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Original Article

Cancer-specific dose and fractionation schedules in stereotactic body radiotherapy for oligometastatic disease: An interim analysis of the EORTC-ESTRO E^2-RADIatE OligoCare study

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Abbreviations: BC, Breast cancer; BED, Biologically effective dose; CRC, Colorectal cancer; CTV, Clinical target volume; E^2-RADIATE, EORTC-ESTRO RADiotherapy InfrAstrucTure for Europe; ECOG, European Cooperative Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; ESTRO, European Society for Radiotherapy; EQD2, Equivalent dose in 2 Gy single fractions; ITV, Internal target volume; MVA, Multivariate analysis; NCCN, National Comprehensive Cancer Network; NSCLC, Non small-cell lung cancer; OMD, Oligometastatic disease; PC, Prostate cancer; PET, Positron emission tomography; RT, Radiotherapy; SBRT, Stereotactic body radiotherapy; SRT, Stereotactic radiotherapy; UVA, Univariate analysis.

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ABSTRACT

Background and introduction: Optimal dose and fractionation in stereotactic body radiotherapy (SBRT) for oligometastatic cancer patients remain unknown. In this interim analysis of OligoCare, we analyzed factors associated with SBRT dose and fractionation.

Materials and methods: Analysis was based on the first 1,099 registered patients. SBRT doses were converted to biological effective doses (BED) using α/β of 10 Gy for all primaries, and cancer-specific α/β of 10 Gy for non-small cell lung and colorectal cancer (NSCLC, CRC), 2.5 Gy for breast cancer (BC), or 1.5 Gy for prostate cancer (PC).

Results: Of the interim analysis population of 1,099 patients, 999 (99.5 %) fulfilled inclusion criteria and received metastasis-directed SBRT for NSCLC (n = 195; 19.5 %), BC (n = 163; 16.3 %), CRC (n = 184; 18.4 %), or PC (n = 457; 47.5 %). Two thirds of patients were treated for single metastasis. Median number of fractions was 5 (IQR, 3–5) and median dose per fraction was 9.7 (IQR, 7.7–12.4) Gy. The most frequently treated sites were non-vertebral bone (22.8 %), lung (21.0 %), and distant lymph node metastases (19.0 %). On multivariate analysis, the dose varied significantly for primary cancer type (BC: 237.3 Gy BED, PC 300.6 Gy BED, and CRC 84.3 Gy BED), and metastatic sites, with higher doses for lung and liver lesions.

Conclusion: This real-world analysis suggests that SBRT doses are adjusted to the primary cancers and oligometastasis location. Future analysis will address safety and efficacy of this site- and disease-adapted SBRT fractionation approach (NCT03818503).

Introduction and background

Stereotactic body radiotherapy (SBRT) has become a standard-of-care in the multidisciplinary management of patients with oligometastatic disease (OMD) [1]. Today, definitive local treatment of distant metastases is recommended in several National Comprehensive Cancer Network (NCCN) guidelines, for example, for colorectal cancer (CRC), non-small cell lung cancer (NSCLC), renal cell cancer, sarcoma, and selected pediatric malignancies [2–4]. Consequently, the use of SBRT in patients with OMD has markedly increased and is commonplace in many radiation oncology centers around the world nowadays. A recent survey among 1,000 radiation oncologists practicing globally found that more than 60 % of participants planned to increase their use of SBRT to treat OMD [5]. To date, several prospective randomized phase II trials assessing metastasis-directed local treatment in OMD patients were completed successfully: all trials showed favorable toxicity profiles and the majority reported promising efficacy data [6–13], with only two trials reporting no outcome benefit [14,15]. SBRT was the most frequently used metastasis-directed local treatment modality across all these trials. Currently, several phase III trials are ongoing, whose results are awaited eagerly.

Despite the widespread use of SBRT, there is no consensus on the optimal SBRT regimen with respect to dose and fractionation schedules. There is wide variation in the number of fractions, dose per fraction, and total delivered dose across centers and individual patients reported in retrospective and prospective studies [6–10,12,14–16]. For example, in the phase II study by *Iyengar et al. (2018)*, patients with oligometastatic NSCLC received 1–5 fractions with 6–26 Gy per fraction [7]. In the trial conducted by *Wang et al. (2022)*, patients with oligometastatic NSCLC were treated in 5 fractions with 6–8 Gy per fraction [10]. And in the trial by *Gomez et al. (2019)*, the SBRT dose-fractionation was at the discretion of the treating radiation oncologist [17]. Whereas patients with oligometastatic prostate cancer (PC) were treated homogeneously in 3 fractions of 10 Gy in the phase II trial by *Ost et al. (2018)* [13], patients with oligometastatic PC who were included into the study conducted by *Phillips et al. (2020)* were treated in 3–5 fractions of 7–12 Gy [8]. And in the SABR-COMET phase II basket trial run by *Palma et al. (2019)*, the number of SBRT fractions varied between 1 and 8 and dose per fraction varied between 7 and 24 Gy [9].

The reasons for this heterogeneity in dose and fractionation schedules remain poorly understood. One might hypothesize that dose-fractionation regimens depend on the different OMD states and treatment intents, the different primary cancers, metastasis location and target size, concurrent systemic therapy, and the experience of the different centers. Against this background, we analyzed SBRT dose and fractionation and factors associated with SBRT clinical practice leveraging the OligoCare trial data.

Materials and methods

Study design of OligoCare

OligoCare represents a cohort within the E^2-RADIatE trial (NCT03818503), which is designed as a prospective, non-interventional, multicenter cohort study. Its primary goal is to collect real-world data on cancer patients treated with radiotherapy, to support research in radiation oncology, and to provide more evidence on the role of radiotherapy in modern cancer care. The OligoCare cohort enrolls patients with oligometastatic NSCLC, breast cancer (BC), CRC, and PC treated with metastasis-directed radiotherapy. The primary objective of OligoCare is to identify patient, tumor, staging and treatment characteristics impacting overall survival. The secondary objective is to identify patterns-of-care of SBRT for OMD and to determine factors influencing outcomes.

Patient selection and OligoCare database review

This interim analysis is based on the first registered 1,099 patients. For the purposes of this analysis, key items of the OligoCare database were analyzed. The clinical cut-off date for this analysis was set on December 17th, 2021, based on the last SBRT treatment date for these patients. The database was locked on April 8th, 2022, with 99.8 % of the required forms available for all patients, and with approximately 90 % (range, 82–97 %) of the available forms filled and clean.

Statistical analysis and ethical approvals

Minimum criteria for patients to be included into the interim statistical analysis required the availability of data on primary disease site, location and number of oligometastatic lesions and the type of treatment. SBRT doses were converted into equivalent dose in 2 Gy fractions (EQD2) and biologically effective dose (BED). BED was calculated as $n \times d[1 + \frac{d}{\frac{\alpha}{\beta}}]$, with n = the number of fractions, d = dose per fraction to the clinical target volume (CTV)/internal target volume (ITV). Two assumptions were used for the $\frac{\alpha}{\beta}$ value: a homogenous value of 10 Gy for all cancer types, and values of $\frac{\alpha}{\beta} = 10$ Gy for CRC and NSCLC, and $\frac{\alpha}{\beta} = 2.5$ Gy for BC and $\frac{\alpha}{\beta} = 1.5$ Gy for PC [18]. Non-cancer specific EDQ2 was calculated as $EQD2 = \frac{BED}{1+\frac{2}{\frac{\alpha}{\beta}}}$. For NSCLC and CRC, $EQD2 = \frac{BED}{1.2}$, for BC and

PC, it was calculated as $EQD2 = \frac{BED}{1.8}$ and $EQD2 = \frac{BED}{2.33}$, respectively. Concomitant therapy was taken to refer to chemotherapy, targeted therapy, immunotherapy, hormonal therapy and/or other systemic treatments. Its administration was not halted over the course of SBRT in the majority of cases, yet usually occurred on other days than radiation therapy. Descriptive statistics were calculated for all relevant variables under study. Subsequently, a 3-level hierarchical multivariate linear mixed model [19] with fixed effects and random effects was used to assess associations with SBRT dose (Supplementary Table 1). The effect of each factor was estimated via the difference in least-squares means. The confidence interval and the p-value were adjusted for multiplicity using the Dunnett approach [20]. The degrees of freedom were determined via the Satterwaithe method. The overall significance level was set at 0.05 two-sided. Statistical significance was set at 0.001475. This was calculated using the current number of irradiated lesions (n = 1,456 lesions for n = 999 patients) in the SBRT population including patients with at least one irradiated oligometastatic lesion and the total estimated number of lesions to be included into the final analysis (n = 3,800 lesions of n = 2,600 patients). Based on an information fraction on irradiated lesions of 38 % (n = 1,456/n = 3,800) and a spending function Lan-de-Mets [21], the significance level was set at 0.001475. Statistical analysis was conducted by the EORTC statistics team using *SAS version 9.4*. Study procedures, research governance and study ethics follow the E^2-RADIatE protocol.

Results

Of the 1,099 first patients registered in the OligoCare trial database, 80 (n = 80/n = 1,099; 7.3 %) were ineligible, because they finally did not participate in OligoCare (n = 18), did not fulfill inclusion criteria (n = 51) or had an empty OligoCare eligibility check form (n = 11). Of the 1,019 eligible patients, 15 (n = 15/1,019; 1.5 %) had to be excluded from the analysis because of withdrawn consent, treatment modification or missing data. The interim analysis population comprised of a total of 1,004 (100 %) patients, 459 (45.7 %), 196 (19.5 %), 184 (18.3 %), and 165 (16.4 %) of which were treated for oligometastatic PC, NSCLC, CRC, and BC, respectively (Fig. 1). Most patients were accrued in Italy (n = 558; 54.8 %), Belgium (n = 156; 15.3 %), and Switzerland (n = 125; 12.6 %) (Supplementary Table 2). Few additional patients had to be excluded because of undocumented SBRT regimens (n = 5), resulting in n = 999 ("SBRT population") patients included into statistical analyses concerning patterns of OMD and SBRT, respectively.

Median age of all patients in the analysis population was 69 (range, 28–91) years. More than two thirds (n = 689; 68.6 %) of patients were male. For NSCLC (60.7 %), BC (53.3 %) and PC (70.2 %), de-novo OMD was most common. With CRC, the repeat OMD status was the most frequent status, occurring in 43.5 % of patients. Across all four primary tumor sub-groups, more than four fifths of patients had one (n = 654; 65.3 %) or two (n = 238; 23.8 %) distant metastases. In the large

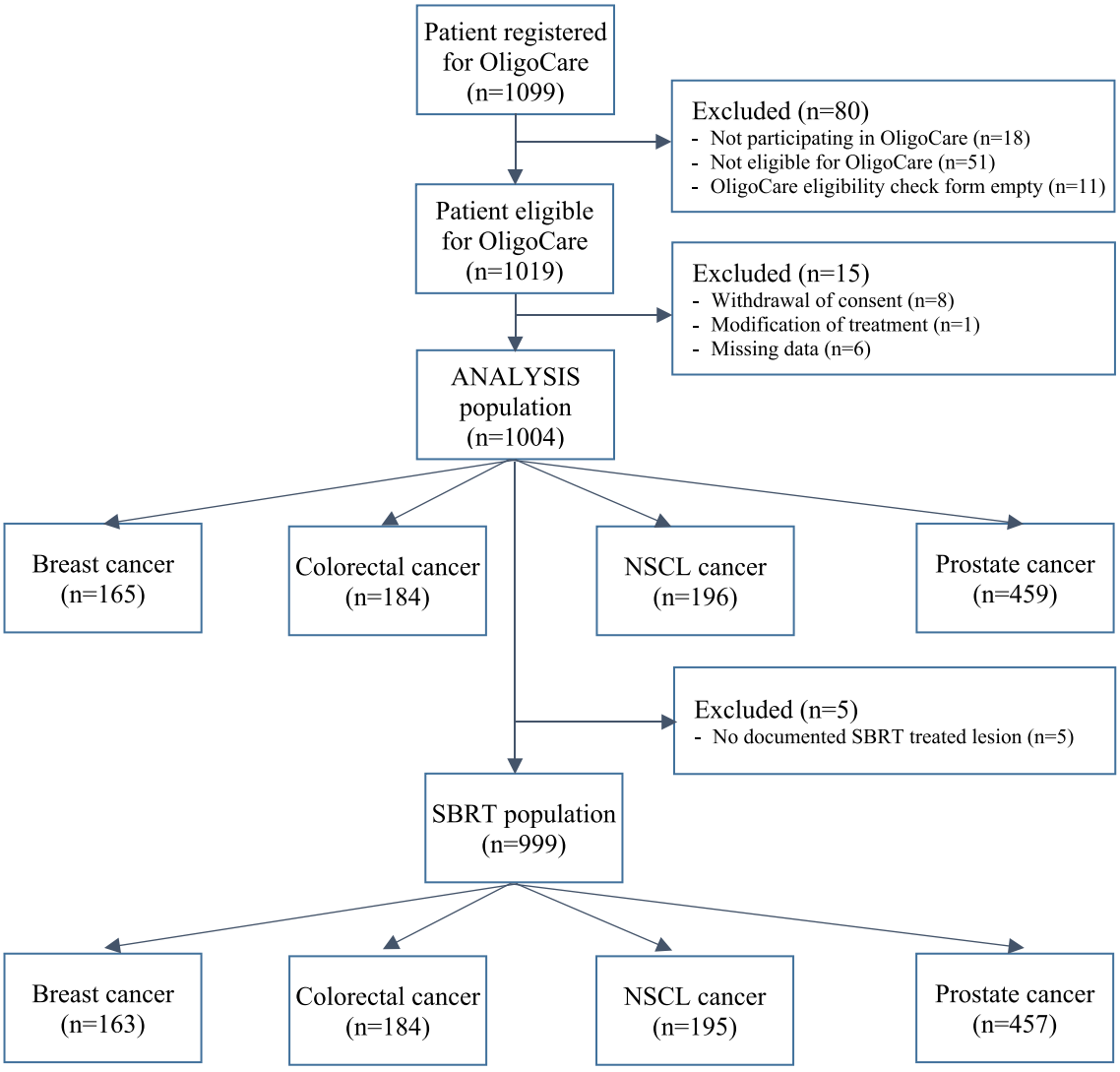


Fig. 1. CONSORT diagram.

majority of patients (n = 896; 89.2 %), metastatic lesions were confined to one single organ. For about one third of patients, a concomitant systemic therapy was part of the treatment regimen; this was the case in almost half of the BC patients (n = 78; 47.3 %), yet only in 12.5 % (n = 23) of CRC patients (Table 1). Fig. 2

More than two thirds of patients (n = 676; 67.7 %) were irradiated for a single distant lesion. The three most frequently irradiated organ sites were non-vertebral bone (n = 332; 22.8 %), lung (n = 306; 21.0 %), and lymph node metastases (n = 276; 19.0 %). Non-vertebral bone (n = 235; 35.6 %) and lymph node (n = 206; 31.2 %) metastases occurred most frequently in PC patients, while lung metastases were most frequently irradiated in CRC patients (n = 174; 59.2 %). Median CTV/ITV was 3.9 (interquartile range (IQR), 1.3–13.1) cm^3, with median values ranging between 2.9 cm^3 for PC and 7.3 cm^3 for BC patients. Median number of fractions was 5 (IQR, 3–5); median dose per fraction (median CTV/ITV dose) was 9.7 (IQR, 7.7–12.4) Gy. Median dose per fraction for NSCLC, BC, CRC, and PC patients was 10.6 (IQR, 8.0–15.1) Gy, 9.0 (IQR, 7.1–11.9) Gy, 13.1 (IQR, 9.0–21.5) Gy, and 8.6 (IQR, 7.1–10.2) Gy, respectively. Using a homogenous value of $\frac{\alpha}{\beta}$ = 10 Gy, median BED across all primary cancers was 74.4 (IQR, 60.6–105.0) Gy. The median BED for NSCLC, BC, CRC, and PC patients was 85.3 (IQR, 69.7–123.6) Gy, 70.2 (IQR, 59.5–81.6) Gy, 126.1 (IQR, 99.4–164.7) Gy, and 63.9 (IQR, 59.0–75.2) Gy, respectively. Cancer-specific median BED across all primary cancers was 173.9 (IQR, 114.1–241.6) Gy. Cancer-specific median BED for NSCLC, BC, CRC and PC was 85.3 (IQR, 69.7–123.6) Gy, 169.5 (IQR, 131.0–233.9) Gy, 126.1 (IQR, 99.4–164.7) Gy, and 237.2 (IQR, 198.3–284.5) Gy, respectively. Cancer-specific median EQD2 across all primary cancers was 96.8 (IQR, 76.5–122.6) Gy. Cancer-specific median EQD2 for NSCLC, BC, CRC, and PC was 71.0 (IQR, 58.0–103.0) Gy, 94.2 (IQR, 72.8–129.9) Gy, 105.1 (IQR, 82.8–137.3) Gy, and 101.7 (IQR, 85.0–121.9) Gy, respectively (Table 2). Only BED was used for further analysis. For technical SBRT treatment details, refer to Supplementary Table 3. Fig. 3

On multivariate analysis (MVA) using a non-cancer-specific BED, one patient-related (primary cancer, p <.0001) and two lesion-related (location of metastases, p <.0001; size (CTV/ITV) of SBRT-treated metastases, p <.0001) factors were statistically significantly associated with BED (Table 3). BED was lower when the primary tumor was BC, NSCLC or PC with an estimated decrease of 13 Gy (99.85 % confidence interval (CI), 2–23 Gy), 13 Gy (99.85 % CI, 3–23 Gy), and 15 Gy (99.85 % CI, 4–26 Gy), respectively, when compared to metastatic CRC lesions (Supplementary Table 4a, Supplementary Fig. 3a). BED was significantly lower if the oligometastatic lesion was located in the adrenal gland, brain, non-regional lymph nodes, non-vertebral bones, pancreas or spine with an estimated decrease of 33 Gy (99.85 % CI, 12–55 Gy), 52 Gy (99.85 % CI, 36–69 Gy), 50 Gy (99.85 % CI, 38–63 Gy), 58 Gy (99.85 % CI, 45–70 Gy), 46 Gy (99.85 % CI, 2–90) and 61 Gy (99.85 % CI, 48–74), respectively, when compared to liver lesions. No significant difference in BED was found for kidney, lung, pleura or soft tissue lesions when compared to liver metastasis (Supplementary Table 4a, Supplementary Fig. 4a). BED was also found to decrease with increased CTV/ITV size, with an estimated decrease of 1.4 Gy (99.85 % CI, 0.4–2.4 Gy) when the CTV/ITV size doubles (Supplementary Table 4a). Factors such as site accrual capacity, age at registration, performance status at baseline, OMD state or number of oligometastases treated with SBRT did not show a statistically significant association with BED.

On MVA using cancer-specific BEDs, primary cancer (p <.0001) and location of metastasis (p <.0001) remained the only two statistically significantly associated variables (Table 3). Cancer-specific BED was higher for BC and PC with an estimated increase of 153 Gy (99.85 % CI, 128–178) and 216 Gy (99.85 % CI, 192–241), respectively, in comparison to CRC (Supplementary Fig. 3b). Cancer-specific BED was statistically significantly lower if the oligometastatic lesion was located in the adrenal gland, brain, kidney, non-regional lymph nodes, non-vertebral bones, other sites and spine with an estimated dose decrease of 60 Gy (99.85 % CI, 13–106), 90 Gy (99.85 % CI, 54–126), 64 Gy (99.85 % CI, 1–130), 91 Gy (99.85 % CI, 63–118), 123 Gy (99.85 % CI, 96–151), 112 Gy (99.85 % CI, 72–152) and 138 Gy (99.85 % CI, 109–167), respectively, as compared to liver lesions. No significant difference as compared to liver lesions was detected for metastases located in the lung, pancreas, pleura or soft tissue. The association of BED with CTV/ITV size did not persist on MVA with cancer-specific BEDs (Supplementary Table 4b).

Table 1
Patient demographics (analysis population).

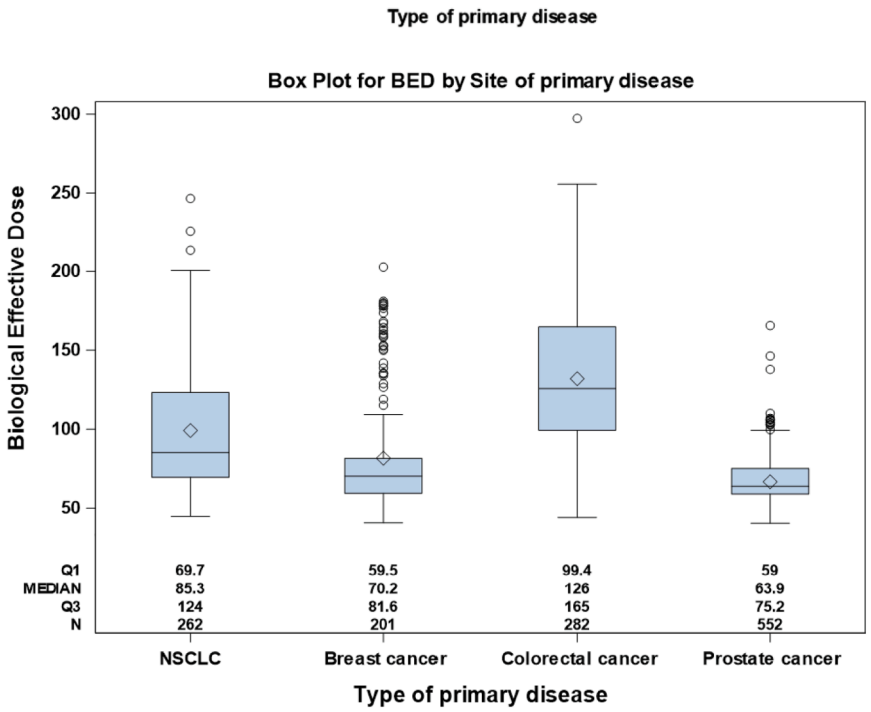
Variable	NSCLC (n = 196)	BC (n = 165)	CRC (n = 184)	PC (n = 459)	Total (n = 1,004)
Age, median (range)	68 (28–90)	60 (28–91)	70 (34–89)	71 (46–91)	69 (28–91)
Gender, n (%)					
• Female	74 (37.8)	163 (98.8)	78 (42.4)	0 (0.0)	315 (31.4)
• Male	122 (62.2)	2 (1.2)	106 (57.6)	459 (100)	689 (68.6)
ECOG, n (%)					
• ≤1	161 (82.1)	130 (78.8)	162 (88.1)	373 (81.3)	826 (82.2)
• >2	9 (4.6)	2 (1.2)	8 (4.3)	3 (0.7)	18 (1.8)
• Unknown	26 (13.3)	33 (20.0)	14 (7.6)	83 (18.0)	156 (15.5)
OMD state, n (%)					
• De-novo	119 (60.7)	88 (53.3)	62 (33.7)	322 (70.2)	591 (58.9)
• Repeat	51 (26.0)	51 (30.9)	80 (43.5)	112 (24.4)	294 (29.3)
• Induced	26 (13.3)	26 (15.8)	42 (22.8)	25 (5.4)	119 (11.9)
# of distant lesions, n (%)*					
• 1	128 (65.6)	120 (72.7)	108 (59.0)	298 (65.1)	654 (65.3)
• 2	47 (24.1)	31 (18.8)	47 (25.7)	113 (24.7)	238 (23.8)
• 3	14 (7.2)	13 (7.9)	17 (9.3)	33 (7.2)	77 (7.7)
• 4	2 (1.0)	0 (0.0)	9 (4.9)	8 (1.7)	19 (1.9)
• 5	3 (1.5)	0 (0.0)	2 (1.1)	5 (1.1)	10 (1.0)
• 6	1 (0.5)	1 (0.6)	0 (0.0)	1 (0.2)	3 (0.3)
# of affected sites, n (%)					
• 1	171 (87.2)	151 (91.5)	167 (90.8)	407 (88.7)	896 (89.2)
• 2	24 (12.2)	14 (8.5)	17 (9.2)	51 (11.1)	106 (10.6)
• 3	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)
• 4	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Concomitant therapy**	58 (29.6)	78 (47.3)	23 (12.5)	178 (38.8)	337 (33.6)

Abbreviations: BC = Breast cancer; CRC = Colorectal cancer, ECOG = European Cooperative Oncology Group; NSCLC = Non-small cell lung cancer; OMD = Oligometastatic disease; PC = Prostate cancer.
Based on a n = 1,001 OMD population, after excluding three patients with duplicated OMD lesions.
Includes chemotherapy, targeted therapy, immunotherapy, hormonal therapy and/or other systemic treatments.

Discussion

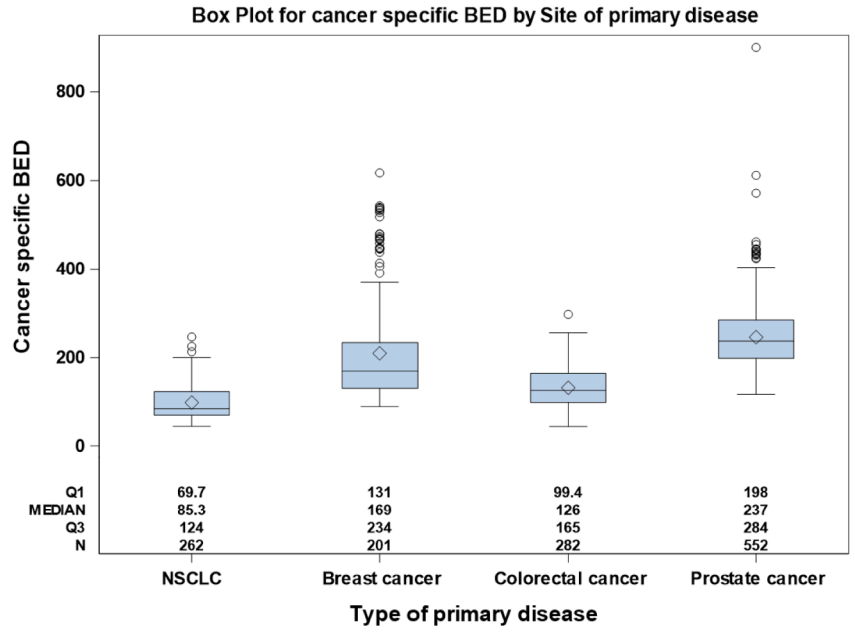
A large heterogeneity of SBRT fractions, dose per fraction, and total BED dose was observed. Delivered doses were lower than expected, below the threshold of 100 Gy BED, which has been reported as cut-off for > 90 % local metastases control [22,23]. On MVA with non-cancer-specific BED, three factors (primary cancer, location of metastases, size of metastases) were significantly associated with BED: CRC metastases were treated with higher doses; metastases to the adrenal glands, brain, non-regional lymph nodes, non-vertebral bones, pancreas, and spine were treated with comparably lower doses; and larger distant metastases

Box plot for non-cancer-specific BED by site of primary disease



Abbreviations: BED = Biologically effective dose; NSCLC = Non-small cell lung cancer.

Box plot for cancer-specific BED by site of primary disease



Abbreviations: BED = Biologically effective dose; NSCLC = Non-small cell lung cancer.

Fig. 2. a. Box plot for non-cancer-specific BED by site of primary disease. *Abbreviations:* BED = Biologically effective dose; NSCLC = Non-small cell lung cancer. b. Box plot for cancer-specific BED by site of primary disease. *Abbreviations:* BED = Biologically effective dose; NSCLC = Non-small cell lung cancer.

were treated with comparably lower doses. On MVA with cancer-specific BED, only two factors remained associated with BED: primary cancer and location of metastases. Oligometastatic PC and BC patients were treated with significantly higher cancer-specific BED compared to NSCLC and CRC patients.

The optimal SBRT dose and fractionation schedules for oligometastatic patients with different primary cancers remain a matter of investigation. Dose per fraction in the STOMP trial was 10 Gy; the SABR-COMET trial did not explicitly report the used single dose for the CRC sub-group [9,13]. In this analysis, dose per fraction varied between

Table 2
Treatment details (SBRT population).

Variable	NSCLC	BC	CRC	PC	Total
# of irradiated lesions per patient, n (%)	*n = 195*	*n = 163*	*n = 184*	*n = 457*	*n = 999*
• 1	131 (67.2)	123 (75.5)	114 (62.0)	308 (67.4)	676 (67.7)
• 2	48 (24.6)	28 (17.2)	43 (23.4)	110 (24.1)	229 (22.9)
• ≥3	16 (8.2)	12 (7.4)	27 (14.7)	39 (8.5)	94 (9.4)
# of irradiated sites, n (%)	*n = 284*	*n = 218*	*n = 294*	*n = 660*	*n = 1,456*
• Non-vertebral bone mets	25 (8.8)	68 (31.2)	4 (1.4)	235 (35.6)	332 (22.8)
• Lung mets	94 (33.2)	30 (13.8)	174 (59.2)	8 (1.2)	306 (21.0)
• Distant lymph node mets	32 (11.3)	14 (6.4)	24 (8.2)	206 (31.2)	276 (19.0)
• Spine mets	17 (6.0)	59 (27.1)	1 (0.3)	148 (22.4)	225 (15.5)
• Liver mets	22 (7.8)	24 (11.0)	76 (25.9)	1 (0.2)	123 (8.5)
• Other locations[1]	94 (33.1)	23 (10.6)	15 (5.1)	62 (9.4)	194 (13.3)
CTV/ITV in cm^3, median (IQR)[2]	4.8 (1.6–13.1)	7.3 (2.3–24.0)	3.3 (1.2–12.4)	2.9 (0.9–11.1)	3.9 (1.3–13.1)
Dose per fraction to CTV/ITV, median (IQR)[3]	10.6 (8.0–15.1)	9.0 (7.1–11.9)	13.1 (9.0–21.5)	8.6 (7.1–10.2)	9.7 (7.7–12.4)
BED with $\frac{\alpha}{\beta} = 10$ Gy for all cancer types	85.3 (69.7–123.6)	70.2 (59.5–81.6)	126.1 (99.4–164.7)	63.9 (59.0–75.2)	74.4 (60.6–105.0)
Cancer-specific BED in Gy, median (IQR)[5]	85.3 (69.7–123.6)	169.5 (131.0–233.9)	126.1 (99.4–164.7)	237.2 (198.3–284.5)	173.9 (114.1–241.6)
Cancer-specific EQD2 in Gy, median (IQR)[4]	71.0 (58.0–103.0)	94.2 (72.8–129.9)	105.1 (82.8–137.3)	101.7 (85.0–121.9)	96.8 (76.5–122.6)

Abbreviations: BC = Breast cancer; BED = Biologically effective dose; CRC = Colorectal cancer; CTV = Clinical target volume; EQD2 = Equivalent dose in 2 Gy single fractions; IQR = Interquartile range; ITV = Internal target volume; NSCLC = Non-small cell lung cancer; PC = Prostate cancer; SBRT = Stereotactic body radiotherapy.

[1] Includes metastasis to adrenal glands, brain, kidney, pancreas, pleura, skin, soft tissue, and other sites.

[2] Based on 273 NSCLC, 215 breast cancer, 292 colorectal cancer, and 617 prostate cancer lesions.

[3] Based on 262 NSLC, 201 breast cancer, 282 colorectal cancer, and 552 prostate cancer lesions, which had all necessary data for dosimetric analysis.

[4] For NSCLC and colorectal cancer, $\alpha/\beta = 10$; for breast cancer, $\alpha/\beta = 2.5$; and for prostate cancer, $\alpha/\beta = 1.5$.

[5] For NSCLC and colorectal cancer, $EQD2 = \frac{BED}{1+\frac{2}{\frac{\alpha}{\beta}}} = \frac{BED}{1.2}$; for breast cancer, $EQD2 = \frac{BED}{1+\frac{2}{\frac{\alpha}{\beta}}} = \frac{BED}{1.8}$; and for prostate cancer, $EQD2 = \frac{BED}{1+\frac{2}{\frac{\alpha}{\beta}}} = \frac{BED}{2.33}$.

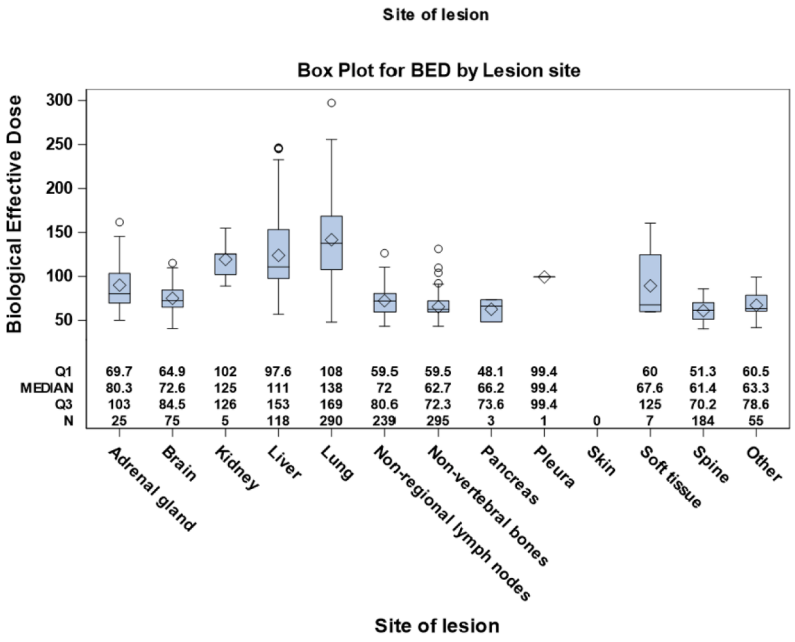
different primary tumors, with the lowest median dose observed in PC (8.6 Gy) and the highest median dose in CRC (13.1 Gy) patients. Consequently, in our SBRT population, non-cancer-specific median BED varied by primary tumor, with the lowest median BED being observed in PC (63.9 Gy) and the highest in CRC cancer (126.1 Gy) patients. A systematic review and *meta*-analysis of 686 patients from 15 studies with pulmonary metastases from CRC indeed suggested that SBRT for distant metastases for CRC may require higher BEDs than in other primary cancers [24]. For patients with NSCLC, non-cancer-specific median BED was 85.3 Gy in our SBRT population. In the *Iyengar* trial, various fractionation schedules were allowed, all of which reflect a similar BED dose range (21–27 Gy / 1 Fx; 26.5–33.0 Gy / 3 Fx; 30.0–37.5 / 5 Fx) [7]. Recent systematic reviews on oligometastatic NSCLC such as the one conducted by *Brandão et al. (2021)* did not feature an assessment of SBRT dose and fractionation schedules [25], thus reinforcing the relevancy of the current study. When using cancer-specific BEDs in regression analysis, variation in BED was more pronounced for primary cancers, suggesting that SBRT doses are adjusted to the primary cancers and oligometastasis location. This observation of higher cancer-specific SBRT BEDs in oligometastatic BC and PC fits well with observations of excellent local control of metastases from these primary cancers, especially as compared to CRC [26]. Additionally, the different distribution of distant metastases sites by primary tumor might also play a role.

Furthermore, in our SBRT population, metastatic lung and liver target sites were treated at higher cancer-specific BED compared to all other targets, independent of the primary tumor. Median dose per fraction and non-cancer-specific BED for lung and liver lesions were 13.2 (IQR, 10.1–22.9) Gy and 11.3 (IQR, 8.7–18.0) as well as 137.6 (IQR, 107.8–168.5) Gy and 110.7 (IQR, 97.6–153.5) Gy, respectively. *Mendez-Romero et al. (2020)* previously reported a large variation in BED for liver metastases from the Dutch-Belgian SBRT registry, where 668 liver metastases in 515 patients were treated with either 60 Gy / 5 Fx, 55–60 Gy / 5 Fx, 60 Gy / 8 Fx or 60 Gy / 3 Fx [27]. *Andratschke et al. (2018)*, in reporting on 474 patients with 623 liver oligometastases from the SBRT database of the German Radiation Oncology Society, also reported a high variance in dose-fractionation schedules (median: 3; range, 1–13) and dose per fraction (median: 18.5 Gy; IQR, 3–37.5 Gy), with a consistently high BED after an initial adoption phase of the treatment technique by the respective radiation oncology department [28]. A similar observation holds true for lung metastases, with, for example, *Rieber et al. (2016)* seeing large dose and fraction heterogeneity in 700 patients with medically inoperable lung metastases who were treated with SBRT. The authors found a median dose of 12.5 Gy (range, 3.0–33.0) and a median number of 3 fractions (range, 1–13) [29]. Besides the large dose and fractionation heterogeneity in liver and lung SBRT, *Viani et al. (2021)*, who conducted a systematic review and *meta*-analysis of 467 patients with 653 oligometastatic lesions from BC receiving local ablative therapy, and they found a 10 Gy higher BED for liver and lung lesions as compared to bone-only metastases [30]. The fact that the lungs and liver are parallel organs-at-risk and thus have relatively higher dose tolerances as well as the large and long-term experience from primary NSCLC and liver cancers have contributed to this practice.

Limitations of this analysis might consist in the fact that the top three accruing institutions were located in Italy, thus potentially introducing a bias with respect to varying SBRT dose and fractionation schedules across different countries. Moreover, the clinical consequences of different dose-fractionation regimens in terms of efficacy and safety have not been evaluated yet. Another potential reason for bias could be different cost-reimbursement models that can affect the median number of fractions. In fact, this consideration could have limited more pervasive use of single-dose or ultra-short schedules of hypofractionation.

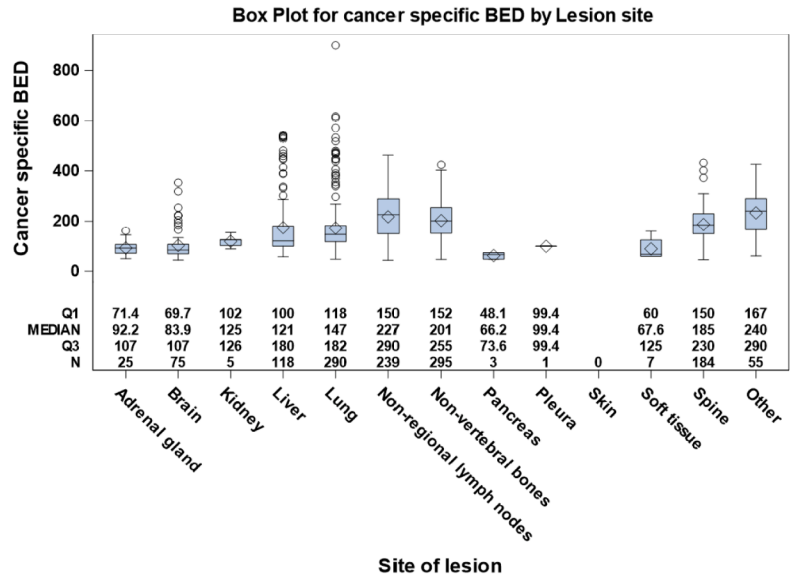
In conclusion, SBRT dose and fractionation schedules are heterogeneous across participating institutions. A first analysis suggested that non-cancer-specific BED was associated with primary cancer, location of metastases, and size of metastases, yet only the effects of the primary cancer and location of metastases persisted when using cancer-specific BEDs. Whereas OMD PC and BC patients were treated with lower non-cancer specific SBRT BED doses as compared to CRC, this changed using cancer-specific alpha/betas: Cancer-specific SBRT BED doses were then higher for PC and BC as compared to CRC and NSCLC. This real-world analysis suggests that SBRT doses are adjusted to the primary cancers and oligometastasis location. Future analysis will address safety and efficacy of this adapted SBRT fractionation approach.

Box plot for non-cancer-specific BED by lesion site



Abbreviations: BED = Biologically effective dose.

Box plot for cancers-specific BED by lesion site



Abbreviations: BED = Biologically effective dose.

Fig. 3. a. Box plot for non-cancer-specific BED by lesion site. *Abbreviations:* BED = Biologically effective dose. b. Box plot for cancers-specific BED by lesion site. *Abbreviations:* BED = Biologically effective dose.

Declarations

Ethical approval: All study procedures, research governance, study ethics and other research considerations regarding OligoCare will follow the EORTC 1811-E^2-RADIatE protocol.

Availability of data and material: Collected patient data are confidential and not available for publication.

Code availability: Not applicable for this publication.

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CRediT authorship contribution statement

Sebastian M. Christ: Writing – review & editing, Writing – original

Table 3
Results of univariate and multivariate linear mixed regression model (fixed effects).

Variable	Num DF	Non-cancer-specific BED		Cancer-specific BED	
		UVA p-value	MVA p-value	UVA p-value	MVA p-value
Accrual rate per month *Categorical variable*	1	0.360	0.345	0.432	0.441
Age at registration (years) *Continuous variable*	1	0.672	0.375	0.003	0.994
WHO performance status 0 vs. ≥ 1	2	0.041	0.083	**0.001**	0.614
Type of primary disease *Reference category*: CRC	3	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
ESTRO/EORTC OMD classification *Reference category*: Repeat	2	**<0.0001**	0.543	0.041	0.127
Number of irradiated lesions *Continuous variable*	1	0.217	0.194	0.253	0.444
Concomitant systemic therapy *Reference category*: Yes	1	**<0.0001**	0.310	0.019	0.611
Site of lesion *Reference category*: Liver	11	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
CTV/ITV (log2 transformed) *Continuous variable*	1	0.017	**<0.0001**	**<0.0001**	0.010

Abbreviations: BED = Biologically effective dose; CRC = Colorectal cancer; CTV = Clinical target volume; DF = Degrees of freedom; EORTC = European Organisation for Research and Treatment of Cancer; ESTRO = European Society of Radiation Oncology; ITV = Internal target volume; MVA = Multivariate analysis, OMD = Oligometastatic disease; UVA = Univariate analysis; WHO = World Health Organization.
Note: Bolded p-values are < 0.001475 and therefore statistically significant in the context of this study.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: BAJF received grants from Accuray, AIRC, IBA and Fondazione IEO-CCM, lecture payments/honoraria from Bayer, Accuray, Astellas, IBA, IPSEN, Astra Zeneca, Tecnologie Avanzate, Recordati, and Novartis, and has board appointments at Astra Zeneca, Bayer, and Seagen. MG and PO are PIs of the ESTRO-EORTC 1811-E^2-RADIatE OligoCare trial. MG is president-elect of ESTRO.

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Prior publication

Some of this data has been orally presented as OligoCare data at ESTRO's Annual Congress in May 2022 in Copenhagen, Denmark. Yet none of this data has previously been published in the peer-reviewed, scientific literature.

Authors' contributions

All authors made substantial contributions to this project and manuscript. MG and PO are the PIs of the ESTRO-EORTC 1811-E^2-RADIatE OligoCare trial. SMC supported the development of this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2024.110235.

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