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The continuing conundrum in oligometastatic breast carcinoma: A real-world data

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ABSTRACT

The optimal management in Oligometastatic (OM) breast carcinoma is not defined.
Objectives: To identify the prognostic factors influencing OM and the effect of Locoregional treatment (LRT) on survival in OM.
Methodology: Patients with ≤5 metastases and each with ≤ 5 cm size were defined as OM. Data of OM were extracted from the Institute Registry between 2012 and 2018. The impact of prognostic factors on survival was analysed by univariate and multivariate Cox regression. The Kaplan Meier survival curves were used to plot PFS and OS.
Results: There were 170 patients with OM. The median follow-up was 61 months. Median OS was 43.3 months. The median OS was 74 months in OMD vs 22.7 months in Oligorecurrent disease (ORD) with 5year OS rate of 55.3% vs 16.5% respectively. In the multivariate analyses of OMD both Ki67 ≤ 50% and hormone therapy (HT) showed significant favourable survival outcome. While premenopausal status and HT showed significant survival benefits in ORD. The worse survival outcome in ORD could be because of their aggressive biology and deficit in LRT compared to literature review. The prognostic factors were swayed by the uneven distribution of HR status, grade and Ki67.
Conclusion: The survival of OM was influenced by OMD, Ki67 ≤ 50%, premenopausal status and HT. The lesser survival rates of OM in the long term suggest the need for curative LRT to metastatic sites and primary tumor. The potential role of HT and targeted therapy with or without LRT need to be assessed in future randomised trials.

1. Introduction

Breast cancer is one of the leading sites of cancer worldwide. As per GLOBOCAN, the age-standardised incidence (ASR) per 100,000 person-years is 47.8 [1]. It is also one of India's common leading cancer sites [2]. Around 10% of breast cancers present with stage IV at diagnosis. Distant metastases will eventually develop in 20–30% of those with localised disease [3,4]. The five-year overall survival (OS) rates of stage IV patients are approximately 20%–25%, with a median OS of about three years [3,4].

The term "Oligometastasis" (OM) was coined by Hellman and Weichselbaum in 1995 for patients with limited metastatic burden [5]. The definition of oligo-metastasis is not well defined [6]. There are various definition of what constitutes OM. The OM comprises 10%–20% of all the metastases [3,7].The Advanced Breast Cancer (ABC) guidelines proposed by the European School of Oncology and the European Society for Medical Oncology (ESO-ESMO) task force defined it as a low volume metastatic disease with a limited number (up to five in number and not necessarily in the same organ) and size (<5 cm) of metastatic lesions potentially amenable for local treatment [6,8–10]. The European Society for Radiotherapy and Oncology (ESTRO) and the American Society for Radiation Oncology (ASTRO) consensus document proposed that "Oligometastasis can be defined as 1–5 metastatic lesions, a controlled primary tumor being optional, but where all metastatic sites must be

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Table 1
Baseline characteristics of patients with Oligometastatic disease.

Baseline characteristics	Number (%)
Total no. patients	170
Age (years)	50 (Average), Range (27–84)
Nulliparous	
Yes	8 (5)
No	162 (95)
Comorbidities [b]	
Yes	64 (38)
No	106 (62)
Menopausal status	
Postmenopausal	103 (61)
Premenopausal	67 (39)
ECOG	
1	157 (92)
2	12 (7)
3	1 (1)
Receptor status	
ER/PR + ve only	59 (34.7)
HER2neu 3+ (±ER/PR + ve)[a]	87 (51.2)
TNBC	24 (14.1)
No. of metastases	
1	52 (31)
2	40 (24)
3	39 (23)
4	21 (12)
5	18 (11)
Metastatic sites	
Bone	76 (44.7)
Lung	32 (18.8)
Liver	26 (15.3)
Non -regional LN only	57 (33.5)
Brain only	5 (2.9)
Other Sites (choroid, breast, chest wall)	5 (2.9)
Single organ involvement	
Yes	136 (80)
No	34 (20)
Denovo Oligometastatic disease (OMD)	124 (73)
Oligorecurrent disease (ORD)	46 (27)
Stage grouping (at initial diagnosis) for ORD	
I	2 (1)
IIA	8 (5)
IIB	5 (3)
IIIA	7 (4)
IIIB	13 (8)
IIIC	11 (6)
Grade of tumor	
1	2 (1)
2	37 (22)
3	131 (77)
Ki-67(%)	
≤20	10 (6)
>20	154 (90.6)
>20-50	70 (41)
>50	84 (49.4)
Unknown	6 (4)
Systemic therapy received	
Anthracycline + Taxane based (sequential)	29 (17)
Anthracycline based	42 (25)
Taxane based	40 (24)
Other regimens (CMF, CTX/VP16, Capecitabine, Eribulin, Carboplatin/Gemcitabine, Palbociclib, Trastuzumab based)	29 (17)
Palbociclib + letrozole	1 (0.6)
Trastuzumab based	3 (1.8)
Radiotherapy	
PMRT	19 [11]
Preop CCRT	15 (9)
Preop Sequential RT	42 (25)
Palliative	20 (12)
Nil	90 (53)
Surgery	
MRM	47 (28)
Metastasectomy	3 (2)
Nil	120 (71)
Treatment modality	
S + C + RT ± HT	32 (18.8)
S + C ± HT	14 (8.2)
C + RT ± HT	28 (16.5)
LRT (curative)+C	74 (43.5)
C ± HT (without LRT)	55 (32)
C + palliative S/RT ± HT)	22 (12.9)
HT	
Alone	19 (11.2)
with S or RT (palliative)	19 (11.2)
with S or RT (curative)	2 (1.2)
with C	27 (15.9)
with S + C + RT	19 (11.2)
Nil	56 (33)

Abbreviations: ECOG PS-Eastern cooperative oncology group performance status, ER -Estrogen receptor, PR - Progesterone receptor, TNBC -Triple negative breast cancer,LN- lymph node,MRM-Modified Radical mastectomy, S -Surgery, C-Chemotherapy,RT- Radiotherapy, HT- Hormone Therapy, CCRT- Concurrent Chemoradiotherapy, PMRT-post mastectomy radiotherapy, CMF – Cyclophosphamide/Methotrexate/5fluorouracil, CTX/VP16 – Cyclophosphamide/Etoposide (oral Tablet), LRT- Locoregional Therapy(surgery or definitive or CCRT).
[a] FISH-Fluorescent in situ hybridisation in case of HER2neu 2+.
[b] Comorbidities-Diabetes mellitus, hypertension and cardiac disease).

safely treatable" from the perspective of metastasis-directed radiotherapy (MDRT) [11]. The term Oligometastasis is usually described for denovo metastases at diagnosis. The term Oligorecurrent disease is used for the patients who were initially treated for localised breast cancer and then relapsed later as oligometastases [12–14].

1.1. Role of locoregional treatment in stage IV disease

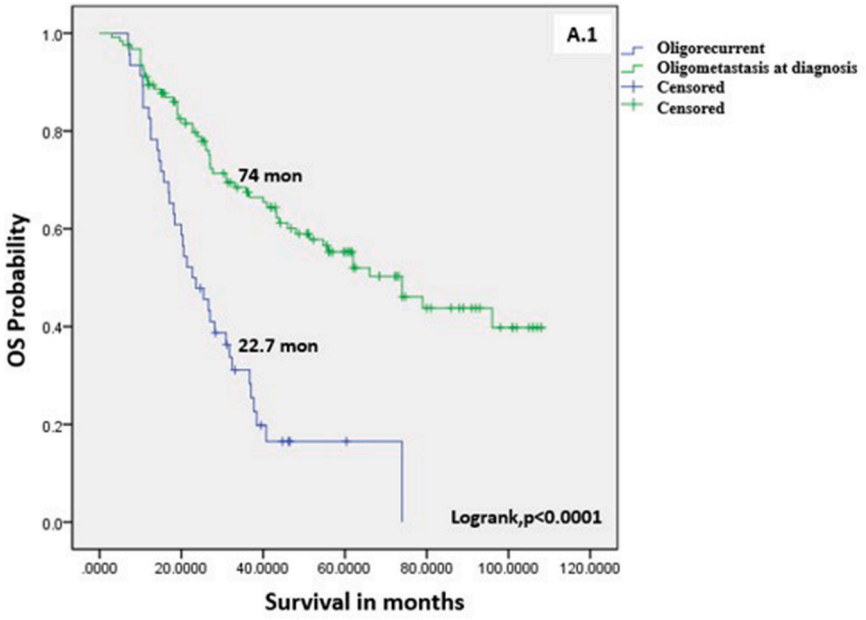
The MF07-01 phase III randomised controlled trial comparing locoregional treatment (LRT) with standard of care therapy for de novo stage IV patients demonstrated statistically significant improvement in median OS (46 months vs 36 months). Although more than one third of the study population had OM the multivariate analysis did not reveal significant impact from this subset [15]. In contrast an Indian randomised study failed to reveal significant benefit from LRT in stage IV vs standard of care (median OS 19.2 vs 20.5 months). Here too the subgroup analysis failed to show OS benefit for those with OM [16].

1.2. Perspectives in oligometastases

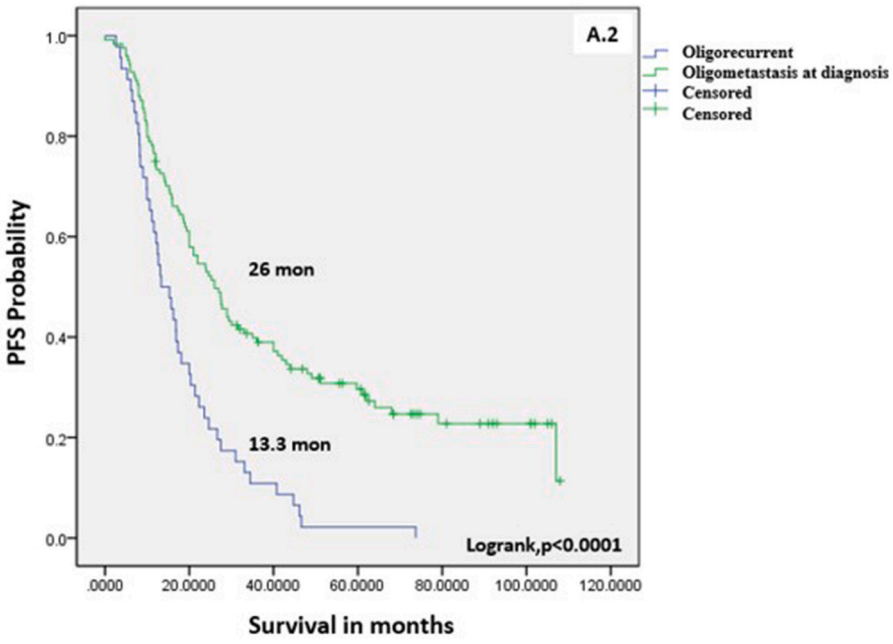
Kelly et al. proposed criteria to standardise the definition of number of metastatic sites. Each radiologically identified lesion was considered as one site for the lesions in the brain, bone, lung, and liver. For lesions in the lymph nodes, each radiological echelon involvement of axillary, cervical, or mediastinal lymphatics was considered as single site, even if there were multiple nodes in an echelon. Similarly recurrent lesions of the ipsilateral breast or chest wall were considered as a single site irrespective of numbers [12,17].

Compared to breast cancer with multiple metastases, OM has displayed favourable outcomes. Jain SK et al. showed superior survival rates for OM compared to multiple metastatic patients (44.7 vs 18.1 months) [7]. The literature reviews demonstrated that, presence of single metastasis, OM, good performance status (ECOG 0 or 1), hormone-receptor (HR) positivity, >24 months interval between primary tumor and OM and no or limited involvement of axillary lymph nodes at primary diagnosis were found to be favourable prognostic factors in metastatic settings [18,19].

Steenbruggen et al. examined the impact of the number of metastases on survival to determine the optimal threshold. Their study found improved survival with statistical significance for no more than 3 distant metastases. According to this large retrospective analyses ≤3 metastasis should be considered as oligometastases. This study failed to



Survival in months	12	24	36	48	60	72
Numbers at risk(OMD)	109	86	67	53	43	27
Numbers at risk(ORD)	38	22	11	3	2	1



Survival in months	12	24	36	48	60	72
Numbers at risk(OMD)	95	65	45	35	26	16
Numbers at risk(ORD)	28	11	5	0		

Fig. 1. Kaplan-Meier Survival curves -Oligometastatic disease at diagnosis vs oligorecurrent disease. **Abbreviations:** A.1 OS – Overall survival, A.2 PFS - Progression free survival, OMD- Oligometastasis at diagnosis (denovo), ORD- Oligorecurrent disease.

Table 2
Distribution of metastatic sites and their survival rates.

	Bone[a]		Lung[b]		Liver[c]		NLN only	
	OMD	ORD	OMD	ORD	OMD	ORD	OMD	ORD
Number	58	8	24	7	14	11	27	10
%	46.7	17.3	19.3	15.2	11.3	24	21.8	21.7
2years survival rate (%)								
OS	89.4	37.5	87.1	71.4	26.5	45.5	75.2	30
PFS	67.2	25	58.3	42.9	7.1	9.1	39.2	20
3years survival rate (%)								
OS	75.9	37.5	73.3	28.6	17.7	45.5	70.2	20
PFS	40.6	12.5	41.3	14.3	7.1	9.1	35.3	10
5years survival rate (%)								
OS	58.5	18.8	60.5	28.6	17.7	30.3	64.8	0
PFS	34.7	0	26.7	0	0	0	35.3	0

Abbreviations: NLN-nonregional lymph node.
[a] Bone (± other sites excluding lung, liver, brain metastases).
[b] Lung (± other sites excluding lung, liver and brain metastases).
[c] Liver (± other sites excluding liver and brain metastases), OMD- Oligometastasis at diagnosis (denovo), ORD- Oligorecurrent disease.

demonstrate OS benefit in patients with no more than 5 metastases However, in multivariate analyses of patients with ≤3 metastases, premenopausal status, absence of lung metastases, and local therapy to metastases or primary tumor with systemic therapy demonstrated favourable OS and progression-free survival (PFS) with statistical significance. Single organ metastasis did not show significant OS benefit [20].

In another large retrospective series, performing surgical resection for all metastatic lesions along with standard systemic was an independent prognostic factor. Those with solitary metastases and HR positive subtype benefited more with surgical resection [21]. A prospective study in <5 metastases showed significant improvement in OS and PFS for those who received stereotactic ablative radiation/stereotactic body radiotherapy (SABR/SBRT) compared to palliative conventional RT dose [22]. Similarly in a systematic review on local radiotherapy (RT) use of SABR, presence of <5 metastases, local RT to metastases and bone only metastases were found to have prognostic significance [23].

There is sparse evidence in literature regarding the prognostic factors and therapeutic outcomes in oligometastatic breast cancer. Hence, this study aims to identify the prognostic factors and benefit of LRT in OM.

2. Methodology

This study is a single-center, retrospective analysis of oligometastatic breast carcinoma. This is a consecutive series. The Institute tumor registry has 100% coverage. All the metastatic breast carcinoma case records were retrieved from Institute Cancer Registry between 2012 and 2018. Those with ≤5 metastases in total and ≤ 5 cm metastasis were considered as OM and became eligible for the study as per the ABC guidelines to maintain uniformity in reporting. The number and size of metastases were confirmed by reviewing the radiological reports and the discussions with radiologist as mentioned in the case records. The number of metastases were measured from CT (computed tomography) chest/abdomen, bone scan, MRI (magnetic resonance image) for brain, 18f-FDG-PET/CT (Positron Emission Tomography with fluorodeoxyglucose) or USG (ultrasonogram) images for abdomen.

All biopsy-proven primary breast carcinoma patients with OM were included. The biopsies from metastases were not mandatory if there was clinical/radiological correlation. The data of all patients who underwent therapy irrespective of either single or multi-modality treatment (curative or palliative) were included. Those who failed to receive any treatment or those with incomplete case records were excluded. The HR status, human epidermal growth factor receptor 2 (HER2neu) positivity and triple negative breast cancer (TNBC) were defined by immunohistochemistry (IHC). In cases where the HER2neu positive results were equivocal by IHC, the fluorescence in situ hybridization (FISH) was performed. The data for the presence of comorbidities like diabetes mellitus, hypertension and cardiac disease was collected from the case records. Response assessments were extracted from case records which were based on RECIST version 1.1 (response evaluation criteria in solid tumours).

Table 3
The univariate analyses of prognostic variables in OMD.

Variables	Median OS (months)	P value (log rank)	Median PFS (months)	P value (log rank)
Age (in years)				
≤40	NR	0.96	21	0.84
41–50	66		22	
51–60	62		21	
>60	86		27.7	
Comorbidities				
Yes	66	0.16	27	0.66
No	54.7		26	
Nulliparous				
Yes	22.8	0.07	27	0.40
No	74		9.5	
Menopausal status				
Pre	79	0.61	26	0.98
Post	62		27	
Number of metastases				
1	74	0.32	33	0.05
2–3	56		20	
4–5	66		29	
Single organ involvement				
Yes	74	0.16	27.6	0.58
No	56		21	
Site of Metastasis				
Bone[a]	74	<0.0001	35	<0.0001
Lung[b]	NR		27	
Liver[c]	19		10	
NLN only	NR		18.5	
Grade				
1	NR	0.14	14.2	0.13
2	NR		40	
3	56		22	
Ki67(in %)				
≤50	NR	0.002	42	0.01
>50	46		20	
Receptor status				
ER/PR + ve	74	0.18	42	0.02
HER2neu3+	62		18.7	
TNBC	43		24.6	
Type of chemotherapy regimen				
Anthracycline based and Taxane (Sequential)	79	0.19	36	0.03
Taxane based	46		18.5	
Anthracycline based	54.7		22	
Others (CMF, CTX/VP16, Capecitabine, Eribulin, Carboplatin/ Gemcitabine, Palbociclib, Trastuzumab based)	66		33	
Hormone therapy				
Yes	79	0.007	31.4	0.004
No	33		15.4	
Locoregional therapy				
C + S + R	74	0.66	22	0.58
C + S or R	56		20	
C	62		22	
Palliative R + HT ± C	62		60	
HT only	28.5		27	

Abbreviations: OMD-denovo oligometastasis, ER -Estrogen receptor, PR - Progesterone receptor, TNBC -Triple negative breast cancer, NLN-nonregional lymphnode, S -Surgery, C-Chemotherapy,RT- Radiotherapy, CMF – Cyclophosphamide/Methotrexate/5fluorouracil, CTX/VP16 – Cyclophosphamide/Etoposide (oral Tablet), HT- Hormone Therapy.
[a] Bone (± other sites excluding lung, liver, brain metastases).
[b] Lung (± other sites excluding liver and brain metastases).
[c] Liver (± other sites excluding lung and brain metastases),NR-not reached.

Table 4
Multivariate analyses in OMD.

Variables	OS				PFS			
	HR	95% CI		Sig.	HR	95% CI		Sig.
		Lower	Upper	P < 0.05		Lower	Upper	P < 0.05
Number of metastases				0.870				0.068
1	0.844	0.342	2.084		0.665	0.331	1.336	
2–3	1.034	0.515	2.077		1.303	0.758	2.242	
4–5	referent				referent			
Site of Metastasis				0.078				0.060
Bone[a]	1.677	0.640	4.390		0.919	0.469	1.799	
Lung[b]	1.028	0.347	3.042		0.715	0.327	1.565	
Liver[c]	3.108	0.979	9.872		1.547	0.664	3.605	
NLN only	referent				referent			
Receptor status				0.650				0.130
ER/PR + ve	1.420	0.408	4.941		1.215	0.476	3.098	
HER2neu3+	1.669	0.530	5.254		1.884	0.811	4.374	
TNBC	referent				referent			
Ki67(in %)				0.022				0.129
<50	0.140	.026	.755		0.297	0.063	1.405	
≥50	referent				referent			
Type of chemotherapy regimen				0.299				0.077
Anthracycline based and Taxane (Sequential)	0.581	0.157	2.143		0.725	0.272	1.935	
Taxane based	1.442	0.450	4.616		1.475	0.582	3.737	
Anthracycline based	0.712	0.220	2.300		0.653	0.255	1.675	
Others[d]	referent				referent			
Hormone therapy				0.135				.023
No	2.022	0.803	5.088		2.182	1.116	4.264	
Yes	referent				referent			

Abbreviations: OMD-denovo oligometastasis, ER -Estrogen receptor, PR - Progesterone receptor, TNBC -Triple negative breast cancer, NLN-nonregional lymphnode, CMF – Cyclophosphamide/Methotrexate/5fluorouracil, CTX/VP16 – Cyclophosphamide/Etoposide (oral Tablet).

[a] Bone (± other sites excluding lung, liver, brain metastases).

[b] Lung (± other sites excluding liver and brain metastases).

[c] Liver (± other sites excluding lung and brain metastases).

[d] CMF, CTX/VP16, Capecitabine, Eribulin, Carboplatin/Gemcitabine, Palbociclib, Trastuzumab based.

Progression of the disease or death from any cause was defined as an event. Progression-free survival (PFS) was calculated from the date of oligo-metastasis diagnosis to the event's occurrence. The OS was calculated from Oligometastasis diagnosis to death due to any cause or until the last follow-up. The intent of treatment was decided in the multidisciplinary tumor board discussions. Chemotherapy regimen was delivered before LRT as neoadjuvant with curative intent. In case of curative intent sequential Anthracycline-Taxane based chemotherapy or Taxane based doublet regimen was delivered. Monotherapy was preferred in case of palliative intent. The LRT can be surgery(S) and/or RT delivered to the primary tumor and/or the metastatic site depending on the site and response. The preop sequential RT (after neoadjuvant chemotherapy) or concurrent chemoradiation (CCRT) was delivered in case of stable disease/borderline operability of primary tumor before surgery. Palliative LRT was defined based on the intent of treatment, dose of RT or if provided for symptom relief. Palliative LRT need not be provided with chemotherapy or targeted therapy as with curative LRT.

Factors like age, comorbidities, nulliparity, menopausal status, denovo OM at diagnosis (OMD), oligorecurrent disease (ORD), number of metastases, single organ involvement, treatment received, type of chemotherapy regimen, LRT, Hormone therapy (HT), Grade of tumor, Ki67(in %), hormone receptor (HR) and HER2neu receptor status were analysed for prognostic significance.

Following were the primary objectives of this study:

1. To identify prognostic factors influencing the OS/PFS in oligometastatic breast carcinoma.
2. To find the effect of LRT on OS/PFS vs standard systemic therapy in OM.

3. Statistical analysis

Baseline characteristics were reported as descriptive analytics in the form of frequency distribution. Kaplan Meier survival curves were used for plotting PFS and OS. Factors influencing survival were initially assessed for prognostic significance by log rank univariate analyses. Statistical significance was defined as p value < 0.05. This was followed by multivariate cox regression analysis with a p-value of <0.05 considered as statistically significant. The statistical analysis was performed with SPSS software Version 20. The study was conducted after approval from the Institutional Ethics Committee (IEC). This study has been carried out in accordance with Declaration of Helsinki.

4. Results

Data of 736 patients with metastases were retrieved from 2012 to 2018. Out of these 736 patients, 170 (23.1%) had an oligometastatic disease. Two patients were excluded while data retrieval as they came only for second opinion and wanted to get treatment elsewhere. None of them were excluded because of treatment default or incomplete case records. The baseline characteristics of 170 oligometastases patients were represented in Table 1. Out of 170 patients 124 (73%) were OMD and 46 (27%) were ORD. The average age of these patients was 50 years. Majority were ECOG-1 (92%), postmenopausal (61%), Grade 3 (77%), >20% Ki67 (90.6%), HER2neu positive (51.2%), OMD (73%) and had bone metastases (44.7%). The solitary metastases were less (31%) and single organ involvement (80%) were more commonly found. The nonregional lymph node (NLN) metastases were seen as second most common site of metastases. The HER2neu status was assessed by FISH in 39 patients with equivocal results. FISH positive results were equally distributed between ER/PR+ and ER/PR -ve HER2neu cases. Among HER2neu patients 64 (73.5%) were HR positive and 23 (26.4%) were HR negative. Bisphosphonates were offered to patients with bone metastases. In the OMD group 15 received palliative LRT to the metastatic site and 76 received curative LRT (44.7%) to the primary tumor. Among ORD group 14 patients received palliative LRT to metastatic site and the

Table 5
The univariate analyses of prognostic variables in ORD.

Variables	Median OS (months)	P value (logrank)	Median PFS (months)	P value (logrank)
Age (in years)				
≤40	31.7	0.17	15.3	0.67
41–50	22.7		16.9	
51–60	18.1		9.9	
>60	15.7		11.6	
Comorbidities				
Yes	16.9	0.10	12.2	0.26
No	30.9		16.8	
Nulliparous				
Yes	26.7	0.90	21.4	0.55
No	22.7		13.1	
Menopausal status				
Pre	32.4	0.006	16.9	0.20
Post	17		12.2	
Number of metastases				
1	22.7	0.92	13.3	0.92
2–3	25.4		11.1	
4–5	18.1		16.2	
Single organ involvement				
Yes	23.6	0.49	13.1	0.52
No	20.3		16.2	
Site of Metastasis				
Bone[a]	20.3	0.30	16.2	0.65
Lung[b]	30.9		23.6	
Liver[c]	20.5		12.5	
Brain only	22.7		21.4	
NLN only	14.6		10	
Grade				
2	26.7	0.44	15.3	0.81
3	22.7		13.3	
Ki67(in %)				
≤50	74	0.008	24.6	0.016
>50	20.3		12.6	
Unknown	14.6		9.9	
Receptor status				
ER/PR + ve	28.2	0.038	16.3	0.005
HER2neu3+	20.3		15.2	
TNBC	10.6		8	
Type of chemotherapy regimen				
Taxanes	37	0.03	16.8	0.017
Others (CTX/VP16, Capecitabine, Eribulin)	17		8.3	
Hormone therapy				
Yes	28.2	0.003	17.3	<0.0001
No	14.1		8.2	
Locoregional therapy				
C	17	0.15	9.9	0.015
C + Palliative S or R	26		20.3	
HT	23.6		13.3	

Abbreviations: ORD-oligorecurrent disease, ER -Estrogen receptor, PR - Progesterone receptor, TNBC -Triple negative breast cancer, S -Surgery, C-Chemotherapy, R- Radiotherapy, CTX/VP16 – Cyclophosphamide/Etoposide (oral Tablet), HT- Hormone Therapy.

[a] Bone (± other sites excluding lung, liver, brain metastases).

[b] Lung (± other sites excluding liver and brain metastases).

[c] Liver (± other sites excluding lung and brain metastases).

rest received chemotherapy. Out of 170 cases 40 patients (23.6%) received HT without chemotherapy. The chemotherapy regimens were based on physician discretion. Out of 170 patients 88.2% achieved partial response and only 5.9% achieved complete response after chemotherapy. All received ≥2 lines of therapy on disease progression. The anti-HER2neu targeted therapy was received by 1.8% of HER2neu patients due to financial constraints.

The median follow-up was 61 months. The overall median OS was 43.3 months (range 29.6–56.9 months), and median PFS was 21months (range 16.8–25.2 months). The 2year, 3year and 5year OS rates were 70.7%,57.2% and 46.2% respectively. For PFS, they were 45.1%,31.3% and 22% respectively. The median OS/PFS were better in the OMD group (74/22.7months respectively) compared to ORD group (26/13.3months respectively). The OMD group achieved statistically significant favourable survival outcome versus ORD in the univariate analysis as depicted in Fig. 1. We analysed OMD and ORD groups separately for the influence of prognostic factors as most of OMD received curative LRT to the primary and none received curative LRT in ORD which might have influenced their outcome. The decision on LRT was based on multidisciplinary tumor board discussions.

We did not perform univariate analyses for ECOG status as majority were ECOG 1. With respect to Ki 67 only few patients were <20% or 30% and hence we took all patients with ≤50% for analyses to compare with >50%. The frequency distribution of metastatic sites and their survival rates with respect to OMD and ORD are depicted in Table 2. Presence of both liver and lung metastases were seen in only one patient with OMD and it was not included in the analysis. The brain metastases were seen in ORD group (5 out of 46) and their 2year OS/PFS rates were 40%. None of the brain metastases patients survived beyond 2.5 years. Other sites of metastases as mentioned in Table 1 were too small to analyse.

5. Results in OMD

Out of 124 patients 8 received palliative LRT to the metastases and 74 (59.7%) received curative LRT to the primary tumor. The palliative LRT was delivered in the form of RT. The 2years, 3years and 5years OS/PFS rates were 78.8%/53.3%, 67.5%/39% and 55.3%/29.7% respectively. The univariate analyses depicted better OS/PFS trends for ≤40years age, non-nulliparous, premenopausal patients, solitary metastasis, single organ involvement, grade2 tumours, ≤ 50% Ki67 HR positivity, sequential Anthracycline-Taxane based therapy, curative LRT and HT. Both Ki67 ≤ 50% and HT showed statistically significant OS and PFS benefits. With respect to site of metastases the liver metastasis showed significant worse survival outcomes in both OS and PFS. The HR positive status and type of chemotherapy regimen significant PFS benefits. All these 5 prognostic variables were further calculated in multivariate cox regression. As the number of metastases showed borderline PFS benefit ($p = 0.05$) it was included in multivariate analyses. The univariate analyses are represented in Table 3. The multivariate analyses revealed a better survival outcome with statistical significance for Ki67 ≤ 50% (in OS) and for those who received HT (in PFS). This is shown in Table 4.

6. Results in ORD

Out of 46, only 13 received palliative LRT to metastases and three underwent metastasectomy. Rest of the ORD group received only chemotherapy (±HT). The 2years, 3years and 5years OS/PFS rates with ORD were 47.8%/23.9%, 31.1%/10.9% and 16.5%/2.2% respectively. The univariate analyses found better OS/PFS trends for ≤40years age, nulliparous, premenopausal patients, solitary metastasis, single organ involvement, grade2 tumours, ≤ 50% Ki67 HR positivity, Taxane based therapy, palliative LRT and HT. The favourable OS/PFS benefits were seen for Ki67 ≤ 50%, HT, HR positivity and Taxane chemotherapy with statistical significance. Significant OS benefit was seen with premenopausal women. The addition of palliative LRT showed significant PFS benefit. All the above said factors were further considered for multivariate analyses. The univariate analyses results are depicted in Table 5. The multivariate analyses revealed a significantly better OS outcome for premenopausal patients and significantly better PFS outcome for HT received cases. This is shown in Table 6.

7. Discussion

Oligometastasis has always been debated for curative intent, especially in providing LRT. However, most of the available literature is retrospective data pointing to favourable outcomes with OM, HR

Table 6
Multivariate analyses in ORD.

Variables	OS				PFS			
	HR	95% CI		Sig.	HR	95% CI		Sig.
		Lower	Upper	P < 0.05		Lower	Upper	P < 0.05
Menopausal status				0.001				0.449
Pre	0.256	0.110	0.593		0.746	0.349	1.595	
Post	referent				referent			
Receptor status				0.080				0.140
ER/PR + ve	0.255	0.072	0.904		0.860	0.184	4.018	
HER2neu3+	0.474	0.133	1.687		0.328	0.090	1.197	
TNBC	referent				referent			
Ki67(in %)				0.324				0.252
<50	0.218	0.078	5.088		0.545	0.117	2.541	
≥50	referent				referent			
Type of chemotherapy regimen				0.217				0.167
Taxane based	0.396	0.136	1.155		0.446	0.178	1.119	
Others^	referent				referent			
Hormone therapy				0.694				0.008
No	1.225	0.446	3.363		4.759	1.493	15.164	
Yes	referent				referent			
Locoregional therapy				0.680				0.754
C	2.855	.050	.3.314		0.405	0.038	4.297	
C + Palliative S or R	1.944	.535	15.240		1.639	0.350	7.668	
HT only	referent				referent			

Abbreviations: ORD-oligorecurrent disease -Estrogen receptor, PR - Progesterone receptor, TNBC -Triple negative breast cancer, S -Surgery, C-Chemotherapy, R-Radiotherapy, CTX/VP16 – Cyclophosphamide/Etoposide (oral Tablet), ^ - CTX/VP16, Capecitabine, Eribulin.

positivity and a lesser number of OM [18–20,24,25]. The historical comparison of the present study with the available literature on OM was done and is shown in Table 7.

7.1. Present study vs literature review

The baseline characteristics of this study were almost similar to literature except the higher proportion of grade 3, Ki67 > 50%, HER2-neu positivity and lesser LRT. The other distinguishing feature of this study was higher proportion of HR positive HER2neu cases.

The median OS (43.3 months) and 5-year OS rate (46.2%) in this study were similar to the literature review on oligometastases (Table 7) [18,20]. Similarly, the OS outcomes of OMD were comparable with that of literature but not ORD. Also, this study had a lesser PFS rate (16.5–29.7%) when compared to others (21.6–57%) [18,20]. The possible reasons for the latter could be lesser proportion of LRT to metastatic sites and lesser targeted therapy due to financial constraints.

Unfortunately, the evidences from available studies are from denovo OMD, and the data on ORD is lacking as most of the studies did not stratify and analyse the results for ORD. This study clearly showed better survival outcomes with OMD in patients who have not received LRT compared to ORD patients who received chemotherapy alone as shown in Table 3 and E. This explains the intrinsic aggressive biology of ORD. In a study by Nagasaki et al. the 5year OS/PFS rates were 81.1% and 56.8% with an updated OS rates of 18.9% at 25 years [26]. The definition of OM was different in that study with 1–2 organs involved (<5 metastases per organ each with <5 cm). With only 18% denovo OM and the rest being ORD Nagasaki et al. demonstrated excellent survival rates. This was because almost 47% received curative LRT to all metastatic lesions (either S or RT) in that study [26]. Administration of Taxanes and ≤3 metastatic lesions per organ were found to influence relapse free disease and response rates in their multivariate analyses which is not seen in this series [26].

Prognostically significant better OS outcomes were seen in Ki67 ≤ 50% (in OMD) and premenopausal patients (in ORD) and for those who received HT (in terms of PFS). However, the prognostic factors like age, HR positivity, low grade, good performance status, number of metastases, site of metastases, type of chemotherapy, and LRT were not prognostically significant compared to other retrospective studies [18,20,26]. This is again explained by the lesser number of LRT in the present series.

As per the literature review those with ≤5 metastases had 5year OS/PFS rates of 49%/25% similar to the present study [18]. With respect to the site of metastases the 5year OS/PFS rates reported in literature for bone (73%/33%), lung (54%/-), liver (33–78%/23–36%) were better compared to the present study (as in Table 2). In addition, the present study showed better median OS/PFS for brain metastases (22.7/21.4months) compared to 11 months in the literature [27]. Higher number of brain lesions (>5) and extracranial metastases might have contributed to the lesser survival rates seen in the study by Berghoff et al. [27] The OMD group had poor survival outcomes in case of liver or brain metastases. In contrary the liver and NLN metastases in ORD showed better survival rates. This is because of the uneven distribution in HR status, grade and Ki67 of the tumor.

Cha et al. in their study failed to show OS benefit for local therapy in presence of HT in HR positive oligometastases [28]. With or without LRT better survival outcomes were seen in HR positive cases. But they did not analyse in HR positive HER2neu patients as this study had higher proportion of the same and HT was provided to all HR positive cases. The study by Falato et al. demonstrated significant OS benefit in Ki67 ≤ 20% compared to >20%. But this study was conducted in metastatic breast cancer not in oligometastases [29]. Though this study showed better OS outcomes for Ki67 ≤ 50% we do not have enough literature to compare.

The present study has longer follow-up data and is one of the most extensive second Indian data on oligometastases. However, selection bias, information bias due to retrospective nature of this study cannot be denied. The higher proportion of grade 3, Ki67 > 50% and HER2neu positivity observed in this series might have affected the overall survival and imply the aggressive intrinsic disease biology of OM in Indian scenario. The disproportionate distribution of HR positivity, grade and Ki67 might explain the non-significant results in the prognostic factor analyses. The major limitations of this study were lesser LRT and limited targeted therapy usage due to financial constraints as this could have improved the survival outcomes. This is because of the paucity of evidence from prospective studies, which affects physician choice in managing OM.

8. Conclusion

This study showed the positive impact of OMD, Ki67 ≤ 50%,

Table 7
Comparison of characteristics and outcomes for oligometastatic breast carcinoma (literature review vs present study).

Characteristics	Systematic review@ [18]	Steenbruggen et al.@ [20]	Kobayashi et al.@ [24]	Gogia et al. @ [19,25]	Present study
Number of patients	1041 Combined population of <5, <3 and solitary metastases	517-oligometastasis ≤3 metastases out of 3535 metastatic patients retrospective (2000–2007)	75 oligometastatic patients (<5sites and <5 cm) retrospective (1980–2010)	128 oligometastatic patients out of 375 metastatic patients (<5sites and <5 cm) retrospective (2012–2018)	170 oligometastatic patients out of 736 metastatic patients (<5sites and <5 cm) retrospective (2012–2018)
Age in years mean (range)	27–84		48 (28–69)	49 (22–80)	50 (27–84)
Receptor status (%)					
HR positive (ER/PR) in %	56.9–68.3	60.9 (includes HER2neu unknown)	64 (includes unknown-4)		34.7 (64.7% if we include those with HR + HER2neu + ve)
HR and HER2/neu positive (in %)		12.2			37.6
HR -ve and HER2/neu positive (in %)	20	12.7	17 (includes unknown 9)		13.6
TNBC (in %)		7	24		13.5
Proportion with **oligometastatic disease (%)**		19.5		34.1*	23.1
Proportion with **poly-metastatic disease (%)**		80.1		65.9	76.9
Site of metastasis (%)					
Bone metastases	12.6–50	55.9	39		44.7
Visceral	37–73.6		48		37
Lung	Nil	10.4	55 (soft tissue metastases)		18.8
Liver	Nil	34			15.3
Nonregional lymph node	9–30	7.5			33.5
Brain	4	5.6			2.9
Others	4	2.7			3
Chemotherapy (%)					
Single-agent Taxane			1		24
Taxane plus anthracycline			3		17
Taxane plus platinum					
Anthracycline plus cyclophosphamide					25
Endocrine therapy			7		67
Tamoxifen					
Aromatase inhibitor					
Targeted therapy (%)					
AntiHER2neu (%)			1		1.8
CDK4/6 inhibitors (%)					0.6
Median OS	(11–185 months)		185 months		43.3months (29.6–56.9months) For OMD- 74 months For ORD-22.7months
OS rate (%)	30–79% at 5 years	10year OS ≤3 metastases-14.9% 4 to 5 metastases −7.4% (Median follow up-15.2years)	5year OS 79.2% 10year OS 59.2% (Median follow up-103 months)	2year OS 91.1% and 66.8% of estimated 5year OS (Median follow up-21.4months)	2year OS 70.7%, 3year OS 57.2%, 5year OS 46.2%, and estimated 8year OS of 30.7% (Median follow up-56.3months) For OMD 2year OS 78.8%, 3year OS 67.5%, 5year OS 55.3%, and estimated 8year OS of 39.8% (Median follow up-57 months)
Median PFS	11–52months		Median 48 months		21months (16.8–25.2months) For OMD-26 months For ORD -13.3months
PFS rate	25–57% at 5 years		5year RFI-56.8% 10year RFI-27.4%	Estimated 2year PFS 54.6% and 5year PFS 21.6%	2year PFS 45.1%, 3year PFS 31.3%, and 22% 5year PFS For OMD 2year PFS 53%, 3year PFS 39% and 29.7% 5year PFS

Abbreviations: OMD-denovo Oligometastasis, ORD-oligorecurrent disease, TNBC -Triple negative breast cancer, HR-Hormone Receptor, ER -Estrogen receptor, PR -Progesterone receptor RFI – Relapse free interval, OS – Overall survival, PFS - Progression free survival, @-references.

premenopausal status, and HT in survival. The improved trend towards OS and PFS for age, premenopausal patients, single organ involvement, solitary metastases, site of metastases, grade2 tumours, HR positivity and type of chemotherapy observed in this study need to be confirmed in future prospective trials. The lesser survival rates observed in this study for ORD hints toward the importance of adding curative LRT with chemotherapy in OM. Therefore, OM has to be considered for curative intent with LRT for both primary tumor and metastatic disease along with chemotherapy in future prospective randomised trials with the stratification for HR status and targeted therapy. We need to determine the role of LRT in the present era of targeted therapies showing improvement in survival. Multimodality management will remain a continuing hitch in oligometastases. Till then, the conundrum in Oligometastatic breast cancer will persist.

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Declaration of competing interest

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