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Prognostic factors and clinical outcomes after stereotactic radiotherapy for primary lung tumors

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ABSTRACT

Aim: To characterize the population treated with SBRT for early-stage primary lung tumors in our institution, determine their outcomes, and identify potential prognosis factors.
Background: Stereotactic radiotherapy (SBRT) is an alternative treatment for inoperable patients with early-stage lung cancer. It confers a local control rate around 90% at 3 years, and 2–3 year overall survival rates of 43–60% in this population.
Materials and methods: We retrospectively analyzed all patients treated in our department between 2012 and 2017 and evaluated local progression-free survival (L-PFS), nodal or distant progression-free survival (ND-PFS), global progression-free survival (G-PFS), overall survival (OS), and disease specific survival (DSS). Univariate (UVA) and multivariate (MVA) models were built to assess the influence of each variable.
Results: We identified 218 patients with 233 tumors. Most were male (78.9%) with a median age of 73 years. Median follow-up was 22 months. At 18 months, L-PFS was 93.7%, ND-PFS was 82.2%, G-PFS was 76.0%, DSS was 90.5%, and OS was 78.0% in ≤T2 tumors. On UVA, T2 tumors were associated with lower L-PFS, G-PFS and DSS than T1, with no significant impact on ND-PFS or OS, an effect that persisted on MVA. On UVA, L-PFS and G-PFS were negatively influenced by female gender and a 5-fraction schedule was associated with worse G-PFS, which was not confirmed on MVA.
Conclusion: Our local and distant control rates and survival were similar to those previously reported. On MVA, T2 tumors displayed lower L-PFS, G-PFS and DSS, with no difference in OS.

1. Introduction

Lung cancer is the main global cause of death by cancer. Most are diagnosed in advanced stages. However, around 16% are early-stage when diagnosed (confined to the thorax with a maximum diameter less than 5 cm), a number expected to rise as a result of the implementation of screening programs.[1] Surgery remains the most widely adopted treatment for these early-stage lung cancers. Many patients are inoperable – most for medical reasons, which can be understood given the average age at diagnosis of 70 years and the prevalence of tobacco-related comorbidities in this population.[1] In this setting, stereotactic body radiation therapy (SBRT) is the alternative treatment modality, with a reported local control similar to that obtained with a surgical approach and low toxicity rates (also in the elderly population).[2,3] As such, it should be offered in inoperable patients or those who refuse surgery.[4] SBRT confers a local control rate of 90% at 3 years, and 2–3 year overall survival rates of 43–60% for medically inoperable patients.[5] Its adoption for larger tumors (>5 cm) has been reported in retrospective studies and, in spite of conferring an acceptable toxicity profile and disease control, is associated with lower local and distant control.[6] As such, our purpose was to retrospectively characterize the population that was treated with SBRT for early-stage primary lung tumors in our department, to determine their clinical outcomes, and to identify the influence of potential prognosis factors.

2. Methods

We retrospectively analyzed all patients treated with SBRT for primary early-stage lung tumors in our department between 1st January 2012 and 31st December 2017, and evaluated the influ-

Abbreviations: L-PFS, local progression-free survival; ND-PFS, nodal or distant progression-free survival; G-PFS, global progression-free survival; DSS, disease specific survival; OS, overall survival; UVA, univariate analysis; MVA, multivariate analysis; AC, Adenocarcinoma; SCC, Squamous Cell Carcinoma.

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ence of potential prognostic factors related to patient/tumor or treatment characteristics. Information about age, gender, Charlson score, tumor size, location (central vs peripheral; abutting the thoracic wall or not), histology, number of treated lesions, treatment technique and fractionation was collected and analyzed. Patient selection criteria included inoperable patients (due to medical comorbidities or tumor characteristics) or who refused surgery, without clinical evidence of lymph node spread (cN0). All lesions were biopsied and patients were staged by computed tomography (CT) and PET/CT, according to the AJCC 7th edition. Treatment was planned using free-breathing 4D-CT images and respiratory gating (with a vacuum cushion, and abdominal compression when appropriate). Cone beam CT and fluoroscopy image guidance were used. Four different fractionation schedules were used, based on RTOG protocols 0813 (5 alternate-day fractions of 10 Gy),[7] 0236 (3 fractions of 18–20 Gy)[8] and 0915 (1 fraction of 30–34 Gy; 4 fractions of 12–12.5 Gy)[9]—all delivering a biologically effective dose (BED) >100 (100 Gy, 113–180 Gy, 120–150 Gy and 106–113 Gy, respectively, for an α/β ratio of 10 Gy).

2.1. Response and toxicity evaluation

Treatment response was evaluated by CT scan with contrast, employing the RECIST criteria,[10] every 3 months during the first two years, every 6 months until the fifth year, and annually thereafter. When there was significant uncertainty in CT evaluations due to the confounding effect of radiation pneumonitis, cases were discussed with trained radiologists and, if needed, PET/CT and/or biopsy were requested. Toxicity was recorded on medical visits with the same periodicity using the CTCAE scale (v5.0). Treatment toxicity was considered acute when in the first 6 months after treatment and late when thereafter.

2.2. Statistical procedures

Data was stored and analyzed using IBM SPSS Statistics Version 25. Several clinical outcomes were evaluated. Initial time was considered as the first day of SBRT and the event day defined as follows: local progression-free survival (L-PFS, by tumor), until progression on the treated lesion; nodal or distant progression-free survival (ND-PFS, by patient), until nodal or distant progression; global progression-free survival (G-PFS, by patient), until progression in any location; overall survival (OS, by patient), until death by any cause; disease specific survival (DSS, by patient), until death caused by lung cancer. Survival curves were estimated via the Kaplan-Meier estimator and the Log-Rank test was used to compare survival between groups. Hazard ratios were calculated using Cox proportional hazards regression models. First, univariate models were built to determine individual contribution of each of the following variables: gender, Eastern Cooperative Oncology Group Performance Status (ECOG), histology, tumor stage, smoking status (former/current smoker or never smoker), number of treated lesions, location within the lung (centrality; proximity to chest wall), fractionation and SBRT technique. In a second stage, multivariable models retaining only the significant variables (p value < 0.05) were built.

3. Results

SBRT was performed in 218 patients with 233 tumors in the analyzed period. Most were males (78.9%) with a median age of 73 years (from 51 to 91 years) and a median Charlson score of 5.5 (from 1 to 13). Most patients had an ECOG of 0 or 1 (70.7%) and had a history of tobacco exposure (81.7%). Median follow-up time was 22 months (from 0 to 67 months). Information regarding response evaluation was not available for 4 patients, who were excluded from outcome analysis. Most patients had one lesion undergoing SBRT (93.6%) – 13 patients had two and 1 had three. The majority of tumors were adenocarcinomas (67.8%), followed by squamous cell carcinomas (29.2%). The majority of lesions were peripheral (81.5%) and about half were located > 1 cm from the chest wall (49.8%). Median maximum diameter was 2.3 cm, varying from 0.5 to 7.5 cm – 76.4% were T1(a, b or c) and 21.9% were T2(a or b). Median internal target volume (ITV) was 10.5cc (from 0.2 to 163.9cc) and median planning target volume (PTV) was 31.1cc (from 4 to 264.9cc). Three-dimensional conformal radiation therapy (3DCRT) was the most frequently used planning technique (in 63.1%), followed by VMAT (in 22.3%) and IMRT (in 14.6%). The four-fraction schedule was used on 38.2% of tumors, the five-fraction on 29.2%, the one-fraction on 23.2% and the three-fraction on 9.4% [Tables 1 and 2].

The most frequently observed acute toxicities were grade I pneumonitis (in 22.0%), grade I cough (in 6%) and grade I asthenia.

Table 1
Demographic variables by patient (n = 218).

Gender (n) (%)	
Male	172 (78.9%)
Female	46 (21.1%)
Median Age (y) (range)	73 years (51–91)
Charlson Comorbidity Score Index (median) (range)	5.5 (1–13)
Number of lesions (n) (%)	
1	204 (93.6%)
2	13 (6.0%)
3	1 (0.5%)
ECOG	
0	22 (10.1%)
1	132 (60.6%)
2	53 (24.3%)
3	11 (5.0%)
Smoking Status	(10 Missing)
Former/Current Smoker	178 (81.7%)
Never Smoker	30 (13.8%)

Table 2
Demographic variables by tumor (n = 233).

Histology (n) (%)	
Adenocarcinoma	158 (67.8%)
Squamous Cell Carcinoma	68 (29.2%)
Small-Cell Carcinoma	2 (0.9%)
Non-Small Cell Carcinoma	2 (0.9%)
Carcinoid	1 (0.4%)
Adenosquamous Carcinoma	1 (0.4%)
Large-Cell Neuroendocrine Carcinoma	1 (0.4%)
Maximum diameter (median) (range)	2.3 cm (0.5–7.5 cm)
Stage (n) (%)	
T1	178 (76.4%)
T1a	19 (8.2%)
T1b	90 (38.6%)
T1c	69 (29.6%)
T2	51 (21.9%)
T2a	36 (15.5%)
T2b	15 (6.4%)
T3	3 (1.3%)
T4	1 (0.4%)
Location	
Peripheral (Versus Central) (n) (%)	190 (81.5%)
> 1 cm from Chest Wall (Versus < 1 cm) (n) (%)	116 (49.8%)
ITV (median) (range)	10.5cc (0.2–163.9)
PTV (median) (range)	31.1cc (4–264.9)
Fractionation (n) (%)	
8–10 Gy × 5 fractions	68 (29.2%)
12–12.5 Gy × 4 fractions	89 (38.2%)
18–20 Gy × 3 fractions	22 (9.4%)
30–34 Gy × 1 fraction	54 (23.2%)
Planning Technique (n) (%)	
3DCRT	147 (63.1%)
IMRT	34 (14.6%)
VMAT	52 (22.3%)

Table 3
Toxicity.

ACUTE	
Pneumonitis	
G1	48 (22.0%)
Cough	
G1	13 (6%)
G2	1 (0.5%)
Asthenia	
G1	14 (6.4%)
Dyspnea	
G1	8 (3.7%)
Chest Wall Pain	
G1	6 (2.8%)
Esophagitis	
G1	1 (0.5%)
LATE	
Pneumonitis	
G1	87 (39.9%)
G2	6 (2.8%)
Dyspnea	
G1	14 (6.4%)
G2	3 (1.4%)
G3	1 (0.5%)
Chest Wall Pain	
G1	14 (6.4%)
G2	2 (0.9%)
Cough	
G1	13 (6%)
G2	1 (0.5%)
Asthenia	
G1	10 (4.6%)
G2	1 (0.5%)
Pleuritic Pain	
G1	4 (1.8%)
G2	1 (0.5%)
Rib Fracture	5 (2.2%)
Dermatitis	
G1	3 (1.4%)

No grade ≥ III acute toxicities were noted. In a late setting, the most common was grade I pneumonitis (39.9%), grade I chest wall pain (6.4%) and grade I dyspnea (6.4%). Five rib fractures were identified in follow-up imaging evaluation. The only grade III late toxicity registered was dyspnea in 1 patient [Table 3].

At follow-up, a complete local response was obtained in 19% of lesions, a partial response in 22%, and stable disease in 46%. Disease progression was observed in the treated site in 11.5% patients, elsewhere in the lung in 8.4%, in hilar or mediastinal nodes in 10.7% and a distant progression was verified in 12.1%. In ≤ T2 tumors, respectively at 18 and 24 months, L-PFS was 93.7% and 89.2%, ND-PFS was 82.2% and 78.2%, G-PFS was 76.0% and 68.5%, DSS was 90.5% and 84.4%, and OS was 78.0% and 67.6%.

On univariate analysis, when analyzing T1 versus T2 lesions, a higher tumor stage was significantly associated with lower 18-month L-PFS (95.3% for T1 vs. 90.4% for T2, with a p value of 0.029), G-PFS (80.2% for T1 vs. 65.3% for T2, $p < 0.001$) and DSS (92.3% for T1 vs. 86.2% for T2, $p = 0.009$). However, it had no significant impact on OS ($p = 0.302$) or ND-PFS ($p = 0.085$), with a trend towards worse prognosis in T2 tumors **[**Fig. 1**]**. On a multivariate analysis model including tumor stage (T1 vs. T2), gender, fractionation schedule and location within the lung (central vs. peripheral), a T2 tumor stage was the only predictor of worse L-PFS (HR 2.524, $p = 0.037$), G-PFS (HR 2.371, $p = 0.001$) and DSS (HR 2.348, $p = 0.016$). OS and ND-PFS were not influenced by any variable in multivariate analysis.

Three T3 and one T4 tumors underwent SBRT (staged as such due to tumor size), with a median maximum diameter of 6.25 cm (from 5.5 to 7.5 cm). One patient was lost at follow-up and died 16 months post-treatment, two died after relapse (7 and 19 months after SBRT – one relapsed on the treated lesion and hilar/mediastinal lymph nodes, and the other developed other lesions on the same lobe), and one died 5 months after SBRT with no evidence of disease relapse (with partial response on the treated lesion). Since they were a minority, they were not included in the Kaplan-Meier model for size comparison.

On univariate analysis, female gender seemed to have a negative influence on L-PFS and G-PFS ($p = 0.048$ and $p = 0.044$, respectively), with no influence on ND-PFS, DSS and OS ($p = 0.222$, $p = 0.564$ and $p = 0.205$). However, this effect did not translate into multivariate analysis.

Fractionation also did not influence outcome, both in univariate and multivariate analysis when analyzing for L-PFS, ND-PFS, DSS and OS ($p > 0.05$). We did observe a statistically significant difference for G-PFS in univariate analysis, with worse outcomes for patients undergoing the 5-fraction schedule (80.3% for 1-fraction, 90.7% for 3-fraction, 75.3% for 4 fraction and 70.9% for 5-fraction schedules; $p = 0.008$), but that finding was not observed in multivariate analysis.

Location within the lung also influences the choice of fractionation (along with tumor size) and was, therefore, included in the multivariate model. It did not seem to independently influence any of the outcomes. We also did not observe any significant effect of histology (when comparing adenocarcinoma with squamous cell carcinoma), ECOG, smoking history, SBRT technique or number of treated lesions for any of the outcomes [Table 4].

4. Discussion

The aim of this study was to determine the outcome of patients with early-stage lung cancer treated with SBRT in our Institution, and to evaluate the influence of several factors on prognosis. Our progression-free survival, disease-specific survival and overall survival rates are in line with literature reported outcomes.[11] A review by Tandberg et al. described 3-year local control rates of around 90% in most studies.[5] A study by Hörner-Rieber et al. also reported 2-year local control rates of 90%, distant control of 79% and overall survival of 68%, which are in line with those of our series.[12] Similarly, Giuliani et al. reported 2-year DSS of 89.9% and OS of 63.7%, both aligning with our findings.[3]

Tumor size has been previously studied as a prognosis factor in lung SBRT. By comparing T1 and T2 tumors, Dunlap et al. observed that T2 tumors had significantly lower local control rates and a shorter mean time to local recurrence, and trended towards lower overall survival rates.[13] Baumann et al. also compared T1 with T2 tumors and concluded that patients with T2 tumors had a significantly higher risk of failure in any location (local, nodal or distant). However, there was no difference in overall survival, progression-free survival or disease-specific survival. Several other studies have also concluded that larger GTVs are associated with more frequent local recurrences.[2,14] Nevertheless, this association between tumor size and outcome after lung SBRT is not consensual. Allibhai et al. found that tumor size did not relate to local failure, but only to regional and distant failure, as well as overall and disease-free survival.[15] In the other hand, Marhawa et al. did not observe any significant differences when comparing nodal failure rates between patients with different sized primary tumors (except when comparing cT1a with cT1b tumors).[16]

The absence of association between T-stage and OS possibly relates to population characteristics. Since most patients undergo SBRT for lack of clinical eligibility criteria for surgery, it can be understood that their comorbid conditions could also play an important role in limiting their life expectancy. In fact, in a Dutch

Table 4
Univariate (UVA) and Multivariate (MVA) Analysis for each outcome. L-PFS: local progression-free survival; ND-PFS: nodal or distant progression-free survival; G-PFS: global progression-free survival; DSS: disease-specific survival; OS: overall survival AC: Adenocarcinoma; SCC: Squamous Cell Carcinoma.

	L-PFS			
	UVA		MVA	
	HR [95% CI]	*p-value*	HR [95% CI]	*p-value*
T Stage				
(T1 vs T2)	2.536 [1.065–6.039]	**0.029**	**2.524 [1.059–6.015]**	**0.037**
Gender				
(Male vs Female)	2.533 [1.119–5.734]	**0.021**		0.079
Fractionation Schedule				
1 fraction	1			
3 fractions	0.367 [0.040–3.343]	0.209		0.622
4 fractions	1.078 [0.325–3.575]			
5 fractions	2.038 [0.638–6.509]			
Location Within the Lung				
(Peripheral vs Central)	1.638 [0.650–4.130]	0.291		0.650
Histology				
(AC vs SCC)	0.865 [0.343–2.185]	0.759		–
Technique				
3DRT (Reference)	1			
IMRT	0.598 [0.136–2.632]	0.782		–
VMAT	0.870 [0.256–2.963]			
Smoking Status				
(Non-smoker vs Smoker)	0.541 [0.212–1.379]	0.191		–
ECOG				
0 (Reference)	1			
1	1.535 [0.351–6.719]	0.854		–
2	1.442 [0.279–7.454]			
3	2.380 [0.333–17.006]			
Number of treated lesions				
(1 vs 2)	1.115 [0.331–3.754]	0.861		–

	ND-PFS			
	UVA		MVA	
	HR [95% CI]	*p-value*	HR [95% CI]	*p-value*
T Stage				
(T1 vs T2)	1.761 [0.917–3.384]	**0.085**		0.093
Gender				
(Male vs Female)	1.607 [0.852–3.032]	0.139		0.223
Fractionation Schedule				
1 fraction	1			
3 fractions	0.591 [0.119–2.935]	0.081		0.115
4 fractions	1.842 [0.735–4.615]			
5 fractions	2.455 [0.967–6.236]			
Location Within the Lung				
(Peripheral vs Central)	1.836 [0.944–3.569]	0.069		0.131
Histology				
(AC vs SCC)	0.604 [0.289–1.260]	0.174		–
Technique				
3DRT (Reference)	1			
IMRT	1.211 [0.549–2.716]	0.873		–
VMAT	0.962 [0.400–2.313]			
Smoking Status				
(Non-smoker vs Smoker)	1.608 [0.574–4.503]	0.362		–
ECOG				
0 (Reference)	1			
1	2.600 [0.615–10.990]	0.183		–
2	4.013 [0.903–17.841]			
3	4.237 [0.775–23-152]			
Number of treated lesions				
(1 vs 2)	1.363 [0.487–3.810]	0.554		–

	G-PFS			
	UVA		MVA	
	HR [95% CI]	*p-value*	HR [95% CI]	*p-value*
T Stage				
(T1 vs T2)	2.421 [1.454–4.029]	**<0.001**	**2.371 [1.425–3.947]**	**0.001**
Gender				
(Male vs Female)	1.730 [1.041–2.875]	**0.041**		0.075
Fractionation Schedule				
1 fraction	1			
3 fractions	0.412 [0.114–1.487]	**0.008**		0.191

Table 4 (*Continued*)

	L-PFS			
	UVA		MVA	
	HR [95% CI]	*p-value*	HR [95% CI]	*p-value*
4 fractions	1.336 [0.661–2.698]			
5 fractions	2.176 [1.077–4.395]			
Location Within the Lung				
(Peripheral vs Central)	1.839 [1.073–3.153]	**0.024**		0.113
Histology				
(AC vs SCC)	0.761 [0.439–1.319]	0.329		–
Technique				
3DRT (Reference)	1			
IMRT	1.123 [0.556–2.270]	0.228		–
VMAT	1.714 [0.921–3.192]			
Smoking Status				
(Non-smoker vs Smoker)	0.854 [0.436–1.673]	0.645		–
ECOG				
0 (Reference)	1			
1	1.719 [0.678–4.356]	0.346		–
2	2.326 [0.861–6.288]			
3	2.258 [0.651–7.830]			
Number of treated lesions				
(1 vs 2)	1.570 [0.718–3.434]	0.255		–
	DSS			
	UVA		MVA	
	HR [95% CI]	*p-value*	HR [95% CI]	*p-value*
T Stage				
(T1 vs T2)	2.464 [1.225–4.658]	**0.009**	**2.348 [1.175–4.691]**	**0.013**
Gender				
(Male vs Female)	1.343 [0.646–2.791]	0.428		0.583
Fractionation Schedule				
1 fraction	1			
3 fractions	0.590 [0.113–3.089]	0.117		0.588
4 fractions	1.408 [0.501–3.956]			
5 fractions	2.355 [0.855–6.490]			
Location Within the Lung				
(Peripheral vs Central)	1.505 [0.707–3.203]	0.285		0.670
Histology				
(AC vs SCC)	1.086 [0.531–2.220]	0.821		–
Technique				
3DRT (Reference)	1			
IMRT	1.376 [0.550–3.444]	0.694		–
VMAT	0.808 [0.281–2.326]			
Smoking Status				
(Non-Smoker vs Smoker)	1.050 [0.408–2.702]	0.920		–
ECOG				
0 (Reference)	1			
1	1.730 [0.520–5.758]	0.813		–
2	1.396 [0.359–5.421]			
3	1.491 [0.248–8.967]			
Number of treated lesions				
(1 vs 2)	2.079 [0.807–5.351]	0.121		–
	OS			
	UVA		MVA	
	HR [95% CI]	*p-value*	HR [95% CI]	*p-value*
T Stage				
(T1 vs T2)	1.315 [0.780–2.218]	0.303		0.346
Gender				
(Male vs Female)	0.699 [0.386–1.267]	0.236		0.264
Fractionation Schedule				
1 fraction	1			
3 fractions	0.474 [0.187–1.203]	0.192		0.325
4 fractions	0.726 [0.403–1.306]			
5 fractions	1.094 [0.613–1.952]			
Location Within the Lung				
(Peripheral vs Central)	1.113 [0.642–1.930]	0.703		1.000

Table 4 (*Continued*)

	L-PFS			
	UVA		MVA	
	HR [95% CI]	*p-value*	HR [95% CI]	*p-value*
Histology				
(AC vs SCC)	1.164 [0.727–1.863]	0.526		–
Technique				
3DRT (Reference)	1			
IMRT	1.102 [0.581–2.092]	0.852		–
VMAT	1.178 [0.641–2.163]			
Smoking Status				
(Non-Smoker vs Smoker)	0.998 [0.527–1.890]	0.994		–
ECOG				
0 (Reference)	1			
1	2.152 [0.853–5.431]	0.114		–
2	2.744 [1.032–7.294]			
3	0.929 [0.179–4.822]			
Number of treated lesions				
(1 vs 2)	1.280 [0.589–2.782]	0.532		–

In bold: Values that reached significance (p-value < 0.05).

study it was found that more than two-thirds of deaths in a lung cancer cohort occurred due to unrelated causes.[17]

We observed a gender difference in L-PFS and G-PFS with a significant trend towards inferior outcome on females, only in univariate analysis. In our series, this does not translate into multivariate analysis, probably owing to the influence of other variables. In opposition, in a study by Pham et al., female gender was associated with more favourable OS in univariate analysis, with borderline significance in multivariate analysis ($p = 0.0535$).[18] The SPACE trial also reported a trend towards better OS in females ($p = 0.13$),[11] which was also described by Jeppesen et al. and statistically significant in their retrospective series.[19] It became known from screening studies that women have a higher incidence of lung cancer than men (almost double after adjusting for smoking history and age). However, they have shown to have a lower hazard ratio of fatal outcome (HR 0.48, 95% CI 0.25–0.89).[20] These findings are not corroborated by our data.

Our in-house protocol for lung SBRT encompasses four different treatment schedules based on three RTOG protocols,[7–9] selected on a case-by-case basis according to tumor size and location. One-fraction schedules are preferred for small peripheral lesions located away from the chest wall (>1 cm). Three or four-fraction schedules are used for larger lesions or those close to the chest wall, respectively. Central tumors, when eligible for SBRT, undergo five-fraction schedules, according to tolerance doses to organs at risk determined during planning. Recent ACROP-ESTRO guidelines suggested different fractionation schedules, not including the one-fraction schedule.[21] However, according to our results, and with appropriate patient selection and image verification procedures, no fractionation schedule entails inferior survival outcomes. The low number and severity of side effects in our cohort also did not allow us to infer any influence of fractionation. Therefore, when appropriately performed, one-fraction schedules do not seem to be inferior to multiple-fraction schedules. This has also been reported in prospective studies, such as RTOG 0915 and I-124407, which did not identify any significant increase in toxicity or decrease in tumor control rates or survival when comparing one-fraction schedules with three or four-fraction schedules.[9,22] We did, however, observe a difference in G-PFS in univariate analysis, with a lower prognosis after 5-fraction schedules. These patients have typically larger lesions, which could account for this difference, especially since this was not a significant variable in multivariate analysis. The BED delivered by this fractionation schedule is also slightly lower than that of other schedules in our protocol, which could also contribute to this difference.

Although histology has previously been described as a prognosis factor, we observed no difference in outcome between adenocarcinomas and squamous cell carcinomas in our population, both in univariate and multivariate analysis. On the first retrospective study demonstrating an eventual effect of histology on outcome, Woody et al. found that a squamous histology was a strong predictor of local failure (with a twofold higher incidence of local relapse).[23] Another unicentric study with similar findings determined that this effect was not evident when EQD2 (2 Gy equivalent dose) was ≥150 Gy.[12] Although other studies did not observe this influence, a multi-institutional analysis also noted more frequent local, regional and distant failures, a shorter median time to recurrence and a higher risk for death in squamous cell tumors when compared to adenocarcinomas after SBRT.[24] We did not observe a significant difference in outcome between the two, and therefore cannot corroborate the possibility that squamous cell carcinomas may be more radioresistant to SBRT than adenocarcinomas.

Other predictors of worse prognosis reported in the literature are higher maximum SUV (standard uptake value) on PET evaluation,[25,26] age[27] and cardiac dose.[28] These were not analyzed in our study.

In our population, the dominant patterns of recurrence were distant and nodal spread. This finding aligns with literature-reported patterns, with reported distant recurrence rates of around 20% at 3–4 years and regional recurrences in about 10% patients.[3] Verma et al. also observed distant recurrence in 21% patients (with tumors larger than 5 cm), accounting for 33% disease recurrences, the main pattern of recurrence in this series.[6] Adjuvant systemic therapies, especially with well tolerated drugs (given the comorbid burden of the population that is usually treated with SBRT) could have a role in improving disease-specific survival and decreasing nodal and distant relapse, especially in larger tumors.

This study has some limitations. Its retrospective nature could eventually imply some missing data, in case they were not registered in the clinical records for appropriate collection. On the other hand, the low number of cases with G2–3 toxicity did not allow any correlation between significant toxicity and patient or treatment characteristics. Also, this is a heterogeneous patient population, typically with several comorbidities that could shorten their life expectancy (and therefore decrease the follow-up time for disease progression evaluation).

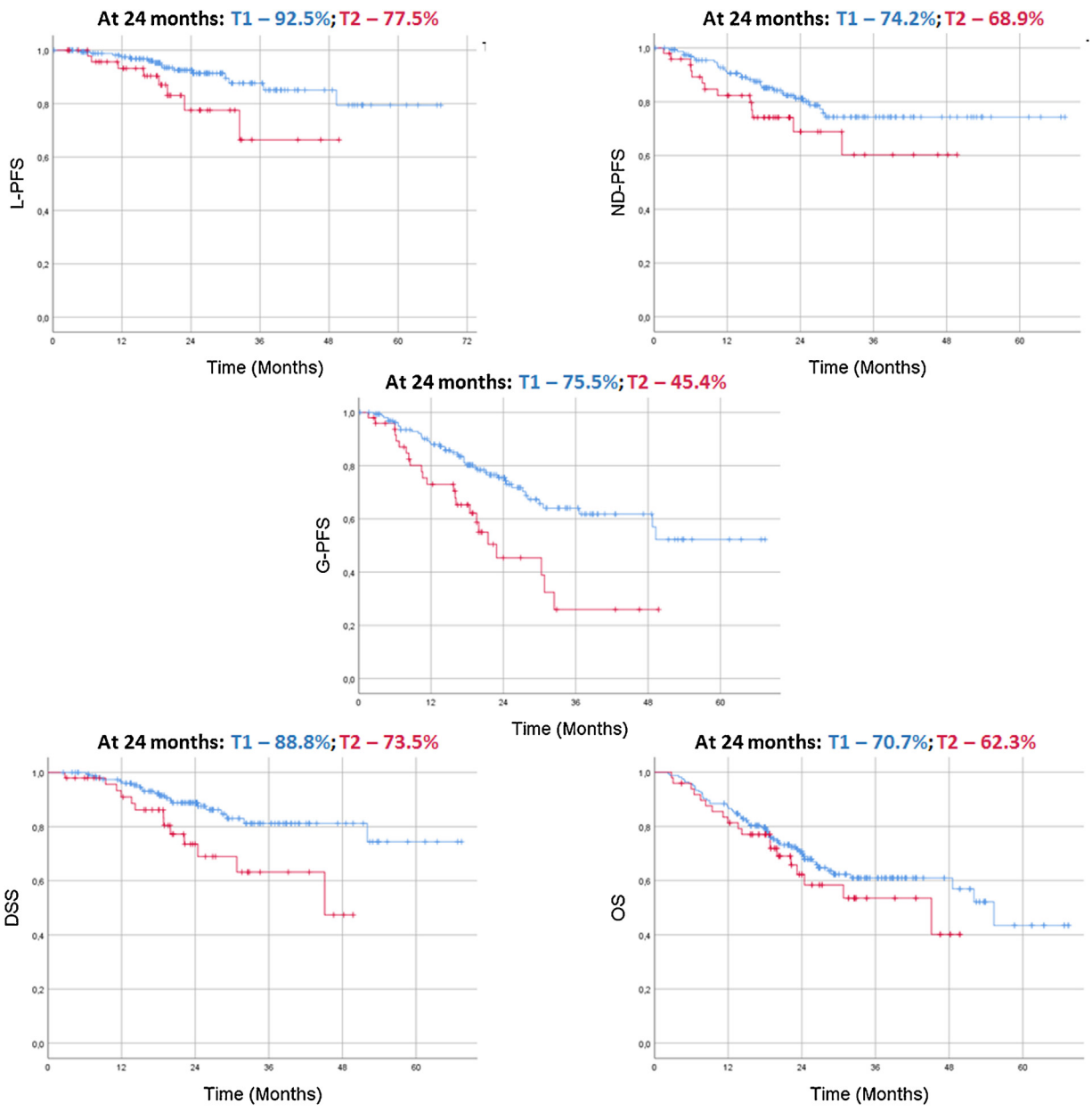

Fig. 1. Survival outcomes (comparison between T1 and T2 tumors). L-PFS: local progression-free survival; ND-PFS: nodal and distant progression-free survival; G-PFS: global progression-free survival; DSS: disease-specific survival; OS: overall survival.

5. Conclusion

In our series, we observed local and distant control rates and survival similar to those reported in the literature. T2 tumors displayed lower L-PFS, G-PFS and DSS rates when compared to T1 tumors, both in univariate and multivariate analysis. They did not, however, show any difference in OS in multivariate analysis, which can be understood given the characteristics of the population treated with SBRT, typically older and more fragile. Other potential factors tested (namely gender, ECOG, smoking history, histology, number of treated lesions, location within the lung, fractionation schedule and radiotherapy planning technique) did not seem to influence prognosis.

Conflict of interest

None declared.

Financial disclosure

None declared.

Ethics approval

Approval was obtained from the local institutional ethics committee.

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