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A population-based study on treatment and outcomes in patients with gastric adenocarcinoma diagnosed with distant interval metastases

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ABSTRACT

Background: In patients with gastric or gastroesophageal junction (GEJ) cancer treated with curative intent, distant interval metastases may be detected after start of neoadjuvant chemotherapy or during surgery. The aim of this study was to explore characteristics, allocated treatment and overall survival (OS) in gastric/GEJ cancer patients with interval metastases, and to compare OS with synchronous metastatic gastric/GEJ cancer patients who started palliative chemotherapy.
Methods: Patients with interval metastases were selected from the Netherlands Cancer Registry by including patients with potentially curable gastric/GEJ adenocarcinoma (2010–2018) who started chemotherapy without concurrent radiotherapy. The OS since start of neoadjuvant treatment of patients with interval metastases was compared with a propensity score-matched cohort of patients with synchronous metastases who received palliative systemic treatment.
Results: 164 patients with interval metastases diagnosed in 2010–2018 were included. Metastases were most frequently detected during surgery (83%) and most frequently located in the peritoneum (77%). Peritoneal interval metastases were observed in 63% and 80% of the patients who did and did not have a diagnostic laparoscopy prior to neoadjuvant treatment, respectively (P = 0.041). Median OS was 8.9 months (IQR 5.5–13.4), compared to 8.0 months (IQR 4.1–14.1) in matched synchronous metastatic patients calculated from start of neoadjuvant and palliative systemic treatment, respectively (P = 0.848).
Conclusion: This population-based study shows that gastric/GEJ cancer patients who started neoadjuvant treatment and were diagnosed with interval metastases most frequently suffered from peritoneal metastases detected during (exploratory) surgery, even when a diagnostic laparoscopy was performed before start of treatment. OS was comparable to patients with synchronous metastatic gastric/GEJ cancer.

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1. Introduction

Patients with gastric cancer without distant metastases or tumor invasion in surrounding organs at initial diagnosis (i.e. $cT_{1-4a}N_{0-3}M_0$) are eligible for treatment with curative intent [1–3]. Currently, in most western countries a surgical resection with perioperative chemotherapy is the preferred treatment strategy [1–4].

Unfortunately, data show that recurrence of disease is found in nearly 30% of the gastric cancer patients within a year after gastrectomy [5], mostly consisting of distant metastases [5,6]. Although several studies describe the rate of recurrence in patients after a gastrectomy [5–7], distant metastases can also be detected during, or even before surgery in patients who started neoadjuvant treatment, so-called interval metastases.

The exact number of patients that develop interval metastases, as well as their characteristics, management of these patients and their overall survival (OS) in daily clinical practice is unknown. The primary aim of this population-based study was to explore the characteristics, the use of palliative treatment and OS of a nationwide cohort of gastric or gastroesophageal junction (GEJ) cancer patients who started with preoperative chemotherapy and developed interval distant metastases. The secondary aim was to compare OS of the patients with interval metastases with gastric or GEJ cancer patients who had distant metastases at initial diagnosis, i.e. synchronous metastases, and received palliative systemic treatment.

2. Materials and methods

2.1. Data collection

Patients of ≥18 years with a histologically confirmed adenocarcinoma of the GEJ or stomach (C16 according to the ICD-O-3 [8]) diagnosed in 2010–2018 with a potentially curable tumor at initial diagnosis ($cT_{1-4a,X}N_{0-3}M_0$) who started systemic treatment without concurrent radiotherapy were identified from the Netherlands Cancer Registry (NCR). The NCR is a population-based registry that covers the total Dutch population of more than 17 million people and is directly linked to the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA) [9] that comprises all histologically confirmed cancer diagnoses. Data were extracted from medical records by trained registrars. Data on vital status were obtained by annual linkage to the Dutch Personal Records Database and updated until February 1, 2020.

Patients diagnosed in 2015–2018 were included, as well as patients diagnosed in a subset of Dutch hospitals between 2010 and 2014. This subset was selected because of logistic limitations, and can be regarded as a representative sample of all Dutch hospitals [10]. Because the number of patients with a gastric/GEJ adenocarcinoma who started neoadjuvant systemic treatment was available for 2015–2018 only, we were able to calculate the proportion of patients with interval metastases in these years.

2.2. Staging

Clinical and pathological staging was performed according to the TNM 7th (2010–2016) and 8th edition (2017–2018). Dutch guidelines recommend initial staging with gastroscopy with biopsies, endoscopic ultrasonography on indication and CT scan in all patients, and from 2016 onwards fluorodeoxyglucose positron emission tomography (FDG-PET)/CT and a pre-chemo diagnostic laparoscopy in patients with locally advanced gastric and GEJ tumors, i.e. cT_{3-4a} or cN_{1-3} [1,2]. Before 2016, a diagnostic laparoscopy was recommended in patients with cT_{3-4a} tumors [11].

2.3. Interval metastases

Interval metastases were defined as distant metastases detected five days after start of neoadjuvant chemotherapy and the day of the surgery (regardless of whether surgical resection of the primary tumor took place). In case no surgery was performed, distant metastases detected >120 days after stop of neoadjuvant chemotherapy were not considered interval metastases because this time interval is considered too long, as surgical resection is generally scheduled within 42 days after the last neoadjuvant treatment cycle [4,12]. Distant metastases detected <5 days after start of systemic treatment were considered synchronous metastases, as described earlier [10].

Metastases locations were categorized in peritoneal, liver, distant lymph nodes, lungs, bones, other, and unknown. Metastatic dissemination was categorized in distant lymph nodes only, peritoneum only, and hematogenous if other sites were affected.

2.4. Neoadjuvant systemic treatment

The first cycle of systemic treatment after the diagnosis of the primary tumor was considered neoadjuvant treatment. Patients were excluded if they did not receive a regimen that consisted of at least a platinum compound and a fluoropyrimidine, because these regimens are generally used for neoadjuvant treatment. Neoadjuvant treatment was categorized in anthracycline triplets (anthracycline, fluoropyrimidine and platinum compound, e.g. epirubicine, oxaliplatin and capecitabine [EOX]), taxane triplets (taxane, fluoropyrimidine and platinum compound, e.g. 5-FU, leucovorin, oxaliplatin and docetaxel [FLOT]) or fluoropyrimidine-platinum doublets (e.g. capecitabine and oxaliplatin [CapOx]) [13].

2.5. Palliative treatment

Treatment that was initiated at the day of or after the detection of metastases was considered palliative treatment, and categorized in surgical resection (with or without metastasectomy or hyperthermic intraperitoneal chemotherapy [HIPEC]), systemic treatment, radiotherapy on the primary tumor, and radiotherapy on metastases. Palliative systemic treatment strategies were categorized in anthracycline triplets, fluoropyrimidine-platinum doublets, paclitaxel and ramucirumab, taxane monotherapy and other strategies. Systemic treatment regimens in which an agent of a drug group was included that was not used as neoadjuvant treatment were regarded second line, e.g. CapOx to paclitaxel [14].

2.6. Statistical analysis

Patient and tumor characteristics were displayed with counts and percentages for categorical variables, and means and standard deviations or medians and interquartile ranges (IQRs) for continuous variables. Differences between groups were analyzed using chi-squared tests, Fisher's exact tests or Mann-Whitney U tests, whichever was appropriate.

OS was analyzed using the Kaplan Meier method with log-rank test. OS of patients with interval distant metastases was compared with gastric/GEJ adenocarcinoma patients with synchronous metastases who received palliative first-line systemic treatment by performing a propensity score matching using NCR data. Matching was performed at a one-to-one ratio according to the nearest neighbor method without replacement, i.e. striving for the best possible matches. The within-pair difference was minimized by setting a caliper of 0.25 of the standard deviation of the logit of the propensity score. After matching, the balance per item between patients with interval and synchronous metastases was assessed by

the standardized mean difference and displayed in Supplementary Table 2. The following matching variables were included: sex, age, performance status, number of comorbidities, primary tumor location (GEJ/vs. non-cardia stomach), clinical tumor stage, clinical nodal stage, Lauren classification, number of metastatic locations and period of diagnosis. P values < 0.05 were considered statistically significant. Analyses were performed using SAS software (version 9.4, SAS institute, Cary, NC, USA).

3. Data availability

The data that support the findings of our study are available from the Netherlands Cancer Registry. Restrictions apply to the availability of these data, which were used under license for our study.

4. Results

4.1. Baseline characteristics

A total of 164 patients with interval metastases were included over the period 2010–2018 (Fig. 1). Of all patients diagnosed in 2015–2018 who had started neoadjuvant systemic treatment for gastric cancer (n = 1316), 114 (9%) were diagnosed with interval metastases. Patients with interval metastases more frequently had a cT_{4a} or a $cN_{2\text{-}3}$ stage, a diffuse histology type and a poor or unknown differentiation grade compared to patients in whom no interval metastases were detected (Supplementary Table 1).

Of all 164 included patients with interval metastases, 40% were women and median age was 66 years (IQR 58–72; Table 1). Before start of neoadjuvant treatment, most patients had a WHO performance status of 0–1 (70%), whereas 5% had a performance status of 2 and performance status was unknown in 26%. The majority had a non-cardia stomach tumor (71%). The majority received a neoadjuvant anthracycline triplet (84%); others received a taxane triplet (13%) or a fluoropyrimidine-platinum doublet (3%).

4.2. Staging

Staging information was available in patients diagnosed in 2015–2018 (n = 114). Initial staging with a CT scan and gastroscopy was reported in 111 patients (missing: n = 3). A diagnostic laparoscopy before start of treatment was performed in 36% and an FDG-PET/CT scan in 48% of 114 patients, and in 41% and 55% of patients with a $cT_{3\text{-}4a}$ or $cN_{1\text{-}3}$ tumor (n = 83), i.e. patients in whom this was indicated since 2016, respectively. Peritoneal interval metastases were observed in 58 of 73 patients (80%) who did not have a diagnostic laparoscopy prior to neoadjuvant treatment, compared to 26 of 41 patients (63%) who received a diagnostic laparoscopy (P = 0.041). Of the 49 patients with diffuse histology who started neoadjuvant chemotherapy and in whom interval metastases were detected, 35% underwent a pre-chemo diagnostic laparoscopy, which did not differ from patients with a different histology (P = 0.270).

4.3. Location of metastases

Information on metastases detection was available in all patients. In 83% of patients, distant metastases were detected during (exploratory) surgery. In the majority of the patients (77%), peritoneal metastases were found, followed by liver metastases (12%) and distant lymph node metastases (10%). In 70% of all patients, the peritoneum was the only metastasis location, whereas metastatic dissemination was limited to the distant lymph nodes in 7% of the patients. A total of 20% had hematogenous metastases, and metastasis location was unknown in 3% (Table 2).

4.4. Palliative treatment

Fifty-three (32%) of 164 patients underwent a complete surgical resection of the primary tumor (Table 3). Surgical treatment for interval metastases and the primary tumor was performed in 8 patients (5%), including 7 patients undergoing a metastasectomy

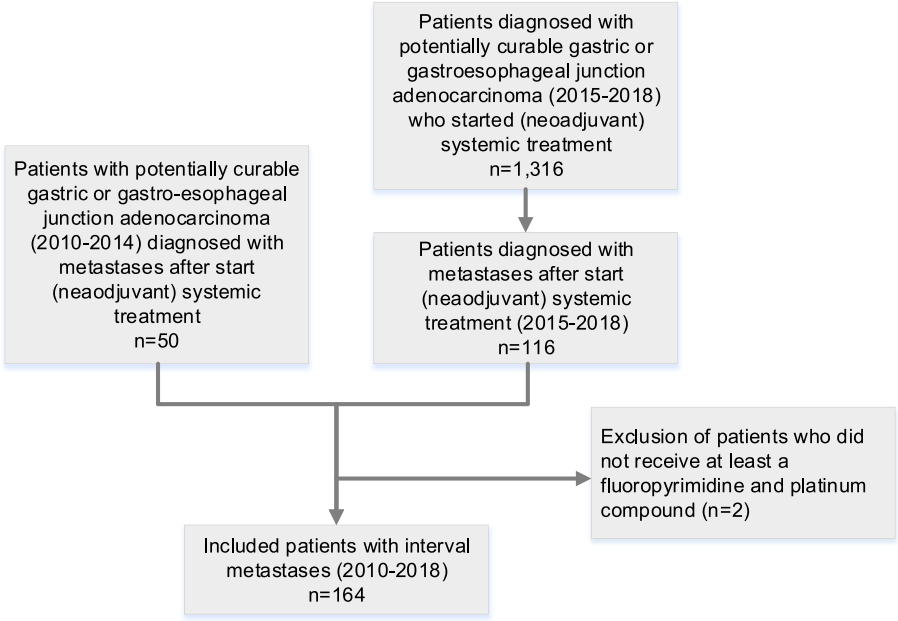

Fig. 1. Patients with interval metastases receiving neoadjuvant therapy for gastric cancer.Flowchart of patient selection. Patients who did not receive at least a fluoropyrimidine and platinum compound received a regimen containing capecitabine in combination with docetaxel, or 5-FU monotherapy.

Table 1
Patient characteristics before start of neoadjuvant treatment in patients with interval metastases (n = 164).

	Patients (n = 164) No. (%)
Female	66 (40%)
Age, years, median (IQR)	66 (58, 72)
<60	48 (29%)
60-69	61 (37%)
70-79	51 (31%)
≥80	4 (2%)
Performance status	
0 or 1	114 (69%)
2	8 (5%)
Unknown	42 (26%)
Number of comorbidities	
0	93 (57%)
1	45 (27%)
≥2	17 (10%)
Unknown	9 (5%)
Tumor location	
Gastro-esophageal junction or cardia	47 (29%)
Stomach	117 (71%)
Clinical tumor stage	
1-2	50 (30%)
3	74 (45%)
4a	15 (9%)
X	25 (15%)
Clinical nodal stage	
0	66 (40%)
1	48 (29%)
2-3	41 (25%)
X	9 (5%)
Lauren classification	
Intestinal	46 (28%)
Diffuse	75 (46%)
Mixed	7 (4%)
Indeterminate	4 (2%)
Unknown	32 (20%)
Signet ring cell histology	32 (20%)
Differentiation grade	
Good	4 (2%)
Moderate	16 (10%)
Poor	114 (70%)
Unknown	30 (18%)
Period of diagnosis	
2010–2014	50 (30%)
2015–2018	114 (70%)
Neoadjuvant treatment	
Anthracycline triplet (ECC, ECF, EOX, EOF)	138 (84%)
Taxane triplet (FLOT, DOC)[a]	21 (13%)
Fluoropyrimidine-platinum doublet (CapOx, FOLFOX, SOX, CapCis)	5 (3%)

IQR = interquartile range; ECC = epirubicin, cisplatin and capecitabine, ECF = epirubicin, cisplatin and 5-FU, EOX = epirubicin, oxaliplatin and capecitabine, EOF = epirubcin, oxaliplatin and 5-FU, FLOT = 5-FU, leucovorin, oxaliplatin and docetaxel, DOC = capecitabine, oxaliplatin and docetaxel, CapOx = capecitabine and oxaliplatin; FOLFOX = 5-FU and oxaliplatin; SOX = S1 and oxaliplatin; CapCis = capecitabine and cisplatin .

[a] One patient received neoadjuvant DOC with trastuzumab.

(not otherwise specified) and 1 patient undergoing HIPEC in study context (PERISCOPE-2) [15]. A total of 59 (36%) patients received palliative systemic treatment after detection of interval metastasis. In 20 (34%) of these 59 patients, this was the same regimen which was administered as neoadjuvant treatment, and in 17 (29%) a fluoropyrimidine with or without a platinum was administered (i.e. systemic agents that were administered as neoadjuvant treatment as well). In 22 (37%) of 59 patients, an agent of a drug group that was not used as neoadjuvant treatment was administered, which was regarded second-line treatment. Of these 22 patients, 12 received paclitaxel/ramucirumab, 8 taxane monotherapy, 1 5-FU/irinotecan (FOLFIRI), and one paclitaxel/regorafenib. Radiotherapy to the primary tumor was applied in 13% of the patients, and to metastases in 2%. In 61 patients (37%) no treatment was allocated.

4.5. OS since detection of metastases

Median OS for all patients was 5.5 months (IQR 2.3–10.2) since detection of interval metastases. Both continuation of the systemic treatment regimen that was administered in the neoadjuvant setting (median OS since detection of metastases 9.5 months), and switch to second-line systemic treatment (median OS 9.9 months) were independently associated with improved OS compared to no systemic treatment (median OS 2.8 months; Fig. 2).

4.6. OS compared to synchronous metastatic patients

OS was compared with a propensity score matched cohort of patients with gastric or GEJ adenocarcinoma and synchronous metastases who received palliative systemic treatment. First, 163 patients with interval metastases (regardless of treatment) were matched to 489 synchronous metastatic patients (one interval metastases patient was excluded because less than three matches were found; Supplementary Table 2). Median OS since start of neoadjuvant treatment was 8.9 months (IQR 5.5, 13.4), compared to 8.3 months (IQR 4.0, 14.3) since start of palliative systemic treatment in synchronous metastatic patients (P = 0.956; Fig. 3).

5. Discussion

In our population-based study, interval metastases were observed in nearly one in ten gastric cancer patients who started with neoadjuvant treatment. Metastases were most frequently detected during surgery, and located in the peritoneum. Longer OS was observed in patients who received systemic treatment after interval metastasis detection compared to no treatment. OS of patients with interval metastases who received palliative systemic treatment - irrespective of subsequent treatment -, calculated since start of neoadjuvant treatment, did not differ from OS of patients with synchronous metastatic gastric cancer since start of palliative systemic treatment.

We observed that 9% of all patients who started neoadjuvant chemotherapy between 2015 and 2018 developed interval metastases. In the pivotal MAGIC-trial, 12% of 237 patients who started neoadjuvant chemotherapy did not undergo surgery for unknown reasons, but presumably interval metastases played an important role [12]. In the recent FLOT4-trial, 8% of the 705 patients who started neoadjuvant treatment did not have a surgical resection [4]. In a recent population-based study metastases were observed peroperatively in 4% of patients who received neoadjuvant FLOT [16]. Thus, our population-based results add to earlier findings that in a considerable number of gastric cancer patients metastases are detected soon after start of treatment with curative intent.

Initial staging in gastric cancer is routinely performed using gastroscopy and CT. However, sensitivity of CT to detect peritoneal and distant metastasis is low [17,18]. In our study, the proportion of patients with interval metastases that were located in the peritoneum was 77%. This rate was higher in patients who did not have a diagnostic laparoscopy before neoadjuvant treatment compared to patients who did have a diagnostic laparoscopy, albeit a limited difference (80% versus 63%). This implies that although diagnostic laparoscopy can be helpful to exclude radiologically occult (peritoneal) metastases [19] and is recommended in (inter)national guidelines, in particular in patients with a $cT_{3\text{-}4a}$ tumor [1,2], it cannot sufficiently rule out early peritoneal involvement. Improved

Table 2
Neoadjuvant treatment and interval metastases characteristics in all patients (n = 164).

	Patients (n = 164) No. (%)
Days between start of neoadjuvant treatment and metastasis detection, median (IQR)	90 (77, 109)
Days between stop of neoadjuvant treatment and metastasis detection, median (IQR)	47 (36, 62)
Number of metastatic sites	
1	150 (91%)
≥2	14 (9%)
Location of metastases[a]	
Peritoneal metastases	126 (77%)
Liver metastases	19 (12%)
Distant lymph node metastases	16 (10%)
Bone metastases	3 (2%)
Lung metastases	2 (1%)
Other metastatic sites	10 (6%)
Unknown location of metastases	5 (3%)
Dissemination of metastases	
Distant lymph nodes only	12 (7%)
Peritoneum only	114 (70%)
Hematogenous	33 (20%)
Unknown	5 (3%)
Detection of metastases[b]	
During (exploratory) surgery	136 (83%)
Restaging using (PET-)CT scan	11 (7%)
Unknown	17 (10%)

IQR, interquartile range; PET, positron emission tomography; CT, computed tomography.
[a] As patients can have metastases at multiple locations, the sum of all percentages is greater than 100%.

staging techniques at initial diagnosis may enhance detection of metastases in an early stage and decrease the rate of interval metastases. Currently, the added value of FDG-PET/CT and diagnostic laparoscopy as initial staging in patients with cT3-T4 tumors is investigated in the PLASTIC study [20]. However, it is unlikely that FDG-PET/CT will aid in the detection of peritoneal metastases specifically [17,21]. The implementation of novel methods such as the detection of mRNA in peritoneal lavage fluid [22,23] could contribute to peritoneal metastases detection.

Table 3
Palliative treatment.

	Patients (n = 164) No. (%)
Surgical resection	53 (32%)
Resection primary tumor only	45
Resection primary tumor and metastasectomy	7
Resection primary tumor and HIPEC	1
Palliative systemic treatment	59 (36%)
Anthracycline triplet (ECC, ECF, EOX, EOF)	17
Fluoropyrimidine-platinum doublet (CapOx, FOLFOX, SOX, CapCis)	15
Paclitaxel and ramucirumab	12
Taxane monotherapy	8
Other	7
Palliative radiotherapy primary tumor	22 (13%)
Palliative radiotherapy metastases	4 (2%)
Best supportive care only	61 (37%)

HIPEC, hyperthermic intraperitoneal chemotherapy; ECC, epirubicin, cisplatin and capecitabine; ECF, epirubicin, cisplatin and 5-FU; EOX, epirubicin, oxaliplatin and capecitabine; EOF, epirubcin, oxaliplatin and 5-FU; FLOT, 5-FU, leucovorin, oxaliplatin and docetaxel; CapOx, capecitabine and oxaliplatin; FOLFOX, 5-FU and oxaliplatin; SOX, S1 and oxaliplatin; CapCis, capecitabine and cisplatin.

The median survival time calculated from start of neoadjuvant treatment of 8.9 months was comparable with OS of patients with synchronous metastases who received first-line palliative systemic treatment. These results implicate that interval metastases can be regarded as synchronous metastases in terms of OS, and suggest a similar response to systemic treatment. Importantly, patients diagnosed with synchronous peritoneal metastases are known to have a poor prognosis [24]. These are detected with imaging rather than laparoscopy and may therefore have a higher tumor load than in patients with interval peritoneal metastases detected at a later stage. These interval metastases patients with most likely limited peritoneal dissemination may have a more favorable tumor biology and may be particularly suitable for local peritoneal treatment with HIPEC [25].

Improving the diagnosis of metastatic disease at initial staging could improve decision-making on systemic treatment strategies, and thereby improve patient outcomes. This has several reasons. First, although components of the neoadjuvant treatment are similar to first-line palliative systemic treatment, in contrast to the curative setting, doublet chemotherapy is preferred over triplet chemotherapy in the palliative setting because of similar survival rates, while doublets are less toxic [10]. Furthermore, in neoadjuvant treatment, HER2 is not taken into consideration, whereas the use of trastuzumab in first-line palliative treatment can improve patient outcomes in HER2 positive patients [26,27]. Finally, the use of a taxane triplet as initial treatment (such as FLOT) could impair the use of a taxane in second line, which is currently recommended as second-line monotherapy or in combination with ramucirumab [2].

Patients who received systemic treatment after detection of metastases showed better survival rates compared to no systemic treatment. Although these results clearly suggest that interval metastases patients may benefit from systemic treatment, the question remains what the optimal treatment strategy after detection of metastases is. Our results indicate that both continuing neoadjuvant treatment and switching to second-line systemic treatment seem beneficial, suggesting any of these systemic treatment strategies may improve outcomes in these patients. Interestingly, a remarkable number of patients (63%) did not receive systemic treatment after detection of metastases, despite they were considered eligible to undergo surgery at initial diagnosis. Future studies should focus on reasons for refraining from sequential treatment in these patients, which most probably will include patients' request or performance status, as these were most frequently reasons to refrain from gastrectomy [28].

A limitation of this study includes missing data in the patients diagnosed in 2010–2014, e.g. on staging. In addition, data on peritoneal tumor load was missing, as well as on performance status after neoadjuvant treatment or surgery, and therefore we could not rule out a selection bias. Moreover, we could only analyze the proportion of patients with interval metastases in patients who were diagnosed in 2015–2018. Another limitation is that the study design was retrospective. Furthermore, as FLOT was not state of the art therapy in the period the included patients were diagnosed and treated, only a few patients received a taxane triplet, and as a result we could not analyze results on FLOT treatment. An important limitation is that a considerable number of patients with interval metastases did not undergo laparoscopy, increasing the possibility peritoneal metastases were missed, which could have resulted in an underestimation of synchronous peritoneal metastases. Our analysis is strengthened by the inclusion of a large nationwide cohort.

In conclusion, interval metastases were observed in 9% of gastric cancer patients after start of neoadjuvant treatment in daily clinical practice, of which the majority was located in the peritoneum and

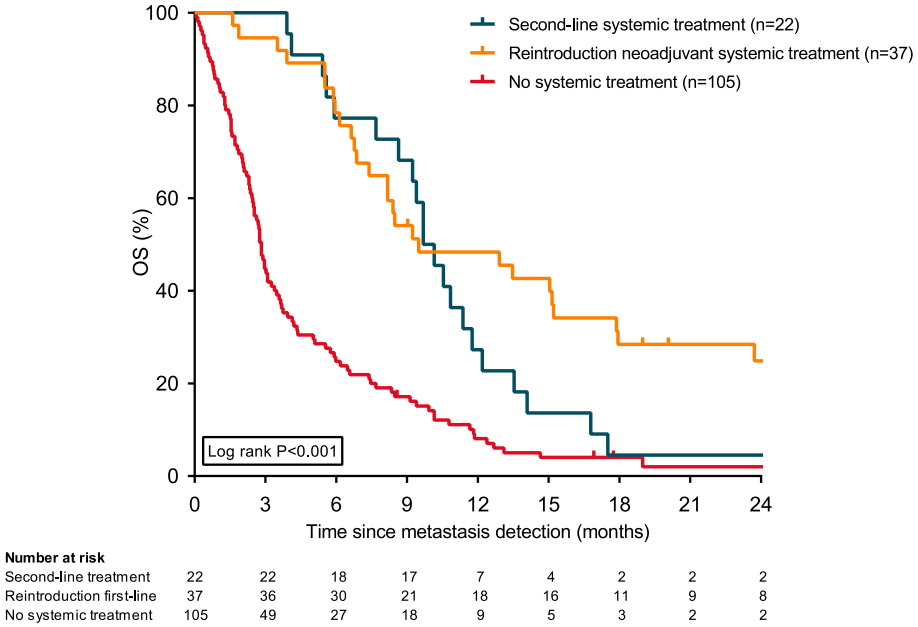

Fig. 2. Kaplan Meier curves showing OS for interval metastases patients stratified for type of treatment after detection of metastasis* Primary tumor resection includes both resection of primary tumor only and resection of the primary tumor with HIPEC or metastasectomy, not followed by systemic treatment.

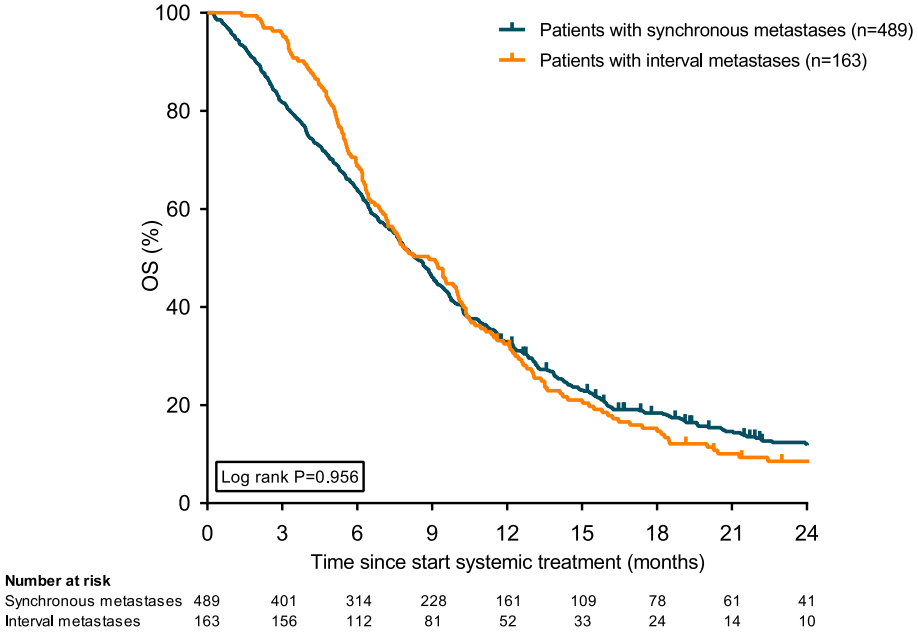

Fig. 3. Kaplan Meier curves for overall survival in patients with interval metastases versus a matched cohort of patients with synchronous metastases who received palliative systemic treatmentOverall survival was calculated since start of neoadjuvant treatment in patients with interval metastases, and first-line palliative systemic treatment in the matched cohort of patients with synchronous metastases.OS = overall survival.

detected during (exploratory) surgery. OS did not differ from synchronous metastatic gastric cancer patients treated with systemic therapy. Use of palliative systemic treatment after detection of metastases could improve survival in these patients.

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Ethical approval

According to the Central Committee on Research involving Human Subjects, this type of study does not require approval from

an ethics committee in the Netherlands. The study was approved by the Privacy Review Board of the NCR and the scientific committee of the Dutch Upper GI Cancer Group. The reporting of this study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [29].

CRediT authorship contribution statement

Willemieke P.M. Dijksterhuis: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, preparation, Writing – review & editing, Resources. **Tiuri E. Kroese:** Conceptualization, Writing – review & editing. **Rob H.A. Verhoeven:** Methodology, Writing – original draft, preparation, Writing – review & editing, Supervision, Resources. **Peter S.N. van Rossum:** Writing – review & editing. **Stella Mook:** Writing – review & editing. **Nadia Haj Mohammad:** Writing – review & editing. **Maarten C.C.M. Hulshof:** Writing – review & editing. **Suzanne S. Gisbertz:** Writing – review & editing. **Jelle P. Ruurda:** Writing – review & editing. **Martijn G.H. van Oijen:** Conceptualization, Methodology, Writing – original draft, preparation, Writing – review & editing, Supervision. **Richard van Hillegersberg:** Conceptualization, Writing – review & editing. **Hanneke W.M. van Laarhoven:** Conceptualization, Methodology, Writing – original draft, preparation, Writing – review & editing, Funding acquisition, Supervision.

Declaration of competing interest

RHAV reports grants from BMS and Roche. NHM reports a consult/advisory role for BMS, MSD Servier, Eli Lilly, reserach grant from Servier. SSG reports a research grant from Olympus and consulting fees from Medtronic. MGHvO reports grants from Amgen, BMS, Lilly, Nordic, Merck, Roche and Servier. HWMvL reports a consult/advisory role for BMS, Celgene, Lilly, Merck, and Nordic, and Servier and has received unrestricted research funding from Bayer, BMS, Celgene, Lilly, Merck Serono, MSD, Nordic, Philips, Roche and Servier. The other authors declare that they have no conflicts 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.ejso.2022.03.003.

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