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RESEARCH ARTICLE

Accelerated hypofractionated radiation therapy (AHRT) for non-small-cell lung cancer: can we leave standard fractionation?

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Abstract
Purpose To report interim results from a single-institution study conducted to assess accelerated hypofractionated radiotherapy (AHRT) delivered with 3D conformal radiotherapy in two groups of patients with non-small cell lung cancer: (1) patients with early stage disease unable to tolerate surgery and ineligible for stereotactic body radiation therapy, and (2) patients with locally advanced disease unsuitable for concurrent chemoradiotherapy.
Methods/patients A total of 83 patients (51 stage I–II, 32 stage III) were included. Radiotherapy targets included the primary tumor and positive mediastinal areas identified on the pre-treatment PET–CT. Mean age was 77.8 ± 7.8 years. ECOG performance status (PS) was ≥2 in 50.6 % of cases. Radiotherapy was delivered in daily fractions of 2.75 Gy to a total dose of 66 Gy (BED_{10} 84 Gy). Acute and late toxicities were evaluated according to NCI CTC criteria.
Results At a median follow-up of 42 months, median overall survival (OS) and cause-specific survival (CSS) were 23 and 36 months, respectively. On the multivariate analysis, PS [HR 4.14, $p = 0.0001$)], stage [HR 2.51, $p = 0.005$)], and maximum standardized uptake values (SUVmax) [HR 1.04, $p = 0.04$)] were independent risk factors for OS. PS [HR 5.2, $p = 0.0001$)] and stage [HR 6.3, $p = 0.0001$)] were also associated with CSS. No cases of severe acute or late treatment-related toxicities were observed.
Conclusions OS and CSS rates in patients treated with AHRT for stage I–II and stage III NSCLC were good. Treatment was well tolerated with no grade three or higher treatment-related toxicity. PS, stage, and SUV max were predictive for OS and CSS.

Keywords Hypofractionation · Radiotherapy · Non-small-cell lung cancer · Performance status

Introduction

Lung cancer is the leading cause of cancer-related death world-wide [1]. Non-small cell lung cancer (NSCLC) accounts for 80 % of all lung cancers and prognosis is poor, even in patients eligible for curative-intent treatment. Surgical resection is the treatment of choice in early stage (I–II) disease, although radiotherapy offers an efficacious alternative in the 20–25 % of patients considered unfit for surgery due to advanced age, poor lung function, or comorbidities, such as cardiopathy, vascular disease, diabetes mellitus, or other comorbid conditions [2] or in patients who refuse surgery. Concomitant chemoradiotherapy is the treatment of choice in locally advanced (stage III) NSCLC, offering improved overall survival compared with sequential treatment schemes. However, concomitant treatment is associated with more treatment-related side effects, primarily in the esophagus, with higher rates (from 4 to 18 % higher) of ≥grade 3 acute esophagitis compared with sequential treatment [3, 4].

The number of elderly patients diagnosed with lung cancer is expected to increase in coming decades due to

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population demographics. Consequently, the percentage of patients with early stage NSCLC considered ineligible for surgery is also expected to increase [5, 6]. Various studies have demonstrated the importance of accurately assessing the patient's general condition, performance status (PS), and comorbidities, because these factors have been shown to be independent predictors of overall survival [7, 8].

The conventional radiotherapy for NSCLC consists of a total dose ≥60 Gy delivered in daily fractions of 2 Gy/day for 6–6.5 weeks. [9] In recent years, various alternative treatment schemes have been evaluated in an effort to improve treatment outcomes. One such strategy—hypofractionated radiotherapy—involves increasing the dose per fraction while reducing the number of sessions, an approach that is believed to limit tumor repopulation [10]. Hypofractionated radiotherapy may be particularly advantageous in patients with poor PS, because fewer treatment sessions are needed. This is an important advantage given that lower survival rates have been reported in elderly patients versus younger patients, possibly due to reduced access to treatment as a consequence of poor PS [8].

In early stage NSCLC, stereotactic body radiotherapy (SBRT) has proven superior to the conventional radiotherapy in inoperable patients [11–13]. However, SBRT must be administered according to a very strict protocol to assure treatment accuracy and safety. In addition, certain patient characteristics—including tumor size and/or location and PS—could complicate the use of SBRT; moreover, SBRT is not available in all centers. For these reasons, accelerated hypofractionated radiotherapy (AHRT) delivered with three-dimensional conformal radiotherapy (3D-CRT) could offer an acceptable alternative to SBRT. Several studies (using slightly different doses and fractionation schemes) have reported promising results for AHRT compared with the conventional radiotherapy [14, 15]. Sakaguchi et al. [16] retrospectively assessed 29 patients, finding that the only factor that was significantly associated with local control was a biological equivalent dose (BED) ≥80 Gy. However, data on AHRT remain limited and all but two of the studies published to date have been retrospective.

Given this context, we conducted the present prospective study to investigate the efficacy of AHRT delivered with 3D-CRT as an alternative to the conventional fractionation in two groups of patients with NSCLC, both of which underwent AHRT. The first group consisted of patients with early stage disease who were ineligible for surgery and unable to undergo SBRT (lack of SBRT technique; comorbidities; elevated PS; refusal to travel to another center; etc.). The second group comprised patients with stage III disease considered ineligible for concomitant chemoradiotherapy and, therefore, treated with sequential chemotherapy and AHRT.

Materials and patients

Patient selection

Inclusion criteria for the first group included a histological diagnosis of stage I–II NSCLC and ineligibility for surgical resection or SBRT. For the second group, inclusion criteria were a histological diagnosis of stage III NSCLC and eligibility for sequential chemoradiotherapy. Exclusion criteria included any of the following: diagnosis of small cell lung cancer; eligibility for surgery or SBRT; history of prior chest irradiation; and eligibility for concomitant chemotherapy treatment. Patients eligible for inclusion were treated between March 2009 and June 2015.

All patients were staged with contrast-enhanced thoraco-abdominal computed tomography (CT), ^{18}F-fluorodeoxyglucose positron-emission-computed tomography (FDG–PET–CT), brain magnetic resonance imaging (MRI), and respiratory function tests. Histologic assessment was performed by endobronchial ultrasound (EBUS) or mediastinoscopy depending on the results of the imaging tests. In general, histological evaluation was performed if the mediastinal nodes had a diameter >1 cm and/or nodal uptake was observed on the PET–CT. The treatment decision was made by a multidisciplinary tumor board. All patients signed the informed consent form prior to treatment. The Research Ethics Board of Parc de Salut Mar gave ethical approval for this project.

Radiotherapy technique

Treatment planning was based on the PET–CT images. The patient was placed in the treatment position (supine decubitus with arms raised above the head) using an immobilization device. No endovenous contrast was used [17]. PET–CT images were interpreted jointly with the nuclear medicine specialist. The gross tumor volume (GTV) was defined as the primary tumor plus the involved lymph nodes (>1 cm on the CT and/or hypermetabolic on the PET–CT). Under our institutional protocol, the GTV and CTV are the same. To obtain the PTV, we applied an automatic 1.5-cm margin to the GTV in the antero-posterior and lateral directions, and a 2-cm margin in the cranial-caudal direction. No elective nodal irradiation was performed.

The following organs at risk (OARs) were contoured: esophagus, heart, spinal cord, and lung. The brachial plexus was contoured when necessary (according to the location of the primary tumor). The lung volume considered as the OAR was defined as the total lung volume minus the GTV (i.e., total lung-GTV).

Treatment planning and dosimetric calculations were performed with the Oncentra Master Plan (Nucletron B.V., Veenendaal, The Netherlands). Radiotherapy was administered in 24 daily sessions of 2.75 Gy/session to a total dose of 66 Gy (BED_{10} 84 Gy). Plan acceptance required that 95 % of the PTV receive 95 % of the prescribed dose and that 50 % of the PTV receive 100 % of the prescribed dose.

Dose restrictions to the OARs were set according to standard limits [18, 19]. Dose limits in the lung were: V20 ≤30 %, and mean lung dose (MLD) <20 Gy. In the spinal cord, the maximum dose was set at <45 Gy. For the heart, the V30 limit was <46 % with a total mean dose <26 Gy. In the brachial plexus, the limit was <66 Gy. Finally, the recommended mean dose to the esophagus was <34 Gy, with V30 <50 %, V50 <40 %, and V70 <20 % [20, 21].

Statistical analysis

The statistical analysis was performed with SPSS version 22 (IBM SPSS, Chicago, IL). A descriptive analysis was performed using means and standard deviations. The survival analysis was performed with the Kaplan–Meier method. Overall survival (OS) and cause-specific survival (CSS) were calculated from radiotherapy initiation to death or final follow-up evaluation. The multivariate analysis was performed with a Cox regression.

Follow-up

During the course of radiotherapy, patients were examined at least once per week (more often if necessary). All patients were scheduled for a follow-up consultation at the following time points: at 3 weeks post-treatment, every 3 months for the first 2 years, and every 6 months thereafter. All follow-up evaluations consisted of a full history and physical examination, including assessment of adverse events. Acute and late radiation effects were evaluated and graded according to Common Terminology Criteria for Adverse Events (http://evs.nci.nih.gov/ftp1/CTCAE). Chest CT was used to assess tumor response at all follow-up consultations except for the first post-treatment follow-up (week 3).

Results

A total of 83 patients with a histologically confirmed diagnosis of NSCLC (62 % stage I–II, 38 % stage III) were included in the study. Patient characteristics are shown in Table 1. Most patients (50/83) had no mediastinal node involvement; of the other 33 patients, 9 were classified as N1, 19 as N2, and 5 as N3. All patients were staged by PET–CT, with a maximum standardized uptake value (SUVmax) of 10.0 ± 6.4. Most (90.6 %) of the stage III patients received sequential chemotherapy, which consisted of platinum-based treatment combined with vinorelbine in most cases.

Table 1 Patient and disease characteristics

Characteristic	
Sex	
Male	71 (86 %)
Female	12 (14 %)
Average age	77.9 ± 7.8 years
Tumor stage	
IA	17
IB	14
IIA	11
IIB	9
IIIA	20
IIIB	12
Histology	
Adenocarcinoma	35 (1 EGFR mutation, 23 EGFR no mutation and 11 unknown)
Squamous cell carcinoma	41
NSCLC	7
Performance status score	
PS 0–1	41 (49.4 %)
PS 2–3	42 (50.6 %)
Lung dosimetric parameters	
Stages I–II	V5 31.9 ± 14.7, V20 16.3 ± 6.1, MLD 10.0 ± 3.5
Stage III	V5 47.3 ± 11.8, V20 22.9 ± 4.8, MLD 14.2 ± 2.8

V5 the total lung volume receiving a dose of 5 Gy, V20 the total lung volume receiving a dose of 20 Gy

MLD mean lung dose

PS ranged from 2 to 3 in 50.6 % of the patients. Respiratory function tests showed the following mean values: forced expiratory volume in 1 s (FEV1), 57.1 ± 23.7 %; diffusing capacity for carbon monoxide (DLCO), 48.2 ± 28.6 %; and carbon monoxide transfer coefficient (KCO), 58.9 ± 36.6 %.

All patients were treated with 6-MV photon 3D-CRT delivered in 24 sessions of 2.75 Gy/day. The final OAR values were as follows: lung: V5 37.8 ± 15.5 %; V20 18.9 ± 6.4 %; mean dose 11.6 ± 3.8 Gy; esophagus: V30 16.5 ± 20.1 %; V50 11.4 ± 16.6 %; mean dose 14.3 ± 11.9 Gy; maximum dose 41.4 ± 24.5 Gy; heart: V30 11.5 ± 14.5 %; mean dose 12.4 ± 10.6 Gy; and maximum dose 53.9 ± 20.6 Gy. In the brachial plexus and spinal cord, the maximum doses in all cases were, respectively, <66 Gy and <45 Gy (Table 1).

At a median follow-up of 42 months, median OS and CSS were, respectively, 23 and 36 months (Fig. 1). By stage, 2-year OS and CSS rates were, respectively, 51.1

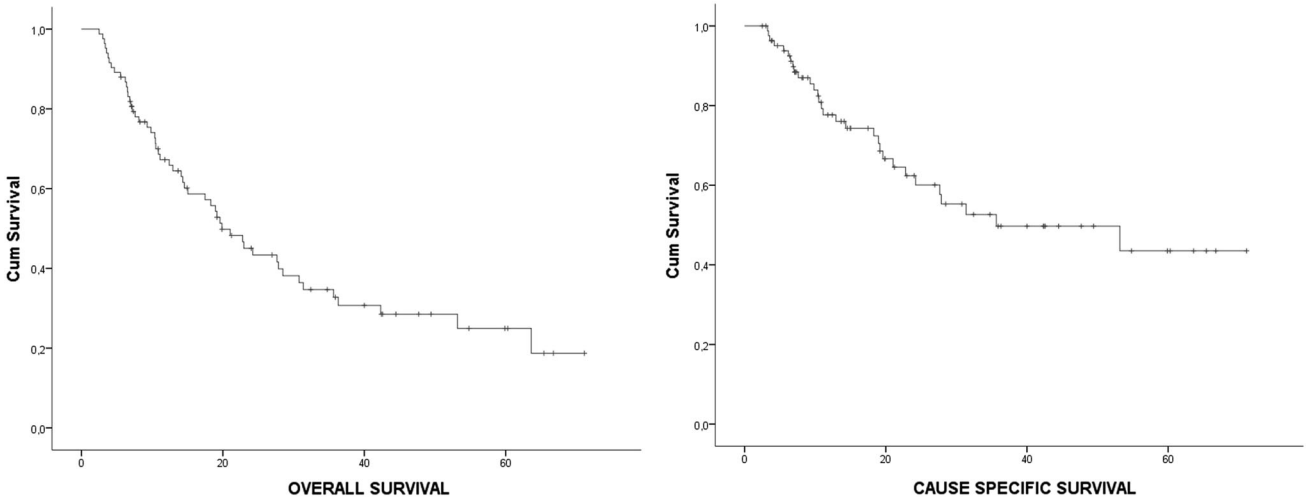

Fig. 1 Actuarial overall survival (OS) and cause-specific survival (CSS) for the entire cohort (83 patients)

and 82.1 % (stage I patients), 50.6 and 70.8 % (stage II), and 37.5 and 41.5 % (stage III).

Thirty-seven patients developed a recurrence, as follows: local (21.6 %), 5 stages I–II and 3 stage III); distant (18.9 %), 3 stages I–II and 4 stage III; or both local and distant (59.5 %), 8 stages I–II, and 14 stage III.

We assessed the impact of the following variables on survival: age, PS, stage, tumor size, SUV max on the PET–CT, FEV1, DLCO, and KCO. As shown in Table 2, the only variables found to be independent prognostic factors for OS and CSS were PS (0–1 vs 2–3), early vs advanced stage disease, and SUV max.

Figure 2 shows the effect of PS on survival in both patient groups. In patients with stage I–II disease, 2-year OS was 20.5 % in the subset of patients with a poor PS (2–3) vs 61 % in patients with good PS (0–1) ($p = 0.002$). For 2-year CSS, the corresponding survival values were 26 vs 68.5 %, respectively ($p = 0.01$).

The treatment was well tolerated and no cases of toxicity >grade 2 were observed. In terms of acute side effects, grade 1 and grade 2 dermatitis, respectively, were observed in 41 and 16.8 % of patients; no dermatitis was observed in the remaining 42.2 % of patients. Most patients (65.1 %) did not develop any esophageal toxicity; however, 25.3 and 9.6 %, respectively, presented grade 1 or grade 2 esophagitis. Most patients (72 %) presented no acute pulmonary toxicity. Acute grade 1 pneumonitis was reported in the remaining 28 % of patients. Chronic grade 1 pneumonitis was observed in 50.6 % of the patients, with one case of grade 2 lung toxicity. No treatment-related deaths were observed.

Discussion

The aim of this study was to assess the role of AHRT as an alternative to the conventional fractionation in NSCLC. We evaluated two groups of patients, both treated with AHRT delivered by 3D-CRT. The first group consisted of patients with early stage NSCLC ineligible for surgery and unable to receive SBRT; this group received AHRT alone. The second group consisted of stage III patients unfit for concomitant chemoradiotherapy and, consequently, treated with sequential chemotherapy and AHRT. Median OS and CSS were good (23 and 36 months, respectively) and consistent with other reports. Moreover, treatment was well tolerated without any severe (≥grade 3) treatment-related toxicity. Taken together, these results support the use of AHRT in patients ineligible for SBRT or concomitant chemoradiotherapy.

Table 3 summarizes the most relevant studies published to date on AHRT for NSCLC. As that table shows, most studies conducted to date have been retrospective, with highly heterogenous doses schemes among those studies. Similarly, treatment planning (2D, 3D, or even 4D in the most recent studies) is also heterogeneous. As a result of this variability, it is difficult to reliably compare the available studies [14–16, 22–28, 30].

Soliman et al. [24] used a hypofractionated treatment regimen (4 Gy/day; total dose 48–60 Gy) to treat 118 patients with stage T1–3 N0M0 NSCLC, reporting favorable local control and survival rates. They observed 45 recurrences, of which 13 were exclusively local. They did report, however, one death due to radiation pneumonitis, five cases of pneumonitis requiring corticosteroid therapy, and four rib fractures. Yung et al. [25] evaluated 60 patients with T1–2 N0 disease, most of which (70 %) were treated with 20 fractions of 3 Gy/day. Survival rates were similar to those reported by Soliman et al., but with a better tolerance (no cases of ≥grade 3 toxicity). Two other studies used a daily fractionation schedule similar to ours [14, 15]. Din et al. [15] retrospectively assessed a series of 609 patients (20 fractions of 2.75 Gy; total dose: 55 Gy), reporting a 2-year OS of 72 % (stage IA), 51 % (stage IB),

Table 2 Multivariable cox proportional hazards regression model of factors predicting overall survival (OS) and cause-specific survival (CSS)

	HR	95 % CI	*p*
OS			
PS	4.14	2.20–7.81	0.0001
Stage III vs I–II	2.51	1.31–4.80	0.005
Maximum SUV value	1.04	1.00–1.09	0.04
CSS			
PS	5.22	2.26–12.06	0.0001
Stage III vs I–II	6.31	2.31–17.25	0.0001

PS performance score, *SUV* standardized uptake value, *HR* hazard ratio, *CI* confidence interval

and 40 % (stage III), without any grade ≥3 toxicity. Importantly, less than 20 % of patients developed grade 1 or 2 pneumonitis. Lester et al. [14] evaluated 135 patients, most (72 %) of which received 20 fractions of 2.75 Gy (total dose 50 Gy). At a mean follow-up of 48 months, 2-year OS and CSS were 48.2 and 51.6 %, respectively, in stage I–II patients and 26.1 and 28.6 % in stage III patients. No severe acute or late toxicity was reported. Notably, although the OS and CSS rates reported by those authors showed a little variation, we observed a much greater disparity in our outcomes: 2-year OS and CSS were 51.1 and 82.1 %, respectively, in our stage I patients, 50.6 and 70.8 % in stage II patients, and 37.5 and 41.5 % in stage III patients. This disparity between our results and those reported by Lester et al. could be attributable to differences between the studies in terms of mean PS value: nearly three-quarters (72 %) of patients in this study had a PS of 0–1, whereas 49.4 % of patients in our study had a PS 0–1.

Two prospective studies have been conducted to evaluate hypofractionated 3D-CRT. The CALGB 39904 trial [26] reported favorable results with a total dose of 70 Gy (2.41–4.11 Gy/fraction). Mean survival was 38.5 months with a local failure rate of only 10 %. The NCIC-CTG BR 25 [27] phase II trial assessed 80 patients with peripheral lung tumors (≤5 cm) without nodal involvement. Treatment consisted of 60 Gy of hypofractionated radiotherapy delivered in 15 fractions. At a mean follow-up of 49 months, 2-year local control and OS were 87.4 and 68.7 %, respectively.

More recently, several authors have compared SBRT with AHRT. Lucas et al. [28] analyzed 160 stages I–II NSCLC patients treated with a mean dose of 54 Gy in three fractions (RTOG 0236 regimen) and 70.2 Gy in 26 fractions (CALGB 39904 regimen), respectively. At 3 years of follow-up, there were no significant differences between the groups in terms of local control (87.7 vs 71.7 %) or OS (63.4 vs 56.7 %); however, it is important to note that the groups were not well balanced in terms of PS, tumor size, and tumor localization. Chiang et al. [29], retrospectively, reviewed outcomes in 114 patients diagnosed with stage T1–T4 N0M0 NSCLC. Patients were equally divided into two treatment groups (57 patients per group): SBRT (49.7 ± 1.9 Gy; BED_{10} 100–119.6 Gy) vs AHRT (49.8 ± 2.8 Gy; BED_{10} 67.2–84 Gy). The results of the AHRT group had previously been reported by Soliman et al. [24]. In that group, treatment planning was 3D (3D-CRT), with weekly control via portal imaging. In the SBRT group, 4D treatment planning was utilized and the immobilization systems were more rigid. Daily cone beam CT was used for image guidance. The findings showed that patients treated with SBRT had better OS and local control, although no differences between the groups were observed in terms of progression-free survival and distant failure. Importantly, a higher proportion ($p < 0.001$) of patients in the SBRT group underwent complete staging (i.e., both

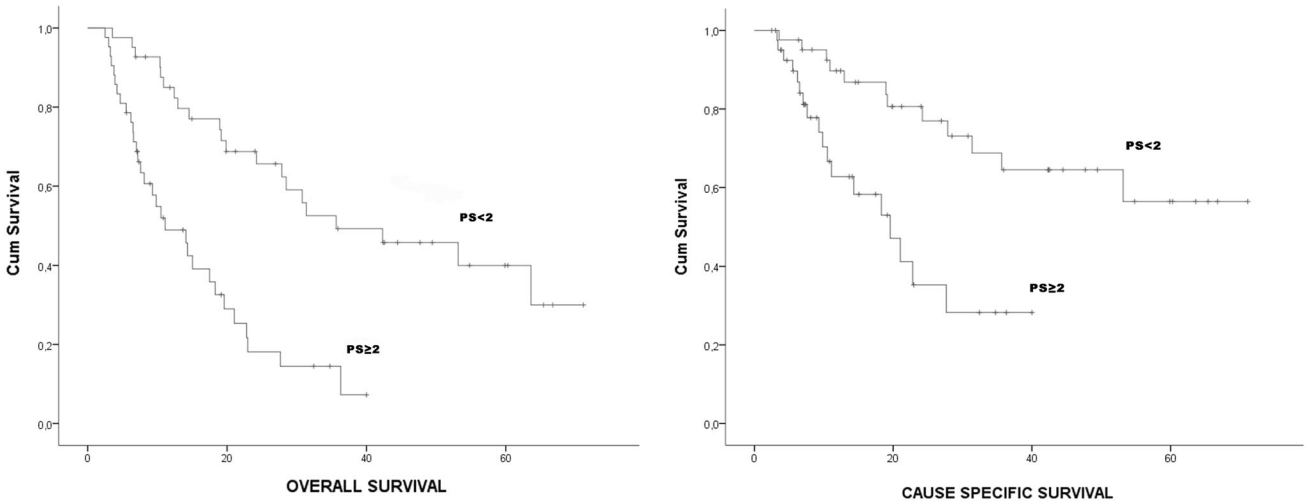

Fig. 2 Overall survival (OS) and cause-specific survival (CSS) as a function of performance status (PS) for the entire cohort (83 patients)

Table 3 Selected series of accelerated hypofractionated radiotherapy for NSCLC

	n	Stage	ECOG PS	Age (years)	Dose	Risk factors	Follow-up	OS 2 years (%)	CSS 2 years (%)	OS months	LC 2 years
Yung 2012 [25]	60	T1–2N0	NR	74	50–60 Gy in 20–25 fr 70 % 60 Gy in 20 fr, 3 Gy/fr	NR	27	61	79	28	8 % LR (2 years)
Faria 2006 [22]	32	T1–2N0–1	NR	76	52.5 Gy in 15 fr, 3.5 Gy/fr	NR	29	56	74	29	LRFS 76 % (2 years)
Soliman 2011 [24]	118	T1–4 N0	82.2 % PS 0–1	76	48–60 Gy in 12–15 fr, 4 Gy/fr	T > 3 cm	23	51	67	26	76.2 % 28 % LR
Westover 2015 [30]	55	I–IV	57 % PS 2–4	70	50–55–60 Gy in 15 fr de 3.3–4 Gy/fr	NR	12.5	20	NR	6	NR
Lester 2004 [14]	135	I–IIIB 83 % I–II	72 % PS 0–1	71	50–55 Gy in 15–20 fr, 2.75 Gy/fr	Stage PS	48	44	47	21	28 % LR
Cheung 2000 [23]	102	T1–4 N0–1	96 % PS 0–1	71	52.5 Gy in 20 fr, 2.6 Gy/fr	NO	86	50	63	24	49 % LR
Din 2013 [15]	609	I–IV	43 % PS 0–1 45 % unknown	71	55 Gy in 20 fr, 2.75 Gy/fr	NO	NR	50	NR	24	37 % LR
Sakaguchi 2016 [16]	29	T2–T3 N0	PS 0–1 83 %	76	48–60 Gy in 3–6 Gy/fr 50 % 60 Gy in 20 fr	BED <80 vs ≥80 Gy	17	45	77 % (1 years)	17	66 % (1 years)
CALGB 39904 2010 [26]	39	T1–2 N0	95 % PS 0–1	75	70 Gy in 17–29 fr, 2.4–4.1 Gy/fr	NR	53	62	NR	38	10 % LR
NCIC-CTG BR 25. 2014 [27]	80	T1–3N0	80 % PS 0–1	76	60 Gy in 15 fr, 4 Gy/fr	T > 3 cm	49	69	NR 39 % died of lung cancer 48 % other causes	41	88 %
Lucas 2014 [28]	160 (79 AHRT)	T1–2b N0	90 % PS 0–1	69	60–72.3 Gy in 17–30 fr, 2.7 Gy/fr	Dose/fr action. Tumor size	19	62	NR 19 % died of lung cancer	35	79 %
Current study	83	T1–4 N0–3	49 % PS 0–1	77.9 ± 7.8	66 Gy in 24 fr, 2.75 Gy/fr	PS, Stage, SUV max	42	45	63	23	21 % LR

PS performance score, *SUV* standardized uptake value, *OS* overall survival, *CSS* cause-specific survival, *LC* local control, *NR* not reported, *NO* not observed, *LR* local recurrence, *LRFS* local recurrence free survival

PET–CT and CNS imaging). On the multivariate analysis, tumor size [HR (per 1 cm increase): 1.29, $p = 0.009$] and complete staging with PET–CT [HR 0.34, $p = 0.004$)] were the only factors significantly associated with OS. Moreover, no differences in OS were observed among the treatment groups. By contrast, in our study, all patients were staged with PET–CT; CNS imaging was performed only in stage III patients and in patients with adenocarcinomas ≥stage IIA. We found that tumor stage and SUV max values were independent prognostic factors for OS. Based on these data and the results of other related studies, we agree with the conclusions of the aforementioned comparative studies: SBRT seems to be superior to AHRT in the treatment of patients with inoperable early stage NSCLC. However, in institutions that lack the equipment necessary to perform SBRT, or in patients who cannot follow the strict protocols necessary for SBRT, AHRT appears to be a reasonable option.

In general, AHRT is well tolerated. Although we did observe some toxicity in our study, it was limited, without any grade 2 or greater acute or chronic side effects. These findings are consistent with the published results of other AHRT studies. Notably, the good toxicity outcomes in our study (≤grade 2) were achieved even in patients with mediastinal involvement (19 patients with N2 disease, and 5 with N3). However, the use of higher dose fractions appears to increase side effects, primarily dyspnea and esophagitis [24], although it should be noted that Westover et al. [30] found no significant association between these side effects and dose levels.

In addition to treatment-related variables, such as dose and toxicity, several studies have demonstrated that assessment of patient-related variables (age, PS, functional status) is very important. Moreover, in most patients, comorbidities associated with tobacco use are also present [5–8, 31]. In our sample, mean patient age was nearly 80 years, and slightly more than half had a PS ≥2 (an independent predictor of poor outcomes). These findings are consistent with those reported by Lester et al. [14], who also found an association between good PS and higher OS. As discussed previously, our results showed a large disparity between OS and CSS—particularly in early stage disease—a finding that indicates that the cause of death in most of our patients was not directly related to the cancer.

Conclusions

AHRT is safe and well tolerated by patients with stage I–II NSCLC who cannot receive SBRT and in stage III patients considered unsuitable for concomitant treatment. Importantly, AHRT does not require any special technology, which means that it can be performed at any radiation oncology department with 3D planning. Poor PS, tumor stage, and SUV max on the PET–CT are all predictors of survival in these patients.

Compliance with ethical standards

Conflict of interest The authors indicate no potential conflicts of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent All patients signed the informed consent form prior to treatment.

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