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ORIGINAL ARTICLE

Stereotactic body radiotherapy for colorectal lung oligometastases: preliminary single-institution results

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Summary

Purpose: *To present the preliminary results of stereotactic body radiotherapy (SBRT) for lung oligometastases originated from colorectal cancer (CRC).*

Methods: *Thirteen patients (9 male, 4 female) with lung oligometastases from CRC were prospectively selected for SBRT between July 2009 and July 2013. We used a dose risk-adapted schedule of radiation.*

Results*: The median follow-up was 9.16 months (range 2-45.6). The median age was 69 years (range 40-84). Three cases (23.1%) were treated with 12.5 Gy in 4 fractions (112.5 biological effective dose/BED). Four cases (30.8%) received 18Gy (151.2 BED), 2 (15.4%) 7.5 Gy in 8 fractions (BED 105) and 4 (30.8%) a monofraction of 34 Gy (149.6 BED). There were 5 (38.5%) complete responses, 5 (38.5%) partial responses and 3 (23%) patients remained with stable disease. During follow-up 6 patients (46.2%) showed distant metastases: liver (N=3, 50%), bone (N=1, 16.6%) and contralateral lung (N=2, 33.3%). Median time to systemic progression was 9 months. One- and two-year distant progression-free survival (DPFS) was 45.8% and 22.9%, respectively. Local control (LC), overall survival (OS), and cause-specific survival (CSS) at one- and two-years were all 92.3%. A tendency for a better local response and DFPS in patients aged ≤70 years and BED > 120 Gy was observed. No grade 3-4 toxicity was noticed.*

Conclusions: *Excellent LC and longer DFS could be achieved with SBRT in oligometastatic lung disease from CRC, delaying thus disease progression and the need for further treatment.*

Key words: *colorectal cancer, lung cancer, oligometastases, stereotactic radiotherapy*

Introduction

SBRT, also known as stereotactic ablative radiotherapy (SABR), is an emerging noninvasive technique developed in the wake of Intracranial Stereotactic Radiosurgery (SRS) and Fractionated Stereotactic Radiotherapy (SRT). The development of SBRT is the result of technological advances in tumor imaging that facilitate guidance, which allows for improved accuracy in radiation delivery and patient immobilization, thus enabling the use of conformal radiation techniques [1].

The term oligometastases, first introduced in 1995 by Hellman and Weichselbaum in relation to the natural history of breast cancer, describes an intermediate state of cancer spread that lies between localized disease and widespread metastases; in this intermediate stage, DFS and OS can both be improved if local control is achieved [2,3]. This term has been recently updated [4] to include a new state of clinical cancer history called oligo-recurrence, which describes a situation in which the primary cancer is controlled but in which some isolated metastases (all of which are suitable for local therapies) are present in one or more organs.

The main use of SBRT is typically local treatment designed to achieve high rates of LC with minimal toxicity. SBRT can be delivered as a single fraction ablation or hypofractionated multi-beam conformal radiotherapy (CRT), in combination with image-guided radiotherapy (IGRT)

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[5]. Many non-randomized studies have shown that SBRT is safe and effective in the treatment of oligometastases, with variable but acceptable LC and OS rates [6,7]. In addition, some authors suggest that SBRT has the potential to increase PFS, thus delaying the need for further systemic therapies [8] and possibly even offering the possibility of cure [9].

The management of metastatic solid tumors has historically focused on systemic treatment given with palliative intent, without expectation of long-term survival [10]. However, there is evidence that patients with limited metastatic disease, such as liver metastasis from CRC, can be cured, drawing increased focus on the potential for intermediate states of metastatic cancer involvement. The lung is another common site for CRC metastases and the emergence of SBRT and other techniques is promising for both lung and liver metastases. However, unlike SBRT in CRC liver metastasis, few studies have investigated the use of this technique in lung metastases of CRC origin.

In the present report, we describe our preliminary results with SBRT in lung oligometastasis from CRC. We demonstrate that this technique is both feasible and efficacious and offers a new management tool for metastatic solid tumors that historically have been treated with systemic rather than local therapies.

Methods

Thirteen consecutive patients with lung oligometastases from CRC were prospectively analyzed and treated with SBRT between July 2009 and July 2013. Patients who met the criteria for our ongoing phase II trial and who consented were enrolled in this clinical study [11].

A multidisciplinary tumor board for thoracic malignancies and the Clinic of Advanced Techniques at our hospital approved the treatment. All patients provided written informed consent, after receiving an explanation for possible benefits and complications, and the need for patient's cooperation with the technique.

Patient selection criteria

Patients eligible for SBRT for lung oligometastases were required to fulfil the following criteria: histologically-proven CRC, age ≥18 years, radical treatment of the primary tumor, life expectancy >6 months, and Karnofsky performance status ≥80%. Other inclusion criteria included the following: inoperable metastasis (assessed by a thoracic surgeon); solitary lung metastases (amenable to local radical treatment such as SBRT and radiofrequency ablation); maximum tumor diameter 5 cm; adequate lung function (FEV_1 >30% of predicted). All patients underwent a positron-emission tomography (PET)-CT scan prior to SBRT to confirm the oligometastatic status.

Treatment (SBRT technique)

During simulation and on the treatment day, patients were immobilized with a thermoplastic mask (Lorca Marin, Murcia, Spain S.A), and treatment setup was reproduced using an end-expiratory breath hold technique. A planning CT chest scan (3mm thickness, without contrast) was obtained using 4-dimensional (4D) CT imaging so that each slide included a complete respiratory cycle. The gross tumor volume (GTV) was identified in the lung parenchyma window and delineated in each 4D-CT phase; the clinical target volume (CTV) was defined as coincident to the GTV. The internal target volume (ITV) was defined as the envelope of the CTVs from each respiratory phase. The final planning treatment volume (PTV) was defined as the ITV plus an isotropic margin of 5 mm. When indicated (particularly in patients with atelectasis) fusion PET-CT was performed.

SBRT was delivered using conformal arcs or multiple fixed coplanar beams, shaped with multileaf collimators. The prescription was designed to encompass the 85% isodose line (permitted between 60-90%). In case of doses >105%, the dose was required to be within the PTV; in cases with doses outside the PTV, only a volume <15% of the PTV volume was allowed. The ideal conformity index was <1.2 (a range of 1.2-1.4 was permitted).

Constraints for organs at risk (OAR) were based on RTOG-0236 recommendations [7]. Cone Beam CT was performed before each session to verify set-up errors. Different types of fractionations were used according to tumor size, target location, and risk of toxicity (Table 1).

Dose risk adapted characteristics

We used a dose-risk adapted schedule (Table 1) that included lesion size and distance from critical structures. The aim of this risk adapted protocol was to minimize toxicity by maintaing BED higher than 100Gy.

Treatment schedule distribution was as follows: 3 cases (23.1%) were treated with 12.5 Gy x4 fractions (112.5 BED). Four cases (30.8%) received 18 Gy x3 fractions (151.2 BED), 2 cases (15.4%) 7.5 Gy x8 fractions (BED 105) and 4 cases (30.8%) received a monofraction of 34 Gy (149.6 BED).

Total treatment time ranged between 1 to 15 days, with a minimum separation between fractions of 40 hrs and a maximum of 8 days. Moreover, in a frame of 7 days only 2 fractions were given. One hour before each fraction, patients were given a single dose of corticosteroid (dexamethasone, 8 mg) to decrease the inflammatory effects of SBRT in the lungs.

Table 1. Patient and treatment characteristics

Characteristics	*N*	*% or range*
Age (years)		
Median	66.46	40-84
>70	5	38.5
≤70	8	61.5
Sex		
Male	9	69.2
Female	4	30.8
Nodule size (mm)		
Median	10	7-27
$BED_{10\ (Gy)}$		
Median	149.6	105-151.2
≤120	5	38.5
>120	8	61.5
Fractionation		
12.5 Gy x 4	3	23.1
18 Gy x 3	4	30.8
34 Gy x 1	4	30.8
7.5 Gy x 8	2	15.4
Local response		
Partial	5	38.5
Complete	5	38.5
Stable	3	23.0
Distant progression		
Yes	6	46.2
No	7	53.8

Response and toxicity assessment

The aim of this retrospective sample study was to assess LC and toxicity.

Secondary end points included OS and PFS.

Follow up included CT scans of the chest, abdomen, and pelvis and 18-FDG PET-CT if local relapse was suspected.

Metastatic lesion response was evaluated using RECIST [12] (Response Evaluation Criteria for Solid Tumors) at 1, 3, 6, 12 months after SBRT. Local failure was defined as an increase in tumor size during the follow-up period or emergence of a new solid lesion in the radiation field. Systemic progression was defined as the appearance of new lesions (distant metastases) outside the irradiation field. Acute and late toxicities were scored using the National Cancer Institute Common Terminology Criteria for Adverse Events version (NCI CTC AE) 3.0, and late toxicities were scored using the Radiation Therapy Oncology Group (RTOG) late toxicity scoring system.

Statistics

Continuous variables were described as mean, median, standard deviation, and range. Categorical variables were presented as frequencies and percentages. The LC, PFS, OS and CSS rates were obtained by the Kaplan–Meier product limit method and Cox regression analysis was used to assess the prognostic factors. CSS refers to the actuarial rate of freedom from death due to CRC. For OS, all causes of death were considered as an event. The Cox regression analysis was performed to identify significant prognostic factors for LC and survival. The following parameters were evaluated to determine their influence on LC and survival: age (> or ≤70 years old), gender, nodule size, BED (≤ or > 120 Gy) and the use of monofraction (34 Gy) vs other types of fractionation.

Local-regional control time was measured from the day of irradiation to the date of failure. Survival was measured from SBRT delivery to the last follow-up date or death (whichever occurred first).

Statistical significance was set at $p<0.05$. Data were analyzed using Statistical Package for the Social Sciences (IBM Corp., SPSS Statistics for Windows, v. 20.0. Armonk, NY; USA).

Results

Patient characteristics

Thirteen consecutive patients, all of whom had a single lung metastasis from CRC, were treated from July 2009 to July 2013. Median age was 69 years (range 40-84). Of the 13 patients, 9 were male (69.5%) and 4 (30.8%) female.

Median follow-up was 9.16 months (range 2-45.6). There were 2 cases (15.4%) that were subjected to surgery and radiofrequency as primary treatment and developed relapse for which they received STRT . The rest of the lesions (N=11, 84.6%) were treated primarily with SBRT.

Lesion locations were as follows: 4 lesions (30.8%) in the superior right lobe, 4 (30.8%) in the superior left lobe, 3 (23.1%) in the lower left lobe, and 2 in the right medium and lower lobes. Median nodule size was 10 mm (range 7-27). Patients were treated either with multiple fractions (69.2%) or monofraction of 34 Gy (30.8%). Median BED_{10} was 149.6 Gy (range 105-151.2).

Patient and treatment characteristics are described in Table 1.

Treatment outcomes

Response to treatment was as follows: complete response in 5 patients (38.5%), partial response in 5 patients (38.5%), and stable disease in the remaining 3 patients (23%). During follow-up

6 patients (46.2%) developed distant progression with the liver (N=3.50%) being the most common site, followed by the contralateral lung (N=2, 33.3%) and bone (N=1,16.6%). One (16.6%) of the patients that developed systemic progression also experienced a concurrent local relapse.

Only one out of 13 patients showed local progression during follow-up, at 5-months post-SBRT. Therefore, 1- and 2-year LC rates were 92.3%. One patient died 31 months after treatment due to CRC. Consequently, the 1- and 2-year OS and CSS survival rates were 92.3%. After 31 months of follow-up, OS and CSS remained 66.7% (Figure 1). A total of 6 patients (53.8%) presented distant/systemic progression during follow-up.

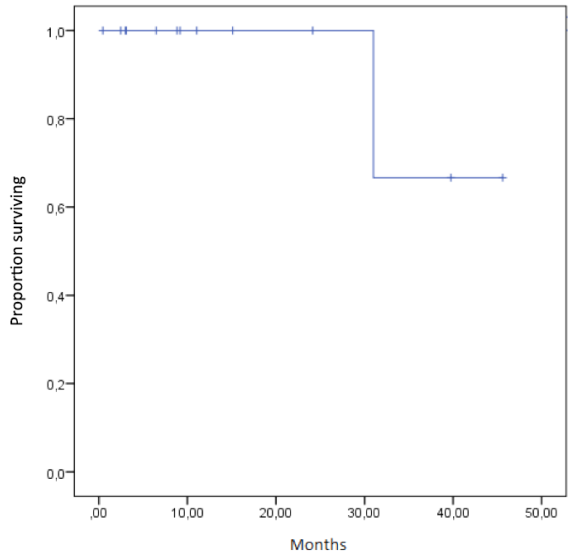

Figure 1. Overall survival.

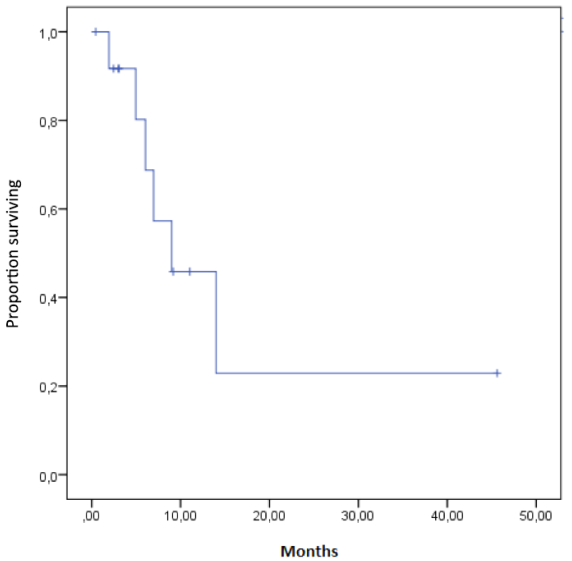

Figure 2. Distant progression-free survival.

Table 2. Responses related to fractionation, age and BED

	Response (%)		
	Partial	*Stable*	*Complete*
Monofraction	44.4	22.2	33.3
Other type	25	25	50
BED ≤ 120	60	20	20
BED > 120	25	25	50
Age, years ≤ 70	37.5	12.5	50
Age, years >70	40	40	20

Median time to systemic progression was 9 months whereas 1- and 2-year DPFS rates were 45.8% and 22.9%, respectively (Figure 2).

Age, gender, nodule size, total BED administered, and the type of fractionation were analyzed to evaluate their influence on LC, survival and treatment response. Complete response rate was higher in younger patients (age ≤ 70) treated with monofraction and a BED >120 Gy. Patients with those characteristics accounted for 50% of complete responses (Table 2). However, none of these associations was statistically significant.

Although patients aged ≤70 presented a higher DPFS compared to patients >70 years (14 months vs 9 months, respectively), this result was not significant (Figure 3).

The total BED was ≤ 120 Gy in 8 patients (61.5%) and >120 Gy in 6 (38.5%). Mean DPFS in patients with total BED >120 was higher than in patients whose total BED was ≤120 Gy (16.6 vs 7.7 months, respectively), although this clinical difference was not significant (Figure 4).

Patients treated with fractionated therapy achieved a DPFS of 14 months vs 7 months in patients treated with a monofraction of 34 Gy. However, this result was not significant either.

We were unable to identify any clinical or statistically significant associations between LC/OS and any of the patient- or treatment-related parameters.

Finally, although no statistically significant results were obtained in this study, we did observe a tendency for better local response in patients aged ≤70 years and a BED >120 Gy, and in patients treated with a 34 Gy monofraction. Moreover, we found a clinical tendency for better DPFS in patients ≤ 70 years of age that received a total BED >120 Gy.

Toxicity

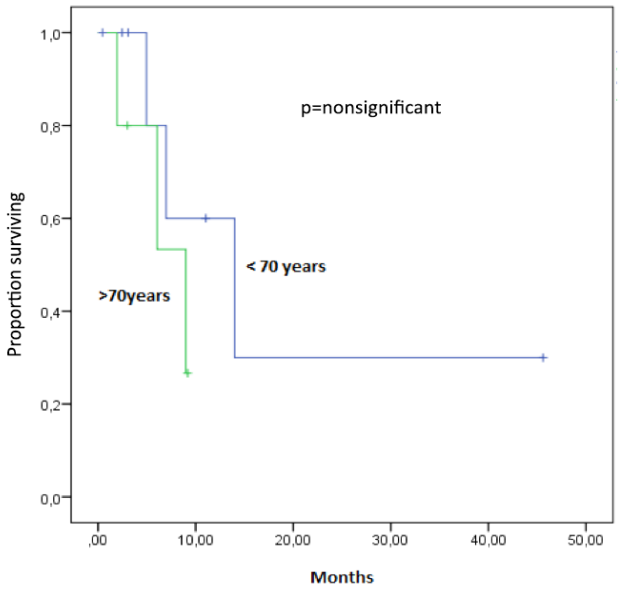

Figure 3. Association between distant progression-free survival and age.

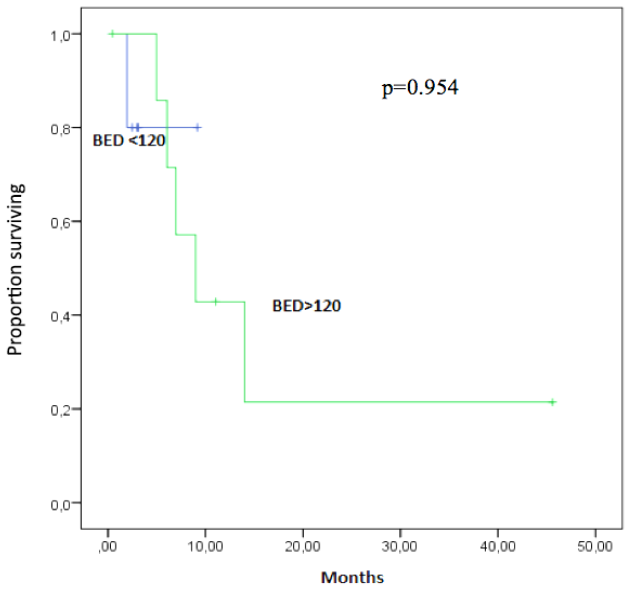

Figure 4. Differences in distant progression-free survival according to total BED.

No patient experienced grade ≥3 toxicity in the subsequent follow-up period. The most common acute toxicities were radiodermatitis, asymptomatic pneumonitis, and grade 1-2 asthenia. All toxicities resolved during follow-up.

Discussion

Our preliminary results in CRC patients with lung oligometastaes treated with SBRT show promising results in terms of LC and survival, with limited morbidity. We found that local ablative treatment with SBRT is a feasible option, with excellent rates of LC (92.3%) and OS (92.3%) at both 1- and 2-year follow-up.

Systemic therapy is the standard of care for patients with metastatic CRC and may prolong survival. However, it is not considered a curative option for most patients. For this reason, it has been hypothesized that some patients are in a transition stage, between localized and widespread systemic disease; in such patients, LC may help improve systemic control [13].

Lungs are among the most common sites for disease spread. This is especially true for epithelial metastases from CRC, as shown in the International Registry of Lung metastases, in which 5206 lung metastasectomies were recorded [14].

Although the presence of lung metastasis is usually a manifestation of widespread disease, carefully selected patients can, nevertheless, benefit from local treatments. At present, surgical resection is recommended as the standard of care because this treatment modality yields 5- and 15-year OS rates of 30-65% and 22%, respectively [14-16]. However, many patients who either refuse or are unsuitable for surgery may be candidates for less invasive techniques, such as radiofrequency ablation [17] or SBRT delivered with curative intent. Indeed, the existing literature indicates that high levels of LC are achievable with SBRT (74-100%) [2,18-23]. Widder et al. recently presented the first study comparing pulmonary metastasectomy (PME) vs SBRT: at a median follow-up of 43 months (range 36-60), there were no significant differences in OS, with 39% and 45% of patients remaining free from failure after 3 years of PME and SBRT, respectively [24]. The preliminary results of that study suggest that the number of patients who can benefit from non-invasive techniques is growing. Nevertheless, the wide variety of treatment techniques and dose fractionation schemes reported in the literature indicates that there is, as yet, no consensus for a standard approach for stereotactic radiotherapy of pulmonary metastases.

Siva et al. published a recent review about pulmonary oligometastases treated with SBRT. Median follow-up ranged from 9 to 22 months. That study reported a 2-year LC and OS of 77.9% and 53.7%, respectively, and grade 3 or higher toxicity of 2.6% [5]. The majority of the studies included in that review evaluated metastases from mixed primary tumors. Indeed, only 6-29% of the lesions originated from CRC.

Histology seems to be an important factor

of LC. Takeda et al. [25] published their experience regarding LC with CRC lung metastases and lung metastases from other primaries and primary lung tumors. In a multivariate analysis they showed that metastases from CRC had poorer LC. Milano et al. [26] prospectively analyzed 121 patients with 1-5 metastatic lesions in 1-3 metastatic regions. Breast primary had better LC at 1 year (87%) compared to non-breast primary tumors (74%). As a result, it appears that histology is an important prognostic factor to consider when treating lung metastases. In our study, our homogeneous sample of CRC lung metastases had high rates of LC.

Other authors have also reported good results. Oh et al. showed a LC rate of 94.5% with a 2-year OS of 57.2% [27], while Osti et al. reported 1- and 2-year LC rates of 89.1% and 82.1%, respectively. In terms of LC and survival, our rates are similar to figures reported by other authors [5,20,27]. However, we could not find any clinical or statistically significant association between LC or OS and any patient- or treatment-related parameters. This is probably due to the small sample size but also because there was only one death and one case of local progression in our small sample.

Some series have shown that there might be a relationship between large lesions and propensity of treatment failure [20,28]. However, there is a considerable variation in the target size, and this is important because a larger size has been associated with severe toxicity [5]. According to Oh et al., tumors < 2.5 cm had a more favorable survival profile (64 vs 38.9% at 2 years; p=0.032) [26]. In our study, median nodule size was rather small (10 mm) and only one patient showed local failure. This may be why we found no correlation between nodule size and LC or survival. Some authors [29] are using dose risk adapted schemes that account for lesion location and size, with reported LC rates at 1 and 2 years of 95 and 89%, respectively, without >2 grade toxicities.

Another important factor for LC in CRC metastases is the dose per fraction and nominal dose. Bae et al. [30] showed LC at 3 years of 64% in 41 patients with 51 CRC metastases. However, only 12 metastases in that study were lung metastases.

BED has been studied as one of the factors that influences LC and survival. Recently, Wulf et al. stated that there is a steep increase in tumor control probability for isocenter doses >94 Gy BED [28]. Although our results did not achieve statistical significance, there was a tendency towards better complete response and higher DPFS in patients with a total dose >120 Gy BED. Similar results have been reported by other authors [20] .

Single-dose schemes have been used successfully for lung metastases by some authors. Ricardi et al. [31] published a study with 55 patients with a single dose of 26 Gy and 22 who received 45 Gy in 3 fractions and 3 with 36 Gy in 4 fractions. In that study, LC rates at 2 years were 89% with only one case of grade 3 toxicity. In our study, the monofraction (34 Gy) results should be interpreted with caution as the linear quadratic (LQ) equation, used to calculate BEDs at very large doses per fraction, failed to predict tumor control [20]. Only one patient died during follow-up. Thus, we could not find any statistically significant association between survival and the previously-mentioned parameters.

In terms of age, although we found that the patients aged ≤ 70 years had a better DPFS, this result was not significant. Interestingly, the median time to systemic progression in the entire patient sample was 9 months. In contrast, patients with more favorable parameters (such as BED >120, age ≤70 and fractionated treatment) had a notably longer DPFS (14 months). In our opinion, DPFS is highly important for this group of patients. OS and LC are assuredly two of the most relevant endpoints in the oligometastatic setting. However, DPFS is also an important end point to be considered, especially given that the longer the DFS, the less the systemic treatment will be needed (and this supports the benefits of SBRT in terms of its low toxicity profile and efficacy). This issue may be even more important for older patients, whose quality of life is often adversely affected by their treatment as well as the disease itself.

Finally, the objective of SBRT in most patients is to control metastases and to delay disease progression and, therefore, the need for further treatment. However, it is important to keep in mind that, for some authors [9,30], there is sufficient evidence accumulated to date to believe that even cure is possible for a subgroup of patients. To identify the population with oligometastatic disease and better outcomes, De Vin et al. [33] presented 4 prognostic factors from different primary sub-sites which impaired OS: non adenocarcinoma, intracranial metastases, synchronous oligometastatic disease at diagnosis, and male sex. However, to assess whether SBRT really does improve PFS or cure some patients, randomized trials will be essential.

Limitations and considerations

This study has a number of shortcomings. The most obvious is the small sample size, which impedes valid multivariate analysis; similarly, the short follow-up us precludes us from drawing any definitive conclusions regarding outcomes and late toxicity. Despite these limitations, it is important to note that the present study addresses an area - lung metastases of CRC origin treated by SBRT- about which very little research has been carried out. Although many studies have evaluated outcomes of both primary non-small cell lung cancer (NSCLC) and oligometastatic lung lesions, most have done so with a wide variety of treatment techniques [5] and primary tumors. In fact, most of the published series report heterogeneous data that include patients with lung metastases from different type of primary tumors [18,20,30]. In contrast, although our study was small, it included a homogeneous, prospectively evaluated cohort of patients with solitary lung metastases from CRC.

Based on the preliminary findings presented herein, SBRT should be considered as a treatment option in selected patients with lung oligometastases from CRC. Certain parameters may be associated with a better DPFS, such as age ≤70 years, BED >120 and a fractionated treatment. We are currently carrying out a phase II Dose-Risk Adapted trial which will validate the initial results presented herein [11]. We also expect the current trial will help determine the prognostic factors that may help to design new treatment strategies in this subset of patients.

Conclusion

Our data show that SBRT is a safe and effective treatment for highly selected patients presenting lung oligometastases from CRC. The preliminary data suggest that this technique may even be considered a non-invasive alternative to surgery. SBRT appears to offer excellent LC and survival in this patient subset. Our findings also suggest that younger patients (≤70 years) who received larger doses (total BED >120 Gy) in a fractionated regimen have improved DPFS outcomes. Further recruitment and follow-up is necessary to assess the long-term outcomes.

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