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REVIEW

Knowing When to Use Stereotactic Ablative Radiation Therapy in Oligometastatic Cancer

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Abstract: Oligometastatic patients are a heterogeneous and yet not well-defined population. The actual definition identifies as oligometastatic, patients with 1–5 metastases in 1–3 different organs. However, only a proportion of these patients are "true" oligometastatic and therefore derive some kinds of benefit from local ablative approaches like stereotactic ablative radiation therapy (SABR). Since SABR is an easily accessible, effective and well-tolerated treatment, it is widely employed in the oligometastatic scenarios, without a particular focus on selection criteria. However, it should be crucial to identify predictive and prognostic features that could be clinically implemented. Therefore, we conducted this narrative review of the available literature to summarize all clinical, radiomic, genetic and epigenetic features found to be predictive of overall survival, progression-free survival or local control of oligometastatic patients treated with SABR.

Keywords: stereotactic ablative radiation therapy, oligometastases, prognostic factors, selection criteria

Introduction

Despite 25 years have passed since the existence of an oligometastatic state was firstly postulate.[1] The first clinical experiences of successful local treatment of metastatic patients are even older, being dated almost one century ago.[2] Notwithstanding this quite impressive historical tradition and the constant increase in interest towards this clinical scenario in the last 20 years with hundreds of publications, very few step forwards were done for the identification of the "true" oligometastatic patient. A low number of metastases (one to five) in few organs (1 to 3) are still the most used definition for these patients. However, it is common thinking among the experts in the field that this numerical characterization is just a part of a more complex scenario, in which biological aspects, mostly still unknown, probably play a major role in determining the course of the disease. Recently, ESTRO and EORTC tried to standardize the definition of oligometastatic state according to available evidences, but the same authors conclude that much remains to be done for a more precise and accurate identification.[3]

Stereotactic ablative radiation therapy (SABR) is playing a crucial role in the treatment of oligometastatic patients. Although the first historical series are for the most part based on surgical metastasectomy, the most recent publications on the topic utilize SABR as the treatment of choice. There are different reasons for this trend in our opinion. Indeed, SABR is an effective and safe option (high local control rates and low toxicity reported in thousands of patients), and potentially feasible in almost

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all body sites. Moreover, SABR allows the simultaneous treatment of different lesions located in different organs, is non-invasive and does not require hospitalization. Lastly, but not less important, the large majority of oligometastatic patients treated with local ablative approaches in prospective trials are SABR patients, making SABR the only treatment with high level of evidence in this clinical scenario.[4–7] However, the crucial question "who is the oligometastatic patient" is still to be answered. Therefore, in this review, we want to summarize the most recent findings in the identification of significant parameters for this clinical scenario. We chose to focus on the four major solid tumors (breast, lung, colorectal and prostate), looking not only for clinical features, but also with a special focus on biological, genetic and radiomic parameters that could enrich clinical evaluation.

Materials and Methods

A literature review of SABR in oligometastatic disease was performed. PubMed, Web of Science and MedLine were used for research.

Studies focusing on oligometastases treated with definitive SABR and reporting data on prognostic factors were included in the current analysis.

The following keywords were combined for the search: SABR/SBRT/stereotactic body radiotherapy AND oligometastases/oligometastatic AND pulmonary/lung OR prostatic/prostate OR colorectal OR breast cancer.

The correlation between prognostic factors and local control (LC), progression-free survival (PFS) and/or overall survival (OS) after SABR was evaluated.

SABR-Related Predictors of Response in Primary Tumor-Specific Oligometastatic Disease

Colorectal Cancer

More than half patients with colorectal cancer (CRC) will develop metastatic disease despite definitive radical surgery at diagnosis.[8,9] Among the local therapies, surgery is the most frequently used in oligometastatic disease. About 85% of patients with oligometastatic CRC have liver and lung localization and a surgical approach improves survival in this setting.[10–13] SABR is an alternative ablative local therapy when surgery is not feasible or patients refuse metastasectomy. In a review of SABR in colorectal oligometastases, liver and lung 2-years LC rates were 32–91% and 53–92%, respectively.[14] In a recent meta-analysis of CRC pulmonary metastases treated with SABR, Choi et al showed that LC rate at 1, 2, 3, and 5 years was 81%, 72%, 56%, and 62%, and the OS rate was 87%, 70%, 58%, and 43%, respectively.[15]

The selection of patients who could benefit from local therapies is crucial in order to obtain the largest benefit from the treatments. However, factors related to long-term survival of CRC oligometastatic disease are not yet clearly defined in SABR setting.

We identified 16 articles reporting the analysis of prognostic factors after SABR in patients with CRC oligometastases. Two were prospective studies and 14 retrospective series. Overall, 1429 patients for a total of 2384 lesions were included. The details are described in Table 1.

According to our review, LC rates after SABR varied from 70% to 95% at 1 year and 64% to 81% after 3 years. Five series reported 5-year LC rate ranging from 24% to 77%. The OS rates ranged from 67% to 95.5% at 1 year. The 3- and 5-year OS rates were 43–57% and 26–43%, respectively. PFS ranged from 37% to 56% at 1 year and 64% to 81% after 3 years.

Treatment-related factors affecting LC and survival were doses. In particular, biological effective dose (BED) ≥ 100 predicted better LC in 5 series[16–20] and BED ≥ 75 in one study.[21] Sharma et al observed poorer LC in patients treated with BED < 100.[22] Only two studies found correlation between higher OS and BED >100.[20,22] In a prospective trial, LC was better in patients treated with SABR dose ≥ 60 Gy in 3 fractions at univariate analysis ($p= 0.04$).[23] SABR dose also improved LC in a little retrospective study.[24] CRC metastases are assumed to be radioresistant and it may explain why higher doses related to better outcomes. Volume of metastases correlated with LC in 3 series[21,24,25] and with OS in 6 studies.[19,23,25–28] Total number of metastases treated with SABR was not a clear prognostic factor according to our analysis. Limited number (< 3) of metastases improved LC in one study[29] and OS in two.[22,28] In a retrospective study LC was significantly better for pulmonary oligometastases from rectal cancer compared to those from colon cancer.[17] The reason is unknown. The same authors concluded that this difference in response could be due to the heterogeneous molecular patterns between the two primary sites such as microsatellite instability, BRAF/KRAS status, etc. Lung location was correlated with better LC than liver metastases also in Thomson et al study.[19] The liver microenvironment which gives a higher tumor radioresistance may be

Table 1 Summary of Colorectal Oligometastases Treated with SABR

Author, Year	Study Design	Number of Patients/ Lesions	Median Age (Years)	Site of Metastases	Median Dose/ Fractions	Median BED	Median Follow-Up, (Months)	LC	OS	PFS	Prognostic Factors		
											Patient Factors	Tumour Factors	Treatment Factors
Li,[16] 2019	Retrospective	53/105	61	Lung	48–75 Gy/ 4–10 fr	100 Gy	14	90.4% (1y) 90.4% (2yrs)	95.5% (1y) 74.5% (2yrs)	N.A.	N.A.	N.A.	LC: -BED ≥100Gy (p-value 0.047) OS: -Radiological response (p-value 0.006)
Sharma,[22] 2020	Retrospective	118/202	N.A.	Lung	N.A.	N.A.	31	83% (2yrs) 81% (3yrs) 77% (5yrs)	69% (2yrs) 55% (3yrs) 36% (5yrs)	38% (2yrs) 29% (3yrs) 21% (5yrs)	OS: - male gender (HR 0.52, p-value 0.025) -age < 70 years (HR 0.52, p-value 0.024)	OS: -single metastasis (HR 0.37, p-value 0.046)	LC: -BED < 100 Gy (HR 3.67, p-value < 0.001) -pre-SABR chemotherapy (HR 2.66, p-value 0.020) OS: -BED ≥100Gy (HR 0.52, p-value 0.017)
Ji,[28] 2021	Retrospective	94/162	61	Lung (29%) Liver (23%) Nodes (26%) Other (22%)	N.A.	100 Gy	36.4	94.1% (1y)	26.9 mos (median)	7 mos (median)	OS: -Performance Status 2–3 (HR 3.51, p-value 0.001) PFS: -Performance Status 2–3 (HR 1.86, p-value 0.020)	PFS: Number of metastases > 2 (HR 2.76, p-value 0.001) -pre-SABR CEA > 100 ug/L (HR 2.08, p=0.013) OS: -pre-SABR CEA > 100 ug/L (HR 2.60, p-value 0.011)	OS: -PTV ≤ 30cc (HR 3.69, p-value 0.000)

(*Continued*)

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Table 1 (Continued).

Author, Year	Study Design	Number of Patients/ Lesions	Median Age (Years)	Site of Metastases	Median Dose/ Fractions	Median BED	Median Follow-Up, (Months)	LC	OS	PFS	Prognostic Factors		
											Patient Factors	Tumour Factors	Treatment Factors
Thomson,[19] 2020	Retrospective	165/262	69	Lung (47%) Liver (36%) Spine (10%) Other (7%)	24–60 Gy/ 2–5 fr	107 Gy	22	90.5% (1y) 76.2% (2yrs) 73.1% (3yrs)	49.3 mos (median)	12.4 mos (median)	N.A.	LC: -lung metastases (HR 0.41, p-value 0.011) OS: -CEA (HR 1.46, p-value 0.001) -Primary in situ (yes vs no: HR 4.35, p-value 0.009) -Oligoprogression vs Oligometastases (HR 3.35, p-value)	LC: -mean BED 107 (HR 0.99, p-value 0.042) OS: -Lines of previous systemic therapy (HR 1.56, p-value 0.016) - PTV volume (HR 1.83, p-value 0.002)
Franzese,[27] 2018	Retrospective	270/437	69	Lung (49%) Liver (36%) nodes (12%) Other (3%)	48 Gy/ 1–8 fr	105.6	23	95% (1y) 73% (3yrs) 73% (5yrs)	88.5% (1y) 56.6% (3yrs) 37.2% (5yrs)	39.2% (1y) 14.3% (3yrs) 13.5% (5yrs)	N.A.	LC: -Time from metastases to SABR, >12 months (HR 1.62, p-value 0.023) OS: -Lesion > 30 mm (HR 1.56, p-value 0.030) -non-lung metastases (HR 1.67, p-value 0.020)	OS: - systemic therapy pre-SABR (HR 1.82, p-value 0.023) -progression of treated metastases (HR 1.80, p-value 0.007)

Dell'Acqua,[21] 2019	Retrospective	102/150	67	Lung (53%) Liver (15%) Node (13%) Other (19%)	45	112.5	11.4	70% (1y) 55% (2yrs)	90% (1y) 90% (2yrs)	37% (1y) 27% (2yrs)	N.A.	N.A.	LC: -BED10 ≥ 75 Gy (HR 0.12, p-value 0.0004) -PTV volume < 42 cm3 (HR 0.46, p-value 0.02)
Nicosia,[34] 2020	Retrospective	38/107	75	Lung	30–70Gy/ 3–10 fr	105	28	91.5% (1y) 80% (2yrs)	39.5 mos (median)	7 mos (median)	N.A.	PFS: -BRAF wild-type (p-value 0.046)	N.A.
Jethwa,[26] 2020	Retrospective	85/109	58	Liver Lung Nodes Bone Other	50 Gy/ 3–5 fr	113	50	70% (2yrs)	69% (2yrs) 26% (5yrs)	14% (2yrs) 5% (5yrs)	OS: -age > 60 years (HR: 2.4, p-value 0.01)	LC: -KRAS and TP53 mutation (HR: 4.5, p-value 0.04) OS: -lesion size per 1 cm (HR: 1.3, p-value < 0.01) -KRAS mutation (HR: 2.2, p-value < 0.01)	N.A.
Hoyer,[30] 2006	Prospective	64/141	67	Liver (69%) Lung (19%) Others (12%)	45 Gy/ 3 fr	N.A.	24	95% (1y) 79% (2yrs)	67% (1y) 38% (2yrs)	N.A.	PFS: -performance status < 1 (p-value 0.008) OS: -Male gender (p-value 0.03)	PFS: -metachronous metastases (p-value 0.04) OS: -extrahepatic localization (p-value 0.01) -metachronous metastases (p-value 0.04) -size metastasis less than 35 mm (p-value 0.02)	PFS: -No neoadjuvant chemotherapy (p-value 0.01)

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Table 1 (Continued).

Author, Year	Study Design	Number of Patients/ Lesions	Median Age (Years)	Site of Metastases	Median Dose/ Fractions	Median BED	Median Follow-Up, (Months)	LC	OS	PFS	Prognostic Factors		
											Patient Factors	Tumour Factors	Treatment Factors
Yu,[20] 2019	Retrospective	48/88	58	Lung (60%) Liver (35%) Nodes (5%)	45–72 Gy/ 3–10 fr	45–72 Gy/3–10 fr	15	85% (1y) 69% (2yrs)	87.2% (1y) 63.2% (2yrs)	46.2% (1y) 23.7% (2yrs)	N.A.	N.A.	LC: -BED≥100 Gy (HR, 0.19; p-value 0.048) OS: -BED ≥100 Gy (HR, 0.19; p-value 0.05)
Kang,[25] 2010	Retrospective	59/78	57	Lung 22% Liver 17% Nodes 52% Others 9%	45 Gy/3 fr	N.A.	32	66% (3yrs) 24% (5yrs)	49% (3yrs) 29% (5yrs)	25% (3yrs) 19% (5yrs)	N.A.	LC: -GTV < 23 mL (p-value 0.05) OS: - GTV < 23 mL (p-value 0.014) -Lesion site (p-value 0.04)	N.A.
Bae,[24] 2012	Retrospective	41/50	56	Lung 29% Liver 27% Nodes 44%	48 Gy/3 fr	N.A.	28	64% (3yrs) 57% (5yrs)	60% (3yrs) 38% (5yrs)	40% (3yrs) 40% (5yrs)	N.A.	LC: -GTV (HR 8.5, p-value 0.003)	LC: -SABR dose (HR, 0.12; p-value 0.010)
Jingu,[17] 2017	Retrospective	93/104	69	Lung	50 Gy/3–15 fr	105.6	28	65% (3yrs) 56% (5yrs)	56% (3yrs) 43% (5yrs)	N.A.	LC: -age > 70 (HR=0.416, p-value 0.044)	LC: -Rectal primary tumor (HR=0.375, p-value 0.025)	LC: -BED_{10} ≥100 Gy (HR=0.100, p-value 0.027) -chemotherapy after SABR (HR=0.246, p-value 0.003)

Joo,[18] 2017	Retrospective	70/103	65	Liver	45–60/3–4 fr	60–180	34.2	93% (1y) 73% (2yrs) 68% (3yrs)	75% (2yrs)	35% (2yrs)	LC: -age (HR 1.05; p-value 0.02)	LC: -liver MRI (HR 3.35; p-value 0.03) OS: -Extrahepatic recurrence (HR 4.77; p-value < 0.01)	LC: -BED 132–180 (HR 0.24; p-value 0.03) -chemotherapy lines > 3 (HR 3.34; p-value <0.01)
Ottaiano,[29] 2018	Retrospective	47/174	67	Liver lung Nodes	60 Gy/ 3 fr	180	48.8	N.A.	44 mos (median)	13 mos (median)	N.A.	LC: -lung metastases (HR 0.36, p-value 0.0014) -KRAS mutation (HR 2.02, p-value 0.0093) - lesions < 3 (HR 0.14, p-value <0.0001) PFS: -KRAS mutation (HR 2.47; p-value 0.0012) -lesions < 3 (HR 0.23; p-value <0.0001) -Localization of primary tumor (right vs left colon: HR 2.03; p-value 0.0008) -lung metastases (HR 0.28; p-value <0.0001)	LC: -Reduction of deltaSUV max (p-value <0.001) -Response to first-line chemotherapy (Response complete: HR 0.35, p-value <0.0001) PFS: -Response to first-line chemotherapy (Response Complete: HR 0.23, p-value <0.0001) OS: -Reduction of delta SUV max after SABR (p-value 0.003)
Comito,[23] 2014	Prospective	82/112	68	Liver Lung	48–75 Gy/ 3–4 fr	N.A.	24	90% (1y) 80% (2yrs) 75% (3yrs)	85% (1y) 65% (2yrs) 43% (3yrs)	56% (1y) 40% (3yrs)	N.A.	OS: -GTV > 3 cm (p-value < 0.02)	LC: - dose ≥ 60 Gy (p-value 0.04)

Abbreviations: SABR, stereotactic ablative radiotherapy; LC, local control; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; BED, biologically effective dose; GTV, gross tumor volume; PTV, planning tumor volume; FR, fractions; Y, year; YRS, years; SUV max, maximum standardized uptake value; N.A., not available; MRI, magnetic resonance imaging; MOS, months; vs, versus; CEA, carcino embryonic antigen; BRAF, B-rapidly growing fibrosarcoma; KRAS, Kirsten rat sarcoma virus; TP53, tumor protein p53.

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the reason for this. The difficulty of finding all liver lesions on Cone Beam Computed Tomography (CBCT) was another explanation reported by authors. The same result was reported in another retrospective analysis.[29] Franzese et al showed that non-lung metastases predicted poor OS in a large retrospective study.[27] The metachronous timing of metastases was a positive prognostic factor for OS and PFS in a Phase II trial.[30] Sixty-four patients with 141 metastases were included. Male gender, extrahepatic localization and size of the metastasis less than 35 mm were also significantly correlated with better OS on univariate analysis. Advanced age was an unfavorable prognostic factor in oligometastases disease treated with SABR in 3 retrospective series.[17,22,26] The role of chemotherapy in CRC oligometastases treated with SABR is unclear. Thomson et al reported that number of lines of previous systemic therapy improved OS,[19] while it was a poor prognostic factor in Franzese et al analysis.[27] Similarly, poor LC was correlated to pre-SABR chemotherapy in a large retrospective study of CRC pulmonary metastases.[22] A complete response after first-line of chemotherapy at radiologic evaluation improved PFS in a retrospective study.[29] The conflicting results on pre-SABR systemic therapy could be related to the retrospective nature of these studies and patients selection bias. Furthermore, Jingu et al showed in multivariate analysis that chemotherapy after SABR improved LC in pulmonary oligometastatic disease from CRC.[17] Usually, response to SABR is assessed by Computed tomography (CT) or Magnetic Resonance Imaging (MRI). However, the [18F]-fluorodeoxyglucose positron emission tomography computed tomography ([18F]-FDG-PET/CT) is often used to discriminate necrotic tumor tissue from actively replicating tumor tissue after SABR. An Italian retrospective study investigated the role of [18F]-FDG-PET/CT among prognostic factors after SABR in patients with metastatic colorectal cancer. Notably, all patients were evaluated by [18F]-FDG-PET/CT before and after SABR and the reduction in delta maximum standardized uptake value (SUV_{max}) was significantly correlated with LC > 12 months (p <0.001) and OS > 24 months (p 0.003) at analysis.[29] Li et al reported a correlation between radiological response to CT-scan and OS after SABR. The first radiology evaluation was at a median time of 1.8 months (0.5–8.0, range) and the second at 5.3 months (1.9–12.5, range). The 2-years OS rate was correlated with radiological response at second assessment (Complete Response vs Partial Response vs Stable Disease vs Progressive Disease: 100 vs 85.7 vs 53.3 vs 25%; P = 0.006).[16]

Biomarker-based patient selection could be the right way to proceed, however published studies are rare.[31–33] Pitroda et al classified patients with CRC liver metastases into 3 subgroups based on a molecular risk score.[31] Patients with immune activation, p53 pathway and NRAS mutation had better OS. KRAS signaling, angiogenesis and SMAD3 mutation correlated with worse survival. The intermediate subgroup showed activation of E2F/MYC signaling, DNA damage and NOTCH1 and PIK3C2B mutations. Narayan et al reported poor disease-specific survival if peripheral circulating tumor DNA with TP53 mutation was found prior to resection of CRC liver metastases.[32] In a review of resectable and unresectable colorectal liver metastases, KRAS and BRAF mutations were a negative prognostic factor for survival.[33] According to our review, KRAS and TP53 mutations correlated with worse survival outcomes including OS in CRC oligometastases treated with SABR.[26,29] Nicosia et al found at univariate analysis that BRAF wildtype status was predictive for a longer local progression-free survival.[34]

Prostate Cancer

Androgen deprivation therapy (ADT), chemotherapy and palliative or ablative radiotherapy, alone or combined, are among the therapeutic strategies in metastatic prostate cancer (PCa).[35,36] As two randomized trials have shown, therapeutic approach to use depends on the tumor burden.[37,38] According to CHARTEED trial, ADT combined with docetaxel resulted in improved OS compared to ADT alone in patients with high-volume metastatic PCA. Notably, the authors defined “high-volume” as presence of visceral metastases and/or more than 4 bone metastases (at least one outside of spine and pelvis).[37] On the other hand, LATITUDE trial defined the high tumor burden as a high-risk disease characterized by at least 2 of the following criteria: Gleason score ≥8, number of lesions ≥3 on bone scan, presence of measurable visceral lesion. In this setting, Abiraterone Acetate (AA) plus prednisone associated with ADT showed better OS than ADT alone.[38] On the contrary, PCa oligometastatic disease has a limited tumor burden (presence of up to 3–5 metastases) and may benefit from use of metastases-directed therapy (MDT).[39] In particular, the use of surgery or SABR in PCa oligometastases could delay the progression of the disease, postpone the start of systemic therapy and improve the patient's quality

of life and survival.[40,41] In a prospective trial, Ost et al showed a median ADT-free survival of 21 months for patients undergoing MDT (SABR or surgery) compared to 13 months for the surveillance group in PCa oligometastatic disease with ≤3 lesions.[6]

Nine studies reporting data on prognostic factors for PCa oligometastases treated with SABR were included in the current analysis. Seven were retrospective studies and 2 were prospective. A total of 1471 lesions treated with SABR in 916 patients were evaluated. The details are described in Table 2.

The LC rates in these studies are highly variable: some authors reported the data at 1, 2, 3 or 5 years, others even at 6 months or 18 months. In 2 cases, the LC is not reported.[42,43]

According to our review, majority of SABR studies only investigate LC and PFS, and not OS. Patients with PCa have a long survival and OS is rarely analyzed in most studies. PFS represents a valid surrogate endpoint. Only one study reported 5-years LC, OS e PFS rates,[44] which were 92%, 88% and 15%, respectively. All 9 studies assessed PFS among outcomes, but its definition was not the same. Increased Prostate Specific Antigen (PSA) may be a sign of progression even in the absence of radiological or clinical evidence of disease. Schick et al reported biochemical relapse-free survival as a surrogate of PFS (bRFS).[42] They described biochemical recurrence as an increase in PSA value >1 ng/mL. In another prospective trial, the primary endpoint was the treatment escalation-free survival (TE-FS).[43] It was defined as initiation of ADT, chemotherapy or palliative radiation therapy following PSA recurrence, radiological progression, or onset of symptoms.

Prognostic LC-related factors were described in 2 studies. Franzese et al showed that oligoprogressive versus oligorecurrent patients correlated with worse LC at univariate analysis. However, the 2 groups were unbalanced and 97% of patients had oligorecurrent disease. Time to SABR was also associated with poor LC.[45] BED < 100 predicted a higher local recurrence rate at 3 years in a multi-institutional retrospective analysis of 119 PCa patients.[44] The role of BED > 100 in improving outcome was also highlighted for PFS.[46,47] A normalized total dose >64 Gy improved three-year bRFS in PCa patients with less than five metastases treated by SABR and ADT.[42] Bowden et al reported 5-year follow-up of a prospective phase II study evaluating SABR for oligometastatic PCa patients with up to 5 lesions. SABR was delivered in 199 patients, 82.9% of whom had up to 3 lesions. At median follow-up of 35.1 months, prior ADT and increasing age correlated with poor TE-FS.[43] Opposite results were shown by Jereczek-Fossa et al at multivariate analysis: age over 75 years and ADT administration for up to 12 months were associated with a longer PFS. Pelvic lymph nodes involvement and pre-SABR PSA < 10 ng/mL were the other factors that improved PFS.[48] These differences 2 studies could be partially explained by their opposite nature, one prospective and the other retrospective, and by selection of patients. In the prospective trial, the same authors commented that many patients probably had occult poly-metastases at the time they started ADT. This plausibly led to early disease relapse.

Use of ADT before SABR was related to worse OS in a retrospective study on 92 patients (HR 1.16, 95% CI 7.55–17.9; p= 0.000). In addition, PSA velocity (defined as annual increase of PSA) correlated with poor PFS (HR 1.01, 95% CI 1.00–1.02, p=0.049).[49]

With recursive partitioning analysis, the patients were stratified into risk groups based on OS and PFS. Castration-sensitive group was related with better 3-years OS (p = 0.0003). PFS was longer in patients with disease-free interval ≥34 months and low-intermediate risk disease (3 years PFS of 60.2%, p = 0.016).

A multi-institutional retrospective study evaluated 176 oligometastatic PCa patients (pts) treated by MDT (SABR in 129 pts or convention radiotherapy in 47 pts) based on Gallium-68–labeled prostate-specific membrane antigen (PSMA) PET. An increased number of metastases related to poor OS (HR=1.44, p=0.02) at multivariate analysis. Untreated primary PCa was negative predictor of both PFS (HR 2.22, p 0.03) and OS (HR 3.3, p 0.02). Finally, MDT with conventional fractionation was associated with worse PFS compared to SABR (HR 3.80 p <0.001).[47]

In oligometastatic PCa, sensitivity or not to castration was a factor influencing PFS after SABR in a retrospective study.[45] In particular, poor PFS was observed in metastatic castration-resistant PCa (mCRPC) (HR 2.12; p 0.02). The cause is uncertain. However, in patients with mCRPC at the time of SABR there may be a subclinical disease, which will become evident soon after treatment, making the research for the right combination of SABR and systemic therapy crucial. The ARTO trial is an ongoing phase II randomized study investigating the role of ablative radiation therapy in addition to next-generation hormone therapy (AA) in patients with metastatic castration-resistant PCa.[50] At 6-month follow-up, an interim analysis was

Table 2 Summary of Prostatic Oligometastases Treated with SABR

Author, Year	Study Design	Number of Patients/ Lesions	Median Age (Years)	Site of Metastases	Median Dose/ Fractions	Median BED	Median Follow-Up, (Months)	LC	OS	PFS	Prognostic Factors		
											Patient Factors	Tumour Factors	Treatment Factors
Schick,[42] 2013	Retrospective	50/76	63	Nodes bone visceral	64/N.A.	N.A.	31	N.A.	92% (3yrs)	54.5% (3yrs)	N.A.	N.A.	PFS: -SABR dose > 64 Gy (HR 0.37, p-value < 0.034)
Ost,[44] 2016	Retrospective	119/163	61	Nodes bone visceral	N.A.	From 80 to >140	36	93% (3yrs) 92% (5yrs)	95% (3yrs) 88% (5yrs)	31% (3yrs) 15% (5yrs)	N.A.	N.A.	LC: -BED >100 Gy (p-value 0.01)
Hurmuz,[47] 2020	Retrospective	176/353	65	Nodes bone	27 Gy/1–5 fr	N.A.	22.9	98% (1y) 93% (2yrs)	88% (2yrs)	63% (2yrs)	N.A.	OS: -number of metastases (HR=1.44, p-value 0.02)	PFS: -BED < 108 (HR 2.52, p-value 0.03) -conventional RT (HR 3.80, p-value <0.001) -Untreated primary PCa (HR 2.22, p-value 0.03) OS: -Untreated primary PCa (HR 3.37, P-value 0.02)
Triggiani,[46] 2019	Retrospective	86/117	65	Nodes bone	Nodes: 45–36 Gy/ 6 fr bone: 24 Gy/ 3 fr	116	30.7	80% at time of analysis	N.A.	52% (1y) 34% (2yrs)	N.A.	N.A.	PFS: -BED > 100 Gy (p-value 0.004

Franzese,[45] 2018	Retrospective	64/90	72	Nodes bone lung	42 Gy/ 2–8 fr	157	15.2	94% (6mos) 88% (12mos) 84% (18mos)	100% at time of analysis	70% (6mos) 38% (12mos) 25% (18mos)	N.A.	LC: oligoprogressive vs oligorecurrent disease (HR 9.10, p-value 0.049) -Time to SABR (HR 1.03, p-value 0.047) PFS: -Castration sensitive vs resistant (HR 2.12; p-value 0.02)	N.A.
Bowden,[43] 2020	Prospective - interim analysis	199/429	67	Nodes bone Other	50 Gy/10 fr	N.A.	35.1	N.A.	N.A.	27.1 mos (median)	PFS: -Increasing age (HR 1.39; p-value < 0.001)	N.A.	PFS: -Prior ADT (HR 1.97; p-value 0.005)
Phillips,[54] 2020	Prospective	36/N.A.	68	Bone soft tissue	19.5–48 Gy/ 3–5 fr	N.A.	18.8	98.9% (6mos)	N.A.	Not reached	N.A.	PFS: -Greater peripheral baseline clonality (p-value 0.03)	N.A.
Jereczek-Fossa,[48] 2017	retrospective	94/124	70	Nodes	24 Gy/ 3 fr	152	18.5	84% (2yrs)	N.A.	30% (2yrs)	PFS: -Age > 75 years (HR 0.30, p-value < 0.01)	PFS: -Pre-SABR PSA (ng/mL): 4–10 (HR 2.27, p-value 0.01)	PFS: -Primary treatment: RT (HR 2.44; p-value 0.03) -ADT < 12 months (HR 0.35; p-value 0.03)
Franzese[49], 2019	Retrospective	92/119	71	Nodes bone lung	42 Gy/ 5 fr	157.5	22.2	91% (1y) 85% (3yrs)	97% (1y) 88% (3yrs)	43% (1y) 17% (3yrs)	N.A.	LC: -PSA velocity (HR 1.01; p-value 0.049)	OS: -previous ADT (HR 1.16; p-value 0.000)

Abbreviations: SABR, stereotactic ablative radiotherapy; LC, local control; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; BED, biologically effective dose; FR, fractions; Y, year; YRS, years; N.A, not available; PSA, prostate-specific antigen; MOS, months; ADT, androgen deprivation therapy; RT, radiotherapy; PCa prostate cancer.

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recently presented. The treatment group (SABR + AA) consisted of 13 patients and the control group (AA) of 18 patients. In the treatment group, complete response (PSA level <0.2 ng/dL) and biochemical response (PSA reduction >50% from baseline) were observed in 46% and 77%, respectively. In the control group, the same were achieved in 22% and 44%, respectively.[51]

More advanced tests such as the count of circulating tumor cells (CTC) or the evaluation of genomic aberrations in circulating tumor DNA (ctDNA) can be useful for the identification of the oligometastatic patient who can benefit from MDT and therefore from SABR. However, the clinical use and practical application of genomic markers in the oligometastatic setting is unclear because solid data is lacking.

A recent review focused on role of blood-based liquid biopsy in metastatic PCa.[52] The authors observed that both CTC count and ctDNA could be prognostic factors in metastatic PCa predicting patient resistance to treatment. In the CTC count, the presence of androgen receptor splice variant 7 (AR-V7) was a biomarker for resistance to treatment with Abiraterone/Enzalutamide/Apalutamide (androgen receptor-targeted therapy) in mCRPC. Also, the aberrations of the androgen receptors present in the ctDNA were predictors of a poor response to the aforementioned drugs in mCRCP. On the other hand, AR-V7 correlated with a better response to chemotherapy.

Recently, Bjerre et al investigated the use of ctDNA in de novo metastatic PCa. Three methylation markers (DOCK2/HAPLN3/FBXO30) were elevated in high-volume versus low-volume metastatic PCa ($p < 0.001$). Furthermore, methylated ctDNA was associated with rapid progression of hormone-naïve disease.[53] The ORIOLE Phase 2 randomized trial investigated oligometastatic patients with hormone-sensitive PCa enrolled to received SABR or observation.[54] Clonal expansion of T-cell receptors was found in the SABR arm after ablative treatment. The baseline clonality related to progression after SABR (p 0.03). In addition, all patients who received SABR to all lesions detectable by PSMA PET had better metastasis-free survival and PFS ($p = 0.006$).

Lung Cancer

At the time of diagnosis in patients with non-small-cell lung cancer (NSCLC) metastatic disease occurs in about half of cases, and the most frequent presentation, after progression in patients with localized NSCLC undergoing radical treatment, is the spread of distant metastases.[55,56,59]

In our review, we identified 7 articles analyzing SABR in patients with NSCLC oligometastases. Three were prospective studies and 4 retrospective analyses. Overall, 737 patients were included. The details are described in Table 3.

In our analysis, LC rates after SABR ranged from 84.32% to 91.9% at 1 year. OS rates ranged from 67% to 81.5% at 1 year. The 2-year OS rate was from 38% to 80.8%. PFS ranged from 33.3% to 45% at 1 year and from 8% to 22% after 2 years.

Surely, the number of metastases turns out to be a determining factor. In 2012, Salama et al presented the results of a dose escalation study (SABR). In analysis, they evaluated 61 patients with one to five metastases (total: 113 metastatic lesions) but only 11 patients with stage IV NSCLC. We have the survival outcomes of the entire population of patients and not of NSCLC subgroup. The median follow-up was 20.9 months. Treatment was well tolerated. At 2 years, the PFS and OS rates were 22% and 56.7%, respectively. After SABR, the 72% of patients had a further oligoprogression with a better 2-year OS for patients with 1–3 metastases compared to patients with 4–5 metastases.[57] In their systematic review and pooled analysis of the literature, Ashworth et al included 49 studies that analyzed 2176 oligometastatic NSCLC patients with up to 5 lesions and treated with surgery or radiotherapy. The 83% of patients, at the time of treatment, had controlled thoracic disease. About 53% of studies focused on patients with single metastasis, and 60% of studies included patients with brain metastases only. The median survival was 13.8 months, median PFS was 12 months, and the 5-year survival was 23%. The prognostic factors were the control of the primary tumor, the thoracic lymph nodes stage, and disease-free interval of more than 12 months (6 months for adrenal metastases) prior to oligometastatic presentation.[58] A meta-analysis of individual patient data by Ashworth and colleagues included 757 patients with stage IV NSCLC with 1 to 5 synchronous (76%) and metachronous (24%) metastases treated with ablative therapies (metastasectomy, SABR or stereotactic radiosurgery or radical external beam radiotherapy and curative intent treatment of the primary chest disease). Median survival was 26 months, and the median PFS was 11 months. The OS at 5 and 8 years the rates were 29% and 23%, respectively. The analysis was performed stratifying the patients into low (metachronous metastasis; 5-year survival, 48%), intermediate (synchronous metastasis, no thoracic metastatic lymph nodes; 5-year survival,

Table 3 Summary of NSCLC Oligometastases Treated with SABR

Author, Year	Study Design	Number of Patients/ Lesions	Median Age (Years)	Site of Metastases	Median Dose/ Fractions	Median BED	Median Follow-Up, (Months)	LC	OS	PFS	Prognostic Factors		
											Patient Factors	Tumour Factors	Treatment Factors
Salama,[57] 2012	Prospective	11/na	N.A.	Nodes bone visceral	24–60/3	N.A.	20.9	N.A.	81.5% (1y) 56.7% (2yrs)	33.3% (1y) 22% (2yrs)	N.A.	OS: -1–3 metastases vs 4–5 metastases (p-value 0.22)	N.A.
Griffioen,[63] 2013	Retrospective	61/74	N.A.	Nodes bone visceral	N.A.	N.A.	26.1	N.A.	54% (1yr) 38% (2yrs)	32% (1y) 8% (2yrs)	N.A.	OS: -Bone metastases (yes vs no; HR 3.66, p-value 0.007) -Brain metastases (yes vs no; HR 3.66, p-value 0.004)	PFS: -Lung PTV ≥639 cc vs < 639 cc (HR 2.49 p-value 0.007) OS: -Lung PTV (≥639 cc vs < 639 cc; HR 2.89, p-value 0.006) -Surgery for primary lung tumor (HR undefined due to insufficient events, p-value <0.001)

(*Continued*)

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Table 3 (Continued).

Author, Year	Study Design	Number of Patients/ Lesions	Median Age (Years)	Site of Metastases	Median Dose/ Fractions	Median BED	Median Follow-Up, (Months)	LC	OS	PFS	Prognostic Factors		
											Patient Factors	Tumour Factors	Treatment Factors
Parikh,[61] 2014	Prospective	186/N.A.	61	Nodes Bone Brain	45–70 Gy/ N.A.	N.A.	24	N.A.	19 mos	N.A.	OS: -Performance status (1 or lower vs 2 or higher; HR 2.42 p-value <0.001)	OS: - nodal status (N0-1 vs N2-3; HR 1.91 p-value 0.001) -pathology (p-value 0.001) -Number of metastatic organs (1 vs 2–3; HR 2.33 p-value <0.001).	N.A.
Collen,[60] 2014	Prospective	26/N.A.	62	Nodes bone, visceral	N.A.	N.A.	16.1	N.A.	67% (1y)	45% (1 y)	N.A.	OS: -Synchronous metastases (better OS; p-value 0.014)	PFS: - PET response (p-value 0.03)
Chin,[66] 2018	Retrospective	67/114	68	Nodes bone visceral	18–74 Gy/ 1–37 fr	87.5 Gy	13.8	91% at time of analysis	27 mos	6.3 mos	N.A.	OS: - pre-SABR Higher MTV (better OS; p-value 0.009) - pre-SABR higher TLG (shorter OS; p-value 0.004)	N.A.

Franceschini,[62] 2019	Retrospective	85/N.A.	63.6	Nodes, visceral	20–75Gy/ 1–8 fr	105	31.8	6 mos 94.63% 12mos 84.32%, 24mos 78.94%	6mos 96.07%, 1y 85.22%, 2yrs 63.57	6mos 66.10%, 1 y 36.3%, 2 yrs 18.43%	LC: -Age at diagnosis (HR 1.02, p-value 0.032) OS: -performance status (HR 1.45, p-value 0.001)	LC: - number metastases treated (>1; HR 1.62, p-value 0.014) OS: -Lung (HR 0.67, p-value 0.016) -nodal metastases (HR 0.47, p-value 0.001)	N.A.
Horner-Rieber,[65] 2019	Retrospective	301/336	68.5	Lung	19.5–48 Gy/ 3–5 fr	N.A.	16.1	1 y 91.9% 2 yrs 82% 5 yrs 70.3%	2 yrs 80.8% 3 yrs 62.2% 5 yrs 48.1%	N.A.	OS: -Age (HR 1.023, p-value 0.036)	OS: -histological subtype (adenocarcinoma; HR 0.69, p-value 0.038)	LC: -BED at PTV isocenter (HR 0.98, p-value 0.032)

Abbreviations: NSCLC, non small cell lung cancer; SABR, stereotactic ablative radiotherapy; LC, local control; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; BED, biologically effective dose; PTV, planning tumor volume; FR, fractions; Y, year; YRS, years; N.A., not available; vs, versus; PET, positron emission tomography; MOS, months; MTV, metabolic tumor volume; TLG, total lesion glycolysis.

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36%) and high-risk disease (synchronous, thoracic metastatic lymph nodes; 5-year survival, 14%), and better survival was observed in oligometastatic patients with metachronous oligometastases.[59]

On the contrary, in the prospective study by Collen et al, patients with synchronous presentation of metastases were associated with better OS.[60]

The performance status (PS) of the metastatic patient plays a predominant role. In a retrospective study, Parikh et al demonstrated that patients with Eastern Cooperative Oncology Group (ECOG) PS >2, with squamous cell histology and with multiple organ metastases, had an increased risk of death. Instead, the definitive treatment of the primary cancer may confer a survival benefit.[61] One of the predictors of response to SABR is certainly also the site of metastases.

In a retrospective analysis, Franceschini et al evaluated a possible correlation between the characteristics of patients undergoing radiotherapy treatments with the response to SABR and survival. They included 358 patients with oligometastatic disease (23,7% with NSCLC). Median follow-up was 31.8 months. LC and PFS at 24 months were, respectively, 78.9% and 18.4%, and the OS at 24 months was 63.5%. On the multivariate analysis, a better OS was reached in patients with pulmonary and nodal metastases. But the primary lung cancer, older age and the presence of metastatic sites other than the irradiated were all independent predictors of shorter OS.[62] Griffioen et al conducted a retrospective analysis of patients with synchronous oligometastases treated with radical intent at all disease sites and found a correlation between survival and site of metastasis at initial presentation. Notably, survival was better in patients with brain metastases than in those with bone metastases. In addition, other prognostic factors correlated with better survival were primary tumor surgery and smaller radiotherapy planning target volume.[63]

Li et al, in their meta-analysis, analyzed 24 studies to find prognostic factors in oligometastatic NSCLC. They included 1935 patients. Female sex, (y)pN0 stage and adenocarcinoma histology were significant prognostic factors for survival in the univariate analysis. In the multivariate analysis, (y)pN0 was associated with better OS when compared with disease at the (y)pN1 stage, but not at the (y)pN2 stage. Furthermore, patients receiving radical treatments on the primary tumor or on oligometastases had better OS.[64] The correlation between OS and histological subtype was also found in the retrospective study by Hörner-Rieber et al on 301 patients with oligometastatic NSCLC.[65]

The use of FDG PET could give useful information on the response to radiotherapy treatment.

Chin et al, in a retrospective cohort study, analyzed 67 radiotherapy-treatment courses in 55 patients with oligometastatic NSCLC. They evaluated the metabolic tumor volume (MTV), total lesion glycolysis (TLG) and SUV_{max} of all lesions on pretreatment FDG-PET. In the univariate and multivariate analysis, high MTV and TLG were predictors for shorter OS.[66] Moreover, in the study by Collen et al a FDG PET response was positively correlated with better PFS.[60]

Lastly, the molecular profile seems to have an important prognostic role. In a single-center study published by Lussier et al, the expression of MicroRNAs (miRNAs) of lung lesions was analyzed in 63 oligometastatic patients undergoing radical curative treatment. Patients were then distinguished by relapse rate. The authors demonstrated that each different subset of patients expressed specific miRNAs, finding a profile able to predict response and prognosis of oligometastatic patient.[67]

Breast Cancer

Metastatic breast cancer is defined as an incurable disease.[68] Historically, the role of systemic therapies has been predominant, while local radiotherapy was limited to a palliative setting.[69,70] Primarily, breast cancer-related mortality is attributed to complications related to distant recurrence or metastasis. Approximately 6% of breast cancer cases are reported to have metastases at diagnosis and approximately 20–30% of early-stage breast cancers develop distant metastases.[71] In recent years, the use of local therapies for oligometastatic disease has undergone a rapid increase. From a recent survey, with more than 1000 radiotherapists, it emerged that about 60% of participants use ablative radiotherapy treatment if the patient has a limited number of metastases[72] and a similar result was also found in the case of surgical choice.[73]

However, the metastatic breast cancer population has significant variability depending on various factors. In fact, from the clinical trials carried out, the overall results can be influenced by various characteristics, such as age, PS, hormonal status, the stage of disease at diagnosis, the execution of adjuvant chemotherapy or the response to systemic treatments.[74]

In our review, we identified 8 articles analyzing SABR in patients with breast cancer oligometastases. Four were

prospective studies and 4 retrospective analyses. Overall, 323 patients were included. The details are described in Table 4.

According to our analysis, LC rates after SABR ranged from 92.2% to 100% at 1 year and from 69.6% to 90% after 2 years. OS rates ranged from 85.2% to 100% at 1 year. The 2-year OS rate ranged from 57% to 100%. PFS ranged from 38.7% to 75% at 1 year and from 16.6% to 65% after 2 years.

The number of lesions is a fundamental criterion for defining the response to ablative radiotherapy treatments. A correlation between the number of lesions and survival was evaluated in some studies. In Milano et al, patients with a single metastasis (vs >1) were found to have better OS.[75] In the retrospective study by Yoo et al, in which 50 patients were treated with radiotherapy at oligometastatic sites, an association with better OS was found in patients with a single bone metastasis.[76] In Franzese et al, in a retrospective analysis of 72 patients treated with ablative radiotherapy on liver metastases (1–5 metastases), the number of treated liver lesions in the univariate analysis predicted worse control of liver disease (1 metastasis vs >1 metastasis).[77] Also, in the retrospective study by Weykamp et al, in which 46 patients treated with SABR were analysed, the presence of a solitary metastasis was an independent prognostic factor for better disease control and PFS in multivariate analysis.[78] Also, the localization of the lesions becomes a fundamental parameter for predicting survival. In a prospective observational study by Scorsetti et al, SABR was used in patients with oligometastatic breast cancer, affected by liver and lung metastases. Among the inclusion criteria, the presence of stable extrapulmonary or extrahepatic disease was allowed and it correlated with worse PFS as found by the authors. In the univariate analysis, they also demonstrated a correlation between disease free interval >12 months and better survival.[79] An advantage in OS was found in the study of Milano et al, in which patients with bone disease had better OS than patients who also had other sites of disease.[75] The table shows how the OS at 2 years differs between the different studies, and the lowest survival was found in the study by Onal et al (2-years OS 57%), which retrospectively analyzed patients with liver metastases undergoing SABR.[80] In Yoo et al retrospective analysis, a correlation was found between high RT (≥50 Gy10) and increased LC and better distant-PFS.[76] In a study performed using a large multi-center database from German society of radiation Oncology, Klement et al show that breast cancer metastases treated with SABR (with BED_{max} of 157 ± 80 Gy_{10} or 80 ± 62 Gy_{10} with and without prior chemotherapy) have a significantly higher probability of tumor control over the entire dose-response, and this shows that this subtype could be particularly radiosensitive to high doses per fraction such as in SABR.[81] Furthermore, the pooled analysis by Hong et al, which also included patients with oligometastatic breast cancer, also showed a correlation between BED >75 Gy and better OS and PFS.[82]

The biomolecular factors of breast disease also predict a different response to radiotherapy treatments.

In our analysis, we found various studies showing these predictors. Hormone receptor positivity of patients undergoing SABR was found to be linked to improved OS in 3 of the studies included in our analysis.[75,76,79] A worse survival was instead demonstrated by Franzese et al for the patients who presented a HER-2 positivity.[77] It is also very important to note that the Karnofsky Performance Status Scale was a significant positive prognostic factor for survival and disease control. Indeed, some studies included high KPS as an inclusion criterion with a range between 70% - 100%.[75,78,83] The timing of systemic medical treatment was evaluated by Scorsetti et al, who demonstrated a significant impact on OS in case of systemic treatment after SABR.[79] In the study by Franzese et al, a correlation was found between systemic therapy administered before local treatment on metastases and PFS.[77] We also found interesting data from a prospective study. In a phase II study, published by Trovò et al, the authors sought to demonstrate whether radical radiotherapy on all metastatic sites could increase PFS in patients with oligometastatic breast cancer. They included 54 patients with a total of 92 metastatic lesions, treated with radical radiotherapy, in their analysis. After a median follow-up of 30 months, the PFS at 1 and 2 years was 75% and 53%, respectively. They did not identify prognostic factors associated with improvement in PFS. However, they showed that patients treated with radical radiotherapy on all metastatic sites may reach long-term PFS without significant treatment-related toxicity increase. Therefore, the choice of stereotactic ablative radiotherapy can be considered a valid option.[84]

Conclusion

Through this review, we provide a state of the art summary of predictive factors that can help deciding whether oligometastatic patients deserve SABR. It is evident that a lot is still to be done, as reflected by the various and heterogeneous results

Table 4 Summary of Breast Oligometastases Treated with SABR

Author, Year	Study Design	Number of Patients/ Lesions	Median Age (Years)	Site of Metastases	Median Dose/ Fractions	Median BED	Median Follow-Up, (Months)	LC	OS	PFS	Prognostic Factors		
											Patient Factors	Tumour Factors	Treatment Factors
Yoo,[76] 2015	Retrospective	33/N.A.	43	Bone, nodes, visceral	20–60Gy/ N.A.	N.A.	53.6	3 yrs 69.6%, 5 yrs 66.1%	2 yrs 85.2%, 5 yrs 49%	3 yrs 36.8% 5yrs 24.5%	N.A.	LC: -Her-2 negative (p-value 0.019) PFS: -solitary BM (p-value 0.007) OS: -hormonal receptor positivity (HR 7.558, p-value 0.001) -solitary BM (HR 0.256, p-value 0.015)	LC: -RT dose (<50 vs ≥ $50Gy_{10}$; HR 5.874, p-value 0.055) PFS: -High dose RT (p-value 0.002) OS: -High dose RT (p-value 0.079)
Scorsetti,[79] 2016	Retrospective	33/43	57	Bone, Brain, visceral	48–75Gy/ 3–4 fr	NA	24	1 y 98% 2–3 yrs 90%	1 y 93% 2 yrs 66%	1 y 48% 2 yrs 27%	N.A.	PFS: -extrahepatic or extrapulmonary disease (worse PFS; p-value 0.03) OS: -hormonal receptor positivity (p-value 0.03) -Disease free interval >12 mos (p-value 0.005)	OS: -medical therapies for metastatic disease after SABR (p-value 0.01 and 0.04)
Trovò,[84] 2017	Prospective	54/92	55	Bone, Nodes, Visceral	30–60Gy/ 3–25fr	79.2–112.5	30	2 yrs 97%	2 yrs 95%	1 y 75% 2 yrs 53%	N.A.	N.A.	N.A.
Onal,[80] 2018	Retrospective	22/29	47	Liver	54Gy/3fr	N.A.	16	2yrs 88%	2 yrs 57%	N.A.	N.A.	N.A.	N.A.

David,[83] 2019	Prospective	15/19	61	Bone	20Gy/1fr	N.A.	24	2 yrs 100%	2 yrs 100%	2 yrs 65%	N.A.	N.A.	N.A.
Milano,[75] 2019	Prospective	48/102	60–43.9	Bone nodes, visceral	62,5 Gy - 57,3Gy (median)	N.A.	53	N.A.	2 yrs 74%	2 yrs 53%	N.A.	OS: -Bone metastases (p-value 0.002) -hormonal receptor-positivity (p-value 0.024) -number of lesions (p-value 0.026) -sum GTVs (25cc; p-value 0.026)	N.A.
Franzese,[77] 2020	Retrospective	72/N.A.	55.4	Liver	30–75Gy/ 3–6fr	161,7Gy (range 48–262,5)	26.2	N.A.	1 y 95.5%, 2 yrs 76.9%	1 y 38.7%, 2 yrs 22%	N.A.	OS: - Her-2 positive (HR 1.82, p-value 0.01)	LC: -systemic therapy before metastases directed therapy (HR 2.89, p-value 0.016) -number of systemic therapy lines (HR 1.43, p-value 0.005) -number of liver metastases treated (HR 1.70, p-value 0.004)

(*Continued*)

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Table 4 (Continued).

Author, Year	Study Design	Number of Patients/ Lesions	Median Age (Years)	Site of Metastases	Median Dose/ Fractions	Median BED	Median Follow-Up, (Months)	LC	OS	PFS	Prognostic Factors		
											Patient Factors	Tumour Factors	Treatment Factors
Weykamp,[78] 2020	Retrospective	46/58	55	Bone, brain, nodes, liver	24–60Gy/ 1–10	81,6 (range 45–112)	21	1 y 92.2%, 2 yrs 88.5%	1 y 85.4%, 2 yrs 62.1%	1 y 54.3%, 2 yrs 16.6%	LC: -Performance status (HR 0.962, p-value 0.004) PFS: - Performance status (HR 0.840, p-value 0.024) OS: -Age > 55yrs (HR 2.61, p-value 0.043)	PFS: -Estrogen receptor positivity (HR 0.098, p-value 0.045) -Oligoprogressive disease (HR 11.23, p-value 0.037)	LC: -SABR bone (HR 0.172, p 0.004) -BED_{10gy} (HR 1.019, p-value 0.035) OS: -SABR bone (HR 0.117, p-value 0.038)

Abbreviations: SABR, stereotactic ablative radiotherapy; LC, local control; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; BED, biologically effective dose; GTV, gross tumor volume; FR, fractions; Y, year; YRS, years; N.A., not available; MOS, months; BM, breast metastasis; RT, radiotherapy, HER-2, human epidermal growth factor receptor 2.

of the published series. While clinical parameters are easily accessible, their relevance in predicting outcome of oligometastatic patients is minimal. The research on genetic, epigenetic and radiomic features is still far from a clinical implementation. However, we feel that this is the right way to proceed, since the identification of the biology behind oligometastases is crucial. A significant effort to collect similar data is of paramount importance.

Disclosure

The authors report no conflicts of interest in this work.

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