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Oligometastatic Solid Tumors: Disease Characteristics and Role of Local Therapies

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ABSTRACT

Background: Treatment recommendation and benefit of local therapy in oligometastatic disease (OMD) are an era of interest and debate. However, most of the clinical literature on OMD is cancer site specific.

Objective: To study OMD detailed disease characteristics and outcomes regarding local therapies.

Patients sand methods: This observational prospective cohort study included 234 patients with stage IV solid tumors who met the criteria of OMD (≤ 5 metastatic lesions, and or ≤ 2 organs) with performance status 0-2; we studied disease characteristics and outcomes regarding local therapies of OMD.

Results: 126 (53.8%) patients received local therapies; surgery, radiotherapy (RT) and local ablative therapy (group I). 108 (46.2%) patients didn't receive local therapy (group II). Comparing both groups, in group I, patients had significantly younger age, earlier initial TNM stage, higher rates of metachronous onset, symptomatic disease, soft tissue disease, single lesion and or single organ involvement and complete response, but lower rates of managed pulmonary OMD compared to group II. Regarding survival, local therapy of OMD was associated with better PFS and OS. The mean OS since OMD diagnosis in local therapy group was 64 months vs. 38 months in non-local therapy patients and the median PFS was not reached in local therapy patients vs. 30 months in no local therapy patients. By multivariate regression analysis, local therapy for OMD was an independent prognostic factor for both progression-free survival (PFS) and overall survival (OS).

Conclusions: For selected oligometastatic solid tumor patients, local therapy for OMD could improve PFS and OS.

Keywords: OMD, Solid tumors, Local therapy.

INTRODUCTION

The leading cause of cancer mortality is metastases [(1)]. However, it is known that distant metastases may not always be multiple and extensive [(2)]. An intermediate state exists in between localized cancer and extensive metastatic state, termed oligometastasis, where metastasis targeted therapy has the possibility for cancer cure [(3)].

Oligometastatic state is defined to be a maximum of five metastases at two or three sites [(4-5)]. However, in a meta-analysis conducted by **Rim *et al.*** [(6)], the definition varies, with some studies included less than or equal to three metastases. Other studies included less than or equal to five, & a few trials chose patients according to the capability of local consolidative therapies (LCTs) to cover the lesions [(4, 7)].

The European Organisation for Research and Treatment of Cancer (EORTC) & the European Society for Radiotherapy and Oncology (ESTRO) OligoCare project developed a thorough design for description & categorization of OMD according to the clinical scenarios. Criteria for sub-categorization involve: The timing of OMD, clinical history of previous OMD, initial systemic therapy at OMD diagnosis, response to systemic therapy and previous clinical history of polymetastatic cancer state [(8)]. And it was approved by a retrospective study that included hundreds of patients with OMD [(9)]. The clinical impact of oligometastatic state is that local radical treatment could result in long-term survival or cure [(10, 11)].

In this work we aimed to study OMD detailed disease characteristics and outcomes regarding local therapies.

PATIENTS AND METHODS

Patients: This observational prospective cohort study included patients of stage IV oligometastatic disease (OMD) of different types of solid tumors through the period from January 2015 to January 2019.

Inclusion criteria: Patient with stage IV solid tumors with oligometastatic disease including the following eligibility criteria: ≤ 2 organs involved and ≤ 5 metastatic lesion with male or female sex of any age but with performance status (PS) 0-2 [(12)]. Staging was done according to AJCC cancer TNM staging manual, eighth edition, 2017 [(13)].

Exclusion criteria: Patients with incomplete medical data, patients with decompensated organ functions and polymetastatic disseminated disease at time of recruitment are excluded but patients with previous history of polymetastatic disease and current induced OMD are eligible.

Local therapy done after multidisciplinary team consultation of Menoufia University Hospital and Surgical approach aimed for complete surgical excision of metastatic lesion, metastatectomy of brain metastases required a careful clinical assessment of individual patients.

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Methods:

Patients underwent metastatic work up imaging either by computerized tomography (CT) of chest, abdomen, and pelvis with contrast, or magnetic resonance image (MRI) with or without technetium bone scan, or 18F-FDG-PET/CT. To confirm OMD nature of the disease, all images and reports reviewed and rechecked by participating radiologist. All imaging details as imaging modality used initially and max SUV activity.

Base line information regarding patients characteristics: (age, gender, PS, smoking, comorbidities, family history of cancer), disease characteristics: (tumor site, initial stage, histopathological subtype, grade, molecular subtype of breast cancer, mutational analysis, serum tumor markers, size and number of lesions, number of affected organs, OMD burden, OMD organs, if OMD is symptomatic or not, onset of OMD to differentiate synchronous from metachronous OMD, OMD during active treatment or no active treatment to differentiate oligoprogression from oligorecurrence, previous history of polymetastatic disease to differentiate induced from genuine OMD, previous OMD to differentiate repeated from denovo OMD, all treatment data as treatment intention of OMD, type of systemic treatment received, number of lines of systemic treatment, type of local treatment received, further systemic disease or delay in systemic treatment after local control if done and disease outcome. Responses and survival were collected, tabulated and analyzed. Response was assessed by revised RECIST criteria version (1.1) [(14)]. Patients were followed at least 36 months. PFS was calculated from the date of diagnosis till the date of progression. OS since diagnosis was calculated from the date of primary cancer diagnosis till the date of death or last contact. OS since OMD was calculated from the date of OMD diagnosis till the date of death or last contact.

Ethical approval: A written consents from the patients and approval (IRB number 2/2023ONCO4-2) from The Ethical Committee of Faculty of Medicine, Menoufia University were obtained. The Helsinki Declaration was followed throughout the study's conduct.

Statistical analysis

Data were statistically analyzed using an IBM compatible personal computer with Statistical Package for the Social Sciences (SPSS) version 26 (SPSS Inc. Released 2018. IBM SPSS statistics for windows, version 26.0, Armonk, NY: IBM Corp.). Qualitative data were expressed as Number (N), percentage (%), while quantitative data were expressed as mean and standard deviation (SD).

Chi-square test was used to study association between qualitative variables. Student's t-test was used for comparison of quantitative variables between two groups of normally distributed data, while Mann-Whitney's test was used for comparing quantitative variables between two groups of not normally distributed data.

OS analysis and PFS were done using Kaplan-Meier curve statistics with log rank test to express the significance between two groups. Univariate COX regression analysis was done for each clinical variable separately to determine factors affecting OS & PFS, then significant factors were analyzed together using multivariate COX regression analysis to identify independent predictors for survival and to calculate adjusted hazard ratio. Significant test results were quoted as two-tailed probabilities. Significance of the obtained results was judged at 5% level ($P \leq 0.05$).

RESULTS

This study included 234 patients with OMD of solid tumors. Group I: patients with OMD had local therapy (n= 126) and group II patients with OMD had no local therapy (n= 108). Breast cancer ranking the most frequent cancer type (44.4% of cases), followed by colorectal cancer (12%) and NSCLC (11.5%) (Figure 1). Age of the studied patients ranged from 15 to 86 years old with significantly higher age in group II. Regarding histopathological subtype adenocarcinoma was the most common subtype with 83.3% in group I vs. 78.7% in group II with no significant difference. Undifferentiated carcinoma was significantly higher in group I (9.5%) vs. (0.9%) in group II (p value 0.012).

There was no significant difference regarding any actionable disease mutations. Regarding luminal subtypes in breast cancer patients, both groups were similar with total 66.7% luminal subtype and 22.9% HER2neu overexpressed and 10.4% triple negative subtype. In prostate cancer patients, the median PSA level in group I was 80 ng/ml vs. 55.5 ng/ml in group II. In breast, GIT and lung cancers, the median CEA level in group I was 66.0ng/ml vs. 74.5 ng/ml in group II.

PET/CT was the initial imaging modality in 76 patients (Figure 2) with uptake > 10 in 44.2% in group I vs. 33.3% in group II (all p value > 0.05). There was significant difference of initial TNM stage and onset of OMD between both groups with 66.7% patients was presented with synchronous metastasis in group II vs. 50.8% in group I (p value 0.034 and 0.014 respectively). There was significant difference regarding OMD organs (Figure 3), histopathological assessment of OMD (core or surgical biopsy), number of OMD lesions (Figure 4), and OMD max size between both groups (Table 1).

Table (1): Patients and disease characteristics

		Group I (n= 126)		Group II (n= 108)		Total (n= 234)		χ^2 (P-value)
		No	%	No	%	No	%	
Age (in years)		53.2±13.6		56.7±12.1		54.8±13.0		#2.07 **(0.04*)**
Gender	Male	38	30.2	38	35.2	76	32.5	0.67
	Female	88	69.8	70	64.8	158	67.5	(0.41)
Smoking	Yes	23	18.3	20	18.5	43	18.4	0.003
	No	103	81.7	88	81.5	191	81.6	(0.96)
Comorbidities	Yes	43	34.1	36	33.3	79	33.8	0.02
	No	83	65.9	72	66.7	155	66.2	(0.90)
PS	0	88	69.8	63	58.3	151	64.5	3.37
	1, 2	38	30.2	45	41.7	83	35.5	(0.07)
histopathological grade	G (1, 2)	74	58.7	53	49.1	127	54.3	2.39
	High G	38	30.2	38	35.2	76	32.5	(0.30)
	Unknown/NA	14	11.1	17	15.7	31	13.2	
Initial TNM stage	I	3	2.4	0	0.0	3	1.3	8.68 (**0.03*)**
	II	17	13.5	7	6.5	24	10.3	
	III	42	33.3	29	26.9	71	30.3	
	IV	64	50.8	72	66.7	136	58.1	
Symptomatic OMD	Yes	62	49.2	27	25.0	89	38.0	14.46
	No	64	50.8	81	75.0	145	62.0	**(<0.001**)**
Onset of OMDs	Synchronous	64	50.8	72	66.7	136	58.1	6.02
	Metachronous	62	49.2	36	33.3	98	41.9	**(0.01*)**
OMDs diagnosis during active therapy	Yes oligoprogression	34	27.0	20	18.5	54	23.1	2.35
	No oligorecurrence	92	73.0	88	81.5	180	76.9	(0.13)
Histopathological assessment of OMD	Yes	47	37.3	5	4.6	52	22.2	35.91
	No	79	62.7	103	95.4	182	77.8	**(<0.001**)**
Previous poly-metastatic disease	Yes (Induced)	12	9.5	10	9.3	22	9.4	0.01
	No (genuine)	114	90.5	98	90.7	212	90.6	(0.95)
Previous OMD (No= 212)	Yes (repeated	3/114	2.6	2/98	2.1	5/212	2.4	0.09
	No (denovo)	111	97.4	96	97.9	207	97.6	(0.96)
Number of involved organs	1	100	79.4	66	61.1	166	70.9	9.40
	2	26	20.6	42	38.9	68	29.1	**(0.002*)**
Max no of lesions /organ	1 - 2 lesions	87	69.0	44	40.7	131	56.0	18.91
	3 - 5 lesions	39	31.0	64	59.3	103	44.0	**(<0.001**)**
OMD burden	single lesion	48	38.1	16	14.8	64	27.4	15.86
	multiple lesion/organs	78	61.9	92	85.2	170	72.6	**(<0.001**)**
Serum tumor markers	Normal	45	35.7	32	29.6	77	32.9	2.99
	elevated	40	31.7	29	26.9	69	29.5	(0.22)
	Unknown /NA	41	32.5	47	43.5	88	37.6	
Max SUV activity PET/CT (No= 76)		10.8 ± 6.5		9.7 ± 6.2		10.3 ± 6.4		## 0.87(0.39)
OMD max size groups (No= 157)	≤3cm	48	57.1	55	75.3	103	65.6	5.73
	>3cm	36	42.9	18	24.7	54	34.4	**(0.02*)**
Clinically controlled primary tumor at OM	Yes	95	75.4	79	73.1	174	74.4	0.15
	No	31	24.6	29	26.9	60	25.6	(0.69)
Overall response	CR	37	29.4	15	13.9	52	22.2	8.06
	Other responses	89	70.6	93	86.1	182	77.8	**(0.005*)**
NO of lines of systemic treatment	1-2	98	77.8	77	71.3	175	74.8	1.30
	≥ 3	28	22.2	31	28.7	59	25.2	(0.2)
Delay of systemic treatment	Yes	27	21.4	24	22.2	51	21.8	0.02
	No	99	78.6	84	77.8	183	78.2	(0.88)

Age is expressed as mean ± SD. Co morbidities include (DM, HTN and Hepatic), χ^2: Chi square test; #: student t test; *Significant (P<0.05); **Highly Significant (P<0.001), ##: Mann-Whitney test.

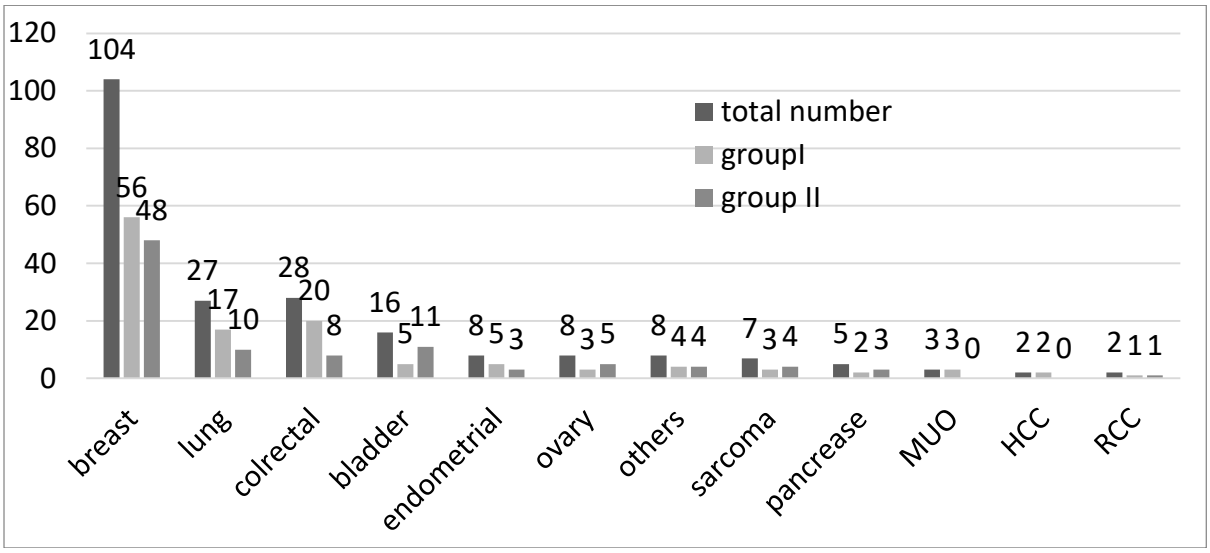


Fig. (1): Patients numbers according to cancer diagnosis (total number and both groups)

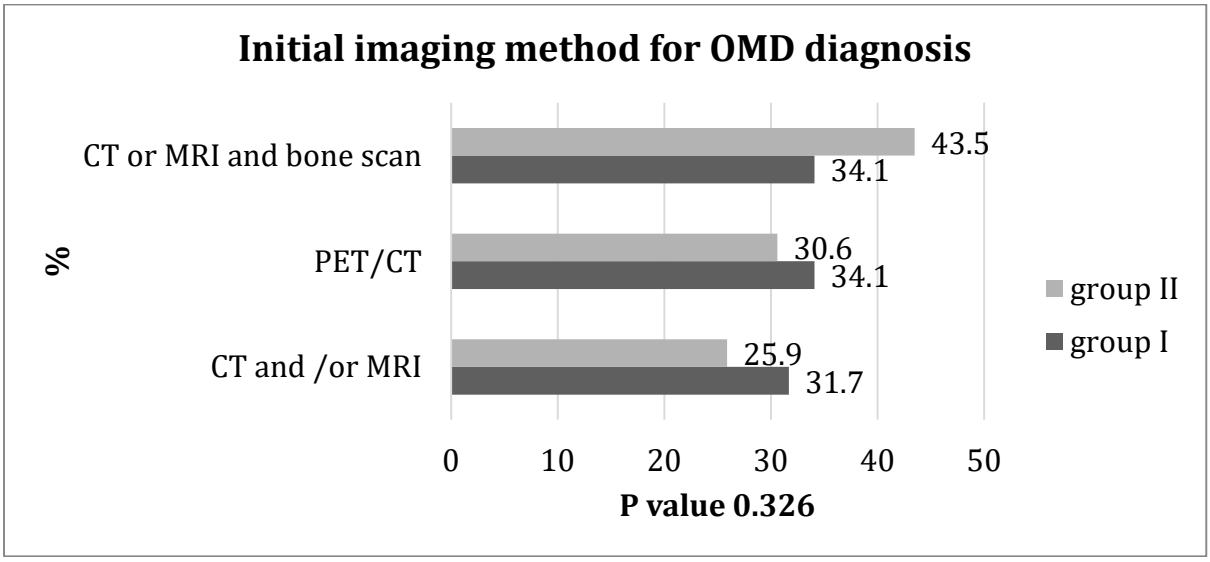


Fig. (2): Initial imaging method for diagnosis of OMD in both groups

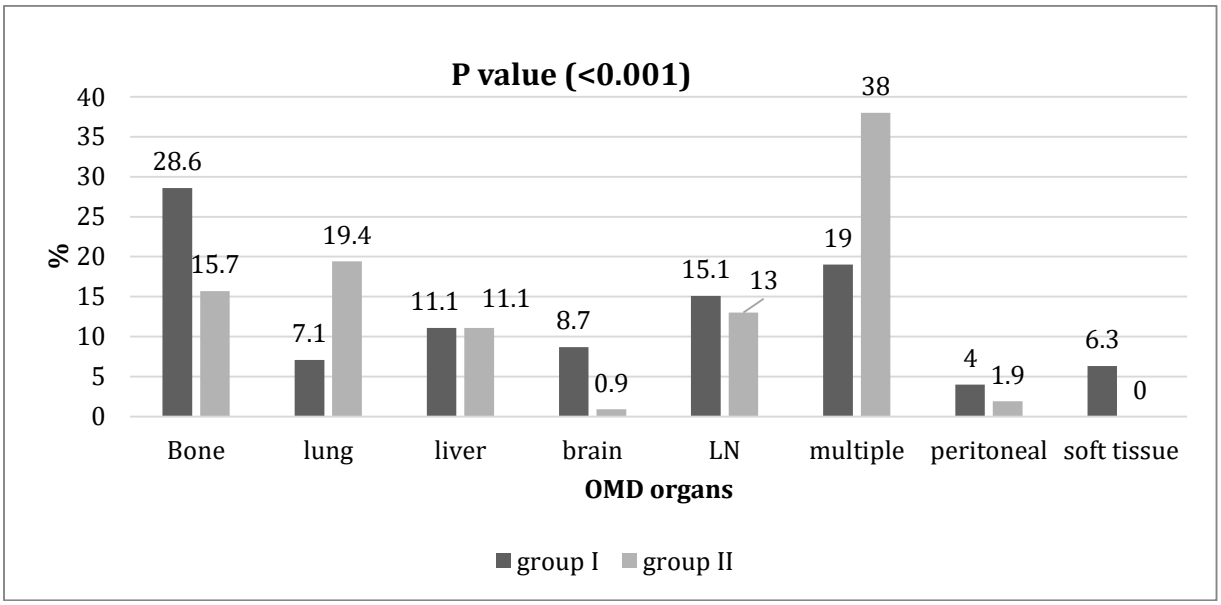


Fig. (3): OMD organs distribution in both groups

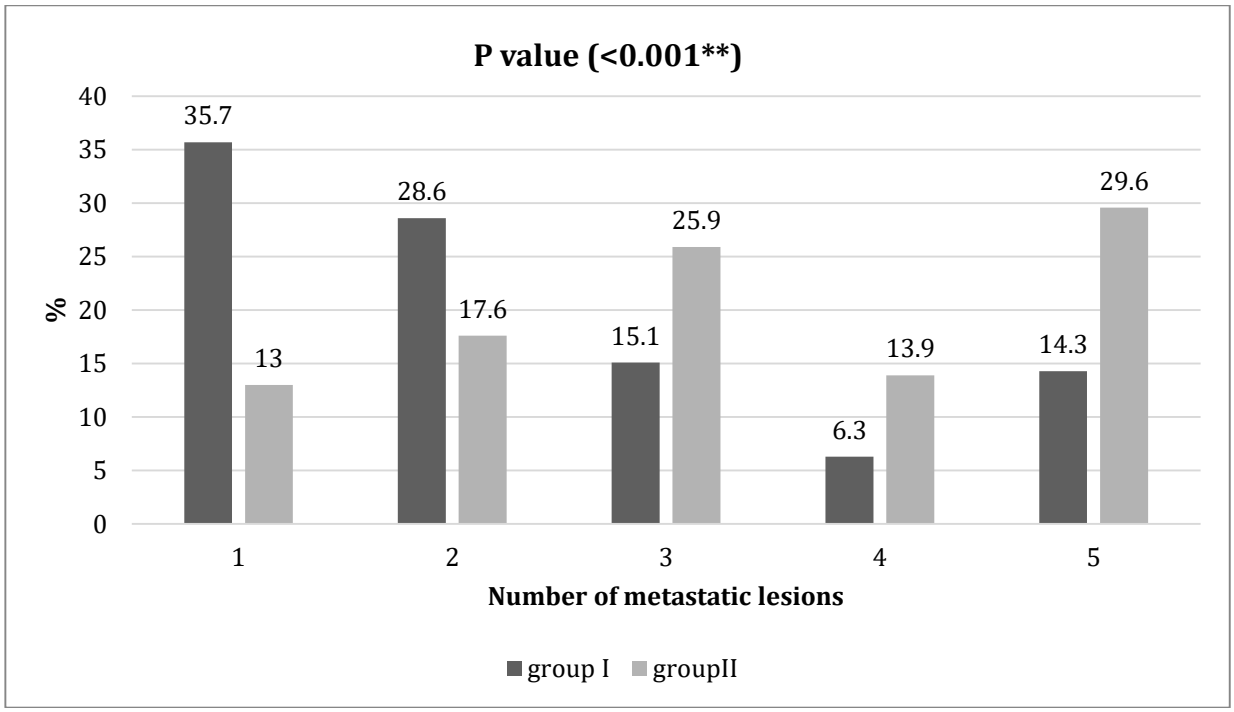


Fig. (4): Number of metastatic lesion in both groups

Local treatment received in 126 patients group I (Table 2); 71 patients received radical fractionated radiotherapy with multiple dose schemes, 37 patients underwent surgery including eleven patients had brain metastatectomy and 17 patients with liver metastases had radiofrequency ablation and 1 patient had microwave ablation (Cases figures 8 & 9). The mean PFS was 55.1 months for both groups with significant difference between them, the mean PFS in group I was 64.9 months vs. 39.2 months in group II (P value 0.001) (figure 5). The mean OS since diagnosis for both groups was 76.3 months, with significant difference between both groups (the mean OS in group I was 87.9 months vs. 60.1 months in group II (P value 0.001) (figure 6 and 7). Univariate COX regression analysis was done for each clinical variable separately then significant factors were analyzed together using multivariate COX regression analysis (Figure 7). Local therapy for OMD was found to be an independent prognostic factor for both PFS and OS (Table 3).

Table (2): Relation between type of local therapy and response of OMD in group I (No= 126)

		Surgery (No= 37)		**Radiotherapy (No= 71)**		**local ablative therapy (No= 18)**		**Chi square test (P-value)**
		No	%	No	%	No	%	
Response of OMD:	CR	18	48.6	13	18.3	6	33.3	23.55 **(0.003*)**
	PR	11	29.7	21	29.6	8	44.4	
	SD	5	13.5	27	38.0	2	11.1	
	PD	3	8.2	10	14.1	1	5.6	
	Unknown/ NA	-	-	-	-	1	5.6	
Complete Response:	Yes	18	48.6	13	18.3	6	33.3	10.95 **(0.004*)**
	No	19	51.4	58	81.7	12	66.7	

Table (3): Univariate and Multivariate analysis for predictors of PFS and OS

	Univariate Cox regression		Multivariate Cox regression	
	P-value	Crude HR (95% CI)	P-value	Adjusted HR (95% CI)
Progression free survival				
N. of OMD lesions (3-5)	**0.005**	2.6 (1.3-5.1)	0.260	0.4 (0.1-2.2)
Max. N. of OMD lesions/ organ (3-5)	**0.001**	3.1 (1.6-5.97)	0.076	4.8 (0.8-26.8)
Elevated serum tumor marker	0.278	1.5 (0.7-3.3)		
Tumor size >5 cm	0.448	1.3 (0.6-2.7)		
OMD burden (few lesions, few organs)	**0.011**	4.6 (1.4-14.9)	0.318	1.9 (0.5-7.2)
treatment of intention of OMDs (palliative)	**<0.001**	5.5 (2.7-11.2)	0.076	2.3 (0.9-5.5)
lines of systemic treatment (> 3 lines)	0.672	1.2 (0.6-2.2)		
Delay of systemic treatment	**<0.001**	5.4 (2.96-9.9)	**<0.001**	3.8 (2.0-7.2)
Complete response	**0.002**	0.2 (0.05-0.5)	0.109	0.3 (0.1-1.3)
Local therapy of OMD	**0.002**	0.4 (0.2-0.7)	**0.023**	0.5 (0.2-0.6)
Overall survival				
Age group: >65 years	**0.004**	2.3 (1.3-4.1)	0.440	1.3 (0.7-2.7)
Male gender	**<0.001**	3.03 (1.8-5.1)	0.556	1.3 (0.6-2.7)
Smoking	**<0.001**	3.6 (2.1-6.2)	**0.002**	3.3 (1.5-6.9)
Performance status (≥1)	**0.005**	2.03 (1.2-3.3)	**0.040**	1.9 (1.03-3.4)
Grading (1&2)	**0.028**	0.6 (0.3-0.9)	0.785	1.1 (0.6-2.1)
Synchronous Onset of OMDs	**<0.001**	2.6 (1.5-4.3)	**0.023**	1.99 (1.1-3.6)
Elevated serum tumor marker	0.492	1.3 (0.7-2.4		
Tumor size >5 cm	0.241	1.5 (0.8-2.8)		
N. of OMD lesions (3-5)	**0.023**	1.8 (1.1-2.9)	0.688	0.8 (0.3-2.5)
Max. N. of OMD lesions/ organ (3-5)	**0.014**	1.9 (1.1-3.1)	0.493	1.5 (0.5-4.4)
Delay of systemic treatment	**0.003**	2.3 (1.3-3.8)	0.163	1.5 (0.8-2.8)
lines of systemic treatment (> 3 lines)	0.742	0.9 (0.5-1.5)		
Complete response	**0.003**	0.3 (0.1-0.7)	**0.011**	0.3 (0.1-0.8)
Local therapy of OMD	**0.001**	0.4 (0.3-0.7)	**0.033**	0.5 (0.2-0.7)

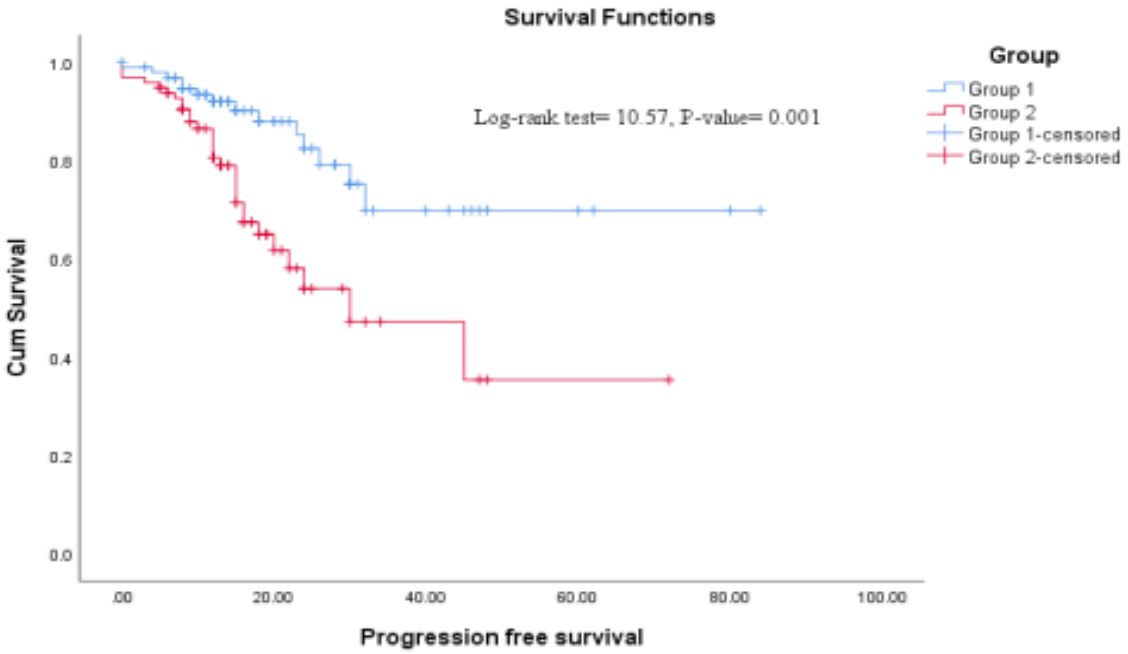


Fig. (5): Kaplan Meier survival curve for PFS in both groups

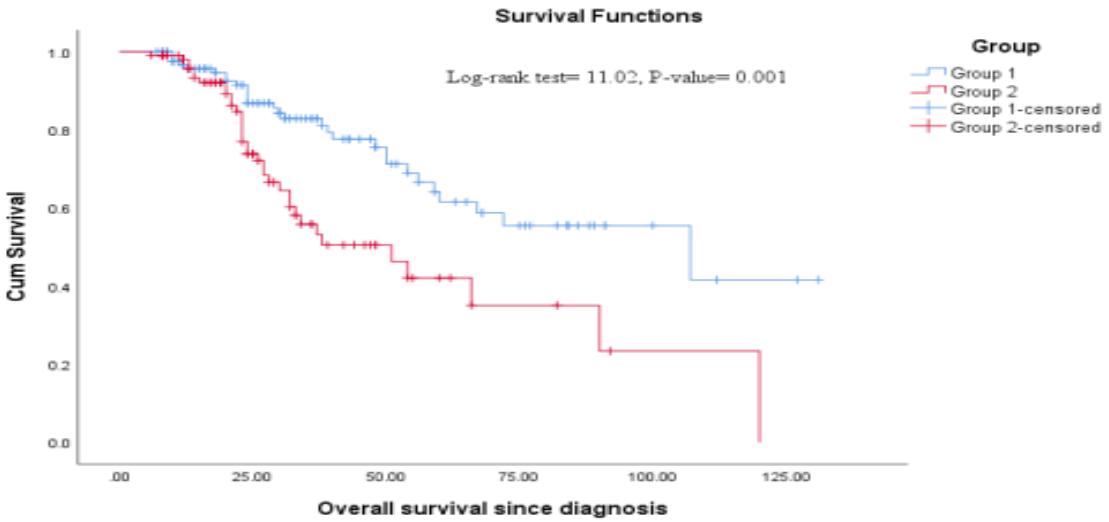


Fig. (6): Kaplan Meier survival curve for OS since diagnosis in both groups

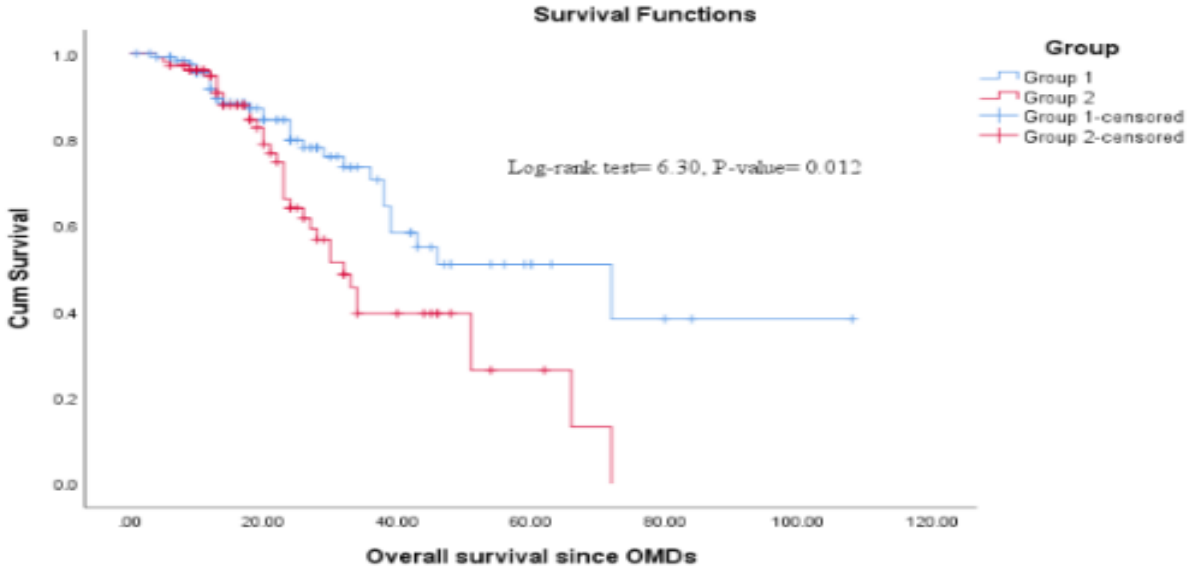
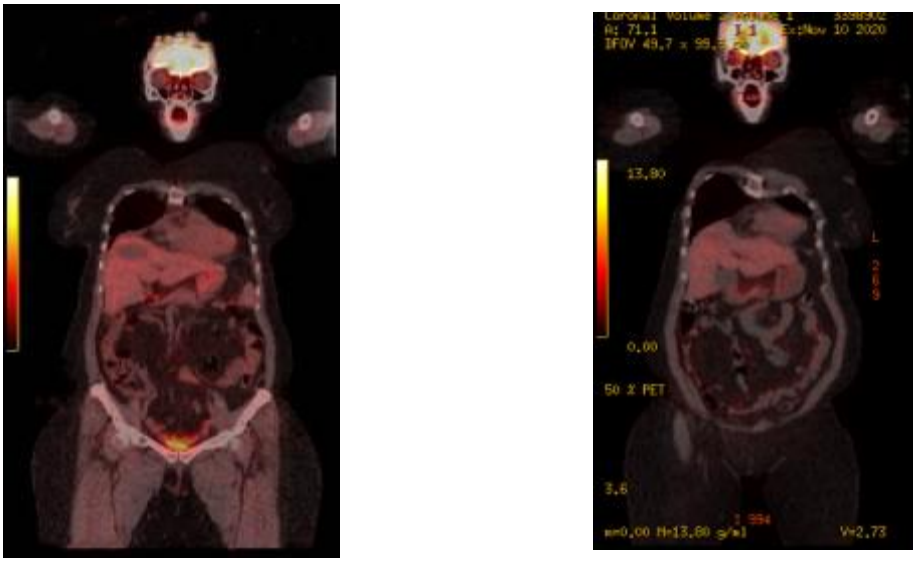
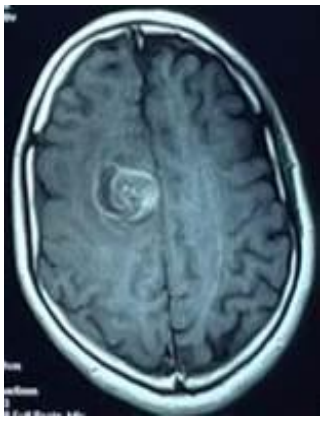


Fig. (7): Kaplan Meier survival curve for OS since OMD in both groups

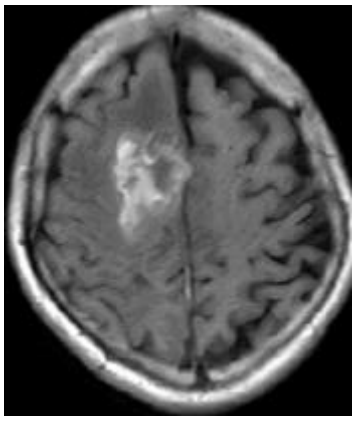


- CT coronal and fusion images of left hepatic lobe OMD (segment IV) the left image shows marginal uptake (before systemic treatment then ablation) & the right image shows no FDG uptake after MWA denoting CR

Fig. (8): PET-CT Images before and after MWA of hepatic lesion breast cancer patient.



a- axial T1 post-gadolinium WI shows right parasagittal space occupying lesion with post-contrast enhancement and surrounding edema representing metastasis.



b-axial T1WI post-total surgical excision showing post-operative intra-axial hemorrhagic signal and surrounding edema and post-operative change

Fig. (9): MRI of RCC case before and after surgical resection of brain lesion.

DISCUSSION

Comprehensive studies have appeared lately regarding local consolidative therapy use for oligometastasis [15, 16], however, most of them are single-arm and or observational trials, as is quite difficult to plan RCTs including metastatic patients due to ethical concerns (e.g., the patients may lose an effective treatment if they are assigned to a control arm) and due to extensively variable clinical characteristics of the patients [3].

Majority of the studies on OMD are cancer specific site, & just only few trials included different tumor types. **Rim *et al.*** [6] conducted a meta-analysis and included studies with multiple cancer types. This is compatible with this study, which included multiple cancer types.

Breast carcinoma is the most common cancer in females & the first cause of cancer related mortality [17]. This is in agreement with this study results that showed that breast cancer was the most prevalent primary cancer in females.

The mean age of patients in group I was younger than in group II. This may explain the possibility of surgical resection of OMD in group I due to younger age.

In a study about the most common first metastatic site in women with non-advanced breast carcinoma; bones were the most frequent site: 41% [18]. This is also compatible with our study results, which revealed that bone was the most common OMD site.

In this study most patients in group II were presented by synchronous onset of metastasis, while the majority of patients in group I was presented by low OMD burden. This may explain less aggressiveness of disease in group I, and so the higher possibility of local ablative therapies.

- Group I patients had a higher percent of brain metastasis, which could be explained by presence of neurological symptoms that require tumor debulking surgery. Group I patients had also a higher percent of soft tissue and lymph node metastasis, which are more amenable for radical excision, while group II patients had more lung metastases, which needs more complicated surgical procedure.

Surgery was associated with more CR rates, which were noted in group I patients, and CR could be translated into better OS. This is compatible with a review conducted by **Suh *et al.*** [19] that showed that a group of patients with metastasis to brain may be long survivors after diagnosis, specifically patients with ≤ four lesions from breast origin.

- The role of the size of metastases in prognosis is still to be defined. In a multicentric trial by **Yamamoto *et al.*** [20], the maximum diameter of OMD tumor (per 1-cm increase) has showed a powerful correlation ($p < 0.001$) with overall survival. Also, three large cohort studies [21, 22, 23] showed that a cut-off level of 3 cm of metastasis diameter significantly associated with better OS. This is compatible with this study although p value was insignificant. However in this study results, metastatic size of ≥ 3 cm was more amenable for local therapy by comparing both groups and that may be explained by the possibility of uncertainty of metastatic nature of small size lesions, which may led to more conservative approach.

- Many trials have established a powerful correlation between OS and PS [20, 24]. This is compatible with this study result, as PS is an independent prognostic factor of OS. In contrast, other large cohort studies [21, 23, 25] showed statistically significant correlation only in the univariate but not in the multivariate analysis.

Fode *et al.* [24] show a good prognosis for metachronous metastases in a group of patients, 98% of them were presented by single organ metastasis. This is compatible with this study results as synchronous onset was considered as independent poor prognostic factor of OS.

- In stage IV CRC, **Thompson *et al.*** [25] showed that pre-SBRT CEA level was a strong indicator of

improved OS, which is agreeable with our results that showed that elevated serum tumor markers may be associated with increased risk of death (HR: 1.3), despite the p. value was insignificant.

Three large cohort studies showed that numbers of systemic therapy lines given before SBRT have a bad prognostic impact on OS and PFS, that could be explained by dominance of more resistant cell lines after chemotherapy [21, 25, 26]. This is compatible to some extent with this study results, by univariate analysis of PFS, although there was no significant association between the number of lines of received systemic therapy & PFS, the hazard ratio was 1.2 , and this means that there was increased risk of progression, but not compatible with OS .

A meta-analysis done by **Rim *et al.*** [6] revealed that local therapy was beneficial. In terms of OS and PFS, there was PFS, and OS benefit for selected oligometastatic patients when radical local therapy whether surgery or radiotherapy was given with systemic treatment, based on results of several phase II trials [27, 28]. These studies are compatible with our study results, which showed that patients in group I was associated with higher response rates, and longer PFS, & OS than patients in group II. Furthermore, local therapy for OMD was an independent prognostic factor for both PFS and OS.

Hepatic metastatectomy with curative intent is the standard therapy for CRC with limited hepatic metastases, resulting in longer OS [29]. This is also compatible with our study results, which showed that surgery of OMD was associated with more CR rates and longer survival.

This study results showed that there was a statistically significant correlation between OS & number of OMD lesions, which is compatible with **Gofrit *et al.*** [30] that revealed that OS was dependent on the number of metastases ($p < 0.0001$).

Also **Fode *et al.*** [24] showed equivocal significance ($p=0.049$) for single metastasis in terms of overall survival. However, **Franceschini *et al.*** [23] concluded that there is no correlation between the number of metastasis & overall survival ($p=0.792$). Similarly, different other recent trials showed that in patients with OMD, the total number of lesions may affect PFS but not OS [25, 31, 32].

Study limitations: the observational nature of the study caused the heterogeneity of systemic treatment received.

CONCLUSIONS

For selected oligometastatic solid tumor patients, local therapy for OMD could improve PFS and OS.

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- **Competing interests:** Nil.

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