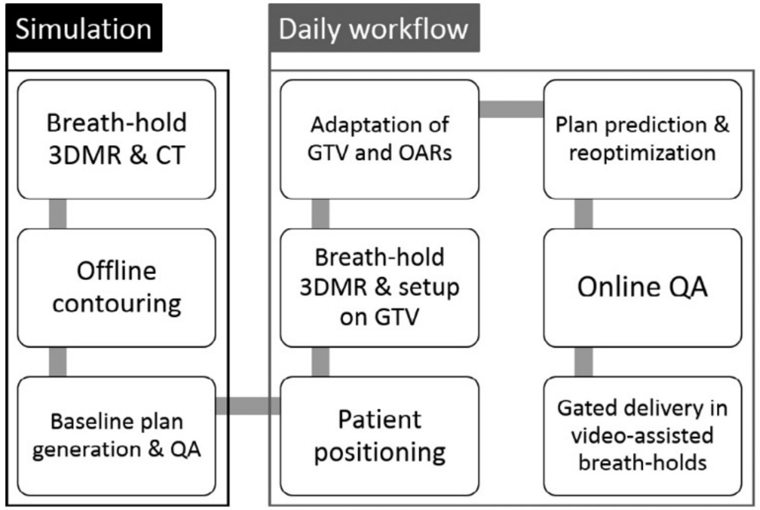
Finazzi T et al. Int J Radiat Oncol Biol Phys. 2019 Jul 15;104(4):933-941

Innovative setting: adaptive MRgRT peripheral lung tumors

25 lesions (23 patients)
3 × 18 Gy (3), 5 × 11 Gy (18), 8 × 7.5 Gy (4)
BH delivery - PTVs approximately half of ITV
12m LC and OS: 89.4% and 95.7%.
2 recurrences

Toxicity profile
OARs constraints varied based on tumor location, fractionation scheme and prior radiotherapy.

CTCAE Grade 2	chest wall pain (3)
	pleural effusion (1)
	radiation pneumonitis (1)
	fatigue (1)
CTCAE Grade 3	pneumothorax (1)



		Violations (112 fractions)	
OAR	**Objective**	**Predicted**	**Reoptimized**
Chest Wall	V60Gy ≤0.1cc	n = 7	n = 4
Chest Wall	Dmax 61 Gy	n = 3	n = 4
Chest Wall	Dmax 60 Gy	n = 2	n = 2
Chest Wall	Dmax 55 Gy	n = 2	n = 2
Chest Wall	Dmax 40 Gy	n = 0	n = 1
Chest Wall	Dmax 30 Gy	n = 2	n = 2
Spinal Cord	Dmax 13.5 Gy	n = 2	n = 0
Total		n = 18	n = 15

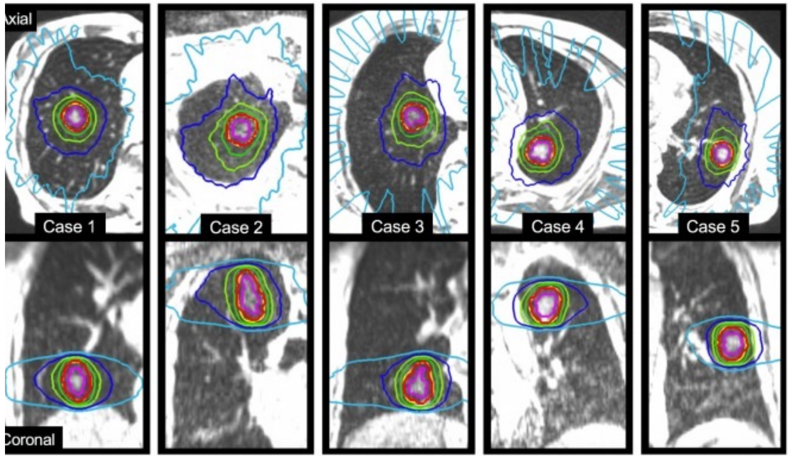
Finazzi T et al. Radiother Oncol. 2020 Mar;144:46-52.

Innovative setting: 34 Gy single fraction SBRT

10 patients affected by lung cancer (8) or M (2) with MRgART
BH gating with visual feedback (2 x 17 Gy plans)
RTOG 0915 study constraints

Case	Threshold-ROI%	Mean GTV_t coverage by the PTV during beam-on (5th–95th percentile)	Duty cycle efficiency	SABR delivery session (min)	Full SMART session (min)
1	10%–15%	99.0% (97.0–100.0%)	54%	38	74
2	10%	100.0% (100.0–100.0%)	85%	28	82
3	10%–15%	99.6% (98.7–100.0%)	34%	59	150
4	10%	99.9% (99.8–100.0%)	72%	34	86
5	10%–15%	99.3% (97.7–100.0%)	58%	36	102
6	10%–20%	99.2% (94.1–100.0%)	37%	57	143
7	10%	99.9% (99.6–100.0%)	52%	48	119
8	10%–15%	99.6% (97.9–100.0%)	56%	39	129
9	10%	99.9% (99.4–100.0%)	60%	37	120
10*	10%	99.9% (99.2–100.0%)	40%	66	185*

* Case 10 required SMART delivery in two sessions due to patient discomfort, and the total duration of both sessions is reported.



Toxicity profile

Median follow-up of 5 months (range 2-12)

CTCAE Grade 2 dyspnea worsening (1)
fatigue (1)

Finazzi T et al. *PhiRO*. 2020;(14):17-23

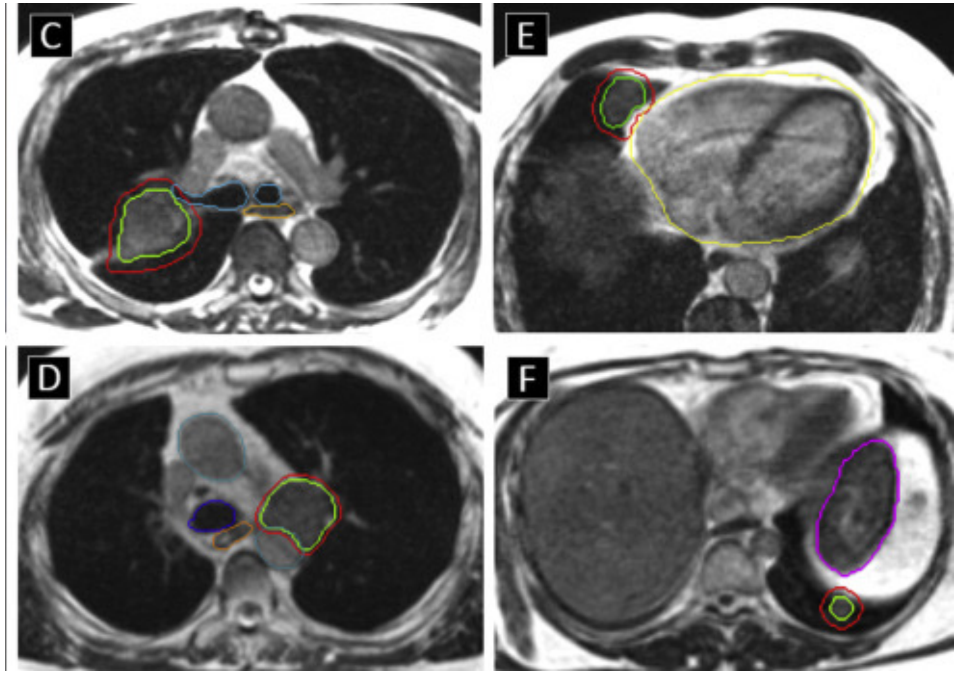
Innovative setting: adaptive MRgRT in high risk

MRgART SBRT lung lesions
50 patients (29 primary, 21 M)

High risk toxicity factors:
- central tumor location (n = 30)
- previous thoracic irradiation (n = 17)
- interstitial lung disease (n = 7)

BED ≥100 Gy to 95% PTV (different fractionations)
12mLC, OS and DFS: 95.6%, 88.0% and 63.6%
4 local failures

Toxicity profile
CTCAE Grade 2 30%
CTCAE Grade 3 8% (despite high risk factors)



Finazzi T et al. Int J Radiat Oncol Biol Phys. 2020 Jun 1;107(2):270-278.

Disease stage	Team	Machine	No. of patients	Tumor location	Fractionation schedule	Sequence used	Immobilization/ positioning	Adaption	Gating/ tracking	Couch time (min)
I/II	Thomas et al. 2018 (32)	MRIdian Cobalt-60	5	Peripheral and central	50–54Gy/3–4#	TrueFISP	NR	NR	Tracking	>20
	Padgett et al. 2018 (34)	MRIdian Cobalt-60	3 (1 primary lung)	Peripheral	50Gy/5#	NR	NR	To anatomy	NR	NR
	De Costa et al. 2018 (Abstract) (35)	MRIdian Cobalt-60	14 (11 primary lung)	NR	40–50Gy/5#	NR	NR	NR	Both	NR
	Henke et al., 2018 (17)	MRIdian Cobalt-60	5 (1 primary lung)	Ultra-central	50Gy/5#	NR	NR	To anatomy	Gating	Median = 69
	Finazzi et al. 2019 (36)	MRIdian Cobalt-60 or MR-Linac	23 (25 tumors - 14 primary lung)	Peripheral	54–60Gy/3–8#	TrueFISP	NR	To anatomy	Gating	Median from changing room to end of delivery: Cobalt-60 = 62 MR Linac = 48
	Finazzi et al. 2020 (37)	MRIdian MR-Linac	10 (8 primary lung)	Peripheral	34Gy/1#	TrueFISP	NR	To anatomy	Both	Median from changing room to end of delivery: 120
	Finazzi et al. 2020 (38)	MRIdian Cobalt-60 or MR-Linac	50 (29 primary lung)	Peripheral and central	54Gy–60Gy/3–12#	TrueFISP	NR	To anatomy	Both	Median from changing room to end of delivery: Cobalt-60 = 60 MR-Linac = 49
	Li et al., 2019 (Poster, 14th Elekta MR-Linac Consortium meeting)	Unity	1	Peripheral	56Gy/7#	T2 3D	Custom vacuum bag	ATP	Intermittent "motion monitoring"	<30
	Merckel et al., 2020 (Private correspondance)	Unity	10	Central/ ultra-central	60Gy/8–12#	T2 3D	Mattress, arms down	ATS	Nil	Median = 39

Crockett CB et al. Front Oncol . 2021 Mar 10;11:617681.

III	Straza et al., 2019 (Private correspondance)	Unity	1	Peripheral and central	60Gy/30#	4D Vane TFE	Vac fix, arms up	ATP	"Real-time monitoring"	30–35
IV	Padgett et al. 2018 (34)	MRIdian Colbalt-60	3 (2 oligo-metastases)	Peripheral and central	48–50Gy/4#	NR	NR	To anatomy	NR	NR
	De Costa et al. 2018 (Abstract) (35)	MRIdian Cobalt-60	14 (3 oligo-metastases)	NR	40–50Gy/5#	NR	NR	NR	Both	NR
	Henke et al. 2019 (17)	MRIdian Cobalt-60	5 (4 oligo-metastases)	Ultra-central	50Gy/5#	NR	NR	To anatomy	Gating	Median = 69
	Finazzi et al. 2019 (36)	MRIdian Cobalt-60 or MR-Linac	23 (25 tumors - 11 oligometastases)	Peripheral	54–60Gy/3–8#	NR	NR	To anatomy	Gating	Median from changing room to end of delivery: Cobalt-60 = 62 MR Linac = 48
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	Finazzi et al. 2020 (38)	MRIdian Cobalt-60 or MR-Linac	50 (21 oligo-metastases)	Peripheral and central	54Gy–60Gy/3–12#	TrueFISP	NR	To anatomy	Both	Median from changing room to end of delivery: Cobalt-60 = 60 MR-Linac = 49

An effort was made to include only the most recent data to avoid duplicate reporting of patients. NR, not recorded; ATP, Adapt To Position; ATS, Adapt To Shape; TFE, turbo field echo; TrueFISP, True Fast Imaging with Steady Precession.

Crockett CB et al. Front Oncol . 2021 Mar 10;11:617681.

Toxicity take home message

- **Toxicities** (such as RILI and/or lung fibrosis) are important **dose limiting factors** with direct impact on patient **outcomes** and **quality of life**.

- To take into account the **complexity of pulmonary toxicities**, optimal models should integrate:

  - Dosimetric variables
  - Technology
  - Individual risk factors such as age
  - Genetic polymorphisms
  - Pre-existing functional impairment of the lung
  - Chemotherapy regimens
  - Smoking status

  } **Adapted dose constraints**

- **Are we constrained by (current) constraints?**

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