Original Article

Long term control stereotactic body radiotherapy (SBRT) for oligometastatic colorectal cancer: a single center study

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Background: To evaluate survival after stereotactic body radiotherapy (SBRT) as radical treatment for metastases of colorectal cancer (CRC) and to identify prognostic factors after treatment.

Methods: Patients with metastatic CRC treated with SBRT on metastatic lesions were retrospectively analyzed between February 2012 and August 2016 at the General University Hospital of Valencia. The follow-up was carried out until July 15, 2018. The data have been collected in a database. Patients may have received prior systemic therapy and/or resection of metastatic disease. Endpoints were timed from end of SBRT and included overall survival (OS) and progression-free survival (PFS). Univariate and multivariate analysis using Cox proportional hazard modeling was used to identify prognostic factors.

Results: A total of 49 patients were identified. Before SBRT, 77.5% of the patients have received systemic therapy and 65.2% surgery for metastatic disease. Of metastatic lesions treated with SBRT 53.1% were located in the lung, 30.6% in the liver and 16.3% in other locations. Median survival were: PFS after treatment with SBRT was 9.9 months (95% CI: 4.64–15.1) and the median OS was 28.9 months (95% CI: 19.0–38.7). No relapses were observed in 20% of the patients after SBRT. The treatment was well tolerated and no patient had grade 3 or 4 adverse effects. Right colon [HR 16.53 (95% CI: 3.11–87.87), P value 0.001] and higher tumor stage (III–IV) [HR 12.30 (95% CI: 2.10–71.92), P value 0.005] showed a lower OS in a multivariate analysis.

Conclusions: SBRT for oligometastatic disease is an effective option for patients with advanced CRC, with encorauging survival outcomes. However, a definitive validation in large randomized studies is required.

Keywords: Stereotactic body radiotherapy (SBRT); colorectal cancer (CRC)

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Introduction

Colorectal cancer (CRC) is the second most commonly diagnosed cancer in Europe and the second cause of death both in Europe and worldwide (1). Early detection of CRC is associated with 5-year survival rates as high as 93% in patients staged T1/2N0M0, but 25% of the patients have metastases at diagnosis and 50% will develop them during the evolution of the disease.

Systemic therapy is the gold standard of care in stage IV CRC with median OS of 30 months approximately (2). Colorectal tumors frequently have solitary or oligometastases

(1–5 lesions), being the liver and lung the most affected organs. Surgical treatment of resectable disease in the metastatic setting has increased OS (3-5). Different alternatives to surgery in non-resectable patients have been explored, such as radiofrequency ablation (RFA) and radiotherapy (6,7). Technological advances in the radiotherapy landscape, have allowed the introduction of stereotactic body radiotherapy (SBRT). SBRT involves a very accurate delivery of a high radiation dose in a small number of fractions to a target with narrow margins. The limited volume of normal tissue exposed to radiation is potentially attractive, and the high dose per fraction, with low number of treatment fractions is appealing because of the potential for immune effects (8). The use of SBRT has reported promising results allowing local control up to 90% at 2 years (9). However, the optimal time of administration is unknown. It is necessary to identify prognostic factors that can be useful to select those patients who can benefit from this treatment.

The aim of this study is to assess the efficacy and toxicity profile of SBRT as a treatment modality in a cohort of patients with metastatic CRC.

Methods

Study population and ethics

Retrospective study of all consecutive patients with diagnosis of metastatic CRC treated with SBRT on metastatic lesions in different locations between February 2012 and August 2016 at the General University Hospital of Valencia. The variables collected in the study were age, sex, location of the primary tumor, date of surgery, stage of the disease at diagnosis (TNM 8th), mutational status of genes *RAS*, location and number of metastases and type of relapse. Patients could have previously received treatment both primary and metastatic disease.

Baseline disease extension and tumor response evaluation was carried out by CT scans. Tumor response was evaluated according to RECIST 1.1 criteria.

Follow-up patient parameters (time of relapse and exitus) were recorded since time of study inclusion until 15 July 2018. The study was approved by The Clinical Research Ethics Committee of General University Hospital of Valencia, in accordance with the Declaration of Helsinki, the Good Clinical Practices and local ethical and legal requirements (Spanish laws). This study complied with all applicable regulations for human participant studies. All authors reviewed and approved the final manuscript.

SBRT treatment

All patients underwent TAC planning gating with WING-BOARD immobilization system and abdominal compression system for respiratory control (Dumpening) that are also used during treatment. The treatment volume (ITV) is generated with the MIM contouring system and the planning is done using Pinnacle.

We define the PTV as the ITV generated from the union of the different GTVs of the TAC 4D plus a volumetric expansion of 5 mm. Dose was prescribed to the isocenter and the PTV was covered by at least 95% of the prescription dose. The patients are treated in a TRUEBEAM linear accelerator, positioning themselves with KV and subsequent verification CONEBEAM, which is performed pre- and post-treatment. SBRT was delivered using conformal arcs or multiple fixed no-coplanar beams, shaped with multileaf collimators, with 6Mv FFF photons. The dose per fraction and total dose were determined using the dose volume histogram (HDV) of the organs at risk.

The fraction dose, in lung metastases, is established following a risk-adapted fractionation of the Dutch Senan group (3×20 Gy in small tumors not close to the costal wall or central location, 5×12 Gy in larger tumors and/or close to the costal wall and 8×7.5 Gy in central tumors location—located less than 2 cm from the main tracheobronchial system). In case of liver or lymph node metastases the dose is established based on the consensus established by SEOR in 2014 with the objective of obtaining total doses with biologically effective dose (BED) 10 Gy >100 Gy. Toxicity was evaluated according to RTOG criteria.

The patients have a follow-up weekly during the treatment and image scans were performed every 3 months during the first year.

Statistical methods

All statistical analyses were performed using the SPSS statistical package, version 22 (SPSS, Inc., Chicago, IL, USA). A descriptive statistics analysis including absolute and relative frequencies for categorical variables was performed. A logistic regression multivariate analysis was performed introducing the variables which were significant in the univariate analysis in the model. The survival curve was estimated using the Kaplan-Meier method and compared using the log-rank test. Statistical survival analyzes were

Table 1 Patient and tumor characteristics

Variable	Number of patients (%)
Sex	
Men	32 (65.3)
Women	17 (34.7)
Age	
Median	74
Range	42–86
Stage at diagnosis	
I	5 (10.2)
II	5 (10.2)
III	10 (20.4)
IV	29 (59.2)
Primary tumor location	
Right	5 (10.2)
Left	43 (87.8)
Timing of SBRT	
Synchronous	8 (16.3)
1st recurrence	14 (28.6)
2nd recurrence	12 (24.5)
3rd or more recurrence	15 (30.6)
Previous chemotherapy before SBRT	
No	11 (22.4)
One line	15 (30.6)
Two lines	14 (28.6)
Three or more lines	9 (18.4)
Previous surgery before SBRT	
No	17 (34.7)
One surgery	20 (40.8)
Two surgeries	5 (10.2)
Three or more surgeries	7 (14.3)
Metastases location	
Lung	26 (53.1)
Liver	15 (30.6)
Other (lymph node, adrenal)	8 (16.3)
CEA level	
≤3	19 (38.8)
>3	30 (61.2)

SBRT, stereotactic body radiotherapy.

performed using the Kaplan-Meier method and the log-rank statistic. The SLP in months was calculated taking into account the date of the end of treatment with SBRT until the date of the tumor recurrence or the last patient follow-up and the overall survival (OS) taking into account the date of surgery of the primary tumor, by means of the following formula: 12 × (End Date – Start Date)/365.25. The multivariate analysis to evaluate the independent prognostic values was performed using the Cox regression method. For this, all variables that were significant in the univariate analysis and those in which the P value was close to statistical significance were included.

All reported P values were the result of two-sided tests, with $P<0.05$ considered statistically significant.

Results

Patient characteristics

A total of 49 patients were included in the study (65.3% men). The average age was 70 years. The main patient and tumor characteristics are summarized in *Table 1*. It should be note that only 10% of primary tumors were located in the right colon. Sixty percent of patients were metastatic at diagnosis. The population was highly pretreated with almost 50% of the patients had received 2 or more previous ChT lines.

Sixty-five point two percent of patients had undergone surgery for metastatic disease prior to treatment with SBRT. Regarding the surgery of the metastases, 65% had been operated in some occasion, with 10% of the patients operated 2 or more times. The main location of the lesions treated with SBRT was pulmonary (53.1%).

Treatment and toxicity

The total dose received in the treatment of SBRT was 45 Gy in 57.4% of the cases (fractionation of 1,500 cGy/session, 3 sessions, BED 93.8 Gy). Twenty-four point five percent received a dose of 60 Gy (fractionation of 2,000 cGy/session, 3 sessions, BED 2,000 Gy). The 18.5% received a total dose between 30 and 40 Gy, and 1.9% a dose of 50 Gy.

The treatment was well tolerated. The most frequent adverse effects are described in *Table 2*. No patient had grade 3 or 4 adverse effects.

OS and progression free survival

The median follow-up was 26.1 months. The PFS after

Table 2 Frequency of toxicities after SBRT treatment

Type of toxicity	Total grade I and II, n (%)
Asthenia	12 (24.5)
Anorexy	4 (8.2)
Pulmonary	0
Cardiac	0
Digestive	1 (2.0)
Cutaneous	1 (2.0)

SBRT, stereotactic body radiotherapy.

Table 3 Univariate analysis of prognostic factors associated with overall survival

Factors	N	Median OS (months)	P value
Stage			0.054
I–II	10	19.94	
III–IV	39	5.7	
Sex			0.020
Men	32	47.9	
Women	17	19.68	
Age			0.846
<65	17	28.87	
>65	32	26.48	
RAS status			0.06
Mutated	21	33.28	
Not mutated	21	19.68	
Tumor location			0.014
Right	6	6.70	
Left	43	30.32	
Type of metastases			0.61
Sincronous	8	9.95	
Metachronous	41	28.87	
Previous chemotherapy			0.285
Non or one line	26	17.38	
Two or more lines	23	30.32	
Previous surgery			0.304
Non or one	37	22.3	
Two or more	12	32.13	

Table 3 (*continued*)

Factors	N	Median OS (months)	P value
Location of metastases			0.397
Lung	26	20.43	
Liver	15	49.11	
Other	8	28.15	
Number of relapse			0.0883
First	14	22.30	
Second or more	35	28.87	
CEA level			0.218
≤3	19	22.30	
>3	30	32.13	
Total doses (Gy)			0.707
<45	9	49.11	
45	27	22.30	
>45	13	28.87	
Stage			<0.053
I–II	10	19.94	
III–IV	39	5.7	

treatment with SBRT was 9.9 months (95% CI: 4.64–15.1) (*Figure 1*) and the median OS was 28.9 months (95% CI: 19.0–38.7) (*Figure 2*). No relapses were observed in 20% of the patients after SBRT. In this subgroup of patients, the median PFS was 41.82 months (95% CI: 24.83–58.81 months).

Factors affecting the treatment outcomes

The univariate survival analysis showed a lower PFS in female (P value =0.05), higher tumor stage (P value =0.054), age more than 70 years (P value =0.012) and previous treatment with chemotherapy (P value =0.07). In multivariate analysis, no factor showed significant influence on PFS.

The univariate survival analysis showed a lower OS in female (P value =0.020), *RAS* mutated tumors (P value =0.06), right colon tumors (P value =0.014) and higher tumor stage (III–IV *vs.* I–II) (P value <0.053). Univariate analysis of prognostic factors associated with OS was shown in *Table 3*.

In multivariate analysis, right colon [HR 16.53 (95% CI:

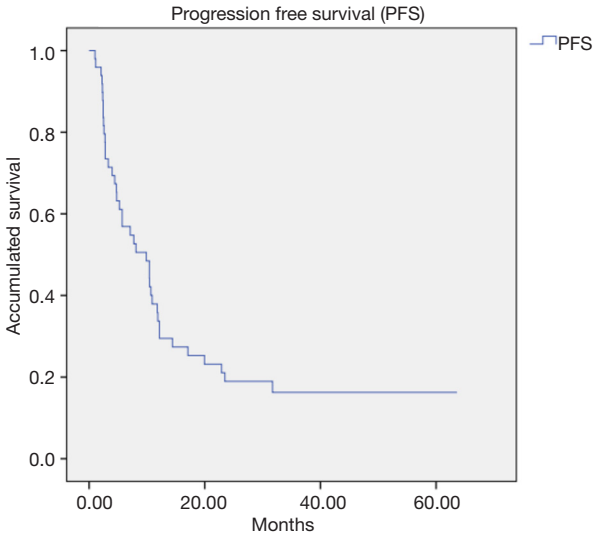

Figure 1 Progression free survival in all population in study with SBRT treatment. SBRT, stereotactic body radiotherapy.

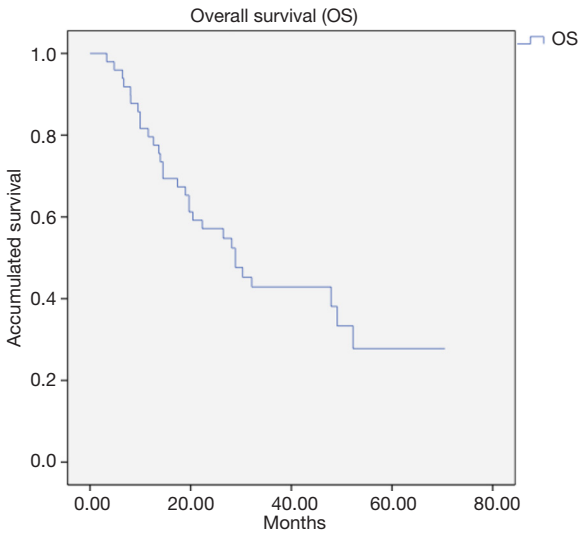

Figure 2 Overall survival (OS) in all population with SBRT treatment. SBRT, stereotactic body radiotherapy.

3.11–87.87), P value 0.001] and higher tumor stage (III–IV) [HR 12.30 (95% CI: 2.10–71.92), P value 0.005] showed a lower OS. No impact on OS was observed regarding sex, *RAS* status or location of metastases.

Discussion

SBRT is a minimally invasive radiation technology that can provide a large dose of highly focused ionizing radiation to the target tumor and reduce normal tissue toxicity. For CRC, some series reported 5-year survival rate of 52% for patients who have one metastasectomy for pulmonary metastasis and 57.9% for patients who have a second surgery (10). However, there are patients in whom surgery is not indicated due mainly to previous interventions, localization of the disease or comorbidities (11-13). In this scenery, it is necessary to develop new local treatment modalities. SBRT as a radical treatment for oligometastatic disease has emerged as a treatment well tolerated by patients, with high rates of local control and that prolong survival. In retrospective series SBRT offers local control (LC) up to 90% at 2 years (14,15).

Several authors have reported a survival benefit with SBRT in oligometastatic disease. So far the liver location is the best studied with both retrospective and prospective studies. OS have been described that vary from 50% to 100% per year, from 32% to 91% at 2 years and from 60% to 85% at 3 years (7,9,11,12). Lung metastases from retrospective studies show a local control of 77% a year and 67% at 3 years with OS data of 64% to 73% at 2 years (14-17).

According to these results, the median OS of the subgroup of liver metastasis and pulmonary metastases of our study was 49.11 (95% CI: 7.8–90.3) and 20.43 (95% CI: 13.2–27.6) months respectively. The results of the cohort including 16.3% of metastases in other locations showed a median OS of 28.9 (95% CI: 19.0–38.7) months. This benefit in survival is clinically relevant considering that it is a population that is generally very pre-treated, both with previous systemic and local treatment. At the same time, the 10-month median PFS obtained allows patients to have long periods of time without receiving systematic treatment, thus decreasing toxicity and improving their quality of life.

It should be noted that 20% of patients did not relapse after treatment with SBRT during the follow-up of the study, opening the door for an important percentage of patients to obtain a lasting control of the disease.

In all analyzed studies, SBRT show a very low rate toxicity, without adverse effects grade 3–4 (16-19), as we have also observed in our study. The most frequent side effect was asthenia (present in 24.5% of patients), being grade I and II. As we said before, our series was composed of a population that had received many previous treatments, both chemotherapy and surgery and that the good tolerability of the SBRT allows lengthening survival while maintaining the quality of life, a very important factor in this patient subgroup.

Some authors have suggested a greater benefit in the local control of the disease and a good survival associated with high doses of treatment and higher BED (11,18,19). However, the multivariate analysis of our series has not shown a correlation of any of these parameters with survival. On the other hand, it is difficult to establish an ideal treatment dose for different locations due to low unification of published results.

This study has some limitations due to the small sample size, the retrospective design, and the heterogeneity of the cohort. Future large and prospective studies and unified reporting protocol are necessary to establish the role of SBRT in the treatment of oligometastatic disease of CRC.

In conclusion, SBRT can contribute to the local control of the disease and increase the survival of patients with oligometastatic CRC. It is important to discuss each case within a multidisciplinary team to establish the optimal therapeutic sequence with systemic treatments and other local treatments.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/cco.2020.01.10). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by The Clinical Research Ethics Committee of General University Hospital of Valencia, in accordance with the Declaration of Helsinki, the Good Clinical Practices and local ethical and legal requirements (Spanish laws). This study complied with all applicable regulations for human participant studies.

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