

Research Article

Stereotactic Body Radiation Therapy for Medically Inoperable Stages I and II Non-Small Cell Lung Cancer. Single Institution Retrospective Analysis of Outcomes and Predictive Factors

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Abstract

Purpose: This retrospective series aims to report the Brazilian single institutional experience and predictive factors for outcomes in patients with early stage and medically inoperable NSCLC treated with SBRT.

Materials/methods: Retrospective analysis of 82 consecutive patients with NSCLC stages IA – IIA (T1aN0M0 – T2bN0M0), by AJCC 8th edition criteria treated from May 2013 to March 2019 with SBRT. All patients were staged with PET/CT and considered medically inoperable. The median age was 77 years old and median tumor size was 2.2cm. Histological subtype was adenocarcinoma in 54 (65.8%), patients, squamous cell carcinoma (SCC), in 25 (30.5%), and 3 (3.7%), had no biopsy. Fifty and six (68.3%), patients were treated with 48Gy in 4 fractions (BED=105.6Gy₁₀), and 26 (31.7%), with 40Gy in 4 fractions (BED=80Gy₁₀) delivered twice a week. Local recurrence free survival (LRFS), disease free survival (DFS) and overall survival (OS), were estimated by Kaplan-Meier method. BED, histological subtype, age and tumor size were factors analyzed for outcomes. Statistical differences in survival curves were calculated by Log Rank test and the hazard ratios were determined by Cox regression model.

Results: With a median follow up of 25 months, the 3-year LRFS, DFS and OS were 82.8%, 68.4%, and 57.9%, respectively. Patients treated with BED=10.6Gy₁₀ had superior 3-year LRFS (89.9% vs 70.0%; p=0.049) and SCC histological subtype was a negative predictive factor for 3-year LRFS compared with adenocarcinoma (90.8% Vs 55.7%; p=0.023). Tumor size and age were not predictive factors for LRFS, DFS and OS. Patients with adenocarcinoma had better 3-year DFS than those with SCC (75.7% Vs 40.9%; p=0.014). Any grade of pneumonitis occurred with a median of 11 months after the last fraction of SBRT. RTOG grades 1 and 2 pneumonitis occurred in 36 (43.9%), and 4 (4.9%), patients, respectively. Four (4.9%) patients developed thoracic pain with no rib fracture and one patient developed rib fracture.

Conclusions: Results of this series are similar to the literature and confirm that BED larger than 100Gy₁₀ is more effective for local control than lower level in the treatment of NSCLC with SBRT. Patients with SCC had lower LRFS and DFS compared with those with adenocarcinoma. The radiation dose of 48Gy in 4 fractions was effective and safe for patients with peripheral early stages tumors.

INTRODUCTION

Radiation therapy alone with SBRT technique is considered the current standard treatment for patients with medically inoperable early stages primary or recurrent NSCLC or for those who refuse surgery as primary treatment. These conclusions were reported by the American Society for Radiation Oncology (ASTRO) evidence-based guideline [1], and were posteriorly endorsed by the American Society of Clinical Oncology (ASCO) [2].

The ideal dose and fractionation schedule of SBRT in the treatment of NSCLC has not yet determined by prospective studies. A Japanese multi institutional retrospective analysis showed that total radiation dose and fractionation with BED larger than 100Gy₁₀ was related to better local control and survival when compared with BED lower than this level [3]. Other institutions also reported the relationship between BED regimens and local control for patients with early stages NSCLC treated with SBRT

[4,5]. These retrospective series are hypothesis generating that SBRT should be used with BED larger than 100 Gy₁₀ to be effective for NSCLC.

Central thoracic structures, such as bronchial tree, esophagus, heart and pericardium, are considered very sensitive to high dose of radiation delivered by SBRT. The phase II study from Indiana University with 70 patients with medically inoperable early stage NSCLC showed 11-fold increase risk of late toxicity among patients with central tumors when compared with those with peripheral tumors [6]. A systemic review of the literature with 315 patients with central primary early stage NSCLC from 20 studies showed that reasonable local control and acceptable level of late toxicities can be achieved when an adequate dose and fractionation radiation schedule is employed [7]. This safe and effective dose has yet to be determined by prospective trials.

In our Institution, we have started to use SBRT for patients with early stages NSCLC and peripheral located tumors with 4 fractions of 12Gy (BED=105.6Gy₁₀), and 4 fractions of 10Gy (BED=80Gy₁₀), for those with central tumors or closed to the thoracic wall in an attempt to avoid late complications. This series aims to report our experience and predictive factors for outcomes in patients with medically inoperable early stage NSCLC treated with SBRT.

MATERIALS AND METHODS

We retrospectively reviewed 82 consecutive patients with medically inoperable stages IA – IIA (T1aN0M0 – T2bN0M0) NSCLC by AJCC 8th edition criteria treated with SBRT from May 2013 to March 2019. All patients underwent PET/CT for staging and were considered medically inoperable by a multidisciplinary team. No patients underwent invasive mediastinal staging procedures, such as EBUS or Mediastinoscopy.

Patient's age ranged from 29 to 89 years, with a median of 77 years old. The size of primary tumor ranged from 0.7cm to 5.0cm and median of 2.2cm. According to histological subtype, 54 (65.8%), patients had biopsy proven adenocarcinoma, 25 (30.5%), had squamous cell carcinoma and 3 (3.7%), had no biopsy due to the clinical conditions that have limited this procedure.

The SBRT technique was performed with Novalis Classic Linac model and IGRT ExacTrac® system. Delineation of Internal Target Volume (ITV), was determined on lung windows from 4D/CT and the Planning Target Volume (PTV), was defined as 5mm margins from ITV. Dose delivered techniques methods included non-coplanar fields, dynamic arcs or static IMRT fields. All plans were approved with prescribed dose covering at least 95% of the PTV volume. Dose constrains for organs at risk were based on RTOG trials.

Fifty and six (68.3%), patients had peripheral located tumor and were treated with 48Gy in 4 fractions (BED=105.6Gy₁₀), twice a week and 26 (31.7%), had primary tumor at central thoracic region or close to thoracic wall and received 40Gy in 4 fractions (BED=80Gy₁₀), twice a week. The use of lower dose for these patients was a physician decision in attempt to decrease the chance of late toxicities.

LRFS, DFS and OS were estimated by the actuarial method of

Kaplan and Meier. Patterns and time of failures after treatment were also measured. Predictive factors analyzed for outcomes included radiation dose prescribed (BED regimen), histological subtype of the tumor, patient age with cohort value of 70 years old and tumor size ($\leq 1.5\text{cm}$ vs $1.5 - 3.0\text{cm}$ vs $> 3\text{cm}$). Differences on survival according to these categorical variables were calculated by the Long Rank test (Mantel-Cox) and the hazard ratios to estimate the impact of these factors were determined by the Cox regression models. Value of $p < 0.05$ was considered statistically significant and the statistical tests were 2-sided. The baseline time for outcomes was the day of the last SBRT fraction. Censoring was considered at the date when the patients were last seen or when we have got news about them. Follow-up was performed with thoracic CT every 3 months during the first two years and every 6 months after this period. Crude incidences of late complications were calculated and pneumonitis was graded by RTOG criteria. The statistical analysis was performed with the Software SPSS v25. Last revision of this series analysis was carried out on November 2019.

RESULTS

The medium follow-up for all patients was 25 months (range: 6 – 77 months). At the time of analysis, 43 (52.4%), were alive and without evidence of disease, 11 (13.4%), were alive with any type of recurrence, 25 (30.5%), have died due to the disease progression, 1 (1.2%), have died due to the clinical cause and 2 (2.4%), were lost to follow up and were censored. A total of 20 patients (24.3%), have developed disease progression of any type. Of these, 11 (13.54%), had local recurrence, 8 (9.7%), had mediastinal node progression and 7 (8.5%), have developed distant metastasis. Sites of distant metastasis were bone in 5 patients, brain in 3 patients and liver and bone in 1 patient. Combined local and mediastinal nodal recurrence occurred in 2 patients, mediastinal and distant metastasis in 1 patient, mediastinal, distant and local failure in 1 patient, and distant and local recurrence in 1 patient. The 2-year and 3-year LRFS were 85.2% and 82.8%, respectively. Disease free survival (DFS), was 73.5% at 2 years and 68.4% at 3 years and overall survival (OS), at 2 and 3 years were 73.9% and 54.6%, respectively (Figure 1).

Radiation dose and histological subtype were predictive factors for LRFS. The 3-year LRFS for patients who received 48Gy in 4 fractions (BED=105.6Gy₁₀) and 40Gy in 4 fractions (BED=80Gy₁₀) were 89.9% and 70%, respectively ($p=0.049$) (Figure 2). The Cox regression analysis showed that the risk of local recurrence was higher for patients treated with 40Gy (BED=80Gy₁₀) but it was not statistically significant [hazard ratio (HR)=3.24, 95% confidence interval (CI): 0.943 – 11.17; $p=0.062$]. Patients with SCC had inferior LRFS at 3 years than those with adenocarcinoma (90.8% vs 55.7%, $p=0.025$ by log-rank test) and HR=5.59 (95% CI: 1.287-16.393, $p=0.019$ by Cox regression model). Age and tumor were not predictive factors for LRFS with p value of 0.386 and 0.980 by log rank test, respectively (Table 1).

Patients treated with higher BED had better 3-year DFS than those treated with lower level but without statistically significance (67.3% vs 52.4%, $p=0.064$). Patients with adenocarcinoma had better 3-year DFS than those with SCC (75.7% vs 40.9%, $p=0.014$) (Figure 3). Age and tumor size were not predictive factors for DFS with p value of 0.770 and 0.954, respectively.

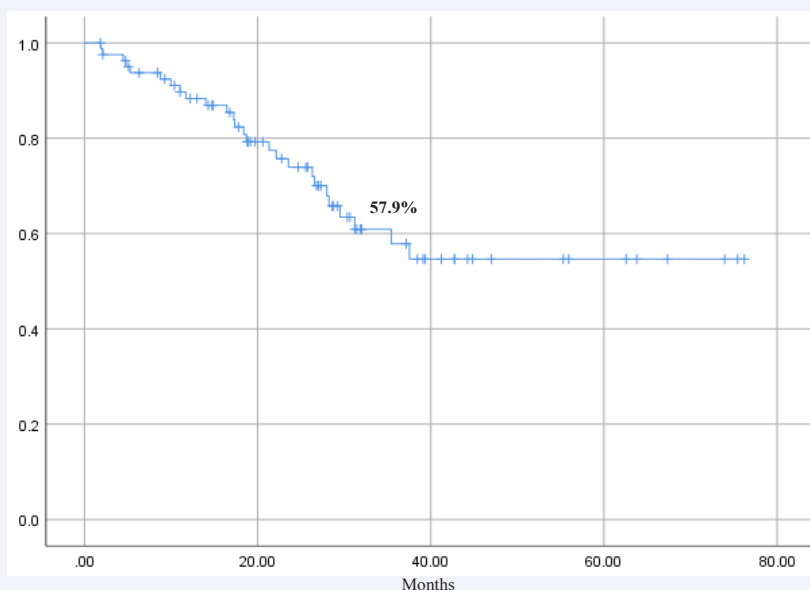


Figure 1 Overall survival (OS) by Kaplan-Meier method.

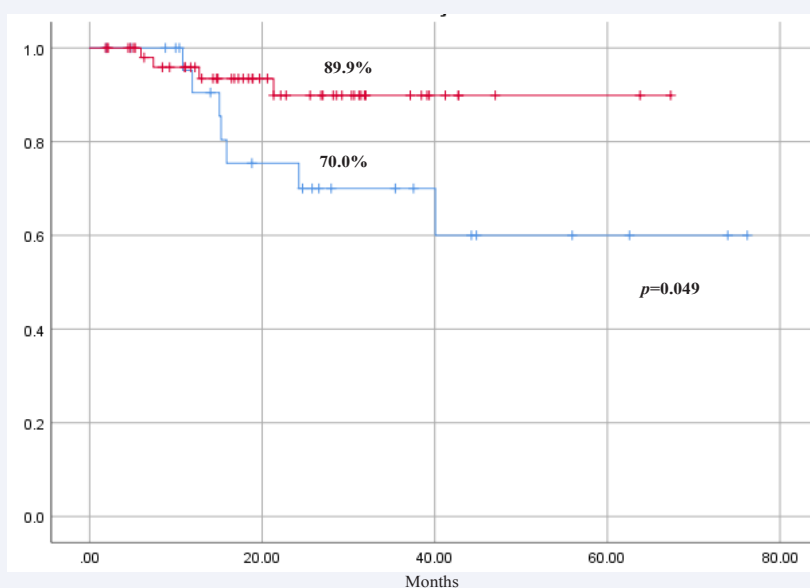


Figure 2 LRFs according to BED regimen by Kaplan-Meier method (Red: BED=105.6Gy₁₀; Blue: BED=80Gy₁₀). Comparison between the curves was calculated by log-rank test.

BED and histological subtypes were predictive factors with marginally statistical significance for OS. Patients treated with higher BED had superior 3-year OS (69% vs 43.9%, $p=0.064$), as such patients with adenocarcinoma than those with SCC (59.2% vs 36.5%; $p=0.057$). Age and tumor size were not predictive factors for OS with p value of 0.211 and 0.365.

Any grade of pneumonitis occurred in 40 (48.8%), patients with a median time of appearance of 11 months after the last fraction of SBRT. Of these, 36 (43.9%), had RTOG grade 1 (asymptomatic or mild symptoms and slight radiographic appearances), and 4 (4.9%), have developed RTOG grade 2 pneumonitis (moderate symptomatic fibrosis, symptom of severe cough, low grade fever

and/or patchy radiographic appearances). All patients with grade 2 pneumonitis had their symptoms recovered after treatment with steroids. Other late toxicities observed were thoracic pain with no rib fracture in 4 (4.9%), patients and painful rib fracture in 1 (1.2%). BED, histological subtype, age and tumor size were not predictive factors for the incidence of any grade pneumonitis with p value of 0.203, 0.785, 0.407 and 0.675, respectively. Late toxicities grades ≥ 3 were not observed.

DISCUSSION

The use of radiation therapy alone with SBRT technique in the treatment of early stage NSCLC has been increasing

Table 1: Influence of predictive factors on local relapse free survival (LRFS) by log-rank test (Mantel-Cox) and Cox regression analysis.

Predictive factor	3-year LRFS	p (log-rank)	HR	95% CI	p (Cox)
BED: 105.6Gy ₁₀ 80Gy ₁₀	89.9% 70.0%	0.049	1.00 3.24	0.94 – 11.17	0.062
Tumor histology: Adenocarcinoma Squamous cell carcinoma	90.8% 55.7%	0.025	1.00 4.59	1.29 – 16.39	0.019
Age: ≤ 70 years > 70 years	95.0% 77.9%	0.386	1.00 0.51	0.11 – 2.38	0.394
Tumor size: ≤1.5cm 1.5 – 3.0cm > 3.0cm	87.5% 77.8% 85.6%	0.980	1.00 1.16 1.13	0.23 – 5.76 0.27 – 4.77	0.860

BED=Biologic effective dose; HR=hazard ratio; CI=Confidential interval

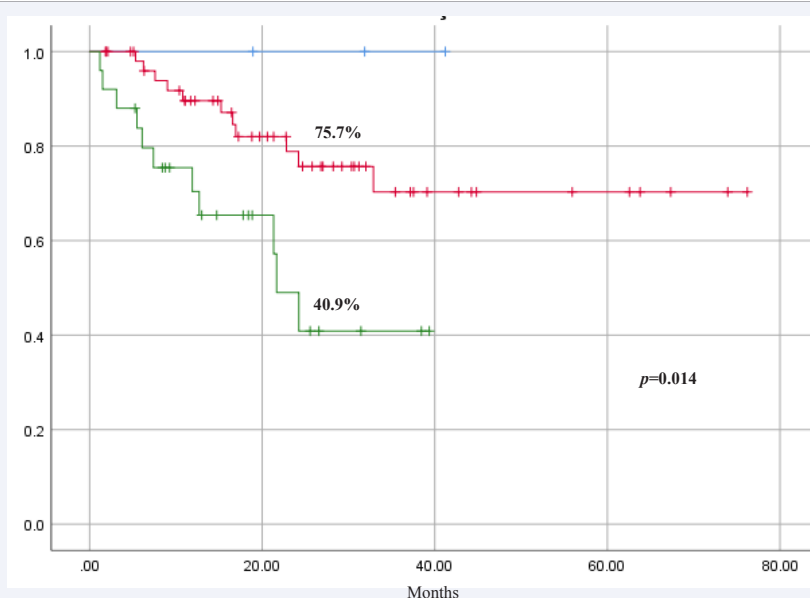


Figure 3 DFS according to histological subtype by Kaplan-Meier method (Blue: no histology; Red: Adenocarcinoma; Green: SCC). Comparison between the curves was calculated by log-rank test.

worldwide and for medically inoperable patients is considered the current standard of care [1,2]. Several radiation schedules have been tried but most studies are retrospective and an ideal total radiation dose and fractionation has yet to be determined by prospective trials.

In our series, patients treated with 4 fractions of 10Gy (BED=80Gy₁₀), had inferior LRFS, even considering the marginally p value by log rank test and Cox regression model analysis. The p value was not significant in Cox regression analysis probably due to the number of patients analyzed and the small number of events for LRFS (local recurrence). Only 11 patients have developed local recurrence among a total of 82 analyzed (13.41%). This small number of local recurrence led to a wide range of 95% CI when we analyze the difference in LRFS according to the categorical variable, such as radiation dose. The main contribution of this series was the confirmation of the hypotheses that we should not deliver radiation dose with BED lower than 100Gy₁₀ in the treatment of early stages NSCLC. Other series also

analyzed the association between BED and local control. Onishi et al., retrospectively analyzed 245 patients from 13 Japanese Institutions with stage I NSCLC treated with SBRT using different total dose and fractionation schedule. Patients treated with BED lower than 100 Gy₁₀ had higher local recurrence (26.4% vs 8.1%; p<0.05) [3]. Olsen et al., in a retrospective analysis of 130 patients with early stages NSCLC from Washington University, compared the efficacy of three SBRT regimens. Patients treated with 5 fractions of 9Gy (BED=67.5Gy₁₀), had inferior local control than those treated with 5 fractions of 10Gy (BED=100Gy₁₀) or with 3 fractions of 18Gy (BED=151.2Gy₁₀). There was no difference in local control among patients treated with BED of 100 Gy₁₀ or 151.2Gy₁₀. The 2-year local control was 75%, 100% and 99% for patients treated with BED of 67.5 Gy₁₀ (8 patients), 100Gy₁₀ (11 patients), and 151.2Gy₁₀ (111 patients), respectively [4]. As in our series, lower BED schedules were used for tumors that were central or near critical structures. Hobbs et al., retrospectively reviewed 282 patients with early stage and medically inoperable

NSCLS treated with SBRT at the Mayo Clinic. Similar local control was observed in patients treated with 4 fractions of 12Gy and 3 fractions of 18Gy, but inferior than those treated with 5 fractions of 10Gy. Two-year local recurrence rates for patients treated with 48Gy (BED=105.6Gy₁₀), 54Gy (BED=151.2Gy₁₀), and 50Gy (BED=100Gy₁₀), were 1.7%, 3.7% and 15.3%, respectively ($p=0.02$) [5].

The 3-year LRFS of 89.9% observed in the current series in patients treated with dose of 48Gy in 4 fractions is reasonable and similar to the main published series in the literature with at least 70 patients with NSCLC treated with SBRT. The 3-year local control observed in these series ranged from 84% to 98% [5,8-14].

Patterns of failure in our series were more frequent in sites outside de primary tumor region (13.4% had local recurrence, 8.5% had mediastinal node progression and 11% have developed isolated distant metastasis). Failures outside the primary tumor region have probably reflected the DFS and OS observed in our series and others in the literature. The most extensive data from single institution about SBRT in the treatment of NSCLC was published by Senthil et al., from VU Medical Center in Amsterdam, Holland. The authors analyzed 676 medically inoperable patients with stages I and II NSCLC. Actuarial 2-year rates of local, regional, and distant recurrence were 4.9%, 7.8% and 14.7%, respectively [8]. The incidence of nodal and distant metastasis was similar to our series. The Mayo Clinic experience with 282 patients with early stages NSCLS treated with SBRT reported on 2-year probability of local, nodal and distant recurrence of 4.9%, 9.8% and 9.7%, respectively [5], also similar to our series. The relatively high incidence of outside primary tumor recurrence has been leading prospective studies to evaluate the association of SBRT and consolidative immunotherapy in the treatment of early stages NSCLC, such as the PACIFIC-4/RTOG 3515. This double-blind phase III study will compare the use of anti-PDL1 Durvalumab or placebo following SBRT for early stage and medically inoperable NSCLC [15].

The 3-year OS of 57.9% observed in our series for all patients was also similar to the main series published in the literature with medically inoperable NSCLC treated with SBRT. The 3-year OS observed in these series ranged from 32% to 69% [5,8-14,25]. The wide range of OS published is probably due to the different causes of death, including those cancer-related and those caused by clinical events.

In our series, the strategy to use lower BED of 80Gy₁₀ for patients with central tumors or close to the thoracic wall has led to a negative impact on local control when compared with patients treated with BED of 105.6 Gy₁₀. For central tumors and for those close to the critical structures, the ideal total dose and fractionation regimen is still a subject of investigation. The RTOG 0813 trial has been testing different doses of 5 fractions for patients with centrally located tumors. This study starts with 5 fractions of 10Gy and has been escalating 2.5Gy per fractions to a maximum of 5 fractions of 30Gy. The authors preliminarily reported on a maximum tolerated dose of 60Gy in 5 fractions with a 7.2% risk of dose-limiting toxicity [16]. A Dutch institution retrospectively analyzed 63 patients with centrally located early stage NSCLC treated with 8 fractions of 7.5Gy (BED=105 Gy₁₀).

With a median follow-up of 35 months, the authors reported on only 2 patients with chest wall pain and 2 patients with increased dyspnea. No grades IV and V toxicities were observed and the 3-year local control was of 92.6% [17]. A systemic review of the literature involving 315 patients with early stage NSCLC and central tumors from 20 publications suggests that tumor location did not impact overall survival and local control rates can reach $\geq 85\%$ when the prescribed BED is ≥ 100 Gy₁₀ [7]. In our institution, we are now using 5 fractions of 10Gy or 8 fractions of 7.5Gy for centrally located tumors or those close to the critical structures until more data from prospective trials will be available.

NSCLC is composed of several histological subtypes and the impact of this heterogeneity on SBRT treatments has not yet established by prospective studies. In our series, patients with SCC histology had inferior LRFS, DFS and trend toward OS compared with those with adenocarcinoma. Several others retrospective series in the literature also have SCC histology as negative prognostic factor for both local control and/or survival among patients with early stage NSCLC treated with SBRT [14,18-22]. The largest series about this issue was published by Woody et al., from Cleveland Clinic. They retrospectively analyzed 740 patients with early stage NSCLC treated with SBRT. Of these, 215 (29%), had SCC tumor histology. On multivariable analysis, SCC histology was the strongest predictor factor for local failure (HR=2.4; $p=0.008$). The 3-year cumulative rates of local failures were 18.9% and 8.7% among patients with SCC and adenocarcinoma, respectively [18]. A Germanic series of 126 patients with NSCLC treated with SBRT also observed histological subtype of SCC as major independent prognostic factor for local control ($p=0.03$), but when patients received SBRT with EQD2 (2Gy equivalent dose) ≥ 150 Gy, no difference in local control was detected anymore ($p=0.355$) [21]. This finding suggests that care must be taken with SBRT dose prescription for patients with SCC histology. The reason why SCC tumors are more resistant to radiation than adenocarcinoma is not clear by the literature. Unknown molecular, genetic and/or microenvironmental features could explain these differences in the future. Some experimental laboratory studies have already showed that SCC histology have distinct patterns of somatic alterations, a propensity for a higher mutational burden, and a higher metabolic rate resulting in hypoxia. These biologic features can lead SCC to be more radio resistant than adenocarcinoma [23-25].

In our series, late toxicity was relatively low and comparable with other series in the literature that have reported on toxicities for patients with peripheral early stage NSCLC treated with SBRT. In these series, grades 1 and 2 toxicities were relatively common and self-limiting. Grades 3 and 4 events were uncommon, occurring in 5% to 10% and grade 5 event (death due to the treatment), have occurred in patients who received high dose of SBRT to centrally located tumors, such as those near the trachea, primary bronchus, major blood vessel and pericardium [3,4,10-14,26-29]. Most patients of our series who developed any type of secondary effect had grade 1 pneumonitis (only radiographic changes on CT with no symptoms), and only 4.9% developed grade 2 pneumonitis (necessity of steroids treatment). The NRG Oncology RTOG 0915 trial compared two SBRT radiation dose schedule for patients with stage I peripheral NSCLC (34Gy in 1 fraction and 48Gy in 4 fractions). Only 5 (11.1%), patients on the

control arm (48Gy), treated with the same dose as those with peripheral tumors in our series, developed grade ≥ 3 toxicity [30].

CONCLUSIONS

This retrospective series confirms the importance of BED regimens equal or higher than 100Gy_{10} to achieve reasonable outcomes, especially local control, for patients with medically inoperable early stage NSCLC treated with SBRT. Total SBRT dose of 48Gy in 4 fractions ($\text{BED}=105.6\text{Gy}_{10}$), was effective and safe for peripheral stages I and II NSCLC.

As the data from the literature, this series also showed SCC histology subtype as negative predictive factor for local control and DFS compared with adenocarcinoma. Care must be taken with this type of tumor, especially the SBRT dose prescription, due its potential higher radio resistance.

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