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Hypo-fractionated stereotactic radiation therapy for lung malignancies by means of helical tomotherapy: report of feasibility by a single-center experience

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Abstract

Background Several experiences in the literature report SBRT as an effective treatment option for medically inoperable early stage non-small cell lung cancer (NSCLC) and oligometastatic disease. The optimal fractionation schedules and total dose remain controversial. In this study, we evaluated the safety in terms of toxicity and efficacy of using of 8–10 fractions schedules with Helical Tomotherapy (HT) for primary and metastatic lung lesions.

Methods Between March 2014 and May 2016, a total of 39 patients (median age 72 years, range 26–91) were treated with HT-SBRT for malignant lung lesions: 22 patients with early stage NSCLC, 17 with oligometastases. Patients received 8–10 fractions with lower daily dose for central and ultracentral lesions. Treatment-related toxicity was evaluated using CTCAE v 4.0 scale. Local control (LC), overall survival (OS) and toxicity rates were prospectively collected.

Results Median duration of RT was 15 days (range 10–26 days) and no interruption occurred. With a median follow-up of 13 months (range 3–29), we reported one G2 pneumonitis (2.6%) and one G2 chest pain (2.6%); no ≥ G2 esophagitis was registered. Actuarial local control rate was 95.5% both at 12 and 24 months for early stage NSCLC and 92.9% both at 12 and 24 months for metastatic patients. OS rate was 94.4 and 92.3% at 1 year, and 94.4 and 83.9% at 2 years in primary and metastatic group, respectively.

Conclusions The use of 8–10 fractions schedule HT-SBRT for lung malignancies results in high LC and OS rates with minimal toxicities reported.

Keywords SBRT · Lung cancer · Helical tomotherapy · Radiotherapy

Introduction

Lung cancer is the second most common malignancy, after non-melanocytic skin cancers, and it causes more deaths than any other malignancy worldwide [1].

Standard treatment includes surgery, RT and chemotherapy, used alone or in combination, depending on stage of disease and clinical conditions. Stereotactic Body Radiation Therapy (SBRT) has allowed an improvement of oncological outcomes with negligible toxicity, compared to conventional RT, specifically for medically inoperable early stage NSCLC patients [2–6]. The efficacy and safety of SBRT have also been documented in patients affected by oligometastatic disease, i.e., the presence of 1–5 lesions [7].

SBRT is typically delivered in a limited number of fractions over the course of 1–2 weeks [8]. Based on the toxicity data following SBRT for centrally located lesions [9], a strategy of risk-adapted dose prescription was proposed to minimize SBRT-related adverse events, depending on the localization of target volumes within the lungs and proximity to mediastinal organs at risk (OARs) [10, 11].

Recent developments in lung SBRT, such as intensity-modulated RT (IMRT) and image-guided RT (IGRT), have allowed a high accuracy of dose distribution to the target volumes and a more precise assessment of tumor volume changes during the course of treatment by means of imaging

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on-board, lowering high doses to nearby normal tissues [12, 13].

Helical tomotherapy (HT) is a platform that combines IMRT with in-built image guidance using megavoltage (MV) CT scanning.

We report a single-center experience of 8–10 fractions schedule HT-SBRT for primary and single metastatic lung lesion.

Materials and methods

This is a retrospective mono-institutional study that received the ethics approval from our institutional ethic committee; informed consent was acquired from all participants enrolled in this series.

Primary endpoint of the present study is the feasibility of HT-SBRT for primary and secondary lung malignancies; Local Control (LC), Disease-Free Survival (DFS) and Overall Survival (OS) are secondary endpoints. SBRT was indicated when the following criteria were satisfied: medically inoperable Early Stage NSCLC, the presence of a single lung metastasis for oligometastatic patients, tumor size ≤ 5 cm, Karnofsky perfomance status ≥ 70, a life expectancy of at least 6 months.

Early stage NSCLC patients were staged with bronchoscopy, enhanced computed tomography (CT) scan of the lung and upper abdomen with contrast-medium and 18-fluorodesossiglucose positron emission tomography (PET). The biopsy was avoided in the presence of severe comorbidities; in this scenario, the metabolic imaging was considered a surrogate of malignancy, according to the literature [14]. Before local treatment, oligometastatic patients were evaluated with CT scan and PET.

HT-SBRT procedures

A 2.5 mm slice thickness CT was performed with the patient in supine position with arms up above the head. Immobilization was obtained with the aid of a breast board and an abdominal pressure mould mask. The Clinical Target Volume (CTV), equal to the Gross Tumor Volume (GTV), was defined merging the treatment planning CT with a megavolt computed tomography (MVCT) scan [15–17].

MVCT is a free breathing slow CT able to give information relative to the full extent of target motion during respiratory movement, as recommended by AAPM Task Group 101 report [16]. Planning CT images were fused with pre-SBRT diagnostic studies when necessary to facilitate GTV contouring.

The planning target volume (PTV) was obtained by adding a 10 mm margin in cranio-caudal direction and a 5 mm margin in all other directions.

Target volumes and OARs were contoured on the Pinnacle Planning system. The CT datasets were then transferred to the Tomotherapy Treatment Planning system (HT, Accuray Inc. Sunnyvale, CA, USA), where IMRT plans were generated with inverse treatment planning. Tumor dose was prescribed to the 95% isodose encompassing PTV. Different dose schedules were used according to the tumor site (central or peripheral) and maximum diameter of lesion: 60–70 Gy in 8–10 fractions for peripheral lesions, 50–60 Gy in 10 fractions for central lesions, 40 Gy in 10 fractions for ultra-central lesions. Also patients' frailty, tumor size and location (especially for lesions whose PTV touches or extends into the ribs/pleura, or unable to meet the 3 or 5 fractions schedules constraints) had an impact in fractionation selection process [18, 19], leading to schedules with $BED_{10} > 100$ Gy administered in 39% of cases, and schedules with $BED_{10} < 100$ Gy in 61%. Dose constraints for OARs were derived from peer-reviewed literature [8, 10, 20]: volume of the lung, excluding PTV, receiving 20 Gy (V_{20}) and 5 Gy (V_5) $\leq$ to 10 and 35%, respectively; mean lung dose (MLD) ≤ 9 Gy; $D_{max} \leq 28$ Gy on spinal cord; central airways, brachial plexus and esophagus Dmax were limited to 40 Gy. Conformity Index (CI) and Homogeneity Index (HI) were assessed using the following formulas [21]: $CI = (TVPIV)^2/(TV \times PIV)$ [TVPIV is the target volume covered by prescription isodose volume; TV is the target volume; PIV is the prescription isodose volume], HI is the [(maximum dose − minimum dose)/prescription dose].

Study design and statistical analysis

LC, DFS, OS and toxicity rates were prospectively collected. Dosimetric findings were retrospectively evaluated. LC, DFS and OS at 12 and 24 months from the end of SBRT were calculated using Kaplan–Meier analysis. The log-rank test was used to compare results between patient subsets and among radiation schedule groups. Fisher's exact test was used to examine differences in LC, DFS, OS and toxicities, according to patients' characteristics. The Wilcoxon rank-sum test and the equality-of-medians test were applied to examine differences in continuous variables among patient groups. A two-sided value of 0.05 or less was considered to assess statistical significance. All statistical analyses were carried out using Stata/SE 14.1 (Stata, Corp LP, Texas, USA).

Toxicity and follow-up

Adverse events were assessed according to the CTCAE version 4.0. Concerning pulmonary toxicity, patients who were asymptomatic with radiologic changes were not considered to have toxicity.

Contrast-enhanced Chest CT was performed every 3 months from the end of SBRT for the first 2 years. PET

scanning was requested in selected cases after CT scan to evaluate tumor response after SBRT.

According to RECIST v1.1 Criteria, complete response (CR) was defined as the disappearance of lesions on the CT scan; a reduction of 30% was considered partial remission (PR); any increase in size ≥ 20% not clearly due to fibrosis was reported as progression of disease (PD); stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters [22]. PERCIST criteria were used to evaluate the metabolic response [23].

Results

Between March 2014 and May 2016, a total of 39 consecutive patients (median age 72 years, range 26–91) were treated with HT-SBRT for malignant lung lesions: 22 patients were treated for early stage NSCLC, 17 for metastatic disease (Table 1).

In early stage NSCLC, pathological confirmation was obtained for 17 patients (77%). Chemo or biological therapy was administered prior to SBRT in 23 patients (59%). At the time of analysis, the median follow-up was 13 months (range 3–29 months). All patients completed SBRT without interruptions. The median overall treatment time was 15 days (range 10–26 days). SBRT was delivered in consecutive days in 19 patients (48.7%) and every other day in 20 patients (51.3%).

Actuarial local control rate was 95.5% both at 12 and 24 months for early stage NSCLC, and 92.9% both at 12 and 24 months for metastatic patients. Overall survival rate was 94.4 and 92.3% at 1 year, and 94.4 and 83.9% at 2 years in primary and metastatic lung cancer, respectively (Figs. 1, 2).

During follow-up, 10 (25.6%) patients developed distant progression, 5 occurred in NSCLC and 5 in metastatic group, leading to 1 year disease-free survival (DFS) rates of 78.9 and 67.9% for primitive lesions and metastases, respectively. 2 years-DFS rates were 52.6% for primitive and 60.4% for secondary lesions (Fig. 3). At the time of the analysis, CR was recorded in 11 (28.2%) lesions, PR in 8 (20.5%) and SD in 18 (46.2%) lesions. In-field irradiation failures were observed in 2 (5.1%) patients, one in the NSCLC group and one in the oligometastatic group.

Acute adverse events were registered as follows (Table 2): G2 chest pain in one (2.6%) patient with peripherally located tumor; no rib fractures were recorded. No patient developed ≥ G3 radiation-induced pneumonitis, reporting only one G2 pneumonitis (2.6%), successfully treated with steroids, in a patient who concomitantly underwent erlotinib after progression through platinum-based chemotherapy. The patient was treated with 10 daily fractions of 6 Gy equal to a BED_{10} to the tumor of 96 Gy_{10}, reporting V_{20}, V_5 and MLD of 8.9, 44.8% and 8.2 Gy, respectively.

Concerning late adverse events, no patient developed any symptoms related to pulmonary fibrosis; a single case of G2 chest wall pain was reported. Regarding the three ultracentral lesions, no toxicity was observed.

A statistical relationship between tumor size, fractionation regimen, timing of fractions and LC or toxicities failed to be found.

Table 1 Patient and tumor characteristics ($n = 39$)

Variables	Patient number (%)
Age (years): median (range)	72 (26–91)
Sex	
Male	30 (76.9)
Female	9 (23.1)
Disease definition	
Primitive	22 (56.4)
Metastasis	17 (43.6)
Histology	
Primitive	
Adenocarcinoma	11 (28.2)
Squamous cell	6 (15.4)
Not performed	5 (12.8)
Metastases histology	
Lung	7 (17.9)
Seminoma	1 (2.6)
Colorectal	4 (10.2)
Bladder	3 (7.7)
Hepatocellular carcinoma	1 (2.6)
Parotid gland	1 (2.6)
Tumor location	
Peripheral	23 (59)
Central	13 (33.3)
Ultracentral	3 (7.7)
Previous chemotherapy	
Yes	19 (48.7)
No	20 (51.3)
Previous biological therapy	
Yes	4 (10.2)
No	35 (89.8)
Treatment time (days): median (range)	15 (10–26)
Dose fractionation regimens	
40 Gy/10fx	3 (7.7)
50 Gy/10fx	12 (30.8)
60 Gy/10fx	9 (23)
70 Gy/10fx	1 (2.6)
60 Gy/8fx	14 (35.9)
Fractionation	
Daily	19 (48.7)
Every other day	20 (51.3)

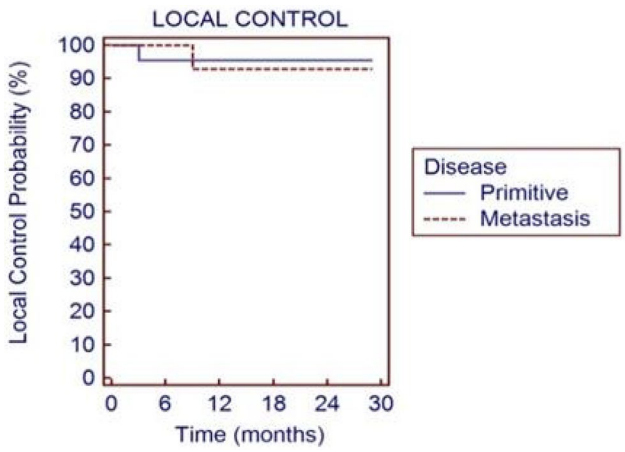

Fig. 1 Local control curves for primitive and metastatic disease. There was no difference between the two groups ($p = 0.928$)

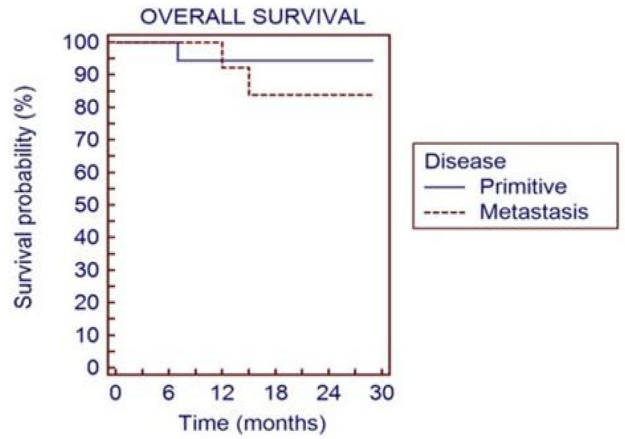

Fig. 2 Overall survival curves according to primitive and metastatic disease. There was no difference between the two groups ($p = 0.731$)

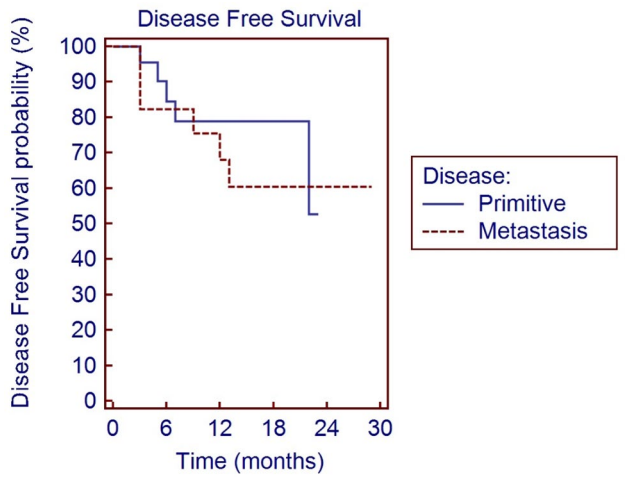

Fig. 3 Disease-free survival curves for primitive and metastatic disease

Planning and dosimetric outcomes

The median GTV was 5.03 cc (range 0.87–47.27 cc) and the median PTV was 28.32 cc (range 7.32–114.21 cc). The median BED_{10} was 96 Gy (range 56–119 Gy). The median HI and median CI were 0.075 (range 0.043–0.136) and 0.84 (0.735–0.906), respectively. Median Total Lung V_5, V_{10}, V_{20} and Mean Lung Dose were 21.3% (range 6.5–45.5%), 13.23% (range 0.08–36%), 5.28% (range 0–19%), and 4.2 Gy (range 1.2–9.4 Gy), respectively (Table 3).

Discussion

In lung malignancies, both isocentric (LINAC-based) and non-isocentric (CyberKnife-based) SBRT techniques are routinely adopted in daily clinical practice. Linacs equipped with Flattening Filter Free delivery allow to reduce the treatment time and, probably, uncertainties related to organ motion during irradiation [24, 25]. Cyberknife system offers a precise tracking during breathing and adjustment to moving targets [26, 27] in order to compensate uncertainties related to the long treatment delivery time. HT could be largely criticized due to the relatively long treatment delivery in the absence of a lesion tracking system. Actually, on the basis of clinical evidence, this technology is safe for treating moving tumors considering that interplay of breathing and tomotherapy delivery motions did not affect significantly plan delivery accuracy [28].

To date, a $BED_{10} \geq 100$ Gy remains a strong predictive factor of long-term LC [29]. Although in our series most patients received a BED_{10} inferior to 100 Gy, we reported an acceptable actuarial 2-years LC. This could be explained with experimental and clinical data supporting the role of the total dose as a more crucial factor comparing to BED_{10}, based on the hypothesis that a moderate protracted schedule fractionation could improve re-oxygenation and, consequently, increase the tumor response [30, 31]. At 12 months, LC and OS rates were greater than 90% in both groups of patients treated with HT-SBRT in the present analysis. Apart from the present experience, other studies reported valuable results both in terms of LC and safety profile by means of HT-SBRT in lung malignancies (Table 4; [15, 18, 32–38]). Looking at HT-SBRT performances for stage I NSCLC, one of the larger data series [37] enrolled 79 patients treated with different doses schedules. Similar to our experience, 12-months LC was superior to 90%.

An Italian study [15], enrolling 56 patients with lung primary or secondary cancer, evaluated clinical outcomes of HT-SBRT in two different subgroups: ablative SBRT for 27 patients with T1–2 NSCLC and palliative SBRT for 29 patients with oligometastases. In their experience, the actuarial 2-years LC was 69.6% in case of primary tumor and

Table 2 Acute toxicity according to CTCAE v4.0

Acute toxicity	CTCAE v4.0				
Symptoms and disorders	0	1	2	3	4
Pneumonitis	20 (51.2%)	18 (46.2%)	1 (2.6%)	0 (0%)	0 (0%)
Esophagitis	36 (92.3%)	3 (7.7%)	0 (0%)	0 (0%)	0 (0%)
Rib fracture	39 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Chest wall pain	38 (97.4%)	0 (0%)	1 (2.6%)	0 (0%)	0 (0%)
Pleural and pericardial effusion	39 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 3 Dosimetric parameters

Dosimetric parameters	Median (range)
GTV volume (cc)	5.03 (0.87–47.27)
D2% (Gy)	62.7 (42.04–73.49)
D98% (Gy)	61.18 (38.96–71.04)
Dmean (Gy)	61.88 (40.00–72.03)
PTV volume (cc)	28.32 (7.32–114.21)
D2% (Gy)	63.23 (43.03–73.88)
D98% (Gy)	59.62 (37.16–69.64)
Dmean (Gy)	61.78 (40.40–71.08)
BED_{10} (Gy)	96 (56–119)
Lung sum	
MLD (Gy)	4.2 (1.2–9.4)
V_5 (%)	21.3 (6.5–45.5)
V_{10} (%)	13.23 (0.08–36)
V_{20} (%)	5.28 (0–19)
Ipsilateral lung	
MLD (Gy)	7.45 (1.34–13.2)
V_5 (%)	36.2 (10–60)
V_{10} (%)	24.14 (0.08–48)
V_{20} (%)	9.96 (0–30.5)
Contralateral lung	
MLD (Gy)	1.52 (0.46–5)
V_5 (%)	5.68 (0–42.5)
V_{10} (%)	0.02 (0–31)
V_{20} (%)	0 (0–18)
Homogeneity Index	0.075 (0.043–0.136)
Conformity Index	0.84 (0.735–0.906)

40% for the oligometastatic group. Regarding the setting of lung oligometastases, the choice of "the right patient" for local treatment remains largely debated. In the present series, we considered the "oligometastatic patient" in case of single lung metastasis in the absence of the primary tumor. At the time of the analysis, 24-months LC and OS were 92.9 and 83.9%, respectively, significantly superior compared to the experience by Marcenaro and colleagues [15] in which a subgroup of patients with multiple lesions was candidate to lung SBRT. These findings reinforce patient selection as a crucial factor in the decision-making process for lung oligometastatic disease.

Regarding the safety profile, the issue of the radiation-induced pneumonitis has been largely investigated during the last years. In fact, several authors [39–41] identified dosimetric parameters that might be useful as predictors of radiation pneumonitis, such as the mean lung dose, V_{20} and V_5. Barriger and colleagues [41], among patients treated with SBRT for a total doses ranged between 42 and 60 Gy given in 8 fractions, reported Grade 2–4 pneumonitis in 4.3% of patients in case of mean lung dose $\leq$ 4 Gy compared to 17.6% for a mean lung dose > 4 Gy ($p = 0.02$); in their experience, a similar risk of moderate-severe pneumonitis was observed for $V_{20} \leq 4\%$ (4.3% of patients) versus $V_{20} > 4\%$ (16.4% of patients, $p = 0.03$). Few authors highlighted the importance of low-dose radiation distribution in the development of lung toxicity with HT; Jo et al. [42] defined the value of V_5 as crucial for the onset of symptomatic RP, recommending to keep its value inferior to 65%. Kim et al. [33] reported a significant dose–response relationship between RP and ipsilateral and contralateral V_5. In the present study, HT allowed to respect available lung dose constraints in the majority of cases: mean lung dose < 9 Gy was respected in 97.4% of cases, $V_{20} < 10\%$ in 92.3%, $V_5 < 35\%$ in 79.5%. The median values of total lung, V_{20} and V_5 and mean lung dose were 5.28 and 21.3% and 4.2 Gy; median values of ipsilateral and contralateral V_5 were 36.2 and 5.68%, respectively. In the present study population, only one patient in the metastatic group with slightly higher values of V_{20} and MLD underwent steroid treatment for respiratory symptoms due to a G2 RP; this patient was concomitantly treated with target agent anti-epidermal growth factor receptor (Erlotinib) after first-line platinum-based chemotherapy and, after a short course period of steroids treatment, continued Erlotinib. According to the data derived from few clinical trials, an increased toxicity is possible when targeted therapy is combined with SBRT [43].

It is also well recognized that lung lesions located in the so-called "No-Fly-Zone" are at particular risk of complications [12]. In this last clinical scenario, mediastinal OARs sparing, in addition to a more fractionated regimen, is crucial to minimize the risk of adverse events, especially in the challenging situation of ultra-central located lesions. As reported by Chi et al. in a dosimetric comparison with 2- and 8-arcs VMAT technique, HT allows sculpting the dose to the

Table 4 HT-SBRT experiences for lung malignancies

Author and publication year [reference]	Years of enrollment	Patients (*n*)	Median Follow-up, range (months)	SBRT schedule (Gy)	Mean BED (Gy)	Primitive/metastases	Primary endpoints	Local Control (LC)	Median Overall survival (OS)	Lung toxicity (pneumonitis)
Hodge 2006 [32]	2005	9	2.1 (1.8–13.3)	60 Gy/5 fx	117	Primitive NSCLC, stage I	Toxicities and local control	33% CR 44% PR 23% SD	Not Reported	No ≥ G2
Kim 2009 [33]	2007–2009	31	13	40–50 Gy/10 fx	65.5	Metastases	Toxicities and local control	1 year, 87.1%	1 year, 60.5%	No ≥ G3
Marcenaro 2013 [15]	2009–2012	56 (27 ablative 29 palliative)	15 (7–30)	48–60 Gy/4–8 fx	100–120	Primitive NSCLC, stage I–IV and lung metastases	Toxicities and local control	Ablative 69.6% Palliative 40.4%	65% at 24 months Ablative 49% Palliative	No ≥ G2
Sole 2013 [34]	2006–2011	42 (60 lesions)	15	60 Gy/3–8 fractions	105	Metastases	Toxicities and local control	1 year, 92% 2 years, 86%	1 year, 84% 2 years, 63%	5 ≥ G3
Aibe 2014 [35]	2007–2013	30 (31 lesions)	36.5 (4–67)	50 Gy/5 fx	100	Primitive NSCLC	Toxicities and local control	1 year, 93% 2 years, 73%	1 year, 92.3%	5 G2 1 G5
Nagai 2014 [36]	2010–2013	72	20	48 Gy/4 fx 50–60 Gy/5–8 fx	105.6 ($n = 37$) ≤ 100 ($n = 35$)	Primitive NSCLC early stage, metastases and recurrence	Toxicities and local control	86% at 2 years	93% at 2 years	No ≥ G3
Rosen 2014 [37]	2005–2010	79	27 (4–82)	48–60 Gy/4–5 fx	100–120	Primitive NSCLC stage I	Toxicities and local control	Overall LC 93.6%	92.3% at 1 year 58.4% at 3 years	No life-threatening radiation pneumonitis or clinically significant pulmonary complications
Casutt 2015 [38]	2011–2012	16	11	60 Gy/5 fx	132	Primitive NSCLC and lung metastases	Toxicities and local control	100% LCR at 6 and 12 months	100% at 6 months 77% at 12 months	12.5% G3 6.2% asymptomatic infiltrates comparable to OP opacities
Arcangeli 2015 [18]	2012–2014	28 (31 lesions)	12 (4–20)	50 Gy/5 fx 50 Gy/10 fx 52.5 Gy/7 fx	≥ 100 (22 pts) ≤ 100 (6 pts)	Early stage NSCLC in elderly patients	Toxicity and Patterns of Radiologic Lung Injury	23% CR 61% PR 16% SD	89.2% at 2 years	4 G2, 1 G3 and none of whom had CT findings at 3 months post-treatment

tumor while sparing nearby OARs offering a safe treatment option, despite the relatively higher low dose to the normal lung remains an issue of debate [18, 44]. In our series, the three ultra-central patients reported no significant toxicity.

In conclusion, the present study has several limitations such as: (1) the retrospective nature of the analysis; (2) the heterogeneity of the population (primary and metastatic lesions) here analyzed; (3) the limited follow-up. However, although the limitations abovementioned could affect the robustness of the present results, LC and OS rates here reported seem comparable to available clinical data, both for primary lung tumors as well as lung oligometastases after SBRT.

A longer follow-up and a wider sample size are advocated for more mature results both in terms of oncological outcomes and toxicity rates. Of course, in consideration of the above-mentioned limitations, keeping in mind the retrospective nature of the current analysis, long-term findings are warranted.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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