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CLINICAL INVESTIGATION

A Systematic Review Into the Radiologic Features Predicting Local Recurrence After Stereotactic Ablative Body Radiotherapy (SABR) in Patients With Non-Small Cell Lung Cancer (NSCLC)



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Purpose

- Radiation-induced lung injury shares a similar appearance to LR after treatment, making the detection of LR on imaging difficult for clinicians.
- Radiologic features of CT and FDG-PET predicting LR and to evaluate radiomics as another tool for detecting LR.

Methods and Materials

Inclusion

- Patient population with NSCLC,
 - Metastases to the lung from either a lung or nonlung primary,
 - LRs within the lung where the treatment modality was SABR
 - Reported on the imaging/radiologic characteristics of local tumor recurrence
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- Either CT or FDG-PET modalities posttreatment.

Exclusion

- Studies that did not report on radio-logic characteristics post-SABR
- Or reported only pre-treatment radiologic characteristics
- Studies that did not report LR as a separate outcome

Search strategy

- Eligible studies were identified by searching the MEDLINE, EMBASE, and PubMed databases. These searches were completed in December 2018 and updated in November 2020.
- A search for abstracts from 2015 to 2020 in the following conferences were also conducted using Web of Science, Wiley Online, and Science Direct databases:

Results

- Overall, the crude incidence of LR was approximately 13% (222/1726) across the 32 studies, over an approximate median follow-up period of 24 months with at least 84 cases reported as being biopsy proven.
- Of the 32 included studies, 19 reported on radiographic findings on FDG-PET imaging, 14 on CT imaging, and 3 on radiomics.

Biopsy or sequential imaging or MDT opinion-LR

Huang et al ²⁶	2013	CT	24 (5-67) mo	Defined radiologically as a growing lesion within the involved lobe on sequential follow-up scans that could not clearly be attributable to lung fibrosis but were definitively considered LR on biopsy	By biopsy in all 12/12 LR patients
Kato et al ²³	2010	CT	24 (18-39) mo	NR	By biopsy in 5/27 LR patients or by "routine workup" inclusive of physical examination or tumor marker examination in 22/27 LR patients
Kimura et al ¹³	2006	CT	18 (6-56) mo	Defined as increasing size during follow-up periods	By sequential imaging
Li et al ¹⁵	2020	CT	36.7 (3-70) mo	Defined as either confirmed by biopsy or by an SUV >5 or an initial value (as measured by FDG-PET) on follow-up FDG-PET scanning	By sequential imaging or by biopsy but number of LR patients confirmed by each mode NR
Matsuo et al ¹⁶	2007	CT	33 (13-65) mo	Defined as either confirmed by biopsy or by an increase in colon tumor markers without other metastases (due to the LR being a metastasis from colon cancer) or from the rapid enlargement	By biopsy in 1/3 LR patients or by increase in colon cancer tumor markers in 1/3 LR patients

(Continued)

Authors	Year	Imaging modality/ies	Total follow-up time median/mean (range)	Definition of local recurrence as defined in study	Method of confirming local recurrence
				of the mass-like consolidation associated with lymph node swelling and increasing of tumor markers	or by sequential imaging and tumor markers in 1/3 patients
Mattonen et al ¹¹	2013	Radiomic	26 (6-44) mo	NR	By biopsy in 8/11 LR lesions and by sequential imaging and multidisciplinary group consensus in 3/11 LR lesions
Mattonen et al ¹²	2014	Radiomic	NR	Defined as either confirmed by biopsy or by an increase in colon tumor markers without other metastases (due to the LR being a metastasis from colon cancer) or from the rapid enlargement of the mass-like consolidation associated with lymph node swelling and increasing of tumor markers	By biopsy in 1/3 LR patients or by increase in colon cancer tumor markers in 1/3 LR patients or by sequential imaging and tumor markers in 1/3 patients
Mohammed et al ³⁸	2011	FDG-PET	9 (0.4-26) mo	Defined as recurrence of tumor at the primary tumor site, within the RT target volume, either based on imaging data or tumor biopsy after a complete radiographic response	By sequential imaging or by biopsy but 0 LR patients
Moore et al ⁴⁷	2015	Radiomic	NR	NR	By consensus of a multidisciplinary lung cancer tumor board and subsequently by biopsy in all 11/11 LR patients
Nakajima et al ⁴⁰	2013	FDG-PET	29 (7-52) mo	Defined as a suspicious mass that showed continuous enlargement on 2 or more follow-up CTs after FDG-PET/CT, with or without the elevation of tumor marker or appearance of new lesions	By biopsy in 7/16 LR patients or by sequential imaging in 9/16 LR patients
Pastis et al ³⁵	2014	FDG-PET	Mean 14 (4-19) mo	Defined as increased tumor size, SUV _{max} >3 (in the absence of known infection) or the presence of new intrathoracic abnormalities beyond expected radiation pneumonitis changes	By consensus of a radiation oncologist and dedicated thoracic radiologist. Disagreements were settled by majority vote among the multidisciplinary tumor board.

CT features post-SABR

Table 2 Gross radiologic CT features post-SABR according to the Ikezoe and Koenig classifications

Study n	LR n	Ikezoe classification				Koenig classification				
		Early radiographic features (<6 mo posttreatment)		Late radiographic features (>6 mo posttreatment)		Late radiographic features (>6 mo posttreatment)		Late radiographic features (>6 mo posttreatment)		Late radiographic features (>6 mo posttreatment)
		Diffuse consolidation n (%)	Patchy consolidation + GGO n (%)	Diffuse GGO n (%)	Patchy GGO n (%)	No evidence of increasing opacity n (%)	Masslike fibrosis n (%)	Modified conventional pattern n (%)	Scarlike fibrosis n (%)	No evidence of increased density n (%)
Li et al ¹⁵ n = 60	7	Total: 22 (37); 12 (20)* LR: 2 (29)	Total: 10 (17); 15 (25)* LR: 4 (57)	Total: 3 (5); 4 (7)* LR: 0 (0)	Total: 19 (32); 24 (40)* LR: 0 (0)	Total: 5 (8); 4 (7)* LR: 1 (14)	Total: 10 (17); 9 (15)* LR: 3 (43)	Total: 37 (62); 37 (62)* LR: 3 (43)	Total: 7 (12); 8 (13)* LR: 0 (0)	Total: 5 (8); 5 (8)* LR: 1 (14)
Kimura et al ¹³ n = 52	4	Total: 20 (38) LR: 0 (0)	Total: 8 (15) LR: 0 (0)	Total: 6 (12) LR: 0 (0)	Total: 1 (2) LR: 0 (0)	Total: 17 (33) LR: 0 (0)	Total: 9 (17) LR: 2 (50)	Total: 32 (62) LR: 0 (0)	Total: 11 (21) LR: 2 (50)	Total: 0 (0) LR: 0 (0)
Matsuo et al ¹⁶ n = 40	3						Total: 27 (68) LR: 3 (100)	Total: NR LR: 0 (0)	Total: NR LR: 0 (0)	Total: NR LR: 0 (0)
Trovo et al ¹⁷ n (at 2-6 mo) = 33 n (at 7-12 mo) = 35	3	Total: 9 (27) LR: 0 (0)	Total: 11 (33) LR: 2 (67)	Total: 4 (12) LR: 1 (33)	Total: 2 (6) LR: 0 (0)	Total: 7 (21) LR: 0 (0)	Total: 7 (20) LR: 0 (0)	Total: 16 (46) LR: 0 (0)	Total: 5 (14) LR: 0 (0)	Total: 7 (20) LR: 0 (0)
Hayashi et al ¹⁴ n = 81	6							Total: 38 (47) LR: 1 (17)	Total: 15 (19) LR: 0 (0)	Total: 7 (9) LR: 0 (0)

Abbreviations: CT = computed tomography; GGO = ground glass opacity; LR = local recurrence; NR = not reported.
* Indicates a second observer's findings.
Results are shown as both the total number of cases and number of LR cases (n) and the proportion of total cases and proportion of total LR cases (%) exhibiting the radiologic feature.

High risk features (HRFs)

Table 4 Incidence of HRFs predictive of LR on CT post-SABR

HRF	Studies measuring HRF	No. of studies measuring HRF	LR n	No recurrence n	LR with HRF n	No recurrence with HRF n	Sensitivity (%)	Specificity (%)
Bulging margin	Frakulli et al, ²⁴ Halpenny et al, ²⁵ Huang et al, ²⁶ Kato et al, ²³ Li et al, ¹⁵ Peulen et al ²⁷	6	58	240	42	38	72	84
Loss of air bronchogram	Frakulli et al, ²⁴ Halpenny et al, ²⁵ Huang et al, ²⁶ Kato et al, ²³ Li et al, ¹⁵ Peulen et al ²⁷	6	58	240	28	35.5	48	85
Enlargement after 12 mo	Frakulli et al, ²⁴ Huang et al, ²⁶ Kato et al, ²³ Li et al, ¹⁵ Peulen et al ²⁷	5	50	157	47	29	94	82
Linear margin disappearance	Frakulli et al, ²⁴ Huang et al, ²⁶ Kato et al, ²³ Li et al, ¹⁵ Peulen et al ²⁷	5	50	157	22	12	44	92
Enlarging opacity at primary site	Frakulli et al, ²⁴ Huang et al, ²⁶ Li et al, ¹⁵ Peulen et al, ²⁷ Takeda et al ²¹	5	48	182	35	70	73	62
Cranio-caudal growth	Frakulli et al, ²⁴ Huang et al, ²⁶ Li et al, ¹⁵ Peulen et al ²⁷	4	45	135	39	26	87	81
New or enlarging unilateral/ipsilateral pleural effusion	Halpenny et al, ²⁵ Kato et al, ²³ Peulen et al ²⁷	3	26	131	10	80.5	38	39
Sequential enlargement	Huang et al, ²⁶ Peulen et al ²⁷	2	25	50	16	6	64	88
New mass	Halpenny et al ²⁵	1	8	83	0	6.5	0	92
Density increase	Halpenny et al ²⁵	1	8	83	4.5	66	56	20
Appearance of lymph node enlargement	Kato et al ²³	1	5	22	3	4	60	82

Combinations of high risk features (HRFs)

Table 5 Number of HRFs predictive of LR on CT post-SABR

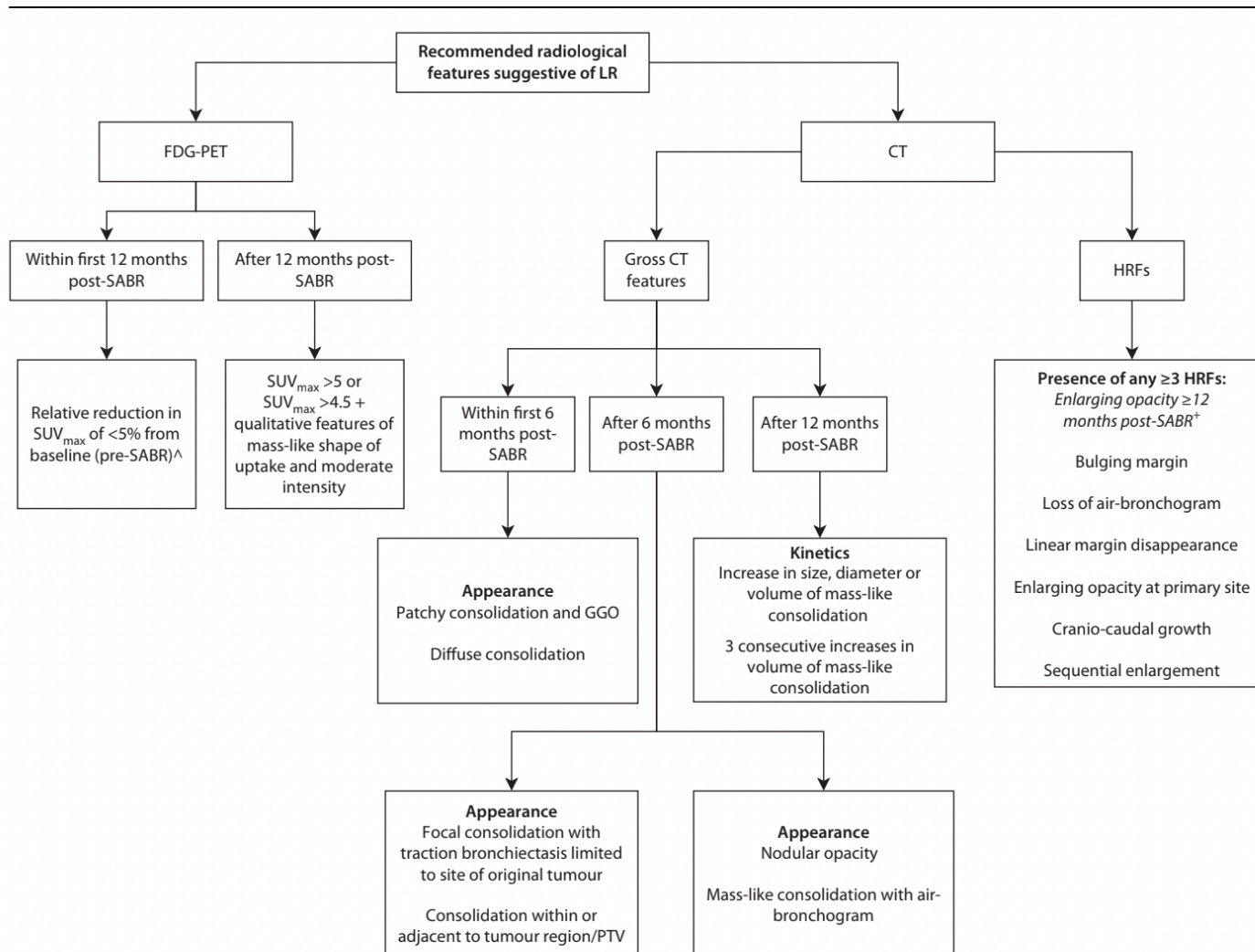
Number of HRFs identified	Studies measuring no. of HRFs	Studies measuring no. of HRFs	LR n	No recurrence n	LR cases n	No recurrence with no. of HRFs specified n	Sensitivity (%)	Specificity (%)
≥1 HRF	Frakulli et al, ²⁴ Huang et al, ²⁶ Li et al ¹⁵	3	32	109	31	47	97	57
≥2 HRF	Frakulli et al, ²⁴ Huang et al, ²⁶ Li et al ¹⁵	3	32	109	31	32	97	71
≥3 HRF	Frakulli et al, ²⁴ Huang et al, ²⁶ Li et al, ¹⁵ Takenaka et al ²⁸	4	40	151	34	13	85	91
≥4 HRF	Frakulli et al, ²⁴ Huang et al, ²⁶ Li et al ¹⁵	3	32	109	22	7	69	94
≥5 HRF	Huang et al, ²⁶ Li et al ¹⁵	2	19	77	12	2	63	97
≥6 HRF	Huang et al ²⁶	1	12	24	7	0	58	100
≥7 HRF	Huang et al ²⁶	1	12	24	4	0	33	100

Abbreviations: CT = computed tomography; HRF = high-risk feature; LR = local recurrence.
 The presence of a number of HRFs, either in isolation or concurrently, was studied by a number of studies as listed. The number of local recurrent cases and nonrecurrent cases with the cumulative presence of these HRFs were totalled and the sensitivities/specificities collated.

PET CT features post-SABR- SUV Criteria

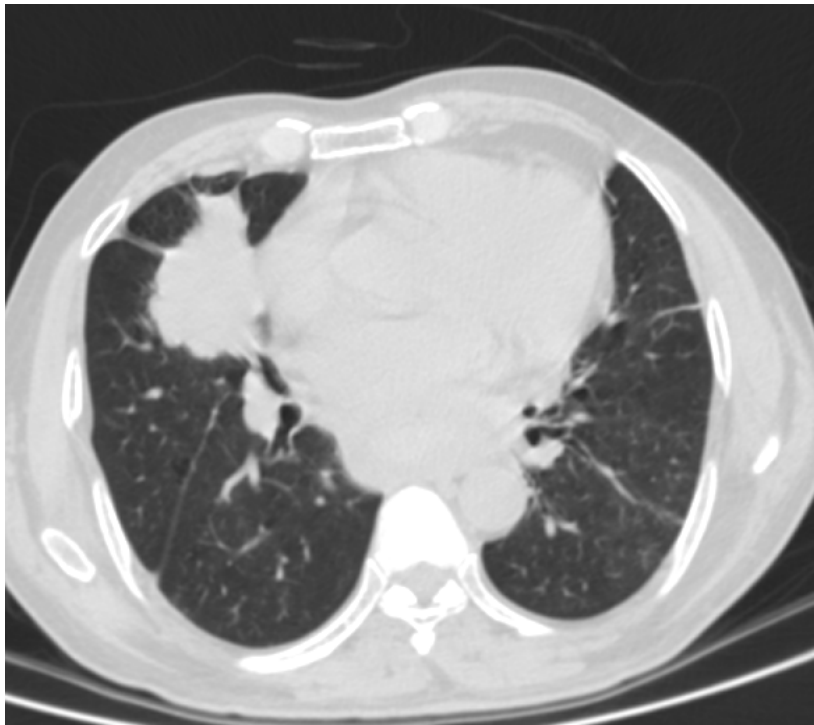
Table 6 Summary of findings on FDG-PET post-SABR

First 12 mo			≥12 mo			
Finding	Study n	LR n	Finding	Study n	LR n	
Relative reduction (from pre- to posttreatment timepoint) of SUV for whole cohort (including patients with LR)	Dahele et al ³⁶ n = 31	1	Relative increase (from pre- to posttreatment timepoint) of SUV _{max} of patients with LR and relative decrease (from pre- to posttreatment timepoint) of SUV _{max} of patients without recurrence	Gill et al ³⁹ n = 20	6	
	Vahdat et al ³² n = 20	1	Persisting residual low-level metabolic activity of SUV range 2.2-5.87 of up to 26 mo posttreatment in patients without recurrence	Hoopes et al ¹⁹ n = 28	0	
Relative reduction (from pre- to posttreatment) of SUV for patients with LR	Coon et al ³⁰ n = 28	2		Takeda et al ²¹ n = 4	1	
	Essler et al ³¹ n = 29	6	SUV _{max} of patients with LR consistently higher than those patients without recurrence in both recurrent and stage I disease at same timepoints	LR vs nonrecurrence (mean SUV _{max} ± SD [range]) 15.1 ± 7.43 [5.7-25.4] vs 2.95 ± 0.81 [1.85-4.5] at 12 mo	Hayashi et al ¹⁴ n = 20	5
Persisting residual low-level metabolic activity in RILI (SUV _{max} >3.5 at 52 weeks)	Henderson et al ³⁷ n = 14	0		LR vs nonrecurrence (SUV _{max} ± SD) 8.0 ± 3.2 vs 2.1 ± 0.9 at 6-12 or 12-24 mo	Nakajima et al ⁴⁰ n = 59	16
	Mohammed et al ³⁸ n = 39	0		<ul style="list-style-type: none"> • LR vs nonrecurrence on early images (obtained 60 mins after injection) (median SUV_{max} [range]) 5.0 [3.2-10.7] vs 1.8 [0.5-4.6] at 12.8 mo • LR vs nonrecurrence on late images (obtained 120 mins after injection) (median SUV_{max} [range]) 6.3 [4.2-13.4] vs 1.7 [0.5-6.1] at 12.8 mo 	Takeda et al ²² n = 214	21
SUV _{max} of patients with LR consistently higher than those patients without recurrence in both recurrent and stage I disease at same timepoints	Tyran et al ²⁹ n = 18	2		LR vs nonrecurrence (median SUV _{max} [range]) 7.5 [3.4-12.4] vs 2.1 [1.7-3.8] at 9-44 mo	Tan et al ⁴¹ n = 42	12
	Zhang et al ³³ n = 128	8		LR vs nonrecurrence in recurrent disease (median SUV _{max} [range]) 14.6 [10.5-18.6] vs 2.35 [1.1-5.2] at 11-14 mo	Tyran et al ²⁹ n = 18	2

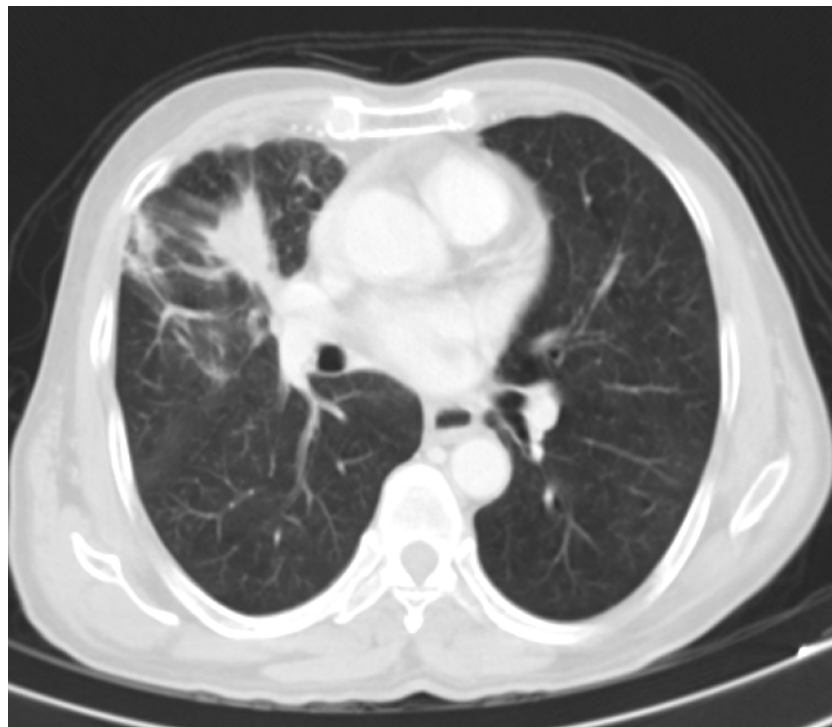


^Caution with using FDG-PET findings as sole indicator of LR within first 12 months

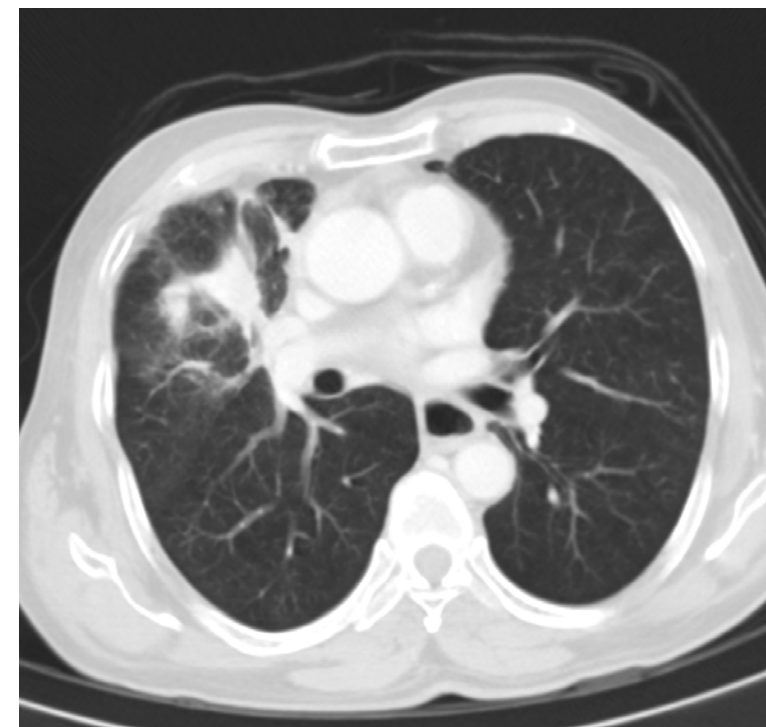
*Presence of the individual HRF of enlarging opacity ≥12 months post-SABR highly suspicious of LR



BASELINE 20.09.2021

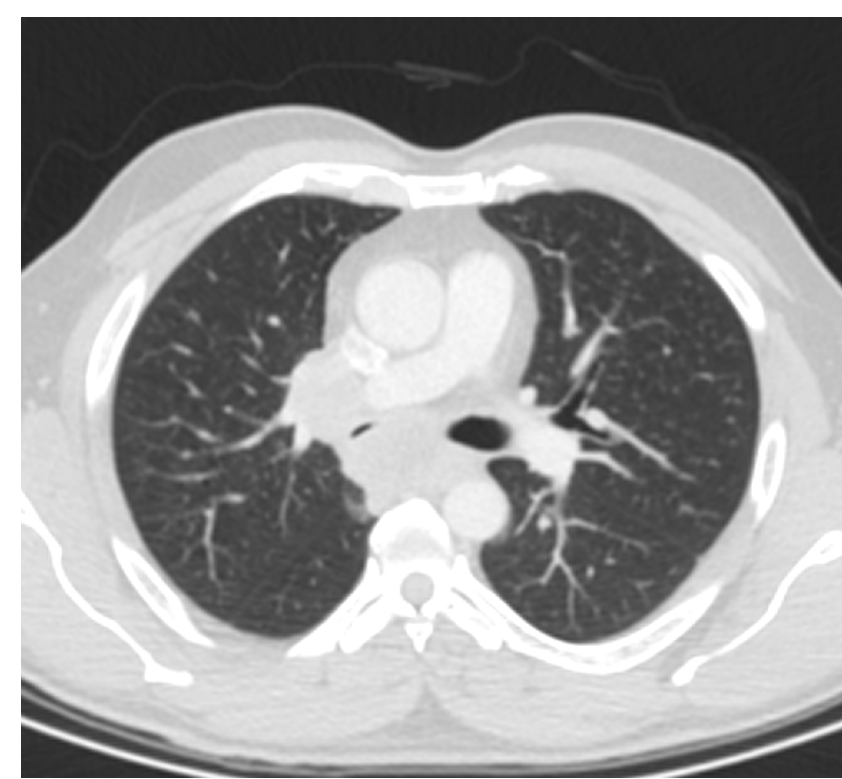


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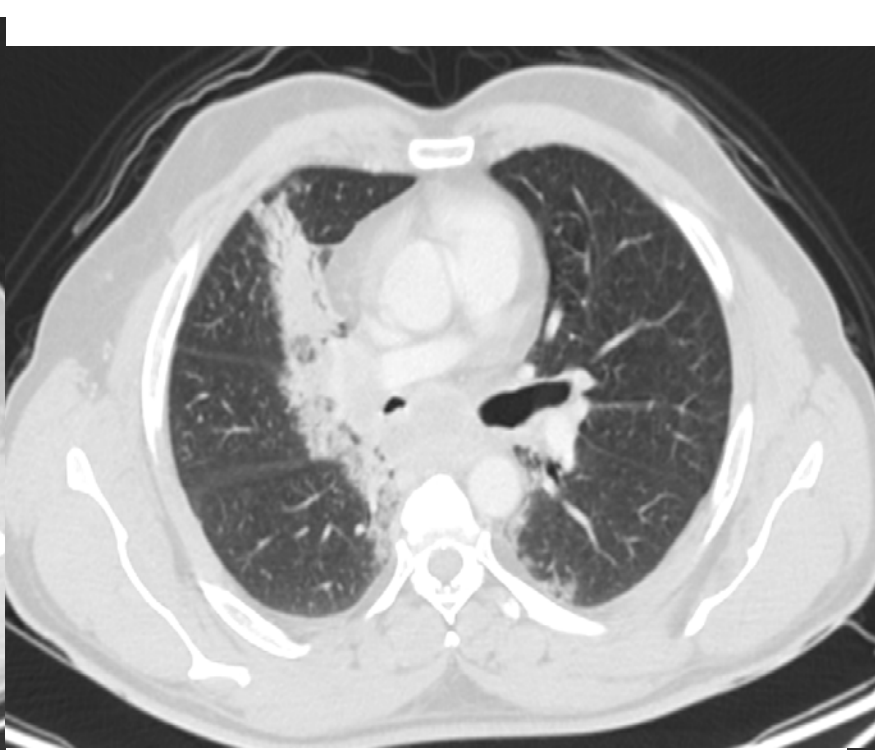


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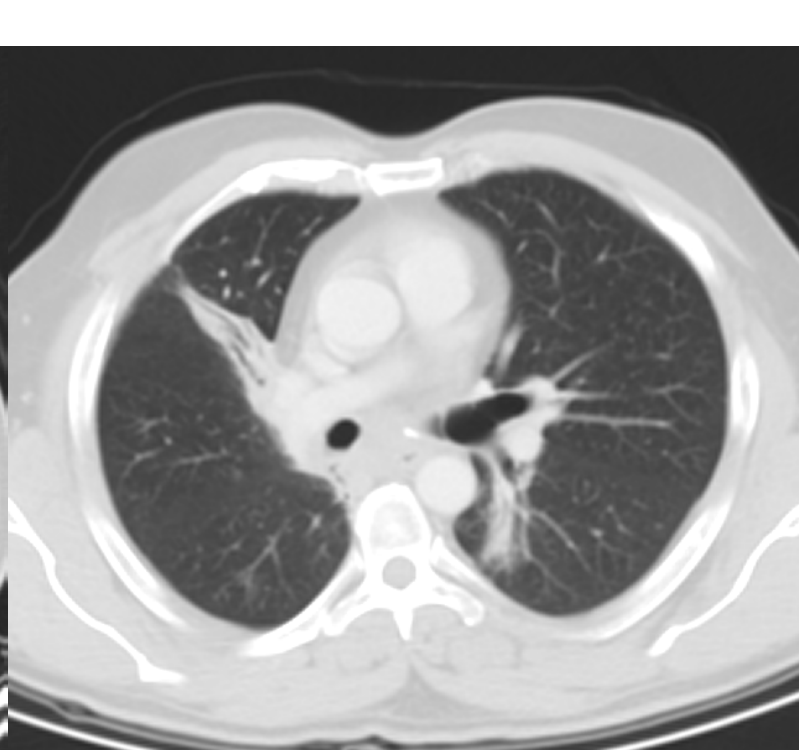
Post RADIATION



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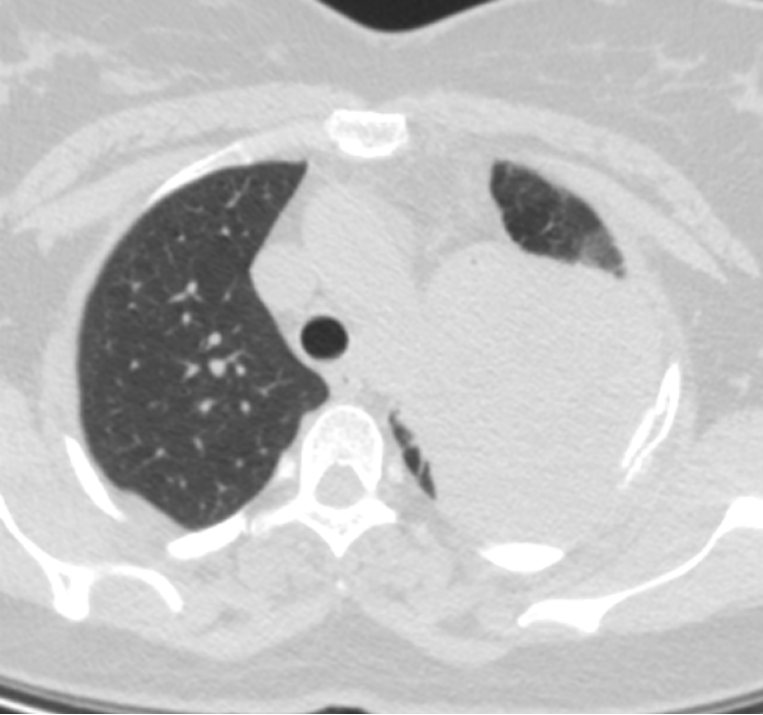
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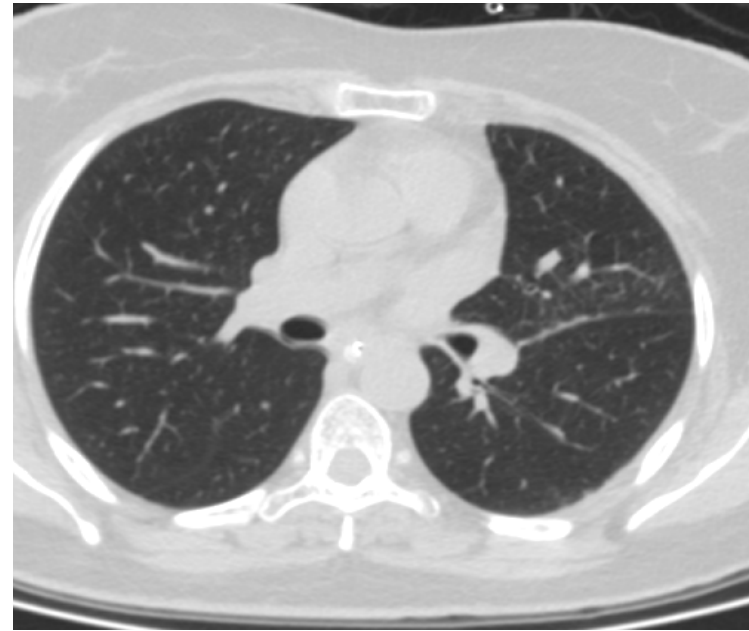
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REGRESSION OF RADIATION PNEUMONITIS

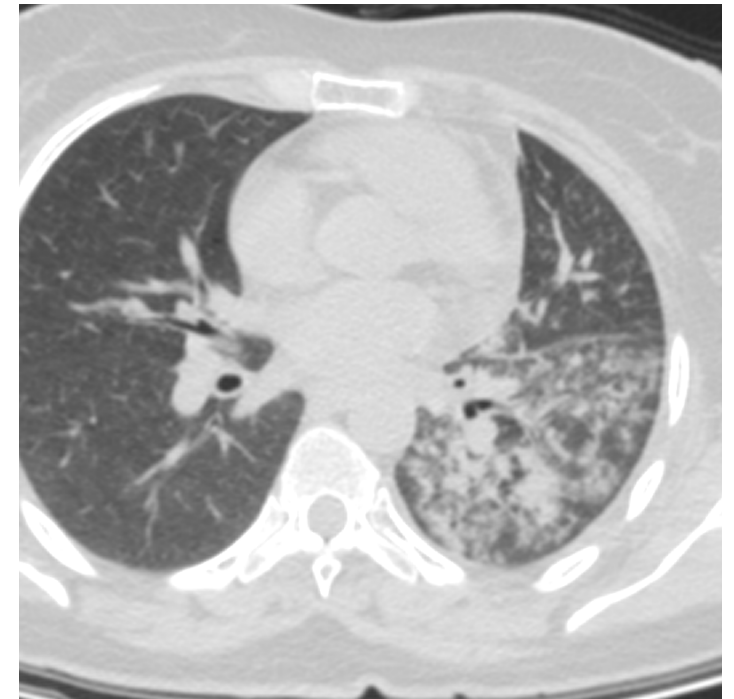
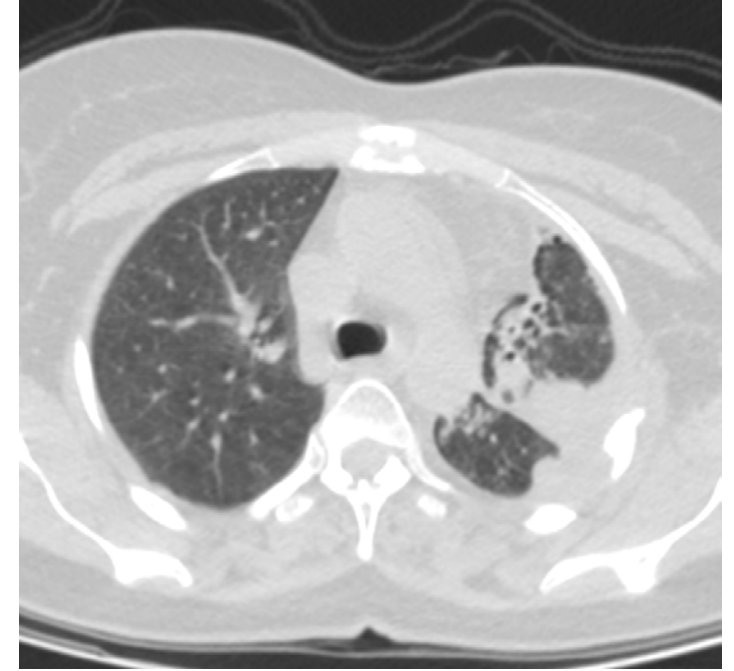
INCREASE IN RT
PNEUMONITIS



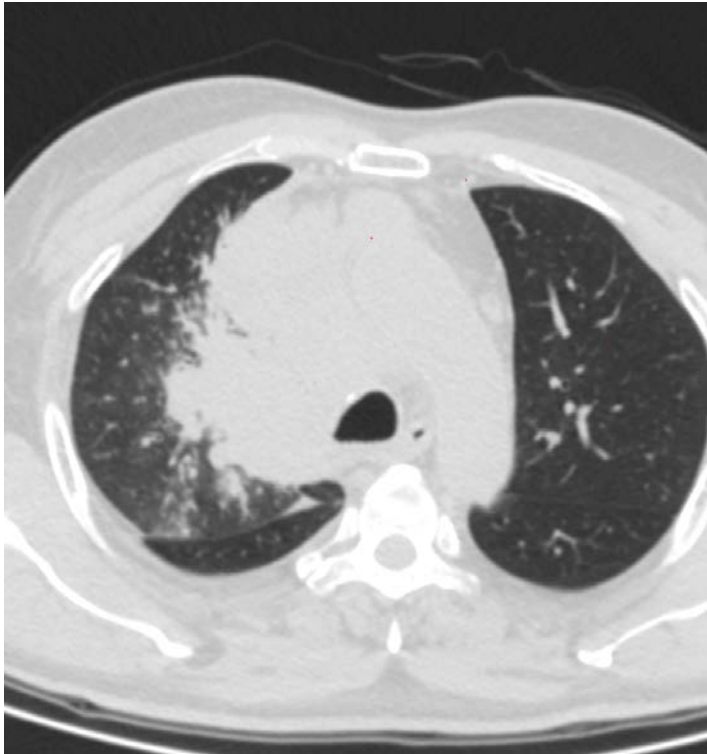
BASELINE



FIRST SCAN POST
RT



SECOND SCAN POST RT



BASELINE
22.06.2021



18.04.2022



25.07.2022

PD in background of radiation pneumonitis

Discussion

- ON CT, more heavily on the HRFs in the detection of LR on CT with the presence of any ≥ 3 HRFs and in particular the presence of the individual HRF of enlarging opacity ≥ 12 months post-SABR (which performed comparably in terms of sensitivity)
- On FDG-PET, within the first 12 months post-SABR, if the relative reduction of SUVmax from baseline is less than 5%, then this lack of reduction in SUVmax is suspicious for LR. The cut-offs of SUVmax > 5 or SUVmax > 4.5 with qualitative features of masslike shape of uptake and moderate intensity being present are more reliably

- first 12 months post-SABR the evidence in support of strongly performing radiologic features was weaker than that after the initial 12-month period.
- Within the first 6 months post-SABR, there are limited data available to support definitive features of LR on CT imaging.
- Gross macroscopic CT changes are likely to fall out of fashion as the area moves further away from RECIST criteria and more toward HRFs.

- Thank you