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

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Umberto Ricardi[a], Giovanni Frezza[b], Andrea Riccardo Filippi[a,*], Serena Badellino[a],Mario Levis[a], Piera Navarria[c], Fabrizio Salvi[b], Michela Marcenaro[d], Marco Trovò[e],Alessia Guarneri[a], Renzo Corvò[d], Marta Scorsetti

caDepartment of Oncology, Radiation Oncology, University of Torino, via Genova 3, 10126 Torino, Italyb
Bellaria Hospital, Radiation Oncology, via Altura 3, 40139 Bologna, Italy
Humanitas Cancer Center, Radiotherapy and Radiosurgery Unit, via Manzoni 56, 20089 Rozzano, Italy
Institute of Cancer Research and Treatment-IST, University of Genova, Radiation Oncology, Largo Benzi 10, 16132 Genova, Italy
Institute of Cancer Research and Treatment-CRO, Radiation Oncology, via Gallini 2, 33081 Aviano, Italy

1 Introduction

Stereotactic Ablative Radiotherapy (SABR) or Stereotactic Body Radiotherapy (SBRT) currently represents a standard of care forinoperable stage I NSCLC, offering a survival advantage overtraditional radiotherapy and cancer-specific survival rates compa-rable to surgical series in retrospective and prospective studies[1–6]. Histological confirmation of lung nodules prior to SABRhas been a concern since the introduction of this treatment, bothin clinical studies and in daily practice. The majority of patients referred to Radiation Oncology Departments are elderly and/orwith comorbidities hence, in most of them, there is contraindi-cation to CT-guided fine needle aspiration or bronchoscopy; inadjunct, peripheral nodules may be difficult to reach by bron-choscopy. In most SABR series, a correct histological diagnosis isavailable in approximately 50% of patients, and this resulted insome criticisms in the oncology community on the true efficacyof SABR as an alternative to surgery. However, other researchersshowed, in mono-institutional cohort studies, that SABR may offerexcellent local control and survival rates in histologically provenNSCLC [7–9]. The lack of robust data on patients with histologicaldiagnosis, 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 overthe last years in most countries: a US survey reported that 57% ofresponding physicians practiced SBRT for lung cancer in 2010 [10],and an Italian survey showed that SABR was used in 41% of depart-ments [11]. Palma et al. [12] analyzed the time trend in SABR use inelderly patients in the Netherlands, showing an incessant increasein indications in patients previously either untreated or addressedto palliative RT. In this frame, few data are available on efficacyand toxicity of SABR outside clinical trials, especially in patientswith histological diagnosis, a subgroup whose disease characteris-tics can be considered analogous to the surgical population (exceptfor the difference in associated comorbidities).Aim of the present retrospective observational study on a Ital-ian multicenter cohort was to provide further data on outcomes andprognostic factors in a quite large group of patients affected withstage I histologically confirmed NSCLC; the analysis was focused onthe possible impact of multiple variables and on either the confir-mation of known

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

2. Materials and methods

2.1. Patients' selection

The SABR database and this study were initiated as a spon-taneous collaboration between five Italian Radiation Oncologycenters of Northern Italy. The whole database includes 356 stageI NSCLC patients treated in the time interval 2003–2011; allcenters adopted analogous eligibility criteria for patients' refer-ral to ablative radiotherapy, and were asked to include patientsconsecutively treated with SABR defined as: stereotactic frame-based or stereotactic frameless treatment (image-guidance based),highly conformal treatment planning, extremely hypo-fractionatedregimens (maximum eight fractions), selective contouring andtreatment of pulmonary nodules without nodal irradiation. Stag-ing 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 than1 cm away from major blood vessels.Patients' information was centralized in a dedicated database,including demographic, clinical and technical data. In 2012, weextracted a cohort of 196 patients with histological/cytologicaldiagnosis of NSCLC, either obtained by fine needle aspiration orbronchoscopy. The Institutional review board of the coordinatingand participating centers approved the study. The cohort included196 patients, 146 males and 50 females, with a median age of 75years (range 48–91). One hundred eighty-one patients (92.3%) weredeemed medically inoperable because of the presence of significantcomorbidities and/or poor pulmonary function; the most com-mon contraindications to surgery included: chronic obstructivepulmonary disease (COPD) in 98 patients (54.1%), cardio-vascularcomorbidity in 58 (32%), and advanced age (>80 years old) in25 (13.9%). Fifteen patients (7.7%) refused surgery after adequatemultidisciplinary discussion. Seventy-six patients (38.8%) had adiagnosis of adenocarcinoma and 61 of squamous cell carcinoma(31.2%); the remaining 59 were classified as non-small cell lungcancer non-otherwise specified (NOS). Eighty-four patients (42.9%)had a T1a, 71 (36.2%) a T1b and 41 (20.9%) a T2a tumor, with155 patients with stage IA (79.1%) and 41 patients stage IB dis-ease (20.9%), according to the 7th edition of the TNM classificationand staging system for lung cancer [13]. Median tumor diameterwas 2.48 cm, median GTV 13.3 cc. In all Departments dose prescrip-tion was at the 80% isodose, and the total dose ranged from 48 to 60 Gy in 3–8 fractions. BED10Gywere calculated using the linearquadratic formula (BED = $nd[1 + d/(\alpha/\beta)]$), where n is the numberof fractions, d is the dose/fraction, and α/β ratio = 10 Gy. MedianBED10Gy,

calculated at 80% dose prescription, was 105.6 Gy (range:100–132 Gy). One hundred seventy-five patients were treated with3D-CRT (89.3%) and 21 with IMRT (10.7%). Three-dimension confor-mal radiotherapy consisted of a minimum of 7 up to a maximum of11 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 latetoxicity) and efficacy (local control, disease-free, overall andcancer-specific survival). Patients were followed-up by periodicalclinical examination and CT scans every 3–4 months. Follow-up CT-PET was performed in a minority of cases, and, generally, only incase of differential diagnosis between tumor recurrence and lungfibrosis. Lung toxicity was graded according to RTOG acute radia-tion toxicity score (for events occurring between day 1 and day 90from the start of radiation treatment) and to RTOG late radiationtoxicity score (for events occurring later than day 90). Late radio-logical toxicity was scored as follows (RTOG): grade 0 = absence ofchanges, grade 1 = slight radiographic appearance, grade 2 = patchyradiographic appearance, grade 3 = dense radiographic appearance.

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

3. Results

Median follow-up time was 30 months. The crude rates of localand 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 survivalsare plotted in Fig. 1a–c. LRFS was 89.7% at 3 years. Fifty-ninepatients (30.1%) had at least one failure, with a disease-freesurvival (DFS) rate at 3 years of 65.5% (Fig. 1d). Median time tolocal recurrence was 14.4 months. Overall and cancer-specificsurvival plots are presented in Fig. 2a and b, and were 68% and82.1% at 3 years, respectively. Median time to any recurrence was15 months, median survival time 54 months. Isolated pulmonary lesions occurring at more than 2 years after SABR were consideredas second primary tumors (7 patients, 3.6%). At univariate analysis, Stage IB (i.e., T2aN0M0) showed worseDFS and CSS, while GTV < 13 cc was associated to better DFS andCSS (Table 2). At multivariate analysis, stage IB was confirmed as the onlyvariable 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). Adifference in survival according to stage was also evident at thelog-rank test (p = <0.0001 for CSS and OS, as shown in Fig. 3).

majority of non cancer-related deaths were secondary to cardiac orpulmonary fatal events (6 chronic heart failure, 4 myocardial infarc-tion, 6 strokes, 11 chronic respiratory insufficiencies, 1 chroniclymphocytic 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 $\geq$2pulmonary toxicity (4 G2 and 2 G3). Late clinical pulmonary toxic-ity 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 eventsincluded: chest wall toxicity (8 cases, 4.1%), with neuropathic painrequiring analgesic therapy, 1 brachial plexopathy (0.5%), 1 mod-erate teleangiectasia (0.5%) and 1 rib fracture (0.5%).

4. Discussion

This retrospective observational study describes toxicity, sur-vival and prognostic factors in a cohort of patients withhistologically proven stage I NSCLC treated with SABR in 5 ItalianRadiation Oncology Departments as part of clinical practice. SABRresulted 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–bvs. T2). Matsuo et al. [8] found, in a series of 101 patients withhistologically proven NSCLC, a significant difference in LC betweenstage IA and IB, while in our study the difference resulted significantonly for survival. In the report by Andratschke et al. [7], including92 patients with histological confirmation, a correlation between Tstage and LC (T1 vs. T2) was evident, but conversely survival was notsignificantly 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 andoutcome analysis on a cohort of 582 patients treated with SABRin Germany between 1998

and 2011 [14]. This study, that has aparallel design and includes a patients' cohort quite analogous toours, showed that stage IA was correlated with a better OS, withonly a trend for a better LC. The prognostic effect of tumor sizehas been recognized in surgical series: in the IASLC database theexpected OS at 2 years for stage IA (tumor size less than 3 cm) is73%, compared to 64% for patients with tumors sized 3–5 cm. Inthe 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 sig-nificant difference in OS and CSS values is a consequence of thequite high number of non cancer-related deaths, hampering a cor-rect comparison with surgical series but also suggesting that theoutcome after SABR is likely to be equal to surgery also in largertumors. At this regard, the negative prognostic impact of tumorsize appears to be mainly related to a higher risk of systemic fail-ures compared to local and loco-regional failures and this patternof relapse emphasizes the potential role of adjuvant systemic treat-ments in stage I. Recently, Allibhai and co-authors, among a seriesof 185 patients, found at recurrence partitioning analysis that largerGTVs were significantly associated with poorer rates of DFS, OS, andCSS. Assuming idealized spherical tumors, the selected GTV cut-point for significance was >2.8 cm (i.e. the approximate size cut-offfor T2 tumors) [15]. Previous studies on surgical series showed thata higher pre-treatment SUVmaxcould be associated to worse sur-vival [16]. After several reports failing to show a correlation, Nairet al. recently reported that a SUVmaxvalue > 7 was an independentprognostic factor for distant metastases-free survival after SABR[17]. In our experience the mean SUVmaxvalue, available in patientswho performed a CT-PET scan before SABR, did not reach statisti-cal significance (a trend toward significance with a cut-off of 7.8 isevident at multivariate analysis, Table 3).The overall clinical outcome of our cohort was satisfactory. The5 participating centers applied homogeneous patients' selectioncriteria, despite data were collected over 10 years. No inter-institutional significant variability in patients' age, performancestatus or comorbidities was recorded. Some intrinsic favorablecharacteristics of our study cohort may be significant for resultsinterpretation, such as the good PS (0 in 58.7%, with no patientswith PS $\geq$ 2), the small median tumor size (2.48 cm) and tumor vol-ume (13.3 cc), a higher percentage of stage IA tumors in comparisonwith other series (79.1% vs. 56.2% in the DEGRO study). Survival esti-mates reflect what emerged from the meta-analysis done by Soldàet al. [18], with OS at 2 years of 70% (81.6% in the present study),emphasizing the potential equivalence between SABR and surgeryfrom clinical trials datasets. Notably, results of our study refer to apatients' population with histological diagnosis.BED10Gydid not emerge as a significant variable for all differ-ent clinical endpoints. The "intermediate" median BED10Gyof ourstudy (105.6 Gy) is associated to a quite high LRFS, comparable tothat achieved by Vrije University researchers in their retrospectiveseries (roughly 90% at 5 years in 672 patients), including a largenumber of patients without histological confirmation

of malig-nancy [1]. This finding confirms that probably lower doses (thanpreviously thought) to the PTV edge may be sufficient to attainhigh control rates, as recently shown by Van Baardwijk et al. in asystematic review of clinical trials [19].As in the DEGRO study, technical parameters did not influenceany clinical endpoint, and also the total number of SABR proceduresper Institution/year did not affect outcomes.Female gender was significantly correlated to a better distantprogression-free survival and OS in a single report [8]. This findingwas not confirmed by our study or by other series, and this maybe due to the low number of female patients enrolled, hamperinga correct statistical evaluation, or to possible intrinsic differencesbetween Caucasian and Asian patients populations.A comparative matched-pair analysis including propensityscore (controlling for all factors affecting treatment selection)between two early stage NSCLC patients cohorts (180 treated withsurgery and 137 with SABR), showed that OS was comparable [20].At univariate analysis, OS was better for adenocarcinomas, smallertumor size and lower Charlson's comorbidity score, with no vari-ables selected as significantly affecting LC. At multivariate analysis,only Charlson's comorbidity index resulted associated to OS, whilelocal control was influenced by tumor size. Apparently, histologi-cal subtype did not have any impact on survival, as in most studies.One of the explanations may be that in the SABR cohort the fractionof NOS diagnoses was higher than in the surgical group, reflectingthe overuse of this pathological category in a patients' populationwhere cytology/histology is only available from small biopsy sam-ples. Also in our cohort the number of NOS was very high, probablyjeopardizing the effect of adenocarcinoma histology on possiblebetter outcomes (we only found a trend toward better OS for ade-nocarcinoma at univariate analysis). In the DEGRO experience, thepositive impact of adenocarcinoma histology was confirmed atmultivariate analysis only on LC, and not on survival endpoints.The findings of the present study confirm that SABR may be avalid alternative to surgery. In clinical practice, a multidisciplinaryapproach could probably be of great value in determining the besttreatment strategy in every single patient, taking into accountclinical factors like respiratory function, tumor's stage, age andcomorbidities, and offering the proper choice in terms of efficacyand morbidity [21,22]. In the study by Palma et al. [12], on elderlypatients with a median age of 79 years old, SABR had a 30-day mor-tality rate of <2%; this result can be of particular importance fordecision making, as patients are obviously reluctant to accept risksthat involve the possibility of short-term death. A Markov-modelbased comparison of surgery versus SABR for patients aged 65 or older predicted that surgery might confer an overall survival bene-fit of 2–3% at 5 years over SABR. However, once operative mortalityincreases above 4%, the survival advantage of surgery was negatedand SABR preferred [23].Our study was designed with the aim of increasing the knowl-edge on SABR safety and efficacy in patients not included inacademic studies. As pointed out by S. Senan, patients enrolledin clinical trials

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

5. Conclusion

This multicenter retrospective observational study, by provid-ing further data on the safety and efficacy of SABR in histologicallyconfirmed stage I NSCLC outside clinical trials, supports the routineuse of SABR for stage I NSCLC in a daily practice environment. Theonly prognostic factor that has been confirmed by our analysis wastumor stage (IA vs. IB).

Conflict of interest

None declared.

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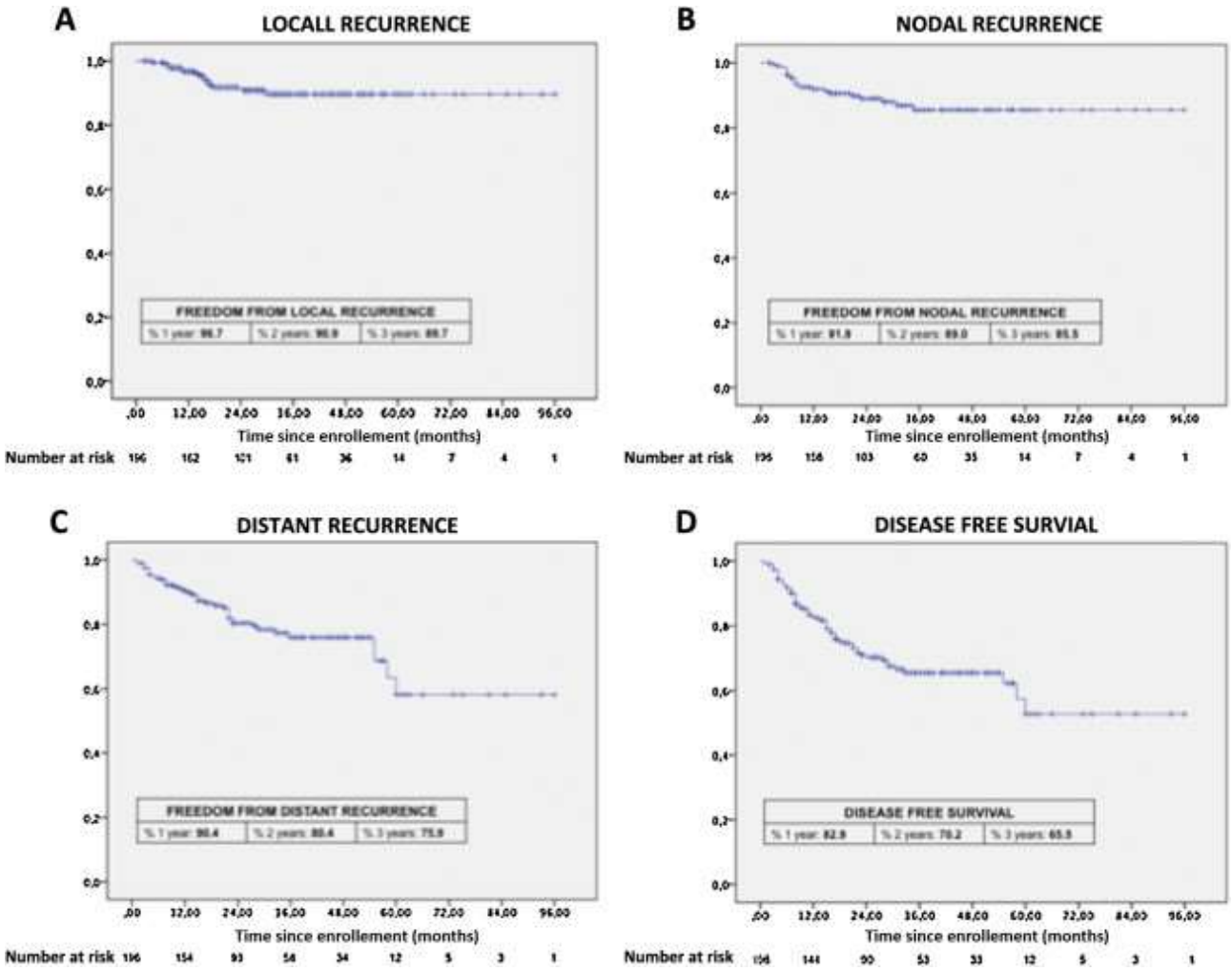


Fig. 1.(a) Local recurrence-free survival; (b) nodal recurrence-free survival; (c) distant recurrence-free survival; (d) disease-free survival.

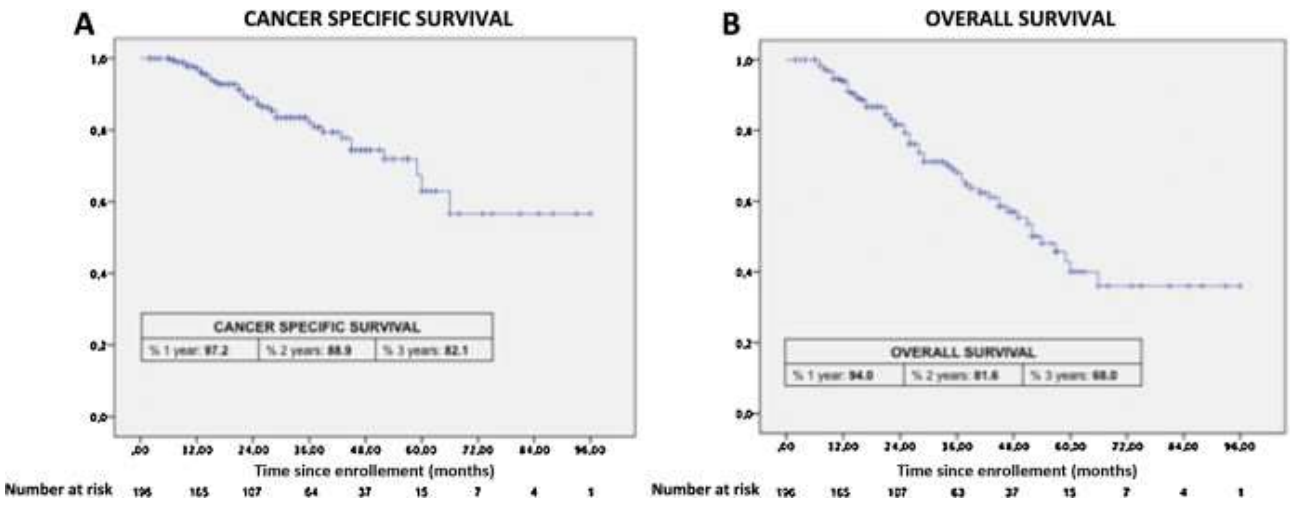
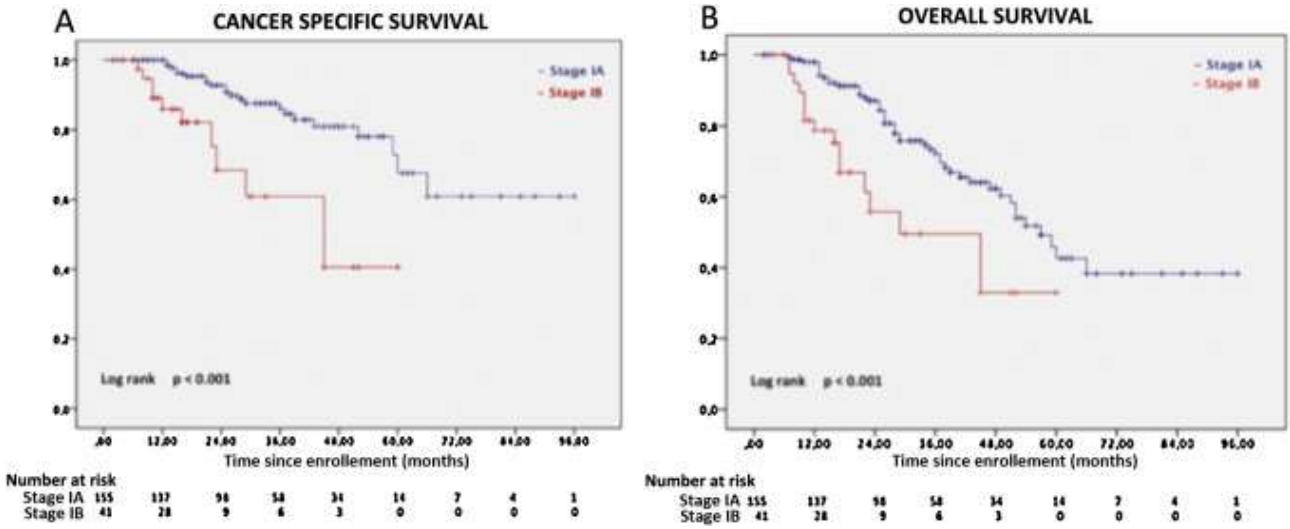


Fig. 2.(a) Cancer-specific survival; (b) overall survival.



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**
	p	***p***	***p***	***p***
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
	p	*p*	*p*	*p*
<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)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
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.