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Stereotactic Ablative Radiotherapy for stage I histologically proven non-small cell lung cancer: An Italian multicenter observational study

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1 Introduction

Stereotactic Ablative Radiotherapy (SABR) or Stereotactic Body Radiotherapy (SBRT) currently represents a standard of care for inoperable stage I NSCLC, offering a survival advantage over traditional radiotherapy and cancer-specific survival rates comparable to surgical series in retrospective and prospective studies [1–6]. Histological confirmation of lung nodules prior to SABR has been a concern since the introduction of this treatment, both in clinical studies and in daily practice. The majority of patients referred to Radiation Oncology Departments are elderly and/or with comorbidities hence, in most of them, there is contraindication to CT-guided fine needle aspiration or bronchoscopy; in adjunct, peripheral nodules may be difficult to reach by bronchoscopy. In most SABR series, a correct histological diagnosis is available in approximately 50% of patients, and this resulted in some criticisms in the oncology community on the true efficacy of SABR as an alternative to surgery. However, other researchers showed, in mono-institutional cohort studies, that SABR may offer excellent local control and survival rates in histologically proven NSCLC [7–9]. The lack of robust data on patients with histological diagnosis, together with the heterogeneity in SABR studies design (patients' number, inclusion criteria and treatment techniques), might jeopardize the clinical results achieved so far. The routine use of SABR outside clinical trials has continuously increased over the last years in most countries: a US survey reported that 57% of responding physicians practiced SBRT for lung cancer in 2010 [10], and an Italian survey showed that SABR was used in 41% of departments [11]. Palma et al. [12] analyzed the time trend in SABR use in elderly patients in the Netherlands, showing an incessant increase in indications in patients previously either untreated or addressed to palliative RT. In this frame, few data are available on efficacy and toxicity of SABR outside clinical trials, especially in patients with histological diagnosis, a subgroup whose disease characteristics can be considered analogous to the surgical population (except for the difference in associated comorbidities). Aim of the present retrospective observational study on an Italian multicenter cohort was to provide further data on outcomes and prognostic factors in a quite large group of patients affected with stage I histologically confirmed NSCLC; the analysis was focused on the possible impact of multiple variables and on either the confirmation of known

prognostic factors or the selection of new ones, if any. Data were extracted from a larger database (including also patients without histological confirmation), allowing for an analysis of long-term safety and efficacy of SABR in multicenter clinical practice setting.

2. Materials and methods

2.1. Patients' selection

The SABR database and this study were initiated as a spontaneous collaboration between five Italian Radiation Oncology centers of Northern Italy. The whole database includes 356 stage I NSCLC patients treated in the time interval 2003–2011; all centers adopted analogous eligibility criteria for patients' referral to ablative radiotherapy, and were asked to include patients consecutively treated with SABR defined as: stereotactic frame-based or stereotactic frameless treatment (image-guidance based), highly conformal treatment planning, extremely hypofractionated regimens (maximum eight fractions), selective contouring and treatment of pulmonary nodules without nodal irradiation. Staging included whole body CT scans and, in the majority of patients, CT-PET scans. All patients were affected with peripheral tumors, defined as located more than 2 cm away from airways or more than 1 cm away from major blood vessels. Patients' information was centralized in a dedicated database, including demographic, clinical and technical data. In 2012, we extracted a cohort of 196 patients with histological/cytological diagnosis of NSCLC, either obtained by fine needle aspiration or bronchoscopy. The Institutional review board of the coordinating and participating centers approved the study. The cohort included 196 patients, 146 males and 50 females, with a median age of 75 years (range 48–91). One hundred eighty-one patients (92.3%) were deemed medically inoperable because of the presence of significant comorbidities and/or poor pulmonary function; the most common contraindications to surgery included: chronic obstructive pulmonary disease (COPD) in 98 patients (54.1%), cardiovascular comorbidity in 58 (32%), and advanced age (>80 years old) in 25 (13.9%). Fifteen patients (7.7%) refused surgery after adequate multidisciplinary discussion. Seventy-six patients (38.8%) had a diagnosis of adenocarcinoma and 61 of squamous cell carcinoma (31.2%); the remaining 59 were classified as non-small cell lung cancer non-otherwise specified (NOS). Eighty-four patients (42.9%) had a T1a, 71 (36.2%) a T1b and 41 (20.9%) a T2a tumor, with 155 patients with stage IA (79.1%) and 41 patients stage IB disease (20.9%), according to the 7th edition of the TNM classification and staging system for lung cancer [13]. Median tumor diameter was 2.48 cm, median GTV 13.3 cc. In all Departments dose prescription was at the 80% isodose, and the total dose ranged from 48 to 60 Gy in 3–8 fractions. BED10Gy were calculated using the linear quadratic formula ($BED = nd[1 + d/(\alpha/\beta)]$), where n is the number of fractions, d is the dose/fraction, and α/β ratio = 10 Gy. Median BED10Gy,

calculated at 80% dose prescription, was 105.6 Gy (range:100–132 Gy). One hundred seventy-five patients were treated with 3D-CRT (89.3%) and 21 with IMRT (10.7%). Three-dimension conformal radiotherapy consisted of a minimum of 7 up to a maximum of 11 non-coplanar static fields; IMRT was planned with a single 360° arc, with VMAT or Rapid Arc. One-hundred and fifty-nine patients (79.6%) were immobilized with a stereotactic body frame and 40 (20.4%) treated with frameless image-guided SABR. Detailed patients' characteristics are summarized in Table 1.

2.2. Follow-up and statistics

Primary endpoints of the study were safety (acute and late toxicity) and efficacy (local control, disease-free, overall and cancer-specific survival). Patients were followed-up by periodical clinical examination and CT scans every 3–4 months. Follow-up CT-PET was performed in a minority of cases, and, generally, only in case of differential diagnosis between tumor recurrence and lung fibrosis. Lung toxicity was graded according to RTOG acute radiation toxicity score (for events occurring between day 1 and day 90 from the start of radiation treatment) and to RTOG late radiation toxicity score (for events occurring later than day 90). Late radiological toxicity was scored as follows (RTOG): grade 0 = absence of changes, grade 1 = slight radiographic appearance, grade 2 = patchy radiographic appearance, grade 3 = dense radiographic appearance.

All statistical analyses were done on SPSS 20.0 (SPSS Inc., Chicago, USA). Univariate logistic analysis was performed using Student's T-test for continuous variables; categorical variables were analyzed by Pearson's chi-square test or Fisher's exact test, as appropriate. Statistical significance was established at $p < 0.05$. Multivariate analysis was performed by using Cox proportional hazard method, with backward exclusion of non-significant variables. Median follow-up time was calculated with reverse Kaplan–Meier method, and Survival curves were generated using Kaplan–Meier method, starting from the end of SABR. Endpoints were defined as follows: local recurrence [event: local relapse; tumor control was defined as the absence of tumor re-growth in the treated area], nodal recurrence [event: hilar and/or mediastinal nodal relapse], distant recurrence [event: distant metastases], disease-free survival [event: local and/or nodal and/or distant recurrence], cancer-specific survival (event: cancer-related death), Overall Survival (event: death for any cause). The log-rank test was used to test for survival differences after subgroups stratification.

3. Results

Median follow-up time was 30 months. The crude rates of local and nodal relapses were 7.6% (15 patients) and 11.2% (22 patients), respectively; 39 patients (20.4%) had distant recurrence. Local (LRFS), nodal (NRFS) and distant recurrence (DRFS)-

free survival are plotted in Fig. 1a–c. LRFS was 89.7% at 3 years. Fifty-nine patients (30.1%) had at least one failure, with a disease-free survival (DFS) rate at 3 years of 65.5% (Fig. 1d). Median time to local recurrence was 14.4 months. Overall and cancer-specific survival plots are presented in Fig. 2a and b, and were 68% and 82.1% at 3 years, respectively. Median time to any recurrence was 15 months, median survival time 54 months. Isolated pulmonary lesions occurring at more than 2 years after SABR were considered as second primary tumors (7 patients, 3.6%). At univariate analysis, Stage IB (i.e., T2aN0M0) showed worse DFS and CSS, while GTV < 13 cc was associated to better DFS and CSS (Table 2). At multivariate analysis, stage IB was confirmed as the only variable associated to worse DFS, OS and CSS (HR 2.77, $p = 0.006$; HR 2.38, $p = 0.009$; HR 4.06, $p = <0.001$, respectively) (Table 3). A difference in survival according to stage was also evident at the log-rank test ($p = <0.0001$ for CSS and OS, as shown in Fig. 3).

majority of non cancer-related deaths were secondary to cardiac or pulmonary fatal events (6 chronic heart failure, 4 myocardial infarction, 6 strokes, 11 chronic respiratory insufficiencies, 1 chronic lymphocytic leukemia, 1 hepatic cirrhosis, 1 melanoma and 1 colo-rectal cancer). The 30 and 60 days mortality rate was 0%. Thirteen patients (6.1%) experienced acute grade 1 and 6 patients (3%) grade ≥ 2 pulmonary toxicity (4 G2 and 2 G3). Late clinical pulmonary toxicity was recorded in 23 patients (11.7%, with 17 G1, 4 G2 and 2 G3), while late radiological toxicity was recorded in 100 patients (51%), as G1 in 68, G2 in 28 and G3 in 4 patients. Other late toxic events included: chest wall toxicity (8 cases, 4.1%), with neuropathic pain requiring analgesic therapy, 1 brachial plexopathy (0.5%), 1 moderate teleangiectasia (0.5%) and 1 rib fracture (0.5%).

4. Discussion

This retrospective observational study describes toxicity, survival and prognostic factors in a cohort of patients with histologically proven stage I NSCLC treated with SABR in 5 Italian Radiation Oncology Departments as part of clinical practice. SABR resulted to be safe and effective. The 3 years LRFS rate was 89.7%, while DFS, OS and CSS rates were respectively 65.5%, 68% and 82.1%. The strongest prognostic factor was tumor stage (stage IA vs. IB, i.e. T1a–b vs. T2). Matsuo et al. [8] found, in a series of 101 patients with histologically proven NSCLC, a significant difference in LC between stage IA and IB, while in our study the difference resulted significant only for survival. In the report by Andratschke et al. [7], including 92 patients with histological confirmation, a correlation between T stage and LC (T1 vs. T2) was evident, but conversely survival was not significantly influenced. The working group “Extra-cranial Stereo-tactic Radiotherapy” of the German Society for Radiation Oncology (DEGRO) conducted a multicenter study on patterns of care and outcome analysis on a cohort of 582 patients treated with SABR in Germany between 1998

and 2011 [14]. This study, that has a parallel design and includes a patients' cohort quite analogous to ours, showed that stage IA was correlated with a better OS, with only a trend for a better LC. The prognostic effect of tumor size has been recognized in surgical series: in the IASLC database the expected OS at 2 years for stage IA (tumor size less than 3 cm) is 73%, compared to 64% for patients with tumors sized 3–5 cm. In the present study, the 3 years OS was 72.2% for stage IA (CSS 86.1%) and 49.5% (CSS 60.1%) for stage IB (log-rank $p < 0.0001$). The significant difference in OS and CSS values is a consequence of the quite high number of non cancer-related deaths, hampering a correct comparison with surgical series but also suggesting that the outcome after SABR is likely to be equal to surgery also in larger tumors. At this regard, the negative prognostic impact of tumor size appears to be mainly related to a higher risk of systemic failures compared to local and loco-regional failures and this pattern of relapse emphasizes the potential role of adjuvant systemic treatments in stage I. Recently, Allibhai and co-authors, among a series of 185 patients, found at recurrence partitioning analysis that larger GTVs were significantly associated with poorer rates of DFS, OS, and CSS. Assuming idealized spherical tumors, the selected GTV cut-point for significance was >2.8 cm (i.e. the approximate size cut-off for T2 tumors) [15]. Previous studies on surgical series showed that a higher pre-treatment SUVmax could be associated to worse survival [16]. After several reports failing to show a correlation, Nair et al. recently reported that a SUVmax value > 7 was an independent prognostic factor for distant metastases-free survival after SABR [17]. In our experience the mean SUVmax value, available in patients who performed a CT-PET scan before SABR, did not reach statistical significance (a trend toward significance with a cut-off of 7.8 is evident at multivariate analysis, Table 3). The overall clinical outcome of our cohort was satisfactory. The 5 participating centers applied homogeneous patients' selection criteria, despite data were collected over 10 years. No inter-institutional significant variability in patients' age, performance status or comorbidities was recorded. Some intrinsic favorable characteristics of our study cohort may be significant for results interpretation, such as the good PS (0 in 58.7%, with no patients with $PS \geq 2$), the small median tumor size (2.48 cm) and tumor volume (13.3 cc), a higher percentage of stage IA tumors in comparison with other series (79.1% vs. 56.2% in the DEGRO study). Survival estimates reflect what emerged from the meta-analysis done by Soldà et al. [18], with OS at 2 years of 70% (81.6% in the present study), emphasizing the potential equivalence between SABR and surgery from clinical trials datasets. Notably, results of our study refer to a patients' population with histological diagnosis. BED10Gy did not emerge as a significant variable for all different clinical endpoints. The "intermediate" median BED10Gy of our study (105.6 Gy) is associated to a quite high LRFS, comparable to that achieved by Vrije University researchers in their retrospective series (roughly 90% at 5 years in 672 patients), including a large number of patients without histological confirmation

of malignancy [1]. This finding confirms that probably lower doses (than previously thought) to the PTV edge may be sufficient to attain high control rates, as recently shown by Van Baardwijk et al. in a systematic review of clinical trials [19]. As in the DEGRO study, technical parameters did not influence any clinical endpoint, and also the total number of SABR procedures per Institution/year did not affect outcomes. Female gender was significantly correlated to a better distant progression-free survival and OS in a single report [8]. This finding was not confirmed by our study or by other series, and this may be due to the low number of female patients enrolled, hampering a correct statistical evaluation, or to possible intrinsic differences between Caucasian and Asian patients populations. A comparative matched-pair analysis including propensity score (controlling for all factors affecting treatment selection) between two early stage NSCLC patients cohorts (180 treated with surgery and 137 with SABR), showed that OS was comparable [20]. At univariate analysis, OS was better for adenocarcinomas, smaller tumor size and lower Charlson's comorbidity score, with no variables selected as significantly affecting LC. At multivariate analysis, only Charlson's comorbidity index resulted associated to OS, while local control was influenced by tumor size. Apparently, histological subtype did not have any impact on survival, as in most studies. One of the explanations may be that in the SABR cohort the fraction of NOS diagnoses was higher than in the surgical group, reflecting the overuse of this pathological category in a patients' population where cytology/histology is only available from small biopsy samples. Also in our cohort the number of NOS was very high, probably jeopardizing the effect of adenocarcinoma histology on possible better outcomes (we only found a trend toward better OS for adenocarcinoma at univariate analysis). In the DEGRO experience, the positive impact of adenocarcinoma histology was confirmed at multivariate analysis only on LC, and not on survival endpoints. The findings of the present study confirm that SABR may be a valid alternative to surgery. In clinical practice, a multidisciplinary approach could probably be of great value in determining the best treatment strategy in every single patient, taking into account clinical factors like respiratory function, tumor's stage, age and comorbidities, and offering the proper choice in terms of efficacy and morbidity [21,22]. In the study by Palma et al. [12], on elderly patients with a median age of 79 years old, SABR had a 30-day mortality rate of <2%; this result can be of particular importance for decision making, as patients are obviously reluctant to accept risks that involve the possibility of short-term death. A Markov-model based comparison of surgery versus SABR for patients aged 65 or older predicted that surgery might confer an overall survival benefit of 2–3% at 5 years over SABR. However, once operative mortality increases above 4%, the survival advantage of surgery was negated and SABR preferred [23]. Our study was designed with the aim of increasing the knowledge on SABR safety and efficacy in patients not included in academic studies. As pointed out by S. Senan, patients enrolled in clinical trials

comprise <2% of all cancer patients, and in this field observational analyses may be an appealing and useful tool in comparative effectiveness research: as an example, results of observational studies could be relevant for determining treatment choices in the frail and so-called “borderline” operable patients, who are the most likely to benefit from SABR but also the least likely to be included in clinical trials [24]. On the other side, it has to be noted that registry studies, as well as observational multicenter studies, have some weaknesses in correctly describing outcomes compared with prospective trials. This is particularly important for toxicity reporting, as some important data may be missing.

5. Conclusion

This multicenter retrospective observational study, by providing further data on the safety and efficacy of SABR in histologically confirmed stage I NSCLC outside clinical trials, supports the routine use of SABR for stage I NSCLC in a daily practice environment. The only prognostic factor that has been confirmed by our analysis was tumor stage (IA vs. IB).

Conflict of interest

None declared.

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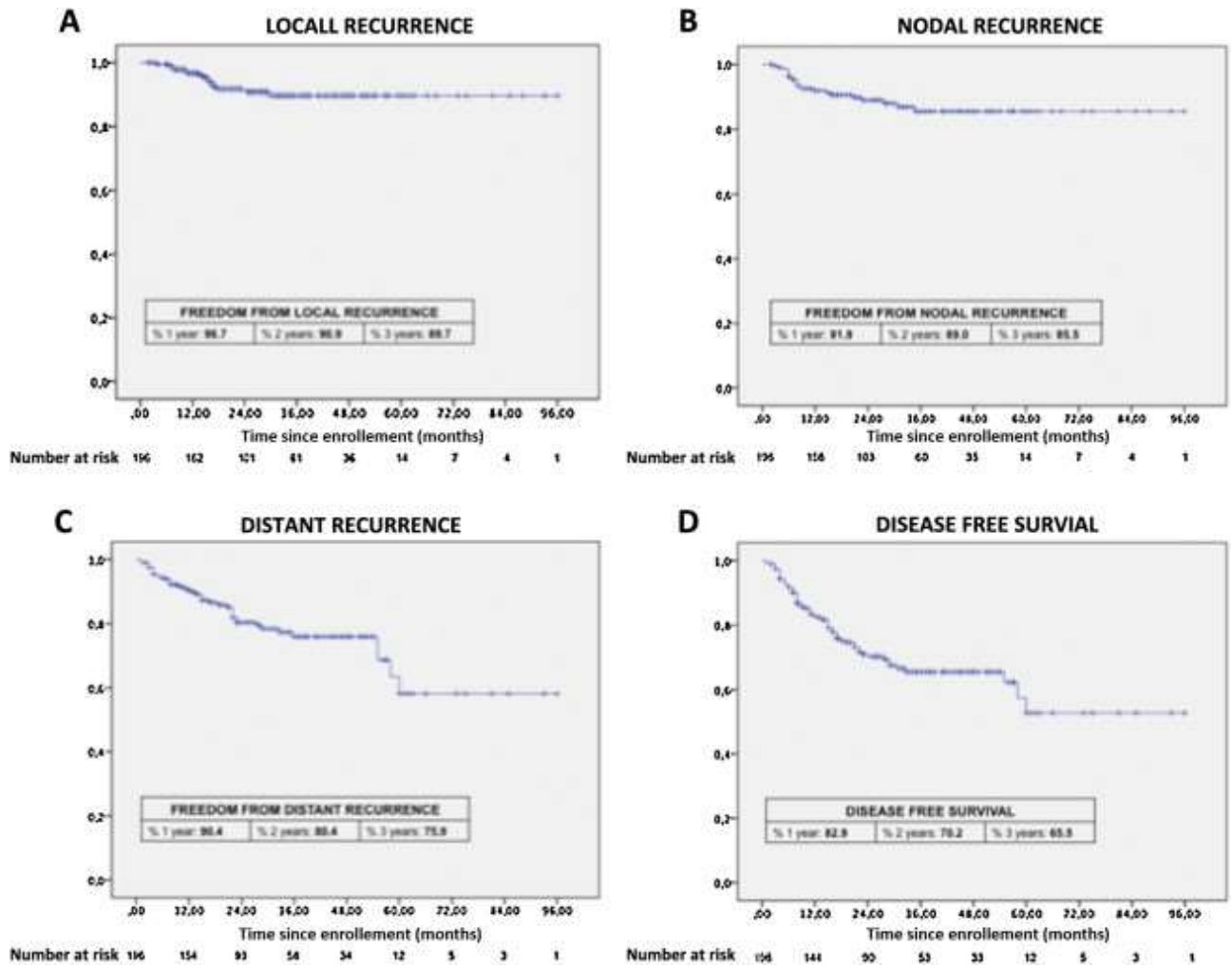


Fig. 1.(a) Local recurrence-free survival; (b) nodal recurrence-free survival; (c) distant recurrence-free survival; (d) disease-free survival.

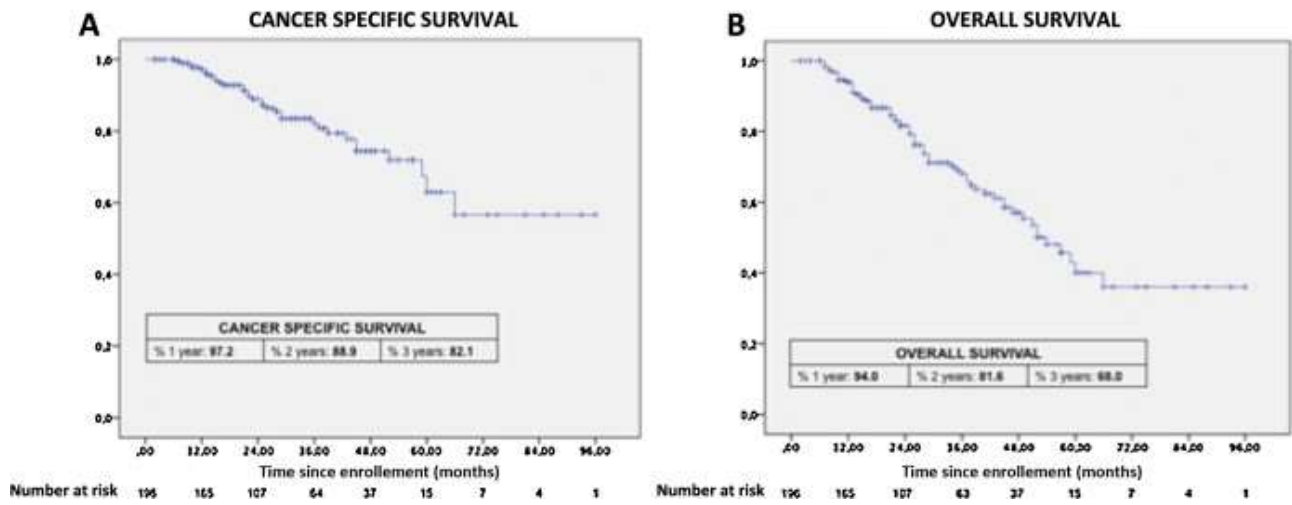
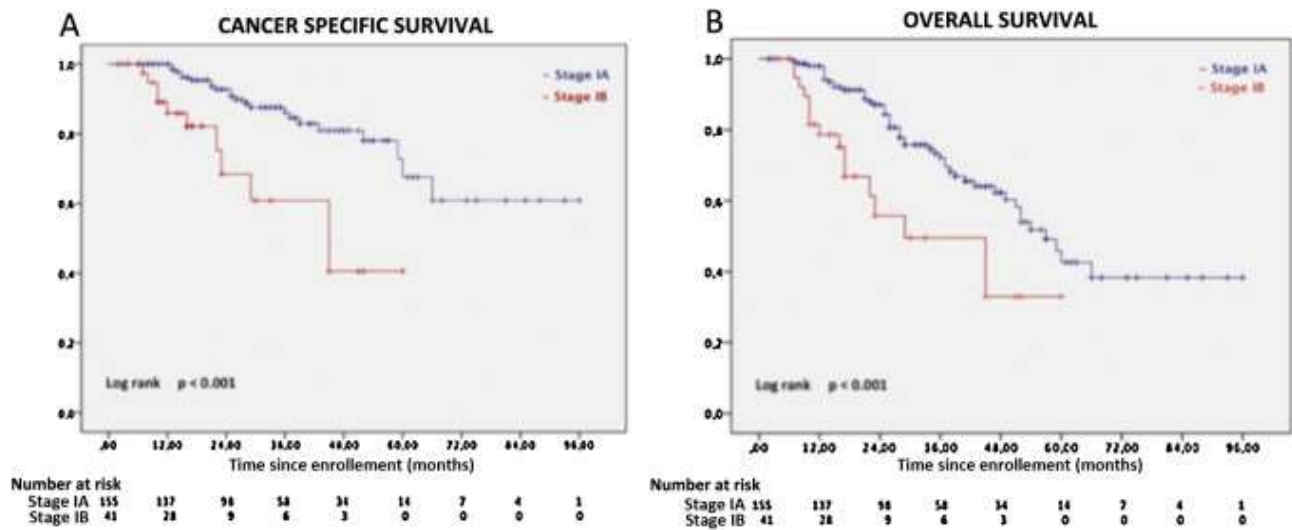


Fig. 2.(a) Cancer-specific survival; (b) overall survival.



The Fig. 3.(a) Cancer-specific survival according to stage (IA vs. IB); overall survival according to stage (IA vs. IB).

Table 1.

Patients characteristics.

	No. (%)	Median (range)
Gender		
Male	146 (74.5)	
Female	50 (25.5)	
Age		75 (48–91)
ECOG performance status		
0	115 (58.7)	
1	76 (38.8)	
2	5 (2.5)	
T stage ^a		
T1a	84 (42.9)	
T1b	71 (36.2)	
T2a	41 (20.9)	
Histology		
Adenocarcinoma	76 (38.8)	
Squamous cell carcinoma	59 (30.1)	

	No. (%)	Median (range)
NSCLC NOS	61 (31.1)	
Tumor diameter (cm)		2.48 (0.9–5)
Tumor volume (cc)		13.3 (1.2–115)
PET-CT staging	147 (75)	
Mean SUV _{max}		7.8 (1.3–25.3)
BED10 Gy		105.6 (100–132)
Dose ^b		
48 Gy/4 fr.	72 (36.7)	
45 Gy/3 fr.	65 (33.2)	
50 Gy/5 fr.	34 (17.3)	
55 Gy/5 fr.	10 (5.1)	
60 Gy/8 fr.	8 (4.1)	
54 Gy/3 fr.	7 (3.6)	

Abbreviations: NSCLC NOS, non-small-cell lung cancer; not otherwise specified; SUV, standardized uptake value; 3D-CRT, 3D-conformal radiotherapy; IMRT, intensity-modulated radiotherapy.

a

No. **Median**
(%) **(range)**

T-stage according to the revised 7th edition of the TNM classification for lung cancer.

b

Prescribed at 80%-isodose.

Table 2.

Univariate analysis.

Parameter	LR	DFS	OS	CSS
	<i>p</i>	<i>p</i>	<i>p</i>	<i>p</i>
Sex				
Male vs. female	0.91	0.98	0.67	0.27
Age				
>75 years vs. ≤ 75 years	0.85	0.33	0.16	0.75
SUV _{max}				
<7.8 vs. ≥ 7.8	0.15	0.25	0.35	0.50
Histology				
Squamous cell vs. others	0.78	0.45	0.12	0.10
Adenocarcinoma vs. others	0.51	0.35	0.07	0.27
NOS vs. others	0.34	0.75	0.64	0.64
Tumor diameter				
T1a vs. T1b	0.76	0.62	0.72	0.62
T1b vs. T2a	0.34	0.04*	0.30	0.14
T1a vs. T2a	0.96	0.01*	0.48	0.06
Stage				
IB vs IA	0.93	0.01*	0.33	0.07
GTV volume				
>13 cc vs. ≤ 13 cc	0.79	0.05*	0.06	0.02*
BED10 Gy				
>100 Gy vs. ≤ 100 Gy	0.25	0.37	0.96	0.70
Institution				

Parameter	LR	DFS	OS	CSS
	<i>p</i>	<i>p</i>	<i>p</i>	<i>p</i>

<20 procedures/year vs. ≥ 20 procedures/year 0.88 0.76 0.26 0.70

Abbreviations: LR, local recurrence; DFS, disease-free survival; OS, overall survival; CSS, cancer-specific survival.

Statistically significant.

Table 3.

Multivariate analysis.

Parameter	LR		DFS		OS		CSS	
	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>	HR (95% CI)	<i>p</i>
Stage								
IB vs IA	0.55 (0.03–10.3)	0.69	3.06 (1.62–5.77)	0.001*	2.46 (1.28–4.74)	0.007*	3.47 (1.50–7.98)	0.003*
GTV volume								
>13 cc vs ≤13 cc	4.4 (0.73–26.7)	0.1	1.04 (0.57–1.88)	0.89	1.04 (0.59–1.82)	0.89	1.37 (0.59–3.16)	0.45
Sex								
Male vs Female	0.5 (0.08–3.2)	0.47	1.05 (0.57–1.92)	0.87	0.94 (0.51–1.74)	0.86	0.79 (0.31–1.98)	0.61
Age								
>75 years vs ≤75 years	0.6 (0.15–2.57)	0.52	1.39 (0.83–2.36)	0.21	1.39 (0.83–2.32)	0.2	1.28 (0.63–2.61)	0.49
Histology								
Adenocarcinoma vs others	2.42 (0.39–14.84)	0.34	1.12 (0.64–1.97)	0.68	1.21 (0.68–2.16)	0.8	1.17 (0.52–2.61)	0.69

Abbreviations: LR, local recurrence; DFS, disease-free survival; OS, overall survival; CSS, cancer-specific survival; HR, hazard ratio; CI, confidence interval.

Statistically significant.