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Review

Definition of oligometastatic esophagogastric cancer and impact of local oligometastasis-directed treatment: A systematic review and meta-analysis

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Abstract ***Background:*** Local treatment (metastasectomy or stereotactic radiotherapy) for oligometastatic disease (OMD) in patients with esophagogastric cancer may improve overall survival (OS). The primary aim was to identify definitions of esophagogastric OMD. A secondary aim was to perform a meta-analysis of OS after local treatment versus systemic therapy alone for OMD. ***Methods:*** Studies and study protocols reporting on definitions or OS after local treatment for esophagogastric OMD were included. The primary outcome was the maximum number of organs/lesions considered OMD and the maximum number of lesions per organ (i.e. 'organ-specific' OMD burden). Agreement was considered to be either absent/poor (< 50%), fair (50%–75%), or consensus (≥ 75%). The secondary outcome was the pooled adjusted hazard ratio (aHR) for OS

Abbreviations: OMD, Oligometastatic disease; OS, Overall survival; aHR, adjusted hazard ratio; SBRT, Stereotactic body radiotherapy.

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after local treatment versus systemic therapy alone. The ROBINS tool was used for quality assessment.

Results: A total of 97 studies, including 7 study protocols, and 2 prospective studies, were included. OMD was considered in 1 organ with ≤ 3 metastases (consensus). 'Organ-specific' OMD burden could involve bilobar ≤ 3 liver metastases, unilateral ≤ 2 lung metastases, 1 extra-regional lymph node station, ≤ 2 brain metastases, or bilateral adrenal gland metastases (consensus). Local treatment for OMD was associated with improved OS compared with systemic therapy alone based on 6 non-randomized studies (pooled aHR 0.47, 95% CI: 0.30–0.74) and for liver oligometastases based on 5 non-randomized studies (pooled aHR 0.39, 95% CI: 0.22–0.59). All studies scored serious risk of bias.

Conclusions: Current literature considers esophagogastric cancer spread limited to 1 organ with ≤ 3 metastases or 1 extra-regional lymph node station to be OMD. Local treatment for OMD appeared associated with improved OS compared with systemic therapy alone. Prospective randomized trials are warranted.

1. Introduction

The general concept of oligometastatic cancer (OMD) was first introduced in 1995 and described a clinical state between locally confined and systemic metastasized disease [1]. OMD reflects distinct tumor biology and implies that local treatment for OMD (e.g. metastasectomy or stereotactic body radiation therapy [SBRT]) could provide long-term disease control or even be curative in a proportion of patients [2]. In 2020, the European Society for Radiotherapy and Oncology (ESTRO) and European Organisation for Research and Treatment of Cancer (EORTC) proposed a classification system of OMD [3]. The first question differentiates between "genuine OMD" and "induced OMD" by analyzing whether or not the patient has had polymetastatic disease before the current diagnosis of OMD ("no" versus "yes", respectively). The second question differentiates between "de-novo OMD" and "repeat OMD" by analyzing whether or not the patient with "genuine OMD" has had OMD before the current diagnosis of OMD ("no" versus "yes", respectively) [3].

In patients with oligometastatic esophagogastric cancer, no RCTs have yet been completed, but several non-randomized trials [4,5] suggested improved OS after local treatment for OMD compared to systemic therapy alone. In the phase II trial by Al-Batran *et al.* the benefit of surgical resection of the primary tumor and metastases plus systemic therapy for patients with gastric or gastroesophageal junction cancer and synchronous OMD limited to the retroperitoneal lymph nodes and/or one organ was assessed [5]. After 4 cycles of FLOT chemotherapy, patients without progression underwent surgical resection of the primary tumor and metastases, which resulted in a median OS of 31.3 months [5]. In addition, the phase II of Liu *et al.* assessed the benefit of SBRT in patients with esophageal squamous cell carcinoma with ≤ 3 metachronous oligometastases [4]. All patients underwent SBRT and 50% underwent systemic therapy after SBRT, which resulted in a median OS of 24.6 months [4]. However, interpretation of these individual studies and translation to clinical practice is hampered by varying definitions of OMD.

A population-based study of autopsy reports of 3,876 patients with esophageal or gastric adenocarcinoma or squamous cell carcinoma between 1990 and 2017 in the Netherlands revealed that the most common metastatic location for esophageal cancer were liver (56%), extra-regional lymph nodes (53%), and lung (50%) and for gastric cancer were extra-regional lymph nodes (56%), liver (53%), and peritoneum (51%) [6]. Esophageal adenocarcinoma more frequently metastasizes to the peritoneum and bone as compared with esophageal squamous cell carcinoma [6]. In addition, diffuse type gastric cancer more frequently metastasizes to the peritoneum as compared with intestinal type gastric cancer [6]. However, for both esophageal and gastric cancer (all histological subtypes) the liver was the most common metastatic site [6]. Peritoneal disease was considered to fall outside the scope of this systematic review and meta-analysis because this reflects a polymetastatic disease state, which requires a different treatment modality (hyperthermic intraperitoneal chemotherapy [HIPEC]) as opposed to OMD (metastasectomy or SBRT) [7,8]. After exclusion of peritoneal disease, we consider esophageal adenocarcinoma and squamous cell carcinoma and diffuse and intestinal gastric cancer as well as patients with cancer of the gastroesophageal junction comparable for this study aim.

The primary aim of this study was to summarize the applied definitions of de-novo oligometastatic esophagogastric cancer in literature and ongoing studies. To this end, as OMEC study group, we performed a systematic review of studies and study protocols reporting on a definition of oligometastatic esophagogastric

cancer or on patients undergoing local treatment for oligometastatic esophagogastric cancer. The secondary aim was to compare local treatment with systemic therapy alone for oligometastatic esophagogastric cancer by performing a meta-analysis of reported hazard ratios (HRs) for OS.

2. Material and methods

This study was prospectively registered in the online PROSPERO database for systematic reviews with registration number CRD42020205306. Reporting is performed in accordance with the PRISMA guidelines (Supplementary File A) [9].

2.1. Search strategy

A systematic search was performed and last updated April 1, 2021 in Medline (via Pubmed), Embase, and ClinicalTrials.gov with the keywords "esophageal cancer" or "gastric cancer" and "oligometastasis" or "SBRT" or "metastasectomy" (and synonyms). Studies or study protocols published after January 1, 2010, that report on a definition of oligometastatic esophagogastric cancer or the local treatment for oligometastatic esophagogastric cancer were identified (Supplementary File B). OMD could be located in a distant organ or the extra-regional lymph nodes (according to the AJCC/UICC 8th edition) [10].

2.2. Study selection

After removing duplicates, 2 authors (PR and TK) independently screened titles and abstracts for eligibility. Studies or study protocols reporting a definition or local treatment of "de-novo OMD" in patients with esophagogastric cancer of adenocarcinoma or squamous cell carcinoma histology were eligible for inclusion. Studies or study protocols reporting on < 7 included patients, "repeat OMD" or "induced OMD", regional lymph node metastasis, hyperthermic intraperitoneal chemotherapy (HIPEC), or conversion surgery were not included. Studies performing local treatment for metastases of esophagogastric cancer without reporting on a definition of OMD (i.e. maximum number of organs and metastases) were excluded. Any disagreements were resolved by consensus. Finally, the references of included articles were screened for other potentially relevant articles by cross-referencing. The inter-rater reliability was not assessed.

2.3. Data extraction

From the selected studies, data were extracted on first author, year of publication, country of origin, inclusion years, type of study (i.e. retrospective or prospective, single- or multi-center), location, and histology of the primary tumor, number of patients treated with local treatment or systemic therapy, the timing of detection of OMD (i.e. synchronous versus metachronous), the maximum number of organs and metastases considered OMD, and the modality of imaging for detecting OMD (i.e. computed tomography [CT], ^{18}F-fluorodeoxyglucose positron emission tomography [^{18}F-FDG PET], or magnetic resonance imaging [MRI]). The disease-free interval was extracted from studies on metachronous OMD (i.e. time interval between definitive treatment of the primary tumor and detection of OMD). Finally, survival outcomes in terms of median OS, 1-year and 5-year OS rates, and the HR comparing OS after local treatment with systemic therapy alone for oligometastatic esophagogastric cancer were retrieved.

2.4. Outcomes

The primary outcome was the maximum number of organs and metastases considered OMD and the maximum number of mestases per specific organ (i.e. 'organ-specific' OMD burden). In addition, liver oligometastases were further categorized according to unilobar or bilobar involvement, lung and adrenal gland oligometastases according to unilateral or bilateral involvement, and extra-regional lymph node oligometastases according to the number of affected lymph node regions (i.e. cervical, thoracic or abdominal/retroperitoneal extra-regional lymph nodes) and the number of extra-regional lymph node stations (according to the AJCC/UICC 8th edition) [11]. The secondary outcome measure was the pooled adjusted hazard ratio (aHR) comparing OS after local treatment to OS after systemic therapy alone for oligometastatic esophagogastric cancer.

2.5. Quality assessment

Quality assessment of comparative studies eligible for inclusion in the quantitative synthesis (meta-analysis) was assessed by 2 authors using the ROBINS tool [12]. "Confounding" was considered a serious risk of bias if studies did not measure or control for important baseline confounders such as performance status and number and distribution of metastases. 'Selection bias' was considered at serious risk if studies selected patients retrospectively without a pre-specified study protocol. "Classification of intervention bias" was considered at serious risk if studies did not clearly define treatment in both groups. "Assignment to intervention bias" was considered at serious risk if studies reported substantial deviations from the intervention and this was not controlled for. "Missing data bias" was considered at serious risk if $> 10\%$ of subjects had missing data. Publication bias was checked by visual assessment of funnel plots.

2.6. Statistical analysis

The agreement between studies was scored to be either absent/poor (< 50%), fair (50%–75%), or consensus (≥75%) [3,13]. According to a recent systemic review, the most common definition for consensus was percent agreement, with 75% being the median threshold to define consensus [14]. From each study, the median OS, 1-year and 5-year OS rates after local treatment for OMD and systemic therapy alone was extracted as well as the adjusted and unadjusted HRs of OS with 95% confidence intervals (CIs) comparing local treatment for OMD with systemic therapy alone.

For meta-analysis of the data, a funnel and forest plot of the adjusted and unadjusted HRs for OS were made. A random-effects model was used to pool the data. Subgroup analyses were only performed in case 3 or more studies were available in each subgroup. Heterogeneity was assessed with the I^2 test. Substantial and considerable heterogeneity were defined as $I^2 \geq 50\%$ and $I^2 \geq 75\%$, respectively [14,15]. A p-value < 0.05 was considered statistically significant. R version 4.1.1 with "Rcurl","metaphor", and "meta" packages were used for statistical analysis.

3. Results

3.1. Study selection

After the removal of duplicates, 7,782 articles were screened on title and abstract for eligibility. Subsequently, the full-text of 236 potentially relevant articles were assessed, of which 72 studies were excluded because no definition of OMD was reported, 47 liver-related studies because no definition of liver oligometastasis was reported, 16 studies because of complete overlap in study population with another (larger) included study, 3 lung-related studies because no definition of lung oligometastasis was reported and 1 lymph node-related study because no definition of extra-regional lymph node oligometastasis was reported. Consequently, 97 studies or study protocols were included in this systemic review, of which 15 studies were included in the meta-analysis (Fig. 1).

3.2. Oligometastatic esophagogastric cancer

A definition of oligometastatic esophagogastric cancer was provided by 21 studies [7,8,15–33] and 7 study protocols [35–41]. The studies were predominantly retrospective (95%) and included a total of 1,439 patients. The median disease-free interval for patients with metachronous OMD was 13 months (interquartile range [IQR] 10–19). Most patients were diagnosed with esophageal cancer (82%) with squamous cell carcinoma histology (53%) and underwent metastasectomy (69%) for metachronous OMD (51%). In addition, 7 study protocols which include patients with synchronous gastric cancer [38–41], synchronous or metachronous esophageal cancer [37], or synchronous esophagogastric cancer [35,36] were included. The imaging modality for detecting OMD was specified by 23 out of 28 studies or study protocols and was CT (100%), and/or PET (35%) and/or MRI (26%, Table 1).

The maximum number of involved organs considered OMD was specified by 26 out of 28 studies or study protocols. Solitary organ involvement was considered OMD by 26 out of 26 (100%, consensus), of which 10 (38%) allowed 1 additional involved organ. Also, 4 studies or study protocols (15%) allowed limited extra-regional lymph node metastases in addition to solitary organ involvement [5,20,38,40]. The maximum number of metastases considered OMD was specified by 17 out of 28 studies or study protocols. A total of ≤ 3 metastases were considered OMD by 17 out of 17 (100%, consensus), of which 11 also allowed ≤ 4 metastases (65%, fair agreement). In 5 studies or study protocols [5,38–41], the maximum number of metastases to be considered OMD depended on the specific organ affected, and these studies or study protocols were included in the 'organ-specific' definition of OMD (Table 2). Fig. 2 shows a summary of definitions of oligometastatic esophagogastric cancer according to literature and study protocols.

3.3. Liver oligometastasis

A definition of liver oligometastasis from esophagogastric cancer was provided by 39 studies [8,31,41–77] and 4 study protocols [38–41]. The studies were predominantly retrospective (97%) and included a total of 1,383 patients. The median disease-free interval for metachronous OMD was 12 months (IQR 10–12). Most patients were diagnosed with gastric cancer (97%) with adenocarcinoma histology (97%) and underwent surgery or radiofrequency ablation (99%) for synchronous (65%) liver oligometastasis. In addition, 4 study protocols which all include patients with synchronous gastric cancer [38–41] were included. The imaging modality for detecting liver oligometastasis was specified by 28 out of 43 studies or study protocols and was predominantly CT (86%) and/or MRI (61%, Supplementary File C1).

The maximum number of liver lobes was specified by 26 out of 43 studies or study protocols. Liver oligometastasis could be present in both liver lobes (i.e. bilobar) according to 23 out of 26 (88%, consensus). The maximum number of liver metastases was specified by 32 out of 43 studies or study protocols. A total of ≤ 3 metastases were considered OMD by 25 out of 32 (78%, consensus; Supplementary File C2).

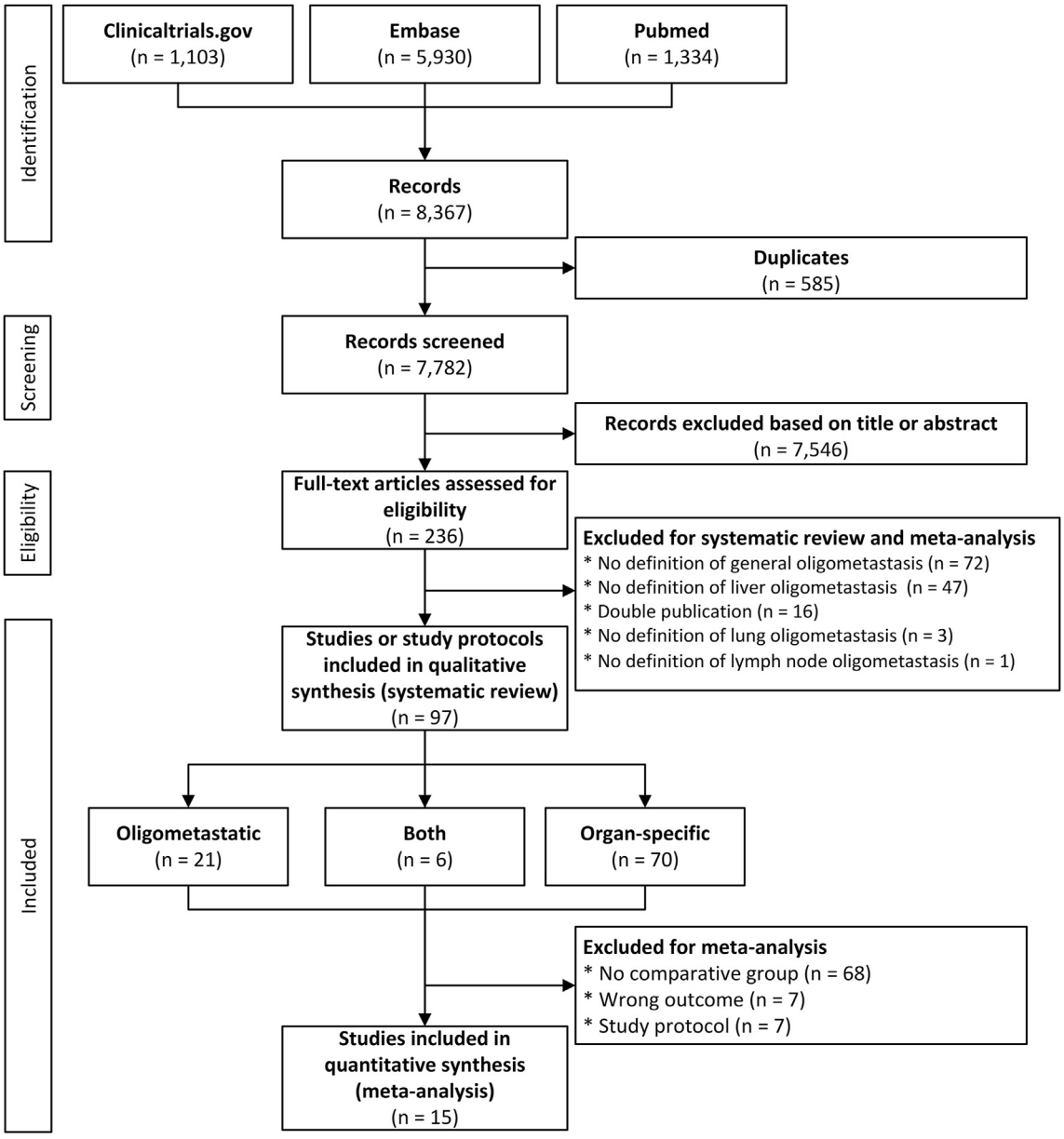

Fig. 1. Flowchart of study selection.

3.4. Lung oligometastasis

A definition of lung oligometastasis from esophagogastric cancer was provided by 22 studies [8,31,76,78–97] and 1 study protocol [38]. The studies were predominantly retrospective (95%) and included a total of 444 patients. The median disease-free interval for metachronous OMD was 17 months (IQR 15–25). Most patients were diagnosed with esophageal cancer (74%) with squamous cell carcinoma histology (72%), and all underwent surgery or radiofrequency ablation (100%) for predominantly metachronous (87%) lung oligometastasis. In addition, 1 study protocol which includes patients with synchronous gastric cancer was included [38]. The imaging modality for detecting lung oligometastasis was specified by 15 out of 23 studies or study protocols and was predominantly CT (80%, Supplementary File D1).

Unilateral or bilateral lung involvement was specified by 16 out of 23 studies or study protocols. Unilateral lung metastasis was considered OMD according to 16 out of 16 (100%, fair agreement), of which 7 (44%) also allowed bilateral involvement. The maximum number of lung metastases was specified by 18 out of 23 studies or study protocols. A total of $\leq$ 2 metastases were considered OMD by 14 out of 18 (78%, consensus), of which 12 also allowed $\leq$ 3 metastases (66%, fair agreement; Supplementary File D2).

Table 1
Study characteristics of oligometastatic esophagogastric cancer.

Study, year or clinicaltrial.gov ID	Country	Inclusion			Included patients/ estimated enrolment	Treatment	Primary tumor				Histology				Type of oligometastasis				Median DFI (months)	Imaging modality
		Type	Center	Period			Esophagus		Gastric		AC (%)		SCC (%)		Synchronous		Metachronous			
							(n =)	(%)	(n =)	(%)	(n =)	(%)	(n =)	(%)	(n =)	(%)	(n =)	(%)		
Nobel, 2021	USA	RNR	Single	1995–2016	104	M/SBRT	104	100%	0	0%	94	90%	10	10%	0	0%	104	100%	8.8	CT
Li, 2021	China	RNR	Single	2009–2018	55	SBRT	55	100%	0	0%	4	7%	51	93%	0	0%	55	100%	ns	ns
Ohkura, 2020	Japan	RNR	Multi	2011–2017	119	M	119	100%	0	0%	ns	ns	ns	ns	0	0%	119	100%	13.2	CT
Li, 2020	China	RNR	Single	ns	163	M/SBRT	163	100%	0	0%	0	0%	163	100%	163	100%	0	0%	ns	ns[a]
Yamashita, 2020	Japan	RNR	Single	2012–2017	18	SBRT	18	100%	0	0%	ns	ns	ns	ns	0	0%	18	100%	ns	PET or CT
Hilal 2020	USA	RNR	Single	2008–2018	197	SBRT	197	100%	0	0%	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Morinaga, 2020	Japan	RNR	Single	2005–2019	43	M/SBRT	43	100%	0	0%	0	0%	43	100%	0	0%	43	100%	12.6	PET/CT or CT
Liu, 2020	China	II NR	Single	2015–2018	34	SBRT	34	100%	0	0%	0	0%	34	100%	0	0%	34	100%	ns	PET or CT
Omari, 2019	Poland	RNR	Single	2010–2016	12	B	0	0%	12	100%	12	100%	0	0%	4	33%	8	67%	ns	MRI or CT
Chen, 2019	China	RNR	Multi	2012–2015	196	SBRT	196	100%	0	0%	6	3%	190	97%	ns	ns	ns	ns	ns	CT
Iwatsuki, 2019	USA	RNR	Multi	2002–2016	85	ns	85	100%	0	0%	85	100%	0	0%	85	100%	0	0%	NA	ns
Depypere, 2018	Belgium	RNR	Single	2002–2015	10	M	10	100%	0	0%	8	80%	2	20%	10	100%	0	0%	NA	PET/CT
Carmona-Bayonas, 2018	Spain	RNR	Multi	2008–2017	92	M	12	13%	80	87%	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns
Hamai, 2018	Japan	RNR	Single	1990–2013	13	M	13	100%	0	0%	0	0%	13	100%	0	0%	13	100%	9.1	(PET)CT
Ghaly, 2018	USA	RNR	Multi	1988–2015	26	M/SBRT	26	100%	0	0%	ns	ns	ns	ns	0	0%	26	100%	19	CT
Depypere, 2017	Belgium	RNR	Single	1990–2012	25	M/SBRT	25	100%	0	0%	ns	ns	ns	ns	0	0%	25	100%	9.9	PET/CT or CT
Al-Batran, 2017	Germany	II NR	Multi	2009–2010	36	M	0	0%	36	100%	36	100%	0	0%	36	100%	0	0%	NA	CT or MRI
Schmidt, 2015	Germany	RNR	Single	2002–2012	123	M	70	57%	53	43%	123	100%	0	0%	123	100%	0	0%	NA	CT
Xu, 2014	China	RNR	Single	2008–2011	19	SBRT	0	0%	19	100%	19	100%	0	0%	0	0%	19	100%	ns	CT
Port, 2012	USA	RNR	Single	1988–2011	27	M/SBRT	27	100%		0%	21	78%	6	22%	0	0%	27	100%	26	CT
Kim, 2011	Korea	RNR	Single	2003–2008	42	M	0	0%	42	100%	42	100%	0	0%	42	100%	0	0%	NA	CT
Pooled (%)					1,439		1,197	83%	242	17%	450	47%	512	53%	463	49%	491	51%	12.6	
NCT04510064*	China	II NR	Multi	2021–2022	40	M	0	0%	40	100%	40	100%	0	0%	40	100%	0	0%	NA	CT or MRI
NCT04248452*	USA	III R	Multi	2020–2023	314	SBRT	ns	ns	ns	ns	314	100%	0	0%	314	100%	0	0%	NA	CT or MRI
NCT04263870*	China	II NR	Single	2020–2021	36	M	0	0%	36	100%	36	100%	0	0%	36	100%	0	0%	NA	CT or MRI
NCT03904927*	China	II NR	Single	2019–2022	102	SBRT	102	100%	0	0%	0	0%	102	100%	0	0%	102	100%		CT
NCT03161522*	USA	II R	Single	2018–2023	100	M	ns	ns	ns	ns	100	100%	0	0%	100	100%	0	0%	NA	PET/CT
NCT03399253*	China	III R	Single	2017–2022	120	M	0	0%	120	100%	120	100%	0	0%	120	100%	0	0%	NA	CT
NCT02578368*	Germany	III R	Multi	2016–2021	271	M	0	0%	271	100%	271	100%	0	0%	271	100%	0	0%	NA	CT/MRI or PET
Pooled (%)					983		102	17%	467	83%	881	90%	102	10%	881	90%	102	10%	NA	

* = Ongoing trial; RNR = Retrospective non-randomized trial; II NR = Phase II non-randomized trial; II R = Phase II randomized trial; III R = Phase III randomized trial; B = Brachytherapy; SBRT = Stereotactic body radiation therapy; M = Metastasectomy; AC = Adenocarcinoma; SCC = Squamous cell carcinoma; ns = Not specified; NA = Not applicable; DFI = Disease-free interval

[a] CT, MRI, PET/CT, bone scan.

Table 2
A definition of oligometastatic esophagogastric cancer.

	Study, year or clinicaltrials.gov ID	Definition		Patients							
		Organ	Lesions	Organ				Lesions			
		Maximum	Maximum	Solitary		Multiple		Solitary		Multiple	
Studies	Nobel, 2021	1	5	98	100%	0	0%	51	52%	47	48%
	Li, 2021	2	5	50	91%	5	9%	31	56%	24	44%
	Ohkura, 2020	1	5	119	100%	0	0%	Ns	ns	ns	ns
	Li, 2020	3	5	ns	ns	ns	ns	Ns	ns	ns	ns
	Hilal, 2020	1 + LN	5	ns	ns	ns	ns	Ns	ns	ns	ns
	Yamashita, 2020	1	3	18	100%	0	0%	ns	ns	ns	ns
	Morinaga, 2020	1	5	ns	ns	ns	ns	ns	ns	ns	ns
	Omari, 2019	2	5	11	92%	1	8%	ns	ns	ns	ns
	Chen, 2019	ns	3	ns	ns	ns	ns	225	49%	236	51%
	Liu, 2019	2	3	32	94%	2	6%	28	82%	6	18%
	Iwatsuki, 2019	1	4	85	100%	0	0%	ns	ns	ns	ns
	Depypere, 2018	1	4	10	100%	0	0%	ns	ns	ns	ns
	Carmona − Bayonas, 2018	2	4	54	59%	38	41%	ns	ns	ns	ns
	Hamai, 2018	1	ns	13	100%	0	0%	ns	ns	ns	ns
	Ghaly, 2018	1	ns	26	100%	0	0%	ns	ns	ns	ns
	Depypere, 2017	1 + RPLN	ns	25	100%	0	0%	ns	ns	ns	ns
	Al − Batran, 2017	1	Organ-specific	36	100%	0	0%	ns	ns	ns	ns
	Schmidt, 2015	2	ns	102	83%	21	17%	ns	ns	ns	ns
	Xu, 2014	2	3	14	74%	5	26%	8	42%	11	58%
	Port, 2012	1	ns	27	100%	0	0%	ns	ns	ns	ns
	Kim, 2011	2	ns	33	79%	9	21%	ns	ns	ns	ns
	Pooled	1	3	753	92%	81	8%	343	56%	324	44%
	NCT04510064*	1	Organ-specific	na	na	na	na	na	na	na	na
	NCT04248452*	ns	3	na	na	na	na	na	na	na	na
	NCT04263870*	1 + RPLN	Organ-specific	na	na	na	na	na	na	na	na
	NCT03904927*	2	4	na	na	na	na	na	na	na	na
	NCT03161522*	1	3	na	na	na	na	na	na	na	na
	NCT03399253*	2	Organ-specific	na	na	na	na	na	na	na	na
	NCT02578368*	1 + RPLN	Organ-specific	na	na	na	na	na	na	na	na

* = Ongoing trial; LN = Limited extra-regional lymph node involved in addition to organ metastasis; RPLN = Limited retroperitoneal lymph node involvement in addition to organ metastasis; ns = Not specified; NA = Not applicable

3.5. Extra-regional lymph node oligometastasis

A definition of extra-regional lymph node oligometastasis from esophagogastric cancer was provided by 6 studies [5,98–102] and 7 study protocols [35–41]. The studies were mainly retrospective (83%) and included a total of 217 patients. The median disease-free interval for metachronous OMD was 12 months (IQR 11–13). Most patients were diagnosed with gastric cancer (59%) with adenocarcinoma histology (70%) and underwent surgery (56%) for synchronous (56%) extra-regional lymph node oligometastasis. In addition, 6 study protocols which include patients with synchronous gastric cancer [38–41], synchronous or metachronous esophageal cancer [37], or synchronous esophagogastric cancer [35,36] were included. The imaging modality for detecting extra-regional lymph node oligometastasis was specified by 11 out of 12 studies or study protocols and was predominantly CT (73%, Supplementary File E1).

The number of extra-regional lymph node regions was specified by 12 out of 12 studies or study protocols. A solitary extra-regional lymph node region with metastases (e.g., cervical, thoracic or retroperitoneal/abdominal extra-regional lymph node) was considered OMD according to 12 out of 12 (100%, consensus), of which 7 allowed 1 additional extra-regional lymph node region (58%, fair agreement). The maximum number of AJCC/UICC lymph node stations was specified by 5 of 12 studies or study protocols. A total of 1 AJCC/UICC extra-regional lymph node station with metastases was considered OMD according to 5 out of 5 (100%, consensus), of which 3 also allowed $\leq$ 3 AJCC/UICC extra-regional lymph node stations (60%, fair agreement; Supplementary File E2).

3.6. Brain oligometastasis

A definition of brain oligometastasis from esophagogastric cancer was provided by 7 studies [103–109]. All studies were retrospective and included a total of 82 patients. The median disease-free interval for metachronous OMD was 8 months (IQR 7–11). Most patients were diagnosed with esophageal cancer (73%) with adenocarcinoma histology (72%) and underwent radiosurgery (82%) for metachronous (88%) brain oligometastasis. The imaging modality for detecting brain oligometastasis was specified by 5 out of 7 studies or study protocols and was predominantly MRI (100%) and/or CT (75%, supplementary File F1). The maximum number of

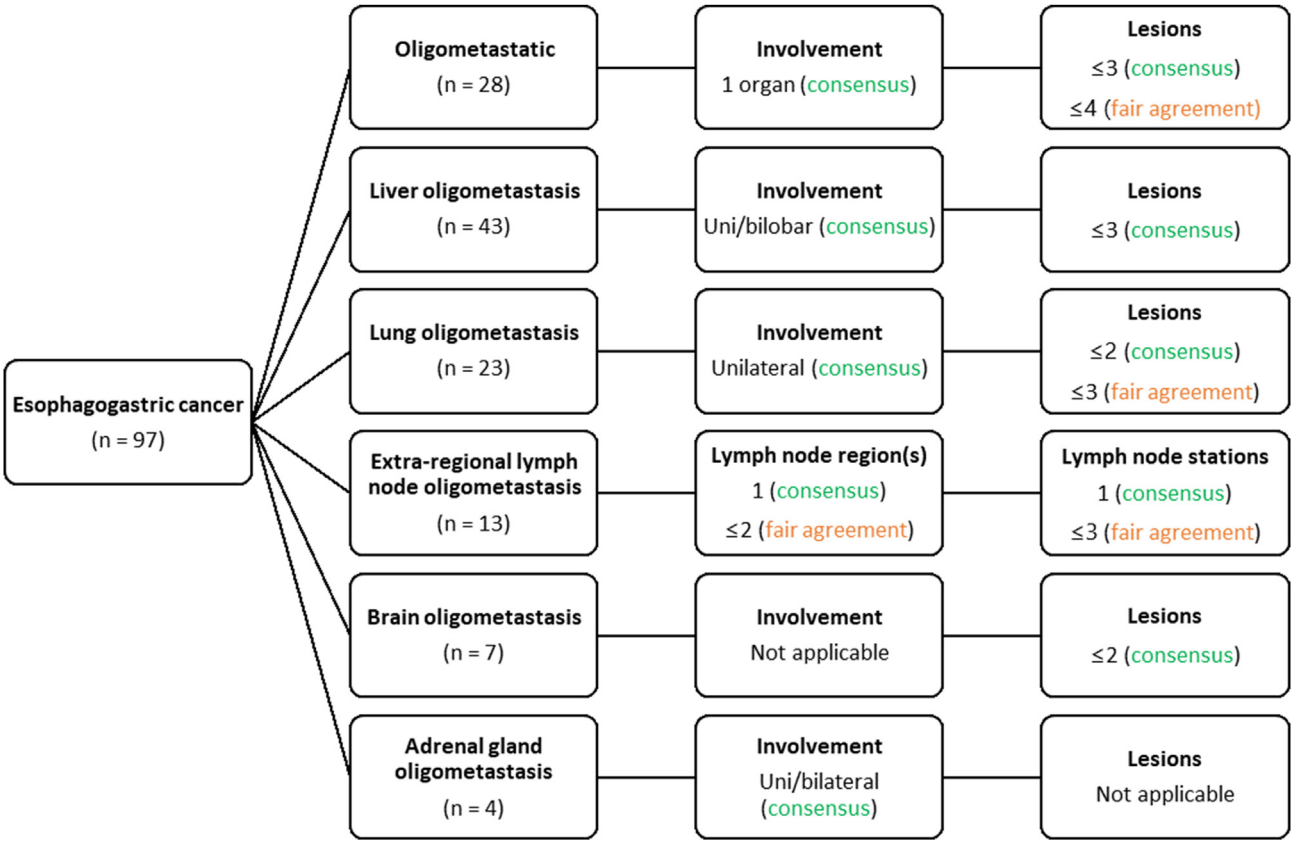

Fig. 2. Summary of definition of oligometastatic esophagogastric cancer according to literature and study protocols.

brain metastases was specified by 7 of 7 studies. A total of ≤ 2 metastases were considered OMD according to 6 out of 7 (86%, consensus; Supplementary File F2).

3.7. Adrenal gland oligometastasis

A definition of adrenal gland oligometastasis was provided by 1 retrospective study [110], 1 prospective non-randomized study [5], and 2 study protocols [5,40]. Studies included a total of 6 patients. The median disease-free interval for metachronous OMD was 11 months (range 8–15). Most patients were diagnosed with esophageal cancer (83%), and all patients underwent surgery for predominantly metachronous (80%) unilateral (100%) adrenal gland oligometastasis. The imaging modality for detecting adrenal gland oligometastasis was specified by 4 out of 4 studies or study protocols and was predominantly CT (100%) or MRI (75%, Supplementary File G1). The unilateral or bilateral involvement was specified by 4 of 4 studies or study protocols. Adrenal gland oligometastasis could be present in both adrenal glands (bilateral) according to 3 out of 4 studies or study protocols (75%, consensus; Supplementary File G2).

3.8. Other sites of oligometastasis

Studies providing a definition of bone, soft tissue, or other oligometastatic sites were not identified.

3.9. OS after local treatment for oligometastasis

The median OS after local treatment for OMD was specified by 16 studies including 740 patients in total. The median OS was 25 months (IQR 21–27), and the median 1-year and 5-year OS rates were 75% and 44%, respectively. The median OS after local treatment for different organ-specific oligometastases are presented in Table 3. In addition, the median OS and 1-year and 5-year OS rates after systemic therapy alone for OMD are presented in Table 3.

3.10. Meta-analysis comparing OS

A total of 16 non-randomized studies [5,18,34,43,45,50,19,21,22,25,27–29,32] compared OS after local treatment to systemic therapy alone for oligometastatic esophagogastric cancer. The overall risk of bias was considered serious. Studies were generally considered at serious risk for confounding bias because of the non-randomized study design and because studies did not adjust for potentially important confounding domains such as performance status [111] or HER2neu [112] and microsatellite instability (MSI) status [113] (Supplementary File H).

Local treatment was associated with improved OS as compared with systemic therapy alone for OMD based

Table 3
Outcomes after local and/or systemic treatment for oligometastatic esophagogastric cancer.

Location		Oligometastatic disease	Liver only	Lung only	Extra-regional lymph node only	Brain only	Adrenal gland only
Local treatment for OMD with or without systemic therapy	Median OS in months [IQR]	25 [21–27]	24 [15–36]	29 [21–41]	19 [13–20]	16 [8–23]	16 [15–40]
	Median 1-year OS rate (%)	75%	76%	80%	52%	80%	80%
	Median 5-year OS rate (%)	44%	27%	42%	25%	20%	20%
Systemic therapy alone for OMD	Median OS in months [IQR]	11.0	7.6	10.0	ns	1.8	ns
	Median 1-year OS rate (%)	63%	30%	40%	ns	ns	ns
	Median 5-year OS rate (%)	2	4%	0%	ns	ns	ns
HR for OS comparing local treatment with systemic therapy for OMD	Unadjusted HR (95% CI)	0.36 (0.22–0.58)	0.33 (0.24–0.46)	na	na	na	na
	Adjusted HR (95% CI)	0.47 (0.30–0.74)	0.39 (0.22–0.69)	na	na	na	na
Number of patients		1,439	1,383	444	217	82	6

OMD = Oligometastatic disease; OS = Overall survival; IQR = Interquartile range; ns = Not specified; NA = Not applicable; CI = Confidence interval, HR = Hazard ratio.

on 8 studies without multivariable adjustment (pooled HR for OS 0.36, 95% CI: 0.22−0.58) and 6 studies with multivariable adjustment (pooled aHR for OS 0.47, 95% CI: 0.30−0.74). There was considerable heterogeneity among these studies (I^2 = 84% and I^2 = 75%, respectively). In addition, local treatment was associated with improved OS as compared with systemic therapy alone for liver oligometastasis based on 4 studies without multivariable adjustment (pooled HR for OS 0.33, 95% CI: 0.24−0.46) and 5 studies with multivariable adjustment (pooled aHR for OS 0.39, 95% CI: 0.22−0.69). There was no substantial heterogeneity among these studies (I^2 = 0% and I^2 = 56%, respectively). No comparative studies were identified for other sites of OMD from esophagogastric cancer. The forest plots of HRs for OS with and without multivariable adjustment are presented in Fig. 3. In addition, the funnel plots of unadjusted and adjusted HRs for OS after local metastasis-directed treatment versus systemic therapy alone for OMD are presented in Supplementary Files I and J. Both funnel plots reveal an asymmetrical appearance with a gap in the right corner, suggesting that studies with HRs closer to 1 (indicating less or no benefit of local metastasis-directed treatment) more often remained unpublished. This points to a certain extent of publication bias with a tendency towards overestimating the effect of local metastasis-directed treatment in the current meta-analysis.

4. Discussion

The primary aim of this systemic review and meta-analysis was to identify applied definitions of oligometastatic esophagogastric cancer from the available literature and compare local treatment versus systemic therapy alone for oligometastatic esophagogastric cancer. In literature, consensus (i.e. $\geq$ 75% agreement) among 28 available studies and study protocols was observed on considering 1 organ with $\leq$ 3 metastases or 1 extra-regional lymph node station with metastases as OMD . Moreover, fair agreement (i.e. 50%−75% agreement) was observed on considering 1 organ with $\leq$ 4 metastases or $\leq$ 2 extra-regional lymph node stations with metastases as OMD. Furthermore, local treatment for oligometastatic esophagogastric cancer appeared associated with improved OS compared with systemic therapy alone, but the included non-randomized studies generally did not adjust for or report on potentially important confounding domains such as performance status [111], HER2neu [112] or MSI status [113]. Therefore, prospective randomized trials are warranted.

A universal consensus definition of OMD in esophagogastric cancer could aid in the standardization of inclusion criteria in future clinical trials and prospective data collection. In addition, such a definition could guide the treatment decision-making process in

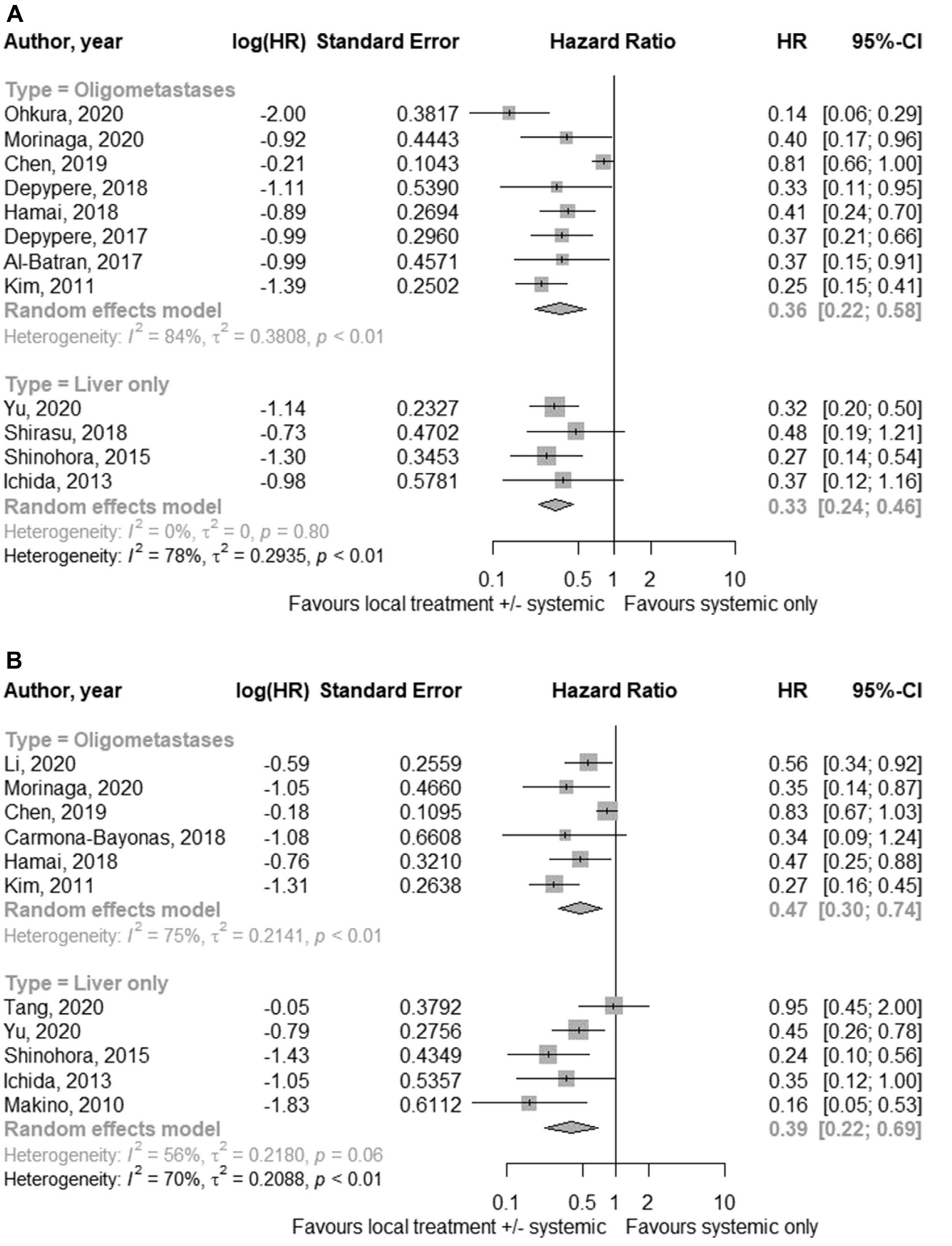

Fig. 3. (A)Forest plot of reported unadjusted hazard ratios for overall survival after local metastasis-directed treatment versus systemic therapy alone in oligometastatic esophagogastric cancer. (B) Forest plot of reported adjusted hazard ratios for overall survival after local metastasis-directed treatment versus systemic therapy alone in oligometastatic esophagogastric cancer.

multidisciplinary tumor board meetings. The current review is the first step in our joint aim within the OligoMetastatic Esophagogastric Cancer (OMEC) consortium to achieve consensus on the definition of oligometastatic esophagogastric cancer (www.OMEC-project.eu). OMEC is a consortium of 50 cancer expert centers in Europe and aims to develop a multidisciplinary European consensus statement for oligometastatic esophagogastric cancer. OMEC has been endorsed by ESDE, ESMO, ESSO, EORTC, ESTRO, IGCA, and DUCG. Subsequent steps of the OMEC-project include real-life clinical case discussions by multidisciplinary teams of esophagogastric cancer experts centers in Europe asking for multidisciplinary team responses on definition and treatment (OMEC-2) [114], Delphi consensus rounds among upper gastrointestinal experts to establish consensus about the definition and treatment of oligometastatic esophagogastric cancer (OMEC-3) and the publication of a consensus statement on this topic (OMEC-4). This consensus statement will result in a prospective study for oligometastatic esophagogastric cancer (OMEC-5).

The definition of oligometastatic esophagogastric cancer identified in the current literature (1 organ with $\leq$ 3 metastases or 1 extra-regional lymph node station with metastasis) was more restrictive than the definition of oligometastatic NSCLC ($\leq$ 3 organs with $\leq$ 5 metastases) [115]. This difference might be explained by the more aggressive tumor biology and lower OS of oligometastatic esophagogastric cancer as compared with oligometastatic NSCLC (i.e. median OS of 25 months versus 41 months) [116].

The observed favorable OS after local treatment for oligometastatic esophagogastric cancer and the apparent survival benefit for local treatment as compared with systemic therapy alone in the current meta-analysis represents supportive evidence for an OMD state in esophagogastric cancer. However, these results could be confounded by publication bias or the response to systemic therapy since patients who respond to systemic therapy are offered subsequent local treatment for OMD and these responders already have an improved OS, irrespective of local treatment for oligometastasis [111]. Therefore, RCTs are warranted to confirm the benefit of local treatment for OMD over systemic therapy alone. Currently, the Renaissance trial by Al-Batran *et al.* addresses the benefit of surgical resection of the primary tumor and metastases plus systemic therapy over systemic therapy alone in patients with gastric or gastroesophageal junction cancer with synchronous OMD [38]. After 4 cycles of FLOT chemotherapy, patients without progression will be randomized to either surgical resection of the primary tumor and metastases plus continuation of systemic therapy or continuation of systemic therapy alone [38]. In addition, the ECOG trial by National Cancer Institute addresses the benefit of radiotherapy plus systemic therapy over systemic therapy alone in patients with esophageal or gastric cancer with metachronous OMD [35]. After 4 cycles of CapOx or FLOT chemotherapy, patients without progression will be randomized to either radiotherapy of metastases plus continuation of systemic therapy or continuation of systemic therapy alone [35]. Furthermore, the REGATTA trial has previously shown that systemic therapy plus local treatment for the primary tumor only (i.e. no local treatment for metastases) does not improve OS as compared with systemic therapy alone in patients with gastric cancer with one organ with metastases [117]. Therefore, future prospective studies for oligometastasis should always incorporate systemic therapy plus local treatment for primary tumor and metastases.

The studies included in this systematic review represent the currently best available evidence but have certain limitations that warrant consideration for the interpretation of results. First, all studies scored a serious risk of bias because of the retrospective study design or because studies did not measure or control for important baseline confounders such as performance status. Second, considerable heterogeneity in the HR for OS was identified, but this study could not determine the cause of this heterogeneity due to the limited number of studies. Third, no pooling of studies for other oligometastasis sites from esophagogastric cancer was possible. Fourth, the studies included in this systematic review mainly used CT as the imaging modality for detecting OMD. However, CT has a lower sensitivity for detecting distant metastasis than PET/CT, which might have overestimated the proportion of patients with OMD [118]. Fifth, there were not enough studies on SBRT only to evaluate the potential different impacts of local treatment strategies. Sixth, there were too few studies comparing outcomes after local treatment versus systemic therapy alone for OMD in patients with esophageal adenocarcinoma versus squamous cell carcinoma to differentiate the outcomes on histology. Seventh, both funnel plots pointed to a certain extent of publication bias with a tendency towards overestimating the effect of local metastasis-directed treatment in the current meta-analysis. Finally, the evidence on oligometastatic esophagogastric cancer could change over time as new (prospective) studies in this field become available, potentially requiring an update of this review in the (near) future. However, the current study is strengthened by the variety of studies and treatment modalities included. Prospective and retrospective, Asian and Western studies were included, and patients with either synchronous or metachronous oligometastatic esophageal or gastric cancer who were treated with metastasectomy or SBRT. Therefore, we believe this study has excellent multidisciplinary applicability and generalizability.

In conclusion, a consensus was found in the available literature (including predominantly retrospective studies) and ongoing trials that a disease burden of 1 extra-regional lymph node station or 1 organ with $\leq$ 3

metastases could be considered OMD in esophagogastric cancer. These findings will be confirmed or updated in subsequent steps of the OMEC project. An apparent survival benefit was observed for local treatment compared to systemic therapy alone for oligometastatic esophagogastric cancer in non-randomized studies, which supports the idea of an actual OMD state in esophagogastric cancer. As such, improvement in the definition and management of oligometastatic esophagogastric cancer is warranted in prospective randomized studies.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Van Cutsem reports personal fees from Advisory boards forArray, AstraZeneca, Bayer, Biocartis, Bristol-Myers-Squibb, Celgene, Daiichi, Halozyme, GSK, Pierre-Fabre, Incyte, Ipsen, Lilly, Merck Sharp & Dohme, Merck KGaA, Novartis, Pierre Fabre, Roche, Servier, Sirtex, Taiho and research grants from Amgen, Bayer, Boehringer Ingelheim,Bristol-Myers- Squibb, Celgene, Ipsen, Lilly, Merck Sharp & Dohme, Merck KGaA, Novartis, Roche, Servier paid to this institution outside the submitted work; Dr. van Laarhoven reports other from BMS, other from Lilly, other from MSD, other from Nordic Pharma, other from Servier, other from Bayer, outside the submitted work; Dr. Lordick reports personal fees from Astellas , personal fees from Astra Zeneca, grants and personal fees from BMS, personal fees from BioNTech, personal fees from Eli Lilly, personal fees from Elsevier, personal fees from MSD, personal fees from MedUpdate, personal fees from Medscape, personal fees from Roche, personal fees from Servier, personal fees from StreamedUp!, personal fees from Incyte, personal fees from Zymeworks, personal fees from Bayer, outside the submitted work; the remaining authors have declared no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.02.018.

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