

Ablative or Palliative Stereotactic Body Radiotherapy with Helical Tomotherapy for Primary or Metastatic Lung Tumor

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Abstract. *Aim: To evaluate the feasibility and outcomes of stereotactic body radiotherapy (SBRT) by helical tomotherapy (HT) for patients with primary or secondary lung cancer. Patients and Methods: Between March 2009 and January 2012, 56 patients were selected as candidates for the study and were divided into two subgroups. The ablative SBRT group included 27 patients with T1-T2 non-small cell lung cancer who received four to five large-dose fractions in two weeks and the palliative SBRT group included 29 patients with lung metastases treated with eight lower-dose fractions in four weeks. Results: No differences in acute toxicities were found between different fractionation schemes with different overall treatment times. Actuarial local control at 24 months was better for the ablative group (69.6%) than for the palliative one (40.4%) ($p=0.0019$). Conclusion: HT-based SBRT was feasible and well-tolerated. Local control was satisfactory for patients treated with ablative SBRT but unsatisfactory for those treated with palliative SBRT. Outcomes also suggest the use of ablative SBRT fractionation for palliative intent.*

Stereotactic body radiotherapy (SBRT) is a non-invasive treatment that can deliver a high dose of radiation in a few fractions to small neoplastic lesions in the thorax or abdomen. Patient outcomes for SBRT of lung and thorax tumors are very promising and few side-effects have been observed (1). The rationale of SBRT is two-fold: to fully eradicate early-stage primary lung tumors by delivering a ablative SBRT and to inactivate lung metastases or advanced localized disease by

delivering palliative SBRT. Ablative SBRT may play a crucial role, since although conservative lobectomy is still considered the treatment of choice for stage IA-B Non-small Cell Lung Cancer (NSCLC), many patients are medically unfit for, or refuse this surgery (2). Excellent long-term results have been reported for patients with early-stage NSCLC treated with ablative SBRT (3-5). Palliative SBRT can also inactivate lung oligometastases or advanced localized disease and improve the progression-free survival of patients with poor prognoses, or with recurrence from previous NSCLCs (6). Most ablative and palliative SBRT results are strictly correlated with the biological dose escalation and with sharp dose distribution to the target that is achievable with innovative technology (7). However, despite ablative SBRT being associated with lower recurrence rates, the optimal total radiation dose and number of fractions to deliver with this evolving strategy still need to be assessed. This article reports preliminary outcomes from ablative and palliative SBRT delivery with the helical tomotherapy (HT) Hi-Art[®] System (Accuray Incorporated, Sunnyvale, CA, USA) to patients with primary or secondary lung cancer. Feasibility, preliminary local control (LC) and overall survival (OS) rates obtained with different fractionation regimens, individualized according to treatment rationale of ablative SBRT and palliative SBRT, are reported in detail.

Patients and Methods

Patient selection. Between March 2009 and January 2012, 62 patients with lung malignancies were selected as candidates for SBRT. Patients were divided into two subgroups according to their individual clinical and imaging features. The first subgroup, the ablative SBRT group, included patients with T1-T2 NSCLC and the second subgroup, the palliative SBRT group, included patients with lung oligometastases from different primary sites or selected (>T2, N+, or lung cancer recurrence from a previously irradiated tumor) advanced disease with only local extension. The primary general eligibility criteria included the following: older than 18 but younger than 90 years, stage IA-IB NSCLC (8), metastases with maximum diameters of less than 5 cm, a number of metastases (not more than 4 lesions) occurring in one or both

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lungs, contraindication to surgery due to comorbidity or advanced age, and patient refusal of surgery after multidisciplinary discussion. Patients with evident positive mediastinal nodes were included if they were considered unfit for any other medical or surgical treatment. Similarly, patients who had centrally located lesions or previously received chest radiotherapy could receive treatment if other therapeutic options were not indicated. Ineligibility criteria included a Karnofsky performance scale score of less than 80 and/or concomitant metastatic lesion(s) outside the lung and/or inadequate pulmonary function [a forced expiratory volume in the 1st second (FEV1) of less than 40% and a diffusing capacity of the lung for carbon monoxide (DLCO) of less than 40% predicted]. This protocol has been submitted and approved by our institutional Ethics Committee and all patients provided written informed consent before being assigned to treatment.

Patients' characteristics. Median age was 77 years (range of 53-88 years). Data were evaluated for 56 with a minimum follow-up of six months. Twenty-seven out of the 56 patients entered the ablative SBRT subgroup. Twenty-two of them had stage T1N0 disease and five had stage T2aN0 disease. The remaining 29 patients had lung metastases or advanced local disease and entered the palliative SBRT subgroup. Out of these 29 patients, 11 had lung cancer recurrences (six rT1 and five rN+ disease) and eight had lung metastases (two each of bladder and rectal cancer and one each of colon, gastric, kidney, and endometrial cancer). One patient had T1N1 disease, three patients had T2aN1 disease, four patients had T3N0 disease, and two patients had T4N0 disease (all of these last four patients had multiple nodules). In terms of the entire patient population, 42 patients (75%) had a single lung nodule and 14 (25%) had multiple lung nodules (12 patients had two nodules and two patients had four nodules) (Table I). The lung nodules were located in the following areas: 30 patients had a single peripheral nodule, 12 had a single central nodule, four had multiple peripheral nodules, three had multiple central nodules, and seven had both central and peripheral nodules. A total of 74 lung lesions were treated. Forty-eight of these lesions were peripheral and 26 were central. Nine out of the 56 patients had previously received chest irradiation. Histology was available for 28 (61%) of the 56 patients with lung cancer. Seventeen of these patients had adenocarcinoma (61%), seven had squamous cell carcinoma (25%) and three had NSCLC with no other specification (14%). Computer Tomography and Positron Emission Tomography-CT findings diagnosed the malignancy (defined as "progression" in subsequent radiologic of examination) for the remaining 28 patients (10 of these patients had oligometastases) who did not undergo biopsy due to the high risk of complications. No patient underwent a concomitant chemoradiotherapy treatment.

Patient setup and planning. In order to account for nodule motion during all phases of the respiratory cycle, each patient underwent a slow CT scan simulation in the supine position. The All-in-One (AIO) system (Orfit Industries n.v. Antwerp, Belgium), which includes thermoplastic masks, was used for immobilization. Permanent marks on the skin and mask were used to align patients to the laser and AIO systems. The Eclipse™ (Varian Medical Systems, Inc., Palo Alto, CA, USA) treatment planning system was used to contour target volume and organs at risk (OARs). The clinical target volume (CTV) corresponded to the gross target volume (GTV). The planning target volume (PTV) was obtained by

Table I. *Patients' characteristics.*

	Ablative	Palliative	Total
Number of patients	27	29	56
Median f/u (months)	13 (7-25)	17 (7-30)	15 (7-30)
Age (years) median	77 (61-88)	72 (50-86)	77 (53-88)
Male/female	18 (67%)/ 9 (23%)	23 (79%)/ 6 (21%)	41 (73%)/ 15 (23%)
Stage			
T1N0	22		
T1N1		1	
T2aN0	5		
T2aN1		3	
T3N0		4	
T4N0		2	
rT1		6	
rN+		5	
Metastases from			
Rectal cancer		2	
Colon cancer		1	
Gastric cancer		1	
Renal cancer		1	
Endometrial cancer		1	
Bladder cancer		2	
Multiple lesions		14	
Single lesion	27	15	

adding a 10-mm margin in the cranio-caudal direction and a 5-mm margin in all other directions from the CTV. In order to calculate the dose volume histogram, the spinal cord, lungs, esophagus, heart, and ribs adjacent to the target were contoured as OARs.

Total doses and fractionations. Patients were treated with different fractionation schemes depending on the tumor stage (T), tumor location inside the chest (peripheral vs. central), and evidence of a primary lung tumor or metastatic disease. For patients in the ablative SBRT subgroup (Table II), T1 peripheral tumors were treated with 48 Gy/4 fractions (fx)/2 weeks, T2 peripheral tumors were treated with 52 Gy/4 fx/2 weeks, and T1-T2 central tumors were treated with 50 Gy/5 fx/3 weeks due to their higher risk of major toxicity (9). Patients with oligometastases or advanced local disease (*i.e.* patients with multiple nodules or previous irradiation) entered the palliative SBRT subgroup and received 60 Gy/8 fx/4 weeks. The biological effective dose (BED) for tumor and normal tissues was estimated for each adopted fractionation schedule according to the linear-quadratic formula (Table I). An α/β ratio equal to 10 Gy was used for primary and secondary tumors, while an α/β equal to 3 Gy was used for late-responding normal tissues.

SBRT delivery. All patients were treated with HT. The setup was checked with a daily Mega Voltage CT scan (obtained with TomoTherapy's image guidance capability) that was matched to the simulation CT scan. For the delivery planning, the following parameters were used: field width 1 cm-2.5 cm depending on the size of the PTV, pitch 0.096-0.143, modulation factor of 2-3 (to enable a beam-on time of less than 15 min). Figure 1 shows the dose distribution delivered by HT for ablative and palliative SBRT.

Table II. Fractionation schedule and corresponding biological effective dose (BED) delivered for ablative and palliative stereotactic body radiotherapy (SBRT) subgroups.

Clinical disease	Fractionation (single dose/ number of fx)	Total dose (Gy)	BED with α/β of 10 Gy (tumor)	BED with α/β of 3 Gy (late toxicity)
Ablative SBRT				
T1-T2 NSCLC central site	10 Gy×5 fx	50 Gy	100	216
T1 NSCLC peripheral site	12 Gy×4 fx	48 Gy	106	240
T2 NSCLC peripheral site	13 Gy×4 fx	52 Gy	120	277
Palliative SBRT				
Lung oligometastases [recurrence of previously irradiated lung cancer or advanced disease (selected T3, T4)]	7.5 Gy×8 fx	60 Gy	105	210

fx: Fractions, NSCLC: non-small cell lung cancer.

Table III. Post-treatment outcomes for ablative and palliative stereotactic body radiotherapy (SBRT) subgroups.

SBRT modality	Local control*	Disease progression		
		Only “in-field”	Only “out-of-field”	Both “in-field” and “out-of- field”
Ablative SBRT	69.6%	1/27 (4%)	5/27 (18%)	3/27 (11%)
Palliative SBRT	40.4%	0	9/29 (31%)	9/29 (31%)

*Local control (complete response, partial response, and stable disease).

End-points and follow-up. This study’s primary end-point was the feasibility of ablative and palliative SBRT as assessed three months after the completion of HT. Lung toxicity was graded according to the Radiation Therapy Oncology Group (RTOG) Acute Radiation Morbidity Scoring Criteria (10) for events occurring 1-90 days from the start of radiation treatment. Secondary end-points were LC and OS rates at 24 months. LC was defined as the absence of local progression, as made evident by tumor growth or regrowth after initial shrinkage. The factors that were investigated for LC probability were: age (younger *vs.* older than 70 years old), lesion location (central *vs.* peripheral), number of treated lesions (single *vs.* multiple), single dose fraction (<10 Gy *vs.* ≥10 Gy), total treatment time (<20 days *vs.* ≥20 days), and number of weekly fractions (one *vs.* two per week). Outcome curves were defined as LC probability (end-points: local and/or nodal failure) or OS (end-point: death for any cause). In order to determine median follow-up and time-to-event (survival), follow-up time was derived from the first day of treatment. Outcome rates were calculated using a Kaplan Meier analysis. The log-rank test was used to compare OS and LC rates between patient subsets. Data were analyzed using the JMP® 9 software (SAS Institute Inc., Cary, NC, USA). Each patient underwent a clinical examination and CT scan six weeks after the end of treatment and every six months thereafter. A CT-PET scan was prescribed in follow-up for patients who completed the examination with a CT-PET scan before receiving SBRT, and when a differential diagnosis between radiation fibrosis and tumor progression was needed.

Results

At the time of writing the median follow-up for all 56 patients was 15 months (range of 7-30 months). All patients were assessed for feasibility, LC, and OS. According to the fractionation schedule design, 25, 4, 9, and 18 patients were treated with 48 Gy/4 fx, 52 Gy/4 fx, 50 Gy/5 fx, and 60 Gy/8 fx, respectively. Forty-three patients were treated twice a week. The 13 patients that were treated once a week were not fit enough (*i.e.* patients were older than 80 years) to complete twice-weekly treatment. Compliance with ablative and palliative SBRT delivery was excellent in 52 (93%) out of the 56 patients. One patient experienced acute dorsal pain after the first treatment fraction but felt relieved after 24 h and without analgesic therapy. Mild treatment-related dysphagia was observed in three (5%) patients. According to the RTOG criteria, no cases of grade 2+ acute or late/consequential toxicity were recorded. In eight (14%) patients, lung fibrosis that was confined to the PTV was detected on a CT scan six months after treatment; all eight patients are now doing well and not suffering lung function impairment. Actuarial LC at 24 months for all 56 patients was 55.4%. The tumor response and failure that was observed in the two patient subgroups is shown in Table III.

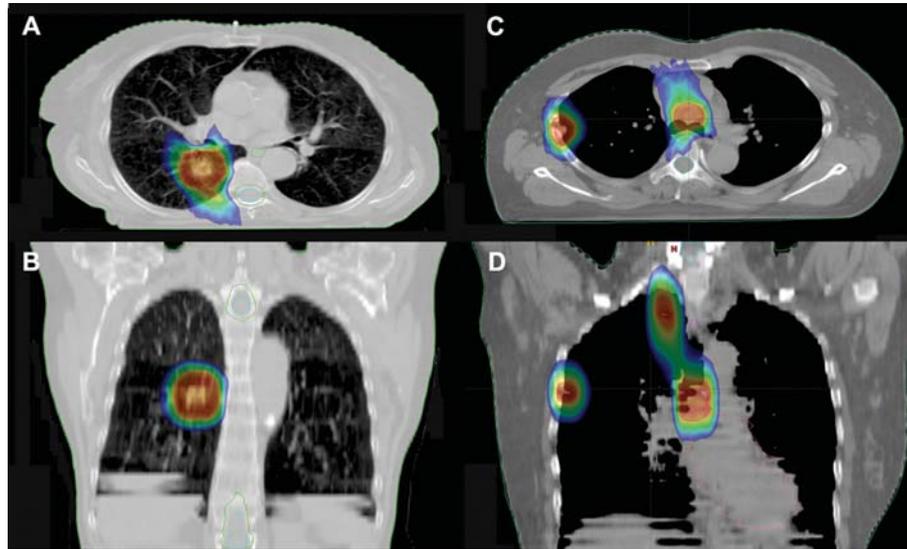


Figure 1. Axial and coronal dose distribution in ablative (A, B) and palliative (C, D) treatment. Doses are represented up to 50% of the prescription dose.

Actuarial LC at 24 months for the SABR subgroup was 69.6% vs. 40.4% ($p=0.0019$) for palliative SBRT (Figure 2). The LC rate was higher when patients were treated for a single lesion [vs. multiple lesions (63% vs. 24%, $p=0.0034$)], for lesion(s) located peripherally [instead of centrally (80% vs. 66%, $p=0.15$)], and with single-fraction doses higher than 10 Gy [vs. <10 Gy (70.5% vs. 46% $p=0.16$)]. In terms of total treatment time, LC was 47% and 63% for treatments longer or shorter than 20 days, respectively ($p=0.23$) (Figure 3). No differences in LC at 24 months were observed between patients receiving either one, and those receiving two fractions per week (59% vs. 48%, $p=0.30$), or those younger and those older than 70 years old (85.7% vs. 62.4%, $p=0.5$). At the time of this report, OS at 24 months was 58% for all 56 patients [65% for the ablative SBRT group vs. 49% for the palliative SBRT group ($p=0.57$)].

Discussion

Many studies have shown encouraging outcomes for curative ablative SBRT for patients with lung malignancies (1-5). A recent ASTRO Technology Committee report points out that although there are many ablative SBRT treatment options that use innovative linear accelerators and advanced technology (7) to provide good planning and delivery solutions for lung cancer, only minimal data are available from a single-treatment delivery system, especially in the case of HT (11-13). To our knowledge, our study is one of the larger data sets pertaining to delivery of SBRT by HT to primary or metastatic lung cancer (12). Treatment fractionation was individualized mainly according to

treatment rationale (ablative vs. palliative) and tumor site (central vs. peripheral). In order to obtain good tumor control but avoid severe late toxicity, all fractionation schedules had a BED of greater than 100 Gy, but less than 280 Gy (9). Metastatic patients were treated with lower-dose fractions because they had multiple lesions and we wanted to minimize the amount of normal lung tissue received a toxic dosage. Primary peripheral lesions that were not near critical structures received the highest doses in the fewest fractions. The primary end-point of this prospective study was to assess the feasibility of HT for ablative and palliative SBRT. In response, all 56 patients completed treatment without interruptions due to intrafraction intolerance or interfraction acute toxicity. Additionally, because beam-on time for each session might exceed 15 min and patient comfort during that time was a high priority for us, great care was given to the patient setup. Because half of all treated patients were more than 77 years old and affected by age-related physiological morbidities, we specifically stressed out on correct patient positioning. HT treatment was generally well-tolerated with reports of only mild dysphagia, minimal lung fibrosis, and no clinical lung impairment. In contrast to several warnings in the literature, central or multiple targets were not a challenge for SBRT delivered with HT (9). Our data also confirm the observations of Chi and colleagues about clinical implication of lung SBRT (14). In summary, because our results show that good feasibility and low toxicity can be achieved independently from tumor size, number of tumors, fractionation schedule, and patient age, our study supports the use of HT to deliver lung SBRT. The second end-point

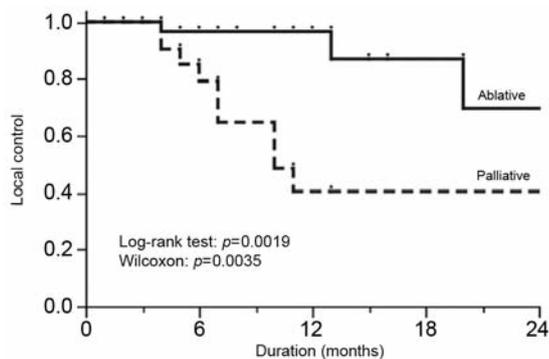


Figure 2. Local control for ablative stereotactic body radiotherapy (SBRT) and palliative SBRT (40.4% and 69.6%, 24 months respectively).

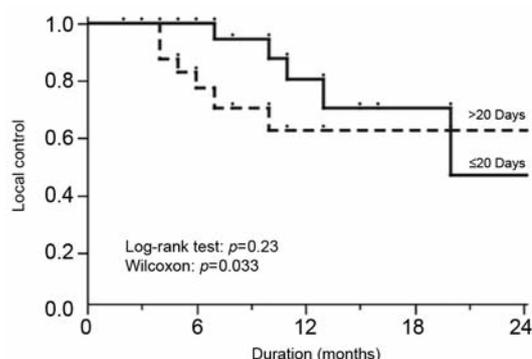


Figure 3. Relationship between local control (LC) and overall treatment time (OTT). LC for an OTT shorter than 20 days was 47% and LC for an OTT longer than 20 days was 63%.

of this study was to assess preliminary clinical outcomes (LC and OS). As expected, our analysis showed statistically significant and improved outcomes for patients treated with ablative SBRT as compared to those treated with palliative SBRT. Results for those patients who were treated for primary, early-stage tumors were comparable to those recently reported by other authors (15). It is also important to note that comparable LC was obtained even though five patients (19%) with stage T2N0 disease were included in the ablative SBRT group. Conversely, as compared to patients in other studies, the patients with metastatic disease that we treated with palliative SBRT had a slightly lower LC rate. However, because the patients that we enrolled in this subgroup had multiple lung metastases or more advanced (*e.g.* relapse) local lung cancer (and thus a worse probability of achieving LC for all irradiated lesions), our study results could be due to differences in patient selection. Specifically, because other authors reported on patients with oligometastases that usually received treatment for a single nodule (6). However, OS rates at 24 months, for patients with metastatic disease, were quite similar to those reported by other authors and thus suggest that the most common reason for failure was distant disease progression (15). As shown by the data of those receiving palliative SBRT (Table II), these patients only had distant or distant and in-field concomitant failure. In other words, no patient with metastases failed exclusively in-field. Interestingly, our investigation showed that different SBRT-by-HT variables, such as fraction size (more than or less than 8-10 Gy), total treatment time (more than or less than 20 days), and target location (central *vs.* peripheral) did not affect outcomes. These results suggest that a shortening of total treatment time, especially for patients receiving palliative SBRT with a major pattern of distant failure, might not be detrimental to LC or OS, but could improve a patient's quality of life.

Conclusion

SBRT by HT delivered with either ablative intent to patients with stage IA IB NSCLC or in a palliative role to patients with oligometastases is feasible and very well tolerated. Preliminary LC results for patients with early-stage primary tumors treated with ablative SBRT appear excellent, especially when considering the large majority of elderly patients in our study. Conversely, but as expected and due to their being strongly affected by distant failure rather than local progression, clinical outcomes after palliative SBRT appear less satisfactory than those of ablative SBRT. Finally, for patients that receive palliative SBRT by HT, LC can be best achieved by shorter treatment times and a limited number of high, single-dose fractions.

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