MasterClass

Radioterapia
en cáncer de pulmón
2025

ORGANIZADO POR:

GRUPO ONCOLÓGICO ESPAÑOL
DE CÁNCER DE PULMÓN (GOECP)

GOECP

22
MAY
2025

4ª Sesión:
Protonterapia: un horizonte al alcance

Protonterapia:

un enfoque innovador y preciso en el tratamiento oncológico

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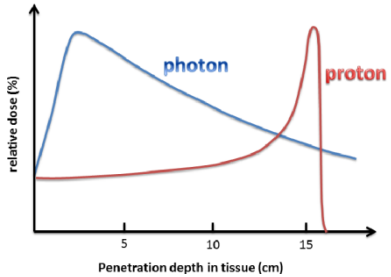
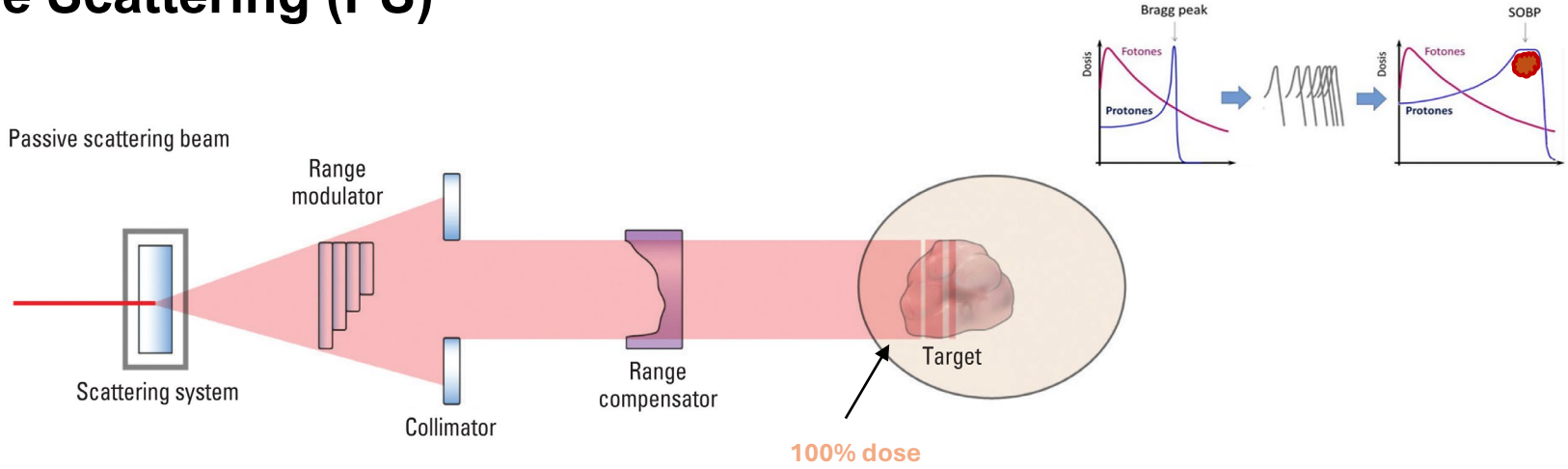
Rationale and potential benefits of proton theraphy for NSCLC

Rationale	Potential benefit
Reduce dose to normal tissue	Reduce treatment toxicities
Safer delivery of high-dose radiation to tumors close to critical organs (i.e. spinal cord or heart)	Increased chance of cure not attainable with photon treatment or chemotherapy alone, without attenuation of survival secondary to treatment toxicities (i.e. cardiovascular events)
Safer delivery of dose escalation	Improvement in local tumor control and survival
Allows for a safer combination of radiation therapy with chemotherapy and surgery for trimodality treatment	Improvement in local tumor control and progression-free survival compared with definitive radiation alone or bimodality chemoradiation
Safer treatment of locoregionally recurrent tumors with radiation in patients who previously had radiotherapy	Chance of cure not attainable with photon therapy or chemotherapy alone

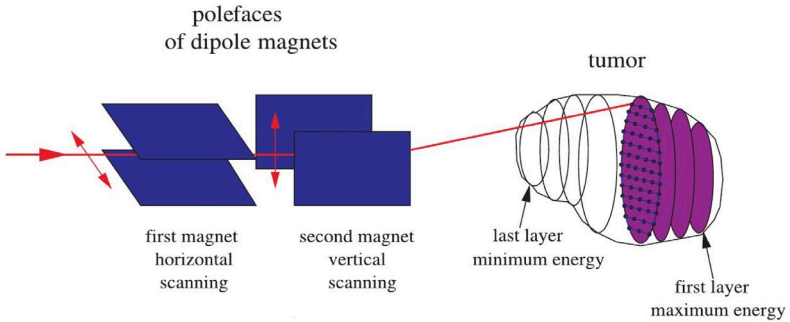


Pasive Scattering (PS)



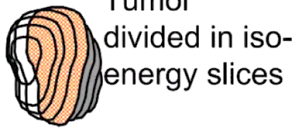
- Need for beam spreading elements to laterally and in-depth shape the beam
- Need for specific patient devices to conform the beam to the tumor

Pencil beam Scanning (PBS)



Optimized dose distribution

- **Better tissue sparing** (lungs, heart and esophagus) and superior **dose distribution conformality** both distal and proximal to the tumor.
- Allows for the delivery of intensity modulated proton theraphy **(IMPT)**



Absence of personalized accessories

- faster beam set-up
- neutron reduction at the patient level
- less radioprotection issues

ASTRO
AMERICAN SOCIETY FOR RADIATION ONCOLOGY

Group 2

While PBT is not a new technology, there is a need for continued clinical evidence development and comparative effectiveness analyses for the appropriate use of PBT for various disease sites. All other indications not listed in Group 1 are suitable for Coverage with Evidence Development (CED). Radiation therapy for patients treated under the CED paradigm should be covered by the insurance carrier as long as the patient is enrolled in either an IRB-approved clinical trial or in a multi-institutional patient registry adhering to Medicare requirements for CED2. At this time, no indications are deemed inappropriate for CED and therefore Group 2 includes various systems such as, but not limited to, the following:

THORACIC
Early-stage lung cancer in which a photon-based plan cannot meet the prespecified constraints or is associated with higher risk of toxicity
Locally advanced lung cancer

Early-Stage NSCLC: Central and Ultra-Central Tumors

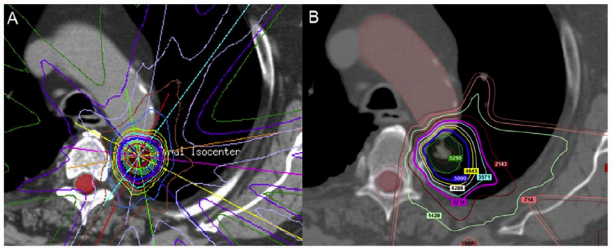
Phase 2 Study of Stereotactic Body Radiation Therapy and Stereotactic Body Proton Therapy for High-Risk, Medically Inoperable, Early-Stage Non-Small Cell Lung Cancer

CLOSED

	SBRT	SBPT
OS median	28 months	NR
OS (3-years)	27.8 %	90%
LC (3-years)	87.5%	90%
RC (3 –years)	47.6%	90%

*Medically inoperable NSCLC with **high-risk features** (centrally located or <5 cmT3 tumor or isolated lung parenchymal recurrences)*

50 Gy([RBE]) in 4 x 12.5-Gy/fracc. (9 SBRT vs 10 SBPT, PS)



- One patient in the SBPT group developed grade 3 skin fibrosis (only 3 fields)
- No patients experienced grade 4/5 toxicity.

Nantavithya, IJROBP2018

Early-Stage NSCLC: Large (> 5 cm)Tumors

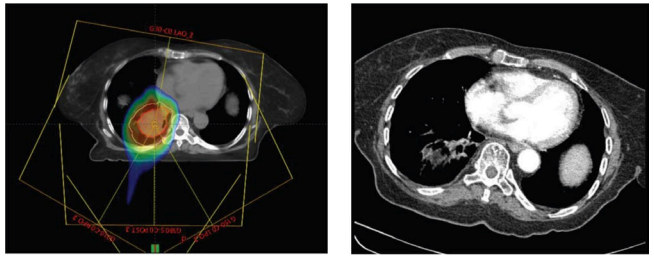
Comparison of particle beam therapy and stereotactic body radiotherapy for early stage non-small cell lung cancer: A systematic review and hypothesis-generating meta-analysis

72 SBRT studies and 9 hypo-fractionated PBT studies from North America, Europe and Asia

cT1-T3N0M0

PBT patients had larger tumors (2.92cm vs. 2.41cm, p=0.02) and more advanced T stages (T2-T3: 43% vs. 29%, p=0.05),

Toxicity type	PBT (N = 614) Events percentage (95% CI)	SBRT (N = 4805) Events percentage (95% CI)	*p* value
Grade 3–5 toxicity	4.8% (3.4%, 6.7%)	6.9% (6.1%, 7.9%)	0.05
Grade 5	0% (0%, 0.6%)	0.2% (0.1%, 0.4%)	0.41
Grade 4	1.8% (1.0%, 3.1%)	1.3% (1.0%, 1.6%)	0.34
Radiation Pneumonitis (≥grade 3)	0.9% (0.4%, 1.9%)	3.4 % (2.9%, 4.0%)	<0.001
Chest wall toxicity (≥grade 3)	1.9% (1.1%, 3.3%)	0.9% (0.6%, 1.3%)	0.03
Rib fractures	13% (11%, 16%)	3.2% (2.7%, 3.8%)	<0.001



- **PBT had improved OS** (5yOS 60% vs. 41.3%, p=0.05) **and PFS** (57.2% vs.37.7%, p=0.01) on univariate analysis.
- **3-year local control improved for PBT** on multivariate analysis (p=0.03).

Chi, Radiother Oncol 2017

Early-Stage NSCLC and Intrathoracic Oligometastatic disease:
Idiopathic Pulmonary Fibrosis and Interstitial Lung Disease

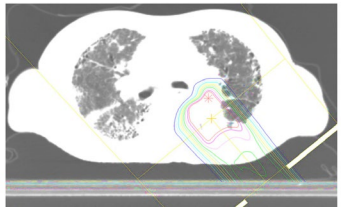
Preliminary result of definitive radiotherapy in patients with non-small cell lung cancer who have underlying idiopathic pulmonary fibrosis: comparison between X-ray and proton therapy

30/264 (11.4% IPF) 2010-2017

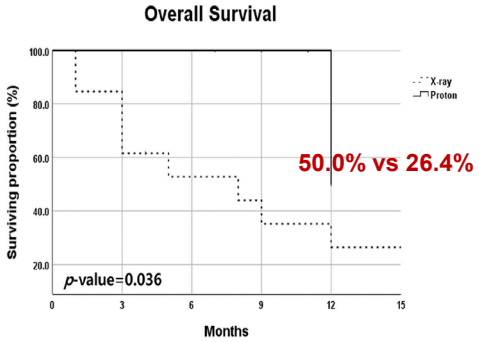
Survival outcomes in patients having IPF ($N = 30$)

Characteristics	X-ray ($n = 22$)	Proton ($n = 8$)	p value
All patients			
Treatment-related death	4/22 (18.2%)	0/8 (0%)	0.140
6 months OS	67.9%	100%	0.081
1 year OS	46.4%	66.7%	
GAP stage I	$n = 9$	$n = 1$	
6 months OS	88.9%	100%	0.501
1 year OS	76.2%	100%	
GAP stage II-III	$n = 13$	$n = 7$	0.036
6 months OS	52.7%	100%	
1 year OS	26.4%	50.0%	

IPF idiopathic pulmonary fibrosis, *OS* overall survival



patients with more advanced IPF (GAP) index stages II-III)



Kim, Radiat oncol 2019

Early-Stage NSCLC: Dose escalation

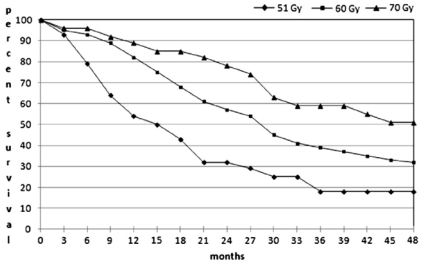
High-Dose Hypofractionated Proton Beam Radiation Therapy Is Safe and Effective for Central and Peripheral Early-Stage Non-Small Cell Lung Cancer: Results of a 12-Year Experience at Loma Linda University Medical Center

- Phase II proton dose escalation
- 111 early stage (T1-2N0M0) medically inoperable/refuse Sx

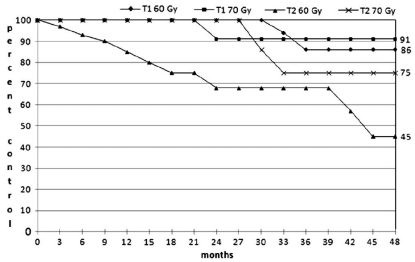
Table 1 Patient characteristics, n=111

Characteristic	n
Gender	
Male	59
Female	52
Age	
Mean	73.2
Range	53-91
T-Stage (6th edition)	
T1	47
T2	64
Tumor size (cm)	
Mean	3.6
Range	1.1-9
0-2	9
2-3	38
3-5	42
5-7	17
7+	5
Histology	
Adeno	39
Squamous	40
Large Cell	6
Unspecified	26
Location	
Right	63
Left	48
Upper lobe	66
Middle lobe	10
Lower lobe	35
Central	33
Peripheral	50
Dose	
51 Gy	29
60 Gy	56
70 Gy	26

OS according to dose



Local control by dose and T-stage

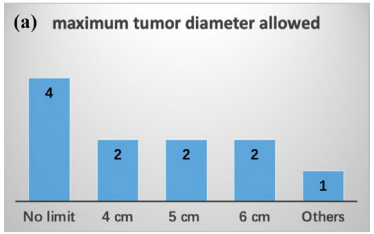


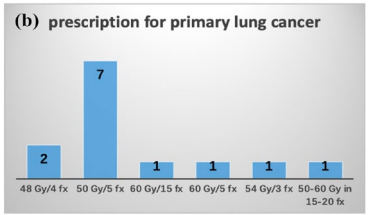
Conclusions: High-dose hypofractionated proton therapy achieves excellent outcomes for lung carcinomas that are peripherally or centrally located. The 70-Gy regimen has been adopted as standard therapy for T1 tumors at our institution. Larger T2 tumors show a trend toward improved outcomes with higher doses, suggesting that better results could be seen with intensified treatment.

Bush, IJROBP 2013

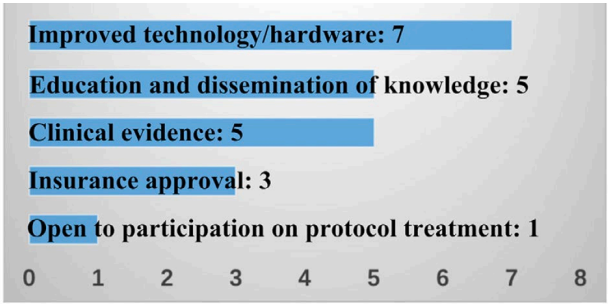
Particle Therapy Co-Operative Group

NRG Oncology and PTCOG Patterns of Practice Survey and Consensus Recommendations on Pencil-Beam Scanning Proton Stereotactic Body Radiation Therapy and Hypofractionated Radiation Therapy for Thoracic Malignancies

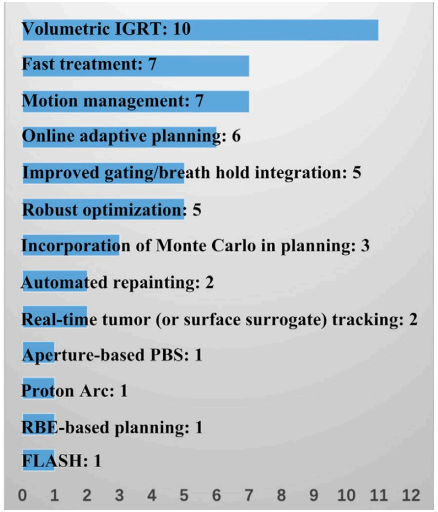




How can increase the use of proton SBRT in lung cancer treatment?



What are the most important technologies to improve lung tretament quality?



Liu, IJROBP 2024

Proton therapy trials for Locally Advanced- NSCLC

Title	ClinicalTrials.gov identifier	Status	Sponsor	Primary outcome
Phase III Randomized Trial Comparing Overall Survival After Photon Versus Proton Chemoradiotherapy for Inoperable Stage II-IIIB NSCLC	NCT01993810	Recruiting	RTOG	OS
Phase I/II Trial of Image-Guided, Intensity-Modulated Photon (IMRT) or Scanning Beam Proton Therapy (IMPT) Both with Simultaneous Integrated Boost (SIB) Dose Escalation to the Gross Tumor Volume (GTV) With Concurrent Chemotherapy for Stage II/III Non-Small Cell Lung Cancer (NSCLC)	NCT01629498	recruiting	MDACC	MTD
Proton Therapy to Reduce Acute Normal Tissue Toxicity in Locally Advanced Non-small-cell Lung Cancer	NCT02731001	Recruiting	TU Dresden	Acute and intermediate radiation induced side effects
A Phase I/II Study of Hypofractionated Proton Therapy for Stage II-III Non-Small Cell Lung Cancer	NCT01770418	Closed	PCG	Phase I: establish MTD Phase II: 1-year OS rate
Phase II Trial of Standard Chemotherapy (Carboplatin & Paclitaxel) +Various Proton Beam Therapy (PBT) Doses in Order to Determine the Optimal Dose of PBT for Unresectable Stage 2/3 Non-Small Cell Lung Cancer	NCT03132532	Recruiting	Mayo Clinic	PFS
Phase I Study of Hypofractionated Proton Radiation Therapy in Thoracic Malignancies	NCT01165658	Ongoing, not recruiting	MDACC	MTD
Feasibility and Phase I/II Trial of Preoperative Proton Beam Radiotherapy with Concurrent Chemotherapy for Resectable Stage IIIA or Superior Sulcus NSCLC	NCT01076231	Recruiting	UP/UMD	Feasibility, dose-limiting toxicity, pathologic complete response rate, late toxicity
Phase I Dose Escalation Trial of Proton Beam Radiotherapy with Concurrent Chemotherapy and Nelfinavir for Inoperable Stage III NSCLC	NCT01108666	Ongoing, not recruiting	UP	Feasibility, acute toxicity, late toxicity
Phase II Trial of Consolidation Pembrolizumab After Concurrent Chemotherapy and Proton Reirradiation for Thoracic Recurrences of Non-Small Cell Lung Cancer	NCT03087760	Recruiting	UP	PFS

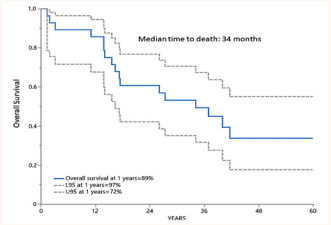
NSCLC, non-small cell lung cancer; RTOG, Radiation Therapy Oncology Group; OS, overall survival; MDACC, MD Anderson Cancer Center; MTD, maximum tolerated dose; TUD, Tehcnische Universität Dresden; PCG, Proton Collaborative Group; PFS, progression-free survival; UP, University of Pennsylvania; UMD, University of Maryland.

32 patients enrolled (28 met criteria)

- Dose ranged from 2.5-4 Gy for total dose of 60 Gy
- Concurrent platin-based doublet chemotherapy
- Median follow-up of 31 months
- Trial closed when PACIFIC trial survival results were available

✓ Majority of patients received 2.5 Gy (14) and PS (18)

✓ No acute grade ≥ 3 esophagitis, 14% grade ≥ 3 pulmonar toxicity

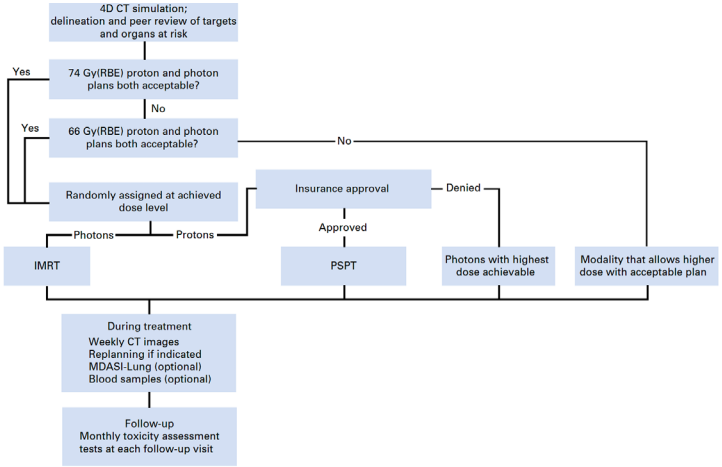


Hoppe, IJROBP 2022

Locally Advanced- NSCLC: Randomized data

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Bayesian Adaptive Randomization Trial of Passive Scattering Proton Therapy and Intensity-Modulated Photon Radiotherapy for Locally Advanced Non–Small-Cell Lung Cancer



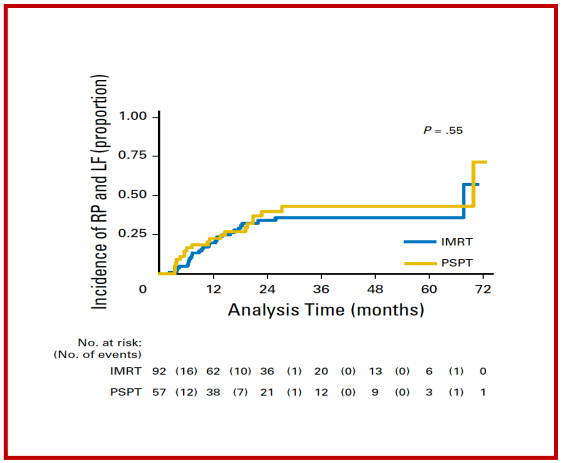
Stage II-IIIB and IV (single brain M1), recurrences after surgery (2009-2014)

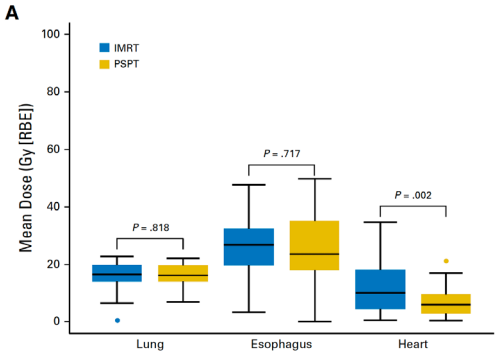
- **1º end points:** G≥ 3 radiation neumonitis or local failure

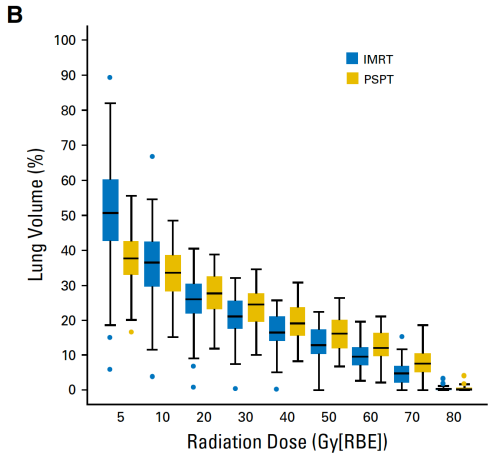
272 enrolled patients, 149 were randomly allocated to **IMRT** (n=92) or **PSPT** (n=57) (insurance denials, dosimetric differences)

Liao, JCO 2018

No statistically significant difference in the primary end points (grade ≥ 3 RP or LF) after IMRT or PSPT

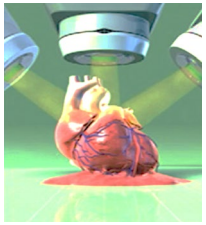




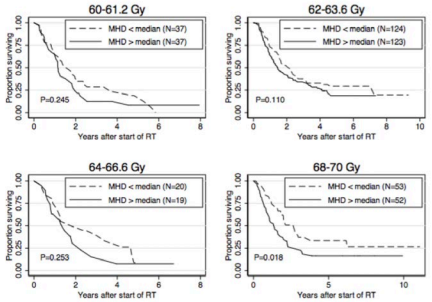


Liao, JCO 2018

Heart dose reduction with protons

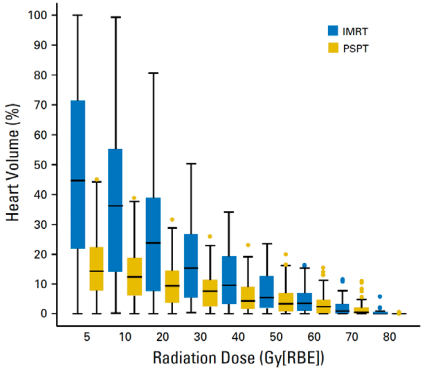


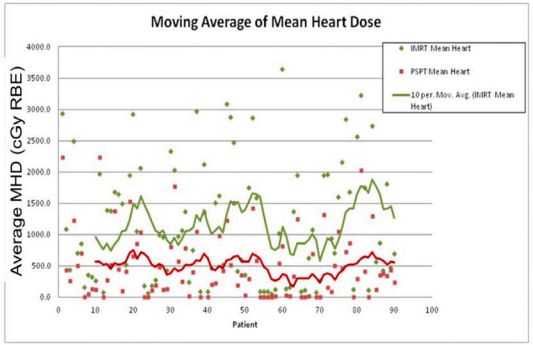
- 532 patients with NSCLC treated with concurrent chemoradiation
- **Mean Heart dose**: 22.3 Gy (3DCRT)
  5.1 Gy (IMRT)
  6.5 Gy (PBT)
- Retrospective multivariate analysis: mean heart doses > 25th percentile associated with increased risk of death (HR 1.4)



OS with mean heart dose above or below the median per RT dose subgroup

Liao ASTRO 2012





Liao, JCO 2018

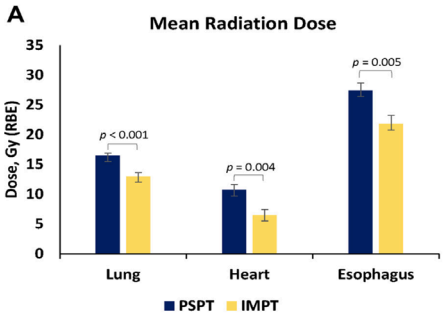
Some considerations !!

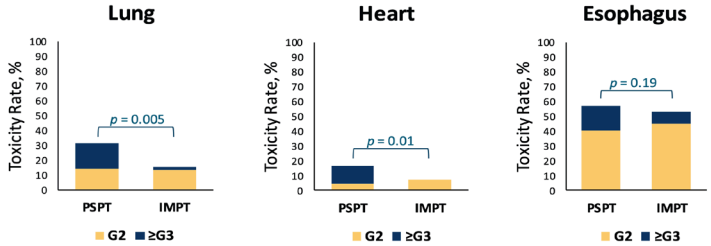
- All patients received **passive scattered protons**

IMPT vs Passive Scattering

- Non-randomized comparison of two prospective cohorts of **139** patients with stage II-IIIB and IV (solitary brain metastases)
- Concurrent chemotherapy and IMPT (53) or PSPT (86)

➢ IMPT had **lower mean lung , heart and esophagus doses**





➢ IMPT had lower rates of **grade ≥ 3 pulmonary and cardiac toxicities**

➢ IMPT had fewer **grade ≥ 4 toxicities** (0 vs. 7%)

➢ IMPT had **longer median OS** (36.2 vs. 23.9 months, p=0.09)

Gjyshi, J Th Oncol 2020

Scanning beam vs IMRT

64 patients (34 SPT + 30 IMRT)

Table 2 Dosimetric comparison between SPT and IMRT

Characteristic	All	Proton	IMRT	*P*
Prescription dose (Gy/CGE)	61.2 (50.4-74.0)	61.2 (50.4-74.0)	61.5 (50.4-66.6)	.820
Median target volumes, cm^3 (range)				
PTV	599.1 (94.10-1639)	607.9 (94.10-1243)	587.6 (135.30-1639)	.845
GTV	156.1 (1.39-647.8)	173.5 (1.39-486.3)	131.5 (28.16-647.8)	.445
CTV	370 (37.49-1202)	382.5 (37.49-729.3)	334.2 (45.81-1202)	.755
Lung-PTV				
Mean dose in Gy (CGE)	13.09 (1.28-19.77)	9.70 (4.87-17.53)	15.77 (1.28-19.77)	<.001
V5 (%)	39.14 (5.01-70.67)	29.02 (15.55-70.67)	57.53 (5.01-69.34)	<.001
V10 (%)	34.42 (3.41-55.19)	23.58 (13.86-47.19)	41.66 (3.41-55.19)	<.001
V20 (%)	24.69 (1.66-35.55)	18.81 (9.51-35.44)	27.98 (1.66-35.55)	<.001
V30 (%)	18.1 (1.10-27.17)	14.27 (4.22-27.17)	19.69 (1.10-26.82)	.015
Heart				
Mean dose in Gy (CGE)	11.65 (0-39.51)	6.95 (0-39.51)	14.04 (0-35.43)	.001
V5 (%)	32.16 (0-100.0)	22.12 (0-100)	55.44 (0-98.39)	<.001
V10 (%)	28.32 (0-99.80)	18.87 (0-99.80)	41.9 (0-85.60)	<.001
V20 (%)	19.98 (0-94.63)	14.49 (0-94.63)	26.68 (0-71.33)	.006
Esophagus				
Mean dose in Gy (CGE)	29.76 (10.78-60.43)	28.19 (10.78-54.14)	30.91 (17.67-60.43)	.023
V10 (%)	58.28 (30.39-98.50)	56.1 (30.39-97.06)	64.53 (37.99-98.50)	.007
V20 (%)	52.76 (16.46-95.18)	51.5 (16.46-95.18)	59.54 (34.89-94.10)	.028
V30 (%)	48.80 (13.57-93.49)	45.5 (13.57-93.49)	53.1 (18.5-90.88)	.038

Scanning Beam Proton Therapy versus Photon IMRT for Stage III Lung Cancer: Comparison of Dosimetry, Toxicity, and Outcomes

- **Reduced lung and heart dose** across most clinically relevant parameters
- Trend toward **lower grade ≥ 2 pneumonitis** rate with protons (40 vs .21%, p=0.107)
- **Greater use of immunotherapy** (44% vs 27%) in proton patients
- Long term impact of 50% reduction in mean heart dose with protons remains to be determined

Zhou, Advances Rad Onc 2020

Some considerations !!

- Futility with **74 Gy** was not yet known

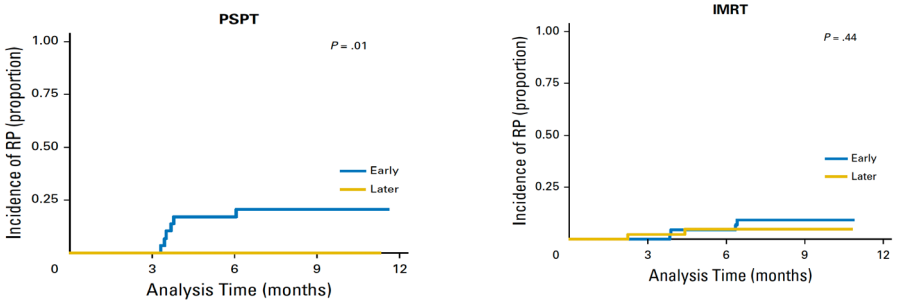
- **Arm imbalances**: proton target volumes were larger (p=0.071) and more patients received higher doses to tumors.

- The **study design** in terms of end point definition, control of confounding factors, and dealing with the lung dosimetric restriction

- **Clear learning curve**:

- Pneumonits G ≥3, was significantly lower in proton arm among patients who were enrolled after the trial mid-point .

- No such difference observed with IMRT



- **18%** of patients required **adaptive plans** during treatment (12% for IMRT and 29% for PSPT). Having a large tumor and receiving **PSPT** independently predicted the need for adaptive planning.

PHASE III RANDOMIZED TRIAL COMPARING OVERALL SURVIVAL AFTER PHOTON VERSUS PROTON CHEMORADIOTHERAPY FOR INOPERABLE STAGE II-IIIB NSCLC RTOG-1308

STRATIFY	RANDOMIZE		
Stage 1.II 2.IIIA 3.IIIB Histology 1.Squamous 2.Non-Squamous Concurrent Chemotherapy Doublet Type 1.Carboplatin/paclitaxel 2.Cisplatin/etoposide 3. carboplatin/ pemetrexed	Arm 1: Photon dose—70 Gy*, at 2 Gy (RBE) once daily plus platinum-based doublet chemotherapy** 158 Arm 2: Proton dose—70 Gy (RBE), at 2 Gy once daily plus platinum-based doublet chemotherapy** 172	Both Arms: Durvalumab or Consolidation chemotherapy x 2 cycles required for patients who receive concurrent carboplatin and paclitaxel***	

*The highest total prescribed dose will be 70 Gy (Relative Biological Effectiveness (RBE)) **without exceeding tolerance dose-volume limits of all critical normal structures**. The dose range can be 60-70Gy provided the dose constraints of OARs are met.

Primary Objectives:

1. Overall survival (OS)
2. Cardiac AE and lymphocyte reduction (lymphopenia)

Secondary Objectives:

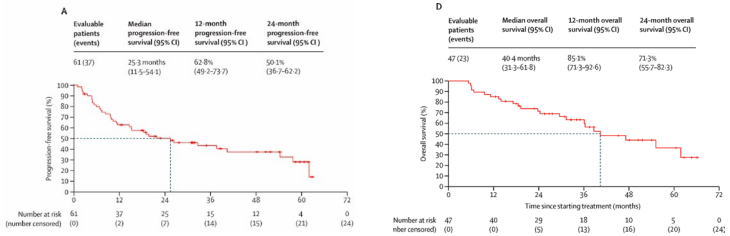
1. 2-year progression-free survival (PFS)
2. Grade ≥3 other AEs (definitely, probably, or possibly related to treatment)
3. QOL: primarily on the development of **shortness of breath** at 6 ms; and secondarily on the development of **sore throat** at the end of chemoRT (as measured by the MDASI-Lung), and breathing related functioning impairments as measured by the Shortness Breath Questionnaire [SOBQ];
4. Cost-effectiveness outcomes
5. Pulmonary function changes by treatment arms and response;
6. The most appropriate and clinically relevant technological parameters to ensure quality and effectiveness throughout RT processes,

Accrual completion: October 2023

Primary endpoint results: December 2026

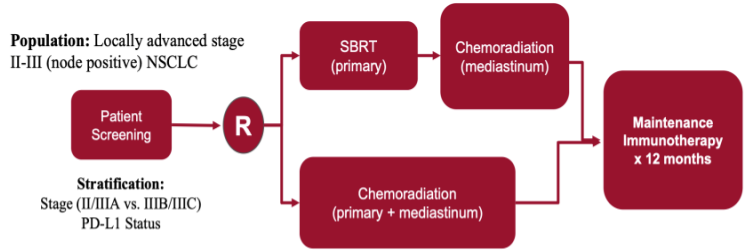
Primary lung tumour stereotactic body radiotherapy followed by concurrent mediastinal chemoradiotherapy and adjuvant immunotherapy for locally advanced non-small-cell lung cancer: a multicentre, single-arm, phase 2 trial

John H Heinzerling, Kathryn F Mileham, Myra M Robinson, James T Symanowski, Raghava R Induru, Gregory M Brouse, Christopher D Corso, Roshan S Prabhu, Daniel E Haggstrom, Benjamin J Moeller, William E Boba, Carolina E Fasola, Vipul V Thakkar, Sridhar E Pal, Jenna M Gregory, Sarah L Norek, Xhevahire J Begic, Aparna H Kesarwala, Stuart H Burri, Charles B Simone 2nd



Heinzerling, Lancet Oncol 2025

LU008 - Phase III Prospective Randomized Trial of Primary Lung Tumor Stereotactic Body Radiation Therapy Followed by Concurrent Mediastinal Chemoradiation for Locally-Advanced Non-Small Cell Lung Cancer



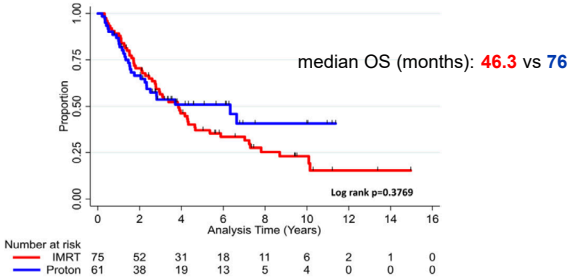
- Control arm: chemoradiation to the primary and mediastinal disease (60 Gy/2 Gy) → immunotherapy maintenance x 12 months
- Experimental arm: SBRT to the primary (standard BED ≥100 Gy dose regimen) → chemoradiation to mediastinal disease (60 Gy/2 Gy) → immunotherapy maintenance x 12 months
  - SBRT to primary tumor:
    - 3 fractions to 54 Gy (BED10 of 151.2 Gy) [peripheral]
    - 4 fractions to 50 Gy (BED10 of 112.5 Gy) [peripheral]
    - 5 fractions to 50 Gy (BED10 of 100 Gy) [peripheral or central]
  - Radiation to involved hilar/mediastinal lymph nodes: 2 Gy x 30 fx to 60 Gy, IMRT or proton therapy
  - Concurrent chemotherapy: carboplatin + paclitaxel, cisplatin + etoposide, cisplatin + pemetrexed, or carboplatin + pemetrexed
  - Maintenance immunotherapy: durvalumab x 12 months [if durvalumab is NOT given, carbo/paclitaxel pts receive 2 cycles of consolidation]

NRG ONCOLOGY™

Adjuvant Proton vs IMRT

136 patients : 61PBT (90% PSPT) and 75 IMRT

Variable	All Patients (n = 136)	IMRT (n = 75)	Proton (n = 61)	*P* Value
Max cord dose, Gy				
Median	7.20	8.97	3.10	< .001
Range	0-24.4	0.06-24.4	0-12.9	
Max esophagus dose, Gy				
Median	56.1	54.4	59.6	< .001
Range	0.9-102.1	0.9-102.1	47.4-79.2	
V50 esophagus				
Median	28.0%	28.3%	26.2%	.251
Range	0.0-80.0%	0.3%-80.0%	0.0-60.0%	
Mean esophagus dose, Gy				
Median	21.6	22.0	19.2	.345
Range	0.2-47.5	0.2-47.5	4.5-43.3	
Mean lung dose, Gy				
Median	9.50	10.4	7.90	.014
Range	0.8-25.7	2.2-25.7	0.9-20.7	
V5 lung				
Median	35.0%	42.0%	23%	< .001
Range	1.0%-70.0%	10.0%-70.0%	10.0%-40.0%	
V10 lung				
Median	27.0%	30.0%	20.0%	.002
Range	1.0%-50.0%	7.0%-50.0%	1.0%-40.0%	
V20 lung				
Median	17.0%	18.0%	16%	.124
Range	0.2%-40.0%	2.0%-40.0%	0.2%-30.0%	
Mean heart dose, Gy				
Median	5.23	7.42	2.00	< .001
Range	0.0-41.7	0.1-41.7	0.0-15.2	
V30 heart				
Median	8.0%	11.0%	3.0%	< .001
Range	0.0-60.0%	0.1%-60.0%	0.0%-20.0%	



- Total toxicity burden (grade ≥2 pneumonitis, cardiac or esophageal toxicity) **was lower with PBT** (OR 0.35; 95% CI 0.15-0.83; p=0.017)
- V30 heart and V5 lung were **the only factors associated with OS** on multivariate analysis

Boyce-Fappiano, Clin Lung Cancer 2021

Potential value in the era of immunotherapy

Radiation-induced lymphopenia risk model predicts durvalumab benefit in non-small cell lung cancer

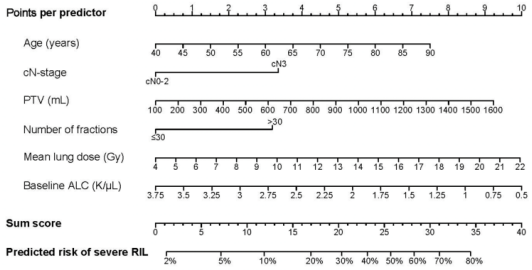
Peter S.N. van Rossum, MD, PhD[1,2], Pim J .J . Damen, MD[1,2], Ting Xu, PhD[1], Brian P. Hobbs, PhD[3], Zhongxing Liao, MD[1], Radhe Mohan, PhD[1], Steven H. Lin, MD, PhD[1].

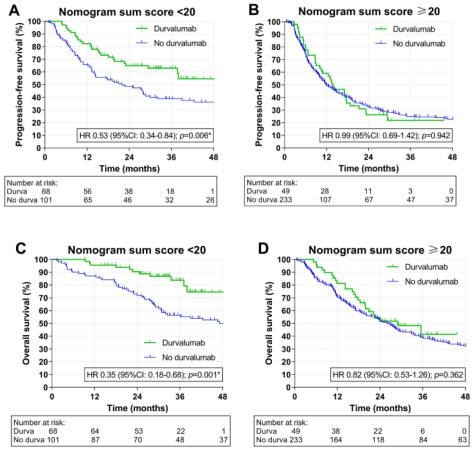
1. The University of Texas MD Anderson Cancer Center, Houston (Texas), United States of America. 2. Amsterdam UMC, location VUmc, Amsterdam, The Netherlands. 3. Dell Medical School, The University of Texas at Austin, Austin (Texas), United States of America.

Severe RIL was defined as a lowest ALC during CRT (ALCnadir) of <0.24 K/µL.

164/451patients **(36%) experienced severe RIL.**

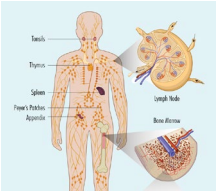
A nomogram was created with a sum score ranging from 0 to 40





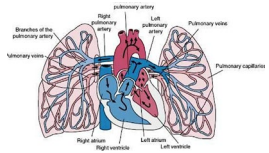
- Adjuvant durvalumab benefit was observed only in patients with a **low predicted risk of severe RIL**, not in high risk patients
- Prediction model has the potential to select high-risk patients who may benefit from lymphopenia-mitigating strategies to improve immunotherapy efficacy and survival.

LOAR
(lymphocyte related organs at risk)



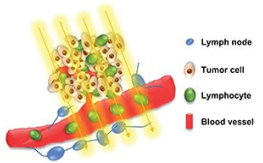
- Lower lymphocyte nadirs during definitive RT were associated with **larger GTVs** and worse patient outcomes.
  Tang, IJROBP 2014

- Therere is a negative correlation between **body integral dose and mean lung and heart dose**, and post-treatment decline in ALC, which is an adverse prognostic factor in lung cancer.



- **Heart V50 >25%** were associated with a higher NLR 4 months post-RT and worse patient outcomes.
  Contreras, Radiother Oncol 2018

- Severe lymphopenia during RT is a significant poor prognostic factor for OS in lung cancer patients and could be mitigated by minimizing **vertebrae V20, mean lung and heart dose.**
  Abravan, J Th Oncol 2020

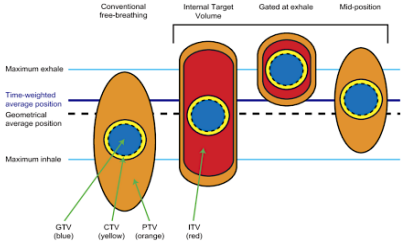


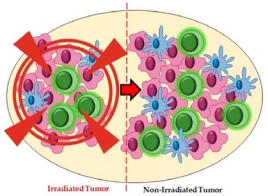
- **Baseline ALC** is strongly associate with severe radiation-associated lymphopenia and it was related to OS and PFS
  Joo, IJROBP 2016; Abravan, J Th Oncol 2020

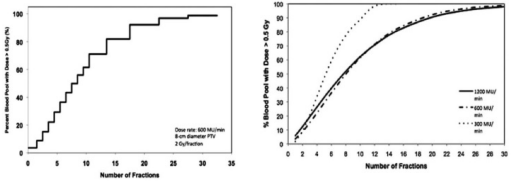
- **EDIC** is associated with inferior disease outcomes, treatment-related toxicity, and the development of severe lymphopenia.
  Friedes Radiat Oncol 2024

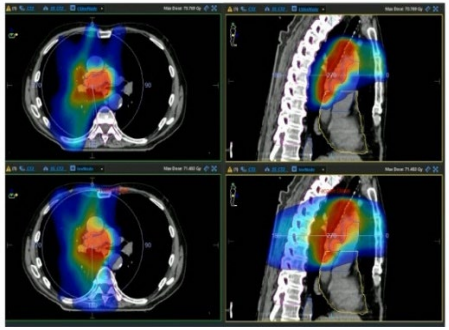
Lymphocyte sparing radiotherapy

- **Reduced planning target volume (PTV):** IGRT, Gating/tracking
- **Partial tumor irradiation (SFRT)** (bystander effect)
- **Hypofractionation**

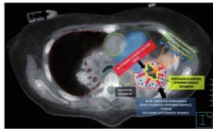


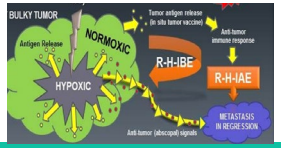




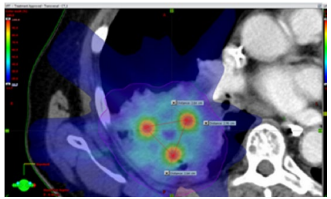


PATHY





GRID/ LATTICE

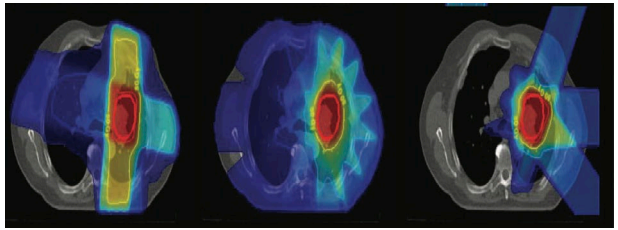


- A single fraction delivered 0.5 Gy to 5% of circulating cells
- **30 fractions expose 99% of circulating blood to ≥ 0.5 Gy**

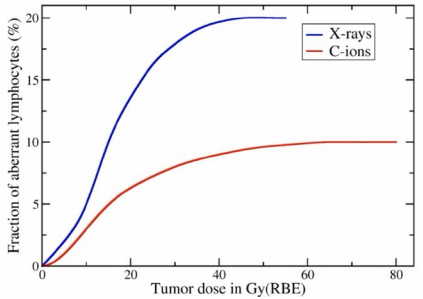
Yovino, Cancer Invest 2013

Charged particle may better spare lymphocytes

- Radiation field sizes can dramatically impact responses to immunotheraphy
  - Large field irradiation may impair responses to immunotherapy
  - Irradiation of lymph nodes can decrease immune cell infiltrates into tumors

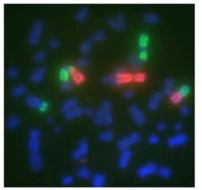


Roelofs, J Thorac Oncol 2012



Reduced integral CIRT to healthy tissue

Result: circulating blood lymphocytes are better spared and are available for an efficient immune response

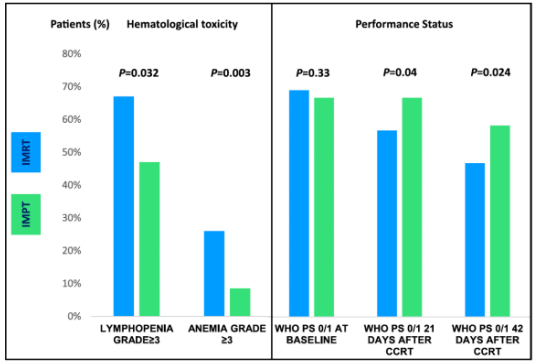


Durante, IJROBP 2000

Original Article

Proton and photon radiotherapy in stage III NSCLC: Effects on hematological toxicity and adjuvant immune therapy

1º endpoint: the incidence of lymphopenia G≥ 3 in IMPT vs IMRT



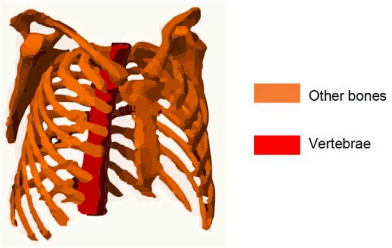


Fig. 1. Bone marrow delineation.

Durvalumab eligibility and safety after IMPT or IMRT.

Characteristics	IMPT (n = 51)	IMRT (n = 77)	Total (*N* = 128)	*P* value
Median time from end CCRT start Durvalumab – days (range)	31 6–97	41 10–156	37 6–156	**0.013**
Durvalumab within 14 days – %	12	4	7	0.09
Durvalumab within 28 days – %	40	25	30	0.057
Durvalumab within 42 days – %	72	51	57	**0.015 OR 2.57 (95 % CI: 1.19–5.5)**
All grade irAEs	29.4	36.6	33.6	0.87
Grade ≥ 2 irAEs	21	26	24.2	0.36
Grade ≥ 3 irAEs	5.9	7.8	7	0.48
Grade ≥ 4 irAEs	0	0	0	–
Immune related pneumonitis	9.8	7.8	8.6	0.48
All cause pneumonitis during Durvalumab (Grade ≥ 2)	23.5	22.1	22.7	0.51

IMPT was associated with a lower incidence of severe lymphopenia and anemia, better PS after CCRT and a higher probability of receiving adjuvant durvalumab.

Cortiula?Radiat Oncol.8680

Increased antigenicity ?

- Photon RT has ben shown to induce mutational neoatigens that function as targets for CD8+ T cells
- Proton RT **differential cell death pattern**
- Protons shows **unique molecular and celular responses** compared to photon, e.g induction of more complex DNA damage, differential gene expression, and epigenetic modulation and induction of distinct signaling pathways
- Proton RT might further **improve the mutagenic landscape** of tumors with **low mutattional burden**

Ritter and Durante, Mut Res 2010

Table 1. Currently ongoing or initiated clinical trials regarding proton RT (PrRT) and carbon ion RT (CIRT) in combination with immunotherapy (IO).

	Identifier	Pathology	RT Dose	IO	Dose	Status	Study Type
PrRT	NCT02648997	Meningiomas	Unknown	Nivolumab * Ipilimumab *	N: 1 mg/kg for 3 weeks I: 3 mg/kg for 3 weeks	Recruiting	Open-label Phase-II
	NCT03267836	Meningiomas	fRT; 5 × 0.04 Gy Total 0.2 Gy	Avelumab *	Concurrent RT, 10 mg/kg, every 2 weeks for 3 months	Recruiting	Phase I
	NCT03539198	Head and neck cancer	fRT; 5× Total 35–45 Gy	Nivolumab *	Before and after RT, Q2/week for 2 weeks	Recruiting	Observational
	NCT03764787	Unknown	Unknown	a-PD-1	Unknown, for 1 year	Not yet recruiting	Phase I/II
	NCT03765190	Neoplasm metastasis	Unknown	a-PD-1	Unknown	Not yet recruiting	Phase I/II
	NCT03818776	Non-small cell lung cancer	fRT; 20–23× Total 60–69 Gy (cardiac sparing)	Durvalumab	1500 mg QW, max. 12 months (to 13 doses/cycles)	Recruiting	Early Phase I
	NCT03087760	Non-small cell lung cancer	Reirradiation, unknown	Pembroluzimab	Unknown	Recruiting	Phase II
	NCT02444741	Non-small cell lung cancer	fRT, 15× low dose, Total unkown	Pembroluzimab	Unknown dose for 21 days, up to 16 cycles	Recruiting	Phase I/II
	Identifier	Pathology	RT Dose	IO	Dose	Status	Study Type
CIRT	NCT04143984	Locally recurrent nasopharyngeal carcinoma	fRT; 21 × 3 Gy Total 63 Gy	Camrelizumab *	C: 200 mg i.v. every 2 weeks for a year maximum	Not yet recruiting	Phase II/III
CIRT	NCT03705403 **, [102]	Non-small cell lung cancer	SABR	Darleukin	C: 15 Mio IU, 6 cycles, 3 infusions within one cycle, every 3 weeks	Not yet recruiting	Phase II

* Nivolumab and durvalumab are PD-L1 antibodies, ipilimumab is a CTLA-4 antibody, pembroluzimab, avelumab and camrelizumab are PD-1 antibodies, darleukin is the immunocytokine L19-IL2. ** CIRT treatment arm is currently being under consideration by BfS (Federal Office for Radiation Protection, Germany). fRT: fractionated RT, Q: dose per week (Q4 is 4 doses a week), i.v.: intravenous administration.

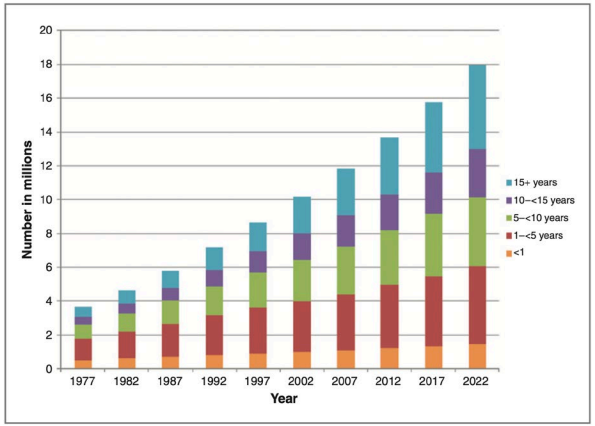
CIRT	NCT05229614	Non Small Cell Lung Cancer Head and Neck Squamous Cell Carcinoma Melanoma Urothelial Carcinoma	fRT; 3 x 8 Gy[RBE] Total 24 Gy [RBE]	Pembrolizumab (unknown dose)	Not yet recruiting	Phase II

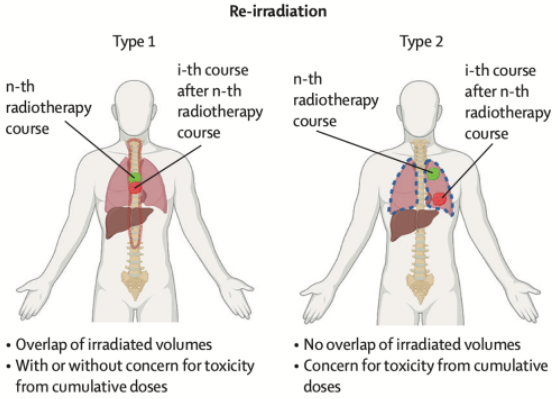
Marcus, Cancers 2021

Relevance for Protons in the era of immunotherapy

- reduction in acute adverse events involving peripheral organs **may facilitate ICI** introduction and continuous administration.
- reduction in hematopoietic bone/normal LN exposure may **prevent immune deficiency**
- more potent antitumor effects may lead to **increased immune antigen presentation**
- extensive tumors that are difficult to treat by photons **can be treated.**

Re-irradiation





Estimated and projected number of cancer survivors in the United States from 1977 to 2022 by years since diagnosis.

de Moor, CEBP 2013

Re-irradiation for recurrent NSCLC

Reference	Sample size	Technique	Reirradiation dose [Gy (RBE)]	Median time to reirradiation	Patients with concurrent chemotherapy	Median follow-up	Outcomes	Grade ≥3 toxicities
McAvoy *et al.* (74) [2013]	33	PSPT	66 Gy (RBE) in 32 fractions	17 months	24%	11 months	1 yr: OS 47%, PFS 28%, DMFS 39%	9% grade ≥3 esophageal, 21% grade ≥3 lung
McAvoy *et al.* (76) [2014]	102	PSPT, IMRT	60.48 EQD2 Gy	36 months	33%	6.5 months	2 yr: OS 33%, DMFS 37%, LFFS 34%	7% grade ≥3 esophageal, 10% grade ≥3 lung
Chao *et al.* (77) [2017]	57	PSPT, IMPT	66.6 Gy	19 months	68%	7.8 months	2 yr: OS 43%, PFS 38%	42% grade ≥3 toxicity (acute n=22, late n=7)
Ho *et al.* (78) [2018]	27	IMPT	66 EQD2 Gy	29.5 months	48%	11.2 months	1 yr: OS 54%, LFFS 78%, PFS 51%	7% late grade 3 lung
Badiyan *et al.* (79) [2019]	79	PBT	60–62.7 Gy	19.9 months	30%	10.7 months	1 yr: OS 60%, PFS 43%, LFFS 56.3%	6% and 1% acute and late grade 3 toxicities

PSPT, passive scattering proton therapy; IMRT, intensity-modulated radiation therapy; IMPT, intensity-modulated proton therapy; PBT, proton beam therapy; Gy (RBE), Gray (relative biological effectiveness); EQD2, equivalent dose in 2-Gy fractions; OS, overall survival; PFS, progression-free survival; DMFS, disease-free survival; LFFS, local failure-free survival.

- Central overlapped volume
- Mean heart dose
- Mean esophagus dose
- Concurrent chemotherapy

Effective use of IMPT to improve outcomes for patients with NSCLC depends on:

REAL-TIME volumetric image guidance

Effective management of **TUMOR AND NORMAL ORGAN MOTION**

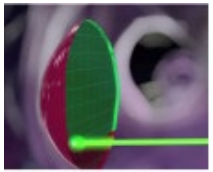
Accurate modeling of **PARTICLE-MATTER INTERACTIONS** and **SET-UP UNCERTAINTIES**

Better understanding of the **RADIOBILOGY** of protons (differential DNA damage along the beam path)

Better understanding of the **IMMUNOMODULATORY EFFECT** of protons

Increased need to account for mitigate motion from respiration

- **Motion encompassmemt**: commonly 4DCT



- **Motion mitigation:**

✓ Margins
✓ Rescanning
✓ Gating/ Tracking
✓ Breath hold/ compression
✓ 4D optimization
✓ 4D reconstruction/adaptation

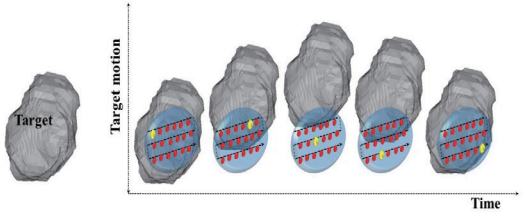
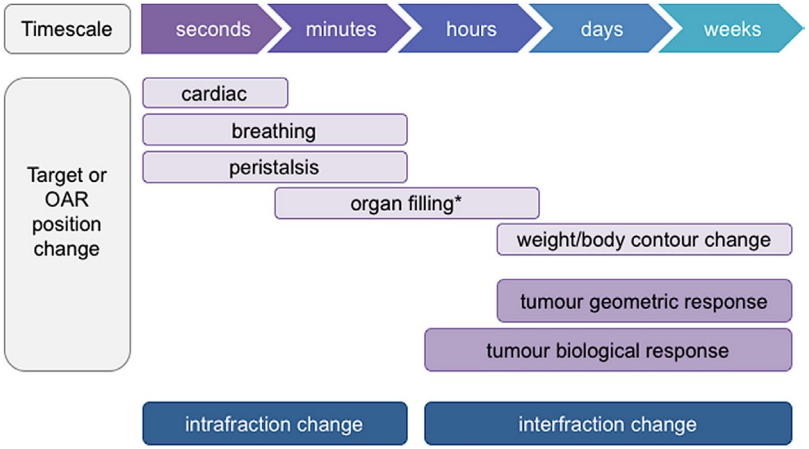
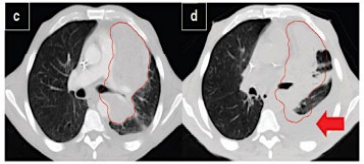


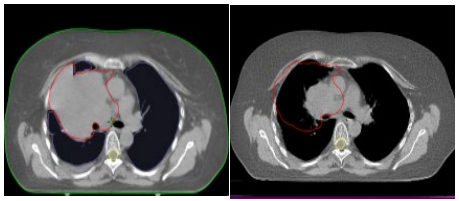
Fig. 3. Schematic diagram showing the beam and target motion interplay. The red colored spots represent the planned spot sequence and the yellow colored spot represent the spot being irradiated at the specific time.

Chang IJROBP 2017, Pakela Front Oncol 2022

Changes within course of radiation therapy

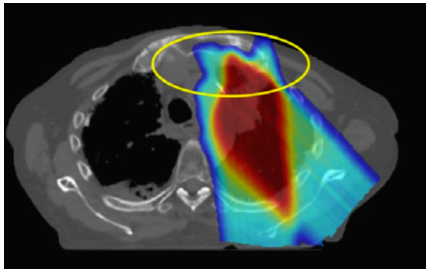


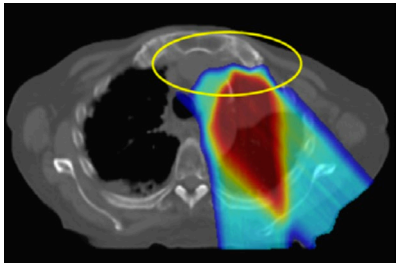


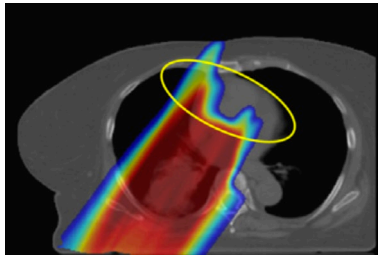


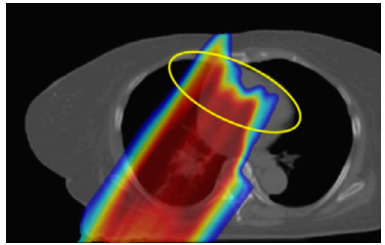
The aim of **Adaptive RT** is to account for these changes and deliver the radiation dose to the tumor as accurately possible

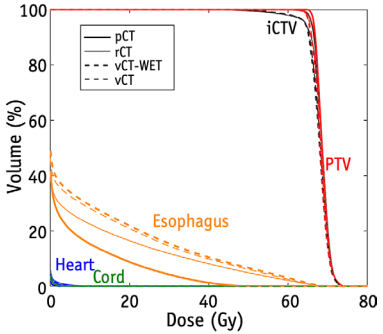
Impact of tumor changes on organs at risk



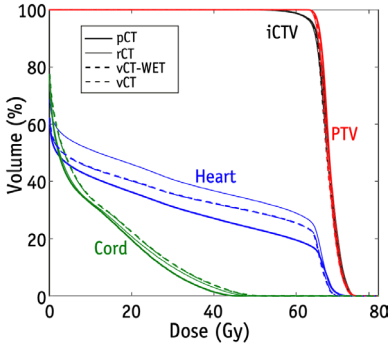




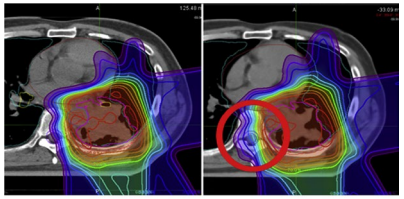




Veiga IJROBP 2016



Concurrent Chemo-Proton Therapy Using Adaptive Planning for Unresectable Stage 3 Non-Small Cell Lung Cancer: A Phase 2 Study

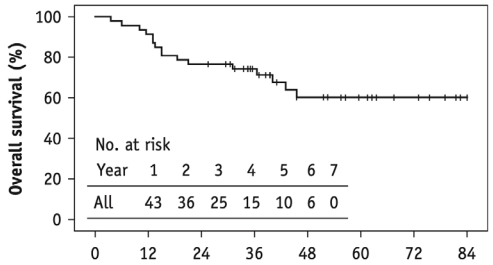


pre-treatment | CCPT; 10 days (16 GyRBE/8 fraction)

- 47 patients; 70/2 GyRBE to primary lesion, 66/2 GyRBE to LN
- QA verification scans :**10, 20, 30** days after RT start.
- Adaptive replanning: when dose to **esophagus and spinal cord increased and exceded the limit dose and/ or when lung dose adjacent to tumor increased 10%**
- Mean number of replanning sessions **2.5** (range 1-4)

➢ **Results:**

- **OS**: 2-yr 77%, 5-yr 59%
- Local control: 2-yr 84%, 5-yr 61%
- PFS: 2-yr 43%, 5-yr 37%



24 patientss were not indicated for radical Ch-RT with photons *

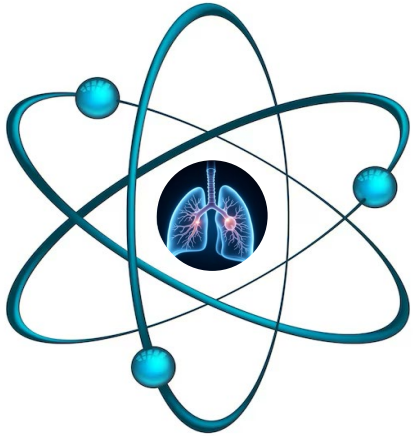
** "No" indicates lung V20 >35% or mean lung dose >20 Gy when a total dose was set at 66 Gy in 33 fr. for primary lesion and lymph node metastasis using involved field technique.*

➢ **Toxicities/QoL:**

- No grade≥ 3 penumonitis
- No significant deterioration in the QoL scores after 24 months except alopecia

Iwata, IJROBP 2020

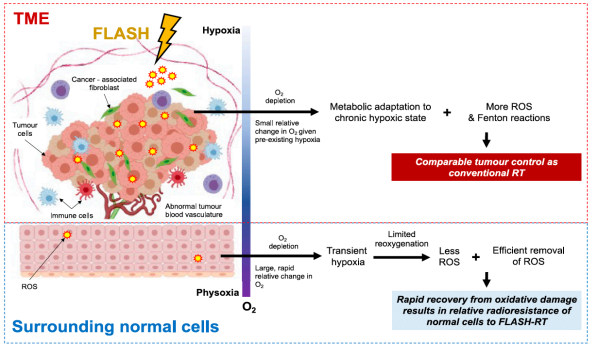
Future perspectives

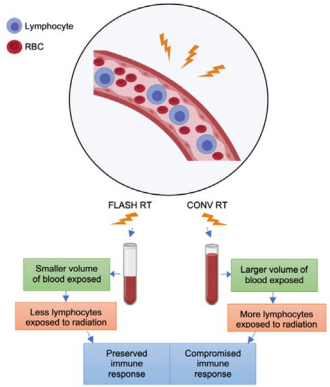


Radiation delivery at ultra-high dose rates (FLASH)

- Enables full treatments (or fractions) in a few hundreds/tenths of a second
  - No motion during treatment
  - Could mimimize treatment (PTV) margins related to motion
  - Less normal tissue exposed to the treatment dose

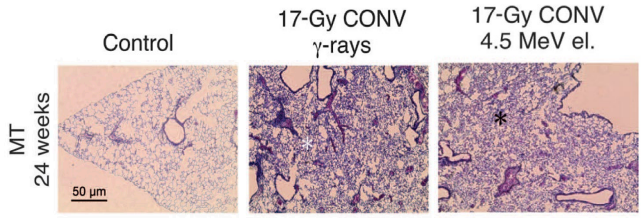
- Pre-clinical studies show:
  - Less normal tissue toxicity
  - Similar tumor control



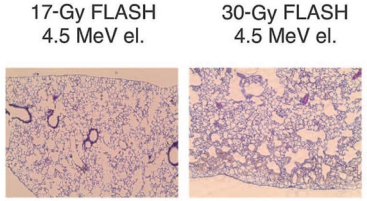


A long way to go….more research is needed

➢ Flash protects normal lung tissue from radio-induced fibrosis

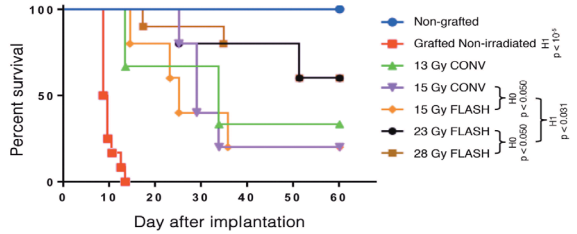


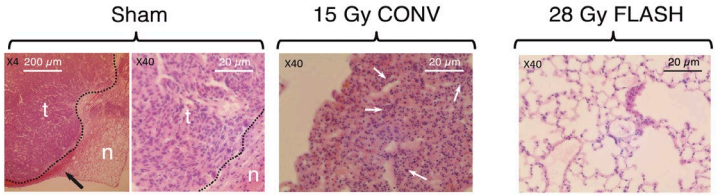
C57BL/6J mice were subjected to **bilateral thorax exposure** to CONV (g-rays or 4.5-MeV electrons**, 0.03 Gy/s**) in a single fraction.



or FLASH irradiation (4.5-MeV electrons, **60 Gy/s)**

➢ Flash is as efficent as CONV in repressing tumor growth





The 15-Gy CONV survivors (n = 2) were free of tumors but presented with inflammatory and fibrotic remodeling, whereas the 28-Gy FLASH survivors (n = 7) did not initiate fibrosis over the same time frame.

Favaudon Science Transl Med 2014

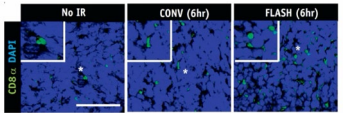
FLASH as immunomodulator

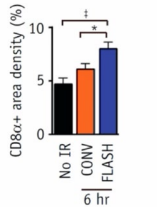
Healthy tissue

- Reduced exposure of circulating cells to RT
- Reduced acute inflamation
- Less chronic activation immune response

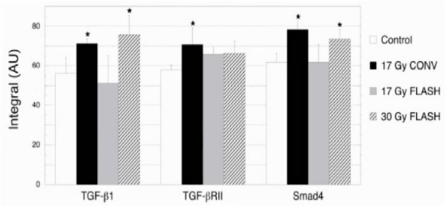
Tumor and its micro-enviroment

- Increase immune infiltration
- Particularly CD8+ effector cells
- Synergize with immunotheraphy without increased toxicity

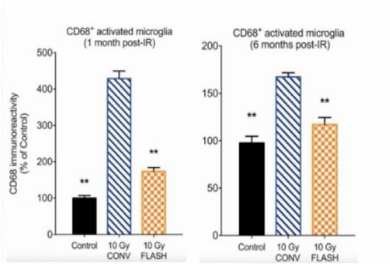




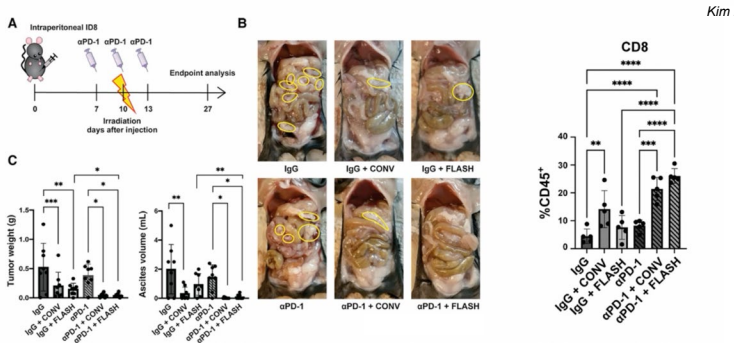
Kim IJROBP 2020



Favaudon Science Translat Medicine 2014



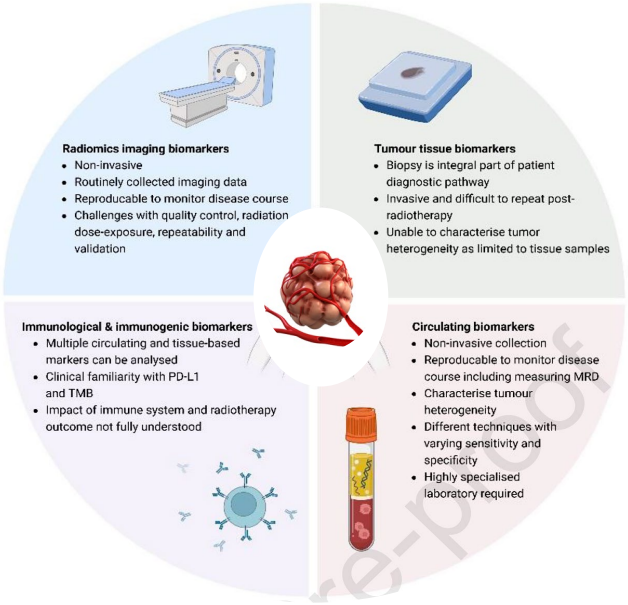
Montay-Gruel PNAS 2019



Eggold Mol Can Ther 2021

Biomarkers for treatment individualization

- **Non-invasive** biomarkers could reduce the reliance on invasive biopsies
- They could be used to describe tumor **heterogeneity**, clonal evolution and identify tretament **resistance mechanisms**
- Its crucial to **incorporate** traditional prognostic and predictive features into the analyses
- Considering **cost-effectiveness** in the design of studies
- **Integration** of biomarker research with modern data science methodologies



Horne, J Thor Oncol 2024

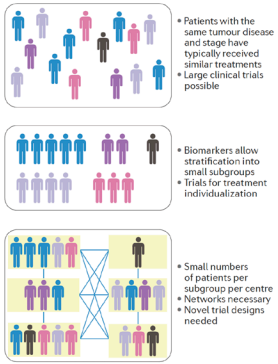
Evaluation of Innovations in Radiation Oncology

Cancer treatment outlook

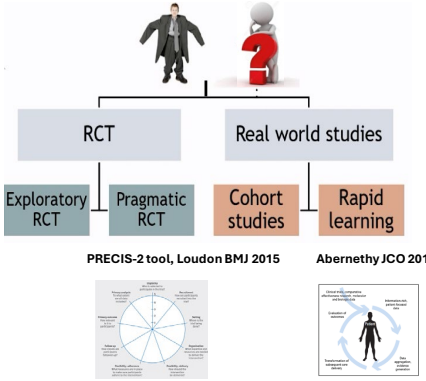
Randomized trials are for yesterday

Pitting new treatments against old, ineffective agents is neither ethical nor economical, says Elaine Schattner.

Nature | Vol 629 | 30 May 2024



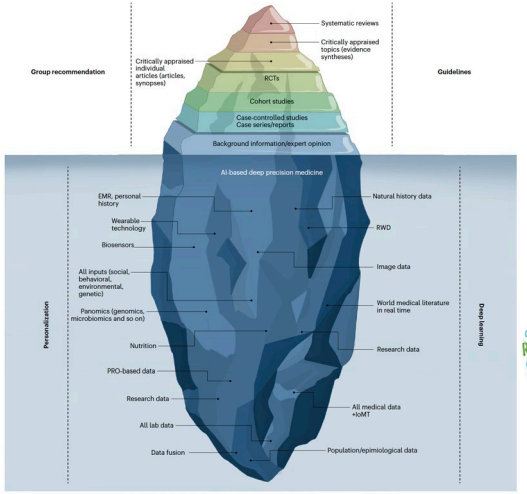
Bauman, Nature 2026



PRECIS-2 tool, Loudon BMJ 2015 | Abernethy JCO 2010

Help trialists design pragmatic trials

Evidence-based deep medicine iceberg.



TAKE HOME MESSAGES…

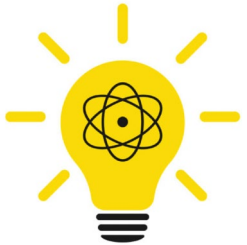
- Proton therapy can **reduce dose** to normal critical thoracic structures , allowing for a potential reduction in **toxicities**, better preservation of **quality of life**, and safer **dose escalation**, integration with **systemic therapy**, and **reirradiation.**

- **Prospective trials** are underway to further evaluate the true value of PBT in this clinical setting

- **PBS offers even greater dosimetric benefits** over scattered protons

- PBT is potentially a powerful tool for improving the therapeutic ratio for subsets of patiens with NSLC:

  - Large (≥ 5 cm) tumors, T4/N3
  - Tumor near critical organs: Central and Ultra-central; peripherally located and close to the brachial plexus, spinal cord,…
  - Patients with interstitial lung disease/ idiopathic pulmonary fibrosis
  - Recurrent or new primary NSCLC after prior radiotherapy
  - Dose escalation
  - Radiation combined with immunotherapy and one or more risk factors for the development of severe lynphopenia
  - Post-operative radiotherapy to the mediastinum



THINK LIKE A PROTON

AND STAY POSITIVE