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RESEARCH ARTICLE

Stereotactic body radiation therapy in the treatment of cancer patients with oligometastatic disease: a real world study

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Abstract

Purpose Stereotactic body radiation therapy (SBRT) is a treatment modality with curative intent for oligometastatic cancer patients, commonly defined by a low-burden metastatic disease with 1–5 systemic metastases. Better knowledge of the clinical profile and prognostic factors in oligometastatic cancer patients could help to improve the selection of candidates who may obtain most benefits from SBRT. The objective of this study was to describe the clinical data and outcome in term of overall survival (OS) of patients with oligometastatic disease treated with SBRT over a 6-year period.

Methods From 2013 to 2018, 284 solid tumor cancer patients with 1–5 oligometastases underwent SBRT at a large university-affiliated oncological center in Barcelona, Spain. Variables related to the patient profile, tumor, oligometastatic disease, and treatment were evaluated.

Results A total of 327 metastatic tumors were treated with SBRT. In 65.5% of cases, metachronous tumors were diagnosed at least 1 year after diagnosis of the primary tumor. The median age of the patients was 73.9 years and 66.5% were males. The median follow-up was 37.5 months. The most common primary tumors were lung and colorectal cancer, with lung and bone as the most commonly treated metastatic sites. Ninety-three percent of patients showed a Karnofsky score (KPS) between 80 and 100. Adenocarcinoma was the most common histological type. The median overall survival was 53.4 months, with 1-, 2- and 5-year survival rates of 90.5%, 73.9% and 43.4%, respectively. Overall survival rates of breast (67.6 months, 95% CI 56.4–78.9), urological (63.3 months, 95% CI 55.8–70.8), and colorectal (50.8 months, 95% CI 44.2–57.4) tumors were higher as compared with other malignancies (20 months, 95% CI 11.2–28.8 months) ($p < 0.001$). Patients with Karnofsky score (KPS) of 90 and 100 showed a significantly better survival than those with impaired performance status ($p = 0.001$).

Conclusion SBRT appears to be well tolerated and safe approach in oligometastatic patients. Patients with good performance status and with primary breast, urological and colorectal cancer have higher OS compared with other malignancies. More studies are necessary to evaluate the prognostic factors in oligometastatic disease (OMD) in order to select patients who could benefit more from this therapeutic approach.

Keywords Oligometastases · Oligometastatic disease · Stereotactic body radiation therapy · Risk factors · Survival

Introduction

Oligometastatic disease (OMD) is characterized by a limited metastatic spread (between 1 and 5 metastases) and low tumor burden and has been described as an intermediate state between localized cancer and wide-spread metastatic disease [1–3]. The appearance of this stage is related to the aggressiveness of clones, tumor mutations, site and characteristics of the primary tumor, and localization of possible metastases. In clinical practice, early detection of OMD is important for a radical therapeutic approach, better control of the disease, delay of systemic treatment, decrease of morbidity, and improvement of oncological outcome [1–7]. Although patients with OMD can undergo metastasectomy and other ablative techniques, such as radiofrequency

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ablation and cryotherapy, currently radiotherapy remains the most effective tool for the treatment of OMD.

Stereotactic body radiation therapy (SBRT) also known as stereotactic ablative radiotherapy (SABR) is a treatment modality in radiation oncology that delivers a very high dose of radiation to the tumor target with high precision using single or a small number of fractions, which could reduce or eradicate tumor burden [1, 9–11]. High radiation doses not only induce tumor hypoxia, but also can increase inflammatory immune response with the release of tumor antigens and activation of proinflammatory factors that can be detected by the immune cells and, synergically, leading to a higher response [1, 9]. Local high dose radiation therapy also triggers systemic effects and reduces tumor-induced immune suppression [12–14].

SBRT has been associated with optimal control of OMD even with curative intent and lower toxicity [1, 5] and is especially useful in bone, lung, liver or brain metastatic locations [3, 15], although studies of more than 5 metastatic lesions are scarce [4]. Total dose and number of fractions should be individualized according to the radiosensitivity index related to histologic type and location of the primary tumor and oligometastatic sites.

The objective of this study was to describe the clinical data and overall survival of a cohort of cancer patients with OMD treated with extracranial SBRT over a 6-year period.

Methods

This was a retrospective observational cohort study of all consecutive cancer patients diagnosed with OMD treated with extracranial SBRT at the Catalan Institute of Oncology (ICO) in Barcelona (Spain) between 2013 and 2018. Inclusion criteria were patients with solid malignancy and OMD (between 1 and 5 metastatic lesions) who received at least one SBRT treatment in one or more metastatic sites. Patients who had been treated with stereotactic radiosurgery (SRS) for brain metastasis were excluded. The study was approved by the institutional review board and was waived of informed consent as data were collected from a retrospective review of electronic medical records.

Study variables included age and gender; Karnofsky performance status score (KPS); tumor-related variables (primary tumor type, histology, time of diagnosis of OMD); data related to first SBRT (total number of metastases, number of metastases treated, metastatic site (s), systemic treatment prior to SBRT, radiation doses and number of fractions); and oncological outcome (overall survival, and survival by gender, primary tumor, time at diagnosis of OMD, and Karnofsky score). Overall survival (OS) was calculated from the date of initiation of SBRT until the date of death or last follow-up.

Categorical data are expressed as frequencies and percentages, and continuous data as median and interquartile ranges (IQR, 25th–75th percentiles). OS was estimated using the Kaplan–Meier method and differences in survival curves were analyzed with the log-rank test. Median OS and 95% confidence interval (CI) were reported. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 20 for Windows.

Results

284 patients treated with SBRT for a total of 327 metastases were analyzed. Patient and tumor characteristics are summarized in Table 1. The median age of the patient population was 73.9 years (IQR, 67.3–79.9 years). Most patients were male (66.5%) and 93.7% had good performance score (KPS 80–100). The median follow-up was 37.5 months (IQR, 23.4–55.6 months) and 152 patients were still alive at the time of data collection. Colorectal and lung cancer were the most frequent primary tumors, 33.5% and 29.2%, respectively. The most frequent histologic type was adenocarcinoma (75.4%). Most patients in our cohort present metachronous metastases with more than 12 months of latency (65.5%).

Most patients had one metastatic site treated (86.3%) and the main sites were lung (52.8%) and bone (25.5%) (Table 2).

Concerning the heterogeneity in tumor sites, there were diversity of SBRT dose and fractionation schedules applied. The range of the radiation dose was 23.6–54 Gy, with 7.5–12.5 Gy per fraction in 1–8 fractions. Prescribed doses are reported in Table 3.

The median OS was 53.4 months (95% CI 49.2–57.6) (Fig. 1). The median survival rates were 90.5% at 1 year, 73.9% at 2 years and 43.3% at 5 years. Differences in survival rates according to sex were not statistically significant, with 51.6 months (95% CI 41.3–61.9) in men and 64.4 months (95% CI 39.4–89) in women ($p = 0.259$) (Fig. 2A).

Concerning the primary tumor, overall survival rates of breast (67.6 months, 95% CI 56.4–78.9), urological (mostly prostate cancer) (63.3 months, 95% CI 55.8–70.8) and colorectal (50.8 months, 95% CI 44.2–57.4) tumors were higher as compared with other malignancies (20 months, 95% CI 11.2–28.8 months) ($p < 0.001$) (Fig. 2,B). The median OS for synchronous OMD, metachronous OMD diagnosed < 12 months and metachronous OMD diagnosed > 12 months after diagnosis of the primary tumor was 59.3 months (95% CI 27.5–91.1), 29.3 months (95% CI 21.5–37.1) and 52.3 months (95% CI 43.5–62.1), respectively ($p = 0.096$) (Fig. 2C). Patients with Karnofsky score of

Table 1 Baseline clinical characteristics of cancer patients diagnosed with OMD treated with extracranial SBRT ($n=284$ patients)

Data	Number patients (%)
Sex	
Male	189 (66.5)
Female	95 (33.5)
Age, years, median (IQR)	73.9 (67.3–79.9)
Karnofsky performance status score	
60	2 (0.7)
70	13 (4.6)
80	56 (19.7)
90	168 (59.2)
100	42 (14.8)
Missing	3 (1.1)
Origin of the primary tumor	
Colorectal	95 (33.5)
Lung	83 (29.2)
Urological	45 (15.8)
Breast	27 (9.5)
Gynecological	9 (3.2)
Upper gastrointestinal tract	8 (2.8)
Head and Neck	8 (2.8)
Melanoma	4 (1.4)
Other	5 (1.8)
Histological type	
Adenocarcinoma	214 (75.4)
Squamous cell carcinoma	33 (11.6)
Other	37 (13.0)
Time of diagnosis of oligometastatic disease	
Synchronous	46 (16.2)
Metachronous (< 12 months)	52 (18.3)
Metachronous (≥ 12 months)	186 (65.5)
Number of initial metastasis	
1	217 (76.4)
2	54 (19.0)
3	12 (4.2)
4	1 (0.4)

Data as frequencies and percentages in parenthesis unless otherwise stated

90 and 100 showed a significantly better survival than those with impaired performance status ($p=0.001$) (Fig. 2D).

Discussion

SBRT is widely used in the management of cancer patients with OMD, improving oncological outcomes. After a median follow-up of 37.5 months, the overall survival in our cohort was 53.4 months, which is higher than survival rates reported in the literature.

Table 2 Characteristics of treatment with stereotactic body radiotherapy (SBRT)

Data	Number (%)
Previous systemic treatment	
None	203 (71.5)
Consolidation SBRT	25 (8.8)
SalvageSBRT	56 (19.7)
Treated metastatic sites	
1	245 (86.3)
2	36 (12.7)
3	2 (0.7)
4	1 (0.4)
Localization of treated metastases	
Lung	150 (52.8)
Bone	72 (25.4)
Lymph nodes	33 (11.6)
Liver	12 (4.2)
Adrenal glands	8 (2.8)
Combined treatment (more than 1 site)	9 (3.2)

Consolidation SBRT: partial response after systemic treatment; salvage SBRT: stable or progressive disease after systemic treatment

Table 3 Stereotactic body radiotherapy (SBRT) schedule according to localization of oligometastatic disease

Data	Median (interquartile range)
Liver	
Total dose, Gy	50 (32.25–50)
Fractions number	5 (3–5)
Dose per fraction, Gy	8.75 (5–10)
Lung	
Total dose, Gy	54 (50–60)
Fractions number	5 (4–8)
Dose per fraction, Gy	11 (7.5–12.5)
Lymph nodal regions	
Total dose, Gy	39
Fractions number	6
Dose per fraction, Gy	6.5
Bone	
Total dose, Gy	22.5 (16–22.5)
Fractions number	3 (1–3)
Dose per fraction, Gy	7.5 (7.5–16)
Adrenal glands	
Total dose, Gy	36
Fractions number	3
Dose per fraction, Gy	12
All sites SBRT schedules	
Total dose, Gy	50 (23.6–54)
Fractions number	4 (3–8)
Dose per fraction, Gy	7.5 (7.5–12.5)

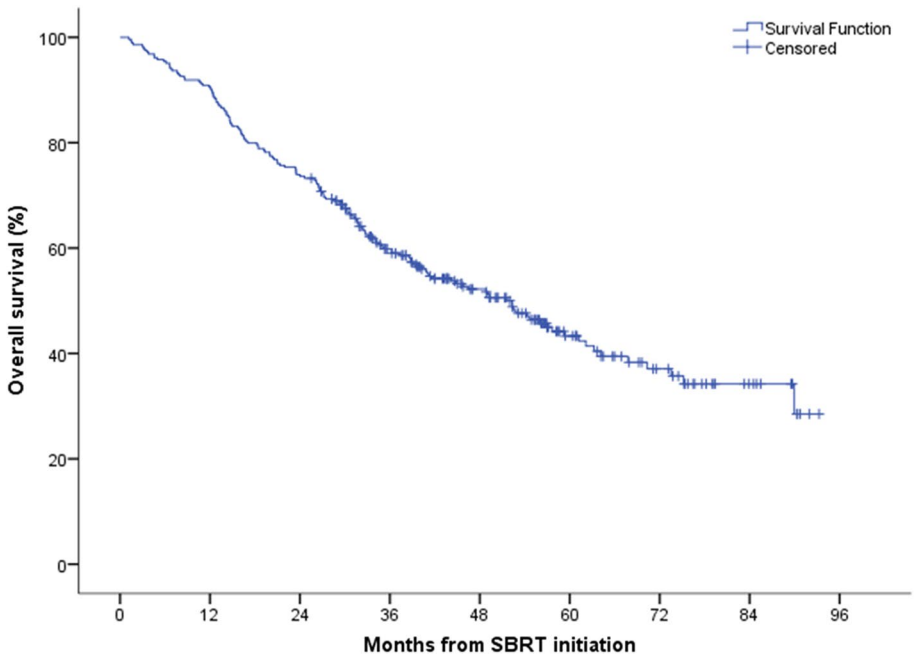

Fig. 1 Overall survival curve estimated by the Kaplan–Meier method

In a study of 757 patients with oligometastatic non-small-cell lung cancer treated with surgical metastasectomy, stereotactic radiotherapy/radiosurgery, or radical external-beam radiotherapy, and curative treatment of the primary lung cancer, the median overall survival was 26 months, with 70.2% and 29.4% rates at 1 and 5 years, respectively [16], as compared to 90.5% and 43.3% in our study. In a study of 670 patients treated with SBRT for lung metastases, the 2-year and 5-year overall survival was 52.6% and 23.7%, respectively [17], also lower than in our study. However, in these two studies [16, 17], oligometastatic lesions were exclusively lung metastases. Fode et al. [18] reported OS of 28.8 months (95% CI, 27.6–32.4) in 321 patients treated for 587 metastases with SBRT over 13 years. In this study, the treatment sites were mainly liver (68%) and lung (29%).

In another study of 403 patients treated with stereotactic radiotherapy for 760 metastases, including brain metastatic tumors in 26% of cases, the median overall survival was 26.6 months, with survival rates of 54% and 22% at 2 and 5 years, respectively [19]. In 309 patients with OMD treated by SBRT (n = 209) and/or by intracranial single or fractionated stereotactic radiotherapy (n = 107), the median OS was 24.4 months and the 5-year survival rate was 19% [20]. In 85 women with oligometastatic breast cancer treated with SBRT, the 5-year overall survival was 83% for patients with bone-only oligometastases vs. 31% for non-bone oligometastases [6]. In a group of cancer patients with OMD from primary sites other than breast or prostate cancer, the overall survival at 5 years was 13.4% [9], which is substantially lower than 43.3% found in the present study. The inclusion of patients with primary breast and prostate cancer in our cohort may account for a higher survival, suggesting that primary tumor has high correlation with OS. A comparison of oncological outcomes in different studies of cancer patients with OMD treated with radiotherapy is shown in Table 4.

Different prognostic factors involved in the local control of the disease, progression-free survival and overall survival have been reported. Age [20, 21], male gender [19, 20], and synchronous OMD [18–21], may be associated with a poor prognosis. On the other hand, histological type of adenocarcinoma [16, 19–21] and breast cancer metastases showed better survival rates as compared to other primary tumors [6, 9, 15, 20]. Also, bone and lymph node metastatic lesions present favorable response to radiotherapy [6, 10, 20] as opposite to intracranial metastasis and metastatic lesions in the adrenal glands [19, 20, 22] in terms of both progression-free survival and overall survival. Control of the primary tumor and previous chemotherapy contribute to improve the results of treatment of OMD [8, 9, 18, 23, 24]. In the presence of 1–3 metastatic tumors, the survival is higher [9, 17, 21]. On the contrary, Karnofsky score lower than 80% is associated with worse prognosis [6, 17–19]. Finally, the dose per fraction administered, the number of fractions and the biological equivalent dose ≥ 75 Gy, in particular > 100 Gy, increase local control and overall survival [10, 20, 21, 23, 24].

According to these factors, the high survival rate obtained in our cohort may be explained by the fact that brain metastases were excluded, the high percentage of adenocarcinomas, the use of SBRT for the treatment of bone and lymph node metastatic lesions, and the high

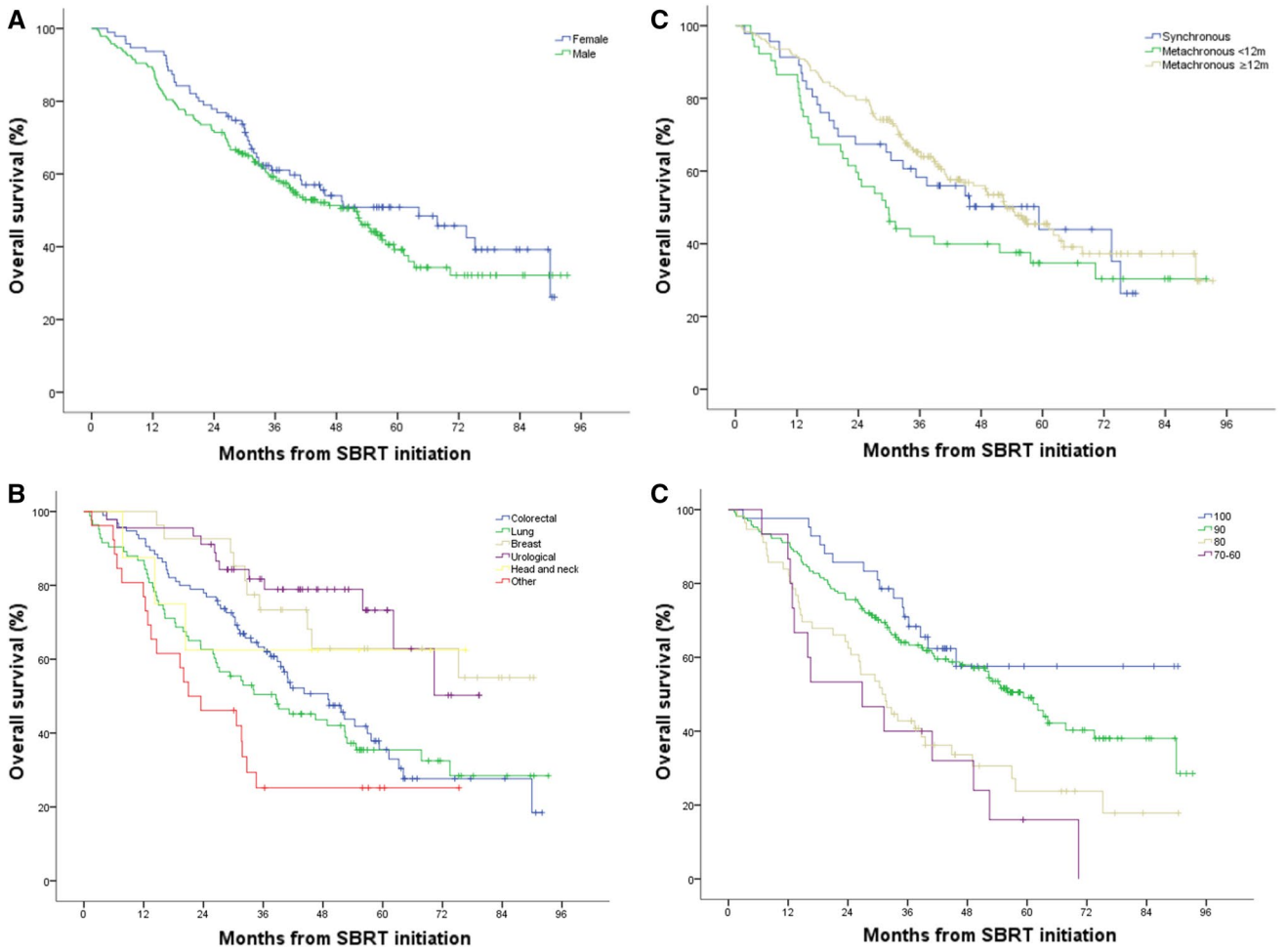

Fig. 2 Overall survival according to different prognostic factors: sex (**A**), primary tumor (**B**), synchronous vs. metachronous diagnosis of OMD (< 12 months or ≥ 12 months after treatment of the primary tumor) (**C**), and Karnofsky performance status score (**D**)

Karnofsky score of the patient population. Other factors that may account for differences in survival may be associated with treatment schedules, selection of candidates for SBRT (consolidation or salvage treatment), the use of previous systemic treatment, or the time of diagnosis of OMD with metachronous OMD (65.5% of the patients) favoring a better survival. Limitations include the retrospective design and the single-center nature of the study.

In summary, numerous studies have shown the efficacy of SBRT for treating cancer patients with OMD. Raising awareness of factors influencing survival would enable clinicians to select the candidates who would obtain maximum benefit of SBRT and improve oncological outcomes in oligometastatic patients.

Table 4 Comparison of overall survival rates among different studies of radiation therapy for the treatment of oligometastatic disease

Frist author (year) [reference]	Patients no	Characteristics of the primary tumor	Oligometastases	Survival
Ashworth 2014 [16]	757	Non-small-cell lung cancer	Different localizations	Overall: 26 months 1-year: 70.2% 2-years: 51.1% 5-years: 29.4%
de Vin 2014 [20]	309	Different primary tumors (colorectal 33%, lung 33%)	Different localizations (brain 35%)	Overall: 24 months 5-years: 19%
Fode 2015 [18]	321	Colorectal cancer (63%)	Different localizations (no brain tumors)	Overall: 28.8 months 1-year: 80% 5-years; 23%
Tanadini-Lang 2017 [17]	670	Different primary tumors	Pulmonary	Overall: 14.3 months 2-years: 52.6% 5-years: 23.7%
Van den Begin 2019 [19]	403	Different primary tumors	Different localizations	Overall: 26.6 months 2-years: 54% 5-years: 22%
Aujla 2019 [19]	82	Different primary tumors (non-breast or prostate)	More frequent localizations liver (50%) and lung (48%)	5-years 13.4%
Milano 2019 [6]	43	Breast cancer	Different localizations (no brain tumors)	5-years 83% in bone metastases and 31% in other localizations
Our cohort 2022	284	Different primary tumors	Different localizations (no brain tumors)	Overall: 53.4 months 1-year: 90.5% 2-years: 73.9% 5-years: 43.3%

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Data availability Data will be made available on request to the authors.

Declarations

Conflicts of interest None of the authors have any conflicts of interest to declare.

Ethical approval Institutional Review Board of Institut Català d'Oncologia (ICO), L'Hospitalet de Llobregat, Barcelona, Spain.

Consent to participate The study was waived of informed consent as data were collected from retrospective review of electronic medical records.

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