



SYSTEMATIC REVIEW

Better survival of patients with oligo- compared with polymetastatic cancers: a systematic review and meta-analysis of 173 studies [version 1; peer review: awaiting peer review]

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V1 First published: 27 May 2021, 10:423
<https://doi.org/10.12688/f1000research.52546.1>

Latest published: 27 May 2021, 10:423
<https://doi.org/10.12688/f1000research.52546.1>

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 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 cell carcinoma (RCC) the reduction in the risk of death for OM patients were 35, 38,

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Reviewer Status AWAITING PEER REVIEW

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30 and 42%, respectively.

Conclusions. Patients with oligometastases have a significantly better prognosis than those with more widespread stage IV tumors. We suggest that a treatment strategy that involves both the primary and the metastases should be identified at the time of diagnosis.

Keywords

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

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Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

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How to cite this article: Petrelli F, Ghidini A, Ghidini M *et al.* **Better survival of patients with oligo- compared with polymetastatic cancers: a systematic review and meta-analysis of 173 studies [version 1; peer review: awaiting peer review]** F1000Research 2021, 10:423 <https://doi.org/10.12688/f1000research.52546.1>

First published: 27 May 2021, 10:423 <https://doi.org/10.12688/f1000research.52546.1>

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 1995¹ to describe patients with a low burden of disease (e.g. one to five 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 In some circumstances, the 8th Tumor Node Metastasis (TNM) staging system distinguishes between patients with a single metastasis and those with multiple such metastases. Large consensus on the definition and management of OM patients is currently lacking. Recently, 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 prostate, kidney, lung and melanomas.^{4,5} In these settings oligometastatic cancers may be treated in oligoprogressive sites continuing systemic therapy that control the remaining disease. Also, oligometastatic tumors at presentation can receive local treatments on the primary tumor and on any single oligometastases. 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 defined as tumors with up to three to five metastatic sites.

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 "oligometastatic" 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 from inception up to October 30th, 2020. To be eligible, studies needed to have evaluated survival of patients with metastatic cancers 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 to 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).

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 I² (I² = 0% to 25%, no heterogeneity; I² = 25% to 50%, moderate heterogeneity; I² = 50% to 75%, high heterogeneity; I² = 75% to 100%, extreme heterogeneity). When I² 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 patients¹⁰ (Figure 1). Baseline characteristics of the included studies and treatments received are presented in Table 1.

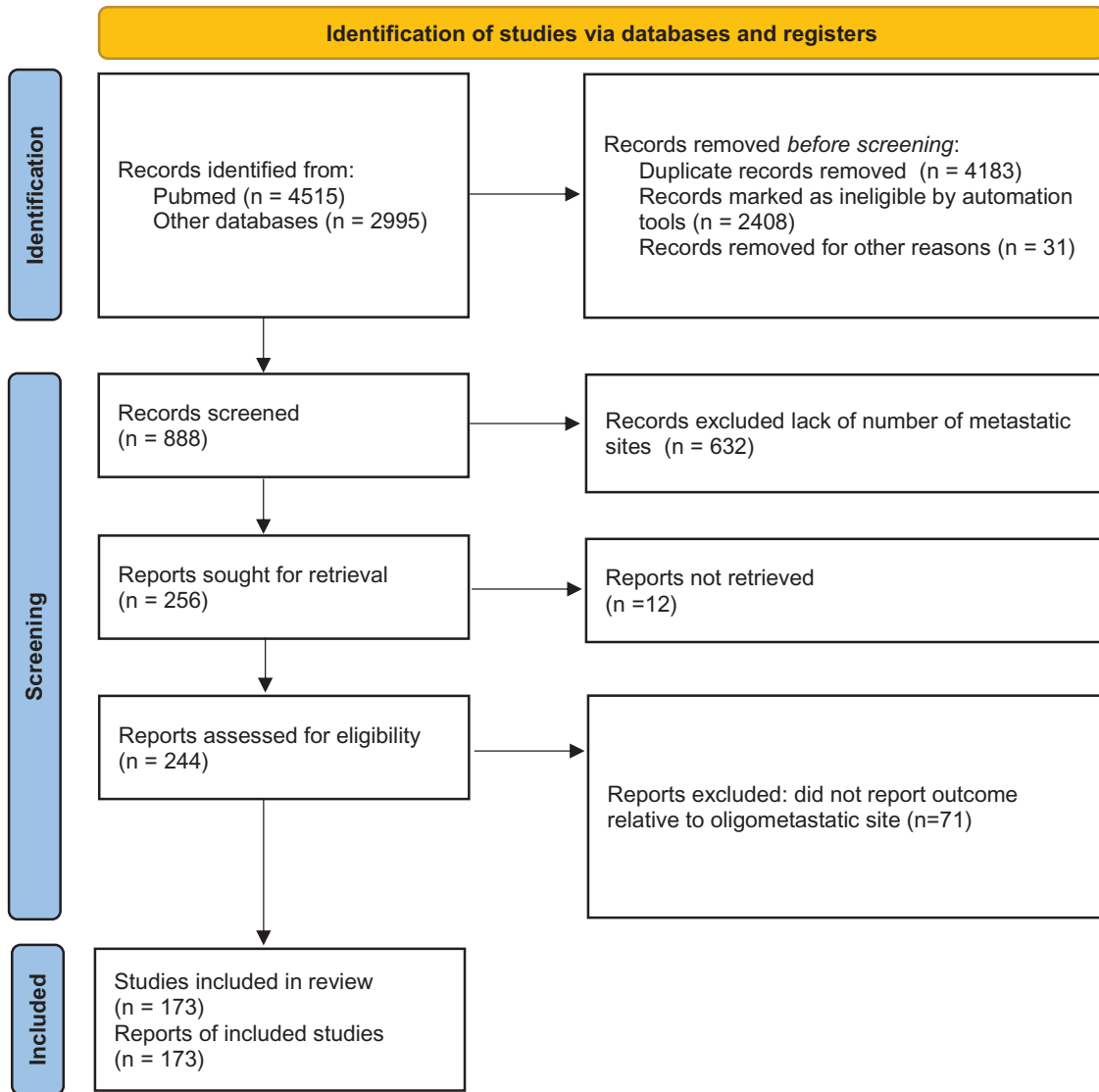


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 flow diagram showing the process of study inclusion.

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 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.

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
Afshari/2019	281	CRC	62/NR	Retrospective	NR	1 (85)	Various	-	-	MVA	-	5
Ai/2017	3245	Esophageal	66/NR	Retrospective	NR	1-3 (NR)	Various	-	-	MVA	-	5
Alf/2011	887	RCC	62.5/85	Retrospective	33.6	2 (16.5)	Various	58/42	S (14)	MVA	-	8
Amikura/2017	342	CRC	NR/NR	Retrospective	52.7	1-4 (75.7)	Liver	63/37	S ± CT (100)	MVA	MVA	8
Anraku/2003	133	Utherine	56/NR	Retrospective	40	1 (58)	Lung	6/94	S (100)	MVA	-	7
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
Armstrong/2007	686	Prostate	68.5/88	Retrospective	70	1-2 (88)	Various	-	CT (100)	MVA	-	9
Atzpodien/2003	425	RCC	NR/100	Retrospective	20	1-2 (82)	Various	0/100	Various	MVA	-	7
Bachet/2019	249	CRC	62.9/NR	Retrospective	28.7	1-3 (66)	Liver	79/21	S ± CT (100)	UVA	MVA (DFS)	6
Baldim/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
Bartosch/2016	130	Utherine	52/NR	Retrospective	48	1 (54)	Various	-	Various	MVA	-	7
Bates/2011	96	Breast	NR/NR	Retrospective	NR	1-2 (NR)	Various	-	CT (100)	MVA	MVA (TTP)	5
Beau-Faller/2019	228	NSCLC	NR/42	Retrospective	NR	1-2 (65)	Various	0/100	TKI (100)	MVA	MVA	5
Beppu/2014	137	CRC	63/NR	Retrospective	NR	1-5 (NR)	Liver	-	CT ± S (100)	MVA	-	5
Beuselinck/2014	200	RCC	59/85	Retrospective	67	1 (83)	Various	38/62	Systemic tx (100)	UVA	UVA	8
Bian/2016	401	Melanoma	NR/83	Retrospective	35	1-4 (87)	CNS	-	SBRT (100)	MVA	-	7
Blanchette/2018	154	Breast	56/NR	Retrospective	34	1 (55)	Various	25/75	CT (100)	MVA	-	7
Blazer III/2008	305	CRC	57/NR	Retrospective	25	1 (32)	Liver	-	CT + S (100)	MVA	-	6
Bollig/2020	283	Head & neck	59.8/NR	Retrospective	NR	1 (18.7)	Various	-	Various (100)	MVA	-	5
Bolm/2015	39	Pancreatic	NR/56	Retrospective	5	1 (56)	Various	-	RT (100)	MVA	-	6
Bossé/2020	3454 1061	RCC	62/81 61/97	Retrospective 2-cohort	34 24.9	1 (19.5) 1 (17.2)	NR	-	TKI (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
Brandi/2013	151	CRC	61.5/100	Retrospective	42	1 (61)	Lung/Liver	51/49	S ± CT (100)	-	MVA	8
Buhl/2018	140	Breast	62/NR	Retrospective	6.2	1 (40)	Various	-	CT (100)	-	MVA (TTP)	5
Cai/2017	143	RCC	60/NR	Retrospective	22	1 (72.7)	Various	-	TKI (100)	UVA	UVA	6
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
Chen/2019	3981	Various	60.84/40.8	Retrospective	44.3	1 (16.5)	Various	-	Various (100)	MVA	-	7
Co/2019	172	Breast	53/NR	Retrospective	NR	1-3 (96)	Various	100/0	Systemic tx ± S (100)	MVA	-	5
Cornella/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
Dai/2020	146	RCC	56.5/71.9	Retrospective	36	1 (56.8)	Various	45.9/54.1	TKI (100)	MVA	MVA	6
Daniel/2017	109	CRC	58.4/NR	Retrospective	NR	1-4 (46)	Liver	100/0	S ± CT (100)	MVA	-	5
de Baere/2015	566	Various	62.7/NR	Retrospective	35.5	1-2 (78)	Lung	-	RFA (100)	MVA	MVA	7
de Geus-Oei/2006	152	CRC	61.5/NR	Prospective	17	1 (NR)	Liver	-	Various	UVA	UVA	6
Derclle/2016	251	Various	52/NR	Retrospective	10.5	1-2 (40)	Various	-	ICIs (100)	MVA	-	6
Ding/2017	85	NSCLC	66/75	Retrospective	9.8	1-3 (48)	Various	-	TKI (94)	MVA	MVA	6
Dudek/2019	33	Sarcoma	55/NR	Retrospective	37	1-3 (72.7)	Lung	36/64	S (100)	UVA	-	7
Efficace/2008	742	CRC	62/92	Retrospective analysis	NR	1 (40)	Various	-	CT (100)	MVA	-	5
Faroni/2015	810	CRC	63/83	Pooled analysis of n = 4 trials	33	1-2 (85)	Various	100/0	CT ± S	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
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
Ghiringhelli/2014	409	CRC	65/59	Retrospective	32	1 (63)	Various	62/38	S ± CT (100)	MVA	-	6
Gobbini/2018	16702	Breast	61/NR	Cohort	48.5	1-3 (92.6)	Various	28.5/71.5	-	MVA	-	8
Gu/2017	184	RCC	54	Retrospective	23.3	1 (85)	Various	-	Various	UVA	MVA	6
Gu/2018	102	CRC	62/NR	Retrospective	NR	1 (36)	Liver	0/100	RFA ± CT (100)	MVA	-	5
Gu/2020	1888	Breast	NR/NR	Retrospective	NR	1 (NR)	Various	100/0	Various	MVA	-	5
Han/2011	61	SCLC	65/71	Phase 2	33.6	1-2 (NR)	Various	-	CT (100)	MVA	-	7
Hashimoto/2010	466	Gastric	60/85	Retrospective	NR	1-2 (NR)	Various	71.7/28.3	CT (100)	UVA	-	5
Hebbbar/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
Iacono/2019	162	Melanoma	NR/82	Retrospective	48	1-2 (66)	Various	-	Systemic tx (100)	MVA	-	7
Ikeda/2018	116	RCC	66/NR	Retrospective	19.4	1 (66)	Various	-	TKI (100)	MVA	MVA	6
Ishiguro/2006	111	CRC	NR/NR	Retrospective	43	1-3 (81)	Liver	100/0	S (100)	MVA	-	9
Ishihara/2017	118	RCC	NR/NR	Retrospective	NR	1 (NR)	Various	100/0	S	UVA	-	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
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

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
Kadokura/2013	208	Gastric	64/81.3	Retrospective	26.9	1 (69.7)	Various	-	CT	MVA	-	6
Kawamoto/2020	98	Sarcoma	NR/NR	Retrospective	NR	1-2 (43.9)	Lung	-	Various	-	MVA (PMS)	
Keizman/2014	278	RCC	63/NR	Retrospective	55	1 (18)	Various	82/18	TKI ± S	UVA	UVA	8
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
Kikawa/2019	134	Breast	63.5/85.8	Retrospective	NR	1-2 (73.9)	Various	24.6/75.4	Everolimus (100)	UVA	UVA	5
Kim/2008	304	Gastric	54/73.3	Retrospective	NR	1 (81.2)	Various	-	CT (100)	MVA	-	5
Kim/2017	177	RCC	62/92.6	Retrospective	19.2	1-3 (NR)	Various	-	TKI (100)	MVA	UVA	6
Kimura/2019	103	Gastric	67/NR	Retrospective	NR	1-2 (89)	Various	-	CT (100)	MVA	-	5
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
Konopke/2009	201	CRC	65/NR	Prospective	31	1-3 (94)	Liver	34.8/65.2	S (100)	MVA	MVA	6
Kroger/2006	187	Breast	45.5/NR	Phase 3	63	1-2 (41.5)	Various	29.5/70.5	CT (100)	MVA	MVA	7
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
Le Scodan/2009	581	Breast	60.2/NR	Retrospective	39	1 (58.9)	Various	100/0	RT ± S	MVA	-	7
Leal/2016	513	CRC	64.1/NR	Retrospective	37	1 (61.6)	Liver	100/0	S	MVA	MVA	7
Lee/2009	2247	Melanoma	51/NR	Retrospective	22.5	1-2 (67.4)	Various	-	-	MVA	-	6
Leone/2017	9143	Breast	61/NR	Retrospective	13	1 (36.2)	Various	100/0	-	MVA	-	6
Li/2019	100	Lung	60/96.1	Retrospective	39	1-3 (13.7)	Brain	100/0	TKI ± CT	UVA	-	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
Liou/2017	266	RCC	61/NR	Retrospective	12	1 (43)	Various	-	S (100)	MVA	-	6
Lipton/2010	102	Breast	55.4/100	Retrospective	34	1-2 (NR)	Various	-	Trastuzumab (100) ± CT (88)	MVA	MVA (TTP)	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
Liu/2010	52	CRC	70/NR	Retrospective	35.5	1 (58)	Liver	0/100	S + CT (100)	MVA	MVA (DFS)	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
Liu/2018	216	NSCLC	57/NR	Retrospective	7	1-3 (NR)	Brain	-	RT ± Systemic tx	MVA	-	6
Liu/2020	125	Osteosarcoma	17/100	Retrospective	NR	1-2 (72)	Lung	-	CT ± S	-	MVA (PRS)	5
Liu/2020	182	CRC	59.5/NR	Retrospective	32.5	1-3 (NR)	Liver	65/35	S ± CT	MVA	MVA (RFS)	6
Lo/2017	120	Head & neck	NR/NR	Retrospective	51	1-3 (68.3)	LNs	-	S ± CT/RT	MVA	MVA (DFS)	8
Lobbezoo/2015	815	Breast	62.5/NR	Retrospective	37.1	1 (67)	Various	19/81	Systemic tx (100)	MVA	-	6
Lu/2016	67	RCC	58/95.5	Retrospective	NR	1-4 (32.8)	Bone	-	TKI (100)	MVA	-	5
Luzzago/2019	1592	Bladder	68/NR	Retrospective	NR	1 (44)	Various	-	CT ± S	MVA	-	5
Makiyama/2018	444	Gastric	75/NR	Retrospective	28.7	1 (37.3)	Various	-	CT (100)	-	MVA	5
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
Mazzaferro/2009	1556	HCC	55/NR	Retrospective	53	1 (26)	Liver	-	S (100)	MVA	-	7
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
Moreau/2012	115	Melanoma	59/NR	Retrospective	19	1-3 (64)	LNs	93/7	S (100)	MVA	MVA (DMFS)	6
Morino/2020	232	Biliary	66/NR	Retrospective	12.6	1-3 (52)	Various	-	± Locoregional ± Systemic tx	UVA	-	5
Narayan/2020	357	CRC	60/NR	Prospective	127	1 (NR)	Liver	100/0	S ± HAI	-	UVA (RFS)	9

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
Nataraj/2016	102	Sarcoma	18/60	Retrospective	23	1-3 (31)	Lung	31/69	S ± CT (100)	MVA	MVA (EFS)	6
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
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
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
Nie/2017	209	NPC	45/81.3	Retrospective	16.6	1 (49.8)	Various	24.9/75.1	CT (100)	UVA	UVA	6
Niibe/2016	61	NSCLC	NR/100	Retrospective	NR	1-2 (89)	SNC	18/82	SBRT or SRS (100)	MVA	-	5
Niikura/2012	314	Breast	51.9/90.4	Retrospective	33	1 (23.8)	Bone	100/0	Bisphosphonates	MVA	MVA	6
Nojiri/2011	31	CRC	63.3/NR	Retrospective	62	1-2 (64.5)	Lung	3.2/96.8	S (100)	MVA	-	8
Paccagnella/2006	324	NSCLC	62/93.7	Phase 2-3	19	1 (30.5)	Various	100/0	CT (100)	UVA	-	6
Park/2009	317	Breast	48/93	Retrospective	NR	1-2 (36)	Various	-	Various	MVA	-	5
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
Park/2017	134	Biliary	61/90	Retrospective	26	0-1 (90)	Various	-	CT (100)	MVA	MVA	6
Park/2019	517	NSCLC	64/NR	Retrospective	NR	1 (57)*	Various	100/0	Various	MVA	-	5
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	MVA (100)	-	MVA	6
Pons-Tostivint/2019	4276	Breast	60/NR	Retrospective	45.3	1-2 (77)	Various	100/0	Various	MVA	-	7
Prasanna/2020	513	CRC	63/NR	Retrospective	NR	1 (NR)	Various	51/49	S ± CT	UVA	-	5
Prelaj/2019	193	Lung	65/88	Retrospective	43	1-3 (NR)	Various	-	IT (100)	UVA	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
Ran/2020	49	Breast	50/NR	Retrospective	29	1-2 (NR)	Various	-	Trastuzumab based (100)	UVA	-	6
Rhu/2014	262	Breast	47/NR	Retrospective	29.6	1-2 (84.7)	Various	100/0	Various	MVA	-	6
Rhu/2017	410	CRC	60/NR	Retrospective	34	1 (63)	Liver	-	S (100)	MVA	-	6
Richey/2011	188	RCC	60.8/65	Retrospective	6.9	1 (36)	Various	100/0	S + Systemic tx (100)	MVA	-	6
Robelin/2019	162	Neuroendocrine	61/90	Retrospective	56	1-2 (85)	Various	49/51	Various	MVA	UVA	7
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
Schmidt/2005	321	RCC	51/NR	Retrospective	52	1-2 (60)	Various	-	Citokines (100)	UVA	-	7
Schneeweiss/2002	118	Breast	44/NR	Retrospective	48	1-2 (86)	Various	-	CT (100)	UVA	MVA	7
Seremet/2019	85	Melanoma	57/91	Retrospective	21	1-2 (44.7)	Various	-	ICIs (100)	MVA	UVA	6
Sharma/2015	93	RCC	61/76	Retrospective	13	1 (60)	Various	100/0	S ± Systemic tx (100)	MVA	-	6
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
Shimizu/2019	160	CRC	66/NR	Retrospective	64	1-3 (88)	Lung	18/83	S (100)	MVA	-	7
Shin/2016	1024	NSCLC	64/85.5	Retrospective	42.2	1 (14.8)*	Various	-	Systemic tx (100)	MVA	-	7
Shinoda/2020	48	Liposarcoma	43/NR	Retrospective	27.5	1 (52.1)	Various	-	Various	UVA (DSS)	-	5
Shirasawa/2019	141	SCLC	70/62	Retrospective	NR	1-5 (34.7)	Various	100/0	CT (100)	MVA	-	5
Shoushtari/2016	215	Sarcoma	56/26	Retrospective	175	1-2 (67)	Various	39/61	CT (100)	MVA	UVA	9
Silva/2019	61	Various	66.3/NR	Retrospective	13.58	1-5 (35)	Spine	-	SBRT (100)	-	MVA (LC 1y)	6
Smart/2019	66	BTC	76/55	Retrospective	21	1-2 (54)	Liver	-	RT (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
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
Sperduto/2016	1481	NSCLC	NR/69.2	Retrospective	NR	1-4 (81)	Brain	-	Various	MVA	-	5
Stang/2016	113	CRC	70/NR	Retrospective	99	1-3 (77)	Liver	21/79	RFA (100) CT (95)	MVA	MVA	8
Stephens/2011	81	Sarcoma	43.5/NR	Retrospective	27	1-2 (33)	Lung	-	S (100)	MVA	-	7
Stremtizer/2015	154	CRC	62/NR	Retrospective	34	1-2 (NR)	Liver	-	S (100)	MVA	MVA	6
Tablazoni/2019	837	Prostate	76/NR	Retrospective	26	1 (NR)	Bone	-	-	MVA	-	7
Takagi/2019	71	RCC	66/99	Retrospective	NR	1 (45)	Various	-	TKI (100)	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
Tarpgaard/2014	566	CRC	NR/96	Retrospective	37	0-1 (29)	Various	-	CT (100)	MVA	MVA	6
Thiery-Vuillemin/2017	224	RCC	67/82	Retrospective	18.3	1 (51)	Various	-	Systemic tx ± S (100)	UVA	-	6
Van Cutsem/2004	1207	CRC	64/NR	Retrospective	NR	1 (25)	Various	76/24	CT (100)	MVA	-	5
Wang/2016	310	Gastric	58/100	Retrospective	NR	1 (70.6)	Various	-	Various	MVA	-	5
Wang/2017	163	CRC	65/NR	Retrospective	37	1-2 (41)	Liver	82/18	S + CT (100)	MVA	MVA	6
Wang/2018	321	Gastric	57/85	Retrospective	32	0-1 (83)	Various	-	CT (100)	MVA	MVA	6
Wei/2005	395	CRC	63/NR	Retrospective	31	1-3 (65)	Liver	51/49	S (100)	MVA	MVA	6
Weide/2012	855	Melanoma	62/NR	Retrospective	25	1-2 (74.7)	Various	-	Various	MVA	-	6
Wong/2019	483	Breast	49/NR	retrospective	66	1 (88)	Various	100/0	Systemic tx (100)	MVA	-	7
Xie/2018	332	CRC	58/NR	Retrospective	27.7	1 (65.2)	Various	72/18	Various	MVA	-	6
Yamamoto/2018	51	RCC	65/80	Retrospective	NR	1 (45)	Various	-	TKI (100)	UVA	UVA	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
Yamashita/2017	74	CRC	59/NR	Retrospective	25	1 (74)	Liver	-	RFA/MWA + CT (100)	MVA	MVA	6
Yin/2019	99	Cervix	53/51.6	Retrospective	11.6	1-3 (37.3)	Various	-	-	MVA	MVA	6
Yoon/2010	52	HCC	49/NR	Retrospective	16.3	1 (75)	Lung	-	S (100)	MVA	-	6
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
Zhang/2020	160	Prostate	68/NR	Retrospective	47.2	1-4 (39.4)	Bone	-	RT + OT (100)	UVA	-	7
Zhao/2017	289	CRC	57/NR	Retrospective	34	1 (51)	Liver	66/34	S (100)	MVA	MVA	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, 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, post-relapse 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.

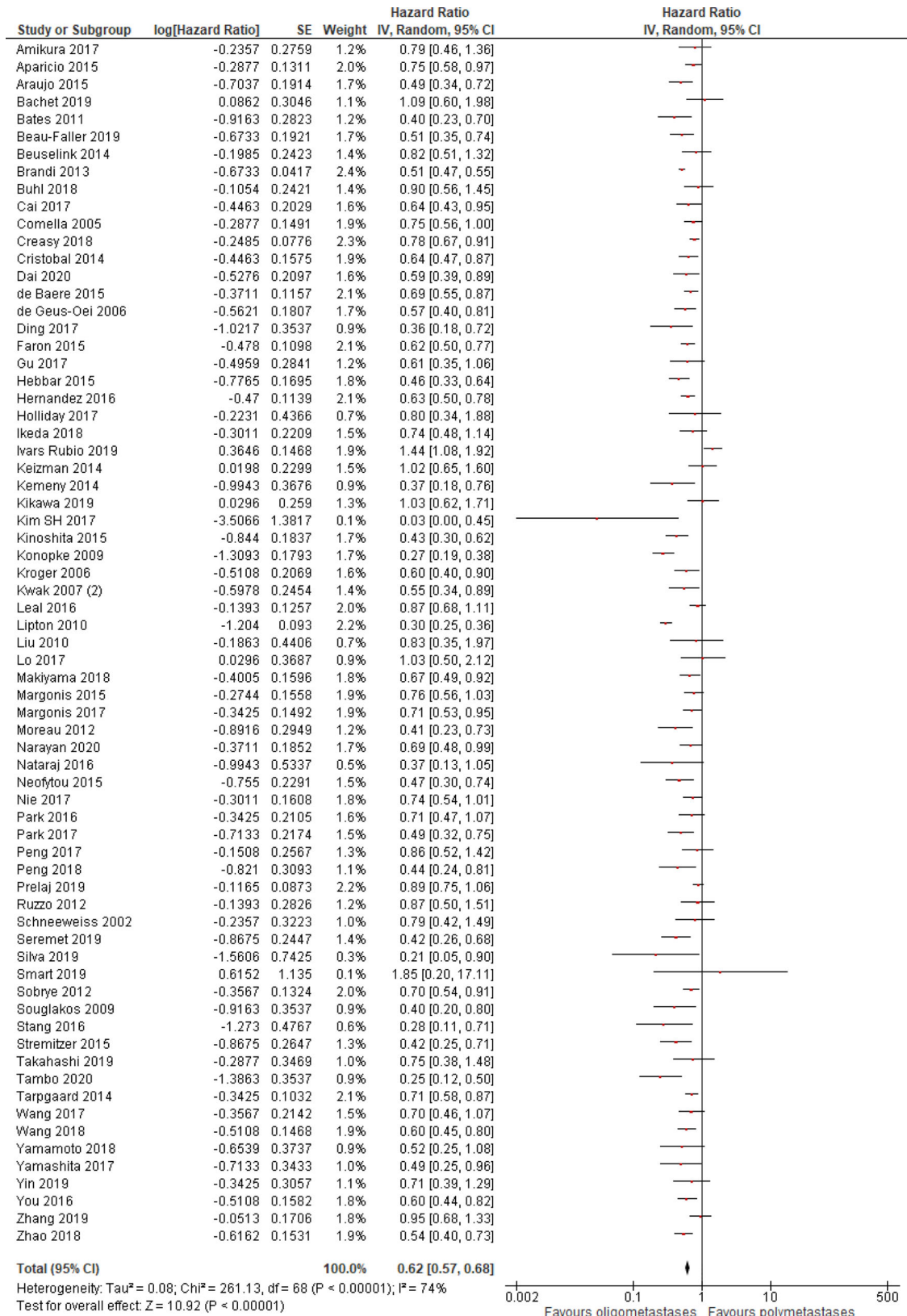


Figure 2. Progression-free survival of oligo- compared to non-oligometastatic cancers.

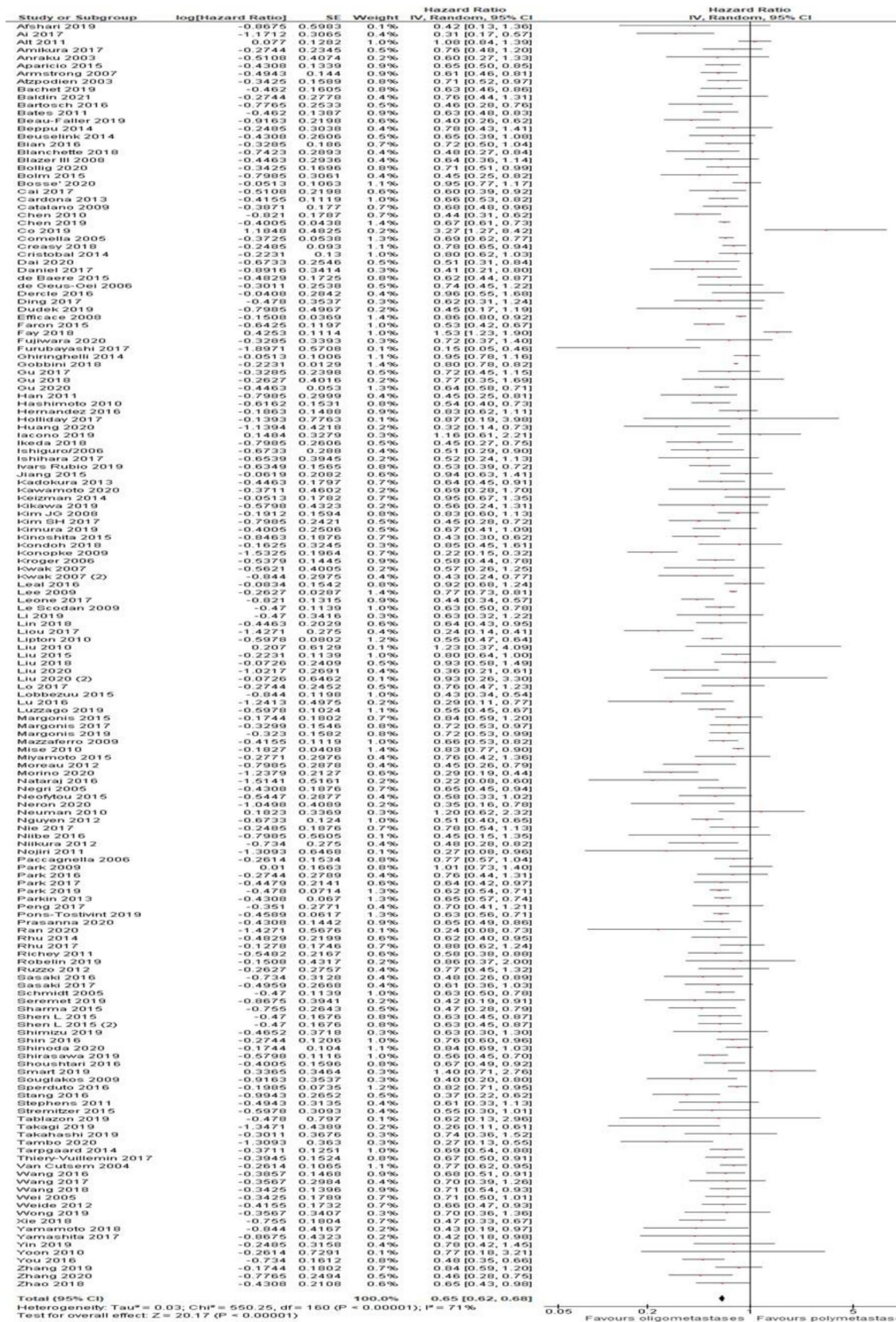


Figure 3. Overall survival of oligo- compared to non-oligometastatic cancers.

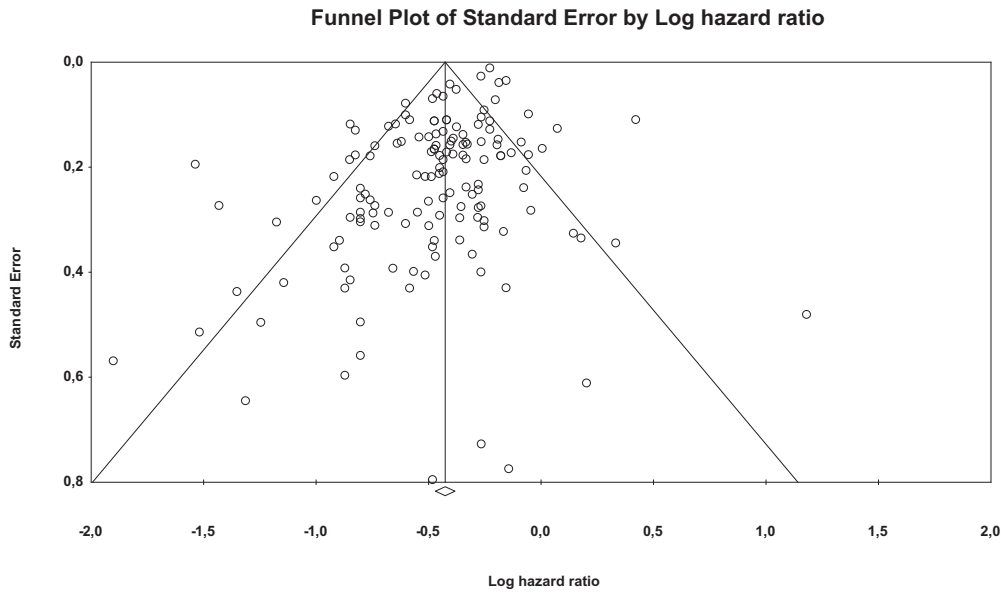


Figure 4. Funnel plot of publication bias for overall survival analysis showing standard error by log hazard ratio.

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 burden.

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.

There is evidence from randomized clinical trials¹²⁻¹⁴ that ablative therapies improve survival in patients with OM cancer. For example, in some cancers small randomized studies¹²⁻²⁰ 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 trials.¹² Furthermore, Gomez *et al.*¹³ 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.¹⁴ 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.^{15,16} 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.¹⁷ 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.¹⁸ Oligometastatic cancers can also be 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.^{19,20}

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. 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.²¹

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>).

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. Also, we propose that these patients should be stratified when included in clinical trials.

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/10.17632/8kycvdp6v.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/10.17632/8kycvdp6v.1>.¹⁰

Data are available under the terms of the Creative Commons Attribution 4.0 license (CC-BY 4.0).

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