SYSTEMATIC REVIEW

REVISED Better survival of patients with oligo- compared with polymetastatic cancers: a systematic review and meta-analysis of 173 studies [version 4; peer review: 2 approved]

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Abstract

Background: The modern concept of oligometastatic (OM) state has been initially developed to describe patients with a low burden of disease and with a potential for cure with local ablative treatments. We systematically assessed the risk of death and relapse of oligometastatic (OM) cancers compared to cancers with more diffuse metastatic spread, through a meta-analysis of published data.
Methods: PubMed, the Cochrane Library, and EMBASE were searched for studies reporting prognosis of patients with OM solid tumors. Risk of death and relapse were extracted and pooled to provide an adjusted hazard ratio with a 95% confidence interval (HR 95%CI). The primary outcome of the study refers to overall mortality in OM vs. polymetastatic (PM) patients.
Results. Mortality and relapse associated with OM state in patients with cancer were evaluated among 104,234 participants (n=173 studies). Progression-free survival was better in patients with OM disease (hazard ratio [HR] = 0.62, 95% CI 0.57–0.68; P <.001; n=69 studies). Also, OM cancers were associated with a better overall survival (OS) (HR = 0.65, 95% CI 0.62-0.68; P<.01; n=161 studies). In colorectal (CRC), breast, non-small cell lung cancer (NSCLC) and renal

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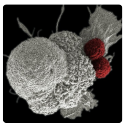
cell carcinoma (RCC) the reduction in the risk of death for OM patients were 35, 38, 30 and 42%, respectively. Biliary tract and cervical cancer do not significantly better in OM stage likely for paucity of data. **Conclusions**. Patients with OM cancers have a significantly better prognosis than those with more widespread stage IV tumors. In OM cancer patients a personalized approach should be pursued.

Keywords
cancer, oligometastases, survival, review, meta-analysis, tumours



This article is included in the Oncology gateway.

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Any reports and responses or comments on the article can be found at the end of the article.

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REVISED **Amendments from Version 3**

We have updated the table data as requested. We have changed a sentence in the final abstract section. We modified introduction by shortening the length. We also improved discussion by discussing the emergent problem of oligometastatic disease in light of the new imaging modalities. We discussed also the potential curative role of targeted local therapies (e.g. RT) in some disease (lung, renal carcinoma) supported by recent clinical trials. Some requests of the reviewer are not satisfied because data lack into included studies (exact burden of disease, treatments received in oligo vs polymetastatic subgroups). We extracted only data about timing of metastases (synchronous vs metachronous) that is reported in the table.

Any further responses from the reviewers can be found at the end of the article

Introduction

The vast majority of metastatic solid tumors are incurable, and despite the evolution of treatments, patients ultimately die because of their disease. The modern concept of oligometastatic (OM) state was initially developed in 1995[1] to describe patients with a low burden of disease (e.g. 1 to 3-5 metastases) with a potential for cure with local ablative treatments. This assumption also relies on the hypothesis that metastatic spread follows a hierarchical pattern in time and number of localizations.[2] Large consensus on the definition and management of OM patients is currently lacking. Clinically, those cancers with a lower burden of metastatic disease have a favorable prognosis and they may be amenable of local treatment for the primary and distant tumors. Recently, infact, advances in imaging and local ablative therapies have permitted the treatment of these patients with additional locoregional treatment in addition to systemic therapies, and some patients may be cured and attain long term survival.[3] This scenario has been best elucidated in genitourinary, lung and melanomas.[4,5] In these settings oligometastatic cancers may be treated in oligoprogressive sites continuing systemic therapy that control the remaining disease. One of the first published trials proving benefit of an aggressive local treatment of oligometastases was published in Lancet during 2019. In the SABR-COMET randomized study median overall survival (OS) was 28 months (95% CI 19-33) in the control group versus 41 months (26-not reached) in the stereotactic body radiotherapy to all metastases group (hazard ratio 0.57, 95% CI 0.30-1.10; P = .09).[6]

The aim of this systematic review and meta-analysis was to investigate and establish the prognostic survival of OM compared to non-OM solid tumors. In particular, we evaluated if patients with oligometastatic solid tumors do better than patients with non-oligometastatic tumors.

Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

Search strategy and inclusion criteria

A comprehensive search was performed with the following terms: (*advanced or metastatic or recurrent or relapsed or synchronous or metachronous) and (site or oligo* or "oligometastastic" or oligorecurrence or oligoprogression or single or multiple or 1-3 or >3 or >4 or >5 or 1-2 or 1-3 or 1-5 or number) and (synchronous or metachronous or metastases or relapse or recurrence or progression) and (tumor or tumour or cancer or carcinoma or melanoma or sarcoma) and ("hazard ratio") and (cox or multivariate or multivariable) and survival.* We searched PubMed, the Cochrane Library and EMBASE for studies eligible for this meta-analysis published in English language from inception up to October 30th, 2020. To be eligible, studies needed to have evaluated survival of patients with OM cancers (1 up to 3/5 metastases regardless of anatomic sites) regardless of line of therapy and to provide data of outcome according to the number of OM sites used by each author. Studies were excluded if they enrolled less than 10 patients, pediatric subjects, and hematological diseases. Commonly we define polymetastatic cancer as any disease with more than three or more than five metastases. Studies were searched and screened independently by three authors (FP, MG and GT).

Quality of studies and endpoints

The primary endpoint was overall survival (OS) and the secondary endpoint was progression-free survival (PFS). Quality assessment of the included studies was performed using the Newcastle-Ottawa Scale (NOS) for observational or retrospective studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). With NOS scale, studies were defined as poor, sufficient or good quality if scores (the sum of points attributed to each domain) were <6, 6 or 7-9 points, respectively.

Data extraction and statistical analysis

The extracted data (from six reviewers) included the type of study, number of patients, cancer type, median age of included patients, performance status 0-1 (rate), treatment received, timing of oligometastases (synchronous or

metachronous), number of OM sites used for comparison, and median follow up. Hazard ratios (HR) for OS and PFS with their 95% CIs, were extracted preferentially from multivariate analyses where available. The heterogeneity in the included studies was evaluated by the Chi-square-based Q-test and I^2 (I^2 = 0% to 25%, no heterogeneity; I^2 = 25% to 50%, moderate heterogeneity; I^2 = 50% to 75%, high heterogeneity; I^2 = 75% to 100%, extreme heterogeneity). When I^2 was larger than 50%, a random effects model was used; otherwise, the fixed effects model was used. Sensitivity analyses for OS were performed according to type of cancer, timing and number of oligometastases to find the potential heterogeneity among the included studies. If the number of studies was less than or equal to one, we did not carry out the subgroup analysis. The possibility of publication bias was explored by the Egger's and Begg's tests and Trim and Fill method.[7,8] Begg's test explores bias with a funnel plot, conversely Egger's test is a linear regression of the effect estimates (OS) on their standard errors weighted by their inverse variance. The trim-and-fill method aims at estimating potentially missing studies due to publication bias in the funnel plot and adjusting the overall effect estimate. All analyses were performed using RevMan v.3 software.[9]

Results

Among the publications retrieved using electronic search (n = 7510), 173 studies were eligible for meta-analysis, for a total of 104,234 patients[10] (Figure 1). Baseline characteristics of the included studies and treatments received are presented in Table 1.

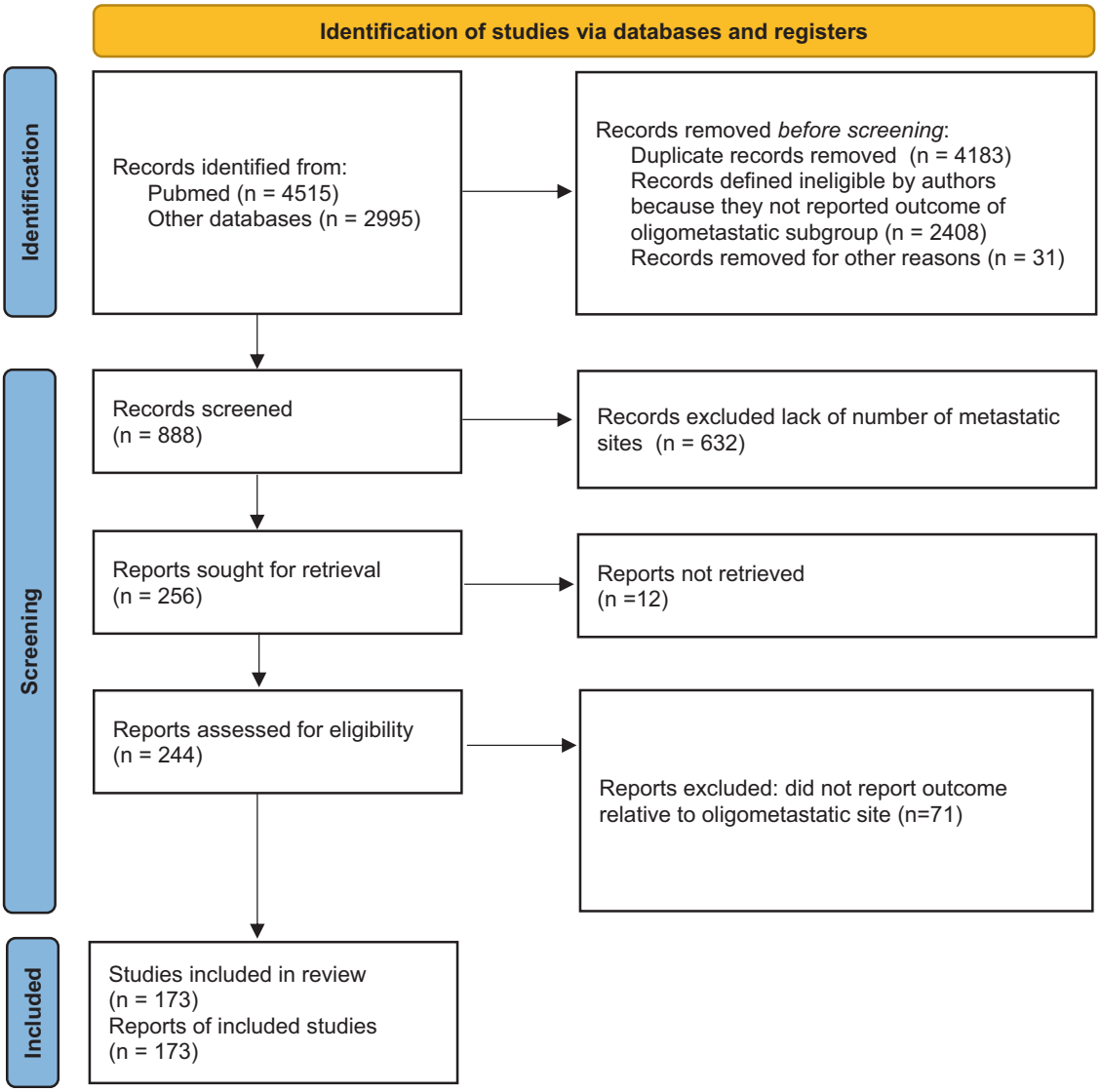


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 flow diagram showing the process of study inclusion.

Table 1. Characteristics of included studies.

Author/year	N° pts	Disease	Median age (years)	PS 0-1 (%)	Type of study	Median follow up (months)	Definition of OM (n° of lesions)/%	Site of OM	De novo / metachronous (%)	Treatment for OM (%)	OS (UVA or MVA)	PFS (UVA or MVA)	Quality
Morino/2020	232	Biliary	66	NR	Retrospective	12.6	1-3 (52)	Various	-	± Locoregional ± Systemic tx	UVA	-	5
Park/2017	134	Biliary	61	90	Retrospective	26	0-1 (90)	Various	-	CT (100)	MVA	MVA	6
Luzzago/2019	1592	Bladder	68	NR	Retrospective	NR	1 (44)	Various	-	CT ± S	MVA	-	5
Bates/2011	96	Breast	NR	NR	Retrospective	NR	1-2 (NR)	Various	-	CT (100)	MVA	MVA (TTP)	5
Blanchette/2018	154	Breast	56	NR	Retrospective	34	1 (55)	Various	25/75	CT (100)	MVA	-	7
Buhl/2018	140	Breast	62	NR	Retrospective	6.2	1 (40)	Various	-	CT (100)	-	MVA (TTP)	5
Co/2019	172	Breast	53	NR	Retrospective	NR	1-3 (96)	Various	100/0	Systemic tx ± S (100)	MVA	-	5
Gobbini/2018	16702	Breast	61	NR	Cohort	48.5	1-3 (92.6)	Various	28.5/71.5	-	MVA	-	8
Gu/2020	1888	Breast	NR	NR	Retrospective	NR	1 (NR)	Various	100/0	Various	MVA	-	5
Ivars Rubio/2019	263	Breast	59	81.4	Retrospective	44.9	1 (57.8)	Various	44.5/55.5	OT (19.8) CT (50.7) CT + Bio (29.5)	UVA	UVA	7
Kikawa/2019	134	Breast	63.5	85.8	Retrospective	NR	1-2 (73.9)	Various	24.6/75.4	Everolimus (100)	UVA	UVA	5
Kroger/2006	187	Breast	45.5	NR	Phase 3	63	1-2 (41.5)	Various	29.5/70.5	CT (100)	MVA	MVA	7
Le Scodan/2009	581	Breast	60.2	NR	Rerospective	39	1 (58.9)	Various	100/0	RT ± S	MVA	-	7
Leone/2017	9143	Breast	61	NR	Retrospective	13	1 (36.2)	Various	100/0	-	MVA	-	6
Lipton/2010	102	Breast	55.4	100	Retrospective	34	1-2 (NR)	Various	-	Trastuzumab (100) ± CT (88)	MVA	MVA (TTP)	6
Lobbezoo/2015	815	Breast	62.5	NR	Retrospective	37.1	1 (67)	Various	19/81	Systemic tx (100)	MVA	-	6
Neuman/2010	186	Breast	56	NR	Retrospective	52	1 (13)	Various	100/0	CT (100)	MVA	-	8
Nguyen/2012	692	Breast	60	68.9	Retrospective	22.8	1-4 (33.6)	Various	-	± Locoregional ± Systemic tx	MVA	-	6
Niikura/2012	314	Breast	51.9	90.4	Retrospective	33	1 (23.8)	Bone	100/0	Bisphosphonates	MVA	MVA	6
Park/2009	317	Breast	48	93	Retrospective	NR	1-2 (36)	Various	-	Various	MVA	-	5
Pons-Tostivint/2019	4276	Breast	60	NR	Retrospective	45.3	1-2 (77)	Various	100/0	Various	MVA	-	7
Ran/2020	49	Breast	50	NR	Retrospective	29	1-2 (NR)	Various	-	Trastuzumab based (100)	UVA	-	6

Table 1. *Continued*

Author/year	N° pts	Disease	Median age (years)	PS 0-1 (%)	Type of study	Median follow up (months)	Definition of OM (n° of lesions)/%	Site of OM	De novo / metachronous (%)	Treatment for OM (%)	OS (UVA or MVA)	PFS (UVA or MVA)	Quality
Rhu/2014	262	Breast	47	NR	Retrospective	29.6	1-2 (84.7)	Various	100/0	Various	MVA	-	6
Schneeweiss/2002	118	Breast	44	NR	Retrospective	48	1-2 (86)	Various	-	CT (100)	UVA	MVA	7
Wong/2019	483	Breast	49	NR	retrospective	66	1 (88)	Various	100/0	Systemic tx (100)	MVA	-	7
Smart/2019	66	BTC	76	55	Retrospective	21	1-2 (54)	Liver	-	RT (100)	MVA	MVA	6
Yin/2019	99	Cervix	53	51.6	Retrospective	11.6	1-3 (37.3)	Various	-	-	MVA	MVA	6
Afshari/2019	281	CRC	62	NR	Retrospective	NR	1 (85)	Various	-	-	MVA	-	5
Amikura/2017	342	CRC	NR	NR	Retrospective	52.7	1-4 (75.7)	Liver	63/37	S ± CT (100)	MVA	MVA	8
Aparicio/2016	282	CRC	80	100	Phase 3	69.8	1-2 (77.8)	Various	-	CT (100)	MVA	MVA	-
Araujo/2015	318	CRC	58	NR	Retrospective	60	1 (43)	Liver	-	S (100) + CT (37)	-	MVA	8
Bachet/2019	249	CRC	62.9	NR	Retrospective	28.7	1-3 (66)	Liver	79/21	S ± CT (100)	UVA	MVA (DFS)	6
Baldin/2021	221	CRC	62	NR	Retrospective	44.5	1-3 (75.6)	Liver	74.2/25.8	S ± perioperative tx (100)	MVA	MVA (TTR)	7
Beppu/2014	137	CRC	63	NR	Retrospective	NR	1-5 (NR)	Liver	-	CT ± S (100)	MVA	-	5
Blazer III/2008	305	CRC	57	NR	Retrospective	25	1 (32)	Liver	-	CT + S (100)	MVA	-	6
Brandi/2013	151	CRC	61.5	100	Retrospective	42	1 (61)	Lung / Liver	51/49	S ± CT (100)	-	MVA	8
Cardona/2013	1004	CRC	NR	NR	Retrospective	59	1 (42)	Liver	-	S (100)	MVA	-	8
Catalano/2009	255	CRC	67	92	Retrospective	45	1 (64)	Various	0/100	CT (100)	MVA	-	8
Chen/2010	255	CRC	NR	NR	Retrospective	11.9	1 (67)	Various	100/0	CT (67)	MVA	-	6
Comella/2005	254	CRC	NR	97	Pooled analysis of n=2 trials	NR	1 (55)	Various	54/46	CT (100)	MVA	MVA	5
Creasy 2018	907	CRC	64	NR	Retrospective	122	1 (52.7)	Liver	-	S + CT (100)	MVA	MVA	8
Cristobal/2014	250	CRC	69.5	81	Retrospective	NR	1-2 (90)	Various	65/35	NR	UVA	MVA	5
Daniel/2017	109	CRC	58.4	NR	Retrospective	NR	1-4 (46)	Liver	100/0	S ± CT (100)	MVA	-	5
de Geus-Oei/2006	152	CRC	61.5	NR	Prospective	17	1 (NR)	Liver	-	Various	UVA	UVA	6
Efficace/2008	742	CRC	62	92	Retrospective analysis	NR	1 (40)	Various	-	CT (100)	MVA	-	5
Faron/2015	810	CRC	63	83	Pooled analysis of n=4 trials	33	1-2 (85)	Various	100/0	CT ± S	MVA	MVA	6
Ghiringhelli/2014	409	CRC	65	59	Retrospective	32	1 (63)	Various	62/38	S ± CT (100)	MVA	-	6

Table 1. *Continued*

Author/year	N° pts	Disease	Median age (years)	PS 0-1 (%)	Type of study	Median follow up (months)	Definition of OM (n° of lesions)/%	Site of OM	De novo / metachronous (%)	Treatment for OM (%)	OS (UVA or MVA)	PFS (UVA or MVA)	Quality
Gu/2018	102	CRC	62	NR	Retrospective	NR	1 (36)	Liver	0/100	RFA ± CT (100)	MVA	-	5
Hebbar/2015	284	CRC	61.7	93	Phase 3	67	1 (48.9)	Various / Liver 83.5	67.7/32.3	S + CT (100)	-	MVA (DFS)	8
Hernandez/2016	522	CRC	64.5	NR	Retrospective	38.7	1 (65.7)	Lung	-	CT	MVA	MVA	6
Holliday/2017	34	CRC	56	NR	Retrospective	25	1-2 (100)	Various	100/0	SCRT	MVA	MVA	6
Huang/2020	179	CRC	62	NR	Retrospective	27.6	1 (51.5)	Lung	-	S (100)	MVA	-	6
Ishiguro/2006	111	CRC	NR	NR	Retrospective	43	1-3 (81)	Liver	100/0	S (100)	MVA	-	9
Kemeny/2014	169	CRC	55	NR	Retrospective	44.3	1-2 (47.3)	Various	66.8/33.2	S + HAI + Systemic tx (100)	-	MVA (RFS)	7
Konopke/2009	201	CRC	65	NR	Prospective	31	1-3 (94)	Liver	34.8/65.2	S (100)	MVA	MVA	6
Leal/2016	513	CRC	64.1	NR	Retrospective	37	1 (61.6)	Liver	100/0	S	MVA	MVA	7
Lin/2018	307	CRC	57.5	NR	Retrospective	31.7	1 (52.8)	Liver	66.4/33.6	S (100) ± RFA (10.1) ± Systemic tx	MVA	-	7
Liu/2010	52	CRC	70	NR	Retrospective	35.5	1 (58)	Liver	0/100	S + CT (100)	MVA	MVA (DFS)	6
Liu/2020	182	CRC	59.5	NR	Retrospective	32.5	1-3 (NR)	Liver	65/35	S ± CT	MVA	MVA (RFS)	6
Margonis/2015	334	CRC	50	NR	Retrospective	28.2	1-2 (NR)	Liver	54.8/45.2	S (100)	UVA	MVA (RFS)	6
Margonis/2017	389	CRC	58.4	NR	Retrospective	20.8	1-2 (NR)	Liver	57.3/42.7	S ± Ablation (18.5) ± CT (71.5)	-	MVA (DFS)	6
Margonis/2019	718	CRC	62.3	NR	Retrospective	30.4	1-3 (36.4)	Liver	51.2/48.8	S ± Systemic tx	MVA	-	6
Mise/2010	98	CRC	62	NR	Retrospective	60	1-3 (68)	Various	0/100	S (100)	MVA	-	8
Miyamoto/2015	78	CRC	65	92	Retrospective	19.2	2 (37)	Various	-	-	UVA	-	6
Narayan/2020	357	CRC	60	NR	Prospective	127	1 (NR)	Liver	100/0	S ± HAI	-	UVA (RFS)	9
Negri/2005	135	CRC	60.5	82.2	Case–control	76.8	1 (60.7)	Various	100/0	CT (100)	MVA	-	8
Neofytou/2015	140	CRC	NR	NR	Retrospective	33	1 (41.4)	Liver	71.4/28.6	± S ± Systemic tx	UVA	UVA	6
Nojiri/2011	31	CRC	63.3	NR	Retrospective	62	1-2 (64.5)	Lung	3.2/96.8	S (100)	MVA	-	8
Park/2016	221	CRC	62	NR	Prospective	34.7	1 (73.3)	Lung	13.1/86.9	S (100) ± CT (79.6)	UVA	MVA (DFS)	6

Table 1. *Continued*

Author/year	N° pts	Disease	Median age (years)	PS 0-1 (%)	Type of study	Median follow up (months)	Definition of OM (n° of lesions)/%	Site of OM	De novo / metachronous (%)	Treatment for OM (%)	OS (UVA or MVA)	PFS (UVA or MVA)	Quality
Parkin/2013	5853	CRC	64	NR	Retrospective	20	1-3 (79)	Liver	37/50	Surgery (100)	MVA	-	5
Peng/2017	150	CRC	58	NR	Retrospective	36	1 (NR)	Liver	67/33	S ± CT (100)	MVA	MVA (RFS)	6
Peng/2018	140	CRC	55	NR	Retrospective	13	1-3 (79)	Liver	70/30	MWA (100)	-	MVA	6
Prasanna/2020	513	CRC	63	NR	Retrospective	NR	1 (NR)	Various	51/49	S ± CT	UVA	-	5
Rhu/2017	410	CRC	60	NR	Retrospective	34	1 (63)	Liver	-	S (100)	MVA	-	6
Ruzzo/2012	59	CRC	NR	100	Retrospective	NR	1 (64)	Various	0/100	CT (100)	UVA	UVA	5
Sasaki/2016	485	CRC	58.5	NR	Retrospective	31	1-3 (65)	Liver	57/43	S / RFA (100)	MVA	-	6
Sasaki/2017	251	CRC	57	NR	Retrospective	30.3	1-3 (NR)	Liver	-	S ± CT (100)	MVA	-	6
Shimizu/2019	160	CRC	66	NR	Retrospective	64	1-3 (88)	Lung	18/83	S (100)	MVA	-	7
Sorbye/2012	342	CRC	NR	98.8	Subgroup analysis of prospective random	NR	1 (53)	Liver	34.5/64.5	Various	-	UVA	5
Souglakos/2009	168	CRC	59	NR	Retrospective	NR	1-2 (53)	Various	-	CT (100)	MVA	MVA	5
Stang/2016	113	CRC	70	NR	Retrospective	99	1-3 (77)	Liver	21/79	RFA (100) CT (95)	MVA	MVA	8
Stremitzer/2015	154	CRC	62	NR	Retrospective	34	1-2 (NR)	Liver	-	S (100)	MVA	MVA	6
Tarpgaard/2014	566	CRC	NR	96	Retrospective	37	0-1 (29)	Various	-	CT (100)	MVA	MVA	6
Van Cutsem/2004	1207	CRC	64	NR	Retrospective	NR	1 (25)	Various	76/24	CT (100)	MVA	-	5
Wang/2017	163	CRC	65	NR	Retrospective	37	1-2 (41)	Liver	82/18	S + CT (100)	MVA	MVA	6
Wei/2005	395	CRC	63	NR	Retrospective	31	1-3 (65)	Liver	51/49	S (100)	MVA	MVA	6
Xie/2018	332	CRC	58	NR	Retrospective	27.7	1 (65.2)	Various	72/18	Various	MVA	-	6
Yamashita/2017	74	CRC	59	NR	Retrospective	25	1 (74)	Liver	-	RFA/MWA + CT (100)	MVA	MVA	6
Zhao/2017	289	CRC	57	NR	Retrospective	34	1 (51)	Liver	66/34	S (100)	MVA	MVA	6
Ai/2017	3245	Esophageal	66	NR	Retrospective	NR	1-3 (NR)	Various	-	-	MVA	-	5
Hashimoto/2010	466	Gastric	60	85	Retrospective	NR	1-2 (NR)	Various	71.7/28.3	CT (100)	UVA	-	5
Kadokura/2013	208	Gastric	64	81.3	Retrospective	26.9	1 (69.7)	Various	-	CT	MVA	-	6
Kim/2008	304	Gastric	54	73.3	Retrospective	NR	1 (81.2)	Various	-	CT (100)	MVA	-	5
Kimura/2019	103	Gastric	67	NR	Retrospective	NR	1-2 (89)	Various	-	CT (100)	MVA	-	5

Table 1. *Continued*

Author/year	N° pts	Disease	Median age (years)	PS 0-1 (%)	Type of study	Median follow up (months)	Definition of OM (n° of lesions)/%	Site of OM	De novo / metachronous (%)	Treatment for OM (%)	OS (UVA or MVA)	PFS (UVA or MVA)	Quality
Kinoshita/2015	256	Gastric	64	NR	Retrospective	65	1-2 (82.8)	Liver	41.4/58.6	S (100) + CT (32.8)	MVA	UVA	8
Kondoh/2018	50	Gastric	67	72	Retrospective	NR	1-2 (74)	Various	-	CT (100)	UVA	-	5
Makiyama/2018	444	Gastric	75	NR	Retrospective	28.7	1 (37.3)	Various	-	CT (100)	-	MVA	5
Wang/2016	310	Gastric	58	100	Retrospective	NR	1 (70.6)	Various	-	Various	MVA	-	5
Wang/2018	321	Gastric	57	85	Retrospecive	32	0-1 (83)	Various	-	CT (100)	MVA	MVA	6
Liu/2015	981	HCC	52.5	NR	Prospective	32.7	1 (70.3)	Liver	-	± S (18.9) ± RFA (19.3) ± TACE (48.2)	-	MVA (RTDS)	7
Mazzaferro/2009	1556	HCC	55	NR	Retrospective	53	1 (26)	Liver	-	S (100)	MVA	-	7
Yoon/2010	52	HCC	49	NR	Retrospective	16.3	1 (75)	Lung	-	S (100)	MVA	-	6
Bollig/2020	283	Head & neck	59.8	NR	Retrospective	NR	1 (18.7)	Various	-	Various (100)	MVA	-	5
Lo/2017	120	Head & neck	NR	NR	Retrospective	51	1-3 (68.3)	LNs	-	S ± CT/RT	MVA	MVA (DFS)	8
Shen L/2015	505	Head & neck	NR	95	Retrospective	20	1 (18.8)	Various	100/0	CT ± RT (100)	MVA	-	6
Shen L/2015 (2)	312	Head & neck	46	89.1	Retrospective	16	1-3 (62.2)	Bone	43.9 / 56.1	Various	MVA	-	6
Shinoda/2020	48	Liposarcoma	43	NR	Retrospective	27.5	1 (52.1)	Various	-	Various	UVA (DSS)		5
Li/2019	100	Lung	60	96.1	Retrospective	39	1-3 (13.7)	Brain	100/0	TKI ± CT	UVA	-	7
Prelaj/2019	193	Lung	65	88	Retrospective	43	1-3 (NR)	Various	-	IT (100)	UVA	MVA	7
Bian/2016	401	Melanoma	NR	83	Retrospective	35	1-4 (87)	CNS	-	SBRT (100)	MVA	-	7
Iacono/2019	162	Melanoma	NR	82	Retrospective	48	1-2 (66)	Various	-	Systemic tx (100)	MVA	-	7
Lee/2009	2247	Melanoma	51	NR	Retrospective	22.5	1-2 (67.4)	Various	-	-	MVA	-	6
Moreau/2012	115	Melanoma	59	NR	Retrospective	19	1-3 (64)	LNs	93/7	S (100)	MVA	MVA (DMFS)	6
Seremet/2019	85	Melanoma	57	91	Retrospective	21	1-2 (44.7)	Various	-	ICIs (100)	MVA	UVA	6
Weide/2012	855	Melanoma	62	NR	Retrospective	25	1-2 (74.7)	Various	-	Various	MVA	-	6
Robelin/2019	162	Neuroendocrine	61	90	Retrospective	56	1-2 (85)	Various	49/51	Various	MVA	UVA	7
Jiang/2015	347	NPC	48	100	Retrospective	NR	1 (28)	Various	100/0	CT (57.9) CT + RT (68.8) RT (3.7)	MVA	-	5
Nie/2017	209	NPC	45	81.3	Retrospective	16.6	1 (49.8)	Various	24.9/75.1	CT (100)	UVA	UVA	6
Beau-Faller/2019	228	NSCLC	NR	42	Retrospective	NR	1-2 (65)	Various	0/100	TKI (100)	MVA	MVA	5

Table 1. *Continued*

Author/year	N° pts	Disease	Median age (years)	PS 0-1 (%)	Type of study	Median follow up (months)	Definition of OM (n° of lesions)/%	Site of OM	De novo / metachronous (%)	Treatment for OM (%)	OS (UVA or MVA)	PFS (UVA or MVA)	Quality
Ding/2017	85	NSCLC	66	75	Retrospective	9.8	1-3 (48)	Various	-	TKI (94)	MVA	MVA	6
Liu/2018	216	NSCLC	57	NR	Retrospective	7	1-3 (NR)	Brain	-	RT ± Systemic tx	MVA	-	6
Niibe/2016	61	NSCLC	NR	100	Retrospective	NR	1-2 (89)	SNC	18/82	SBRT or SRS (100)	MVA	-	5
Paccagnella/2006	324	NSCLC	62	93.7	Phase 2-3	19	1 (30.5)	Various	100/0	CT (100)	UVA	-	6
Park/2019	517	NSCLC	64	NR	Retrospective	NR	1 (57)*	Various	100/0	Various	MVA	-	5
Shin/2016	1024	NSCLC	64	85.5	Retrospective	42.2	1 (14.8)*	Various	-	Systemic tx (100)	MVA	-	7
Sperduto/2016	1481	NSCLC	NR	69.2	Retrospective	NR	1-4 (81)	Brain	-	Various	MVA	-	5
Takahashi/2019	41	NSCLC	67	82	Retrospective	19.6	1 (57)	Bone	100/0	Various (100)	UVA	UVA	6
Tambo/2020	95	NSCLC	72	77.9	Retrospective	8.8	1-2 (80)	NR	-	Pembrolizumab (100)	MVA	MVA	5
Liu/2020	125	Osteosarcoma	17	100	Retrospective	NR	1-2 (72)	Lung	-	CT ± S	-	MVA (PRS)	5
Bolm/2015	39	Pancreatic	NR	56	Retrospective	5	1 (56)	Various	-	RT (100)	MVA	-	6
Neron/2020	51	Phyllodes	56.4	95.9	Retrospective	62.1	1 (51)	Various	13.7/86.3	± S (31.3) ± RT (31.9) ± CT (72.5)	UVA	-	7
Armstrong/2007	686	Prostate	68.5	88	Retrospective	70	1-2 (88)	Various	-	CT (100)	MVA	-	9
Tablazon/2019	837	Prostate	76	NR	Retrospective	26	1 (NR)	Bone	-	-	MVA	-	7
Zhang/2020	160	Prostate	68	NR	Retrospective	47.2	1-4 (39.4)	Bone	-	RT + OT (100)	UVA	-	7
Alt/2011	887	RCC	62.5	85	Retrospective	33.6	2 (16.5)	Various	58/42	S (14)	MVA	-	8
Atzpodien/2003	425	RCC	NR	100	Retrospective	20	1-2 (82)	Various	0/100	Various	MVA	-	7
Beuselink/2014	200	RCC	59	85	Retrospective	67	1 (83)	Various	38/62	Systemic tx (100)	UVA	UVA	8
Bossé/2020	3454 1061	RCC	62 61	81 97	Retrospective 2-cohort	34 24.9	1 (19.5) 1 (17.2)	NR	-	TKI (100)	MVA	-	6
Cai/2017	143	RCC	60	NR	Retrospective	22	1 (72.7)	Various	-	TKI (100)	UVA	UVA	6
Dai/2020	146	RCC	56.5	71.9	Retrospective	36	1 (56.8)	Various	45.9/54.1	TKI (100)	MVA	MVA	6
Fay/2018	4736	RCC	59.2	100	Pooled analysis of n=12 phase 2-3 trials	NR	1 (NR)	NR	-	-	MVA	-	6
Fujiwara/2020	45	RCC	62	82	Retrospective	26.4	1 (36)	NR	-	Nivolumab (100)	UVA	-	6
Furubayashi/2017	59	RCC	67	85	Retrospective	NR	1-2 (86)	Various	-	TKI (100)	MVA	-	5
Gu/2017	184	RCC	54	NR	Retrospective	23.3	1 (85)	Various	-	Various	UVA	MVA	6
Ikeda/2018	116	RCC	66	NR	Retrospective	19.4	1 (66)	Various	-	TKI (100)	MVA	MVA	6

Table 1. *Continued*

Author/year	N° pts	Disease	Median age (years)	PS 0-1 (%)	Type of study	Median follow up (months)	Definition of OM (n° of lesions)/%	Site of OM	De novo / metachronous (%)	Treatment for OM (%)	OS (UVA or MVA)	PFS (UVA or MVA)	Quality
Ishihara/2017	118	RCC	NR	NR	Retrospective	NR	1 (NR)	Various	100/0	S	UVA	-	5
Keizman/2014	278	RCC	63	NR	Retrospective	55	1 (18)	Various	82/18	TKI ± S	UVA	UVA	8
Kim/2017	177	RCC	62	92.6	Retrospective	19.2	1-3 (NR)	Various	-	TKI (100)	MVA	UVA	6
Kwak/2007	186	RCC	58	86.5	Retrospective	17.4	1 (60.2)	Various	39.8/60.2	S ± ICIs	MVA	MVA	6
Kwak/2007 (2)	252	RCC	NR	61	Retrospective	17	1 (37)	Various	19/80	ICIs	MVA	MVA	6
Liou/2017	266	RCC	61	NR	Retrospective	12	1 (43)	Various	-	S (100)	MVA	-	6
Lu/2016	67	RCC	58	95.5	Retrospective	NR	1-4 (32.8)	Bone	-	TKI (100)	MVA	-	5
Richey/2011	188	RCC	60.8	65	Retrospective	6.9	1 (36)	Various	100/0	S + Systemic tx (100)	MVA	-	6
Schmidt/2005	321	RCC	51	NR	Retrospective	52	1-2 (60)	Various	-	Citokines (100)	UVA	-	7
Sharma/2015	93	RCC	61	76	Retrospective	13	1 (60)	Various	100/0	S ± Systemic tx (100)	MVA	-	6
Takagi/2019	71	RCC	66	99	Retrospective	NR	1 (45)	Various	-	TKI (100)	MVA	-	5
Thiery-Vuillemin/2017	224	RCC	67	82	Retrospective	18.3	1 (51)	Various	-	Systemic tx ± S (100)	UVA	-	6
Yamamoto/2018	51	RCC	65	80	Retrospective	NR	1 (45)	Various	-	TKI (100)	UVA	UVA	5
You/2016	325	RCC	NR	NR	Retrospective	NR	1 (37)	Various	55/45	S ± CT	MVA	MVA	5
Zhang/2019	287	RCC	56	NR	Retrospective	28	1 (53)	Various	-	S (100)	MVA	MVA	6
Dudek/2019	33	Sarcoma	55	NR	Retrospective	37	1-3 (72.7)	Lung	36/64	S (100)	UVA	-	7
Kawamoto/2020	98	Sarcoma	NR	NR	Retrospective	NR	1-2 (43.9)	Lung	-	Various	-	MVA (PMS)	
Nataraj/2016	102	Sarcoma	18	60	Retrospective	23	1-3 (31)	Lung	31/69	S ± CT (100)	MVA	MVA (EFS)	6
Shoushtari/2016	215	Sarcoma	56	26	Retrospective	175	1-2 (67)	Various	39/61	CT (100)	MVA	UVA	9
Stephens/2011	81	Sarcoma	43.5	NR	Retrospective	27	1-2 (33)	Lung	-	S (100)	MVA	-	7
Han/2011	61	SCLC	65	71	Phase 2	33.6	1-2 (NR)	Various	-	CT (100)	MVA	-	7
Shirasawa/2019	141	SCLC	70	62	Retrospective	NR	1-5 (34.7)	Various	100/0	CT (100)	MVA	-	5
Anraku/2003	133	Utherine	56	NR	Retrospective	40	1 (58)	Lung	6/94	S (100)	MVA	-	7
Bartosch/2016	130	Utherine	52	NR	Retrospective	48	1 (54)	Various	-	Various	MVA	-	7
Chen/2019	3981	Various	60.84	40.8	Retrospective	44.3	1 (16.5)	Various	-	Various (100)	MVA	-	7
de Baere/2015	566	Various	62.7	NR	Retrospective	35.5	1-2 (78)	Lung	-	RFA (100)	MVA	MVA	7

Table 1. *Continued*

Author/year	N° pts	Disease	Median age (years)	PS 0-1 (%)	Type of study	Median follow up (months)	Definition of OM (n° of lesions)/%	Site of OM	De novo / metachronous (%)	Treatment for OM (%)	OS (UVA or MVA)	PFS (UVA or MVA)	Quality
Dercle/2016	251	Various	52	NR	Retrospective	10.5	1-2 (40)	Various	-	ICIs (100)	MVA	-	6
Silva/2019	61	Various	66.3	NR	Retrospective	13.58	1-5 (35)	Spine	-	SBRT (100)	-	MVA (LC 1y)	6

*M1b single extratoracic organ; CNS, central nervous system; CRC, colorectal cancer; CT, chemotherapy; DMFS, distant metastasis–free survival; DSS, disease-specific survival; EFS, event-free survival; HAI, hepatic artery infusion; HCC, hepatocellular carcinoma; ICIs, immune checkpoint inhibitors; LNs, lymph nodes; MVA, multivariate analysis; MWA, microwave ablation; NPC, nasopharyngeal carcinoma; NSCLC, non-small-cell lung cancer; OM, oligometastatic disease; OS, overall survival; OT, ormonotherapy; PFS, progression-free survival; PMS, post-metastasis survival; PRS, postrelapse survival; PS, performance status; RCC, renal cell carcinoma; RFA radiofrequency ablation; RFS, relapse-free survival; RTDS, recurrence to death survival; S, surgery; RT, radiotherapy; SBRT, stereotactic body radiotherapy; SCLC, small-cell lung cancer; SRS, stereotactic radiosurgery; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor; TTP, time to progression; TTR, time to recurrence; tx, therapy; UVA, univariate analysis.

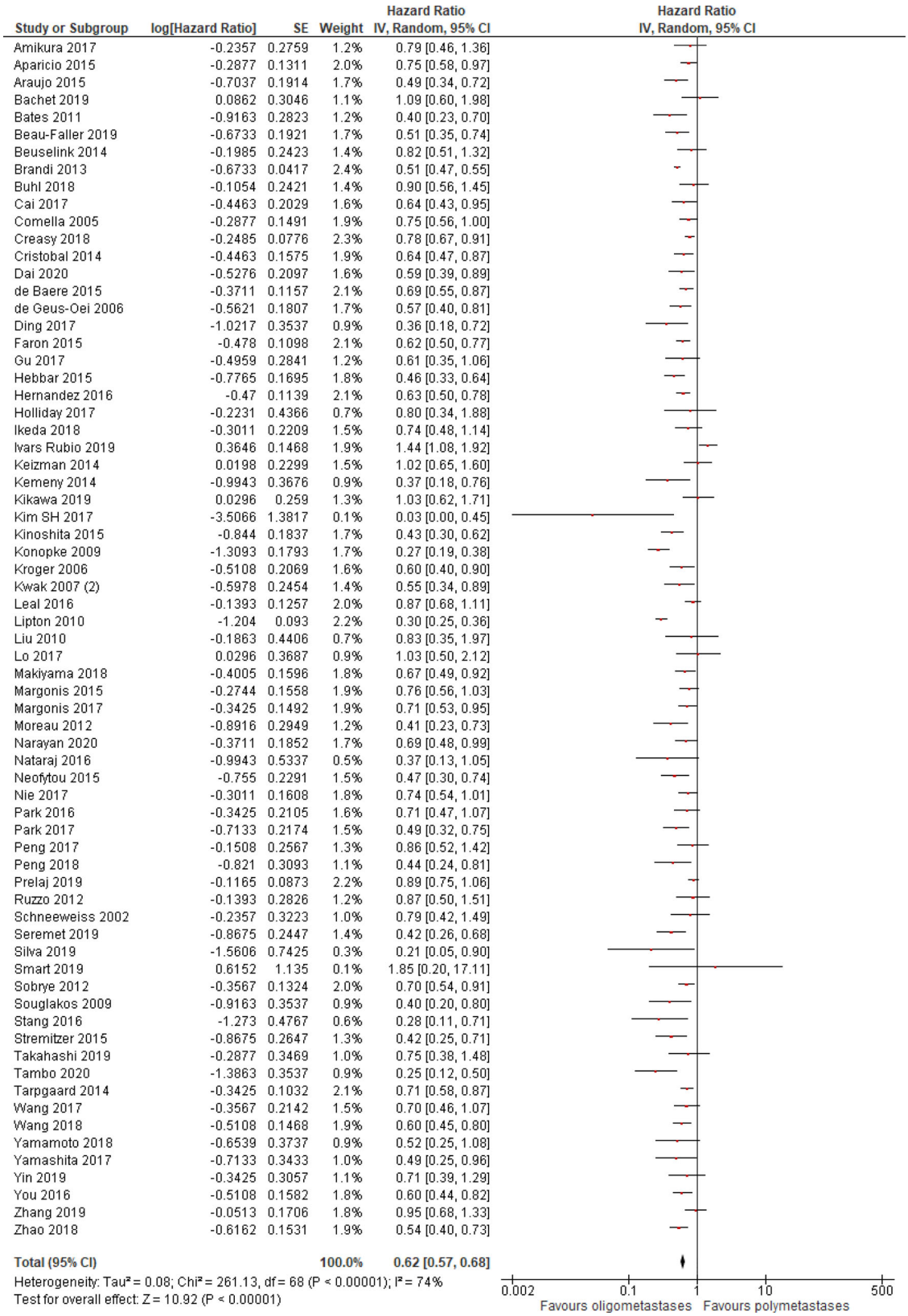


Figure 2. Progression-free survival of oligo- compared to non-oligometastatic cancers.

Progression-free survival was better in patients with OM disease (HR = 0.62, 95% CI 0.57–0.68; P < .01; n = 69 studies; Figure 2). Additionally, in the OS analysis, OM cancers were associated with a better OS (HR = 0.65, 95% CI 0.62–0.68; P < .01; n = 161 studies; Figure 3). Results were significant for all analyzed disease subgroups except biliary tract cancer and cervical cancer (only three studies included). In colorectal (CRC), breast, non-small cell lung cancer (NSCLC) and renal cell carcinoma (RCC), which constituted the more representative series, the reduction in the risk of death for OM patients were 35, 38, 30 and 42%, respectively (Figure 3). Timing of onset (synchronous vs metacronous disease) did not influence the risk of death. Most studies reported OS analysis for up to three metastases (152 out of 161 studies). After exclusion of eight studies that reported outcomes for up to five metastases the final results remained unchanged (HR = 0.64, 95%CI 0.61-0.67; P < .01). No cut-off was associated with a better outcome (1 vs 2 vs 1-2 vs 1-3 metastases).

Risk of bias through Begg's funnel plot was not significant for the OS analysis. Conversely, Egger's test showed evidence of bias (P < .01) (Figure 4). Trim and Fill analysis incorporated 29 missing studies. The overall effect measure (95% CI) based on this analysis was 0.7 (0.67-0.73), which became slightly weaker compared to the originally reported overall effect measure. Compared with cancers with more than three to five metastases, high-certainty evidence indicates OM tumors are associated with better prognosis in particular for CRC, breast, NSCLC and RCC. Despite the subgroup difference is not significant likely for less studies included in other groups, the results for these 4 cancers remain robust.

Discussion

The definition of oligometastatic refers to malignancies with a limited metastatic spread which may be amenable of radical treatment for both primary and each distant site, and that generally have a better prognosis compared to polymetastatic cancers. A very recently published paper clearly explains the timely clonal evolution of somatic mutations and consequently the metastatic process of many cancer types.[11] It may be hypothesized that OM cancer is associated with a more indolent spread and therefore may represent a less fatal disease. With the expansion of the oncological armamentarium, many efforts have been made over the years to improve outcomes of patients with minimal metastatic

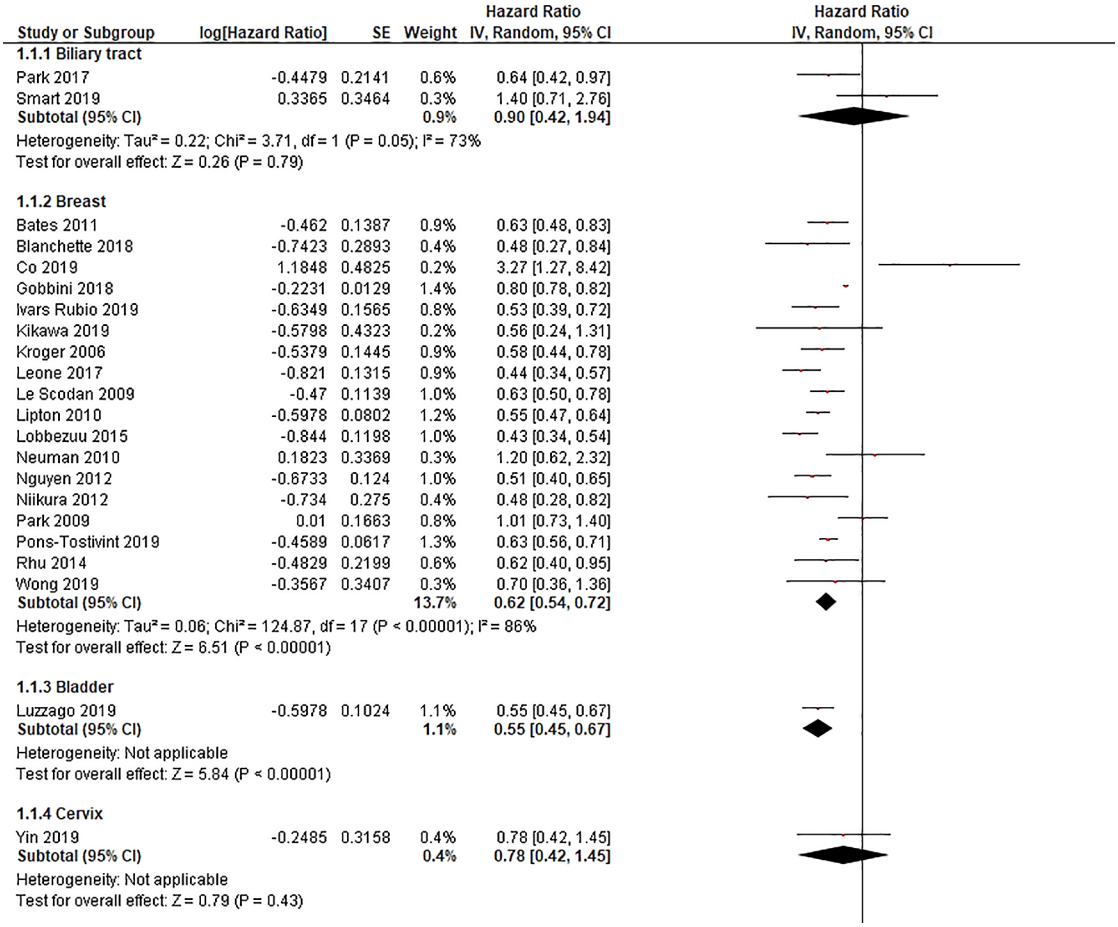


Figure 3. Overall survival of oligo- compared to non-oligometastatic cancers.

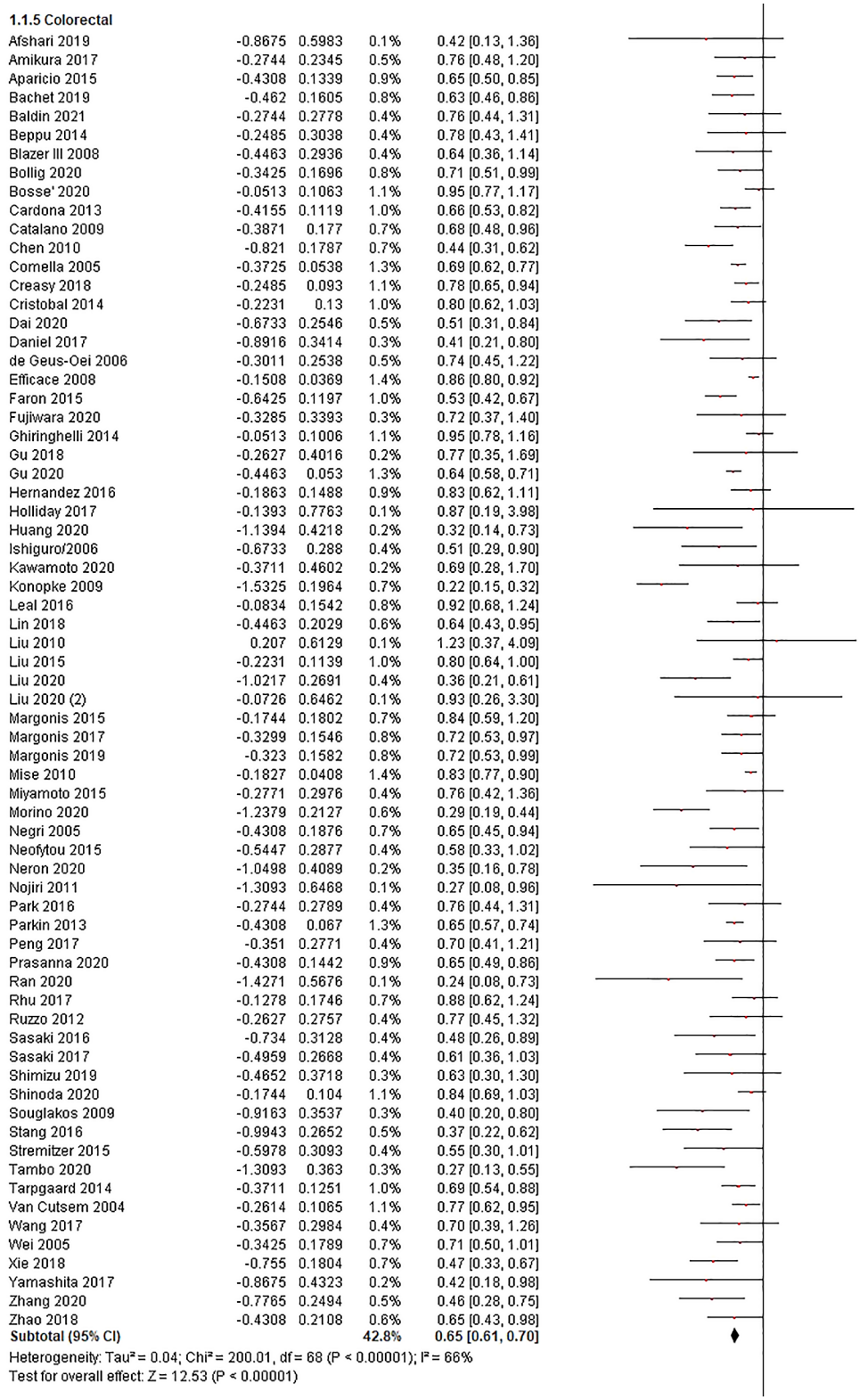


Figure 3. (continued)

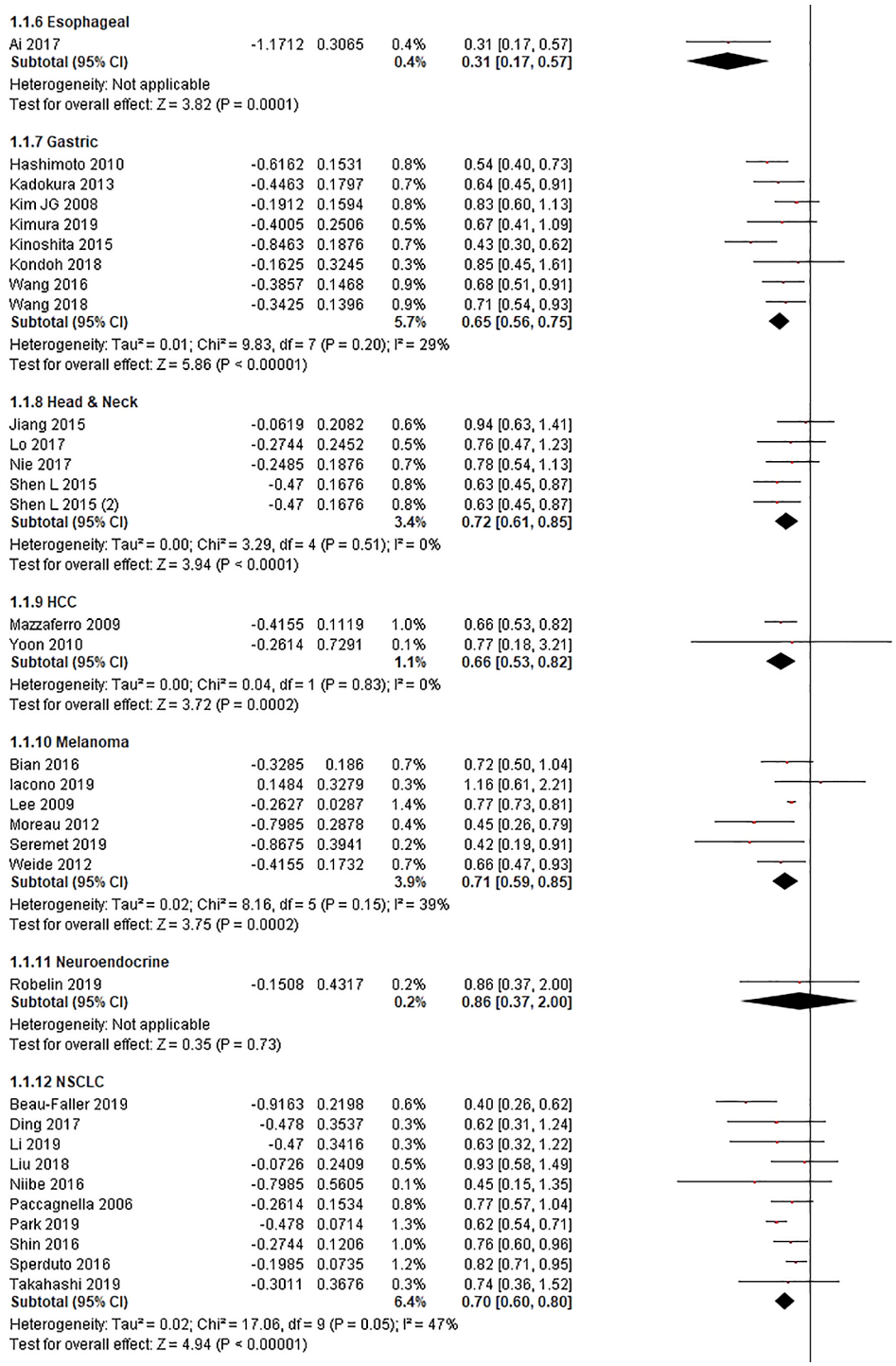
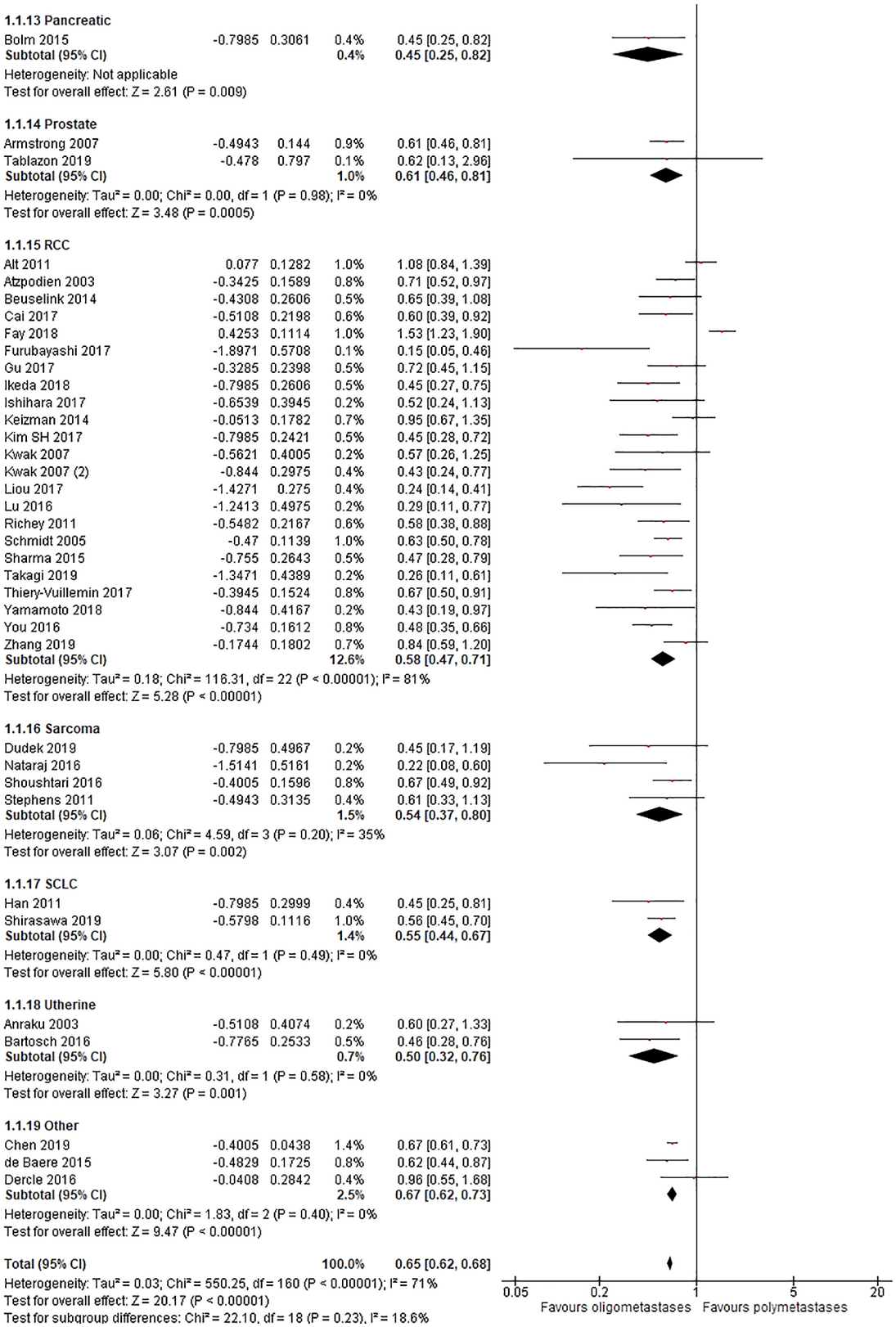


Figure 3. (continued)



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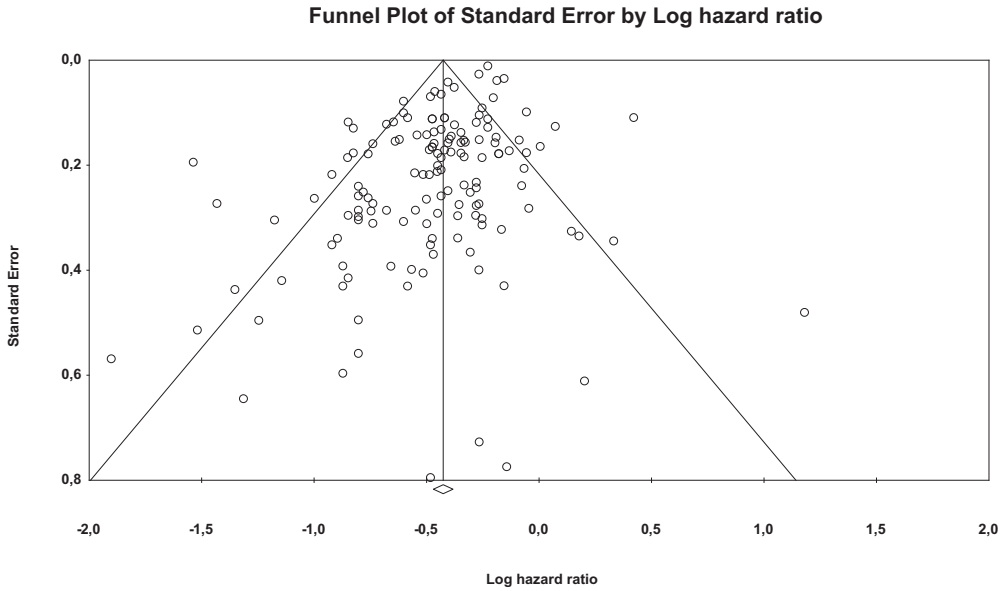

Figure 4. Funnel plot of publication bias for overall survival analysis showing standard error by log hazard ratio.

burden. Advance in imaging may also have improved in the last years the diagnosis of oligometastases with the possibility of a more targeted approach toward primary tumor and every single oligometastatic site. This may have created a bias compared to older series, where less accurate imaging modalities were available and more frequent cases of oligometastases could now be overdiagnosed.

We have performed the most exhaustive systematic review of the literature to quantify the prognostic value of OM stage in various cancers. Overall, OM cancer patients have a risk of death and progression that is a third less than the polymetastatic counterpart. The OM state is frequently calculated as an independent favorable prognostic variable, which means that these patients do well independent from other clinical-pathological characteristics. The effect size was calculated from 173 studies including more than 100,000 patients. The final results were similar in all the most frequent histologies including CRC, breast cancer, NSCLC, RCC and sarcoma with inferior survival in OM gastric, melanoma and head and neck cancers.

Prognosis of OM cancer may be also different according to site of oligometastases. For example in CRC, breast and RCC lung metastases have a generally more favourable outcome than liver (or peritoneal ones in CRC). In our series, sites of oligometasteses were mixed or not described at all so a subgroup analysis was not performed.[12]

There is also evidence from randomized clinical trials[13-15] that ablative therapies improve survival in patients with OM cancer. For example, in some cancers small randomized studies[13-21] already provide evidence of survival improvement in patients that received both systemic and local therapies compared to those that received systemic therapies alone. As a matter of fact, resection of colorectal cancer liver metastases nowadays represents an essential curative option and a primary endpoint in multiple clinical trails.[13] Furthermore, Gomez *et al.*[14] found that in OM NSCLCs, adding local consolidative therapy to active oligometastases and to primary disease may improve OS from 17 to 41 months. Also, in RCC the treatment of indolent lung metastases may permit delaying the start of systemic treatment and obtain an excellent control.[15] A large burden of evidence now supports local therapy for minimal oligoprogressive cancers treated with targeted therapies or immunotherapy. Here, metastases-directed therapy could delay the switch of systematic therapy by radical local treatment of all progressive metastatic sites.[16,17] With the advent of immunotherapy, the combination of immune check point inhibitors and radiotherapy to single OM lesions may facilitate a potentiation of the immune response, increasing the chances of achieving an abscopal effect. This term describes an event in which focalized radiotherapy discharge systemic anti-tumoral action that can result in distant responses.[18] For example, in lung cancer the combination has a good safety profile and achieves high rates of local control and greater chances of obtaining abscopal responses than radiotherapy alone, with a relevant impact on outcome.[19] Oligometastatic cancers can also regarded as extended locoregional disease if, after proper conversion therapy, all sites of metastases and primary tumor may be radically resected with curative purposes. Such a strategy has been employed in largely incurable cancers as gastric and pancreatic carcinomas where selected cases with small liver-limited recurrences were managed with surgery.[20,21]

Melanoma and head and neck OM cancers are also associated with better prognosis. In these settings isolated recurrences (lymph nodes, lung nodules or brain metastases) may be radically treated with surgery or radiotherapy.

This meta-analysis has several limitations. First, our review does not evaluate the absolute benefit of any local treatment and the prognosis and management of oligoprogressive disease or down staged polymetastases to an OM state. Second, the literature search covered a large lifetime span and may include older series where radiological evaluation did not include more advanced modalities that can now increase the accuracy of oligometastases detection. Third, most of studies have an observational design and outcome was retrospectively analysed. Likely publication bias may influenced the prognosis of this population. Finally, the optimal number of lesions defining the OM state cannot be defined in this paper.

A consensus paper of EORTC and ESTRO societies attempted to provide definitions of various OM conditions either naïve or attained after therapy and either synchronous or metachronous.[22]

Some large, randomized studies have included local therapies for OM cancers. An NRG Oncology randomized phase II/III trial study compares therapy with stereotactic radiosurgery and/or surgery with standard of care therapy alone in treating patients with breast cancer that has one or two locations in the body (limited metastatic) that are previously untreated. The PREST study will assess the efficacy of ablative radiotherapy (stereotactic body radiotherapy applied to all oligometastases) administered to all tumor sites (metastases and prostate if applicable), in oligometastatic hormone-sensitive prostate cancer patients. Finally, an ECOG-ACRIn phase III study compared standard chemotherapy to consolidative radiotherapy in patients with oligometastatic HER2 negative esophageal and gastric adenocarcinoma (https://clinicaltrials.gov/ct2/show/NCT02364557; https://clinicaltrials.gov/ct2/show/NCT04115007; https://clinicaltrials.gov/ct2/show/NCT04248452). In all ongoing studies the aim is the optimal timing (after a good shrinkage during systemic therapy) and integration of systemic medical therapy and local ablation/resection with the scope of improving long-term survivals.

Conclusions

In conclusion, this meta-analysis tried to quantify the prognosis associated with OM compared to cancers with more extensive diffusion. Based on our findings, we suggest that every metastatic patient should be accurately evaluated for the number of distant sites of disease, and a treatment strategy that involves both the primary and the metastases should be carefully considered. Patients could be reassured about their life expectancy and about the possibility of integrate both systemic and local therapy with the hope, in certain cases, for definitive cure. In others, focal treatment on the metastases may delay the immediate use of more toxic drugs (for example in elderly or indolent diseases). Also, we propose that these patients should be stratified when included in clinical trials and dedicated studies should be designed.

Data availability

Extended data

Mendeley Data: Extended data for 'Better survival of patients with oligo- compared with polymetastatic cancers: a systematic review and meta-analysis of 173 studies'.

http://dx.doi.org/10.17632/8kycvdnp6v.1.[10]

This project contains the following extended data:

Supplementary Table 1: List of included studies.

Reporting guidelines

Mendeley Data: PRISMA checklist for 'Better survival of patients with oligo- compared with polymetastatic cancers: a systematic review and meta-analysis of 173 studies'.

http://dx.doi.org/10.17632/8kycvdnp6v.1.[10]

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PubMed Abstract | Publisher Full Text

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Open Peer Review

Current Peer Review Status: ✔ ✔

Version 4

Reviewer Report 31 May 2022

https://doi.org/10.5256/f1000research.133866.r137591

✔ **Dario Baratti**
Peritoneal Surface Malignancies Unit, Colorectal Surgical Division, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

The authors carefully revised their manuscript according to this reviewer's comments, resulting in a stronger paper.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Peritoneal surface malignancies, advanced colorectal cancer

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 13 May 2022

https://doi.org/10.5256/f1000research.133866.r137590

✔ **Luca G. Campana**
[1] Department of Surgery, Colorectal and Peritoneal Oncology Centre, The Christie NHS Foundation Trust, Manchester, UK
[2] Department of Surgery, Manchester University NHS Foundation Trust, Manchester, UK

The authors have satisfactorily addressed the majority of the requests, so I recommend the submission for indexing.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: General Surgery; Surgical Oncology; Clinical Research; Melanoma; Colorectal Cancer; Soft Tissue Sarcomas; Skin Cancer

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 3

Reviewer Report 22 November 2021

https://doi.org/10.5256/f1000research.77989.r100190

?

Luca G. Campana
[1] Department of Surgery, Colorectal and Peritoneal Oncology Centre, The Christie NHS Foundation Trust, Manchester, UK
[2] Department of Surgery, Manchester University NHS Foundation Trust, Manchester, UK

The authors of this report deserve praise for their extensive work. The data presented are intriguing and raise some intriguing questions.

- For the included studies, it would be interesting to know the comparator group and its tumour burden. This information would help to appreciate the magnitude of the differences in outcome.

- Additionally, one of the original questions raised with the introduction of the oligometastatic concept relates to the feasibility of local or locoregional treatment in a subset of patients with indolent disease. In this regard, I would present this information as a separate column in Table 1.

- Always in Table 1, the columns on OS and PFS present rather generic information. Therefore, I would suggest including the specific outcomes. Also, the column on Age and PS should be split. Finally, the content of the column “Type of study” should be homogenised.

- Further, the authors need to consider the time bias because modern imaging technologies increase the number of patients labelled as oligometastatic.

- It would be essential to distinguish between different types of oligometastatic disease (e.g., indolent progressive and minimal residual disease after previous treatments). In this regard, in Table 1, the column “De novo or metachronous” seems to provide this information, but it is not entirely clear.

- Please include the authors cited in Table 1 in the reference list.

Minor comments

Abstract
Please revise and use terms consistently (e.g. avoid "overall mortality in OM"). In addition, the conclusions should be reformulated; in particular, the last sentence should be more focused on the results presented.

Introduction
Please revise the language and, wherever possible, shorten the text (e.g. the first sentence is superfluous in this context). Also, please check some definitions such as "prognostic survival" and "with up to three to five metastatic sites."

Methods
Please adjust the definition of polymetastatic accordingly.

Results
Figure 1*:* More than 2,000 reports were excluded from the analysis. The reason needs to be clarified.

Table 1 should indicate more clearly the prevalence of patients with oligometastatic disease.

Page 14: "Timing of onset did not influence the risk of death". The authors should better explain this finding.

Discussion
The discussion could be improved by discussing some general issues first (challenges in the definition of OM, changing scenario in terms of diagnostic tools and available treatments) and then presenting some reflections on the cancer types where the effect of OM on OS was more prominent. For instance, the criterium of OM disease has been long applied in surgical oncology for selecting patients with lung metastases for surgical resection or patients with peritoneal carcinomatosis for cytoreduction and intraperitoneal chemotherapy.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Surgical oncology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 08 May 2022

Fausto Petrelli, asst bergamo ovest, Treviglio (BG), Italy

The authors of this report deserve praise for their extensive work. The data presented are

intriguing and raise some intriguing questions.

- For the included studies, it would be interesting to know the comparator group and its tumour burden. This information would help to appreciate the magnitude of the differences in outcome.
  Data not available (comparator is the non-oligometastatic group but is not known site and number of metastases, for definition > 3-5 metastases).

- Additionally, one of the original questions raised with the introduction of the oligometastatic concept relates to the feasibility of local or locoregional treatment in a subset of patients with indolent disease. In this regard, I would present this information as a separate column in Table 1.
  Data not available.

- Always in Table 1, the columns on OS and PFS present rather generic information. Therefore, I would suggest including the specific outcomes. Also, the column on Age and PS should be split. Finally, the content of the column "Type of study" should be homogenised.
  OS and PFS are not generis but the exact outcomes (what is the meaning of specific outcomes?). Age and PS were split.

- Further, the authors need to consider the time bias because modern imaging technologies increase the number of patients labelled as oligometastatic. **Sentence added in discussion.**

- It would be essential to distinguish between different types of oligometastatic disease (e.g., indolent progressive and minimal residual disease after previous treatments). In this regard, in Table 1, the column "De novo or metachronous" seems to provide this information, but it is not entirely clear.
  Data were not available. Only the information reported were extractable.

- Please include the authors cited in Table 1 in the reference list.
  Due to the high number of studies, ref list is reported in a separated file.

Minor comments

Abstract

Please revise and use terms consistently (e.g. avoid "overall mortality in OM"). In addition, the conclusions should be reformulated; in particular, the last sentence should be more focused on the results presented.
OK sentence modified.

Introduction

Please revise the language and, wherever possible, shorten the text (e.g. the first sentence is superfluous in this context). Also, please check some definitions such as "prognostic survival" and "with up to three to five metastatic sites."
OK sentence modified. Sentences cancelled.

Methods

Please adjust the definition of polymetastatic accordingly.
OK, sentence modified.

Results
Figure 1: More than 2,000 reports were excluded from the analysis. The reason needs to be clarified.
OK reason included.

Table 1 should indicate more clearly the prevalence of patients with oligometastatic disease.
Data already included in the table by the authors.

Page 14: "Timing of onset did not influence the risk of death". The authors should better explain this finding.
OK, sentence modified.

Discussion
The discussion could be improved by discussing some general issues first (challenges in the definition of OM, changing scenario in terms of diagnostic tools and available treatments) and then presenting some reflections on the cancer types where the effect of OM on OS was more prominent. For instance, the criterium of OM disease has been long applied in surgical oncology for selecting patients with lung metastases for surgical resection or patients with peritoneal carcinomatosis for cytoreduction and intraperitoneal chemotherapy.
OK sentences added.

Competing Interests: none

Reviewer Report 22 November 2021

https://doi.org/10.5256/f1000research.77989.r100189

Dario Baratti
Peritoneal Surface Malignancies Unit, Colorectal Surgical Division, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

The authors have thoroughly addressed all my comments, resulting in a stronger paper.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Peritoneal surface malignancies, advanced colorectal cancer

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 2

Reviewer Report 22 September 2021

https://doi.org/10.5256/f1000research.58374.r93920

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Dario Baratti
Peritoneal Surface Malignancies Unit, Colorectal Surgical Division, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

The authors present the results of their systematic review and meta-analysis assessing the prognostic impact of oligometastatic disease on adult patients with solid tumors, as compared with a more diffuse metastatic spread. Overall and progression-free survival were significantly longer in patients with 3-to-5 metastatic lesions, irrespective of anatomic site. This may sound quite obvious in modern oncology, but the authors were able to provide a large amount of clinical data to support such an assumption.

Comments:

Abstract:

- In the Introduction, the main topic of this literature review was described concisely but exhaustively.

- In the Conclusions, please use the term "oligometastatic disease (or OM)" instead of "oligometastases".

Methods:

- The methodology of literature search and data extraction, paper selection criteria, and statistical analyses are thoroughly described. The review was carried out according to international guidelines (PRISMA). Please, clarify if papers not in English language studies were included.

- Also, the Newcastle-Ottawa Scale (NOS) might be briefly described, as a number of readers may be not familiar with it.

Results:

- In the Results section, the authors state that the reduction in the risk of death for oligometastatic patients was 35%, 38%, 30%, and 42% for colorectal, breast, non-small cell lung cancer, and renal cell carcinoma (RCC), respectively. In another part of this section, they state that compared with cancers with more than three to five metastases, “high-

certainty evidence indicates OM tumors are associated with better prognosis in particular for CRC, breast, NSCLC and RCC". However, was such a difference significant? In agreement with Reviewer 1, I would suggest to group studies according to histology, and to graphically depict the risk of oligometastatic vs. more advanced disease for each of the four tumors mentioned above.

- Figure 1: Please, clarify in the Methods section what "Records marked as ineligible by automation tools" means.

- Figure 2 and 3: Please, refer to my comments about the Results section.

Discussion:

- The Discussion was improved according to the suggestions of Reviewer 1, resulting in a stronger manuscript. There is an additional concept that I would address in the paper: the fact that the site of metastatic disease may affect patient prognosis, in addition to the number of metastatic lesions. In colorectal cancer, peritoneal metastases are associated with worse prognosis as compared with liver metastases, and lung metastases are associated with better prognosis. Furthermore, specific areas within the same organ may be related to a worse prognosis, e.g. a metastasis involving the hepatic hilum may be worse than a subcapsular liver metastasis.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Peritoneal surface malignancies, advanced colorectal cancer

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 26 Sep 2021

Fausto Petrelli, asst bergamo ovest, Treviglio (BG), Italy

I have the comments of Reviewer 2:

- I changed the conclusion of the abstract as requested.

- I included a statement in the Methods section about the exclusion of non-English language papers and the NOS scale definition.
- I have modified Fig. 1.
- I have provided a new Fig. 5 with subgroup analysis according to disease histology.
- In the discussion section, I provided a brief discussion about the site of oligometastases (lung vs others), in particular for CRC.

Competing Interests: No competing interests were disclosed.

Author Response 28 Oct 2021

Fausto Petrelli, asst bergamo ovest, Treviglio (BG), Italy

My responses to the comments of Reviewer 2:

- I changed the conclusion of the abstract as requested.
- I included a statement in the Methods section about the exclusion of non-English language papers and the NOS scale definition.
- I have modified Fig. 1.
- I have provided a new Fig. 5 with subgroup analysis according to disease histology.
- In the discussion section, I provided a brief discussion about the site of oligometastases (lung vs others), in particular for CRC.

Competing Interests: No competing interests were disclosed.

Version 1

Reviewer Report 30 June 2021

https://doi.org/10.5256/f1000research.55843.r87329

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Luca G. Campana

[1] Department of Surgery, Colorectal and Peritoneal Oncology Centre, The Christie NHS Foundation Trust, Manchester, UK
[2] Department of Surgery, Manchester University NHS Foundation Trust, Manchester, UK

The authors of this systematic review and meta-analysis assessed the influence of oligometastatic disease status on OS and PFS in adult patients with solid tumours. To do this, they carried out an extensive literature review including all types of studies with at least ten patients with any histology. Patients with OM disease were found to have significantly longer PFS and OS if they had CRC, BC, NSCLC, RCC, and sarcoma.

The literature screening was conducted according to the standard recommendations and the subsequent analysis is methodologically robust. Going across several histotypes, the paper provides a big, and for certain aspects, unique picture of the prognosis of patients with OM. At the same time, however, it makes it challenging summarising and discussing the results.

Here you can find some comments that you may find useful to improve this review:

- In the Abstract, I would mention the histotypes in which the OM status do not correlate with patient outcome. Also, in the Conclusions part, second sentence: this seems to be unrelated to the results presented and anyway not applicable in all cases (consider rephrasing/changing).

- The Introduction needs some input because sentences do not always follow a clear pattern. For instance, there are some general considerations regarding tumour progression, tumour staging according to the TNM, detailed results of a specific trial. It needs to be more homogeneous.

- Given the positive results with ablative therapies in patients with OM disease, the authors should explain what this meta-analysis adds to the literature.

- From the Introduction (and Methods) it is not clear what the definition adopted of OM disease is ("up to 3 to 5" metastatic sites). In this regard, is a patient with 6 liver metastases still considered "oligometastatic"?

- The great majority of the studies were retrospective in nature. This should be clearly stated and critically discussed as well.

- Did the authors detect any imbalance in treatment intensity between OM vs. non-OM patients?

- Table 1, 8th column: some of the included studies have "various" sites of OM. I think this information should be specified in order to be consistent with the inclusion criteria.

- The studies could be regrouped according to the histology. The same could apply to Figure 2 and Figure 3.

- The prognosis of patients with gastric cancer, melanoma, and head and neck cancer should be discussed in light of the results presented.

- In the Discussion, it is not entirely clear if the authors consider the OM status an opportunity to spare patients from systemic treatment or an opportunity to pursue combined treatment. Again, this should be discussed in light of the results presented.

- In the Discussion, the last paragraph seems more like a list of ongoing trials, including some form of local therapies over standard systemic treatment. How does this relate to the findings of the present study? Please discuss.

Are the rationale for, and objectives of, the Systematic Review clearly stated?
Partly

Are sufficient details of the methods and analysis provided to allow replication by others?
Yes

Is the statistical analysis and its interpretation appropriate?
Yes

Are the conclusions drawn adequately supported by the results presented in the review?
Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Surgical oncology, locoregional therapies (limb perfusion/infusion, intraperitoneal chemotherapy, electrochemotherapy), melanoma, sarcoma, breast cancer, peritoneal malignancies, colorectal cancer.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 01 Jul 2021

Fausto Petrelli, asst bergamo ovest, Treviglio (BG), Italy

Reviewer 1: Luca Campana

The authors of this systematic review and meta-analysis assessed the influence of oligometastatic disease status on OS and PFS in adult patients with solid tumours. To do this, they carried out an extensive literature review including all types of studies with at least ten patients with any histology. Patients with OM disease were found to have significantly longer PFS and OS if they had CRC, BC, NSCLC, RCC, and sarcoma.

The literature screening was conducted according to the standard recommendations and the subsequent analysis is methodologically robust. Going across several histotypes, the paper provides a big, and for certain aspects, unique picture of the prognosis of patients with OM. At the same time, however, it makes it challenging summarising and discussing the results.

Here you can find some comments that you may find useful to improve this review:

- In the Abstract, I would mention the histotypes in which the OM status do not correlate with patient outcome. Also, in the Conclusions part, second sentence: this seems to be unrelated to the results presented and anyway not applicable in all cases (consider rephrasing/changing).
  - **Author response: OK - requests accepted.**

- The Introduction needs some input because sentences do not always follow a clear pattern. For instance, there are some general considerations regarding tumour progression, tumour staging according to the TNM, detailed results of a specific trial. It needs to be more homogeneous.
  - **Author response: OK - sentences added or modified.**

- Given the positive results with ablative therapies in patients with OM disease, the authors should explain what this meta-analysis adds to the literature.
  - **Author response: Sentences added in 2nd paragraph of discussion.**

- From the Introduction (and Methods) it is not clear what the definition adopted of OM disease is ("up to 3 to 5" metastatic sites). In this regard, is a patient with 6 liver metastases still considered "oligometastatic"?
  - **Author response: Definition updated.**

- The great majority of the studies were retrospective in nature. This should be clearly stated and critically discussed as well.
  - **Author response: Considerations added in the limitations section.**

- Did the authors detect any imbalance in treatment intensity between OM vs. non-OM patients?
  - **Author response: This data was not reported.**

- Table 1, 8th column: some of the included studies have "various" sites of OM. I think this information should be specified in order to be consistent with the inclusion criteria.
  - **Author response: “Various” means that in those articles, sites of metastases were not specific. Only when explicitly reported they are included (e.g liver or lung). Specific comment in inclusion criteria added.**

- The studies could be regrouped according to the histology. The same could apply to Figure 2 and Figure 3.
  - **Author response: Table and Figure 2 (OS) arranged according to disease.**

- The prognosis of patients with gastric cancer, melanoma, and head and neck cancer should be discussed in light of the results presented.
  - **Author response: Sentences added in the Discussion.**

- In the Discussion, it is not entirely clear if the authors consider the OM status an

opportunity to spare patients from systemic treatment or an opportunity to pursue combined treatment. Again, this should be discussed in light of the results presented.
    - **Author response: In the final paragraph, some sentences were added about this request.**

- In the Discussion, the last paragraph seems more like a list of ongoing trials, including some form of local therapies over standard systemic treatment. How does this relate to the findings of the present study? Please discuss.
    - **Author response: Discussion added.**

Competing Interests: none

Author Response 02 Jul 2021

Fausto Petrelli, asst bergamo ovest, Treviglio (BG), Italy

- We have improved the Introduction and criteria for search.

- We have arranged in the Discussion section a specific discussion about particular settings of patients analysed and the main limitation of the paper (retrospective nature of studies).

- We also discussed the main meaning of the results: improved prognosis and treatment opportunities with locoregional therapies in an oligometastatic setting.

- Table was also ordered according to histology.

Competing Interests: No competing interests were disclosed.