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

Focus on: Lung cancer innovation and compliance

Constraints and toxicity of standard treatment

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Outline

- Standard RT treatments in NSCLC
- Dose limiting toxicities and constraints
  - Early stage NSCLC
  - Locally advanced NSCLC
- Take home messages

Standard RT treatments for NSCLC

Clinical practice guidelines

- **Early stage node-negative inoperable peripheral lung cancer**
  (minimum PS of ECOG 3 and a minimal estimated life expectancy of one year)
  Stereotactic radiotherapy (BED≥100Gy_{10})
  Peripheral location 45 Gy/3 fr.
  Broad chest wall contact 48 Gy/4 fr.

- **Early stage node-negative inoperable central lung cancer**
  More conventional or accelerated schedule
  Avoid 3-fraction SBRT
  Risk adapted strategy: SBRT 4-5 fractions or hypofr. RT (6-15 fractions)

- **Locally advanced NSCLC**
  Concurrent CRT, 60-66 Gy/30-33 fractions, followed by immunotherapy

Postmus PE, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28:iv1-21.
Guckenberger M, et al. ESTRO ACROP consensus guideline on implementation and practice of stereotactic body radiotherapy for peripherally located early stage non-small cell lung cancer. Radiother Oncol. 2017 Jul;124(1):11-17
Videtic GMM, et al. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: Executive Summary of an ASTRO Evidence-Based Guideline Pract Radiat Oncol. 2017 Sep - Oct; 7(5):295-301

Standard RT treatments for NSCLC

Technical guidelines

- **Early stage node-negative inoperable peripheral lung cancer**
  High-resolution multi-leaf collimators (MLC) <10 mm
  volumetric image-guided radiation therapy (IGRT) technology
  4D-CT

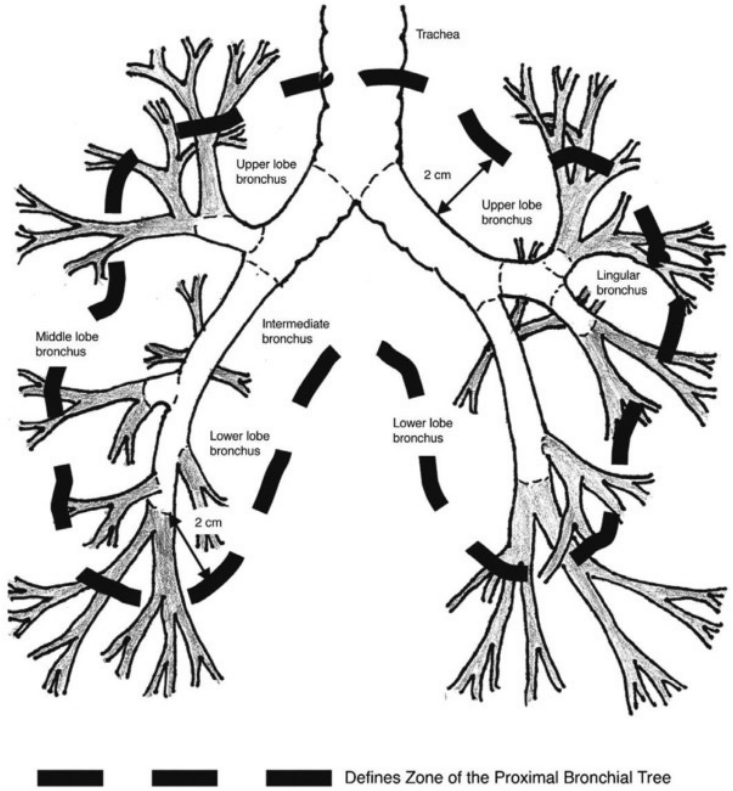
- **Early stage node-negative inoperable central lung cancer**
  As for peripheral tumors

- **Locally advanced NSCLC**
  CT simulation mandatory,
  4D-CT recommended,
  Planning-PET-CT scan recommended
  Elective lymph nodes in the CTV is not recommended (include only biopsy proven or FDG avid lymph nodes)

Guckenberger M, et al. ESTRO ACROP consensus guideline on implementation and practice of stereotactic body radiotherapy for peripherally located early stage non-small cell lung cancer. Radiother Oncol. 2017 Jul;124(1):11-17
Videtic GMM et al. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: Executive Summary of an ASTRO Evidence-Based Guideline Pract Radiat Oncol. 2017 Sep - Oct; 7(5):295-301
Nestle U, et al. ESTRO ACROP guidelines for target volume definition in the treatment of locally advanced non-small cell lung cancer. Radiother Oncol. 2018 Apr;127(1):1-5

Dose limiting toxicities and constraints for peripheral early stage NSCLC

	RTOG 0236
Inclusion criteria	Inoperable T1, T2 (≤5 cm) or T3 (≤5) >2 cm from the PBT
Accrual period	May 2004-October 2006
N of patients eligible	55
RT dose/n fr.	60 Gy/3 fr. (54 Gy/3 fr. *)
BED Dprescr	151 Gy_{10} 378 Gy_3
OARs	Lungs, spinal cord, esophagus, brachial plexus, trachea and bronchus, heart
Median FUP	48 months (86 months for living patients)
5 year primary tumour failure	7.3%
Toxicity incidence	**G3 27%** **G4 4%** **G5 0%**
Most common severe toxicities	**Lung toxicity 16.3%** **Rib fractures 5.6%** **Skin ulcerations 3.6%**



*accounting of density heterogeneity

Timmerman RD, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA. 2010;303(11):1070-1076
Timmerman RD, et al. Long-term Results of Stereotactic Body Radiation Therapy in Medically Inoperable Stage I Non-Small Cell Lung Cancer. JAMA Oncol. 2018 Sep 1;4(9):1287-1288

Dose limiting toxicities and constraints for peripheral early stage NSCLC

	RTOG 0236	RTOG 0915	
Inclusion criteria	Inoperable T1, T2 (≤5 cm) or T3 (≤5) >2 cm from the PBT	Inoperable T1, T2 (≤5 cm) or T3 (≤5) >2 cm from the PBT	
Accrual period	May 2004-October 2006	September 2009-March 2011	
N of patients eligible	55	39	45
RT dose/n fr.	60 Gy/3 fr. (54 Gy/3 fr. *)	34 Gy/1 fr @60-90%	48 Gy/4 fr @60-90%
BED Dprescr	151 Gy_{10} 378 Gy_3	149 Gy_{10} 419 Gy_3	105 Gy_{10} 240 Gy_3
OARs	Lungs, spinal cord, esophagus, brachial plexus, trachea and bronchus, heart	As RTOG, but different dose-volume constraints, **plus ribs (ALARA, but in no way compromise target coverage) and skin**	
Median FUP	48 months (86 months for living patients)	48 months (96 months for living patients)	
5-year primary tumour failure	7.3%	10.6%	6.8%
Toxicity incidence	**G3 27%** **G4 4%** **G5 0%**	**G3 2.6%** **G4 0%** **G5 0%**	**G3 11.1%** **G4 0%** **G5 0%**
Most common severe toxicities	**Lung toxicity 16.3%** **Rib fractures 5.6%** **Skin ulcerations 3.6%**	**Lung toxicity 2.6%** **Rib fractures 0%** **Skin ulcerations 0%**	**Lung toxicity 11.1%** **Rib fractures 0%** **Skin ulcerations 0%**

*accounting of density heterogeneity

Timmerman RD, et al. JAMA. 2010;303(11):1070-1076
Timmerman RD, et al. JAMA Oncol. 2018 Sep 1;4(9):1287-1288
Videtic GM, et al. Int J Radiat Oncol Biol Phys. 2015 Nov 15;93(4):757-64..
Videtic GM, et al. Int J Radiat Oncol Biol Phys. 2019 Apr 1;103(5):1077-1084.

Dose limiting toxicities and constraints for peripheral early stage NSCLC

Yamashita *et al. Radiation Oncology* 2010, **5**:32
http://www.ro-journal.com/content/5/1/32

RADIATION ONCOLOGY

RESEARCH Open Access

Prescreening based on the presence of CT-scan abnormalities and biomarkers (KL-6 and SP-D) may reduce severe radiation pneumonitis after stereotactic radiotherapy

Hideomi Yamashita*, Shino Kobayashi-Shibata, Atsuro Terahara, Kae Okuma, Akihiro Haga, Reiko Wakui, Kuni Ohtomo and Keiichi Nakagawa

From January 2003 to March 2009, SBRT was performed on 117 patients (32 patients before 2005 and 85 patients after 2006) with lung tumors.

After 2006, patients with a high risk for RP who had an obvious IP shadow on CT with a 3- mm slice before SBRT together with a high value of serum KL-6 & SP-D were excluded from receiving SBRT

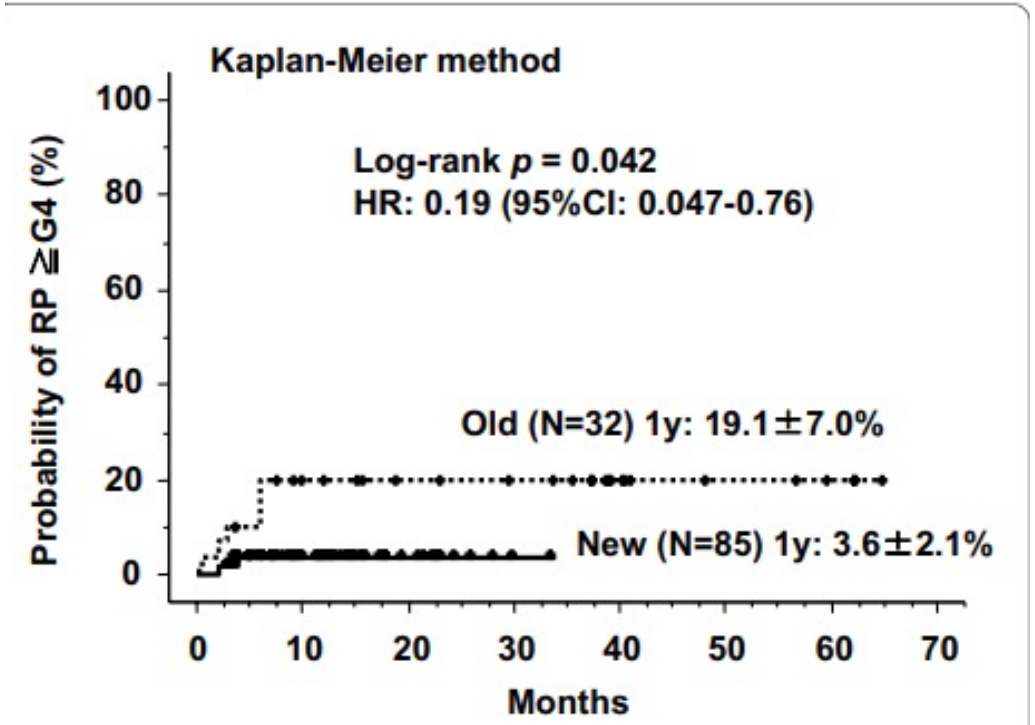


Figure 11 Cumulative probability curves of severe radiation pneumonitis of grades 4-5 divided by pre-2005 (old group) and post-2006 (new group).

Yamashita H, et al. Radiat Oncol. 2010 May 9;5:32.

Dose limiting toxicities and constraints for peripheral early stage NSCLC

Radiotherapy and Oncology 156 (2021) 153–159

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Clinical and dosimetric predictors of radiation pneumonitis in early-stage lung cancer treated with Stereotactic Ablative radiotherapy (SABR) – An analysis of UK's largest cohort of lung SABR patients

Animesh Saha [a,*], Matthew Beasley [b], Nathaniel Hatton [b], Peter Dickinson [b], Kevin Franks [b], Katy Clarke [b], Pooja Jain [b], Mark Teo [b], Patrick Murray [b], John Lilley [c]

[a] Department of Oncology, Apollo Gleneagles Cancer Hospital, Kolkata, India; [b] Department of Oncology; and [c] Department of Medical Physics, St James's University Hospital, Leeds, UK

1266 patients treated with lung SABR between May 2009 and August 2018, in a single United Kingdom (UK) radiotherapy center

Patients were treated according to the UK SABR consortium guidelines

None of the patients had any interstitial lung disease.

Table 1
Organ at risk constraints (based on the ROSEL study [10])

Organ	Volume (cm^3)	Deviation given as cumulative absolute dose (Gy)			
		Three fraction scheme		Five fraction scheme	
		None	Minor	None	Minor
Spinal cord	Any point	18	>18–22	25	>25–28
Oesophagus	1	24	>24–27	27	>27–28.5
Ipsilateral brachial plexus	1	24	>24–26	27	>27–29
Heart	1	24	>24–26	27	>27–29
Trachea and main stem bronchus	1	30	>30–32	32	>32–35

Saha A, et al. Radiother Oncol. 2021 Mar;156:153-159.

Dose limiting toxicities and constraints for peripheral early stage NSCLC

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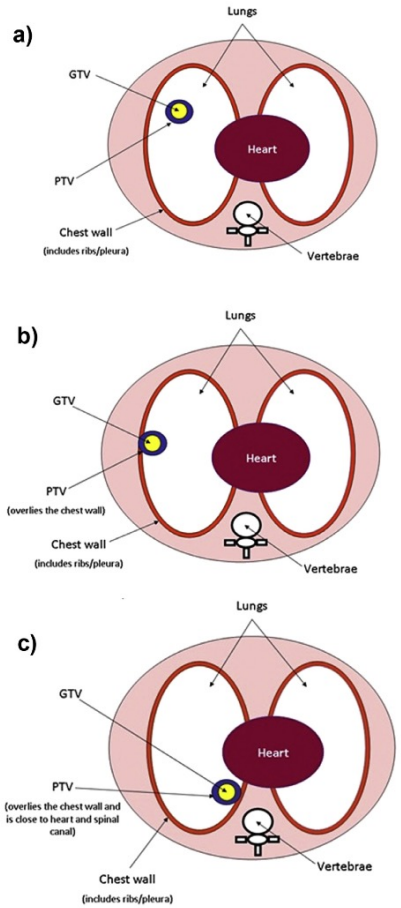

54 Gy/3 fr

55 Gy/5 fr

60 Gy/8 fr

Saha A, et al. Radiother Oncol. 2021 Mar;156:153-159.

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Patients were treated according to the UK SABR consortium guidelines

None of the patients had any interstitial lung disease.

Pulmonary toxicity incidence
grade 2 6.2%
grade 3 0.4%

Grade 3 rib fractures 1.4%

Saha A, et al. Radiother Oncol. 2021 Mar;156:153-159.

Dose limiting toxicities and constraints for peripheral early stage NSCLC

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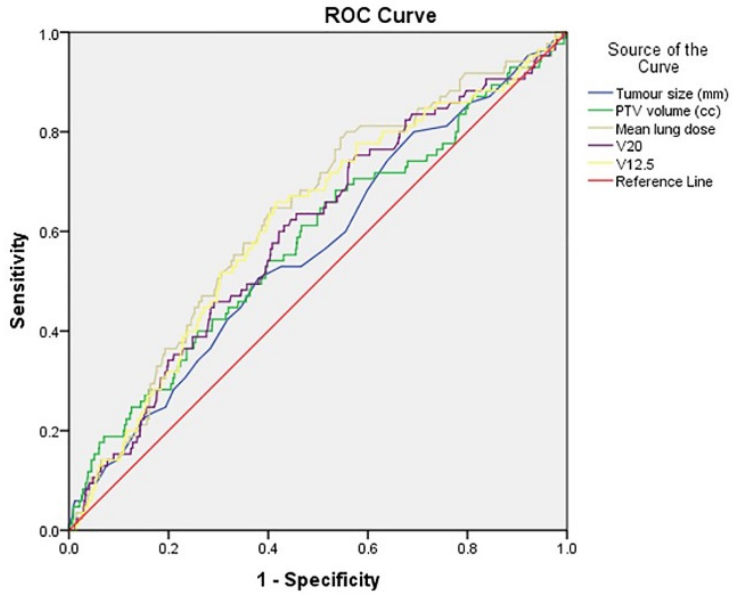


Diagonal segments are produced by ties.

Variable	AUC	Threshold	Sensitivity	Specificity	Gr≥2 RP	p-value
Tumour size	0.565	22.5mm	50.6%	62%	8.7% vs 5.4%	0.022
PTV volume	0.580	27.15cc	68.2%	45%	8.2% vs 4.8%	0.018
MLD	0.633	3.7Gy	80%	44.3%	9.4% vs 3.3%	0.000
V20	0.597	4.6%	74.1%	45.8%	8.5% vs 4.2%	0.002
V12.5	0.616	9.5%	67.1%	55%	9.5% vs 4.2%	0.000

Saha A, et al. Radiother Oncol. 2021 Mar;156:153-159.

Dose limiting toxicities and constraints for central early stage NSCLC

	RTOG 0813
Inclusion criteria	Inoperable T1, T2N0M0 NSCLC (≤5 cm) within the zone 2 cm around the PBT or the mediastinal or pericardial pleura
Accrual period	Feb 2009-Sep 2013
N of patients eligible	120
RT dose/n fr.	40 Gy/5 fr. to 60 Gy/5 fr. by 0.5 Gy/fraction steps, every second to third day, to 60-90% isodose line
BED Dprescr	72 -132 Gy_{10} 146-300 Gy_3
OARs	Lungs, spinal cord, esophagus, brachial plexus, trachea and bronchus, heart, skin (no more than 105% of Dprescr)
Median FUP	38 months
2 year local control rate	87.9%
Toxicity incidence	**G3 10.8%** **G4 0.8%** **G5 5.0%**
Most common severe toxicities	**Respiratory disorders 9.1%** **Broncopulmonary hemorrage 3.2%** **Esophagitis 1.6%** **Esophageal perforation 0.8%**

Bezjak A, et al. J Clin Oncol. 2019 May 20;37(15):1316-1325
Lindberg K, et al. J Thorac Oncol. 2021 Jul;16(7):1200-1210

Dose limiting toxicities and constraints for central early stage NSCLC

	RTOG 0813	HILUS trial
Inclusion criteria	Inoperable T1, T2N0M0 NSCLC (≤5 cm) within the zone 2 cm around the PBT or the mediastinal or pericardial pleura	Inoperable T1, T2N0M0 NSCLC or metastases (≤5 cm) within 1 cm around the PBT
Accrual period	Feb 2009-Sep 2013	July 2011-March 2016
N of patients eligible	120	85
RT dose/n fr.	40 Gy/5 fr. to 60 Gy/5 fr. by 0.5 Gy/fraction steps, every second to third day, to 60-90% isodose line	56/8 fr. to 67% isodose line
BED Dprescr	72 -132 Gy_{10} 146-300 Gy_3	100 Gy_{10} 198 Gy_3
OARs	Lungs, spinal cord, esophagus, brachial plexus, trachea and bronchus, heart, skin (no more than 105% of Dprescr)	Lungs, spinal cord, esophagus, brachial plexus, trachea and bronchus, heart, skin (“soft” for ipsilateral bronchus)
Median FUP	38 months	24 months
2 year local control rate	87.9%	85%
Toxicity incidence	G3 10.8% G4 0.8% **G5 5.0%**	G3 n.a. G4 7.0% **G5 11.7%**
Most common severe toxicities	Respiratory disorders 9.1% **Broncopulmonary hemorrage 3.2%** Esophagitis 1.6% Esophageal perforation 0.8%	Respiratory disorders 10% **Broncopulmonary hemorrage (G5) 9.4%**

Bezjak A, et al. J Clin Oncol. 2019 May 20;37(15):1316-1325
Lindberg K, et al. J Thorac Oncol. 2021 Jul;16(7):1200-1210

Dose limiting toxicities and constraints for central early stage NSCLC

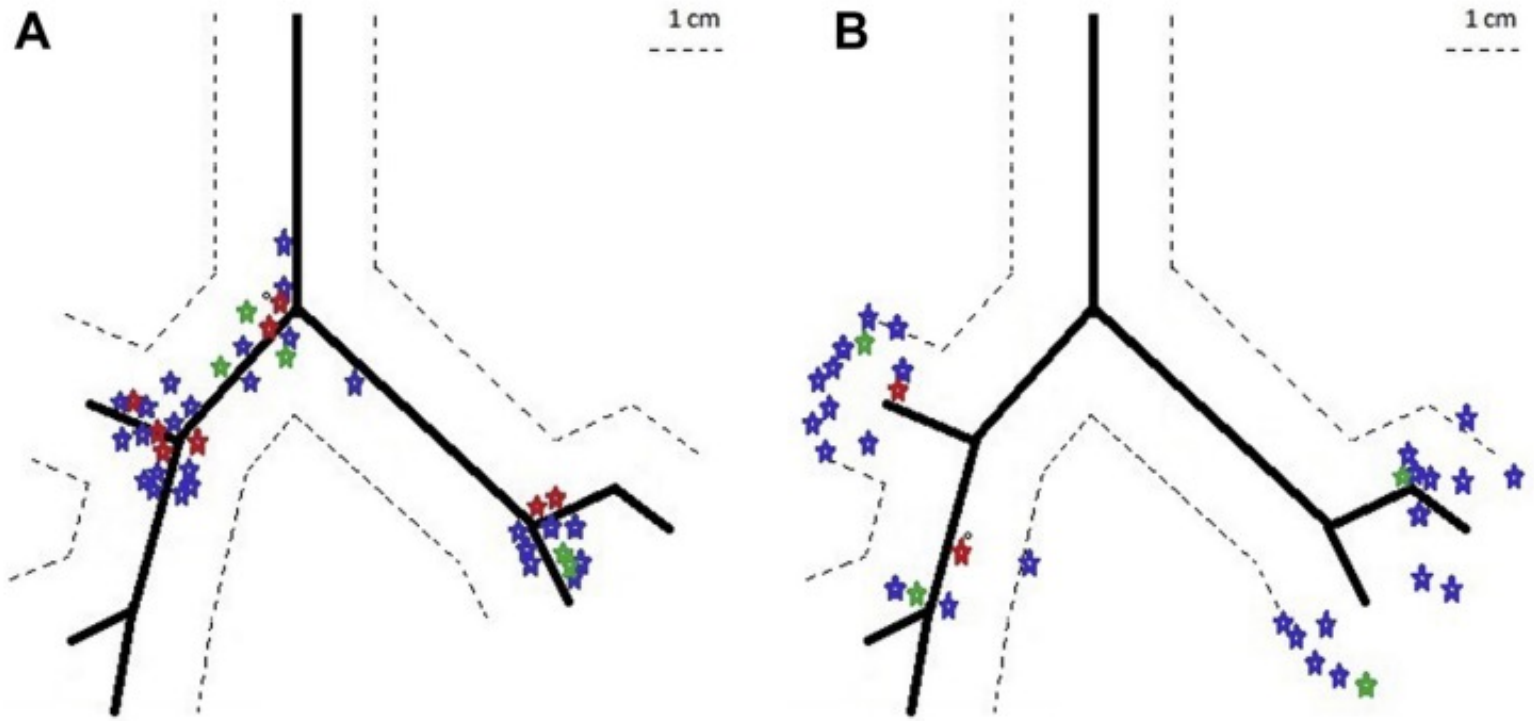
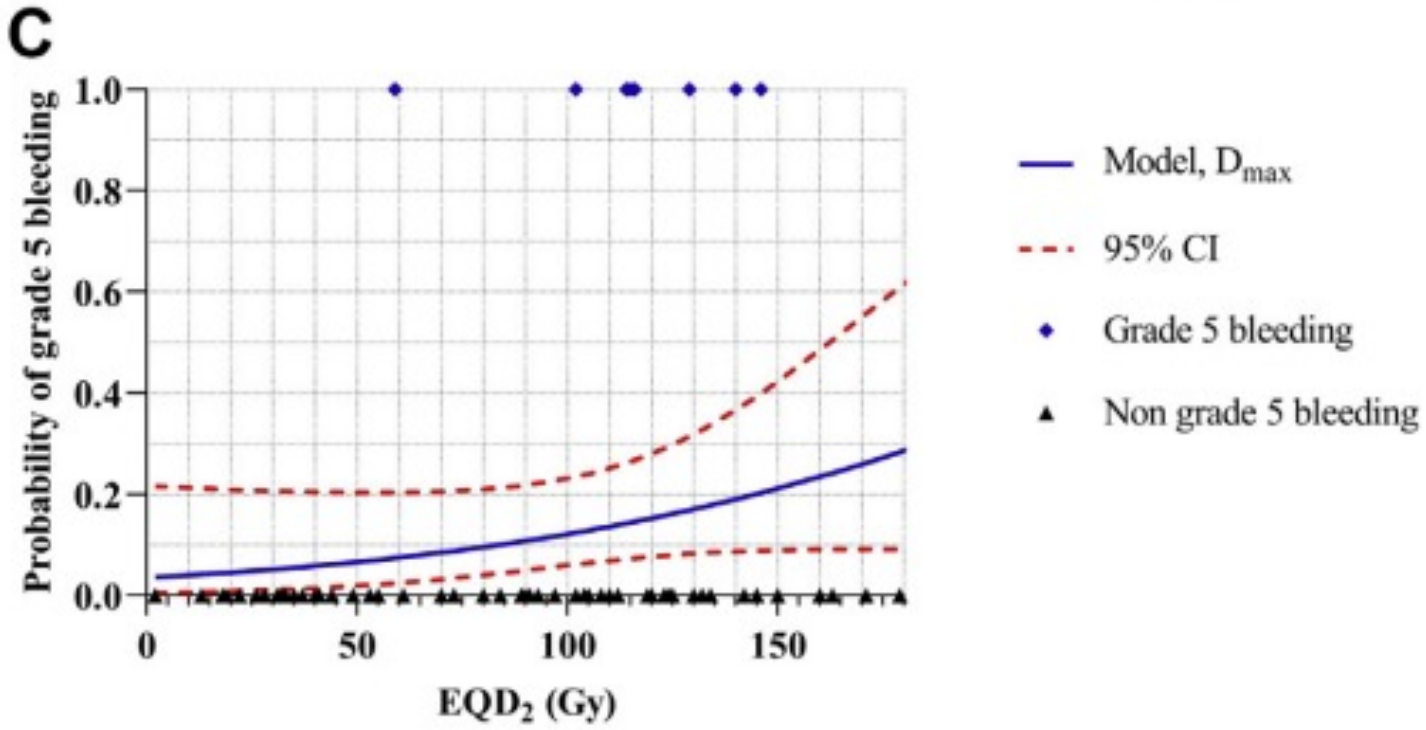


Figure 1. Localization of (*A*) tumors in group A and (*B*) tumors in group B. Red indicates grade 5 toxicity; green, local failure; blue, no grade 5 toxicity + local control.

Lindberg K, et al. J Thorac Oncol. 2021 Jul;16(7):1200-1210

Dose limiting toxicities and constraints for central early stage NSCLC

Estimated probability of bronchopulmonary hemorrhage versus bronchial dose to the main bronchus plus trachea (lumen) in EQD2



Lindberg K, et al. J Thorac Oncol. 2021 Jul;16(7):1200-1210

Dose limiting toxicities and constraints for central early stage NSCLC

Zhao *et al. Radiation Oncology* (2020) 15:0
https://doi.org/10.1186/s13014-020-01491-w

Radiation Oncology

RESEARCH Open Access

Outcomes of stereotactic body radiotherapy 60 Gy in 8 fractions when prioritizing organs at risk for central and ultracentral lung tumors

Yizhou Zhao[1,2*], Eman Khawandanh[3], Steven Thomas[3], Susan Zhang[3], Emma M. Dunne[4], Mitchell Liu[4] and Devin Schellenberg[1]

Abstract

Background: For stereotactic body radiotherapy (SBRT) to central (C) and ultracentral (UC) lung tumors, our provincial practice has been to prioritize organs at risk (OARs) constraints by compromising target volume coverage if needed. The objectives are to report the treatment's efficacy and safety.

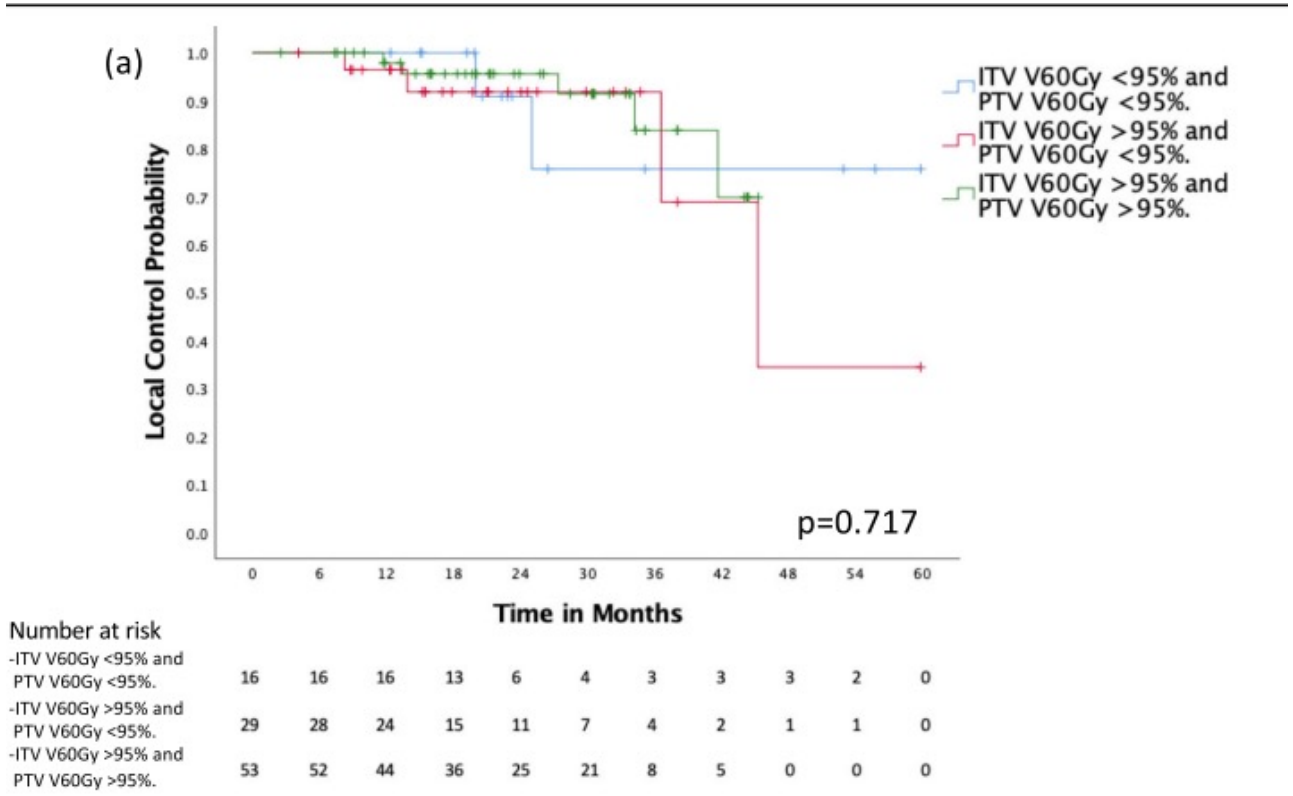
Methods: We conducted a retrospective analysis of all provincial patients who underwent SBRT at 60Gy in 8 fractions to C and UC lung tumors, from 2013 to 2017.

Results: Ninety-eight lesions were treated, 57 (58.2%) C and 41 (41.8%) UC. The median follow-up was 22.9 months (range 2.5–64.8 months). The 1- and 3-year local control (LC) was 97.8 and 84.5% respectively, with no differences between C and UC groups ($p = 0.662$). Fifty-three (54.1%) cases had optimal dose coverage (V60Gy ITV&PTV > 95%), 29 (29.6%) had compromised PTV coverage (V60Gy ITV > 95%/PTV < 95%), and 16 (16.3%) had both compromised ITV and PTV coverage (V60Gy ITV&PTV < 95%). No significant difference in LC was detected at 2 years between the 3 groups (95.6, 91.8 and 90.9%, $p = 0.717$). There were 3 episodes of grade 3 toxicity in the C group (2 dyspnea, 1 pneumonitis) and 2 in the UC group (1 dyspnea, 1 hemoptysis). There were no gr4/5 toxicities. On multivariable Cox regression analysis, ITV size was found to be a predictor for LC ($p = 0.001$).

Conclusions: SBRT at 60Gy in 8 fractions achieves high rates of LC with low risks of significant toxicities, even if target volume coverage is reduced to meet OARs constraints.

Keywords: Stereotactic body radiotherapy, Central, Ultracentral, Lung tumors, 60 Gy in 8 fractions

Proximal bronchial tree and trachea D0.035 cc	< 46.3 Gy/8 fr. (EQD2 81Gy)



Dose limiting toxicities and constraints for locally advanced NSCLC

The NEW ENGLAND JOURNAL of MEDICINE

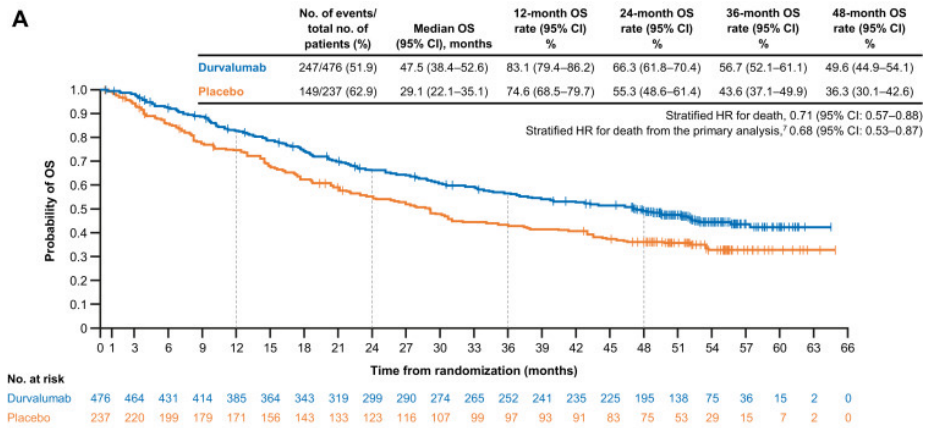
ESTABLISHED IN 1812 NOVEMBER 16, 2017 VOL. 377 NO. 20

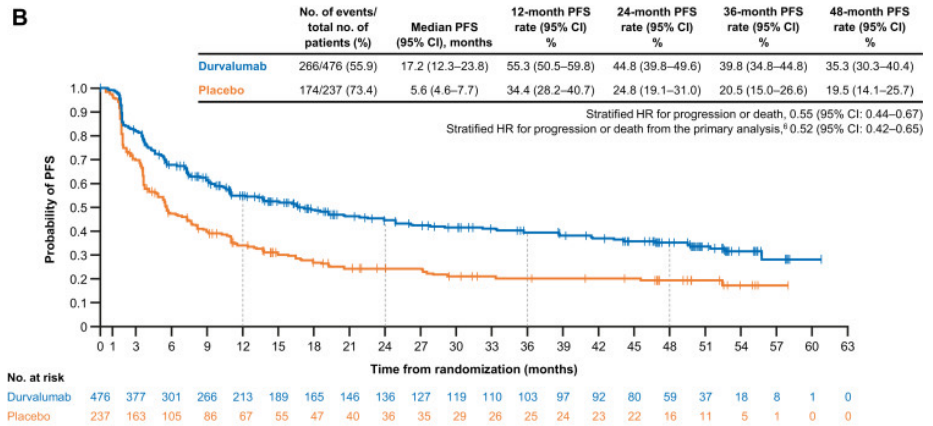
Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer

S.J. Antonia, A. Villegas, D. Daniel, D. Vicente, S. Murakami, R. Hui, T. Yokoi, A. Chiappori, K.H. Lee, M. de Wit, B.C. Cho, M. Bourhaba, X. Quantin, T. Tokito, T. Mekhail, D. Planchard, Y.-C. Kim, C.S. Karapetis, S. Hiret, G. Ostoros, K. Kubota, J.E. Gray, L. Paz-Ares, J. de Castro Carpeño, C. Wadsworth, G. Melillo, H. Jiang, Y. Huang, P.A. Dennis, and M. Özgüroğlu, for the PACIFIC Investigators*

Stage III, locally advanced, unresectable NSCLC, no disease progression after concurrent chemo-RT (54-66 Gy/27-33 fr.).
Mean lung dose less than 20 Gy
Lung V20 less than 35%

May 2014-April 2016
473 patients received durvalumab
236 received placebo





Faivre-Finn C, et al. J Thorac Oncol. 2021 May;16(5):860-867.

Dose limiting toxicities and constraints for locally advanced NSCLC

Table 3. Adverse Events of Any Cause.

Event	Durvalumab (N=475)		Placebo (N=234)	
	Any Grade*	Grade 3 or 4	Any Grade*	Grade 3 or 4
	number of patients with event (percent)			
Any event	460 (96.8)	142 (29.9)	222 (94.9)	61 (26.1)
Cough	168 (35.4)	2 (0.4)	59 (25.2)	1 (0.4)
Pneumonitis or radiation pneumonitis†	161 (33.9)	16 (3.4)	58 (24.8)	6 (2.6)
Fatigue	113 (23.8)	1 (0.2)	48 (20.5)	3 (1.3)
Dyspnea	106 (22.3)	7 (1.5)	56 (23.9)	6 (2.6)
Diarrhea	87 (18.3)	3 (0.6)	44 (18.8)	3 (1.3)
Pyrexia	70 (14.7)	1 (0.2)	21 (9.0)	0
Decreased appetite	68 (14.3)	1 (0.2)	30 (12.8)	2 (0.9)
Nausea	66 (13.9)	0	31 (13.2)	0
Pneumonia	62 (13.1)	21 (4.4)	18 (7.7)	9 (3.8)
Arthralgia	59 (12.4)	0	26 (11.1)	0
Pruritus	58 (12.2)	0	11 (4.7)	0
Rash	58 (12.2)	1 (0.2)	17 (7.3)	0
Upper respiratory tract infection	58 (12.2)	1 (0.2)	23 (9.8)	0
Constipation	56 (11.8)	1 (0.2)	20 (8.5)	0
Hypothyroidism	55 (11.6)	1 (0.2)	4 (1.7)	0
Headache	52 (10.9)	1 (0.2)	21 (9.0)	2 (0.9)
Asthenia	51 (10.7)	3 (0.6)	31 (13.2)	1 (0.4)
Back pain	50 (10.5)	1 (0.2)	27 (11.5)	1 (0.4)
Musculoskeletal pain	39 (8.2)	3 (0.6)	24 (10.3)	1 (0.4)
Anemia	36 (7.6)	14 (2.9)	25 (10.7)	8 (3.4)

Antonia SJ, e al. N Engl J Med. 2017 Nov 16;377(20):1919-1929

Dose limiting toxicities and constraints for locally advanced NSCLC

Original Study

Check for updates

Relationship Between Prior Radiotherapy and Checkpoint-Inhibitor Pneumonitis in Patients With Advanced Non–Small-Cell Lung Cancer

Khinh Ranh Voong,[1] Sarah Z. Hazell,[1] Wei Fu,[4] Chen Hu,[4] Cheng Ting Lin,[5] Kai Ding,[1] Karthik Suresh,[6] Jonathan Hayman,[6] Russell K. Hales,[1] Salem Alfaifi,[1] Kristen A. Marrone,[2,3] Benjamin Levy,[2] Christine L. Hann,[2] David S. Ettinger,[2] Josephine L. Feliciano,[2] Valerie Peterson,[2] Ronan J. Kelly,[2] Julie R. Brahmer,[2,3] Patrick M. Forde,[2,3] Jarushka Naidoo[2,3]

188 NSCLC patients treated with anti PD-1/PD-L1 at a tertiary-care academic cancer center, between June 2011 and July 2017

70% (132/188) received any RT, 53% (100/188) chest RT

Any grade IR pneumonitis occurred in 19% of patients

Predominant Immune-related pneumonitis appearances were ground-glass opacities outside high-dose chest RT regions

IR pneumonitis was more common in patients who received curative-intent chest RT.

No RT parameter was significantly associated with IR pneumonitis.

Voong KR, et al. Clin Lung Cancer. 2019 Jul;20(4):e470-e479.

Take home messages

Dose limiting toxicities and constraints of RT for peripheral early stage NSCLC

- Standard SBRT is safe (less than 10% severe toxicity and no mortality) for peripheral early stage NSCLC even when using high dose single fraction regimens

- Severe radiation induced lung toxicity and/or chest-wall complications might be further reduced by
    - using risk adapted dose prescription strategies
    - optimizing treatment plan (ALARA to lungs and ribs)
    - refining patients selection criteria

Take home messages

Dose limiting toxicities and constraints of RT for central early stage NSCLC

- A risk adapted RT dose fractionation strategy may allow to wide the therapeutic window
- Nevertheless, the risk of bronchopulmonary hemorrage remains not negligible in patients with ultracentral lesions even with more protracted dose fractionation regimens
- Prioritizing the OARs over PTV and/or ITV coverage might allow safer RT treatments without significantly compromizing efficacy

Take home messages

Dose limiting toxicities and constraints of RT for locally advanced NSCLC

- Adjuvant Durvalumab may exacerbate the risk of symtomatic pneumonitis after concurrent chemo-RT

- So far no specific dose constraints have been identified

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