Original Article

# Predictive factors for survival of oligometastatic colorectal cancer treated with Stereotactic body radiation therapy

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ARTICLE INFO

ABSTRACT

*Background and purpose:* Colorectal cancer (CRC) represents one of the major leading causes of death from cancer. Aim of the present study was to analyze outcome of oligometastatic CRC patients treated with stereotactic body radiation therapy (SBRT), and to evaluate predictive factors of survival.
*Materials and methods:* We included patients with maximum 5 metastases. Previous/concomitant systemic treatments were allowed. End points of the present study were the outcome in terms of Local control of treated metastases (LC), progression free survival (PFS), and overall survival (OS).
*Results:* 437 metastases were treated in 270 patients. Lung was site of metastases in 48.5% of cases, followed by liver (36.4%). Systemic treatment was administered before SBRT in 199 patients (73.7%). Median follow-up time was 23 months (3–98.7). Rates of LC at 1, 3 and 5 years were 95%, 73% and 73%, respectively. Time from diagnosis of metastases to SBRT was the only factor predictive of LC (HR 1.62, $p = 0.023$). Median PFS was 8.6 months. Rates of OS at 1, 3 and 5 years were 88.5%, 56.6%, and 37.2%, respectively. Lesion greater than 30 mm (HR 1.82, $p = 0.030$), presence of non-lung metastases (HR 1.67, $p = 0.020$), the use of systemic treatment before SBRT (HR 1.82, $p = 0.023$), and progression of treated metastases (HR 1.80, $p = 0.007$), were all predictive of worse OS.
*Conclusions:* Stereotactic body radiation therapy represents an effective approach in the management of oligometastatic CRC. Control of treated oligometastases seems to be a strong positive predictive factor for both PFS and OS.

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Colorectal cancer (CRC) represents one of the major leading causes of death from cancer [1,2]. Metastases at diagnosis are observed in 20% of patients and up to 50% will develop metachronous metastases [1]. Commonest site of metastases from CRC is liver, followed by lung and bone [2]. The prolongation of survival CRC patients with the introduction of new systemic treatments increased the relevance of local approaches in the oligometastatic setting. Results show that patients resected for liver metastases from CRC can reach 5-year survival rates higher than 50% [3,4], and 10-year survival up to about 40% [5–7]. However, due to disease's or patient's characteristics, a high percentage of cases are not candidate to metastasectomy, thus alternative local approaches are taken into account. Stereotactic body radiotherapy (SBRT) is a high-precision radiation technique that uses ablative doses to treat isolated sites of cancer, both primary and secondary. The main advantages of radiation therapy (RT), compared to surgery, are no need for general anesthesia, lower morbidity, good

immediate tolerance and ambulatory treatment. Moreover, the use of high-dose per fraction results in biologic effects different from what observed with conventional RT and yields optimal rates of control of treated tumor, generally higher than 85%. Ricco et al. [8] evaluated survival and local control (LC) of patients diagnosed with lung metastases treated with SBRT from an RSSearch® Patient Registry. Three hundred four patients with 327 lesions were evaluated and majority of patients had colorectal primary tumor (25.7%). Median overall survival (OS) for the CRC subgroup was 30 months with 3-year rate of 35.8%. The authors didn't observe any difference in LC by primary histologic type ($p = 0.49$) and overall LC at 1-year was 80.4%. However differences in outcome base on primary histology have been found in patients treated with SBRT. Ahmed et al. [9] tested a multigene expression index for tumor radiosensitivity and observed that colorectal adenocarcinoma appeared as one of the most radioresistant tumor compared to others such as breast and lung cancer. The 1- and 2-year rates of LC for colorectal lesions were found to be 79% and 59%, respectively, compared to 100% for non-colorectal lesions ($p = 0.019$). To the best of our knowledge, this study represents the largest monocentric series of extracranial colorectal metastases treated

with SBRT. Our aim was to analyze the outcome of oligometastatic CRC patients treated with SBRT, and to evaluate predictive factors of survival.

## Materials and methods

### Study population

We included in the analysis patients with histologically confirmed diagnosis of colorectal adenocarcinoma, treated with surgery with or without adjuvant chemotherapy, who were diagnosed with metachronous or synchronous metastases. The multidisciplinary team discussed all cases. The local ethics committee approved the analysis. Patients were candidate to SBRT if a maximum of 5 metastases were diagnosed in a maximum of 2 sites. Previous or concomitant systemic treatments were allowed. Patients with lung and liver metastases were treated with SBRT if not suitable for surgery for patients' comorbidities. All patients were staged with CT, MRI or PET scan according to physician choice. The study was conducted in accordance with Good Clinical Practice guidelines, the ethical principles of the Declaration of Helsinki and local regulations.

### Techniques of radiotherapy

The clinical target volume (CTV) was equal to gross tumor volume (GTV) for all lesions and was delineated on simulation CT imaging, co-registered with MRI scan or PET scan when available. In case of disease located into organ subject to internal movement (such as lung or liver), patients were simulated with 4D-CT scan. In case of treatment on liver lesion, an abdominal compression was used in order to reduce organ internal movement. A margin of 5–10 mm, depending on disease site and dimensions, was added to CTV to obtain the planning target volume (PTV).

### Response assessment

First evaluation was planned 3 months after the end of the SBRT and then every 3 months for the first year and every 6 months from the second to the fifth year. Follow-up visits included clinical evaluation and diagnostic imaging (CT, MRI or PET scan) planned at physician's choice. Tumor response was classified according to European Organization for Research and Treatment of Cancer Response Evaluation Criteria In Solid Tumours (EORTC-RECIST) criteria version 1.16. PET Response Criteria in Solid Tumors (PERCIST) [10] were used to evaluate metabolic response in patients who underwent PET scan for restaging.

### Statistical analysis

Data were collected and analyzed retrospectively. End points of the present study were the outcome in terms of LC, progression free survival (PFS), and OS. The analysis of LC was conducted at lesion's level and defined as the time from the beginning of SBRT to the progression of treated metastases or last follow-up. Time from SBRT to the progression of in-field or out-field metastases was defined as PFS. Overall survival was calculated from the SBRT treatment to either death or last follow-up. Univariate analysis was performed with the log-rank test, and Cox proportional hazards regression was used to estimate hazard ratios (HR). Multivariable stepwise cox regression analysis was performed to evaluate the association between clinical factors and survival, with a significance level of $p < 0.05$. Statistical calculations were performed using STATA, version 13.

**Table 1**
Patient's characteristics.

| | N. 270 patients\|437 lesions (%) |
|---|---|
| Age median (range): | 69.1 (31.9–90.6) |
| ≤65 | 82 (30.4%) |
| >65 | 188 (69.6%) |
| Sex | |
| Female | 80 (29.6%) |
| Male | 190 (70.4%) |
| PS: | |
| 0 | 200 (74.1%) |
| 1 | 42 (15.6%) |
| 2 | 26 (9.6%) |
| 3 | 2 (0.7%) |
| Time to metastases, median (range) | 23.5 months (0–126.6) |
| ≤24 months | 139 (51.5%) |
| >24 months | 131 (48.5%) |
| Site of treated metastases (per lesion) | |
| Lung | 212 (48.5%) |
| Liver | 159 (36.4%) |
| Lymph nodes | 54 (12.4%) |
| Adrenal glands | 8 (1.8%) |
| Bones | 2 (0.5%) |
| Pancreas | 2 (0.5%) |
| Metastases in other organs not treated with SBRT | |
| No | 165 (61.1%) |
| Yes | 105 (38.9%) |
| Number of lesion treated simultaneously | |
| 1 | 160 (59.3%) |
| 2 | 69 (25.6%) |
| 3 | 34 (12.6%) |
| 4 | 4 (1.4%) |
| 5 | 3 (1.1%) |
| Number of internal organs treated simultaneously | |
| 1 | 237 (87.8%) |
| ≥2 | 33 (12.2%) |
| KRAS status | |
| Wild type | 44 (16.3%) |
| Mutated | 62 (23%) |
| Unknown | 164 (60.1%) |
| CTV mm (range): | 23 (9–71 mm) |
| ≤30 | 317 (72.5%) |
| >30 | 120 (27.5%) |
| Systemic therapy before SBRT | |
| No | 71 (26.3%) |
| Yes | 199 (73.7%) |
| Systemic therapy after SBRT | |
| No | 202 (74.8%) |
| Yes | 68 (25.2%) |
| Lines of systemic therapies before SBRT | |
| 0 | 71 (26.3%) |
| 1 | 83 (30.7%) |
| 2 | 72 (26.7%) |
| ≥3 | 44 (16.3%) |
| Time from metastases to SBRT median (range) | 10 (0–157.7) |
| ≤12 months | 154 (57%) |
| >12 months | 116 (43%) |
| Total dose Gy, median (range) | 48 (25–75) |
| ≤60 Gy | 332 (76%) |
| >60 Gy | 105 (24%) |
| Dose per fractions Gy, median (range) | 12 (5–30) |
| ≤12 Gy | 278 (63.6%) |
| >12 Gy | 159 (36.4%) |
| Number of fractions, median (range) | 4 (1–8) |
| BED10 Gy, median (range) | 105.6 (37.5–262.5) |
| ≤100 Gy | 94 (21.5%) |
| >100 Gy | 343 (78.5%) |

## Results

From 2008 to 2018 a total of 270 patients were treated with SBRT on 437 metastases from CRC. Patients', disease's and treatment's characteristics are summarized in Table 1. Median age was 69.1 years (31.9–90.6) and majority of the patients was male (70.4%). Median time from diagnosis of primary tumour to metastases was 23.5 months (0–126.6). Lung was site of metastases in 48.5% of cases, followed by liver (36.4%) and lymph nodes (12.4%). Single internal organ was treated in 237 (87.8%) patients. Majority of patients (160, 59.3%) was treated on one lesion. Status of KRAS was analyzed 106 patients and resulted mutated in 23% of cases. Median target volume was 23 mm (9–71 mm). Systemic treatment was administered before SBRT in 199 patients (73.7%) and after SBRT in 68 patients (25.2%). Median time from diagnosis of metastases to RT treatment was 10 months (0–157.7) and median total prescribed dose 48 Gy (25–75) erogated in a median dose per fraction of 12 Gy (5–30). After conversion of dose according to BED10, median value was 105.6 Gy (37.5–262.5) and 343 lesions (78.5%) were treated with more than 100 Gy.

Median follow-up time was 23 months (3–98.7). At reevaluation, best local response was classified as complete response in 249 (56.98%) lesions, partial response in 76 (17.39%) lesions, and stable disease in 71 patients (16.25%). Forty-one (9.38%) lesions didn't receive benefit from SBRT and progressed after first evaluation. In-field local relapse was observed in 89 lesions (20.4%) and 58 patients (21.5%). Median time to lesions' progression was 17.3 months (1.5–98.3). Rates of LC at 1, 3 and 5 years were 95% (95%CI 92–96%), 73% (95%CI 67–77%) and 73% (95%CI 67–77%) as shown in Fig. 1. Median LC was not reached. At analysis of correlation between risk factors and LC, time from diagnosis of metastases to SBRT (HR 1.62, 95%CI 1.06–2.46, p = 0.023) was impacting on control of treated metastases. None of the analyzed factor was significant at multivariable analysis (Table 2).

Median PFS was 8.6 months for the whole group. Rates of PFS at 1, 3 and 5 years were 39.2% (95%CI 33.3–45.2%), 14.3% (95%CI 9.7–19.8%), 13.5% (95%CI 8.9–19%) as shown in Fig. 2. The majority of patients relapse outside the field of irradiation (n = 197, 73%). Among patients with out-field progression, 31.9% relapsed in the same organ, 59.4% relapsed in different organs, and 8.7% in both the same and different organs. Eighty-eight (32.6%) patients had oligometastatic disease at progression. In-field progression (HR 1.81; 95%CI 1.32–2.46, p = 0.000), the administration of systemic treatment before SBRT (HR 1.75; 95%CI 1.26–2.43, p = 0.001), the increasing number of lines of systemic treatment (HR 1.29; 95%CI 1.13–1.47, p = 0.000), more than one treated organs (HR 1.51; 95% CI 1.01–2.24, p = 0.041), and PS (HR 0.81; 95%CI 0.65–0.99, p = 0.049) were impacting on PFS at univariate analysis. At multivariable analysis in-field progression was a significant negative predictive factor (HR 1.86; 95%CI 1.36–2.54, p = 0.000), together with increasing number of lines of systemic treatment (HR 1.32; 95%CI 1.16–1.50, p = 0.000) as shown in Table 3. Median PFS was 7.3 months in patients with progression of treated metastases and 9.8 months in patients with metastases controlled by SBRT.
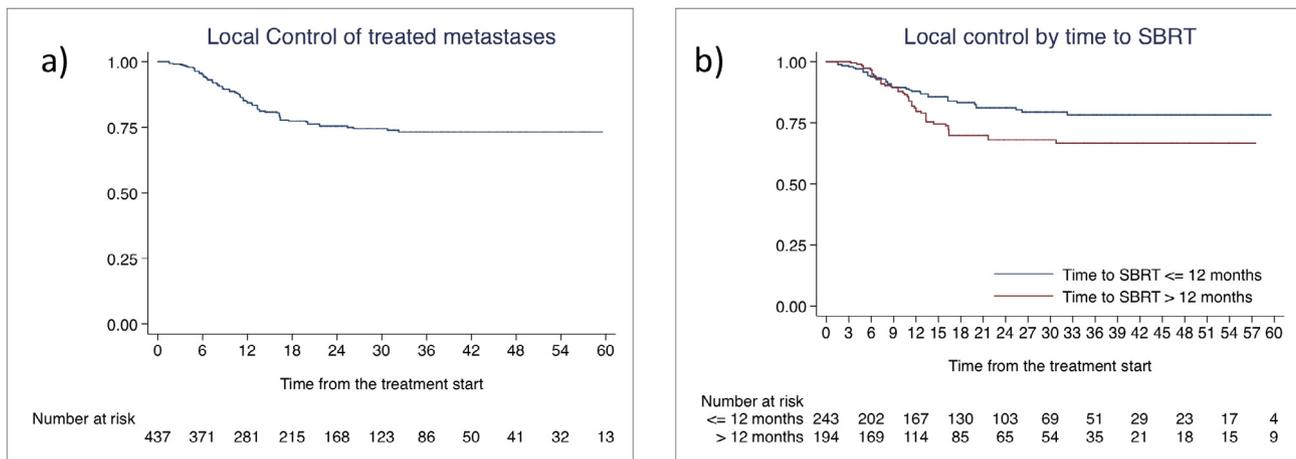


**Fig. 1.** Kaplan–Meier's curves of local control for treated metastases (a) and according to time from diagnosis of metastases to SBRT (b).

**Table 2**
Univariate and multivariable analysis for local control of treated metastas.

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | HR (95% CI) | P value | | |
| Age >65 | 1.03 (0.64–1.66) | 0.884 | – | – |
| Sex, Male | 0.76 (0.49–1.18) | 0.227 | – | – |
| PS | 1.13 (0.86–1.50) | 0.366 | – | – |
| Time to metastases, >24 months | 0.72 (0.47–1.11) | 0.142 | – | – |
| Number of treated lesions | 1.06 (0.88–1.27) | 0.513 | – | – |
| Site of treated metastases, non-lung vs lung | 1.15 (0.76–1.75) | 0.486 | – | – |
| Number of treated organ, ≥2 | 0.93 (0.53–1.62) | 0.807 | – | – |
| CTV mm, >30 | 1.27 (0.80–2.02) | 0.293 | – | – |
| Systemic therapy before SBRT | 0.98 (0.62–1.56) | 0.950 | – | – |
| Lines of systemic therapies before SBRT | 1.05 (0.86–1.27) | 0.610 | – | – |
| Time from metastases to SBRT, >12 months | **1.62 (1.06–2.46)** | **0.023** | **1.62 (1.06–2.46)** | **0.023** |
| BED10 Gy, >100 Gy | 0.77 (0.47–1.27) | 0.316 | – | - |

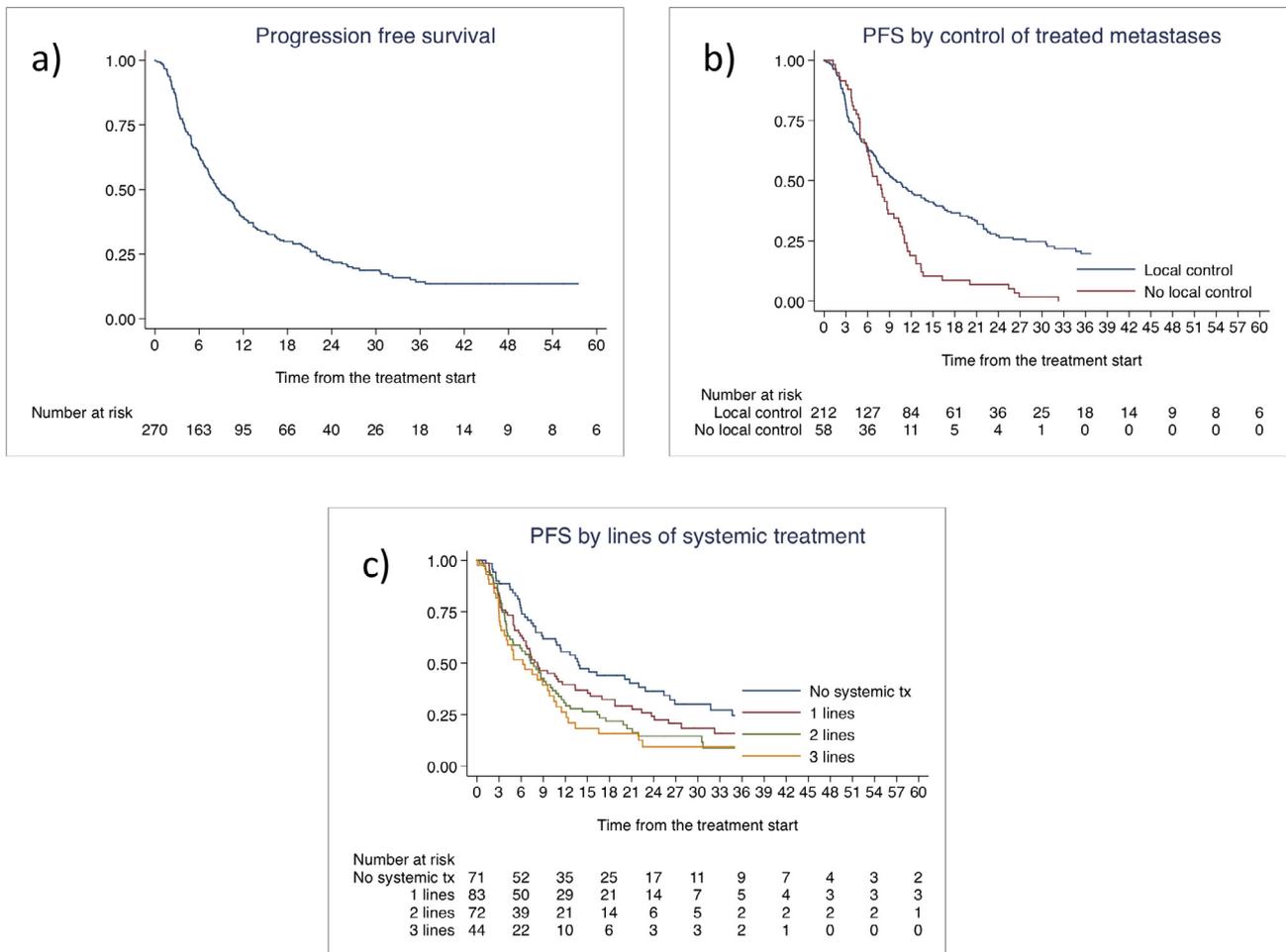In bold values considered as statistically significant (*p* value < 0.05).

**Fig. 2.** Kaplan–Meier's curves of Progression Free Survival for all patients (a), according to control of treated metastases (b) and according to lines of systemic treatments before SBRT.

**Table 3**
Univariate and multivariable analysis for Progression free survival.

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | HR (95% CI) | P value | | |
| Age >65 | 0.89 (0.66–1.20) | 0.476 | – | – |
| Sex, Male | 0.94 (0.69–1.27) | 0.697 | – | – |
| PS | **0.81 (0.65–0.99)** | **0.049** | – | – |
| Time to metastases, >24 months | 0.97 (0.73–1.27) | 0.831 | – | – |
| Number of treated lesions | 1.14 (0.99–1.32) | 0.061 | – | – |
| Site of treated metastases, non-lung vs lung | 1.01 (0.76–1.32) | 0.935 | – | – |
| Number of treated organ, ≥2 | **1.51 (1.01–2.24)** | **0.041** | – | – |
| CTV mm, >30 | 1.00 (0.76–1.34) | 0.947 | – | – |
| Systemic therapy before SBRT | **1.75 (1.26–2.43)** | **0.001** | – | – |
| Lines of systemic therapies before SBRT | **1.29 (1.13–1.47)** | **0.000** | **1.32 (1.16–1.50)** | **0.000** |
| Time from metastases to SBRT, >12 months | 1.10 (0.83–1.44) | 0.495 | – | – |
| BED10 Gy, >100 Gy | 0.74 (0.54–1.01) | 0.065 | – | – |
| Control of treated metastases | **1.81 (1.32–2.46)** | **0.000** | **1.86 (1.36–2.54)** | **0.000** |

In bold values considered as statistically significant (p value < 0.05).

Median OS was 39 months (Fig. 3). Rates of OS at 1, 3 and 5 years were 88.5% (95%CI 83.8–91.9%), 56.6% (95%CI 48.9–63.6%), and 37.2% (95%CI 27.9–46.5%), respectively. At univariate analysis, in-field progression (HR 1.59; 95%CI 1.04–2.43, p = 0.030), presence of non-lung metastases (HR 1.97; 95%CI 1.30–2.99, p = 0.001), CTV bigger than 30 mm (HR 1.73; 95%CI 1.18–2.5, p = 0.005), the use of systemic treatment before SBRT (HR 1.51; 95%CI 1.01–2.57), increasing lines of systemic treatment before SBRT (HR 1.23; 95% CI 1.02–1.48, p = 0.027), high PS (HR 0.66, 95%CI 0.47–0.93, p = 0.019), and male gender (HR 1.63; 95%CI 1.01–2.63, p = 0.044) were all negatively impacting on OS. In-field control (HR 1.80; 95%CI 1.17–2.77, p = 0.007), the use of systemic treatment before SBRT (HR 1.82; 95%CI 1.08–3.06, p = 0.023), presence of non-lung metastases (HR 1.67; 95%CI 1.08–2.59, p = 0.020) and increasing CTV volume (HR 1.82; 95%CI 1.04–2.35, p = 0.030) were all negatively impacting at multivariable analysis (Table 4). Overall
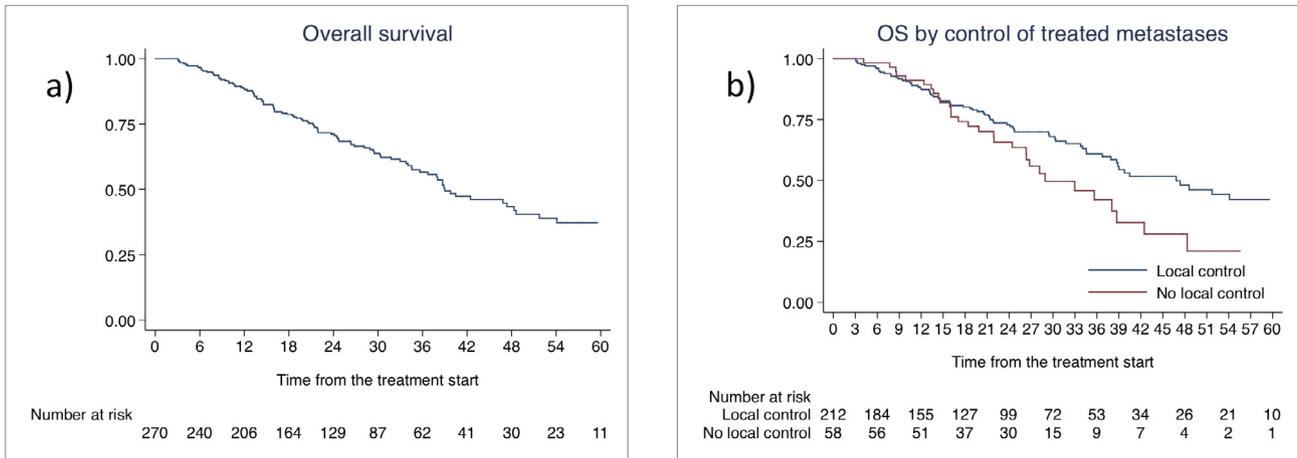
**Fig. 3.** Kaplan–Meier's curves of Overall Survival for all patients (a) and according to control of treated metastases (b).

**Table 4**
Univariate and multivariable analysis for Overall Survival.

|  | Univariate | | Multivariate | |
|---|---|---|---|---|
|  | HR (95% CI) | P value |  |  |
| Age >65 | 1.27 (0.81–1.99) | 0.279 | – | – |
| Sex, Male | **1.63 (1.01–2.63)** | **0.044** | 1.57 (0.96–2.56) | 0.072 |
| PS | **0.66 (0.47–0.93)** | **0.019** | 0.72 (0.50–1.02) | 0.071 |
| Time to metastases, >24 months | 0.80 (0.54–1.18) | 0.266 | – | – |
| Number of treated lesions | 1.08 (0.88–1.33) | 0.425 | – | – |
| Site of treated metastases, non-lung vs lung | **1.97 (1.30–2.99)** | **0.001** | **1.67 (1.08–2.59)** | **0.020** |
| Number of treated organ, ≥2 | 0.78 (0.40–1.51) | 0.473 | – | – |
| CTV mm, >30 | **1.73 (1.18–2.55)** | **0.005** | **1.56 (1.04–2.35)** | **0.030** |
| Systemic therapy before SBRT | **1.61 (1.01–2.57)** | **0.042** | **1.82 (1.08–3.06)** | **0.023** |
| Lines of systemic therapies before SBRT | **1.23 (1.02–1.48)** | **0.027** | – | – |
| Time from metastases to SBRT, >12 months | 0.94 (0.64–1.39) | 0.781 | 0.68 (0.44 – 1.04) | 0.082 |
| BED10 Gy, >100 Gy | 1.52 (0.89–2.59) | 0.123 | – | – |
| Control of treated metastases | **1.59 (1.04–2.43)** | **0.030** | **1.80 (1.17–2.77)** | **0.007** |

In bold values considered as statistically significant (*p* value < 0.05).

survival for patients with liver metastases was 83.5%, 54.7% and 35.5% at 1, 2 and 3 years while patients with lung metastases had rates of 90.2%, 81% and 67.4%. Median OS was 28.9 months for patients who experienced progression of metastases treated by SBRT, while 46.8 months in patients with control of metastases treated with SBRT.

## Discussion

In this large monocentric sample of oligometastatic CRC patients we evaluated the association of risk factors with LC and survival. After a median follow-up of 23 months, we demonstrated high rates of LC after SBRT. We observed 1-year LC rate reaching 95% and 3-years rate above 70%. In a recent systematic review regarding oligometastatic CRC conducted by Kobiela et al., LC rates were reported according to site of disease, ranging from 50% to 100% at 1-year for liver metastases and from 62% to 92% for lung metastases [11]. These results are in line with the outcome reported by several trials of high dose SBRT for metastases from different primary tumors. Hong et al. [12] analyzed a total of 361 patients affected by metastases from primaries including non-small cell lung cancer (17%) and breast cancer (16%). Three years rate of control of treated metastases was 72% and predictive risk factors included histology, interval to metastatic diagnosis and number of treated metastases. Regarding lesions from CRC, Jung et al. [13] evaluated 50 patients affected by 79 metastatic lung lesions and observed a 3-year LC rate of 70.6%. Liver metastases

from CRC treated with SBRT were investigated by Scorsetti et al. [14]. The group analyzed 42 patients with 52 inoperable liver lesions. The liver metastases were treated with 75 Gy in 3 fractions with high in-field control rates (95% and 85% at 1 and 3 years respectively). Lee et al. [15] evaluated 68 patients, of which 40 had inoperable colorectal liver metastases. One-year survival rate for colorectal patients was 63% (95% CI, 44% to 78%). We published a previous experience on 82 patients with 112 lesions from CRC treated with SBRT [16]. With a 1-year LC rate of 90%, we observed a statistically significant improvement of the rate in lesion treated with a BED10 higher than 60 Gy. The delivered dose may play a role in this setting. From the initiative of the German Society for Radiation Oncology (DEGRO), 474 patients with 623 liver metastases were analyzed by Andratschke et al. [17]. Forty-eight percent of patients were affected by CRC and 1-year rate of LC reached 83% if high BED was administered (higher than 150 Gy). In the present analysis we didn't find a correlation between dose according to BED10 and LC, however majority of our patients (78.5%) was treated with a BED10 value higher than 100. The only factor influencing the outcome in terms of LC in our study was the time from diagnosis of metastases to SBRT (HR 1.62, 95%CI 1.06–2.46, *p* = 0.023). The longer the time, the more likely was the progression of treated metastases. Such behavior could find an explanation in biological mechanism of resistance that tumoral cell could acquire during time and after exposition to multiple treatments. We didn't find a correlation between number of systemic treatment administered before SBRT and LC rates; however some studies published in

literature observed different results. Klement et al. [18] evaluated the influence histology and pre-SBRT chemotherapy. They analyzed 452 SBRT treatments in 363 patients and 44.9% were affected by CRC. Patients undergoing chemotherapy before SBRT had a significantly lower LC at 2 years (58% vs 83%); moreover CRC was found to be more radioresistant than other histology, indeed the dose needed to achieve at least 90% tumor control rate was $257 \pm 74$ Gy10. The increasing number of lines of systemic treatment administered before RT was indeed predictive of reduce PFS rates. One-year PFS rates were 55% and 26% for patients not submitted and submitted to $\geq 3$ lines of systemic treatments.

Control of treated metastases increased median PFS from 7.3 to 9.8 months; moreover it influenced positively OS of our sample. Median OS was increased by about 18 months in patients with metastases controlled by SBRT. Short median PFS could be related to a suboptimal selection of the patients, as the majority of patients relapse outside the field of irradiation. Andratsche et al. [17] analyzed 474 patients liver oligometastases and observed that treated metastases control did not affect survival but early local recurrence was significantly associated with worse OS compared to late local recurrence. This behavior of decremented OS in patients not well responding to SBRT could be correlated to a more aggressive disease that could justify the presence of radioresistant cells. The group of Kinji et al. [19] evaluated factors correlated to radioresistance of CRC to SBRT and found that rectal cancer compared to colon cancer was less sensitive to the treatment, while KRAS status was no associated to the outcome. Identification of long-term survival metastatic CRC patients is crucial in order to offer local treatment to patients who can benefit the most from it. The University of Chicago performed a study investigating the biological assessment of curability of oligometastases from CRC [20]. The author found that exhibition of MSI-independent immune activation is associated with a most favorable survival. Hong et al. [21] evaluated the outcome of liver metastases treated with proton-based SBRT focusing on importance of patient's genotype. Thirty-four patients out of 89 analyzed were affected by CRC and median survival was 18.1 months. KRAS oncogene mutation was strongly predictive of lower LC and patients with both mutation of KRAS and TP53 resulted to be radioresistant, with a one-year LC rate of 20.0%, versus 69.2% for other. However no correlation's analysis between mutations and survival was performed. Our study also found different OS according to dimension of disease, with worse survival in patients with big lesions. While some authors [22,23] didn't' observe correlation between dimensions and OS, Ricco et al. [8] found a correlation between both LC and OS rates and tumor volume, with improved outcome for patients with smaller volumes of lung metastases.

Considering the whole group, our study showed 1- and 5-year OS of 88.5% and 37.2%, respectively. These results are comparable to what demonstrated in literature for operated patients. Surgical resection improves OS, with 1- and 5-year rate of 85–95% and 30–60%, respectively for liver and lung metastases [24–28]. Stratifying patients according to lesion's location, OS for patients with liver metastases was 83.5% and 54.7% at 1 and 2 years while patients with lung metastases had rates of 90.2% and 81%%. Results of patients with liver lesions are in line with data showed by the most relevant studies, as shown by the review of Petrelli et al. [29].

Several issues, including the retrospective nature of the analyses and thus the heterogeneity of the patients and lesions included, limit this study.

According to our results, SBRT can prolong survival of metastatic CRC patients, with a median advantage of about 18 months. Only the time from diagnosis of metastases to SBRT was predictive for in-field control while site and dimensions of disease were correlated to OS of oligometastatic CRC patients. This ablative treatment should be offered early at appearance of metastases for a better control of disease. Moreover, patients with lung metastases, smaller than 30 mm, not heavily pre-treated with systemic treatments, could benefit the most from SBRT with longer survival rates.

Prospective trials regarding the treatment of liver metastases are ongoing (NCT03532204, NCT02820194), however the realization of studies evaluating all sites of metastases and the correct integration and sequencing of SBRT and systemic therapy should be considered in the next future.

## Conflict of interest

There are no conflict of interest disclosures from any authors.

## CRediT authorship contribution statement

**Ciro Franzese:** Conceptualization, Data curation, Methodology, Writing - original draft. **Tiziana Comito:** Data curation, Writing - original draft. **Eno Toska:** Data curation. **Angelo Tozzi:** Data curation. **Elena Clerici:** Data curation. **Fiorenza De Rose:** Formal analysis. **Davide Franceschini:** Formal analysis. **Pierina Navarria:** Writing - original draft. **Giacomo Reggiori:** Formal analysis. **Stefano Tomatis:** Formal analysis. **Marta Scorsetti:** Writing - review & editing.

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