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Original Research

Liver oligometastatic disease in synchronous metastatic gastric cancer patients: a nationwide population-based cohort study

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KEYWORDS
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Abstract ***Introduction:*** This population-based cohort study analysed treatment, overall survival (OS), and independent prognostic factors for OS in gastric cancer patients with liver metastases.

Methods: Between 2015 and 2017, patients with synchronous metastatic gastric or gastroesophageal junction adenocarcinoma limited to the liver were included from the prospectively maintained population-based Netherlands Cancer Registry. Liver oligometastatic disease

Abbreviations: OS, overall survival; OMD, oligometastatic disease; HR, hazard ratio; CI, confidence interval; DUCG, Dutch Upper GI Cancer Group; NCR, Netherlands Cancer Registry; EORTC, European Organisation for Research and Treatment of Cancer; PMD, polymetastatic disease; ^{18}F-FDG PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography with integrated CT; BMI, body mass index; SD, standard deviation; IQR, interquartile range.

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Metastasectomy;
Oligometastases

(OMD) was defined as ≤3 liver metastases. The primary outcome was OS. Independent prognostic factors for OS were analysed using multivariable Cox regression analysis.
Results: A total 295 patients with metastases limited to the liver were included. The primary tumour was resected in four patients (1.4%). Treatment for liver metastases consisted of chemotherapy alone (28.1%), trastuzumab plus chemotherapy (4.7%), surgery (1.0%), or best supportive care (67.5%). Median OS across all included patients was 4.0 months (95% confidence interval [CI]: 3.1–4.5). Liver OMD was detected in 77 patients (26%). Treatment for liver OMD consisted of chemotherapy alone (24.6%), trastuzumab plus chemotherapy (5.2%), surgery (3.9%), or best supportive care (67.5%). Median OS among patients with liver OMD was 5.7 months (95% CI: 4.8–7.5). Across all patients, better OS was independently associated with liver OMD (hazard ratio [HR] 0.66, 95% CI: 0.50–0.87), trastuzumab (HR 0.41, 95% CI: 0.23–0.72) but not with triplet compared with doublet chemotherapy (HR 0.94, 95% CI: 0.57–2.87). Worse OS was independently associated with unknown nodal stage versus cN0 (HR 1.74, 95% CI: 1.17–2.60), diffuse-type versus intestinal-type adenocarcinoma (HR 2.06, 95% CI: 1.32–3.20), and monotherapy or best supportive care versus doublet chemotherapy (HR 1.72, 95% CI: 1.03–2.87, and HR 3.61, 95% CI: 2.55–5.10, respectively).
Conclusion: In this population-based cohort study, liver OMD was detected in 26% of patients. Liver OMD and trastuzumab treatment were independently associated with better OS while triplet as compared with doublet chemotherapy was not. OS among patients with liver OMD nevertheless remained poor. The concept of OMD and the benefit of resection of liver OMD may still have been relatively unknown in this disease type during the study inclusion years.

1. Introduction

Gastric cancer is the fifth most common cancer worldwide [1]. Overall survival (OS) in patients with gastric cancer is poor since approximately 35–50% of patients present with synchronous metastatic disease [2]. The most common locations for metastatic disease in patients with gastric cancer are the extra-regional lymph nodes, followed by the liver [3]. More than 95% of gastric cancers are adenocarcinomas, which are commonly classified according to the Lauren classification in diffuse-type or intestinal-type [4]. Liver metastases are more common in intestinal than diffuse-type adenocarcinoma [5].

The recommended first-line systemic therapy regimen for patients with metastatic gastric cancer consists of doublet chemotherapy (platinum and fluoropyrimidine) and trastuzumab in case of HER2 overexpression [6,7]. Triplet chemotherapy (platinum, fluoropyrimidine, and taxane or anthracycline) may be used in patients with metastatic gastric cancer with good performance status although triplet chemotherapy has a higher toxicity rate and unclear OS benefit over doublet chemotherapy [8-10].

In patients with oligometastatic disease (OMD) limited to 1 organ and/or the retroperitoneal lymph nodes, surgery of the primary tumour and metastases may provide an OS benefit. The FLOT-3 trial has shown that the OS of gastric cancer patients with synchronous OMD who underwent resection of the primary tumour and metastases was higher than the OS of patients who underwent chemotherapy alone (31.3 months versus 17.8 months) [11]. However, this comparison is biased because resection of the primary tumour and liver metastases in the FLOT-3 trial was only applied in those patients who responded well to chemotherapy [11].

In patients with OMD limited to the liver (i.e. ≤3 liver metastases and no extra-hepatic metastasis [12]), resection of liver metastases may provide an OS benefit [13–20]. Current Dutch and European gastric cancer guidelines do not incorporate specific recommendations for treatment of liver OMD [7,21] although resection of liver oligometastases is increasingly being performed in high-expertise centres [22]. In addition, because studies have used various definitions of liver OMD [12], the incidence of liver OMD in oesophagogastric cancer is currently unknown.

This population-based cohort study aimed to analyse the incidence and treatment of liver OMD (defined as ≤3 liver metastases and no extra-hepatic metastases), OS, and independent prognostic factors for OS in patients with synchronous metastatic gastric or gastro-esophageal junction adenocarcinoma with metastatic disease limited to the liver.

2. Material and methods

2.1. Ethical statement

This study was approved by the Research Commission of the Dutch Upper GI Cancer Group (DUCG), the Privacy Review Board of the Netherlands Cancer Registry (NCR), the European Organisation for Research and Treatment of Cancer (EORTC) Gastrointestinal Tract Cancer Trials Group, and did not need approval by a medical ethical committee according to the Central Committee on Research involving Human Subjects in The Netherlands. The study was performed in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans, the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Supplementary File 1).

2.2. Patient inclusion

All patients ≥18 years of age with synchronous metastatic gastric or gastroesophageal junction adenocarcinoma diagnosed in the Netherlands between 2015 and 2017 were identified from the prospectively maintained population-based NCR. Patients with metastatic disease limited to the liver were eligible for inclusion. Patients with an unknown number of liver metastases were excluded. Synchronous metastatic disease was defined as metastatic disease detected before the start of primary tumour treatment. Metastatic gastric or gastroesophageal junction cancer was classified according to ICD-0-3 as 16.0–16.9 [23] and according to UICC as stage IV [24]. The NCR covers the entire Dutch population of 17 million inhabitants. The NCR is directly linked to the municipal personal records database to obtain vital status. The vital status was last updated on February 1, 2021. Data on the number of liver metastases could not be retrieved from two hospitals (i.e. 3% of all Dutch hospitals) due to logistical constraints.

2.3. Definition of OMD

The number of liver metastases was obtained by reviewing the imaging reports. Liver OMD was defined as ≤3 liver metastases and no extra-hepatic metastases in accordance with a recent systematic review on definitions of oligometastatic oesophagogastric cancer [12]. Liver polymetastatic disease (PMD) was defined as >3 liver metastases [12]. This systematic review (OMEC-1) was the first subproject of the Oligometastatic Esophagogastric Cancer (OMEC) project to develop a multidisciplinary European consensus statement on the definition, diagnosis, and treatment of oligometastatic oesophagogastric cancer [25]. Subsequent subprojects of the OMEC project include discussion of real-life clinical cases by multidisciplinary teams of oesophagogastric cancer expert centres in Europe (OMEC-2) [22], and Delphi consensus rounds with oesophagogastric cancer experts (OMEC-3). The resulting European multidisciplinary consensus statement (OMEC-4) will lay the foundation for a prospective European clinical trial on the treatment of oligometastatic oesophagogastric cancer (OMEC-5). The OMEC project is endorsed by the EORTC, European Society for Radiotherapy and Oncology (ESTRO), European Society of Medical Oncology (ESMO), European Society of Surgical Oncology (ESSO), European Society for Diseases of the Esophagus (ESDE), the European chapter of the International Gastric Cancer Association (IGCA) and DUCG.

2.4. Staging

Dutch national gastric cancer guidelines recommend baseline staging with computed tomography (CT) for gastric cancer [21]. Since 2016, for patients with ≥cT3 or cN + disease national guidelines recommend baseline ^{18}F-fluorodeoxyglucose positron emission tomography with integrated CT (^{18}F-FDG PET/CT) and diagnostic laparoscopy [21].

2.5. Treatment

Primary tumour resection was defined as total or distal gastrectomy, transhiatal or transthoracic oesophagectomy, or non-specified primary tumour resection. Treatment for liver metastases was categorised into (1) chemotherapy alone, (2) trastuzumab plus chemotherapy, (3) surgery (with or without systemic therapy), or (4) best supportive care. Chemotherapy was categorised into monotherapy (one agent), doublet therapy (two agents), or triplet therapy (three agents). Surgery for liver metastases included radiofrequency ablation and/or metastasectomy. Best supportive care included no anti-tumour treatment for liver metastases.

2.6. Outcomes

The primary outcome of this study was OS. OS was defined as the time interval between the diagnosis of the primary tumour and death or last follow-up. Secondary outcomes were the incidence and management of liver OMD and independent prognostic factors for OS.

2.7. Variables

The primary tumour location was categorised into proximal stomach or gastroesophageal junction (gastroesophageal junction, cardia, or fundus), middle stomach (corpus, small and big curvature), distal stomach (antrum or pylorus), overlapping locations in the stomach, or non-specified location in the stomach. Diffuse-type adenocarcinoma included diffuse-type adenocarcinoma, linitis plastica, and signet ring cell carcinoma. Intestinal-type adenocarcinoma included intestinal-type adenocarcinoma, tubular adenocarcinoma, and mucinous adenocarcinoma. Other adenocarcinoma subtypes were grouped together into ‘other’. Clinical staging was according to the TNM 7th edition [24]. The Charlson comorbidity index was grouped into 1–2, 3–4, and >4 [26].

Body mass index (BMI) was defined as weight in kilograms/height in metres^2.

2.8. Statistical analysis

Parametric data were presented as mean with standard deviation (SD) and were compared with the Student's T-test. Non-parametric data were presented as median with interquartile range (IQR) and were compared using the Mann-Whitney-U test. Categorical data were presented as frequencies with proportions (%) and were compared using Fisher's exact or chi-squared test. Multivariable Cox proportional hazard regression analyses were used to identify prognostic factors for OS. Pre-specified prognostic factors included in the Cox proportional hazard regression analyses were based on a recent systemic review on prognostic and predictive factors for OS in patients with metastatic oesophagogastric cancer [27]. They included age, sex, BMI, performance status, Charlson comorbidity index (1–2, 3–4, >4, or missing), primary tumour location (proximal stomach or gastroesophageal junction, middle stomach, distal stomach, overlapping locations in the stomach, or non-specified location in the stomach), adenocarcinoma subtype (intestinal, diffuse, or other), clinical tumour and nodal stage, liver OMD (yes or no), primary tumour resected (yes or no), and liver metastases treatment (chemotherapy, trastuzumab plus chemotherapy, surgery, or best supportive care) [27]. Prognostic factors for OS were expressed using hazard ratios (HRs) with 95% confidence intervals (CIs). Results of subgroup analyses were reported in case ≥10 patients were included. Kaplan–Meier curves were constructed of independent prognostic factors for OS and categories were compared using the log-rank test. Missing data were not considered missing at random. Therefore, imputation was not performed, but instead missing values were assigned as a separate category. The median follow-up time was estimated using the reverse Kaplan–Meier estimator (i.e. reverse event indicator). Sensitivity analyses were performed for 1 and 2 liver metastases. Subgroup analyses were performed for patients with and without OMD who underwent treatment. Data were analysed using R for Windows, version 3.6.3 [28]. A two-sided p-value <0.05 was considered statistically significant.

3. Results

A total of 2092 patients with synchronous metastatic gastric or gastroesophageal junction adenocarcinoma were identified from the NCR, of whom 318 patients presenting with metastatic disease limited to the liver were eligible for inclusion. Subsequently, 23 patients with an unknown number of liver metastases were excluded. Consequently, 295 patients were included in this nationwide population-based cohort study. There was no loss to follow-up. Fig. 1 demonstrates the flowchart of patient selection.

The median age of included patients was 75 years (IQR: 68–80), median BMI was 25 kg/m^2 (IQR: 23–27), and 74.2% of patients were male. The World Health Organisation (WHO) performance status was 0–1 in 36.9%, and 53.6% had a Charlson comorbidity score of >4. The primary tumour was predominantly located in

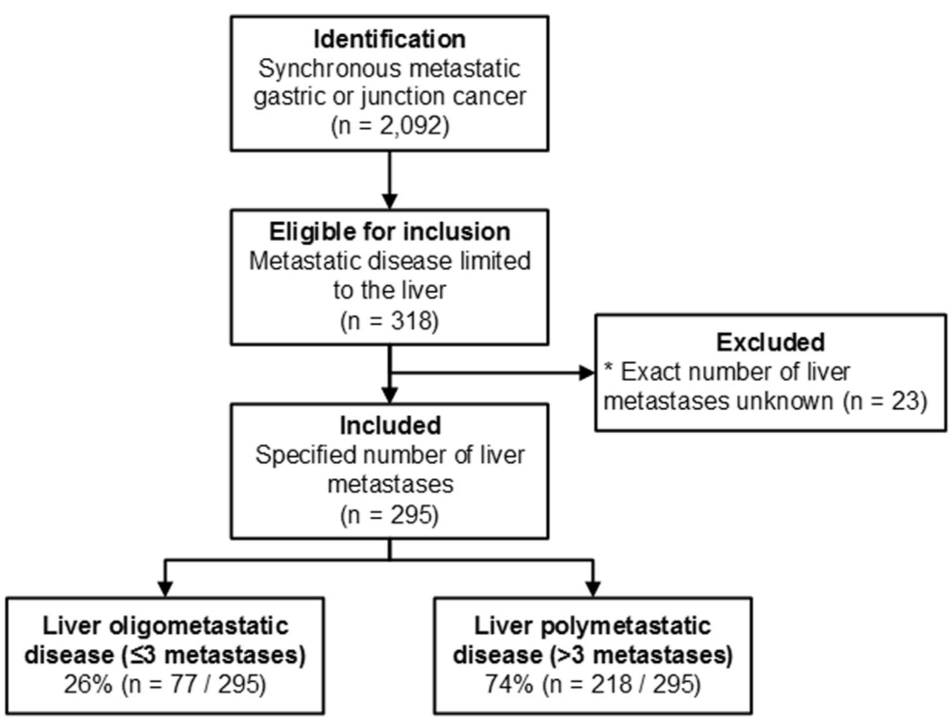

Fig. 1. Patient selection flowchart.

the proximal stomach or gastroesophageal junction (40.3%), and the disease stage was cT1-2 (35.3%) and cN1 (32.5%). The adenocarcinoma subtype was intestinal (40.0%), diffuse (10.8%), or other (49.2%).

Treatment for liver metastases among the 295 patients consisted of chemotherapy alone (28.1%), trastuzumab plus chemotherapy (4.7%), surgery (1.0%), or best supportive care (67.5%). The most common first-line chemotherapy regimen was doublet therapy (11.9% of total), followed by triplet therapy (9.8%), or monotherapy (6.4%). The most common first-line doublet regimens were capecitabine plus oxaliplatin (CapOx, 9.5%), and oxaliplatin, 5-fluorouracil, plus leucovorin (FOLFOX, 2.0%). The most common first-line triplet regimens were epirubicin, oxaliplatin, plus capecitabine (EOC, 7.8%) and docetaxel, oxaliplatin, plus

Table 1
Patient characteristics stratified by liver OMD.

	Liver OMD (n = 77)		Liver PMD (n = 218)		P-value
Median age in years [IQR]	75	[68–80]	74	[67–80]	0.745
Sex					0.553
Male	59	76.6%	160	73.4%	
Female	18	23.4%	58	26.6%	
Year of diagnosis					0.043
2015	32	41.6%	80	36.7%	
2016	23	29.9%	72	33.0%	
2017	22	28.5%	66	30.3%	
Body mass index (kg/m^2) [IQR]	25	[24–29]	25	[23–27]	0.529
WHO performance status					0.023
0	16	20.8%	26	11.9%	
1	23	29.9%	44	20.2%	
>1	10	13.0%	40	18.3%	
Missing	28	36.3%	108	49.6%	
Charlson comorbidity index					0.226
1-2	6	7.7%	16	7.3%	
3-4	26	33.7%	80	36.8%	
>4	44	57.1%	114	52.2%	
Missing	2	2.5%	8	3.7%	
Primary tumour location					0.472
Proximal stomach or GE junction	32	41.6%	87	39.9%	
Middle stomach	11	14.3%	40	18.3%	
Distal stomach	20	26.0%	48	22.0%	
Overlapping regions in the stomach	6	7.8%	27	12.4%	
Non-specified location in the stomach	8	10.3%	16	7.4%	
Clinical tumour stage					0.057
cT1-2	27	35.0%	77	35.3%	
cT3	21	27.3%	38	17.4%	
cT4	11	14.3%	18	8.3%	
cTx	18	23.4%	85	39.0%	
Clinical nodal stage					0.133
cN0	23	29.9%	56	25.7%	
cN1	30	39.0%	66	30.3%	
cN2	13	16.9%	57	26.1%	
cN3	4	5.2%	5	2.3%	
cNx	7	9.0%	34	15.6%	
AC subtype					0.726
Intestinal	28	37.3%	90	41.3%	
AC, intestinal-type	26	33.8%	82	37.6%	
Tubular AC	0	0%	6	2.8%	
Mucinous AC	2	2.6%	2	0.9%	
Diffuse	11	14.3%	21	9.6%	
Linitis plastica	3	3.9%	6	2.8%	
AC, diffuse-type	7	9.1%	11	5.1%	
Signet-ring cell carcinoma	1	1.3%	4	1.8%	
Other	38	50.7%	107	49.0%	
AC NOS	37	48.1%	103	47.2%	
AC with mixed-subtypes	1	1.3%	1	0.5%	
AC with neuroendocrine differentiation	0	0%	3	1.4%	
Median number of liver metastases	1	[1–3]	5	[4,5]	<0.001

OMD: oligometastatic disease (i.e. ≤3 liver metastases); PMD: polymetastatic disease (i.e. >3 liver metastases); GE: gastroesophageal; IQR: interquartile range; AC: adenocarcinoma, NOS: not otherwise specified.

capecitabine (DOC, 1.4%). The most common first-line monotherapy agents were capecitabine (5.8%) and 5-fluorouracil (0.7%). Trastuzumab was combined with doublet chemotherapy (3.7%) or monotherapy (1.0%).

The number of liver metastases was 1 (13%), 2 (7%), 3 (6%), 4 (4%), $\geq$5 (10%), or not liver OMD but with the exact number of liver metastases unknown (60%). Thus, liver OMD was detected in 77 of 295 patients (26%). There were no differences in baseline characteristics between patients with versus without liver OMD, besides a better performance status in patients with liver OMD (0–1 in 51% versus 32%, p = 0.023). Table 1 demonstrates the patient characteristics stratified by liver OMD.

In patients with liver OMD (n = 77), 4 patients underwent resection of the primary tumour (5.2%). These primary tumour resections included 2 distal gastrectomies, 1 transhiatal oesophagectomy, and 1 non-specified primary tumour resection. Primary tumour resection was only performed in patients with liver OMD. Among patients with liver OMD, resection of liver oligometastases was performed in 3 patients (3.9%, 3/77). A patient underwent liver metastasectomy followed by CapOx chemotherapy (n = 1), a patient underwent liver wedge resection and distal gastrectomy (n = 1), and a patient underwent EOC chemotherapy, transhiatal oesophagectomy, and radiofrequency ablation of liver metastases (n = 1). Thus, resection of the primary tumour and liver OMD was performed in two patients with liver OMD (2.6%, 2/77). Resection of liver metastases was only performed in patients with liver OMD.

In addition, in patients with liver OMD chemotherapy alone was performed in 24.6%, trastuzumab plus chemotherapy in 5.2%, and best supportive care in 67.5%. There was no difference in the rate of best supportive care between patients with and without liver OMD (68% versus 67%). Reasons for receiving best supportive care among patients with liver OMD were poor performance status (n = 15), patient request (n = 10), tumour burden (n = 8), or not specified (n = 20). Among patients for whom the reason for best supportive care was not specified (n = 20), the median age was 81 years (IQR: 71–82), and the performance status was 0–1 in 4 patients, 2 in 3 patients, 3 in 2 patients, and not-specified in 7 patients. Table 2 shows the treatment characteristics stratified by liver OMD.

Patients who received best supportive care had higher age, more often male sex, higher Charlson comorbidity index, worse performance status, and more often an

Table 2
Primary tumour and liver metastases treatment stratified by liver OMD.

	Liver OMD (n = 77)		Liver PMD (n = 218)		Total (n = 295)	
Primary tumour resected						
Yes	4	5.2%	0	0.0%	4	1.4%
Distal gastrectomy	2	2.6%	0	0.0%	2	0.7%
Transhiatal esophagectomy	1	1.3%	0	0.0%	1	0.3%
Not-specified primary tumour resection	1	1.3%	0	0.0%	1	0.3%
No	73	94.8%	218	100.0%	291	98.6%
Liver metastases treatment		0%				
<u>Chemotherapy alone</u>	19	24.6%	64	29.4%	83	28.1%
Monotherapy	2	2.6%	17	7.8%	19	6.4%
Capecitabin	1	1.3%	16	7.3%	17	5.8%
5-fluorouracil	1	1.3%	1	0.0%	2	0.7%
Doublet	5	6.5%	30	13.8%	35	11.9%
Capecitabin and oxaliplatin (CapOx)	3	3.9%	25	11.5%	28	9.5%
5-fluorouracil and oxaliplatin (FOLFOX)	2	2.6%	4	1.8%	6	2.0%
Capecitabin and cisplatinum (CX)	0	0.0%	1	0.5%	1	0.3%
Triplet	12	15.6%	17	7.8%	29	9.8%
Epirubicin, oxaliplatin, and capecitabine (EOC)	8	10.4%	15	6.8%	23	7.8%
Docetaxel, oxaliplatin, and capecitabine (DOC)	2	2.6%	2	<1%	4	1.4%
Epirubicin, cisplatinum, and capecitabine (ECC)	1	1.3%	0	0.0%	1	0.3%
Epirubicin, cisplatin, and 5-fluorouracil (ECF)	1	1.3%	0	0.0%	1	0.3%
Unspecified chemotherapy	1	1.3%	0	0.0%	1	0.3%
<u>Targeted therapy (trastuzumab) plus chemotherapy</u>	4	5.2%	10	4.6%	14	4.7%
Trastuzumab plus monotherapy	0	0.0%	3	1.4%	3	1.0%
Trastuzumab plus doublet chemotherapy	4	5.2%	7	3.2%	11	3.7%
<u>Surgery for liver metastases</u>	3	3.9%	0	0.0%	3	1.0%
Metastasectomy followed by CapOx	1	1.3%	0	0.0%	1	0.3%
Wedge resection	1	1.3%	0	0.0%	1	0.3%
EOC followed by radiofrequency ablation	1	1.3%	0	0.0%	1	0.3%
<u>Best supportive care</u>	52	67.5%	147	67.4%	199	67.5%
Resection of primary tumour and liver metastases	2	2.6%	0	0.0%	2	0.7%

OMD: oligometastatic disease (i.e. $\leq$3 liver metastases); PMD: polymetastatic disease (i.e. >3 liver metastases).

unknown clinical T-stage as compared with patients who did not receive best supportive care. Patient characteristics stratified by best supportive care are provided in Supplementary File 2.

The median follow-up time was 61 months (IQR: 56–62). A total of five patients were alive at the end of follow-up (February 1, 2021). Median OS across all patients was 4.0 months (95% CI: 3.1–4.5). Median OS among patients with liver OMD was 5.7 months (95% CI: 4.8–7.5). Superior OS was independently associated with liver OMD (HR 0.66, 95% CI: 0.50–0.87; Fig. 2) and with trastuzumab treatment (HR 0.41, 95% CI: 0.23–0.72; Supplementary File 3). Triplet compared with doublet chemotherapy was not independently associated with improved OS (HR 0.94, 95% CI: 0.57–2.87; Supplementary File 5).

Worse OS was independently associated with unknown nodal stage versus cN0 (HR 1.74, 95% CI: 1.17–2.60, Supplementary File 6), diffuse-type as compared with intestinal-type adenocarcinoma (HR 2.06, 95% CI: 1.32–3.20; Supplementary File 4), and best supportive care or monotherapy as compared with doublet chemotherapy (HR 3.61, 95% CI: 2.55–5.10 and HR 1.72, 95% CI: 1.03–2.87, respectively Supplementary File 5). Table 3 shows the results of the univariable and multivariable Cox regression analyses for prognostic factors for OS as well as median OS with 95% CIs for subgroups with ≥10 patients.

OS of patients with OMD versus without OMD in case of no treatment was 4.8 months (95% CI: 4.1–6.3) versus 1.6 months (95% CI: 1.2–2.1), with monotherapy 6.1 months (95% CI: 4.8-NA) versus 4.8 months (95% CI: 3.8–12.2), with doublet chemotherapy 19.8 months (95% CI: 7.9-NA) versus 9.0 months (95% CI: 6.4–14.8), and with triplet chemotherapy 7.8 months (95% CI: 5.1-NA) versus 5.5 months (95% CI: 4.6–20.7).

Sensitivity analyses demonstrated that having 1–2 liver metastases as compared with >2 liver metastases was independently associated with improved OS (HR 0.60, 95% CI: 0.43–0.83) while 1 liver metastasis as compared with >1 liver metastases was not (HR 0.77, 95% CI: 0.53–1.14).

4. Discussion

This nationwide population-based cohort study included all patients diagnosed with gastric or gastroesophageal junction adenocarcinoma in combination with metastatic disease limited to the liver and a specified number of liver metastases between 2015 and 2017 in the Netherlands. The incidence of liver OMD (defined as ≤3 liver metastases) was 26% among included patients. Patients with liver OMD were rarely treated as such in this cohort since best supportive care was applied in 68% of patients and only 3% underwent resection of the primary tumour and liver OMD. Patients with liver OMD (n = 77) had a 44% lower chance of death overtime as compared with patients without liver OMD (n = 218). Nevertheless, OS in

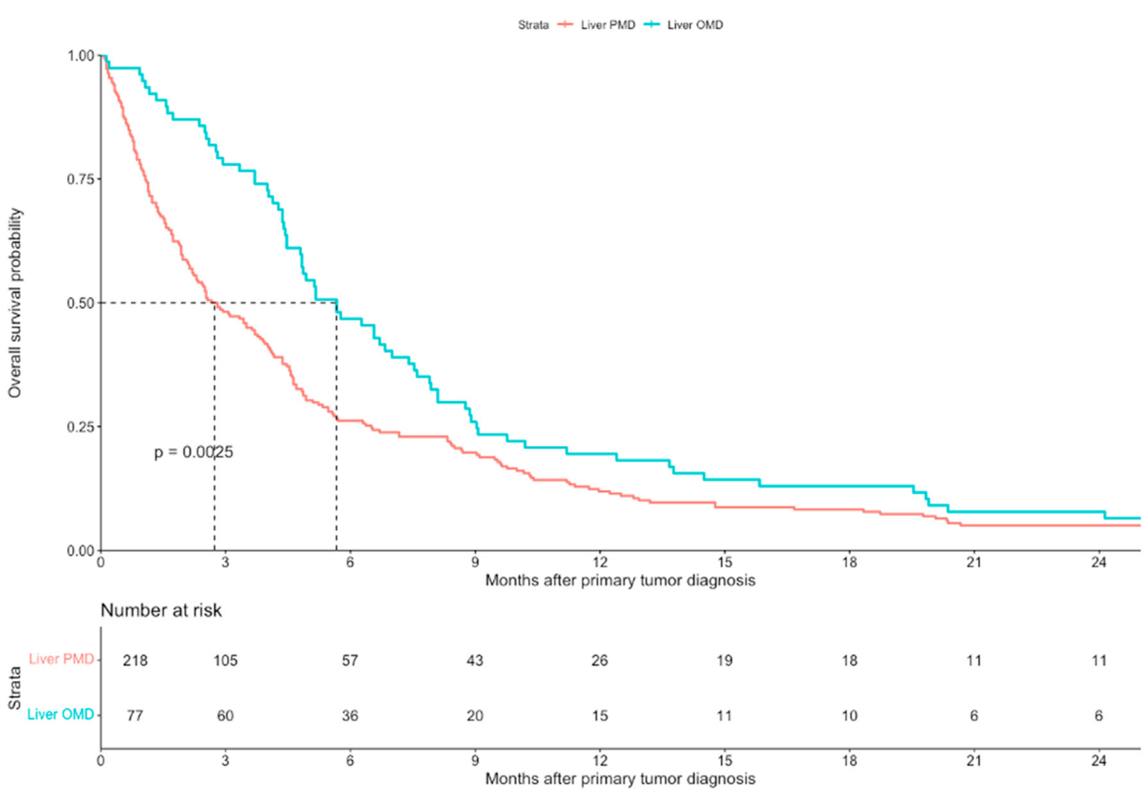

Fig. 2. Overall survival curve stratified by liver oligometastatic disease.

Table 3
Results of univariable and multivariable Cox regression for prognostic factors for OS and median OS of subgroups with ≥10 patients.

	Number	Univariable		Multivariable		OS in months
		HR (95% CI)	p-value	HR (95% CI)	p-value	Median 95% CI
Age		1.03 (1.02–1.04)	**<0.001**	0.99 (0.97–1.01)	0.146	
Sex						
Male	219	Reference	Reference	reference	reference	4.8 (4.4–5.7)
Female	76	1.42 (1.11–1.82)	0.004	1.21 (0.91–1.60)	0.073	3.0 (2.5–4.6)
Performance status						
0	42	Reference	Reference	reference	reference	7.1 (3.9–13.8)
1	67	1.34 (0.94–1.92)	0.103	1.21 (0.76–1.64)	0.763	5.2 (4.5–8.1)
>1	50	2.71 (1.84–3.98)	<0.001	1.61 (1.06–2.45)	0.062	2.7 (1.4–4.4)
Missing	136	2.01 (1.46–2.77)	<0.001	1.23 (0.86–1.77)	0.068	2.4 (1.7–3.8)
Charlson comorbidity index						
>4	158	Reference	reference	reference	reference	3.2 (2.5–4.1)
1-2	22	0.46 (0.29–0.75)	0.002	0.68 (0.33–1.37)	0.282	5.7 (4.1–18.7)
3-4	106	0.76 (0.60–0.98)	0.014	1.28 (0.75–2.19)	0.735	4.2 (2.9–5.2)
Missing	9	0.74 (0.38–1.45)	0.383	0.98 (0.52–1.87)	0.396	4.6 (4.4-NA)
AC subtype						
Intestinal	118	Reference	reference	reference	reference	4.2 (3.1–4.9)
Diffuse	32	1.11 (0.77–1.59)	0.341	2.06 (1.32–3.20)	0.001	2.7 (1.1–5.2)
Other	145	0.91 (0.72–1.70)	0.578	1.30 (0.99–1.69)	0.050	3.9 (2.8–4.6)
Clinical tumour stage						
cT1-2	104	reference	reference	reference	reference	4.4 (2.6–4.9)
cT3	59	0.80 (0.58–1.12)	0.193	1.21 (0.82–3.04)	0.976	6.6 (4.6–8.7)
cT4	29	1.05 (0.69–1.60)	0.803	2.03 (0.99–4.17)	0.500	3.6 (1.9–6.3)
cTx	103	1.34 (1.01–1.76)	0.039	1.79 (0.99–4.22)	0.748	2.4 (1.7–3.7)
Clinical nodal stage						
cN0	79	reference	reference	reference	reference	4.9 (4.4–6.6)
cN1	96	0.82 (0.60–1.05)	0.907	0.80 (0.60–1.07)	0.242	5.2 (4.3–8.3)
cN2-3	79	1.08 (0.66–1.27)	0.144	1.10 (0.78–1.56)	0.848	4.1 (2.9–5.2)
cNx	41	1.71 (1.17–2.49)	0.006	1.74 (1.17–2.60)	0.010	1.4 (1.1–3.0)
Liver OMD						
No	218	reference	reference	reference	reference	2.7 (2.2–3.8)
Yes	77	0.66 (0.52–0.84)	0.003	0.66 (0.50–0.87)	0.001	5.7 (4.8–7.5)
Primary tumour resected						
No	291	NA	NA	NA	NA	4.0 (3.1–4.5)
Yes	4	NA	NA	NA	NA	NA
Liver metastases treatment						
Doublet	46	reference	reference	reference	reference	9.6 (7.9–15.8)
No treatment	200	3.67 (2.67–4.77)	<0.001	3.61 (2.55–5.10)	<0.001	1.9 (3.9–2.8)
Mono	19	1.22 (0.87–2.17)	0.372	1.72 (1.03–2.87)	0.031	4.8 (3.9–12.2)
Triplet	29	1.37 (0.87–2.17)	0.168	0.94 (0.57–2.87)	0.848	6.7 (5.1–9.0)
Not specified	1	NA	NA	NA	NA	NA
Trastuzumab treatment						
No	281	reference	reference	reference	reference	3.7 (2.8–4.3)
Yes	14	0.32 (0.20–0.52)	<0.001	0.41 (0.23–0.72)	0.008	13.3 (7.8–57.8)

HR: hazard ratio; CI: confidence interval; OS: overall survival; liver OMD: oligometastatic disease (i.e. ≤3 liver metastases); AC, adenocarcinoma.

patients with liver OMD remained relatively poor (median OS 5.7 months).

The rate of best supportive care for patients with liver OMD was comparable to patients without liver OMD (68% versus 67%). At first sight, this is surprisingly high, considering that 51% of patients with liver OMD had a performance status of 0–1 which could suggest that these patients potentially could be able to undergo systemic therapy. However, the high rate of best supportive care among these patients could potentially be explained by high age and the patient request to refrain from treatment. Importantly, it should be noted that our perspective on what may be possible in terms of treatment options is biased by the fact that we often do not have a complete picture of the 'real world'. Furthermore, the publication showing that even if patients are considered to be frail, reduced-intensity chemotherapy can provide a better patient experience without significantly compromising cancer control than best supportive care had not been published at the time of our data collection [29].

The proportion of patients undergoing resection of the primary tumour and liver OMD was very low between 2015 and 2017 in the Netherlands (3%). This suggests that in the time period of the study inclusion the concept of OMD treatment was not generally applied in the Netherlands, which may be explained by two factors. First, the results of the FLOT-3 trial were published in 2017 [11], which was at the end of the study inclusion period (2015–2017). Second, this population-based study included older and more fragile patients who would not have been eligible for inclusion in the FLOT-3 trial. For example, 16% of patients included in our study had a WHO performance score of >1, while these patients were excluded from the FLOT-3 trial [11].

In addition, this study suggests that doublet chemotherapy was the preferred first-line systemic therapy regimen in this time period in the Netherlands. Importantly, doublet chemotherapy (mainly CapOx) was associated with comparable OS as triplet chemotherapy (EOC) and improved OS as compared with monotherapy or best supportive care. However, the equipoise in OS between doublet and triplet chemotherapy must be interpreted with care because FLOT chemotherapy was not used in this time period in the Netherlands. FLOT is associated with improved OS as compared with ECF/ECC chemotherapy in the perioperative setting [30]. Nevertheless, for the general metastatic patient population, docetaxel containing triplet chemotherapy provides marginal survival benefit, while toxicity is increased [10, 31]. Thus, FLOT should not be considered the standard of care for all patients with metastatic gastroesophageal cancer.

In addition to best supportive care and monotherapy, other independent prognostic factors for OS identified in the current study, including Lauren classification, are in line with a recent systemic review for prognostic factors for OS in patients with metastatic oesophagogastric cancer [28]. The lower proportion of patients with diffuse-type gastric cancer as compared with population-based cohorts on gastric adenocarcinoma in the Netherlands (11% versus 38% [3] and 44% [32], respectively) confirms previous studies demonstrating that patients with diffuse-type gastric cancer are more likely to develop peritoneal metastases while patients with intestinal-type gastric cancer are more likely to develop liver metastases [3]. The worse OS in patients with an unknown nodal stage is not a known prognostic factor but perhaps could be explained by a higher disease stage which may create increased complexity and less relevance in documenting and extracting all the data elements resulting in more missing data [33].

Recently, the randomised controlled CheckMate 649 trial has shown that the addition of programmed cell death (PD)-1 inhibition to chemotherapy (CapOx or FOLFOX) improves overall and progression-free survival as compared with chemotherapy alone in the first-line palliative setting for advanced or metastatic HER2 negative gastric or gastroesophageal junction adenocarcinoma [34]. Therefore, PD-1 inhibition in combination with chemotherapy can be considered a new standard of care in the first-line palliative treatment for these patients, depending on the PD-L1 expression status of their cancer [35]. Unfortunately, during our study period PD-1 inhibition was unavailable in the Netherlands. Therefore, we could not study the effect of PD-1 inhibition on patients with liver OMD. A potential treatment approach for gastric cancer patients with liver OMD could be local treatment for liver metastases combined with palliative immunotherapy plus chemotherapy, which is currently being investigated in an ongoing phase II trial in China (NCT: NCT04510064).

Strengths of this study include the study design since it is the first population-based study to include data on the number of liver metastases. Therefore, this study uniquely provides information on a nationwide level on (1) the incidence of metastatic disease limited to the liver among patients with synchronous metastatic gastric cancer; (2) the incidence of liver OMD (defined as ≤3 liver metastases) among patients with metastatic disease limited to the liver. Moreover, this study offers real-world generalisability and applicability since frail and elderly patients were included. Other strengths include the register-based follow-up resulting in complete follow-up information for all patients. Potential weaknesses have been partly addressed in the discussion. Additional limitations include missing data on performance status, the size of liver metastases, and toxicity of systemic therapy resulting in a less optimal adjustment in multivariable analyses.

5. Conclusion

In conclusion, liver OMD was detected in 26% of patients with synchronous metastatic gastric limited to the liver. Patients with versus without liver OMD had independently superior OS. Nevertheless, OS in patients with liver OMD remained relatively poor, potentially because best supportive care was applied in 68% of patients, and only 3% underwent resection of the primary tumour and liver oligometastases. This suggests that the concept of OMD and the benefit of resection of the primary tumour and oligometastases may still have been relatively unknown in this disease type during the research years. Triplet chemotherapy (mainly EOC) compared with doublet chemotherapy (mainly CapOx) was not independently associated with improved OS. Future studies are warranted to identify which patients benefit from resection of liver oligometastases.

Author contribution

TK: Data curation, formal analysis, investigation, methodology, visualisation, writing original draft.

YK: Methodology.

FL: Funding acquisition, supervision, review and editing.

PvR: Methodology, formal analysis, supervision, review and editing.

JR: Supervision, review and editing.

SL: Review and editing.

RvH: Methodology, supervision, validation, review and editing.

RV: Methodology, supervision, validation, review and editing.

HvL: Funding acquisition, methodology, supervision, validation, review and editing.

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Data sharing statement

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

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix ASupplementary data

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