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Stereotactic body radiotherapy results for *de-novo* extracranial oligometastatic cancer patients

Ipek Pinar Aral[1], Gonca Altınışık İnan[1], Suheyla Aytac Arslan[1], Ali Kerim Aksakal[2], Huseyin Furkan Ozturk[1], Yasin Caygın[2], Havva Beyaz[1], Muhammet Bülent Akıncı[1], Yılmaz Tezcan[1]

[1]Radiation Oncology, Ankara Şehir Hastanesi, Radyasyon Onkolojisi Bölümü, Ankara Yildirim Beyazit Universitesi Tip Fakultesi, Ankara, Türkiye
[2]Ankara City Hospital, Bilkent Caddesi, Çankaya, Türkiye

ABSTRACT

Background: The aim of study was to evaluate the oncological results of stereotactic body radiotherapy (SBRT) in de-novo oligometastatic (dOM) disease.

Materials and methods: Patients who underwent SBRT for dOM disease in Radiation Oncology Clinic of **XXX** Hospitals were analyzed retrospectively. The endpoints of the study were overall survival (OS) and disease free survival (DFS).

Results: 84 patients with treated between 08.06.2019–15.11.2022 were analyzed. The median follow up was 26 (range 6- 219) months. dOM subgroups were as follows: 37 (44.0%) synchronous dOM (sdOM); 31 (37%) metachronous oligorecurrence (mdOR) and 16 (19.0%) metachronous oligoprogression (mdOP). Grade 1 acute side effects (ASE) were observed in only 1 patient and no grade ≥ 2 a ASE were observed. Progression was observed in 45 (53.6%) of the patients. The median DFS was 8 (range 1–32) mo, 1y DFS was 44.5%; 2y DFS was 26.2%. Significantly higher DFS was obtained in mdOR than sdOM and mdOP [p = 0.020; hazard ratio (HR): 1.6; 95% confidence interval (CI): 0.75–3.68%]. The relationship between response assessment after SBRT and DFS was significant (p < 0.001; HR: 4.8; 95% CI: 1.9–12.2). Twenty-nine (34.5%) patients were ex and 55 (65.5%) were alive. 1y OS was 75.6%; 2y OS —61.2%; 3y OS —57.4% and the median OS value has not yet been reached. Lower OS was observed in sdOM compared to mdOP and mdOR (p = 0.035, HR: 0.45; 95% CI: 0.21–0.96). The relationship between response assessment after SBRT and OS was significant (p = 0.017; HR: 6.6; 95% CI: 1.7–25.7).

Conclusion: Higher DFS was observed in mdOR patients and lower OS was observed in sdOM patients. SBRT response in dOM patients may be a prognostic factor for DFS and OS.

Key words: de-novo; extracranial; oligometastatic cancer; SBRT

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Introduction

The definition of oligometastatic disease was first proposed by Hellman and Weichselbaum in 1995 as an intermediate stage between locally advanced and metastatic stage, which still has a chance of curative treatment [1]. Under this general definition, there are heterogeneous clinical scenarios such as the number of metastases, their localization, and the time of occurrence of metastasis. To standardize these differences, a guideline was published by the European Organisation for Research and Treatment of Cancer (EORTC) in 2020 and the oligometastatic disease was divided

Address for correspondence: Ipek Pinar Aral, Radiation Oncology, Ankara Şehir Hastanesi, Radyasyon Onkolojisi Bölümü, Ankara Yildirim Beyazit Universitesi Tip Fakultesi, Ankara, Türkiye; e-mail: ipekpt@hotmail.com

into three main groups: de novo, induced and repeat. The de novo oligometastatic (dOM) disease, evaluated in this study, is also divided into 3 subgroups according to the duration of metastasis and primary disease control status. The de novo oligometastatic (dOM) disease, which is evaluated in this study, also consists of 3 subgroups according to the duration of metastasis and primary disease control status: synchronous oligometastatic (sdOM), metachronous oligo progression (mdOP), and metachronous oligo recurrence (mdOR) [2]. Progression-free survival or overall survival is improved by adding curative local treatments to systemic treatments in oligometastatic patients. The clinical relevance of the concept of oligometastatic disease is reinforced by the increased survival in patients treated with curative treatment [3–5].

Stereotactic body radiotherapy (SBRT) is a modern RT technique in which curative doses are applied at a short interval. SBRT plays an important role, especially in early stage primary disease and local curative treatment of oligometastatic disease [6].The most remarkable results regarding SBRT in oligometastatic disease were obtained from the SABR-COMET study. Results of the SABR-COMET Phase II randomized trial reported a median OS benefit of 22 months with the addition of SBRT to chemotherapy in patients with controlled primary tumors and 1-5 oligometastases [7]. However, there is heterogeneity in clinical practice of SBRT for oligometastases. Homogenization and standardization are needed in clinical practice of SBRT for oligometastatic disease [8].

Both the concept of oligometastatic disease (de novo, repeat, induced) and the SBRT schemes applied in oligometastatic disease are heterogeneous. This heterogeneity has been ignored in studies; however, significant improvement in oncologic outcomes with SBRT has been noted. Although the role of SBRT in oligometastatic disease is clear, reporting the treatment protocols and oncological outcomes of different subgroups will contribute both to the development and standardization of treatment schemes and to the reveal of the differences between oligometastatic disease subtypes. The current study aims to evaluate the oncological results of SBRT in de novo oligometastatic disease as a homogeneous subgroup of oligometastatic disease.

Materials and methods

The data of patients who underwent SBRT for de novo oligometastatic disease in the Radiation Oncology Clinic of **XXX** Hospital were analyzed retrospectively. Patient interview information, dose volume histograms and electronic system data were used for the study. Demographic status of the patients, radiological and pathological analysis details, Radiotherapy (RT) data, acute side effects (ASE), recurrence status and last status were noted. Staging was performed according to the American Joint Committee on Cancer (AJCC) ver 8. Common Terminology Criteria for Adverse Events (CTCAE) ver 5 was used for acute side effect assessment. The study was conducted in accordance with the Declaration of Helsinki and this was approved by the XXX Hospital Ethics Committee No. 1 with the number E1- at 2022.

Patient population

De novo oligometastatic patients who underwent SBRT for curative purposes, regardless of primary diagnosis and SBRT schemes, were included in the study. The inclusion criteria were as follows: age > 18 years old, Eastern Cooperative Oncology Group (ECOG) 0-3, life expectancy > 6 months, 1–5 metastases, all metastases are suitable for SBRT. The exclusion criteria included: induced or repeat oligometastatic disease, small cell lung cancer (SCLC), brain metastases (BM).

Primary and secondary endpoints

The primary endpoints of the study were overall survival (OS) and disease-free survival (DFS). It was defined that DFS was the time to relapse in or out of the SBRT site, OS was the time to death of patients after end of the SBRT. The SBRT end date was accepted as the start date for the OS and DFS. The endpoint for OS was the last control date for surviving patients and the date of death for ex patients. As the endpoint for DFS, relapse date was the first event date, and last control date or date of death for non-relapsed patients.

SBRT response assessment

The radiological evaluations of the patients in the first 3 months after SBRT were noted as "SBRT response". Response Evaluation Criteria In Solid Tumors (RECIST) criteria were used to evaluate

the response status in imaging [9]. Accordingly, patients were divided into 4 groups as complete response, partial response, stable response and progression. All patients with a heterogeneous primary have a contrast-enhanced CT image. Not all patients had magnetic resonance imaging (MRI) and positron emission tomography (PET) before SBRT. Therefore, response assessment was based on contrast-enhanced computed tomography (CT) imaging before and after SBRT.

Statistical analysis

Data were analysed using SPSS version 26. The conformity of the data to a normal distribution was evaluated with the Shapiro–Wilk test; as the data were not normally distributed, parametric tests were used. The Chi-squared test and Fisher's exact test were used to analyze categorical variables. The Mann–Whitney U test was used for independent two-group analyses. The Kruskal–Wallis test was used for the analysis of 3 or more independent groups and Tukey's post hoc test was performed in cases of significance. For survival analyses, the Kaplan–Meier test was used for univariate analyses and the Cox regression test was used for multivariate analyses. The hazard ratios (HR) and 95% confidence intervals (CI) of results that were significant in our survival analyses were calculated. A HR > 1 denotes an increased relative risk compared to the reference category. The significance limit of this study was set to 0.05

Results

The data of 96 patients who underwent definitive SBRT for extracranial oligometastatic lesions between 08.06.2019 and 15.11.2022 were analyzed retrospectively. Twelve of the patients were excluded from the study because of induced or recurrent oligometastatic disease, and 84 patients were analyzed. 61 (72.6%) of the patients were male, the median age was 67 (range 33-84). The total number of lesions was 136, and the median number of metastatic lesions was 1 (range 1-5). De-novo metastasis subgroups were as follows: 37 (44.0%) synchronous dOM (sdOM); 31 (37%) metachronous oligorecurrence (mdOR) and 16 (19.0%) metachronous oligoprogression (mdOP). The median time for metachronous metastases to occur after primary was 26 (range 6 to 219) months. There was a single metastasis in 52 (61.9%) of the patients. The most common anatomic site for SBRT was the lung (n = 46, 33.8%). The median dose of total SBRT was 35 (16–72.5) Gy. Median follow-up was 18 (1–44) months. Grade 1 (1.2%) acute side effects were observed in only 1 patient during the treatment. Grade 1 gastrointestinal system (GIS) acute side effects were observed in only 1 patient. No grade ≥ 2 a ASE were observed. Patient and treatment details are summarized in Table 1.

SBRT response analysis

Contrast-enhanced CT obtained in the first three months after SBRT and pre-SBRT contrast-enhanced CT were compared and noted as "SBRT response". According to this evaluation, 17 (20.2%) patients had CR; 31 (36.9%) patients had PR, 27 (32.1%) patients had stable response and 9 (10.7%) patients had progression. There was no significant relationship between the SBRT response and the patient's subgroup of de novo oligometastatic disease (sdOM, mdOP or mdOR) (p = 0.530). There was no statically significant relationship between SBRT response and age (p = 0.056); gender (p = 0.787), primary (p = 0.147); SBRT site (p = 0.267); number of metastasis (p = 0.407); immunotherapy status (p = 0.783); total SBRT doses (p = 0.207); BED values (BED < 100 *vs.* BED ≥ 100) (p = 0.398); gross total volume (GTV) volumes (p = 0.063).

DFS analysis

Progression was observed in 45 (53.6%) of the patients. The median DFS was 8 (range 1–32) mo, 1y DFS was 44.5%; 2y DFS was 26.2% (Fig. 1A). There was no statically significant relationship between DFS and age (p = 0.539); gender (p = 0.517); primary (p = 0.529); SBRT site (p = 0.572); number of metastasis (1 *vs.* ≥ 2 met) (p = 0.257); immunotherapy status (p = 0.754), GTV volume (p = 0.487), RT total dose (p = 0.813), BED100 values (BED < 100 *vs.* BED ≥ 100) (p = 0.544). In addition, there was no significant relationship between DFS and the time from primary disease to the oligometastasis for metachronous oligo-recurrence patients (p = 0.842).

Significantly higher DFS was obtained in metachronous oligorecurrence disease (p = 0.020; HR 1.6; 95% CI: 0.75–3.68) (Fig. 1B). The median DFS was 8 (1–28) months in sdOM; 4 (1–14) months for mdOP; 18 (1–32) months for mdOR. The re-

Table 1. Patient and treatment details

Parameters		Results
Sex	Female	23 (27.4%)
	Male	61 (72.6%)
Age	Median(range)	67 (33–84)
	Age < 65	33 (39.3%)
	Age ≥ 65	51 (60.7%)
Primary	NSCLC	25 (29.8%)
	Breast	4 (4.8%)
	Colorectal	11 (13.1%)
	Gynecologic	6 (7.1%)
	Other_GIS	7 (8.3%)
	Other	10 (11.9%)
Immunotherapy	Yes	10 (11.9%)
	No	74 (88.1 %)
Metastasis	Median (range)	1 (aralık 1–5)
	1 metastasis	52 (61.9%)
	≥ 2 metastases	32 (38.1%)
De novo oligometastatic	Synchronous	37 (44.0%)
	Metachronous	47 (56.0%)
	Metachronous oligorecurrence	31 (37%)
	Metachronous oligoprogression	16 (19.0%)
Time from primary disease to metachronous metastasis	Median (range)	26 (6–219) months

Parameters		Results
SBRT site (for 136 metastasis)	Lung	46 (33.8%)
	Bone non vertebra	29 (21.3%)
	Bone vertebra	29 (21.3%)
	Liver	3 (2.2%)
	Soft tissue	4 (2.9%)
	Others	25 (18.4%)
GTV	Median (range)	9.8 (1–96)cc
Total dose	Median (range)	35 (16–72) Gy
Number of fraction	Median (range)	5 (1–8)
BED	BED < 100	55 (65.5%)
	BED ≥ 100	29 (34.5%)
	BED < 75	52 (61.9%)
	BED ≥ 75	32 (38.1%)
Acute toxicity	Yes	1 (1.2%)
	No	83 (98.8%)
SBRT response	CR	17 (20.2%)
	PR	31 (36.9%)
	Stable	27 (32.1%)
	Progression	9 (10.7%)
Progression	Yes	45 (53.6%)
	No	39 (46.4%)
Last status	Alive	55 (65.5%)
	Ex	29 (34.5%)

NSCLC — non-small cell lung carcinoma; GIS — gastrointestinal system; SBRT — stereotactic body radiotherapy; GTV — gross total volume; BED — biological effective dose; CR —complete response; PR — partial response

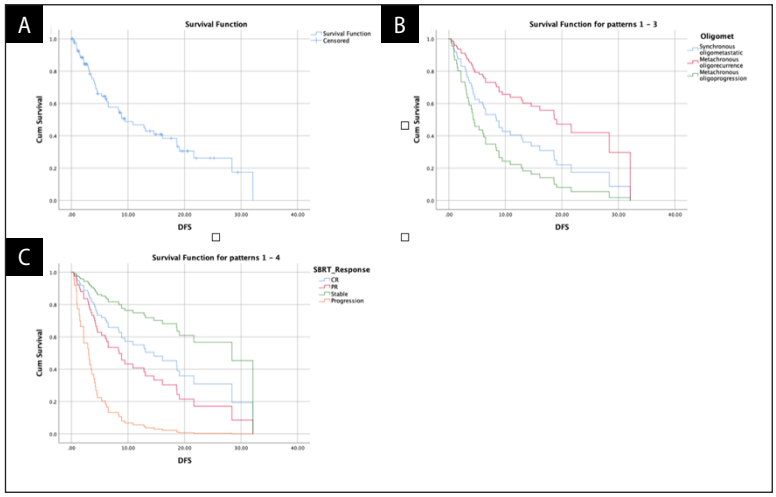

Figure 1. A. Disease-free survival (DFS)-Kaplan Meier survival analysis image; **B.** Significantly higher DFS was obtained in metachronous oligorecurrence disease; **C.** Lower DFS was observed in patients with progression

lationship between first response assessment after SBRT and DFS was significant. Lower DFS was observed in patients with progression. The median DFS was 9 (3–29) months for CR; 6 (1–28) months for PR; 18 (1–32) months for SD and 2 (1–9) months for progression ($p < 0.001$; HR: 4.8; 95% CI: 1.9–12.2) (Fig. 1C).

OS analysis

Twenty-nine (34.5%) patients were ex and 55 (65.5%) were alive. 1y OS was 75.6%; 2y OS 61.2%; 3y OS 57%.4 and the median OS value has not yet been reached (Fig. 2A). There was no statically significant relationship between DFS and age ($p = 0.453$); sex ($p = 0.583$); primary ($p = 0.128$); SBRT site ($p = 0.876$); number of metastasis (1 *vs.* ≥ 2 met) ($p = 0.193$ immunotherapy status ($p = 0.439$), GTV volume ($p = 0.114$), RT total doses ($p = 0.143$), BED100 values (BED < 100 *vs.* BED ≥ 100) ($p = 0.086$).

Lower OS was obtained in synchronous patients compared to metachronous patients. Median OS was 18 (1–44) months in synchronous oligometic patients, and median OS has not yet been reached in metachronous patients ($p = 0.035$, HR: 0.45; 95% CI: 0.21–0.96) (Fig. 2B). The relationship between first response assessment after SBRT and OS was significant. The median OS has not yet been reached in CR; the median OS was 28 (4–44) months for PR; 13 (1–40) months for SD; 5 (3–29) for progression ($p = 0.017$; HR: 6.6; 95% CI: 1.7–25.7) (Fig. 2C; Tab. 2).

Discussion

In our study, SBRT result was evaluated in EORTC de-novo oligometastatic disease as a homogeneous subgroup. The treatment tolerance of the patients was excellent, only 1.2% of grade 1 GIS effects were observed, and no acute side ef-

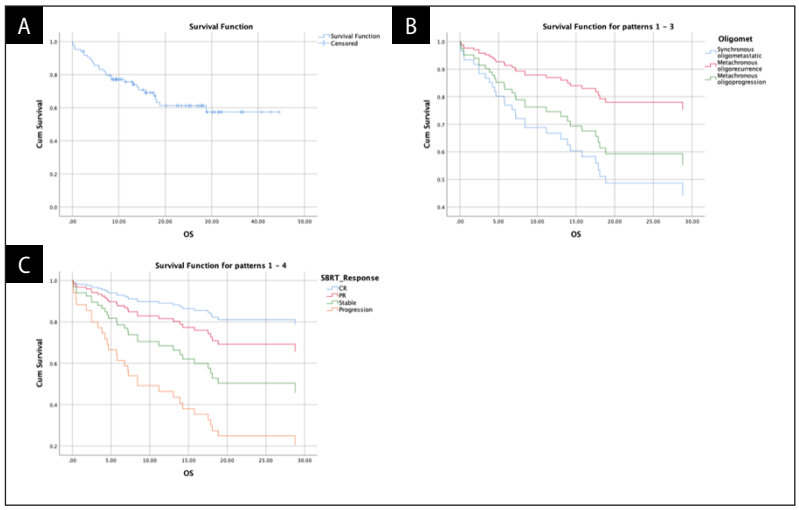

Figure 2. A. Overall survival (OS) — Kaplan Meier survival analysis image; **B.** Lower OS was obtained in synchronous patients compared to metachronous patients; **C.** The relationship between first response assessment after stereotactic body radiotherapy (SBRT) and OS was significant

Table 2. Oncologic outcomes of stereotactic body radiotherapy (SBRT)

	DFS Median (Range)	p	OS	p
Synchronous oligometastatic	8 (1–28) mo	0.020 (HR: 1.6; 95% CI: 0.75–3.68)	18 (1–44)	0.035 (HR: 0.45; 95% CI: 0.21–0.96)
Metachronous oligoprogression	4 (1–14) mo		NR	
Metachronous oligorecurrence	18 (1–32) mo		NR	

DFS — disease free survival; mo — months; OS — overall survey; NR — not reached

fects of grade 2 and above were described. During a median follow-up of 18 months, 53.6% disease progression was observed and 34.5% patients died. mdOR patients had higher DFS, mdOR and mdOP patients had higher OS than sdOM patients (Tab. 2). Evaluation within the first three months after SBRT may be an important predictor for DFS and OS.

Up to 90% locoregional control can be achieved by applying high doses to a limited number of metastatic sites with SBRT [6]. One of the most important study in the widespread use of SBRT in oligometastatic disease is SABR COMET-study, and this study demonstrated the overall survival contribution of SBRT of approximately 22 months. However, this study was criticized for having a heterogeneous primary disease profile. In addition, concepts such as de novo, recurrence or induced oligometastasis were not evaluated under separate subheadings in this study [7]. In some studies that oligometastasis subtypes were noted, the subtypes were not compared with each other in terms of oncological outcomes [4,10]. Different results have been reported in a limited number of articles in which comparisons were analyzed. In the study of Francini et al. in which they analyzed metastatic hormone sensitive prostate cancer (mHSPC) patients, lower OS was observed in synchronous patients, similar to our results [11]. In the study of Baoml et al. in NSCLC patients randomized to surgery and SBRT after chemotherapy, there was no significant difference between PFS (p = 0.10) and OS (p = 0.59) in synchronous (n = 14) and metachronous (n = 31) patients [12]. In the study of Trovo et al. evaluating SBRT in oligometastatic patients, no significant PFS difference was found in synchronous (n = 40) and induced oligomet (n = 14) patients [13]. In our study, there was a difference between SO, MOP or MOR disease in terms of oncological outcomes. Significantly higher DFS was observed in mdOR disease, and higher OS results were seen in mdOP and mdOR compared to sdOM disease. The lower survival rate in synchronous tumors in our study may be due to slightly higher lung primary (32% *vs.* 27%) and lower prostate primary (24% *vs.* 25.5%) in synchronous disease. It is important to determine the expected benefit according to these subgroups for the right patient selection. Therefore, the study results should be repeat with more homogeneous groups in terms of primary disease, prospectively.

Parameters determining the prognosis are important for oligometastatic patients. There are evaluations regarding the number of metastases, primary diagnosis, localization, GTV volume, SBRT dose, BED value as prognostic factors [8]. In this study, initial response assessment after SBRT was evaluated radiologically using RECIST criteria, and the initial response status was significantly correlated with both DFS and OS. These results are consistent with the results of the SABR COMET study. In the SABR COMET study, there was a significant correlation between long-term LC and progression according to RECIST 1 criteria (p = 0.039). Although the RECIST criteria are frequently preferred in the evaluation of response after SBRT, this relationship is not significant in all studies [14, 15]. Additionally, the differences between the SBRT response status and oncologic outcomes of these subgroups are not yet clear. There is a need for additional studies using the same SBRT area and the same doses in patients with homogeneous primary regarding the prognostic significance of response assessment after SBRT in oligometastatic disease.

SBRT is an effective curative treatment option with low side effects. Side effects of SBRT are reduced with technological advances in RT devices, more accurate evaluation of intra-organ movements, and more precise dose delivering [6]. Today, the acute toxicity profile of treatments is more important and is one of the factors in determining treatment schemes. In the meta-analysis of Lehrer et al., 943 patients/1290 lesions treated with SBRT were evaluated. It was reported that acute and chronic grade 3 and higher side effects represented less than 10% [16]. In the SABR COMET study, SBRT results of 99 patients at 10 centers were analyzed, and no side effects of grade 2 and above were reported in any patient. In addition, no change was observed in the quality of life with SBRT [7]. Grade 2 and higher toxicity was not observed in the phase 2 randomized prospective study conducted by Ost et al. and, similarly, no grade 3 and higher side effects were observed in the Bowden et al. study [17, 18]. In our study, only one patient had grade 1 (1.2%) side effects and no acute side effects of grade 2 or higher were observed. Late side effects were not evaluated.

The study has important limitations. First, the study was retrospective and single-center. Late side effects analysis could not be performed. Primary disease, chemotherapy, SBRT site, RT dose and fraction schemes were heterogeneous. Only de novo oligometastatic diseases were evaluated and there was no evaluation for repeat and induced oligometastatic diseases.

Conclusion

SBRT is an effective treatment with a low side-effect profile in oligometastatic disease. In SBRT for de novo oligometastatic disease, significantly higher DFS was obtained in metachronous oligorecurrence disease. Lower OS was obtained in synchronous patients compared to metachronous patients. Evaluation within the first three months after SBRT may be an important predictor for DFS and OS.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of interests

The authors have no relevant financial or non-financial interests to disclose.

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