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Original Article

Incidence and survival of patients with oligometastatic esophagogastric cancer: A multicenter cohort study

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ABSTRACT

Purpose/Objective: This multicenter study assessed the incidence and survival of patients with esophagogastric cancer and oligometastatic disease (OMD) in two tertiary referral cancer centers in The Netherlands and Switzerland.

Materials/Methods: Between 2010 and 2021, patients with metastatic esophagogastric cancer were identified. Patients with de-novo OMD were included (first-time diagnosis of ≤5 distant metastases on ^{18}F-FDG-PET/CT). Control of the primary tumor was considered in patients who underwent primary tumor resection or definitive chemoradiotherapy without locoregional recurrence. Treatment of OMD was categorized into (1) systemic therapy, (2) local treatment (stereotactic body radiotherapy or metastasectomy), (3) local plus systemic therapy, or (4) best supportive care. The primary outcomes were overall survival (OS) and independent prognostic factors for OS. Independent prognostic factors for OS were analyzed using multivariable Cox proportional hazard models.

Results: In total, 830 patients with metastatic esophagogastric cancer were identified of whom 200 patients with de-novo OMD were included (24%). The majority of included patients had esophageal cancer (73%) with adenocarcinoma histology (79%) and metachronous OMD (52%). The primary tumor was controlled in 68%. Treatment of OMD was systemic therapy (25%), local treatment (43%), local plus systemic therapy (13%), or best supportive care (18%). Median follow-up was 14 months (interquartile range: 7–27). Median OS was 16 months (95% CI: 13–21). Improved OS was independently associated with local plus systemic therapy compared with systemic therapy alone (hazard ratio [HR] 0.47, 95% confidence interval [CI]: 0.25–0.87). Worse OS was independently associated with squamous cell carcinoma (HR 1.70, 95% CI: 1.07–2.74), bone oligometastases (HR 2.44, 95% CI: 1.28–4.68), brain oligometastases (HR 1.98, 95% CI: 1.05–4.69), and two metastatic locations (HR 2.07, 95% CI: 1.04–4.12). Median OS after local plus systemic therapy was 35 months (95% CI: 22-NA) as compared with 13 months (95% CI: 9–21, $p < 0.001$) after systemic therapy alone for OMD.

Conclusion: Patients with metastatic esophagogastric cancer present in 25% with de-novo OMD. Local treatment of OMD plus systemic therapy was independently associated with long-term OS and independently improved OS when compared with systemic therapy alone. Randomized controlled trials are warranted to confirm these results.

Oligometastatic disease (OMD) implies that radical local treatment of OMD (e.g., stereotactic body radiotherapy [SBRT] or metastasectomy) could slow down disease progression and improve overall survival (OS) [1]. Indeed, recent randomized controlled trials (RCTs) have demonstrated that local treatment of OMD when compared with systemic therapy alone may improve OS for patients with non-small-cell-lung cancer (NSCLC) [2,3]. In addition, another RCT has shown that local treatment of OMD improves OS when compared with systemic therapy alone or observation in patients with colorectal, breast, prostate, or NSCLC [4].

Up until recently, a consistent definition of OMD did not exist. Therefore, these RCTs [2–4] included quite inhomogeneous patient

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cohorts with regards to the number of metastases, metastatic organs involved, and the disease trajectories. Recent advances in the characterization of OMD have been made by the European Society for Radiotherapy (ESTRO) and European Organisation for Research and Treatment of Cancer (EORTC) by developing a consensus classification and nomenclature of OMD [5]. In addition, ESTRO and the American Society for Radiotherapy (ASTRO) convened a committee to establish consensus guidelines regarding the definition of OMD [6]. Currently, de-novo OMD can be defined as the first-time diagnosis of ≤5 safely treatable metastases, without a previous history of polymetastatic disease, and with a controlled primary tumor regarded as optional [6].

For esophagogastric cancer, no consensus has been reached regarding the definition or treatment of OMD. Therefore, the Oligo-Metastatic Esophagogastric Cancer (OMEC) consortium has initiated the OMEC project to come to a uniform definition. In the OMEC 1 study, the reporting on definitions of oligometastatic esophagogastric cancer in the literature was assessed [7] and in the OMEC-2 study, the multidisciplinary tumor boards of 50 esophagogastric cancer expert centers were asked to judge several real-life cases on the definition and treatment of OMD [8]. These results will be used for input into Delphi consensus rounds (OMEC-3) in order to establish a multidisciplinary European consensus statement on the definition and treatment of oligometastatic esophagogastric cancer (OMEC-4). The lack of a definition might be explained by a lack of RCTs, although a few prospective non-randomized studies have suggested improved OS after local treatment of OMD [9,10]. However, because of the exclusion of OMD patients who underwent systemic therapy alone, these studies do not enable to compare different treatment strategies of OMD [9,10]. In addition, the incidence of de-novo OMD among patients with metastatic esophagogastric cancer remains unclear from both studies [9,10].

Therefore, the primary aims of this European multicenter study were to assess OS and identify independent prognostic factors for OS in patients with esophagogastric cancer and de-novo OMD. Secondary aims were to determine progression-free survival (PFS) and the incidence of de-novo OMD among patients with metastatic esophagogastric cancer.

Methods

Ethical statement

The institutional review boards of the UMC Utrecht and University Hospital Zurich approved this multicenter study and waived the need for informed consent. This study was performed in accordance with the World Medical Association International Code of Medical Ethics, the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, and the STROBE checklist. The completed STROBE checklist is provided in Supplementary File 1.

Patient inclusion

Between 2010 and 2021, consecutive patients diagnosed at the UMC Utrecht or University Hospital Zurich with metastatic esophagogastric cancer were eligible for inclusion in this European multicenter retrospective cohort study. Patients with synchronous or metachronous de-novo OMD were included. De-novo OMD was defined as the first-time diagnosis of ≤5 safely treatable distant metastases on ^{18}F-fluorodeoxyglucose positron emission tomography with integrated computed tomography (^{18}F-FDG-PET/CT) without a previous history of polymetastases (i.e. >5 distant metastases, peritoneal or pleural carcinomatosis) in accordance with recommendations by ESTRO, ASTRO, and EORTC[5,6].

Treatment of primary tumor and OMD

Control of the primary tumor was considered in patients who underwent primary tumor resection or definitive chemoradiotherapy without locoregional recurrence. Treatment of OMD was classified into (1) systemic therapy alone, (2) local treatment alone, (3) local plus systemic therapy (concomitant or sequential within 6 months between both treatments), or (4) best supportive care. Systemic therapy comprised immunotherapy, targeted therapy, chemotherapy, or combinations thereof. Local treatment was defined as SBRT, metastasectomy, radiofrequency ablation (RFA), or combinations thereof. Common SBRT schemes were ≥10 Gy per fraction with ≥1 fraction(s), ≥7Gy per fraction with ≥5 fractions, or ≥5 Gy per fraction with ≥10 fractions. Best supportive care could include no treatment of OMD or palliative (e.g., analgesic) radiotherapy only.

Staging

Patients with esophageal cancer underwent baseline staging with ^{18}F-FDG-PET/CT and patients with gastric cancer patients underwent baseline staging with CT and diagnostic laparoscopy in case of clinical advanced disease stage (i.e. ≥cT3 and/or cN+) [11–15]. Follow-up in The Netherlands was performed without standardized imaging and/or endoscopy protocol according to Dutch national guidelines [14,15]. Follow-up in Switzerland was done with standardized imaging and endoscopy protocol, consisting of contrast-enhanced ^{18}F-FDG-PET/CT or contrast-enhanced CT every 6 months during the first 3 years after primary tumor treatment and subsequently annually ^{18}F-FDG-PET/CT or CT as well as standard annually endoscopies. Clinical and pathological staging was according to TNM 8th edition [16]. Patients with periesophageal cervical lymph node metastases were not included because this was considered to be locoregional lymph node metastases (and not extra-regional lymph node metastases) according to TNM 8th edition [16].

OMD characteristics

The location of OMD was classified into an extra-regional lymph node station, liver, lung, bone, brain, other solitary organ (i.e. adrenal gland, soft tissue, or appendix), or 2 metastatic locations. The state of OMD was categorized into synchronous (i.e. OMD detected before completion of primary tumor treatment) or metachronous (i.e. OMD detected after completion of primary tumor treatment). The disease-free interval was defined as the time interval between the diagnosis of the primary tumor and OMD. The disease-free interval was categorized into 0, ≤6 months, or >6 months [17].

Outcomes

The primary outcomes of this study were OS and prognostic factors for OS. OS was defined as the time interval between the first-time diagnosis of de-novo OMD and death or last follow-up. Prognostic factors for OS were analyzed using multivariable Cox proportional hazard models and expressed with hazard ratios (HRs) with 95% confidence intervals (CIs). Secondary outcomes were PFS and the incidence of de-novo OMD among patients with metastatic esophagogastric cancer. PFS was defined as the time interval between the first-time diagnosis of de-novo OMD and disease progression, death, or last follow-up.

Statistical analyses

Categorical variables were described using frequencies with proportions and compared using Fisher's exact test. Parametric

data were described using mean with standard deviation (SD) and were compared using Student's T-test. Non-parametric data were described using median with interquartile range (IQR) and were compared using the Mann-Whitney U test. OS and PFS were determined using Kaplan-Meier curves. Prognostic factors included in the univariable and multivariable Cox proportional hazard model for OS were based on a systemic review on prognostic factors for OS in patients with metastatic esophagogastric cancer [18]. They included age, performance status, histology (adenocarcinoma or squamous cell carcinoma), number of OMD lesions, location of OMD lesions (extra-regional lymph node, lung, liver, bone, brain, other solitary organ [i.e. adrenal gland, soft tissue, or appendix], or 2 metastatic locations), OMD treatment (systemic therapy, local treatment, local plus systemic therapy, or best supportive care), OMD state (synchronous vs. metachronous), and primary tumor treatment (controlled vs. not controlled)[18]. Complete case analyses were performed. A two-sided p-value < 0.0 5 was considered statistically significant.

Results

Between 2010 and 2021, 1,607 patients with esophagogastric cancer were screened, of whom 830 patients with metastatic esophagogastric cancer were identified. A total of 205 patients with synchronous or metachronous de-novo OMD were eligible for inclusion. Thus, the incidence of de-novo OMD among patients with metastatic esophagogastric cancer was 24.7%. The incidence of de-novo OMD was 25.7% in the Netherlands and 23.1% in Switzerland, and was comparable between hospitals (p = 0.185). A total of five patients with de-novo OMD were lost to follow-up. Consequently, 200 patients were included. Fig. 1 shows the patient inclusion process.

Included patients had a median age of 65 years (IQR: 59–71), 76.5% were male, and 88.5% had a performance score of 0–1. Most patients were diagnosed with a poorly differentiated (49.5%) adenocarcinoma (79.0%) of the esophagus (73.0%). The predominant clinical disease stage was cT3 (63.5%) and cN1 (42.5%). The pathological disease stage was pT3 (50.0%) and pN0 (38.6%), among patients who underwent primary tumor resection. Her2Neu positivity of the primary tumor or oligometastases was found in 15.5% of patients. The majority of patients (52.0%) had metachronous OMD. The number of OMD lesions was 1 (52.5%), 2 (39.5%), 3 (9.5%), 4 (3.5%), or 5 (4.0%). The number of OMD locations was 1 (88.5%) or 2 (11.5%). Patient characteristics are presented in Table 1.

Most patients had only 1 organ or 1 extra-regional lymph node station involved (89%). The most common involved solitary organs were liver (n = 51), lung (n = 23), bone (n = 20), brain (n = 17), adrenal gland (n = 9), soft tissue (n = 9), or appendix (n = 2). The most common solitary extra-regional lymph node stations involved were retroperitoneal (n = 20), supraclavicular (n = 14), paraaortic (n = 11), or axilla (n = 1). Among patients with 2 locations with OMD involved (n = 23), most patients had 1 organ and 1 extra-regional lymph node station (n = 14) or 2 organs involved (n = 9).

The primary tumor was controlled in 66.5%, either after upfront primary tumor resection (9.5%), chemoradiotherapy (10.5%), or neoadjuvant treatment followed by resection (46.5%). In patients with metachronous OMD, the disease-free interval was 15 months (IQR: 10–24), and the median time interval between the completion of primary tumor treatment and OMD was 10 months (IQR: 5–19). In patients with metachronous OMD, 16.3% of patients had no controlled primary tumor because they did not want to proceed to surgery after neoadjuvant treatment or developed recurrence of the primary tumor. Supplementary File 2 lists the patient characteristics stratified by OMD state (metachronous versus synchronous).

Treatment of OMD was local treatment alone (43.5%), systemic therapy alone (25.0%), local plus systemic (13.5%), or best supportive care (18.0%). Local treatment of OMD consisted of patients

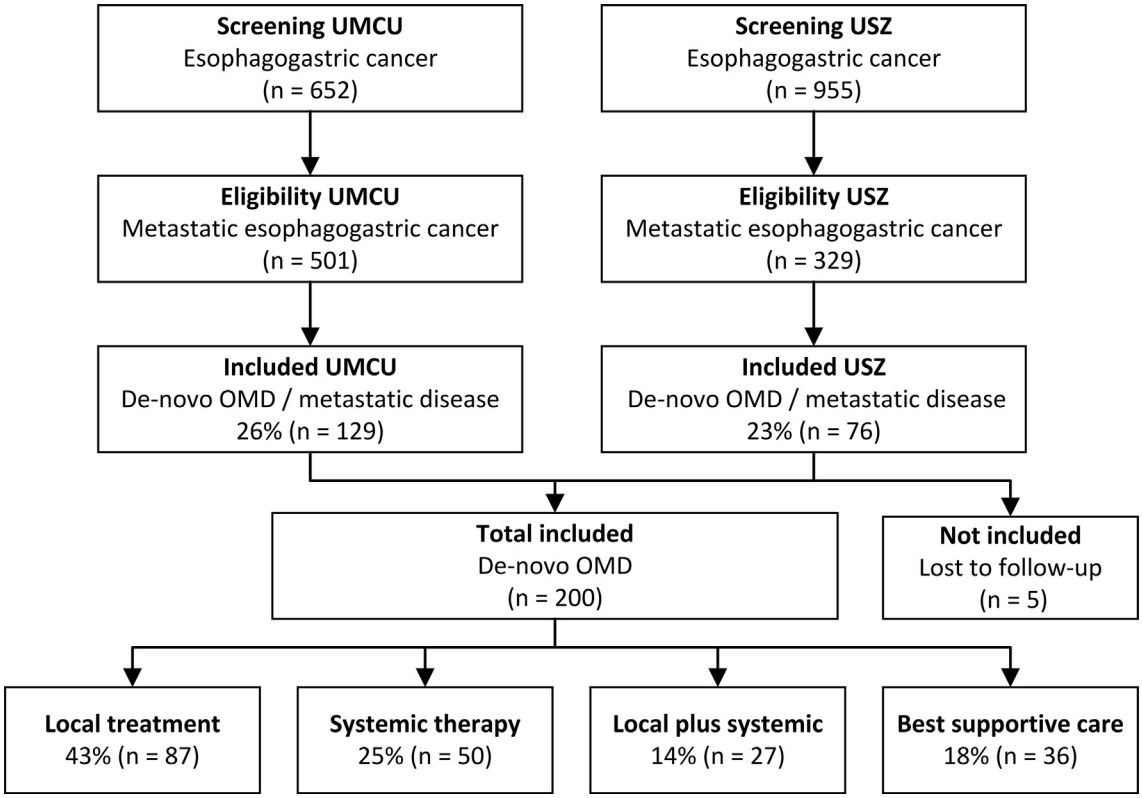

Fig. 1. Overview of patient inclusion.

Table 1
Patient characteristics.

		Overall (n = 200)
Median age [IQR]		65 [59–71]
Sex	Male	153 (76.5)
	Female	47 (23.5)
Performance score	WHO 0–1	177 (88.5)
	WHO >1	22 (11.0)
	Missing	1 (0.5)
Primary tumor location	Esophagus	146 (73.0)
	Cardia	32 (16.0)
	Stomach	22 (11.0)
Clinical tumor stage	cT1	13 (6.5)
	cT2	30 (15.0)
	cT3	127 (63.5)
	cT4	19 (9.5)
	Missing	11 (5.5)
Clinical nodal stage	cN0	53 (26.5)
	cN1	85 (42.5)
	cN2	36 (18.0)
	cN3	19 (9.5)
	Missing	7 (3.5)
Pathological tumor stage*	pT0	20 (15.2)
	pT1	18 (13.6)
	pT2	17 (12.9)
	pT3	66 (50.0)
	pT4	11 (8.3)
	Missing	1 (0.5)
Pathological nodal stage*	pN0	51 (38.6)
	pN1	41 (31.1)
	pN2	24 (18.2)
	pN3	15 (11.4)
Histology	AC	158 (79.0)
	SCC	42 (21.0)
Signet ring cell carcinoma		14 (7.0)
Her2Neu positivity		31 (15.5)
Differentiation grade	Well	16 (8.0)
	Moderate	33 (16.5)
	Poor	99 (49.5)
	Missing	52 (26.0)
Controlled primary tumor	Yes	136 (68.0)
	No	54 (32.0)
OMD state	Synchronous	96 (48.0)
	Metachronous	104 (52.0)
Number of OMD lesions	1	105 (52.5)
	2	61 (30.5)
	3	19 (9.5)
	4	7 (3.5)
	5	8 (4.0)
Number of OMD locations	1	177 (88.5)
	2	23 (11.5)

AC = adenocarcinoma; SCC = squamous cell carcinoma; * = among patients who had primary tumor resection; OMD = oligometastatic disease.

Table 2
Treatment characteristics.

Primary tumor treatment	n = 200	(%)
Controlled	133	66.5%
Upfront resection	19	9.5%
CRT	21	10.5%
Neoadjuvant treatment + resection	93	46.5%
Not controlled	64	32.0%
Treatment of OMD		
Systemic therapy alone	50	25.0%
CapOx	17	8.5%
FLOT	7	3.5%
EOX/ECC	6	3.0%
FOLFOX	4	2.0%
Other	2	1.0%
CapOx + Trastuzumab	7	3.5%
FLOT + Trastuzumab	3	1.5%
Other + Trastuzumab	4	2.0%
Local treatment alone	87	43.5%
SBRT	42	21.0%
Metastasectomy	33	16.5%
RFA	3	1.5%
Metastasectomy + SBRT	9	4.5%
Local plus systemic therapy	27	13.5%
SBRT plus systemic therapy	10	5.0%
Metastasectomy plus systemic therapy	10	5.0%
CRT	7	3.5%
Sequencing of systemic therapy in relation to local treatment		
Systemic therapy before local treatment	16	8.0%
Systemic therapy concomitant with local treatment	7	3.5%
Systemic therapy after local treatment	4	2.0%
Best supportive care	36	18.0%

CRT = chemoradiotherapy; CapOx = capecitabine and oxaliplatin; FLOT = docetaxel, oxaliplatin, leucovorin, and 5-fluorouracil; EOX/ECC = epirubicin, oxaliplatin/ cisplatin, and capecitabine; FOLFOX = leucovorin, fluorouracil, and oxaliplatin; SBRT = stereotactic body radiation therapy; RFA = radiofrequency ablation.

undergoing SBRT (21.0% of total), metastasectomy (16.5%), metastasectomy plus SBRT (4.5%), or RFA (1.5%). Systemic therapy alone consisted of patients undergoing chemotherapy (18.0%) or chemotherapy plus targeted therapy (7.0%). Local treatment plus systemic therapy consisted of patients undergoing systemic therapy plus SBRT (5.0%), metastasectomy (5.0%), or definitive chemoradiotherapy (3.5%). The sequencing of systemic therapy in these patients was before local treatment (8.0%), concomitant (3.5%) or after local treatment (2.0%). Table 2 outlines the treatment characteristics.

Histology, control of primary tumor, and the number of OMD locations were associated with treatment of OMD. Squamous cell carcinoma histology was more common among patients who underwent local treatment of OMD alone as compared with patients undergoing systemic therapy alone or local plus systemic therapy (32.2% versus 10.0% and 7.4%, respectively). Control of the primary tumor was more common among patients who underwent local treatment of OMD or local plus systemic therapy as compared with patients undergoing systemic therapy alone (90.1% and 81.5% versus 34.0%, respectively). Two metastatic locations were more common among patients who underwent systemic therapy alone as compared with patients who underwent local treatment of OMD alone or local plus systemic therapy (24.0% versus 1.1% or 7.4%, respectively). Supplementary File 3 shows patient characteristics stratified by treatment of OMD. Finally, patients undergoing best supportive care had worse performance scores (30.6% versus 6.7%), less often a controlled primary tumor (50.0% versus 72.0%), and more OMD lesions (i.e. $\geq$3 in 30.5% versus 14.0%) as compared with patients undergoing treatment of OMD. Supplementary File 4 outlines the patient characteristics stratified by best supportive care.

The location of OMD was either the liver (25.5%), extra-regional lymph nodes (23.0%), lung (11.5%), bone (10.0%), brain (8.5%), or 2 metastatic locations (11.5%). Systemic therapy alone was mostly used for patients with liver metastases (43.1%). Local treatment of OMD alone was predominantly used as treatment of OMD in extra-regional lymph nodes (56.5%), brain (76.5%), bone (50.0%), or lung (60.8%). Finally, local plus systemic therapy was relatively often used for treatment of adrenal gland OMD (44.4%). Supplementary File 5 shows treatment modalities stratified by the location of OMD and Supplementary File 6 shows the applied SBRT schedules with biologically effective dosage using EQD2.

The median follow-up time was 14 months (IQR: 7–27), and 28% of patients were alive at the end of follow-up. Median

follow-up for surviving patients was 25 months (IQR: 13–39). Median OS across all included patients was 16 months (95% CI: 13–21). Supplementary File 7 shows the OS curve of included patients.

In multivariable Cox regression analyses, improved OS was independently associated with local plus systemic therapy as compared with systemic therapy alone of OMD (HR 0.46, 95% CI: 0.25–0.87). Worse OS was independently associated with squamous cell carcinoma histology (HR 1.70, 95% CI: 1.06–2.73), bone oligometastases (HR 2.65, 95% CI: 1.39–5.06), brain oligometastases (HR 1.98, 95% CI: 1.05–4.69), 2 metastatic locations (HR 2.24, 95% CI: 1.15–4.35), and best supportive care (HR 2.27 95% CI: 1.57–4.75). Table 3 demonstrates the results of the univariable and multivariable Cox regression analyses for prognostic factors for OS.

Median OS in patients undergoing systemic therapy alone was 13 months (95% CI: 9–21), local treatment 24 months (95% CI: 17–35), local plus systemic therapy 35 months (95% CI: 22-NA), and best supportive care 6 months (95% CI: 4–8; p = <0.001). Fig. 2 represents the OS curve stratified by treatment strategy of OMD.

Median OS in patients with adenocarcinoma was 18 months (95% CI: 15–24) as compared with 13 months (95% CI: 11–29) in patients with squamous cell carcinoma (p = 0.180; Supplementary File 7). Median OS in patients with extra-regional lymph node oligometastases was 15 months (95% CI: 12–46) as compared with 13 months (95% CI: 9–29) in patients with bone oligometastases and 11 months (95% CI: 6-NA) in patients with brain oligometastases (p = 0.087, Supplementary File 8).

Finally, median PFS across all patients was 18 months (95% CI: 14–28). Median PFS in patients undergoing systemic therapy alone was 11 months (95% CI: 7-NA), local treatment 16 months (95% CI: 12–28), and local plus systemic 28 months (95% CI: 9-NA; p = 0.56). Fig. 3 shows the PFS stratified by treatment of OMD.

Discussion

This multicenter study showed that approximately 25% of patients with metastatic esophagogastric cancer had de-novo OMD. This portion was comparable between the two tertiary referral cancer centers in The Netherlands and Switzerland (26% versus 23%), despite differences in indications for ^{18}F-FDG-PET/CT imaging (i.e., with or without standardized imaging and endoscopy protocol during follow-up, respectively) and referral criteria (i.e., with or without centralization of esophagogastric cancer surgery, respectively). In addition, this study shows that local treatment of OMD plus systemic therapy resulted in long-term PFS and OS and was independently associated with improved OS as compared with systemic therapy alone, after correction for performance status, histology, number and location of OMD lesions, and primary tumor treatment. In fact, local treatment of OMD plus systemic therapy appeared independently associated with a 56% lower chance of death over time as compared with systemic therapy alone. This benefit of the addition of local treatment over systemic therapy alone must be interpreted with caution because the independently improved OS could also be the effect of confounding-by-indication, or the result of unadjusted confounders in multivariable regression analyses. Therefore, randomized trials are warranted to verify these findings.

Despite the favorable OS associated with local treatment plus systemic therapy, only 13% of patients underwent this treatment in our study. This low portion might be explained by the location of oligometastases since patients with extra-regional lymph node

Table 3
Univariable and multivariable Cox proportional hazard model analyses for overall survival.

	(n =)	Univariable		Multivariable	
		HR (95% CI)	p-Value	HR (95% CI)	p-Value
Age (continuous)		1.02 (0.99–1.03)	0.055	1.00 (0.98–1.02)	0.824
WHO performance score					
0–1	177	reference	reference	reference	reference
>1	22	2.47 (1.54–3.99)	**<0.001**	1.54 (0.86–2.78)	0.149
Missing	1	NA	NA	NA	NA
Histology					
Adenocarcinoma	158	reference	reference	reference	reference
Squamous cell carcinoma	42	1.31 (0.88–1.97)	0.179	4.21 (1.19–15.82)	**0.033**
Number of OMD lesions (continuous)		1.32 (1.13–1.55)	**<0.001**	1.15 (0.97–1.45)	0.087
Location of OMD					
Extra-regional lymph node only	46	reference	reference	reference	reference
Liver only	51	1.37 (0.84–2.26)	0.208	1.78 (0.99–3.20)	0.077
Lung only	23	0.88 (0.47–1.65)	0.698	1.05 (0.55–2.02)	0.877
Bone only	20	1.77 (0.97–3.25)	0.063	2.65 (1.39–5.06)	**0.003**
Brain only	17	1.21 (0.62–2.38)	0.578	1.98 (1.05–4.69)	**0.037**
Other solitary organ*	18	0.47 (1.21–3.79)	**0.008**	2.06 (0.98–3.94)	0.056
Two or more metastatic locations	23	1.28 (0.68–2.40)	0.440	2.24 (1.12–4.35)	**0.023**
Treatment of OMD					
Systemic therapy	50	reference	reference	reference	reference
Local treatment	87	0.56 (0.37–0.86)	**0.007**	0.60 (0.35–1.04)	0.070
Local plus systemic	27	0.44 (0.25–0.79)	**0.005**	0.44 (0.24–0.83)	**0.010**
Best supportive care	36	2.87 (1.79–4.60)	**<0.001**	2.27 (1.57–4.75)	**<0.001**
OMD state					
Synchronous	96	reference	reference	reference	reference
Metachronous	104	0.95 (0.68–1.31)	0.745	1.00 (0.98–1.02)	0.824
Primary tumor controlled					
No	64	reference	reference	reference	reference
Yes	136	0.59 (0.42–0.83)	**0.003**	0.75 (0.48–1.17)	0.212

HR = hazard ratio; 95% CI = 95% confidence interval; OMD = oligometastatic disease; * = adrenal gland, soft tissue, or appendix; **bold** p-value = statistically significant (p < 0.05).

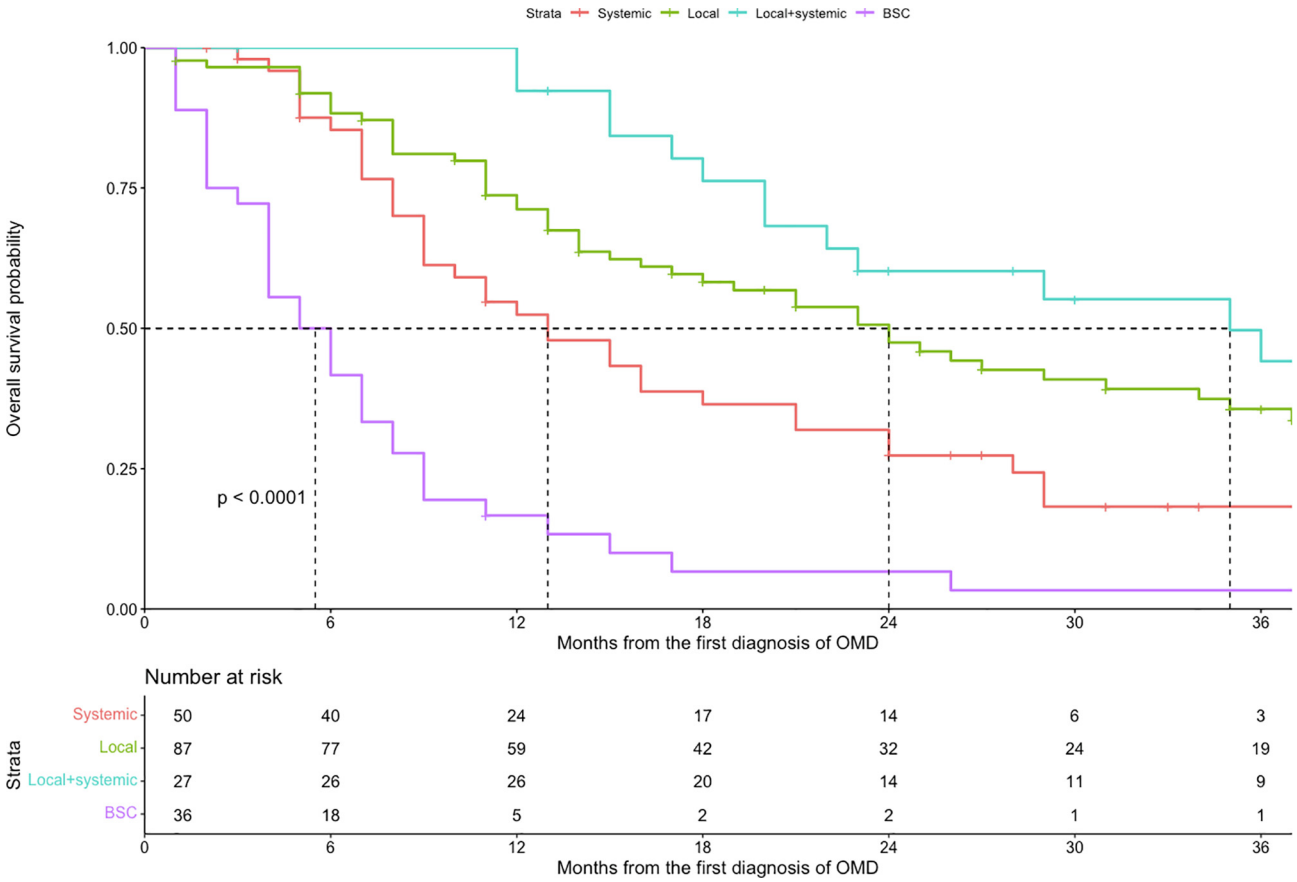

Fig. 2. Overall survival stratified by treatment of OMD.

metastases (22% of the total study population) more often underwent local treatment alone than local treatment plus systemic therapy (44% versus 11%). In addition, the low portion of patients who underwent local treatment plus systemic therapy might be explained by the low tumor burden of the patients included in our study since patients with 1 oligometastasis (53% of the total study population) more often underwent local treatment alone than local treatment plus systemic therapy (74% versus 56%) while patients with >1 oligometastases more often underwent local treatment plus systemic therapy than local treatment alone (44% versus 26%). With the knowledge of the current study, more patients will be offered a local treatment for OMD plus systemic therapy, to improve the chances of survival.

The OS of patients included in our study who underwent local treatment of OMD plus systemic therapy (35 months) was comparable with the phase II trial by Al-Batran et al. (median OS 31 months) [9]. In this phase II trial, patients with gastric cancer with OMD with response to fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) chemotherapy underwent resection of the primary tumor and oligometastases [9]. In addition, the results of our study are comparable with the phase II trial by Liu et al. (median OS 25 months) [19]. In this phase II trial, patients with esophageal squamous cell carcinoma with OMD underwent SBRT of oligometastases [19]. The benefit of local treatment of OMD plus systemic therapy over systemic therapy alone will be confirmed in the ongoing RENAISSANCE trial [20]. In this phase III trial, patients with gastric cancer and OMD with response to FLOT chemotherapy will be randomized to either resection of the primary tumor and oligometastases or FLOT chemotherapy alone [20].

Besides the type of treatment of OMD, independent prognostic factors for worse OS identified in the current study were squamous cell carcinoma histology, bone oligometastases, brain oligometastases, and 2 metastatic locations. Besides squamous cell carcinoma histology, these prognostic factors for worse OS are line with a recent systematic review and meta-analysis on prognostic factors for OS in patients with metastatic esophagogastric cancer [18]. The worse OS in patients with OMD with squamous cell carcinoma as compared with adenocarcinoma histology was in line with American retrospective cohort study by Nobel et al. on patients with lung, brain, or lung oligometastases after R0 esophagectomy [21]. This study also found that squamous cell carcinoma histology was independently associated with worse OS as compared with adenocarcinoma in the OMD setting (HR 2.63, 95% CI: 1.06–6.52) [21]. This suggests that the improved OS associated with esophageal squamous cell carcinoma as compared with adenocarcinoma histology observed in the locally-advanced setting after multimodality treatment (i.e. neoadjuvant chemoradiotherapy plus esophagectomy) is not applicable to the OMD setting [22]. We do not have an explanation for the worse of patients with OMD with squamous cell carcinoma, nor do the authors of the study by Nobel et al. [21]. Future studies are warranted to confirm these results. Furthermore, this study shows that the number of OMD locations (e.g. 1 or 2 organs with metastases) was more important than the total number of OMD lesions, since bone or brain oligometastases or 2 metastatic locations (e.g. 2 organs with metastases) were independently associated with worse OS, while a higher total number of OMD lesions was not.

The results of our study are predominantly applicable to Western countries, since 79% of included patients had an adenocarcinoma while in Eastern countries squamous cell carcinoma histology is more common [23]. Furthermore, the results of our study are applicable to patients with OMD in distant lymph nodes

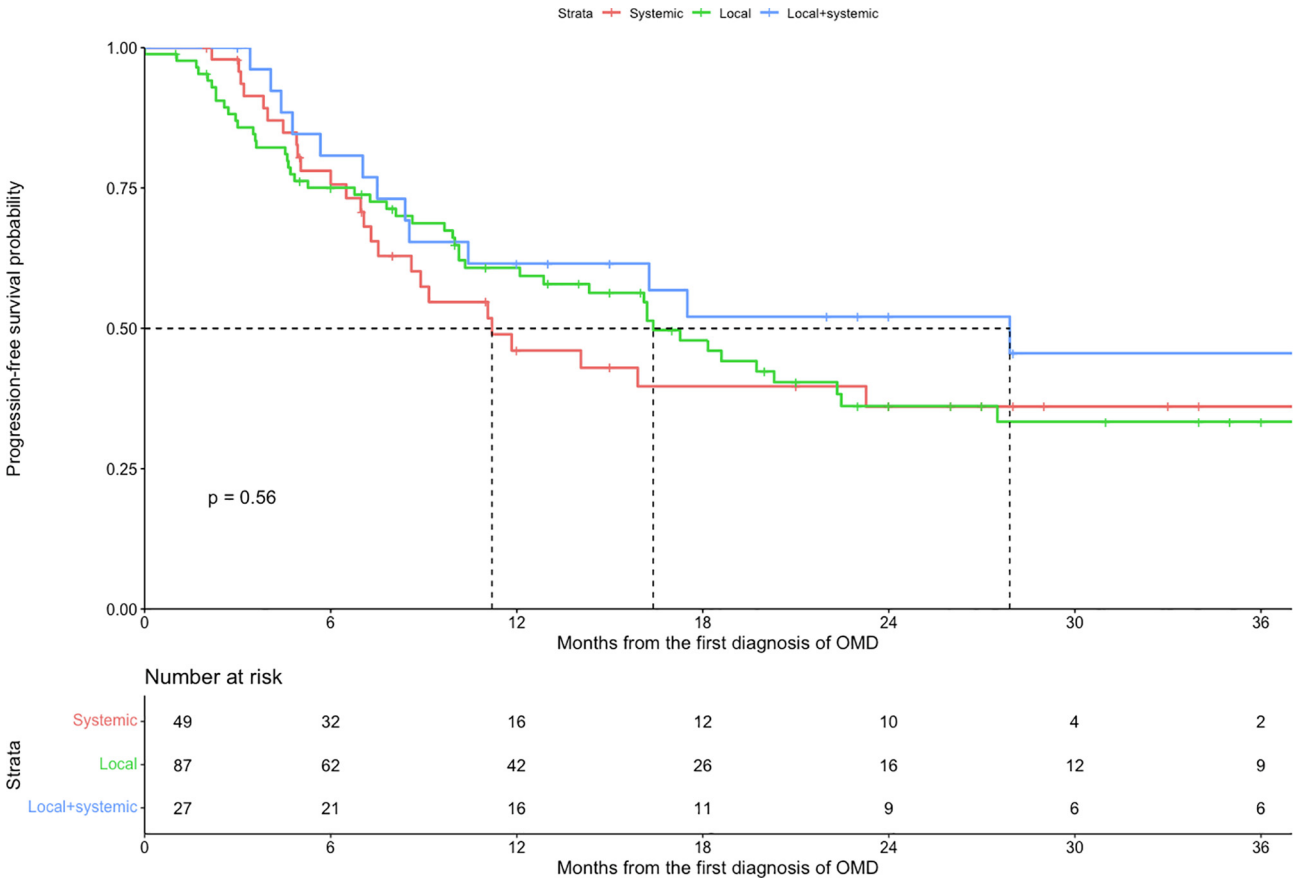

Fig. 3. Progression-free survival stratified by treatment.

and organs only, since patients with peritoneal or pleural carcinomatosis were not included. Such diffuse lesions were not considered OMD, but rather polymetastatic disease [6], requiring a very specific treatment (e.g. cytoreductive surgery and hyperthermic intraperitoneal chemotherapy [HIPEC] [24]), which is not comparable to treatment of OMD in distant lymph nodes or organs.

Strengths of our study include its multicenter study design. In addition, our study uniquely not only included patients who underwent local treatment of OMD but also systemic therapy alone or best supportive care, enabling us to compare different current management strategies of OMD. Another strength is the size of the study population, currently representing the largest multicenter study on oligometastatic esophagogastric cancer (to the best of our knowledge). A limitation includes selection bias caused by confounding-by-indication which could result in an overestimation of OS after treatment of OMD. Another potential limitation is the heterogeneity in the study population, since patients with esophageal or gastric cancer with synchronous or metachronous OMD were included as well as patients with adenocarcinoma or squamous cell carcinoma histology. However, these differences have been addressed and additional data on these differences are provided in the Supplementary Files.

In conclusion, 25% of patients with metastatic esophagogastric cancer with adenocarcinoma or squamous cell carcinoma histology had de-novo OMD. Local treatment of OMD (SBRT or metastasectomy) plus systemic therapy was associated with long-term OS and appeared to improve OS compared with systemic therapy alone in multivariable analyses. However, these results could be confounded by unadjusted confounders in multivariable analyses, or selection bias. Therefore, prospective randomized studies are warranted to confirm these results.

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Conflict of interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2022.06.012.

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