ONCOLOGY

Implementation of advanced radiotherapy techniques: stereotactic body radiotherapy (SBRT) for oligometastatic patients with lung metastasis - a single institution experience

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Abstract

Background and aims. The treatment of oligometastatic disease has become common practice as advanced radiotherapy techniques became more available. Lung is one of the main metastatic sites for a majority of cancers and many of these patients present with a limited metastatic disease burden. For these patients, SBRT (Stereotactic Body Radiation Therapy) represents a non-invasive treatment alternative. In this report we present our experience with our first series of patients with limited metastatic disease treated with lung SBRT. The purpose of this paper is to provide a qualitative and quantitative assessment of the lung SBRT treatment process and algorithm leading up to treatment delivery in a community-based radiotherapy department.

Methods. We have retrospectively reviewed our first series of 41 patients with lung oligometastases from various malignancies, treated using SBRT between March 2019 and December 2020. Demographic, technical and outcome data were analyzed.

Results. A number of 45 lung metastases (in 41 patients) were treated with SBRT during the specified time period. The median age was 65.7 years old (range 33-83). 16 patients (39%) were treated for multiple lesions and the mean number of treated lesions was 1 (range1-3). Median dose prescribed was 50 Gy /5 fractions (median BED_{10} =77 Gy). The median intra-fraction displacements were: Vertical (0.23cm), Longitudinal (-0.27 cm), Lateral (-0.1 cm), Pitch [0.22°], Roll [0.15°], Rotation [0.32°]. The median session time was 40 minutes. All patients completed the prescribed course of treatment.

Preliminary clinical data were recorded. With a median follow-up of 9 months, local control was recorded in all but one patient. At the last known follow-up, local control was recorded for 39 (85%) out of 45 treated lesions.

Conclusion. For lung SBRT, the required corrections at the time of treatment delivery are small, as long as strict protocols are implemented. Preliminary data for lung metastasis in oligometastatic patients support SBRT as a viable method of achieving high rates of early local control. These results need to be further confirmed in a larger cohort of patients with longer follow-up.

Keywords: local control, lung metastases, oligometastatic, SBRT

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Background and aims

Stereotactic body radiation therapy (SBRT), also known as stereotactic ablative radiotherapy (SABR), comprises the delivery of high, ablative dose per-fraction to an extra cranial target in a limited number of treatments (range 3-8), to a rather small volumetric target(s) [1–3]. SBRT is currently among the options for patients with early-stage lung cancer, unsuitable or refusing surgery [4]. In addition, due to an excellent local control and an acceptable toxicity profile, more and more institutions are using this method to treat oligometastatic disease [5]. For patients with genuine de-novo oligometastatic disease (first time diagnosis of oligometastatic disease), the absence of polymetastatic disease in the patient's history indicates a low metastatic capacity of cancer [6]. Lung metastases are widely accepted to be oligometastatic when five lesions or less occur separately in up to three organs [1].

Treatment of metastatic patients has been based on systemic therapies in order to delay progression and extend life, without eradicating the disease completely. Many non-randomized observational studies and randomized phase 2 trials, suggest that the treatment of oligometastatic disease with ablative therapies can lead to better survival, compared to standard of care in metastatic disease. Interest in treating oligometastatic disease is also increasing because of improvements in systemic therapies [7]. The reported toxicity is low, with clinically significant side effects reported in less than 10% of the patients [8–10]. However, these results rely on strict technical requirements during the whole process, from simulation to treatment planning and treatment delivery. Also, there is no current consensus on the ideal dose and fractionation for SBRT in lung metastases, and it is the subject of study in ongoing clinical trials [1].

This technical report aims to show our initial experience using lung SBRT for lung oligometastases. Our objective for this paper was to collect and review the technical aspects and parameters for the SBRT treatment, delivered in this type of patients in our department. We also report our interim initial clinical results of SBRT in patients with lung oligometastases.

Method

We retrospectively reviewed the records of the patients with de-novo oligometastatic disease treated with SBRT in our Radiation Oncology Department between March 2019 and December 2020. All patients were presented and agreed to our code of ethics and agreement to GCP (good clinical practice).

All cases were discussed in a multidisciplinary meeting. Treatment indication was based on available international guidelines (ASTRO, NCCN, ESMO guidelines) Patients included in this study had:

- Good performance status described as performance status between 0 and 2. ECOG scale was used (0: Fully active and able to carry on all pre-disease performance without restriction, 1: Restricted in physically strenuous activity but able to walk and carry out light house work or office work 2: Able to walk and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours)
- Confirmed malignancy. All patients had histologic confirmation of the primary tumor
- Controlled primary site of disease (primary tumor was treated with curative intent whether that is surgery, radiotherapy or radiochemotherapy)
- 1-3 lung metastasis or lung invading into rib metastasis by radiologic criteria only
- Oligometastatic status was confirmed by CT or PET-CT
- Tumor diameter < 7 cm.
- No concurrent systemic treatment

Patients with previous radiotherapy to the chest were excluded from this study and no systemic therapy was administered during SBRT in any patient.

SBRT technique

Patients were immobilized using the Access Supine Breast & Lung or Access Supine MR systems.

All patients underwent non-contrast motion correlated CT simulation (4DCT) using large bore Philips Brilliance CT scanner. Respiration was monitored both at simulation and treatment delivery using the real-time position management system (RPM/RGSC gating system version 1, Varian Medical Systems, USA). The CT slice thickness was 1.8 mm.

Respiratory motion management was employed in all patients. The respiratory motion of the target was evaluated in all phases of the respiratory cycle, and in all planes. Tumors with less than 5 mm of movement during the respiratory cycle, were treated in a free breathing technique. Otherwise, if movement of the tumor was detected to be more than 5 mm, an active respiratory management was employed (deep inspiration breath hold (DIBH) or end expiration breath hold (EEBH)).

For all patients, the gross tumor volume (GTV) was contoured on lung window (level of −300 Hounsfield units (HU) and a window width of 1700 HU). The gross tumor volume (GTV) and the clinical target volume (CTV) were considered to be equal. For patients treated in free breathing, the internal target volume (ITV=iGTV) was defined on all 10 phases of the respiratory cycle and MiP (maximum intensity projection) was generated to account for intra-fractional motion. Our planning target volume (PTV) was defined by adding an isotropic expansion of 5 mm in all directions. For all patients, airways, lungs-PTV, esophagus, spinal cord, heart, great vessels, and chest wall were contoured and dose volume constraints (DVC)

applied as per centralized protocol (NCCN guidelines). The brachial plexus was contoured as an OAR (organ at risk) for patients with upper lung tumors.

The SBRT plan was generated using Eclipse treatment planning system v 15.6, (Varian Medical Systems, USA), with 3D pencil beam superposition-convolution algorithm (AAA) for dose calculations, with heterogeneity corrections. Dose fractionation was at the discretion of the Radiation Oncologist.

All of the patients were treated with VMAT technique and volumetric dose prescription method was employed. The median dose was 50 Gy administered in a median of 5 fractions for the lung metastasis. The median PTV dose, prescribed on the 95% isodose, reflected our objective for the prescribed dose and goal for treatment planning. All the hotspots were within the PTV. All dose for the organs at risk were reviewed and met all constraints according to Chang [11].

Treatment delivery and treatment verification

SBRT was delivered using a True Beam STX linear accelerator (Varian Medical Systems, USA), 6FFF (flattening filter free) photons, in one to three coplanar arcs with the exception of one case where we used IMRT.

Every treatment session was preceded by dual imaging: KV to KV (kilo-voltage) match followed by KV to CBCT (cone beam computed tomography) to account for inter-fractional motion. Additionally, in selected cases we used live fluoroscopy in order to verify intrafractional GTV movement is confined within the PTV boundaries. All necessary alignments were analyzed and applied on 6 axes; X, Y, Z, pitch, roll, rotation for the perfect match to the treatment volume. According to our institutional protocol, shifts larger than 3° for pitch and roll, larger than 6° for rotation and larger than 2cm on X,Y,Z axis, required resetting up of the patient.

Follow-up post-SBRT

All patients, underwent clinical examination and imaging assessment (contrast-enhanced thoracic-abdominal and pelvic CT or PET/CT) for evaluating local and distant control every 3 to 6 months. Access to PET/CT in our national healthcare system is difficult, and this investigation was used only in some cases. Response to treatment and local/distant control was assessed via RECIST criteria v1.1. The median shifts required were calculated and for all patients, overall survival (OS), disease-free survival (DFS), and local control (LC) were analyzed. LC was defined as a lack of tumor regrowth on follow-up CT according to RECIST v1.1. Local control failure was defined as an increase in the sum of the largest diameter of the target lesion by ≥20% from the moment of SBRT treatment. Distant failure was defined as any failure outside the treatment volume, whether this was in the lung or other organs. OS was defined in this case, as the time to cancer related death from the start of SBRT treatment.

Statistical analysis

All data were censored at the date of the last follow-up or death, whichever was recorded first. In order to explore potential differences in RECIST response based on patient and tumor characteristics ANOVA analysis was used. Data were analyzed using IBM SPSS Statistics for Windows, version 20.

Results

Technical aspects of SBRT

For all patients, as described above, all shifts were recorded for each individual treatment session. The required shifts were small. No patients required reset for shifts larger than our accepted variation. Table I presents the median values of the applied shifts. In addition, treatment time was recorded for each individual session from the moment the plan was loaded into the machine up to the end of last monitor unit delivered for that treatment session. The median time spent in our department for this step was 40 minutes per patient (range: 16-166 minutes). The median dose was 50 Gy (range, 30–60) in a median of 5 fractions (range, 3–10) for the lung metastasis, while for costal-lung interface, the median dose was 21 Gy (10–40) in a median of 3 fractions (range, 1–5). Treatment was administered every other day. The median PTV volume was 12.92 cc (3.3–103 cc). The GTV median size was 1.4 cm, however tumors up to 5.6 cm were treated. 36% of the patients were treated in deep inspiration breath hold, and 64% using free breathing. Table II presents dose schedules, simulation and treatment characteristics.

Table I. Median values of the applied shifts.

	kv-kv + CBCT					
	Vrt(cm)	Lng(cm)	Lat(cm)	Pitch[°]	Roll[°]	Rtn[°]
median values	0.23	-0.27	-0.10	0.22	0.15	0.32
minimum values	0.08	0.00	0.00	-0.04	0.02	0.02
maximum values	1.57	-2.41	-1.25	2.20	-2.72	2.96

Table II. Dose schedules, simulation and treatment characteristics.

Dose Schedule	N	%
60Gy/5fr	5	11.1
50Gy/5fr	22	48.8
45Gy/5fr	5	11.1
48Gy/4fr	4	8.8
Others	9	20
Simulation Protocol		
4D-CT	29	64
Breath Hold	16	36
Treatment characteristics		
Dose per fraction (Gy)	9.73 (5-15)	
Tumor volume @Dg	22.7 (6-56)	
PTV volume (cc)	33.7 (1.83-304.9)	

Clinical results

Cohort

A total of 41 patients with 45 lesions were included in this study. Characteristics of the cohort are presented in table III. There were 20 men and 21 women, with a total of 45 lesions, (41 lung metastasis and 4 lung invading into rib metastasis). Median age was 65.7 years (range 33-83). The primary disease sites for these oligometastatic patients were as follows: 16 colorectal, 6 pulmonary; 4 melanoma, 3 renal and 16 other cancers.

Table III. Patient characteristics.

Patient characteristics	
Age	66.45 (33-83)
Males	20
Females	21
Disease characteristics	
No. of lung nodules	41
No. of nodules at the rib-lung interface	4
Size (mm)	23.05 (6-56)
Metastasis in other organs at diagnosis	17
Oligometastases (<5 sites)	45
Primary site	
Colorectal	16
Pulmonary	6
Skin	4
Renal	3
Prostate	3
Others	13
Simulation Protocol	
4D-CT	29
Breath Hold	16
Treatment characteristics	
Dose per fraction (Gy)	9.85 (5-15)
PTV volume (cc)	33.73 (1.83-304.9)

A total of 17 patients (41%) had metastatic disease in other organs outside the lungs at time of SBRT and all patients had oligometastatic disease with 3 or fewer sites of metastasis.

The median PTV volume was 12.92cc (3.3-103cc).

Survival

The median follow-up for this cohort was 9 months (range 3-21). During the follow-up period, 9 patients died: 2 due to causes unrelated to cancer (1 sepsis, 1 major stroke) and 7 patients died from disease progression. For these 7 patients, the median survival after SBRT was 5.3 months. One patient was lost from follow up.

Local control

At least one follow-up imaging was available for all but one patient that has not yet performed first 3-month imaging evaluation. The mean number of follow-up scans of was 3 (range: 1–7). At the last known follow-up, local control was recorded for 39 (85%) out of the 45 treated lesions. Seven patients reached 1 year follow up; local control was maintained for 6 of them. Three patients (7.3%) presented local failure, after a median of 7 months from SBRT.

There were no differences in local control and GTV and PTV volume (one-way ANOVA - table IV and figure 1 and 2).

Table IV. Treatment response according to initial tumor volume and PTV.

RECIST & mean Tu. Volume	N	Mean	Std. Dev.
RC	4	18	20.06
RP	21	24.33	10.92
ST	11	24.27	12.81
Total	36	23.61	12.39
RECIST & mean PTV Volume	**N**	**Mean**	**Std. Dev.**
RC	5	34.54	36.87
RP	22	21.85	20.14
ST	12	27.35	21.99
Total	39	25.17	22.95

Legend: RC - Complete Response; RP - Partial Response; ST - Stable Disease.

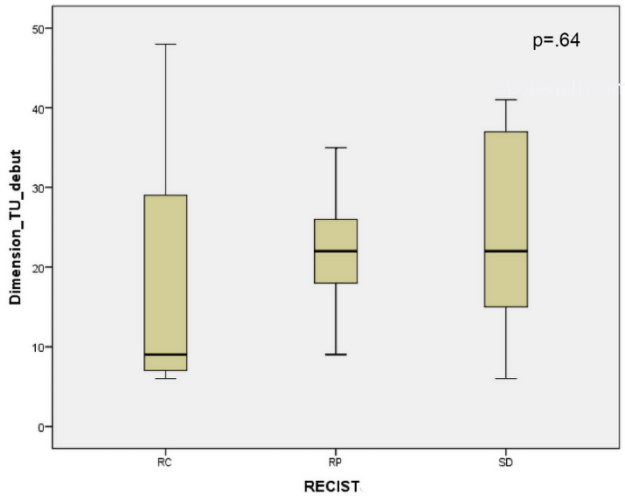

Figure 1. The difference between tumor volume at treatment debut across disease response with SBRT treatment.

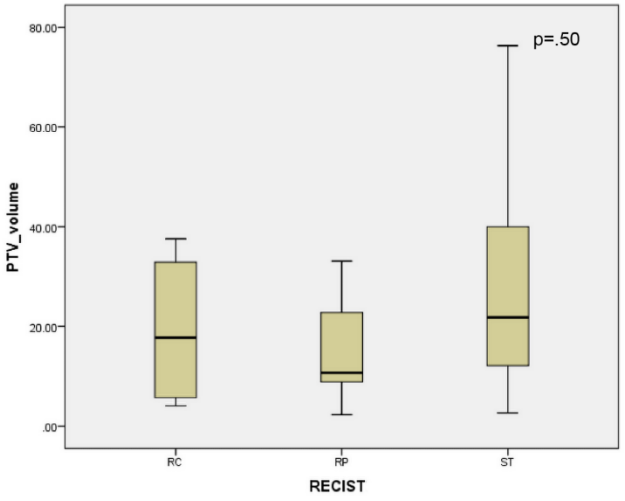

Figure 2. The difference between PTV volume at treatment debut across disease response with SBRT treatment.

We explored the differences regarding initial tumor dimension in between RECIST categories. No differences were observed between groups, F (2,33) = 0.44, p=0.64, as shown in table IV**.** A box plot of the results is shown in figure 1.

Further on, we aimed to analyze whether there were differences of initial PTV volume between RECIST categories at 3 months. Again, no differences were observed, F (2,36) = 0.68, p=0.50. Descriptive statistics are shown in Table 4 and differences are illustrated in figure 2.

Discussion

SBRT is an advanced modern treatment technique that is becoming more used in radiation oncology departments worldwide with the increase of treatment capabilities, quality and safety of administered treatments. SBRT benefits often come with improved quality of life, and positively impact the overall survival, especially in cases with oligometastatic disease that have good life expectancy.

Between 30 and 55% of patients with cancer develop pulmonary metastases [12,13]. Attention and interest in the subject of metastatic treatment of the oligometastatic patients has grown in the past 2 decades. In 1995, Hellman and colleagues defined oligometastatic disease as an intermediate state between the localized and widespread disease, where ablative treatments of all sites of disease result in promising results for disease free interval [14].

The definition of the oligometastatic disease varies and is a continuous subject of debate depending on protocol, institution and publication. However, nowadays the most accepted definition of oligometastatic disease is maximum 5 metastatic lesions in less than 3 organs. Research on the subject is ongoing and other factors such as histology, disease volume, location and genetics or biomolecular marker could potentially aid into a better oligometastatic disease classification. Most recently two articles have tried to bring light into the subject [6,15]. While for patients with aggressive metastatic spread, systemic therapy remains the treatment of choice, for patients with a low metastatic burden, referred to as oligometastatic (OM) disease, local treatment is preferred. In cases where surgery cannot be performed because of unresectable tumor, insufficient medical patient conditions, or patient refusal, stereotactic body radiation therapy (SBRT) reveals a non-invasive alternative treatment. Generally, based on the emerging data, SBRT is considered an effective local treatment alternative to surgery [12].

The issue of the best choice of ablative treatment for oligometastatic patients with lung metastasis whether surgery or SBRT is a subject for consideration. Londero [4] analyzed in his article 79 papers on surgery and SBRT treatment for lung oligometastases. The author advocates that surgical excision of pulmonary oligometastases seems to improve the outcomes in terms of survival, while SBRT has traditionally been reserved for patients unsuitable for surgical treatment. There are consistent differences between surgical excision of metastases and other ablative techniques: excision of lung nodules allows availability of tissue for confirmation of the metastatic nature of nodules, assessment of resection margin while SBRT is an ablative technique that does not allow tissue harvesting. On the other hand, it has been proposed that SBRT might induce not only tumor cell death, but also a tumor-specific response of the host immune system, inactivation of remnant micro metastasis and improved control of disease, in what is known as 'abscopal effect'.

The paper failed to demonstrate a substantial difference between surgery and SBRT in terms of short-term survival while PFS at 1 and 2 years tends to be higher in surgical studies.

A series of prospective and retrospective studies analyzed the role of using ablative therapy in oligometastatic patients and came to be consolidated evidence for using these treatments. The vast majority of the reports on oligometastatic disease were retrospective, either single-center or multicenter. There was large heterogeneity in studies design: studies either reported on a variety of primary tumors or focused on specific tumor entities (e.g. prostate or lung) or metastatic sites (e.g. lymph nodes or lung metastases) [15].

Randomized data emerging from phase 2 trials data are encouraging into using SBRT treatment and paved the way for phase III trials for confirmation of these extraordinary results. Different scientific papers reported encouraging follow up results after SBRT treatment of lung metastases in patients with oligometastatic disease [16].

While the reported results are good, they rely on very strict protocols to be implemented from simulation, to treatment planning and treatment delivery. Image guidance is used to ensure accurate treatment delivery, accurate target positioning and avoidance of organs at risk. There is a significant body of evidence showing that the use of 2D-2D, combined with 3D-3D match offered by the use of CBCT is associated with increased accuracy of the treatment [17]. However, this can result in increased time per fraction time, which can lead to increased patient discomfort, and potential movement of the patient.

Despite long treatment times required for SABR delivery, all our patients completed the prescribed treatment, with no interruptions. At least half of the session time is required for image guidance. Our results show that when strict protocols of immobilization, respiratory motion management are implemented, the recorded displacements are very small. Hence, no patients required re-set-up.

Multidisciplinary approach implemented in all phases of the SABR process is one of the requirements in our center. At the time of treatment delivery, a multidisciplinary team comprised of the treating Radiation Therapists, a physicist and a physician are present. Before beam-on, the whole team must be in agreement with the imaging findings and the required displacements. There were no patients for whom the treatment session was not delivered because of disagreement in the analysis of the image guided findings.

Gomez et al. [18] prospectively showed that local consolidative therapy for patients with metastases from NSCLC improved progression-free survival compared with maintenance therapy alone. Patients in the local SBRT group had significantly longer PFS than patients in the maintenance treatment group: median progression-free survival was 11.93 months versus 3.9 months.

While the updated results of the study [19] showed that PFS benefit was durable (median, 14.2 with LCT versus 4.4 months), the update also showed an OS benefit in the LCT arm (median, 41.2 months versus 17.0 months). Moreover, patients in the LCT group survived longer after progression relative to patients in the MT/O group (37.6 months versus 9.4 months). This study's population comprised of stage IV NSCLC patients and metastasis location varied from brain to lung to liver and adrenal. Consolidative treatment varied from hypo-fractionated radiotherapy or stereotactic ablative body radiotherapy patients; combination surgery and radiotherapy; chemo-radiotherapy; combined hypo-fractionated radiotherapy and chemo-radiotherapy; and surgery to all sites.

In our analysis we enrolled only patients with lung metastases from various primaries and the ablative treatment consisted only of SBRT to those lesions.

Iyengar et al. [20] demonstrated prospectively a three times fold increase in median PFS in limited metastatic NSCLC patients with the addition of SBRT to maintenance chemotherapy for patients with PFS increased from 3.5 months to 9.7 months. Patients were assessed following completion of first-line chemotherapy for limited metastatic disease amenable to SAbR (stereotactic ablative radiotherapy). During follow-up period, for patients presenting with disease progression in the SAbR arm, all lesions were outside the irradiated field. Among the particularities of this study are the fact that only radiation was used as local therapy and no patients underwent surgery. Location of metastases also varied (CNS, mediastinum, liver, etc.).

Rieber et al. [21] retrospectively showed that SBRT for medically inoperable patients with pulmonary metastases from various primaries achieved excellent local control and promising overall survival.

Based on these experiences in primary NSCLC, SBRT has also been introduced in the treatment of oligometastatic disease from various primary tumors and at various metastases locations.

Two-year local control (LC) and overall survival (OS) were 81.2% and 54.4%, respectively. This study included a larger cohort of patients. The primary tumor was controlled in 67% cases. The most frequent primary tumor was NSCLC, followed by colorectal cancer and sarcoma. In our paper we also found colorectal and pulmonary cancers to be the most frequent primaries. Rieber et al. showed a series of other factors influencing local control, mainly pretreatment performance status, biological effective dose (BED) at PTV isocenter and single fraction dose while OS was most significantly influenced by pre-treatment performance status, maximum metastasis diameter, primary tumor histology, time interval between primary tumor diagnosis and SBRT

treatment and number of metastases. Our analysis is also a retrospective one and although these independent factors are generally seen to influence LC and OS, we have not looked into these correlations at this time but they will be analyzed in our follow-up paper on these patients.

Kessel et al. [12] analyzed the long-term outcome, side-effects and the prognostic factors after SBRT of pulmonary lesions. The novelty of the study was the addition of patient-reported outcome (PRO) forms to the follow up routine. The study also correlated a series of prognostic factors in relation to clinical outcomes. Those factors were age, gender, Karnofsky Performance Score, GTV, PTV, PET imaging before treatment, previous chemo, previous external irradiation, number of pulmonary metastases, absence of extra thoracic metastases, controlled primary tumor, primary tumor type, as well as chemotherapy between diagnosis of lung metastases and SBRT. With an LC rate of 78% after 3 years, evaluation of PRO enabled the author to collect comprehensive information about symptoms of patients up to 14 years after SBRT. PROs improve and complement follow-up care. They are an essential measure in addition to the physician-reported outcomes and should be considered in the follow-up workflow. In our study we did not include PRO form evaluation but since this measure of evaluation will improve patient follow-up process, we are inspired into implementation of this practice in the future. Our study looked at the correlation between the PTV volume and initial tumor volume but we could not find any correlation to our early clinical outcomes.

In our study, with a short follow-up period, we could observe our initial findings for local control and survival to the ones reported in these articles. Our initial data showed that among the 7 patients who survived at least one year, 6 maintained local control. Only 3 patients presented local progression, after a median time of 7 months. These data are in agreement with other published studies, reporting further disease progression more often in the same organ, outside the target after a median of 7-9 months. However, longer follow-up is required to confirm the maintenance of long-term benefits.

While different tumor and treatment related factors can impact the clinical outcomes of lung-oligometastatic disease treated by SABR, in our cohort, none of the analyzed factors were associated with the studied clinical outcomes. This might be explained by the limited follow-up, the small number of patients, as well as by the small tumor sizes treated.

The retrospective design of our paper, reviewing a limited number of patients, with a limited follow-up time, were some of the encountered limitations. To our knowledge this is the first data reported from a Romanian cancer center that aimed to evaluate the efficiency of SBRT for the treatment of lung metastasis and lung to rib interface metastasis. Although DFS and OS were prospected for analysis, data collection is ongoing.

This technology and treatment process are among the first ones to be implemented and used on regular basis by our country's healthcare system. Diversifying the radiotherapy options from conventional radiotherapy to SBRT and SRS (stereotactic radiosurgery) is a process that has its learning curve where training and implementation of new safety standards and quality assurance are mandatory requirements.

Conclusion

For lung SABR, the required corrections at the time of treatment delivery are small, when strict protocols are implemented. SBRT for lung metastasis in oligometastatic patients is a viable method of obtaining high rates of early local control. However, these results need to be further confirmed in a larger cohort of patients with longer follow-up.

For this cohort of patients, we intend to do a follow up paper and evaluate the clinical efficacy results with regard to PFS, OS, as well as toxicity of treatment evaluation for a longer follow up period of time.

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