Applying PET-CT for predicting the efficacy of SBRT to inoperable early-stage lung adenocarcinoma: A Brazilian case-series

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Summary

Background Stereotactic body radiotherapy (SBRT) is a treatment option for early-stage inoperable primary lung cancer. Here we report a thorough description of the prognostic value of pre-SBRT SUVmax for predicting the efficacy of SBRT in early-stage lung adenocarcinoma.

Methods This is a retrospective study of consecutive cases of early-stage inoperable lung adenocarcinoma, staged with PET-CT, treated with SBRT between 2007 and 17. Kaplan-Meier (KM) curves were used to assess overall survival and compare time to event between those with PET-CT SUVmax values ≤ 5.0 and those > 5. Fisher's Exact tests and the Mann-Whitney U were used to compare the patient and clinical data of those with SUVmax≤5.0 and >5.0, and those with and without any failure.

Findings Amongst 50 lung carcinoma lesions, from 47 patients (34 (68%)-T1a or <T1b), estimated median overall survival from the KM was 44.9 months (95% confidence interval 35.5−54.3). Five experienced a local failure, which was inadequate for detecting differences between those with PET-CT SUVmax ≤5.0 and those >5 (p = 0.112). In addition, 5 experienced a regional failure and 4 a distant failure. Higher PET-CT SUVmax values before SBRT were associated with an increased risk of any failure (36% versus 0%, p = 0.0040 on Fisher's Exact test) and faster time to event (p = 0.010, log rank test). Both acute and late toxicities profile were acceptable.

Interpretation Patients with early-stage inoperable lung adenocarcinoma present good clinical outcomes when treated with SBRT. We raised the hypothesis that the value of PET-CT SUVmax before SBRT may be an important predictive factor in disease control.

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Keywords: Radiotherapy; Radiosurgery/methods; Lung neoplasms; Positron emission tomography computed tomography; Adenocarcinoma

Abbreviations: RT, Radiotherapy; Lung CA, lung cancer; SBRT, Stereotatic body radiotherapy; Adeno, Adenocarcinoma; PET, PET-CT

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Introduction

Lung cancer has the highest incidence in the world, corresponding to 11.6% of the total cancer cases diagnosed in 2018.[1] Non-small cell lung cancer (NSCLC) represents 80% of all cases of lung cancer, with adenocarcinoma being the most common NSCLC subtype (40−50% of lung tumors).[2,3] For patients with early staged

Research in context

Evidence before this study

For patients with early staged lung cancer, who are inoperable, stereotactic body (SBRT), is a well-established treatment option. However, the prognostic value of pre-SBRT SUVmax value in predicting the efficacy of SBRT in early inoperable staged lung cancer patients has not been broadly investigated, especially in Brazil.

Added value of this study

The current study is the first to report the prognostic value of pre-SBRT SUVmax value in inoperable lung adenocarcinoma treated with SBRT in Brazil. Our findings suggest that patients with adenocarcinoma treated with SBRT have good clinical outcomes. The study also raised the hypothesis that the pre-SBRT PET-CT SUVmax value has potential as a predictor of disease control.

Implications of all evidence available

The article highlights that new radiation technologies are applicable outside high-income countries. It also suggests a role for PET-CT SUVmax in predicting failure post SBRT treatment. Finally, it provides benchmark data for future studies in the region.

(stage I and II) NSCLC, who are inoperable or who present with multiple comorbidities and/or older age, stereotactic body (SBRT) or stereotactic ablative radiotherapy (SABR), is a well-established treatment option.[4,5]

Previously a different case series reported on 54 elderly (median age 75 years) lung cancer patients treated with SBRT.[6] All patients were considered clinically inoperable (mainly due to multiple comorbidities). The results were comparable to those of the main published series, with 90% of local control and 80% of overall 2-year survival, respectively.[6] Despite the rate of local failure after SBRT being low, understanding the histological and imaging characteristics of NSCLC have become important for prognostic definition and management.

In the literature, multiple surgical series described that local failure was lower in early-stage NSCLC patients with adenocarcinoma when compared to other histologies (squamous cell carcinoma or large cell).[7–9] A meta-analysis including thirteen studies indicated that both before-RT and after-RT primary lesion higher Maximum Standard Uptake Values (SUVmax) seen on the Positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro- D-glucose integrated with computed tomography (FDG-PET-CT) can negatively impact the outcome of patients with non-metastatic NSCLC treated with RT.[10] SUVmax integrates knowledge on metabolic and biological activity of the tumour and has been used as a prognostic marker in NSCLC. Some specialized teams have endeavoured to describe the significance of pre-SBRT SUVmax value in the setting of stage I-II NSCLC.[11] However, to our knowledge, there is a lack of data reporting on lung adenocarcinoma alone.

Here we report a thorough description of the prognostic value of pre-SBRT SUVmax value on predicting the efficacy of SBRT in early-stage lung adenocarcinoma.

Methods

We performed a Research Ethics Board approved (REB number HSL 2014-30 under the registry FYdM221) retrospective study which was carried out in the radiotherapy department of Hospital Sírio-Libanês (São Paulo, SP, Brazil). We assessed consecutive lung cancer patients treated between January 2007 and May 2017. We included patients with (1) Biopsy-proven primary lung adenocarcinoma; (2) staged as T1 or T2N0M0, T3N0M0 (more than one lesion in the same lobe) or T4N0M0 (more than one lesion involving lobes other than the ipsilateral lung) according to the 8th edition of the TNM of the International Union for Cancer Control (UICC); (3) staged with FDG-PET-CT and CT (for better T stage definition); (4) considered inoperable by a multidisciplinary team; (5) treated with SBRT. We excluded patients with (1) tumors > 5 cm; (2) pulmonary metastases from other primary tumors; (3) diagnosis of idiopathic pulmonary fibrosis or (4) in treatment for another cancer. The article was organised based on The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.

Demographic, clinical, tumor-related and dosimetric data were collected. Performance status was assessed using the Eastern Cooperative Oncology Group (ECOG) scale (ECOG-PS). Data on comorbidities and cause of non-operability were also collected in addition to the pre and post SBRT FDG-PET-CT SUVmax and the tumor characteristics in CT scans.

To perform lung SBRT, a semi-rigid system for patient positioning and immobilizing was developed and piloted (2007) at our department. As of June 2012, commercial accessories (BodyFIX; Elekta, Stockholm, Sweden) were used for all treatments. All patients were planned with a 3D conformal technique, using non-coplanar fields. Treatment planning followed the protocols of RTOG-0236 (NCT00087438) or RTOG-0813 (NCT00750269). Total dose and fractionation scheme were defined considering the location of the tumor (Figure 1- Imaging representation of the bronchial tree zone), size and the best evidence available at the time of treatment: most commonly, three fractions were used for peripheral lesions and five for central lesions. The dose delivery was performed through stereotactic coordinates by means of using image guided radiotherapy (IGRT) with cone beam computed tomography (CBCT),

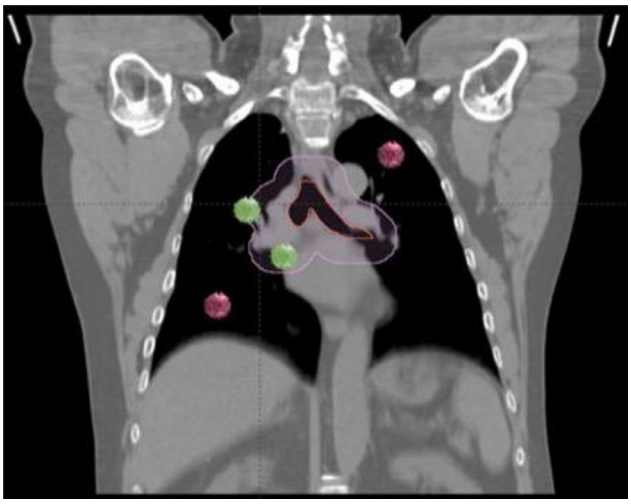

Figure 1. *Imaging representation of the bronchial tree zone*. Bronchial tree zone (light pink) is defined by a 2 cm expansion around the proximal bronchial tree (orange). The Bronchial tree zone was used to define central lesions (inside the light pink zone - green lesions) or peripheral (outside the light pink zone - dark pink lesion).

where not only the patient, but the internal tumor position was evaluated immediately before SBRT. Full description of our department planning, and treatment scheme has been previously described.[6]

Endpoints

The study primary endpoint was to assess the prognostic value of the pre-SBRT SUVmax value for predicting local failure in early-stage lung adenocarcinoma treated with SBRT. The SUVmax was categorized as ≤ 5.0 versus > 5.0 on the basis of a previous meta-analysis.[10] Secondary outcomes included overall survival, incidence of regional, distant, and any failure, and toxicity profile. All outcomes were assessed from the date of the last SBRT fraction to the last follow-up or death date.

The outcomes were defined as follows:

- Local failure: recurrence in a region of up to 1 cm around the treated planning target volume (PTV) which was defined in the presence of one of the following criteria: (1) CT scan with a mass pattern with consolidation patterns increasing in size (cranial-caudal growth on CT imaging ≥25%) without inflammatory signs; and/or (2) FDG-PET-CT study with increased SUVmax uptake in the lung lesion over time (At least 1 PET CT, with 30 days or more from SBRT). Biopsies were not performed due to high risk of complication (elderly patient, inoperable and with multiples comorbidities) or if patient declined it.
- Regional failure: recurrence more than 1 cm away from the PTV, within the parenchyma (same pulmonary lobe) or central structures of the mediastinum.
- Distant failure: metastasis in contralateral lobe or distant organs.
- Acute (≤ 6 months) and late (> 6 months) toxicities were defined based on the Common Toxicity Criteria for Adverse Events (CTCAE) v4.0 and by medical evaluation.
- Any treatment failure: local, regional, or distant failure

The study primary endpoint was to describe the prognostic value of pre-SBRT SUVmax value on predicting local failure in early-stage lung adenocarcinoma treated with SBRT.

Statistical analysis

Descriptive analysis of patients and lung lesions was performed. Categorical variables were summarized by frequency and percentage and quantitative variables by median with quartiles. Follow-up was defined as the time from the end of the SBRT until the death or last seen. Surviving patients were censored on the date of the last chest image. Age, ECOG-PS, size of the lesion in centimetres, duration of SBRT (time interval between the first and last fraction of SBRT), pre and post SBRT FDG-PET-CT SUVmax of ≤ 5.0 versus > 5.0,[10] dosimetric factors, BED_{10}, and response to FDG-PET-CT SUV max were assessed in two ways. Initially their associations with PET SUV ≤5.0 versus > 5.0 were assessed using the Fisher's Exact test (using a two-tailed probability based on double the exact one-tailed probability) for categorical and ordinal data, and the Mann-Whitney U for continuous data. Then their association with any failure (local, regional or distant) was assessed using the

same methodology. The number of events was too small for multivariable analysis. Kaplan-Meier curves with the log rank test were used to compare survival time and time to any failure for PET SUV ≤5.0 versus > 5.0. Statistical significance was established at $p < 0.05$ and no adjustment was made for multiple comparisons. Statistical analysis was performed using the Stata software, version 13.0 (StataCorp, College Station, TX) and IBM SPSS, version 27 (Armonk, NY, 2020).

Role of the funding source
There was no funding for this work.

Results
Between January 2007 and May 2017, 69 unique pulmonary lesions from 65 patients were consecutively treated with SBRT at our institution. Nineteen lesions (18 (28%) patients) were excluded from this study for being > 5 cm, metastatic or non-adenocarcinoma. The final analysed cohort included 50 unique lung lesions from 47 patients. All patients underwent initial staging with CT and FDG-PET-CT while 23 (49%) patients had FDG-PET-CT at follow up. Tables 1 and 2 describe patients' and lesions' characteristics, respectively. The majority (34 or 72%) of the patients were men, and age ranged from 55 to 93 years (median 76 years, IQR 69-82). Twenty-nine (62%) had an ECOG-PS of 1 and 20 (43%) had multiple comorbidities. Previous cancer was reported by 22 (47%) patients. The most common SBRT dose fractionation schedules used were: 18Gy x 3 fractions (28 lesions; 56%), 15Gy x 3 fractions (15 lesions; 30%), 10 Gy x 5 fractions (4 lesions; 8%) and 20 Gy x 3 fractions (4 lesions; 6%). The median total dose (BED_{10}) for the full cohort was 151.2 Gy (IQR 112.5 −151.2).

We also provided a comparison of patient characteristics for those with PET SUV_max ≤ 5.0 versus those > 5.0 (n = 47, Table 1), and none differed significantly. Table 2 provides the same comparison for lung lesions (n = 50), and no lung lesion characteristics differed significantly between the two groups. However, the rate of PET-CT done at follow-up was higher for those with PET SUV_max > 5 (p = 0.017).

The median follow-up for this cohort was 19.1 months (IQR 12.9−33.8). The estimated median overall survival from the Kaplan-Meier curve was 44.9 months (95% CI of 35.5−54.3). Figure 2 provides the survival curves for the 19 patients with SUV_max ≤5.0 versus the 28 with SUV_max > 5.0 and suggests that the two groups are very similar in terms of overall survival (log rank test p = 0.804). Over the total follow-up, we observed 14 (30%) deaths, 6 (43%) being related to lung cancer and 8 (57%) not related.

A total of 5 (5/50 lesions − 10%) local failures (all presenting high risk features on CT) were observed. All occurred within the 28 patients with SUV_max > 5.0,

	N (% total)	PET SUV Max ≤ 5.0 N (%)	PET SUV Max > 5.0 N (%)	*p*-value
Total number of patients	47 (100)	19 (40)	28 (60)	
Age in years (Median, quartiles)	75 (69-82)	80 (71-82)	73 (68-83)	0.66
ECOG PS				
0	11 (23)	2 (18)	9 (82)	0.31
1	29 (62)	14 (48)	15 (52)	
2	7 (15)	3 (43)	4 (57)	
Gender				
Male	34 (72)	16 (47)	18 (53)	0.24
Female	13 (28)	3 (23)	10 (77)	
Comorbidities				
Yes	40* (85)	15 (37)	25 (63)	0.57
No	7 (15)	4 (57)	3 (43)	
Smoking History				
Yes	37 (79)	12 (32)	25 (68)	0.076
No	10 (21)	7 (70)	3 (30)	
Previous Cancer				
Yes	22 (47)	10 (45)	12 (55)	0.72
No	25 (53)	9 (36)	16 (64)	

***Table 1*: Clinical characteristics of patients with inoperable early stage adenocarcinmoa of the lung treated with SBRT and staged with PET-CT.**

* 20 − had multiple comorbidities

N = number; ECOG PS: *Eastern Cooperative Oncology Group* performance status.

P-values are based on the Fisher's Exact test, using double the exact one-tailed probability, or the Mann-Whitney U (age).

	N (% total)	PET SUV Max ≤ 5.0 N (%)	PET SUV Max > 5.0 N (%)	*p*-value
Number of lesions	50 (100)	21 (42.0)	29 (58.0)	
Tumor median max diameter in cm (quartiles)	2.1 (1.5-3.0)	2.1 (1.5-2.9)	2.0 (1.6-3.1)	0.85
T category				
T1a	23 (46)	10 (44)	13 (57)	1.00
T1b	11 (22)	5 (46)	6 (55)	
T1c	0	0	0	
T2a	11 (22)	4 (36)	7 (64)	
T2b	1 (2)	0	1 (100)	
T3	4 (8)	2 (50)	2 (50)	
Tumor location				
Peripheral	39 (78)	16 (41)	23 (59)	1.00
Central	11 (22)	5 (46)	6 (55)	
Tumor lobe				
Superior	37 (74)	15 (41)	22 (60)	0.92
Middle	4 (8)	2 (50)	2 (50)	
Inferior	9 (18)	4 (44)	5 (56)	
Use of 4DCT (n=47, 19, 28)				
Yes	23 (49)	10 (44)	13 (57)	0.77
No	24 (51)	9 (38)	15 (63)	
Median total dose in BED10, Gy (quartiles)	151.2 (112.5-151.2)	151.2 (112.5-151.2)	151.2 (112.5-151.2)	0.32
Median number of fractions (quartiles)	3 (3-3)	3 (3-3)	3 (3-3)	0.48
Median treatment time days (quartiles)	8 (7-10)	8 (7-10)	8 (7-11)	0.92
PET-CT at follow up (n=47, 19, 28)				
Yes	23 (49)	5 (22)	18 (78)	0.017
No	24 (51)	14 (58)	10 (42)	

***Table 2*: Clinical lung lesions treated with SBRT and staged with PET-CT.**
N = number; 4DCT = 4-dimension CT; BED = Biologically effective dose.
P-values are based on the Fisher's Exact test using double the exact one-tailed probability, or the Mann-Whitney U (diameter, dose, fractions, treatment time).
Percentages may total to 101 due to rounding.
Note that two values are at the patient level (Use of 4DCT and PET-CT at Follow-up, $n = 47$) rather than the lesion.

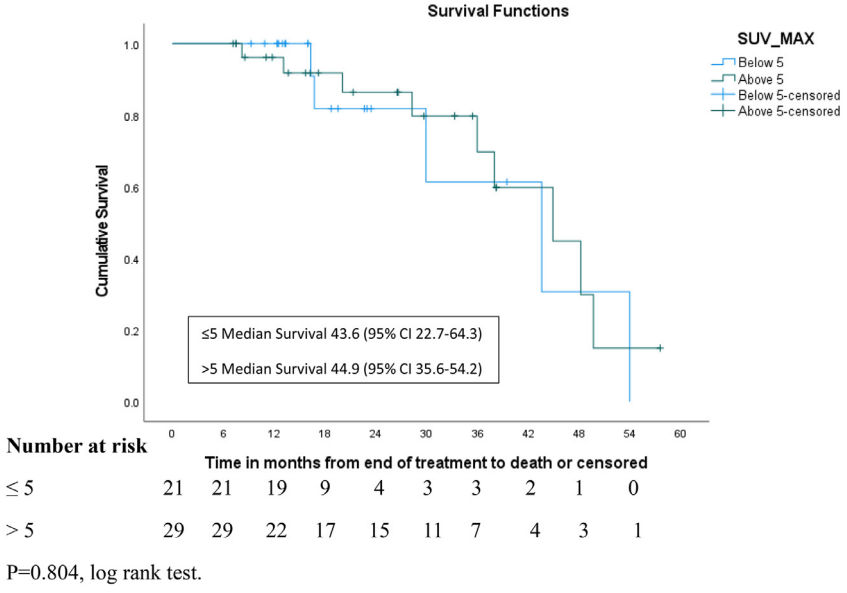

Figure 2. Overall survival curve for early-stage adenocarcinoma of the lung staged with PET-CT and treated with SBRT.

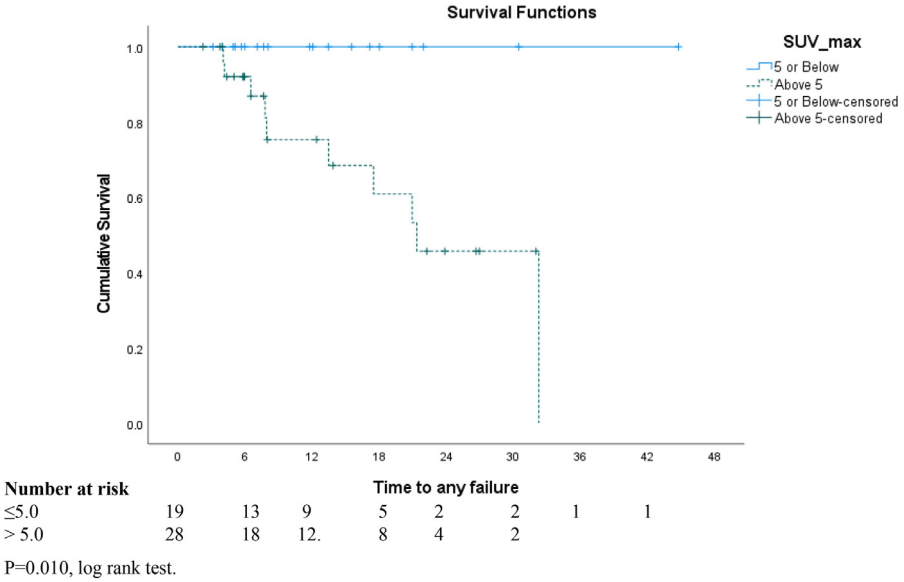

Figure 3. Kaplan-Meier Curve for time to Failure, comparing SUV_max ≤ 5.0 to those > 5.0.

although the numbers were insufficient to demonstrate a statistically significant difference (p = 0.112). In addition, there were 5 (5/47 per patient − 11%) regional failures, 4 distant failures (4/47 per patient − 8%), being 1 liver and peritoneum, 1 liver and bone; 1 liver; 1 liver and brain, and 10 (10/47 per patient − 21%) any failures observed. Figure 3 provides the KM curve for time to any failure for the 19 patients with SUV_max ≤5.0 versus the 28 with SUV_max > 5.0. None of those with SUV_max ≤5.0 experienced a failure over the follow-up period, while 10 of 28 with SUV_max > 5.0 did (p = 0.010, log rank test).

Four (8%) out of the 47 patients received systemic therapy at regional or distant failure. The characteristics of the five patients/lesions who developed local failure are as follow: (1) T1a, BED10 100 Gy (5 fractions), peripheral; (2) T2a, BED10 100 Gy (5 fractions), peripheral; (3) T1b, BED10 151.2 Gy, (3 fractions), peripheral; (4) T1b, BED10 112.5 Gy, (3 fractions), Central; (4) T2a, BED10 112.5 Gy,(3 fractions), peripheral.

Among 47 patients assessed for acute toxicities, 18 (38%) grade 1 or 2 acute toxicities were identified. The reported toxicities were 12 (24%) grade 1 pneumonitis (asymptomatic - diagnosis by image only), 5 (10%) grade 2 pneumonitis (symptomatic, but without the need for supplemental oxygen) and 1 (2%) grade 2 chest pain (moderate pain, limiting daily activities). Additionally, we observed 1 (2%) grade 3 pneumonitis (severe respiratory symptoms that limit daily activities in which the use of oxygen is recommended), for which the patient required hospitalization due to concomitant pneumonia (both resolved) and 1 (2%) grade 4 skin dermatitis (skin necrosis or full thickness dermis ulceration) for which the patient needed local treatment with resolution of the dermatitis. Among 47 patients assessed for late toxicities, 6 (13%) grade 1 or 2 late toxicities were observed, 4 (8%) representing grade 1 chest pain (mild pain without impacting daily activities) and 2 (4%) reporting grade 1 and 2 pneumonitis, respectively. No rib fractures were identified.

Thirty-four (68%) lesions from 23 (49%) patients were evaluated with FDG-PET-CT at diagnosis and during follow-up (when presenting with CT features favouring recurrence). The median time for the first FDG-PET-CT at follow-up ranged from 4.0 to 9.0 months, with a median of 5.5 (IQR 4.6–6.8). The median FDG-PET-CT SUV max at diagnosis was 5.6 (IQR 3.4–8.0) and at follow-up, 3.1 (IQR 1.5–4.9). The median SUV max reduction was 44% (IQR 39–64%). For the 5 (10%) lesions with local failure, the median SUV max reduction was 17% (IQR 16–19%) while the median SUV max for the lesions with no failure was 58% (IQR 56–62%). No lesion with SUV max at diagnosis ≤ 5.0 evolved with local, regional, or distant failure.

The results of univariate analyses performed to explore factors related to any failure (local, regional, and distant) are shown in Table 3. The FDG-PET-CT SUV max value at diagnosis was associated with a significantly higher rate of failure (36% versus 0%, p = 0.0040).

Discussion

Our results reinforce that the use of SBRT for the treatment of inoperable early-stage adenocarcinoma of the lung in elderly patients is safe and effective. SBRT provides prolonged median survival, with low 12-month failure rates. Our primary outcome, number of local

	No Failure $n = 37$	Failure $n = 10$	Indicative p-value*
Gender Male	27 (79)	7 (21)	1.00
Female	10 (77)	3 (23)	
ECOG 0 or 1	30 (77)	9 (23)	0.90
2+	7 (88)	1 (13)	
Median age (quartiles)	78 (69-83)	73 (67-82)	0.49
Smoking history	8 (80)	2 (20)	1.00
	29 (78)	8 (22)	
Median tumour size cm (quartiles)	2.0 (1.5-3.1)	2.2 (1.8-3.2)	0.79
Tumor lobe Superior	28 (78)	8 (22)	1.00
Non superior	9 (82)	2 (18)	
Tumor location Peripheral	29 (78)	8 (22)	1.00
Central	8 (80)	2 (20)	
Use of 4DCT No	17 (71)	7 (29)	0.32
Yes	20 (87)	3 (13)	
PET SUV_max ≤5.0	19 (100)	0 (0)	0.0040
> 5.0	18 (64)	10 (36)	
Median total dose in BED10, Gy (quartiles)	151 (113- 109)	151 (109-158)	0.88
Median SBRT time in days (quartiles)	8 (7-9)	11 (7-14)	0.052
Median interval between SBRT and PET assessment,	5.5 (4.3-6.8)	5.3 (4.9-7.3)	0.814
months (quartiles)	$n = 22$	$n = 10$	

***Table 3*: Factors associated with any failure (local, regional or distant) for PET-CT staged lung adenocarcinoma treated with SBRT. Values are reported as frequencies (%) and medians (quartiles).**

HR = *Hazard ratio*; IC = confidence interval; ref = reference category; ECOG PS = *Eastern Cooperative Oncology Group* performance status; 4DCT = 4-dimension CT; BED = Biologically Effective Dose.

* *P*-value is listed as indicative since length of risk of failure will differ between patients, and hence the strict assumptions for the standard tests are not satisfied.

P-values are based on the Fisher's Exact test using a two-tailed probability based on double the exact one-tailed probability), and the Mann-Whitney U, also based on double the exact one-tailed probability.

failures (5), was too low to demonstrate any statistically significant findings. However, when combined with the regional and distant failures, we were able to report a potential association between the pre-SBRT FDG-PET-CT SUVmax value SBRT and any failure ($p = 0.003$), particularly since there were no failures in the 19 patients with SUV max below 5 at diagnosis.

Our survival rates finding are important and encouraging. In our study the estimated median OS was 44.9 months which is better than prospective studies such as RTOG 0236, with a median OS of 36 months and RTOG 0813, with a median OS of 38 months; but lower when compared to RTOG 0915, with a median OS of 55 months (arm treated with 48 Gy in 4 fractions), respectively.[12–14] It is important to highlight that the patients included in our study presented with adenocarcinoma, a median age of 76 years, 85% had at least one clinical comorbidity, 40% were considered inoperable and a minority received systemic therapy. Thus, we believe that the discrepancy in median OS when compared to the RTOG studies may be related to patient selection, systemic therapy at the time of failure and percentage of adenocarcinoma included (percentage of adenocarcinoma included: RTOG 0236 – 39%, RTOG 0813 – 35%, RTOG 0915 – 58% (longest survival).[12–14]

In the present study we reported 8 (16%; total 50 lesions) local failure and 18 (38%; total 47 patients) any failure events. According to a recent literature review of patients with stage I-II NSCLC treated with SBRT, locoregional recurrence rates are between 0% and 18%, and distant recurrence rates are between 17% and 34% in the first 2 years, which is consistent with our results.[15] When we compare our results with the Cleveland Clinic retrospective series that compared local failure of squamous-type NSCLC versus adenocarcinoma, we noticed that the incidence of local failure was higher in our study, 16% in 2 years versus 8.7% for the adenocarcinoma group of the Cleveland Clinic study.[16] The reported difference in local control is probably related to patient's selection and criteria for local failure definition. In the Cleveland Clinic study, local failure was defined by radiographic progression on CT followed by at least one FDG-PET-CT examination.[16] If failure was defined by imaging, biopsy of the lesion was performed and post biopsy, only 40.3% actually had local recurrence. In our study, local failures were defined by CT in most cases, only 50% of patients underwent FDG-PET-CT at follow-up, and confirmatory biopsies were not performed.

Due to the previous points, we may have overestimated our local failures, as we know from the Cleveland

Clinic study that 59.7% of the cases considered local failures by image were false positives. However, when we analyzed the pre-SBRT FDG-PET-CT SUVmax value, this proved to be an interesting parameter of prognostication on our cohort. No patients with pre-SBRT FDG-PET-CT SUV max ≤ 5.0 developed local, regional or distant failure.

A systematic review, involving 13 studies, showed that both the pre-RT SUVmax and the post-RT SUV max can predict outcomes in patients with NSCLC treated with radiotherapy.[10] The study also showed that patients with higher values of pre-RT SUVmax (> 5.0) usually have worse overall survival and reduced local control.[10] Additionally, some studies reported on the correlation of residual SUV uptake 3 months after SBRT and increased risk of local failure.[17,18]

To our knowledge, when investigating the use of SBRT for early-stage lung disease and FDG-PET-CT we have 2 main published studies, however, none evaluated adenocarcinoma alone. First, the Memorial Sloan Kettering Cancer Center study included 219 stage I NSCLC lesions treated with SBRT and showed that SUVmax > 3.0 is associated with worse outcomes in overall survival, local failure and regional failure.[11] Second, the Mayo Clinic study which included 282 consecutive patients (99 adenocarcinoma) with early-stage NSCLC, showed that Pre-SBRT FDG-PET-CT SUV max value (continuous) was associated with the risk of any failure ($p = 0.02$) but not with local failure only ($p = 0.69$).[19] The results of these two studies are in accordance with our study findings and demonstrate the prognostic importance of pre-SBRT FDG-PET-CT.

Regarding treatment related toxicity, our study showed that grade 1 pneumonitis (asymptomatic) was the most frequent acute adverse event (12 or 24% of the treated lesions). In the literature, acute grade 1 pneumonitis is described in 30–70% of cases treated with SBRT.[20] Grade 2 pneumonitis (symptomatic, but without the need for oxygen) was found in 10% of our cases, which is in accordance with published literature (around 10%). As less frequent acute toxicities, we observed 1 (2%) case of grade 2 chest pain (rate described in the literature around 6–10%), 1 (2%) case of grade 3 pneumonitis, which was justified by an overlapping lung infection (rate described in the literature around 3–5%) and 1 (2%) case of grade 4 skin toxicity (rare event in the literature, < 3%).[20] Regarding late toxicities, we observed only grades 1 and 2 toxicities (6 or 12% of the cases), which is in line with the percentages reported in the literature.[20]

Although the findings reported here are important, our study has limitations that should be discussed and these include its retrospective design, limited sample size, limited number of patients who underwent FDG-PET-CT during follow-up and low statistical power for comparison between groups. Ideally this analysis would involve competing risks (mortality and failure) but the sample size and event size were too small for reliable estimates. Another limitation is the absence of confirmatory biopsy for local recurrence, but this is justifiable as we are reporting on a cohort of elderly inoperable and with multiple comorbidities patients who either were at high risk of patient or declined a biopsy. The lack of biopsy is not a major weakness due to the fact that CT evaluation is recognized in the literature as standard practice for follow up and failure definition. In addition, PET-CT is used for cases presenting with high-risk features of failure on the CT.

Conclusion

Patients with inoperable, early-stage adenocarcinoma of the lung showed good outcomes (low failure rates and prolonged survival) when treated with SBRT. FDG-PET-CT SUVmax value (≤ 5.0) was associated with better outcomes (i.e no failure). The incidence of both acute and late toxicities was low and acceptable. Larger prospective multi-center trials are required for validating our findings.

Contributors

All authors above contributed to conception and design, acquisition of data, or analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; and final approval of the version to be published.

Data sharing statement

The patients' data is stored and protect under the Brazilian privacy law at the Hospital Sirio-Libanes. For assessing the data, please contact the corresponding author so the formal processes for data sharing can be performed.

Declaration of interests

FYM received honoraria from Astra Zeneca and IASLC outside the submitted work. FYM declares grants or contracts from CTAQ Queen's University outside the current work. FYM has received consulting fees from Cancer em foco outside of the submitted work. All other authors have declared no conflicts of interest.

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