



HAL
open science

Stereotactic body radiation therapy (SBRT) as salvage treatment for early stage lung cancer with interstitial lung disease (ILD): An observational and exploratory case series of non-asian patients

J. Pluvy, A. Zaccariotto, P. Habert, J. Bermudez, A. Mogenet, J.Y. Gaubert, P. Tomasini, L. Padovani, L. Greillier

► To cite this version:

J. Pluvy, A. Zaccariotto, P. Habert, J. Bermudez, A. Mogenet, et al.. Stereotactic body radiation therapy (SBRT) as salvage treatment for early stage lung cancer with interstitial lung disease (ILD): An observational and exploratory case series of non-asian patients. *Respiratory Medicine and Research*, 2023, 83, pp.100984. 10.1016/j.resmer.2022.100984 . hal-03962927

HAL Id: hal-03962927

<https://amu.hal.science/hal-03962927>

Submitted on 5 Apr 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

1 Stereotactic body radiation therapy (SBRT) as salvage treatment for early stage
2 lung cancer with interstitial lung disease (ILD): An observational and exploratory
3 case series of non-Asian patients.

4
5
6
7 **Authors:** J.Pluvy, A.Zacariotto, P.Habert, J.Bermudez, A.Mogenet, JY.Gaubert, P.Tomasini, L.Padovani,
8 L.Greillier;

9
10 **Affiliations:**

11 Dr PLUVY Johan, MD, Department of Multidisciplinary Oncology and Therapeutic Innovations Assistance
12 Publique Hôpitaux de Marseille AP-HM, Hôpital Nord, Marseille, France

13
14 Dr ZACCARIOTTO Audrey, MD, Department of Radiation Oncology, Assistance Publique Hôpitaux de
15 Marseille AP-HM, Marseille, France

16
17 Dr. Paul HABERT, MD PhD Radiology department, Hôpital Nord, AP-HM, Aix Marseille Univ, LIIE, Marseille,
18 France; Aix Marseille Univ, CERIMED, Marseille, France

19
20 Dr. Julien BERMUDEZ, MD, Department of Respiratory Medicine and Lung Transplantation, Assistance
21 Publique - Hôpitaux de Marseille APHM, Hôpital Nord, Marseille ; Aix -Marseille University, France

22
23 Dr MOGENET Alice, MD, Aix Marseille University, Department of Multidisciplinary Oncology and
24 Therapeutic Innovations Assistance Publique Hôpitaux de Marseille AP-HM, Hôpital Nord, Marseille, France

25
26 Pr GAUBERT Jean Yves, MD, Radiology Department, Hôpital Nord, Assistance Publique Hôpitaux de
27 Marseille AP-HM, Marseille, France

28
29 Dr TOMASINI Pascale MD, PhD Aix Marseille University, Assistance Publique Hôpitaux de Marseille AP-HM,
30 Department of Multidisciplinary Oncology and Therapeutic Innovations. Marseille, France; Centre de
31 Recherche en Cancérologie de Marseille (CRCM), Inserm UMR1068, CNRS UMR7258, Marseille, France.

32
33 Pr PADOVANI Laeticia MD Department of Radiation Oncology, Assistance Publique Hôpitaux de Marseille
34 AP-HM, Marseille, France

35
36 Pr GREILLIER Laurent MD, PhD, Aix Marseille University, APHM, INSERM, CNRS, CRCM, Hôpital Nord,
37 Multidisciplinary Oncology and Therapeutic Innovations Department, Marseille, France

38
39
40 Address correspondence to Dr Johan PLUVY, Multidisciplinary Oncology and Therapeutic Innovations
41 Department, AP-HM, Marseille, France

42 Landline: +33491965901

43 E-mail: johan.pluvy@ap-hm.fr

44
45 **Author contributions**

46 JP had full access to all of the data in the study and take responsibility for the integrity of the data and the
47 accuracy of the data analysis. Concept and design: JP,AZ,PH,LP,PT,LG Acquisition, analysis, or interpretation
48 of the data: all authors. Drafting of the manuscript: JP,PH Critical revision of the manuscript for important

49 intellectual content: all authors. Statistical analysis: JP Administrative, technical, or material support: all
50 authors Supervision: JYG,LP,PT,LG

51
52 **Declaration of competing interests**

53 JP,AZ,PH,JB,AM,GJY,PT,LP,LG nothing to disclose related to the work

54
55

56 Keywords: Stereotactic Radiation Therapy; Interstitial Lung Disease; Carcinoma, Non-Small Cell Lung,
57 Follow-up Studies

58
59
60
61 **Abstract:** (225 words): Interstitial lung disease (ILD) can coexist with early-stage lung cancer (LC) and may
62 compromise surgery and worsen patients' outcomes. Stereotactic body radiation therapy
63 (SBRT) is the gold standard treatment for medically inoperable early-stage lung cancer, but radiation
64 therapy is contra-indicated for patients with ILD because of the higher risk of severe radiation-induced
65 pneumonitis. SBRT may spare healthy lung tissue, but data are scarce in this rare population. Our
66 exploratory case series aimed to retrospectively identify patients treated with SBRT in this setting: 19
67 patients were diagnosed with early-stage LC-ILD over the past 6 years and 9 received SBRT. Most of them
68 were smokers with a median age of 71, 4 had no pathological documentation. After SBRT, 5 patients had
69 grade I-II respiratory adverse events (AEs), but none had treatment-related grade III-IV respiratory AEs.
70 Two patients died within 6 months of SBRT, and for both, death was related to metastatic relapse. In this
71 case series, the radiological evolution of ILD before radiotherapy and the evolution of the radiotherapy
72 scar on CT-Scan were also explored with different evolutionary models. This exploratory study shows
73 available data that could be studied in a larger retrospective cohort to identify risk factors for SBRT in the
74 LC-ILD population. The use of dosimetric data as a risk factor for SBRT should be done with cautiousness
75 due to heterogeneous and complex dose delivery and different fractionation schedule.

79
80 Introduction:

81 Lung cancer (LC) shares common pathophysiology and risk factors with interstitial lung disease (ILD)
82 (1). LC incidence is increased in patients with idiopathic pulmonary fibrosis (IPF) (2). A French cohort
83 identified ILD in approximately five percent of newly diagnosed LC cases (3). Interstitial lung disease-lung
84 cancer (LC-ILD) refers to patients with co-existing LC and ILD.

85 ILD has an impact on the diagnosis and prognosis of LC: in a French cohort, 19% of patients with
86 combined pulmonary fibrosis and emphysema (CPFE) did not have histologically proven LC (2).
87 Furthermore 42% of patients in this study did not receive the appropriate standard of care. According to a
88 Japanese cohort of LC-ILD patients who underwent surgical resection, death was related to an
89 exacerbation of interstitial pneumonia in approximately 10% of patients (189/1763 patients). Independent
90 predictors of mortality in this study were low forced vital capacity (%FVC), histopathologic stage, male
91 gender, type of surgical procedure, and tumor location (4). These patients also had a higher risk of cancer
92 (50% relapse).

93 Stereotactic body radiation therapy (SBRT) is the preferred treatment for early-stage LCs without a
94 history of ILD refusing surgery, medically inoperable or at high operative risk. SBRT is defined as a
95 radiotherapy technique with modern targeting and planning technologies to deliver higher doses with
96 lower fractions (60Gy 3-8 fractions). This technique can decrease short-term toxicity with higher rates of
97 local control and promising potential long-term cancer control (5,6).

98 Conventional radiotherapy is contraindicated for patients with severe ILD because of the high risk
99 of radiation-induced pneumonia or flare of existing interstitial pneumonia. Data are limited to series
100 showing a higher risk of radiation-induced pneumonia and death (7,8) but these series over represent
101 asian patients. This risk appears to be increased in subclinical ILD (9). SBRT may spare healthy lung but
102 serious and increasing risks of radiation pneumonitis have been reported to date in patients with
103 subclinical ILD. In a nationwide Japanese survey, most of grade V radiation pneumonitis had underlying ILD
104 (10).

105 Despite the risks, a recent international survey (DIAMORFOSIS) (11) identified radiation
106 therapy as the preferred treatment choice (54.1 % of physicians) for patients with mild-to-moderate ILD
107 (DLCO>35% and FVC > 50 %) with stage I or II LC.

108 This leads to a clinical dilemma: on the one hand, SBRT may cause respiratory adverse effects, but the
109 other options are high-risk surgery or even systemic therapy. It is also difficult to identify patients who
110 might benefit from each treatment or avoidance of treatment in this setting.

111 In this study, we aimed to retrospectively identify patients with pre-existing ILD associated with
112 stage I lung cancer or an unproven highly suspicious nodule treated with SBRT and to describe their clinical,
113 functional and radiological outcomes.

114 Materials and methods

115

116 We performed a single-centre retrospective study of a cohort of consecutive patients with LC-ILD
117 managed between April 2015 and December 2021 in the Department of Thoracic Oncology and Radiation
118 Oncology in Marseille. LC-ILD patients were identified through electronic patients' records. We enrolled
119 patients with histologically or cytologically proven LC or with a high probability of LC (evolving nodule, PET-
120 CT hypermetabolism) but a high risk of complication after biopsy as defined by multidisciplinary board
121 discussion according to European guidelines (12).

122 Demographic, clinical and treatment (radiotherapy modality, total dose, total treatment time,
123 number of fractions and dose per fraction, V20, V12.5 and mean lung dose (MLD)) data were collected
124 retrospectively. We performed ILD-GAP when indicated. Available CT scans performed at diagnosis and
125 before/after SBRT were reviewed by a thoracic radiologist to examine the ILD pattern and to assess the
126 evolution of images before and after SBRT.

127 Early death or grade 3-4 respiratory adverse events (AEs) were the co-primary study endpoints. AEs
128 were graded according to the Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0); early
129 death was defined as occurring within 6 months after SBRT.

130 Secondary objectives were the description of disease-free survival (DFS) and overall survival (OS)
131 but also the description of specific clinical, functional, radiological outcomes before and after SBRT. Clinical
132 events were assessed according to CTCAE v5.0. Functional worsening was defined by 10 % decrease in
133 predicted FVC or 15 % decrease in Diffusing Capacity for Carbon monoxide (DLCO) predicted over 12
134 months. Imaging characteristics were assessed by a radiologist as: location of the nodule in healthy or
135 pathological parenchyma; progressive ILD before SBRT; visual quantification of fibrosis: mild (<10%),
136 moderate (10-25%), high (25-50%), severe (50-75%) and extreme (>75%) following the recently published
137 classification to evaluate the severity of COVID-19 pneumonia (13). The radiologist also assessed imaging
138 progression after SBRT: radiotherapy scar (volume and maximum 2D size), occurrence of radiation
139 pneumonitis, progression of the extent of fibrosis and type (densification or new lesions).

140 This is an exploratory study, conducted to design and estimate the feasibility of recruiting a
141 definitive, adequately powered, larger-scale multicenter retrospective cohort. Descriptive analysis was
142 performed using headcounts for discrete variables, median values and interquartile range (IQR) for
143 continuous data. Because of the limited sample size, we could not perform statistical analysis to identify
144 parameters involved in early death or grade III-IV respiratory AEs. OS was defined as the time from Day 1 of
145 SBRT to patient death from any cause. DFS was defined as the time from Day 1 of SBRT and disease
146 progression or death from any cause. Data were censored at the end of the study (December 2021). Kaplan
147 Meier curves were performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk,
148 N.Y., USA).

149 In accordance with French regulation on retrospective observational studies, no objection to the
150 use of anonymously retrospective data was identified. The study was registered at RGPD/AP-HM
151 (registration number #2021-52) and approved by local Institutional Review Board.

152 Results:

153 Between April 2015 and December 2021, 1361 patients with ILD were identified in our center,
154 including 38 patients identified with LC-ILD. Of these, three had small-cell lung cancer and 16 had advanced
155 non-small cell lung cancer. Of the 19 patients with early-stage LC-ILD, three received conventional

156 radiotherapy, seven received surgery and nine SBRT (**Figure 1**). Among these nine patients who received
157 SBRT for the treatment of LC-ILD, 6 were men, with a median age of 71 (range 59–89). 8 out of 9 patients
158 were heavy smokers (> 40 pack-years), including 4 active smokers. All were ECOG Performance Status (PS) 0
159 or 1 at the time of radiotherapy. Baseline demographics, pulmonary characteristics and disease and
160 treatment data of LC-ILD patients treated with SBRT or surgery are detailed in **Figure 1**.

161 4 patients had no cytologically or pathologically proven LC. Of those who had a tissue sample, all
162 were performed by CT-guided Trans-thoracic Needle Aspiration. All were stage I (12 to 21 mm) in various
163 peripheral sites. Baseline clinical, functional, imaging data with pattern and evolution after SBRT are
164 reported in **Table 1**. All patients had a diagnosis of ILD at the time of SBRT and underwent multidisciplinary
165 discussion. Coexisting emphysema was found in 5 patients. All patients underwent a pretherapeutic workup
166 with pulmonary functional test (PFT).

167 After SBRT, 5 patients experienced clinical respiratory AE. None of the patients experienced grade
168 III-IV treatment related respiratory AE. For patient #2, corticosteroid dose was temporarily increased with a
169 one-week course of antibiotics and patient #9 received one week of antibiotics and two weeks of
170 prednisone (20 mg/day).

171 Two patients died within 6 months after SBRT and for both, death was related to metastatic
172 relapse. Median OS was 17.4 months (IC95% 8.4-26.4), and further risk factors analyses were not possible
173 because of the small size of this population. Median DFS was 13.5 month (IC95%:5.7-21.2) (**Figure 2**). Three
174 patients had functional worsening, but data were missing for two patients.

175 All patients had baseline and follow-up imaging. Two patients (#5 and #8) did not have any PET-CT
176 before SBRT. These patients did not experience early relapse. Expert radiologists quantified the extent of
177 ILD by visual assessment ranging from mild to severe and found a deterioration of ILD before SBRT in 5
178 patients. Five other patients had radiation pneumonitis on CT scan during the first year after SBRT and
179 most of them had worsening of ILD (new lesion and extent of ILD) during follow up. Evolution of

180 radiotherapy scar volume (cm³) was also collected (**Figure 3**). For example, we displayed Patient #2 imaging
181 follow-up and parenchyma evolution after SBRT on **figure 4**.

182 Discussion:

183 In this case series, SBRT was performed as salvage therapy for LC-ILD in nine patients. Two of them
184 died less than sixth months after SBRT but in both cases, death was related to metastatic relapse and not
185 to a respiratory AE. An initial assessment of oncologic disease should be performed using PET-CT and brain
186 MRI, especially in such risky circumstances, to prevent early relapse, especially for high-risk treatment. In
187 addition, unlike surgery, SBRT does not assess mediastinal lymph node involvement. It should also be
188 noted that the good outcomes can also be explained by the fact that 4 patients did not have histologically
189 proven LC and that, despite criteria suggesting malignancy, the nodules seen in these 4 patients could be
190 benign. Furthermore, OS was not significantly better than DFS, which could be explained by the fact that 5
191 patients had metastatic relapse and that systemic treatment options after relapse may be limited for these
192 patients due to their general condition and limited access to innovative therapies such as immune
193 checkpoint inhibitors or targeted therapies and a worse expected tolerance to chemotherapy with a higher
194 risk of ILD exacerbation.

195 It is very important to say that 5 patients had respiratory AE but fortunately none of them
196 experienced grade III or IV events. Therapeutic management (by antibiotics, diuretics or corticosteroids) of
197 pulmonary AEs was assessed in our study, but these data are questionable as reports may be missing
198 especially for outpatient management.

199 ILD is considered as a risk factor for severe radiation pneumonitis after conventional 3D conforming
200 radiotherapy: subclinical ILD was associated to grade II to V radiation pneumonitis in previously reported
201 studies (9). Four of the patients who died in a Korean retrospective study had diffuse interstitial change in
202 pre-RT CT-scan (14). Standard radiotherapy is therefore contra-indicated in current guidelines for patients
203 with ILD.

204 SBRT may spare healthy lung, but some studies also identified pre-existing ILD as a risk factor of
205 radiation-induced pneumonitis: pre-existing interstitial pneumonitis shadow, on CT-scan was well

206 correlated to severe radiation pneumonitis (1-year cumulative incidence of 57 % with existing interstitial
207 pneumonitis shadow versus 2 % without) in Yamashita study (15). The implementation of such pre-
208 screening reduced the incidence of radiation pneumonitis. Another Japanese study identified 16 % of
209 subclinical ILD: grade II-V radiation pneumonitis was identified in three out of 16 patients with subclinical
210 ILD. In terms of disease control, no significant differences were identified in OS and 3 years local control
211 rates between the group with and without ILD (16). These results should be taken with caution and further
212 research is needed to clarify this issue (17). Ueki (18) study retrospectively included 157 patients treated
213 with SBRT including 20 ILD patients. Pre-existing ILD was also identified as a risk factor for grade II (HR: 5.52
214 [2.43-12.5]) and grade \geq III (HR 6.96 [0.98-49.7]) radiation pneumonitis.

215 In the LC-ILD population, Median Lung Dose (MLD), V20, V30 and normal tissue complication
216 probability (NTCP) seem well correlated to the incidence and severity of radiation pneumonitis for
217 standard radiotherapy (14).

218 In a systematic review of 13 different studies of SBRT, authors suggest that $V20 \leq 6.5\%$ and mean lung dose
219 ≤ 4.5 Grays (Gy) were associated to reduced mortality (19). In another study, severe radiation pneumonitis
220 was not correlated with dose-volume histogram parameters (15). In our series, only two patients had a V20
221 $>6.5\%$ and MLD > 4.5 Gy, and both had worsening ILD extension and appearance of new ILD lesions
222 without determining the potential SBRT imputability due to the small size of the series. It is very important
223 to understand that the use of dosimetric data as a risk factor for SBRT such as V20 should be done with
224 caution. Indeed, the modalities of SBRT prescription and dose are complex and are not always available in
225 published studies (maximum dose, prescription isodoses, type of radiotherapy, overall treatment course)
226 and therefore the published data are only valid for the patients of the center. This heterogeneity in
227 treatment modalities prevents extrapolation of results presented in the literature. A quality control of
228 dosimetry would be mandatory in order to be able to conclude on this point in future studies.

229 Chronic ILD are heterogeneous. Accurate diagnosis and classification influence both prognosis and
230 treatment. IPF has the poorest prognosis of the fibrosing ILD due to the predominance of fibrosis, whereas

231 inflammation may coexist or pre-exist with fibrosis in non-IPF ILD. Gender, age and lung function tests (FVC
232 and DLCO) are important predictors of survival, but the ILD subtype should be considered as it influences
233 survival in risk prediction models such as the ILD-GAP model (20).

234 A subset of patients may have a progressive decline affecting outcomes and treatment choice: progressive
235 fibrosing interstitial lung disease (PF-ILD) is characterised by a decline over the past 2 years defined as
236 relative FVC of at least 10% of predicted value, decline in relative FVC of 5-10% of predicted value, and
237 worsening of respiratory symptoms or increase in the extent of fibrosis on high-resolution CT.

238 Antifibrotic therapy with nintedanib or pirfenidone can slow down the decline in lung function in IPF, with
239 an expanded indication for PF-ILD with nintedanib (21). We tried to identify the radiological course of ILD
240 before radiotherapy. It might be interesting to study whether such a prior course is associated with a more
241 negative effect of radiotherapy or other local treatments. The evolution of the radiotherapy scar on CT-
242 Scan was also explored (Figure 3) and different evolutionary patterns could emerge such as hypertrophic,
243 stable or regression for this type of population and it could be interesting to correlate it with functional
244 decline and to different isodoses.

245 Remarkably, 8 patients had a LC located in the parenchyma affected by ILD. This seems to be
246 consistent with the literature where tumor nodules are usually found in fibrotic areas in about 68% of
247 cases (1). Whether the treatment of a nodule located in a fibrotic area might have better results compared
248 with a healthy parenchyma by preserving it remains an open question. But on the other hand, a proximal
249 nodule could have a different histology with a worse prognosis, such as small cell lung cancer, or treatment
250 of the fibrotic area could trigger an exacerbation of fibrosis in the healthy parenchyma.

251 Moreover, our study involves non-Asian patients whereas most existing studies in LC-ILD involve
252 Japanese patients. Epidemiological data suggest ethnic differences between the Japanese population, and
253 the rest of the world, potentially related to genetic factors: acute exacerbation of IPF may be more
254 frequent and respiratory AE induced by EGFR (Epidermal Growth Factor Receptor) Tyrosine Kinase

Inhibitors is also more frequent in Japan (22). This suggests the importance of performing the same analysis for non-Japanese patients and determine whether the results are similar.

In our study, radiological patterns were reviewed by expert radiologist and all patients had Multidisciplinary discussion, Heterogeneity of ILD patterns, function status and types of treatments is another important issue for further studies. An effort should be made for accurate collection of these data in order to identify the best predictive model. As already studied before surgery, the role of preventive anti-inflammatory or antifibrotic therapy and the identification of the potential target population has to be studied in this setting.

Here we studied the role of SBRT, but a literature review of different treatments (19) identified that the weighted proportion of treatment-related mortality (and ILD-specific toxicity) depended on the type of treatment: 2.2 (12%) after surgery ,15.6 (25%) after SBRT, 4.3 (18,2%) after particle beam therapy and 8.7 (25%) after radiofrequency ablation (RFA). Efforts must also be made to define the best therapeutic decision for this population.

A prospective Canadian phase II study is recruiting patients treated with SBRT for LC-ILD (T1-2N0M0). Survival and toxicity outcomes of 3 different cohorts stratified by the severity of ILD (ILD-GAP index) are being assessed. In this study, SBRT (50Gy in 5 fractions with pre-specified de-escalation rules) is delivered using rotational therapy (volumetric modulated arc therapy, or Tomotherapy) or static beams (3D conformal or intensity modulated radiotherapy) (23).

Our study was a feasibility study, with some limits since not all patients had histologically proven LC, but this reflects the daily practice with some patients not eligible for biopsy due to the high risk of pneumothorax or haemoptysis induced by the procedure.

Another challenge was to identify these rare patients: we used the ICD-10 diagnosis code. This method unambiguously identifies ILD, it nevertheless involves a selection bias with potentially more severe patients but reflecting the reality of the practice and on the other hand avoiding recall bias. In our cohort, we identified about 3% of lung cancers among the 1361 patients followed for ILD, which means that we

280 could not identify with this method patients with undiagnosed ILD or patients with interstitial lung
281 abnormalities (ILAs) which are an independent risk of mortality with predominantly subpleural fibrosis
282 (24). The prevalence of ILAs is 4 to 9% in smokers over 60 years old. The study of the effects of lung cancer
283 treatments on patients with ILAs is another important research topic.

284 In conclusion this feasibility study has identified various retrospective data that are readily available
285 in order to define what could be useful for a larger retrospective cohort. Defining poor prognosis criteria
286 for such heterogeneous population could be valuable for designing clinical trials with the objective to
287 prevent potential harmful toxicities and adequately select patients who could benefit from the treatment.
288 The use of dosimetric data as a risk factor for SBRT should be done with cautiousness due to
289 heterogeneous and complex dose delivery and various modalities of prescription which is a specific
290 concern to take in account for future studies.

291
292 (3016)

words

Patients Variables	#1	#2	#3	4#	#5	#6	#7	#8	#9
Gender (age year)	M (59)	M (72)	M (80)	M (66)	F (66)	M(75)	M (71)	F(71)	F(89)
Smoking (pack-year)	active(10)	never	former (40)	former (40)	former (75)	former (50)	active (60)	active (60)	active (45)
Date of ILD Diagnosis	2000	2005	2016	2011	2016	1999	2003	2019	2019
Biopsy TTNA	Yes (ADC)	No	No	No	Yes (ADC)	No	Yes (Sq)	Yes (ADC)	Yes (ADC)
Emphysema	Yes	0	Yes	0	Yes	Yes	Yes	0	0
Radiology Pattern	NSIP	UIP	NSIP	UIP	UIP	CBD	UIP	OP	OP
MDD diagnosis	CTD-ILD	CTD-ILD	CPFE	IPF	CPFE	CBD	CTD-ILD	OP	OP induced by statin
Nodule in Pathological parenchyma	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
ILD imaging worsening before radiotherapy	No	No	No	Yes	No	Yes	Yes	Yes	Yes
Visual Fibrosis quantification	Moderate 10-25	Moderate 10-25	High 25-50	High 25-50	Severe 50-75	Severe 50-75	High 25-50	Mild <10%	Moderate 10-25
Date of radiotherapy treatment (type)	01/2019 (IMRT tomotherapy)	09/2019(IMRT tomotherapy)	07/2019 (Cyber knife®)	03/2018 (True Beam®)	04/2018 (True Beam®)	06/2020 (IMRT tomotherapy)	12/2018(IMRT tomotherapy)	11/2019 (IMRT tomotherapy)	01/2020 (IMRT tomotherapy)
Dose (Gy) / Fraction / Dose per fraction	60/8/7.5	60/8/7.5	54/3/18	50/10/5	60/8/7.5	45/5/9	59.5/7/8.5	60/5/12	60/8/7.5
Overall treatment duration (d)	17	13	4	26	13	11	5	8	16
V20/V12,5/MLD	3%/6%/2.5Gy	4.3%/9%/4.2Gy	0.9%/1.3%/1.72Gy	5%/7.5%/3.6Gy	3.6%/7.5%/3,8 Gy	1.5%/3.3%/6Gy	8.9%/13.5%/6Gy	2.7%5.5%/2.5Gy	6.6%13%/4.9Gy
Overall Survival (month)	34.9	19	5.4	17.4	7.8	4.8	20.8	24.3	14.3
Relapse (Vital Status)	Metastatic (Alive)	Metastatic (Dead)	Metastatic (Dead)	Metastatic (Dead)	NO (Dead: COPD exacerbation)	Metastatic (Dead)	Metastatic (Dead)	NO (Alive)	NO (Dead :myeloid Leukemia)
DFS (months)	13.5	7.4	3.7	7.9	7.8	3.6	14.6	24.3	14.3
GAP-Index (%1y mortality)	I (5.6 %)	III (39.2%)	II (16.2%)	III (39.2%)	II (16.2%)	N.A	II (16.2%)	N.A	N.A
PFT before radiotherapy	12/2018	05/2019	11/2018	01/2018	10/2017	06/2020	11/2018	10/2015	01/2020
FVC (%Pred)	3130(77)	2600(63)	2710(77)	2480(52)	1700(79)	2230(61)	1810(66)	3000(114)	2470(103)
DLCO(%Pred)	39	23	24	29	22	24	60	NA	NA
Respiratory AE after RT (grade) Treatment	Yes (1)	Yes (2) -Antibiotics 7days -Temporary Prednisone increase dose	No	No	Yes (2)	No	No	Yes (1)	Yes (2) -Antibiotics 7days -Prednisone 14days (20mg/d)
Lung function decline (%FVC)	Yes (-11%)	Yes (-15%)	No (-9%)	No (-4%)	NA	NA	NA	No (-9%)	Yes (-23%)
Radiation pneumonitis (time to occur)	No	Yes (5m)	No	Yes (11m)	No	No	Yes (11m)	Yes (3m)	Yes (3m)
CT ILD acute worsening	Yes (6m)	No	Yes (3m)	No	No	No	No	No	Yes (3m)
CT ILD chronic worsening; Extent (month)	No	No	No	No	No	No	Yes (11m) Yes (18m)	No	Yes (8m)
CT ILD worsening new lesions (month)	No	Yes (14m)	No	No	No	No	Yes (20m)	Yes (13m)	Yes (8m)

Captions :

Figure 1: Study Flow chart: Distribution of patients with probable lung cancer and Interstitial Lung Disease (LC-ILD) and Baseline Oncological and demographic data of patients with early-stage LC-ILD treated with SBRT and Surgery *N: headcounts, IQR: Interquartile Range, CT : Computed Tomography , TTNA : Trans-thoracic Needle Aspiration , ADK : Adenocarcinoma Sq : Squamous*

Figure 2: Kaplan Meier Curves for Overall survival and Disease-Free Survival for the 9 patients. OS and DFS were considered for all patients: the time origin was set at the first day of radiotherapy treatment and the status of each patient (alive, dead, or lost to follow-up, relapse) was determined on the study termination date (set at December, 2021)

Figure 3: Radiotherapy scar volume evolution after SBRT (cm³)

Figure 4: Example of patient #2 with Sjögren's syndrome and interstitial lung disease (ILD). A) Axial parenchyma view of unenhanced chest CT showing traction bronchiolectasis (arrowhead) and scissural distortion (white thin arrow). B) Two years after during follow-up, ILD was stable but a subpleural nodule appears in the lingula, C) with hypermetabolic activity on PET-CT. This nodule was a biopsy proven adenocarcinoma and was treated by stereotactic body lung radiation therapy, D) follow-up six months after the end of SBRT showed an acute radiation pneumonitis (white arrow with black line) and E) one year after a consolidation of the radiation pneumonitis with a mild extend of ILD without new lesions.

Table: Baseline and evolution of clinical, function and imaging after stereotaxic radiotherapy. *ADC: adenocarcinoma, AE: adverse events, CBD: chronic beryllium disease, CPFE: combined pulmonary fibrosis and emphysema, CTD-ILD: connective tissue disease associated with ILD, DLCO: diffusion capacity of the lung for carbon monoxide, FVC: forced vital capacity, Gy: Gray, ILD: interstitial lung disease, IMRT: intensity-modulated radiation therapy, IPF: idiopathic pulmonary fibrosis, OP: organizing pneumonia, UIP: usual interstitial pneumonia, NSIP: Non Specific Interstitial Pneumonia PFT: pulmonary function test, RT: radiotherapy, Sq: squamous cell, TTNA: Trans-thoracic Needle Aspiration*

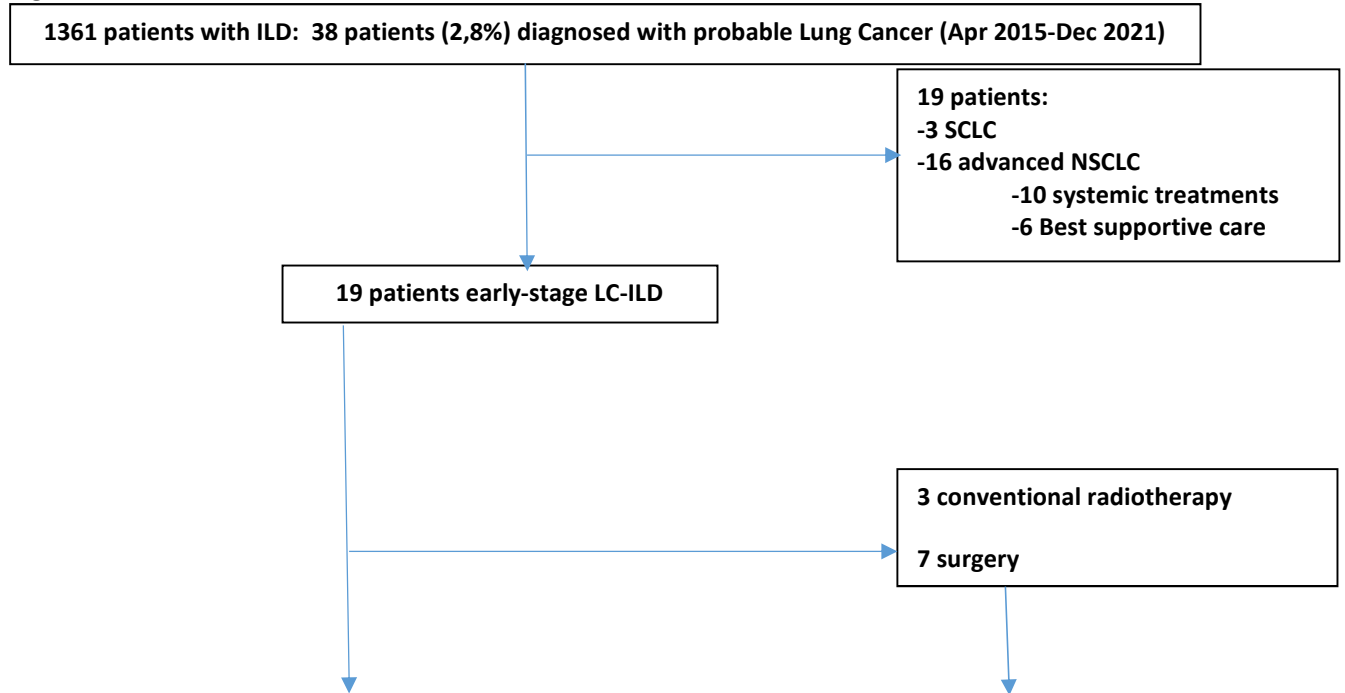
References:

- 1) Naccache JM, Gibiot Q, Monnet I, Antoine M, Wislez M, Chouaid C et al. Lung cancer and interstitial lung disease: a literature review. *J Thorac Dis*. 2018 Jun;10(6):3829-3844. doi: 10.21037/jtd.2018.05.75. PMID: 30069384; PMCID: PMC6051867..
- 2) Girard N, Marchand-Adam S, Naccache JM, Borie R, Urban T, Jouneau S et al . Lung cancer in combined pulmonary fibrosis and emphysema: a series of 47 Western patients. *J Thorac Oncol*. 2014 Aug;9(8):1162-70. doi: 10.1097/JTO.000000000000209. PMID: 25157769.
- 3) Gibiot Q, Monnet I, Levy P, Brun AL, Antoine M, Chouaid C et al. Interstitial Lung Disease Associated with Lung Cancer: A Case-Control Study. *J Clin Med*. 2020 Mar 5;9(3):700. doi: 10.3390/jcm9030700. PMID: 32150840; PMCID: PMC7141363.
- 4) Sato T, Watanabe A, Kondo H, Kanzaki M, Okubo K, Yokoi K et al. Long-term results and predictors of survival after surgical resection of patients with lung cancer and interstitial lung diseases. *J Thorac Cardiovasc Surg*. 2015 Jan;149(1):64-9, 70.e1-2. doi: 10.1016/j.jtcvs.2014.08.086. Epub 2014 Sep 18. PMID: 25439777.
- 5) Videtic GMM, Donington J, Giuliani M, Heinzerling J, Karas TZ, Kelsey CR and 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. doi: 10.1016/j.prro.2017.04.014. Epub 2017 Jun 5. PMID: 28596092.
- 6) Chang JY, Mehran RJ, Feng L, Verma V, Liao Z, Welsh JW et al. Stereotactic ablative radiotherapy for operable stage I non-small-cell lung cancer (revised STARS): long-term results of a single-arm, prospective trial with prespecified comparison to surgery. *Lancet Oncol*. 2021 Oct;22(10):1448-1457. doi: 10.1016/S1470-2045(21)00401-0. Epub 2021 Sep 13. PMID: 34529930; PMCID: PMC8521627.
- 7) Ozawa Y, Abe T, Omae M, Matsui T, Kato M, Hasegawa H et al. Impact of Preexisting Interstitial Lung Disease on Acute, Extensive Radiation Pneumonitis: Retrospective Analysis of Patients with Lung Cancer. *PLoS One*. 2015 Oct 13;10(10):e0140437. doi: 10.1371/journal.pone.0140437. PMID: 26460792; PMCID: PMC4603947.
- 8) Fujimoto T, Okazaki T, Matsukura T, Hanawa T, Yamashita N, Nishimura K et al. Operation for lung cancer in patients with idiopathic pulmonary fibrosis: surgical contraindication? *Ann Thorac Surg*. 2003 Nov;76(5):1674-8; discussion 1679. doi: 10.1016/s0003-4975(03)00966-4. PMID: 14602310.
- 9) Yamaguchi S, Ohguri T, Matsuki Y, Yahara K, Oki H, Imada H et al. Radiotherapy for thoracic tumors: association between subclinical interstitial lung disease and fatal radiation pneumonitis. *Int J Clin Oncol*. 2015 Feb;20(1):45-52. doi: 10.1007/s10147-014-0679-1. Epub 2014 Mar 11. PMID: 24610080.
- 10) Nagata Y, Hiraoka M, Mizowaki T, Narita Y, Matsuo Y, Norihisa Y et al. Survey of stereotactic body radiation therapy in Japan by the Japan 3-D Conformal External Beam Radiotherapy Group. *Int J Radiat Oncol Biol Phys*. 2009 Oct 1;75(2):343-7. doi: 10.1016/j.ijrobp.2009.02.087. PMID: 19735861.
- 11) Tzouvelekis A, Antoniou K, Kreuter M, Evison M, Blum TG, Poletti V et al. The DIAMORFOSIS (DIAGnosis and Management Of lung canceR and FibrOSIS) survey: international survey and call for consensus. *ERJ Open Res*. 2021 Jan 25;7(1):00529-2020. doi: 10.1183/23120541.00529-2020. PMID: 33532484; PMCID: PMC7837280.
- 12) Vansteenkiste J, Crinò L, Doooms C, Douillard JY, Faivre-Finn C, Lim E et al. 2nd ESMO Consensus Conference on Lung Cancer: early-stage non-small-cell lung cancer

- consensus on diagnosis, treatment and follow-up. *Ann Oncol*. 2014 Aug;25(8):1462-74. doi: 10.1093/annonc/mdu089. Epub 2014 Feb 20. PMID: 24562446.
- 13) Revel MP, Boussouar S, de Margerie-Mellon C, Saab I, Lapotre T, Mompont D et al. Study of Thoracic CT in COVID-19: The STOIC Project. *Radiology*. 2021 Oct;301(1):E361-E370. doi: 10.1148/radiol.2021210384. Epub 2021 Jun 29. PMID: 34184935; PMCID: PMC8267782.
 - 14) Lee YH, Kim YS, Lee SN, Lee HC, Oh SJ, Kim SJ et al Interstitial Lung Change in Pre-radiation Therapy Computed Tomography Is a Risk Factor for Severe Radiation Pneumonitis. *Cancer Res Treat*. 2015 Oct;47(4):676-86. doi: 10.4143/crt.2014.180. Epub 2015 Feb 13. PMID: 25687856; PMCID: PMC4614226.
 - 15) Yamashita H, Kobayashi-Shibata S, Terahara A, Okuma K, Haga A, Wakui R, et al. Prescreening based on the presence of CT-scan abnormalities and biomarkers (KL-6 and SP-D) may reduce severe radiation pneumonitis after stereotactic radiotherapy. *Radiat Oncol*. 2010 May 9;5:32. doi: 10.1186/1748-717X-5-32. PMID: 20459699; PMCID: PMC2876174.
 - 16) Yamaguchi S, Ohguri T, Ide S, Aoki T, Imada H, Yahara K et al. Stereotactic body radiotherapy for lung tumors in patients with subclinical interstitial lung disease: the potential risk of extensive radiation pneumonitis. *Lung Cancer*. 2013 Nov;82(2):260-5. doi: 10.1016/j.lungcan.2013.08.024. Epub 2013 Sep 7. PMID: 24054547.
 - 17) Takeda A, Sanuki N, Enomoto T, Kunieda E. Subclinical interstitial lung disease: is it a risk factor for fatal radiation pneumonitis following stereotactic body radiotherapy? *Lung Cancer*. 2014 Jan;83(1):112. doi: 10.1016/j.lungcan.2013.10.009. Epub 2013 Oct 22. PMID: 24199683.
 - 18) Ueki N, Matsuo Y, Togashi Y, Kubo T, Shibuya K, Iizuka Y et al. Impact of pretreatment interstitial lung disease on radiation pneumonitis and survival after stereotactic body radiation therapy for lung cancer. *J Thorac Oncol*. 2015 Jan;10(1):116-25. doi: 10.1097/JTO.0000000000000359. PMID: 25376512.
 - 19) Chen H, Senan S, Nossent EJ, Boldt RG, Warner A, Palma DA et al. Treatment-Related Toxicity in Patients With Early-Stage Non-Small Cell Lung Cancer and Coexisting Interstitial Lung Disease: A Systematic Review. *Int J Radiat Oncol Biol Phys*. 2017 Jul 1;98(3):622-631. doi: 10.1016/j.ijrobp.2017.03.010. Epub 2017 Mar 15. PMID: 28581404.
 - 20) Ryerson CJ, Vittinghoff E, Ley B, Lee JS, Mooney JJ, Jones KD et al. Predicting survival across chronic interstitial lung disease: the ILD-GAP model. *Chest*. 2014 Apr;145(4):723-728. doi: 10.1378/chest.13-1474. PMID: 24114524.
 - 21) Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y et al. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. *N Engl J Med*. 2019 Oct 31;381(18):1718-1727. doi: 10.1056/NEJMoa1908681. Epub 2019 Sep 29. PMID: 31566307.
 - 22) Saito S, Lasky JA, Hagiwara K, Kondoh Y. Ethnic differences in idiopathic pulmonary fibrosis: The Japanese perspective. *Respir Investig*. 2018 Sep;56(5):375-383. doi: 10.1016/j.resinv.2018.06.002. Epub 2018 Jul 27. PMID: 30061050.
 - 23) Palma DA, Chen H, Bahig H, Gaede S, Harrow S, Laba JM, Qu XM, Rodrigues GB, Yaremko BP, Yu E, Louie AV, Dhaliwal I, Ryerson CJ. Assessment of precision irradiation in early non-small cell lung cancer and interstitial lung disease (ASPIRE-ILD): study protocol for a phase II trial. *BMC Cancer*. 2019 Dec 11;19(1):1206. doi: 10.1186/s12885-019-6392-8. PMID: 31829203; PMCID: PMC6905060.

24) Hatabu H, Hunninghake GM, Richeldi L, Brown KK, Wells AU, Remy-Jardin M et al. Interstitial lung abnormalities detected incidentally on CT: a Position Paper from the Fleischner Society. *Lancet Respir Med*. 2020 Jul;8(7):726-737. doi: 10.1016/S2213-2600(20)30168-5. PMID: 32649920; PMCID: PMC7970441.

Figure 1:



9 early-stage LC-ILD treated with Stereotaxic radiotherapy

		Total population	
		N or (median)	[IQR]
Age		(71)	[66-77]
Gender	Women/Men	3/6	
Origin	Caucasian	8	
	North Africa	1	
Smoking Status	Never smoker	1	
	Former smoker	4	
	Active smoker	4	
	Pack-Year	47.5	[40-60]
ECOG PS	0	7	
	1	2	
Histologic biopsy	No biopsy	4	
	Biopsy	5 (all CT-scan guided TTNA) ADC : 4 Sq : 1	
TNM	T1aN0	4	
	T1bN0	3	
	T1cN0	2	
Size (mm)		(16)	[14.5-18.5]
FVC (mL)		(2480)	[2020-2855]
FVC (%Pred)		(77)	[62-91]
VEMS (mL)		(1750)	[1460-2065]
VEMS (%Pred)		(74)	[52-87]
DLCO(%Pred)		24	[23-39]
Overall Survival		17.4	
Relapse		6 relapse/9	
DFS (months)		13.5	

7 early-stage LC-ILD treated with surgery:

		Total population	
		N or (median)	[IQR]
Age		(72)	[67-76]
Gender	Women/Men	1/6	
Origin	Caucasian	5	
	North Africa	2	
Smoking Status	Never smoker	2	
	Former smoker	5	
	Pack-Year	50	[0-60]
ECOG PS	0	4	
	1	3	
Histology		Sq : 6 ADC 1	
TNM	T1cN0	1	
	T2a	1	
	T4	2	
	T1cN2	1	
	T4N1	1	
Size (mm)		(35)	[25-45]
FVC (mL)		(3310)	[2400-3460]
FVC (%Pred)		(99)	[80-108]
VEMS (mL)		(2560)	[1800-2940]
VEMS (%Pred)		(106)	[82-114]
DLCO(%Pred)		(58%)	[56-71]
Overall Survival		Median not reach (2death) 28 &14 months	
Relapse		1 relapse/7 (24 months)	
DFS (months)		Not Reach	

Figure 2:

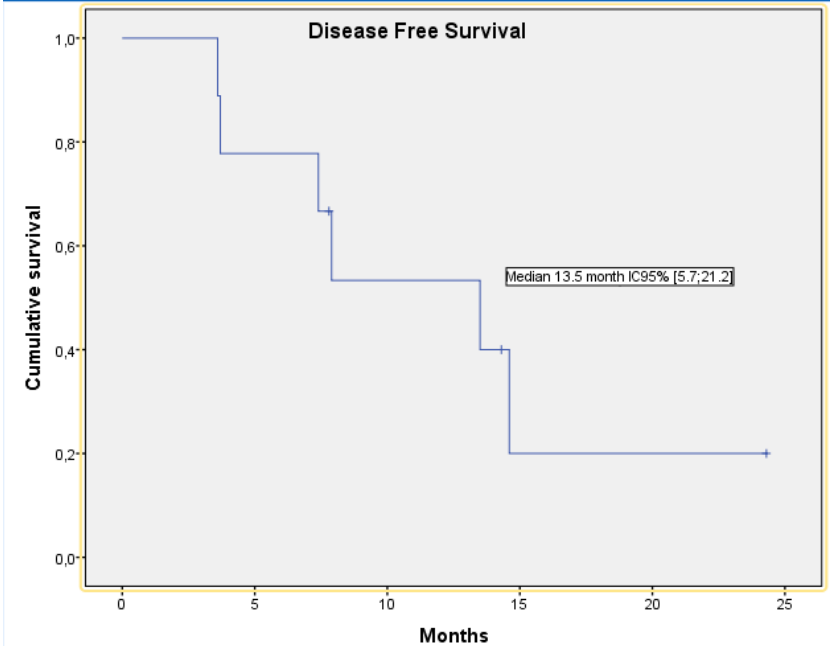
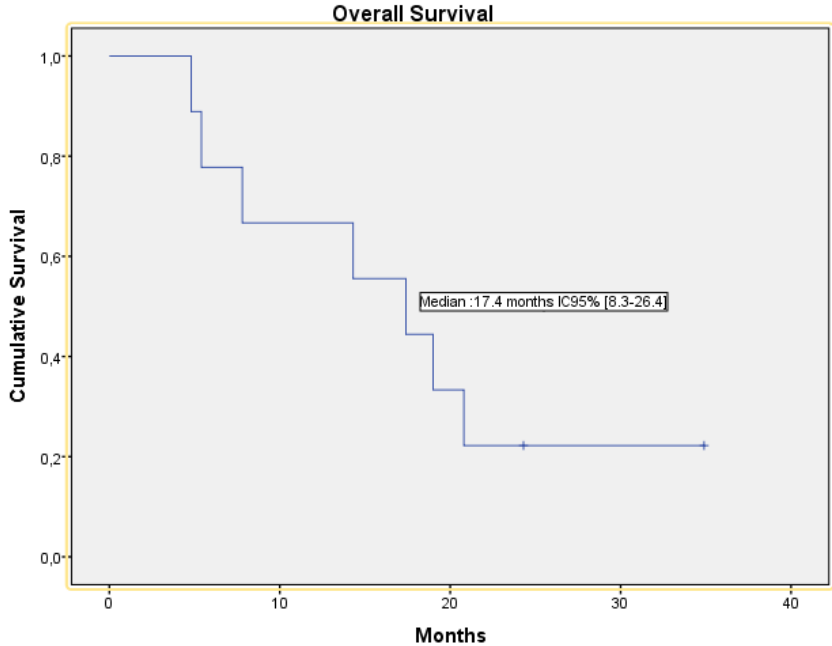


Figure 3:

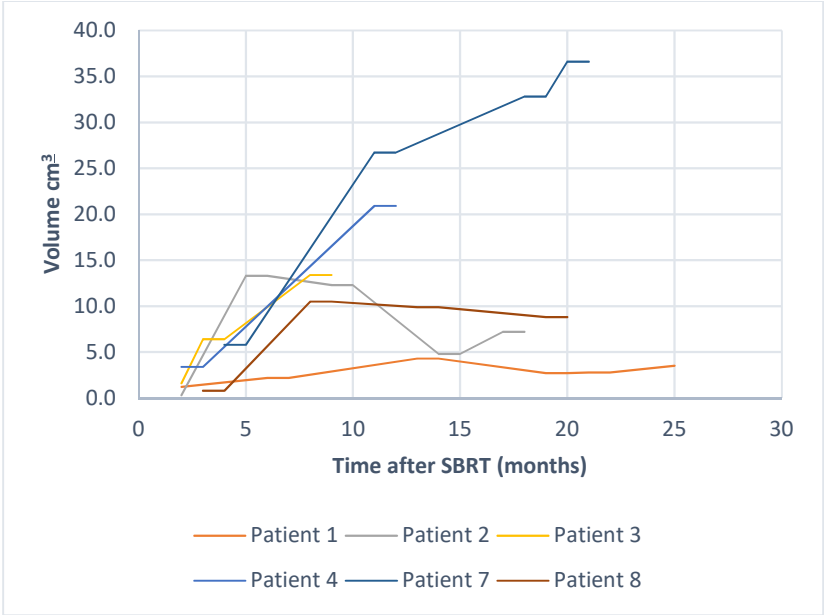


Figure 4 :

