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ORIGINAL ARTICLE

Synchronous peritoneal metastases of gastric cancer origin: incidence, treatment and survival of a nationwide Dutch cohort

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Abstract

Introduction The peritoneum is a predilection site for gastric cancer metastases. Current standard treatment for gastric cancer patients with synchronous peritoneal metastases is palliative systemic therapy. However, its efficacy is largely unknown. The aim of this study was to investigate the incidence, treatment and survival patterns of gastric cancer patients with synchronous peritoneal metastases in the Netherlands.

Methods All newly diagnosed gastric adenocarcinoma patients with synchronous peritoneal metastases between 1999 and 2017 were selected from the Netherlands Cancer Registry (NCR). Incidence, treatment and survival patterns were analyzed.

Results In total, 3,773 patients were identified from the NCR. The incidence of synchronous peritoneal metastases in gastric cancer patients increased from 18% in 2008 to 27% in 2017. The use of systemic therapy increased from 15% in 1999–2002 to 43% in 2013–2017 ($p < 0.001$). The median survival of the entire cohort did not significantly increase over time. Median survival of patients treated with systemic therapy increased from 7.4 months in 1999–2002 to 9.4 months in 2013–2017 ($p = 0.005$). In contrast, median survival of patients *not* treated with systemic therapy decreased from 3.3 months in 1999–2002 to 2.1 months in 2013–2017 ($p < 0.001$). Some clinical and pathological data such as the extent of the peritoneal metastases were not available.

Conclusion Synchronous peritoneal metastases are increasingly diagnosed in gastric cancer patients. In recent years, more patients were treated with systemic treatment and survival of these patients increased. However, as survival of the entire group did not improve over time, the effect of systemic therapy remains unknown.

Keywords Gastric cancer · Peritoneal metastases · Chemotherapy · Survival · Incidence · Treatment

Abbreviations

cN	Clinical nodal stage
cT	Clinical tumor stage
CRS	Cytoreductive surgery
ESR	European standardized rate
HIPEC	Hyperthermic intraperitoneal chemotherapy
HR	Hazard ratio
ICD-O	International Classification of Disease for Oncology
NCR	Netherlands Cancer Registry
OS	Overall survival

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PM Peritoneal metastases
TNM Tumor–node–metastasis system

Introduction

Worldwide, the incidence of gastric cancer has steadily declined over the last 50 years [1]. This has been linked to a decline in *Helicobacter pylori* infections and their treatment, and to dietary changes [1, 2]. In the Netherlands, the incidence of gastric cancer has decreased from 2054 patients in 1999 to 1535 in 2017 [3]. Multimodality treatment consisting of a surgical resection with perioperative systemic therapy has become standard therapy for patients treated with curative intent [4, 5]. However, survival outcomes of gastric cancer patients remain poor with a 5-year overall survival of 18–25% for all stages [6]. A major reason for this dismal survival is the high percentage of patients presenting with metastatic disease at diagnosis. A Dutch population-based study showed that about 40% of patients presented with synchronous metastatic disease [7]. Most common sites for gastric cancer metastases are the liver, the peritoneum, the lung, and the bones [8].

Median survival of all gastric cancer patients with synchronous metastases is around 4 months [9, 10]. For patients presenting with peritoneal metastases, median survival is 3–4 months [11]. Currently, the only treatment option for these patients in the Netherlands is palliative systemic therapy. Its efficacy in improving survival is subject of debate [11, 12].

In the past decade, new diagnostic tools and treatment options were introduced for gastric cancer patients. For example, a diagnostic laparoscopy has become part of the standard diagnostic workup of newly diagnosed locally advanced gastric cancer patients as it was added to the Dutch guideline in 2016 [13]. It is unclear whether these changes in diagnostic workup and treatment options have affected incidence and outcome of patients with synchronous peritoneal metastases of gastric cancer origin. This study aimed to analyze the incidence, treatment strategies and survival of gastric cancer patients with synchronous peritoneal metastases in the Netherlands over the past 2 decades.

Methods

Data collection

A nationwide population-based cohort study with data from the Netherlands Cancer Registry (NCR) was conducted. The NCR registers all newly diagnosed malignancies in the Netherlands through notification by the pathological anatomical national automated archive (PALGA) and administrative hospital data. Specially trained data managers collect patient, tumor and treatment characteristics. Through linkage with the Municipal Administrative Database, in which all records of births, deaths and emigrations in the Dutch population are registered, data on vital status were obtained from all patients until February 2019.

Patient selection

All patients who were diagnosed with a gastric adenocarcinoma (non-cardia only) and synchronous peritoneal metastases between 1999 and 2017 were included. Before 2008, there were regional differences in the registration of certain items, such as the location of the metastases which was not registered in all regions. As a result, the incidence numbers of peritoneal metastases in gastric cancer patients before 2008 are not complete for the entire nation and are, therefore, not reported. As this is only due to regional registration differences, it is not expected to introduce a selection bias in the analyses regarding treatment and survival data of patients with synchronous peritoneal metastases prior to 2008.

Until 2015, the diagnostic methods used to detect peritoneal metastases were not registered in the NCR; this information is, therefore, not included. Topography, morphology and metastatic locations are coded in the NCR according to the third edition of the *International Classification of Disease for Oncology* (ICD-O3) [14]. The tumor location was categorized as follows: proximal/middle stomach (fundus, corpus, and lesser and greater curvature) (C16.1, C16.2, C16.5, C16.6), distal stomach (antrum and pyloric region) (C16.3, C16.4), overlapping regions (C16.8), and not otherwise specified (C16.9). The following ICD-O codes for metastatic locations were categorized as peritoneal metastases: C48.1–C48.8. Additional variables that were collected: age, sex, clinical TNM stage, pathological TNM stage, year of diagnosis, Lauren classification and the administered therapy (gastric cancer resection, systemic therapy, cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC), and 'other', the latter mostly consisting of radiotherapy or local treatment of metastases (by surgery or radiotherapy).

TNM classification

Over the years, the subsequent UICC TNM classifications have been used: the fifth (1999–2002), the sixth (2003–2009), the seventh (2010–2016), and the eighth (since 2017). All TNM classifications were re-coded to establish uniformity (Table S1).

Statistical analysis

European Standardized Rate (ESR) incidence per 100,000 person-years was calculated according to the European standard population. Categorical variables were compared using a Chi-square test. Kaplan–Meier overall survival curves were compared by the log rank test. Overall survival was defined as time from diagnosis to death or until February 2019. A p value $p < 0.05$ was considered statistically significant. Multivariable logistic regression analyses were performed to investigate an association between clinical characteristics and the administration of systemic therapy. Adjustments were made for: year of diagnosis, sex, age, tumor location, clinical tumor (cT) and clinical nodal (cN) stage, Lauren classification and number of metastatic locations. Due to the low number, patients registered with a cT0 tumor were removed from the multivariable analyses. A multivariable Cox-regression analysis was performed to identify prognostic factors for overall survival stratified for systemic therapy and for patients with metastatic disease confined to the peritoneum or at multiple localizations adjusted for year of diagnosis, sex, age, tumor location, Lauren classification, cT stage and cN stage. All statistical analyses were performed using SPSS v25 (IBM, Armonk, United States) or SAS 9.4 (SAS Institute, North Carolina, United States).

Results

Incidence

Between 1999 and 2017, 3773 patients were registered in the NCR with gastric cancer and synchronous peritoneal metastases. In 2437 (65%) patients, the peritoneum was the only metastatic location. Most frequently affected other locations were the liver ($n = 656$, 41%) and extra regional lymph nodes ($n = 558$, 35%). While the ESR of all gastric cancer diagnoses decreased over time, the ESR of gastric cancer patients with synchronous peritoneal metastases remained stable from 2008 (1.19/100,000 person-years) to 2017 (1.10/100,000 person-years), resulting in an increased proportion of gastric cancer patients with synchronous peritoneal metastases over the years; from 18% ($n = 244$) in 2008 to 27% ($n = 276$) in 2017 (Table 1).

Baseline characteristics

Baseline characteristics stratified for time period are summarized in Table 2. The majority of patients was male (54%) and the median age was 68 years. The primary tumor was mainly located in the proximal/middle stomach (26%), distal stomach (26%), or overlapping regions (39%). In most cases, a clinical tumor stage of cT2-3 (30%) or cT4 (23%) and a clinical nodal stage of cN0 (24%) or cN1-2 (36%) was found (Table 2). Of note, the proportion of patients with diffuse type gastric cancer increased over time (34% from 1999 to 2002 to 45% from 2013 to 2017, $p < 0.001$).

Treatment

The use of systemic treatment in gastric cancer patients with peritoneal metastases increased over time. In the period 1999–2002, 15% ($n = 61$) of patients were treated with systemic therapy, whereas in the period 2013–2017, it was administered to 43% ($n = 580$) of patients ($p < 0.001$) (Table 3). Multivariable regression analysis showed that patients diagnosed in the more recent time cohorts (2003–2017), patients of younger age, patients with a primary tumor in the proximal/middle stomach, and patients with metastases confined to the peritoneum were more likely to undergo systemic therapy (Table 4).

The proportion of patients undergoing primary tumor resection decreased over time, from 18% ($n = 76$) in 1999–2002 to 12% ($n = 157$) in 2013–2017 ($p = 0.001$). CRS and HIPEC was only performed in the most recent time cohorts, on a very limited scale. The proportion of patients that received no treatment decreased from 55% ($n = 228$) in 1999–2002 to 46% ($n = 616$) in 2013–2017 ($p < 0.001$).

Table 1 Incidence of gastric cancer patients and gastric cancer patients with synchronous peritoneal metastases as registered in the Netherlands Cancer Registry (NCR)

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Gastric cancer patients (n)	1358	1333	1324	1317	1322	1275	1219	1128	1186	1042
ESR gastric cancer	6.48	6.11	5.99	5.82	5.73	5.47	5.02	4.54	4.63	3.98
Peritoneal metastases (*n*)	244	250	260	236	269	265	261	262	284	276
ESR gastric cancer with synchronous peritoneal metastases	1.19	1.17	1.20	1.07	1.20	1.17	1.11	1.10	1.18	1.10
Proportion (%)	18,0	18,8	19,6	17,9	20,3	20,8	21,4	23,2	23,9	26,5

ESR European Standardized Rate

Table 2 Baseline characteristics of gastric cancer patients with synchronous peritoneal metastases

Time period	1999–2002 $n=413$[a]	2003–2007 $n=753$[a]	2008–2012 $n=1259$	2013–2017 $n=1348$	p value
Median age, years (range)	67 (22–91)	68 (16–92)	68 (19–94)	69 (25–100)	< 0.001
Sex *n* (%)					0.005
Male	230 (56)	370 (49)	658 (52)	765 (57)	
Female	183 (44)	83 (51)	601 (48)	583 (43)	
Tumor location					< 0.001
Proximal/middle stomach	99 (24)	159 (21)	316 (25)	388 (29)	
Distal stomach	118 (29)	186 (25)	332 (26)	352 (26)	
Overlapping	146 (35)	324 (43)	521 (41)	496 (37)	
NOS	50 (12)	84 (11)	90 (7)	112 (8)	
cT stage[b] *n* (%)					< 0.001
T0	1 (0)	3 (0)	2 (0)	1 (0)	
T1	4 (1)	11 (1)	17 (1)	2 (0)	
T2–3	22 (5)	113 (15)	318 (25)	674 (50)	
T4	146 (35)	174 (23)	276 (22)	253 (19)	
Tx	240 (58)	452 (60)	646 (51)	418 (31)	
cN stage[b] *n* (%)					< 0.001
N0	28 (7)	91 (12)	305 (24)	476 (35)	
N1–2	121 (29)	224 (30)	446 (35)	576 (43)	
N3	4 (1)	21 (3)	27 (2)	46 (3)	
Nx	260 (63)	417 (55)	481 (38)	250 (19)	
Lauren classification					< 0.001
Intestinal type	129 (31)	209 (28)	373 (30)	346 (26)	
Diffuse type	139 (34)	295 (39)	567 (45)	601 (45)	
Mixed type	6 (1)	26 (3)	60 (5)	76 (6)	
Unknown	139 (34)	223 (30)	259 (21)	325 (24)	
Metastatic locations *n* (%)					< 0.001
Peritoneal metastases only	288 (70)	508 (67)	809 (64)	832 (62)	
Peritoneal metastases and others	125 (30)	245 (33)	450 (36)	516 (38)	

NOS not otherwise specified, *cT* clinical tumor stage, *cN* clinical nodal stage

[a]Incomplete numbers due to regional registry differences before 2008

[b]After re-coding of four different TNM classifications (as depicted in Table S1)

Table 3 Treatment of gastric cancer patients with synchronous peritoneal metastases

Time period	Systemic chemotherapy *n* (%)	Primary tumor resection *n* (%)	CRS and HIPEC *n* (%)	Other[a] *n* (%)	None *n* (%)
1999–2002	61 (15)	76 (18)	0 (0)	134 (32)	228 (55)
2003–2007	203 (27)	124 (16)	0 (0)	234 (31)	375 (50)
2008–2012	527 (42)	171 (14)	4 (0)	329 (26)	555 (44)
2013–2017	580 (43)	157 (12)	29 (2)	392 (29)	616 (46)
p value	< 0.001	0.001	< 0.001	0.002	< 0.001
Metastatic locations					
Peritoneal metastases only	887 (36)	443 (18)	27 (1)	776 (32)	1102 (45)
Peritoneal metastases and others	484 (36)	85 (6)	6 (< 1)	307 (23)	664 (50)

CRS cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemotherapy

[a]Therapies registered as other, radiotherapy, metastasectomy

Table 4 Multivariable logistic regression analysis for the administration of systemic therapy in gastric cancer patients with synchronous peritoneal metastases

	OR (95% CI)	*p* value
Year of diagnosis		
1999–2002	1.00	
2003–2007	2.45 (1.75–3.43)	< 0.001
2008–2012	5.16 (3.75–7.12)	< 0.001
2013–2017	4.81 (3.46–6.69)	< 0.001
Sex		
Male	1.00	
Female	0.92 (0.79–1.07)	0.25
Age		
< 45 years	1.00	
46–60 years	0.56 (0.41–0.75)	< 0.001
61–75 years	0.23 (0.18–0.31)	< 0.001
> 75 years	0.05 (0.04–0.07)	< 0.001
Tumor location		
Proximal/middle stomach	1.00	
Distal stomach	0.77 (0.63–0.95)	0.02
Overlapping	0.80 (0.67–0.97)	0.02
NOS	0.58 (0.43–0.79)	0.001
cT stage[a]		
T1	1.00	
T2–3	1.51 (0.67–3.42)	0.32
T4	1.10 (0.49–2.49)	0.82
Tx	1.10 (0.49–2.47)	0.82
cN stage[a]		
N0	1.00	
N1–2	1.21 (0.99–1.47)	0.06
N3	0.76 (0.47–1.21)	0.24
Nx	0.73 (0.59–0.9)	0.003
Lauren classification		
Intestinal type	1.00	
Diffuse type	0.94 (0.78–1.14)	0.55
Mixed type	1.11 (0.76–1.62)	0.58
Unknown	1.09 (0.88–1.35)	0.46
Metastatic locations		
Peritoneal metastases only	1.00	
Peritoneal metastases and others	0.87 (0.74–1.02)	0.08

NOS not otherwise specified, *cT* clinical tumor stage, *cN* clinical nodal stage

[a]After re-coding of four different TNM classifications (as depicted in Table S1)

Survival

Median overall survival of all gastric cancer patients with synchronous peritoneal metastases did not change significantly over time (Table 5, *p = 0.065*). In addition, no improved overall survival was seen in patients with metastases confined to the peritoneum ($p = 0.051$). Finally, overall

Table 5 Overall survival of gastric cancer patients with synchronous peritoneal metastases

	1999–2002			2003–2007			2008–2012			2013–2017			*p* value[#]
	n (%)	MS	HR	*n* (%)	MS	HR	*n* (%)	MS	HR	*n* (%)	MS	HR	
All patients	413	3.6		753	3.6		1259	4.1		1348	4.4		0.065
Systemic chemotherapy	61 (15)	7.4	Ref	203 (27)	7.5	0.81	527 (42)	7.6	0.84	580 (43)	9.4	0.77	0.005
No systemic chemotherapy	352 (85)	3.3	Ref	550 (73)	2.6	1.26^	732 (58)	2.2	1.45^	768 (57)	2.1	1.67^	< 0.001
p value*		*p* = 0.002			*p* < 0.001			*p* < 0.001			*p* < 0.001		
Peritoneal metastases only	288	3.9		508	3.8		809	4.9		832	5.3		0.051
Systemic chemotherapy	41 (14)	6.7	Ref	125 (25)	8.0	0.61^	351 (43)	8.3	0.65^	370 (44)	10.0	0.62^	0.001
No systemic chemotherapy	247 (86)	3.6	Ref	383 (75)	2.8	1.34^	458 (57)	2.4	1.60^	462 (56)	2.8	1.79^	< 0.001
p value*		*p* = 0.37			*p* < 0.001			*p* < 0.001			*p* < 0.001		
Peritoneal metastases and other	125	3.0		245	3.0		450	3.1		516	3.1		0.633
Systemic chemotherapy	20 (16)	8.9	Ref	78 (32)	6.7	1.19	176 (39)	6.3	1.23	210 (41)	7.6	1.00	0.533
No systemic chemotherapy	105 (84)	2.5	Ref	167 (68)	2.0	1.18	274 (61)	1.9	1.37^	306 (59)	1.5	1.61^	0.054
p value*		*p* < 0.001			*p* < 0.001			*p* < 0.001			*p* < 0.001		

MS median overall survival in months, *HR* hazard ratio between time periods after multivariable adjustment for sex, age, tumor location, cT stage, cN stage and Lauren classification

^Significant hazard ratio; *systemic chemotherapy versus no systemic chemotherapy; [#]median survival between time periods

survival remained stable in patients with metastases at multiple locations ($p = 0.633$).

Median overall survival increased over time in patients treated with systemic therapy (Fig. 1a, $p = 0.005$). Remarkably, the increase in overall survival was most evident between the latest two time cohorts, where an increase was observed from 7.6 months in 2008–2012 to 9.4 months in 2013–2017, whereas the proportion of patients treated with systemic therapy did not increase concordantly, from 42 to 43%. The same trend was observed in patients with metastases confined to the peritoneum (Fig. 1c, $p = 0.001$), but not in patients with peritoneal metastases and metastases at other locations (Fig. 1e, $p = 0.533$). In patients who did not undergo systemic therapy, the median overall survival decreased over time (Fig. 1b, $p < 0.001$). This trend was also seen in patients with metastases confined to the peritoneum (Fig. 1d, $p < 0.001$), but the trend was not significant in the group of patients with peritoneal metastases and metastases at other locations (Fig. 1f, $p = 0.054$).

After multivariable adjustment for sex, age, tumor location, cT and cN stage, the survival of patients with metastases confined to the peritoneum who were treated with systemic therapy improved over time, while the survival of patients with both peritoneal metastases and systemic metastases who were treated with systemic therapy did not significantly change. In patients who did not undergo systemic therapy, survival decreased over time, both in patients with peritoneal metastases only and in patients with metastases at multiple locations.

Discussion

In this nationwide cohort study, it was found that the proportion of gastric cancer patients diagnosed with synchronous peritoneal metastases increased over time. That is, there was a yearly increase in the absolute number of gastric cancer patients with synchronous peritoneal metastases while the incidence of gastric cancer itself decreased. At the end of the study period, in 2017, 27% of the newly diagnosed gastric cancer patients had synchronous peritoneal metastases, revealing the peritoneal cavity to be a clinically relevant and challenging metastatic site. In addition, an increase in the use of systemic therapy over time was observed. However, this did not result in a significant increase in the overall survival of gastric cancer patients with synchronous peritoneal metastases. A relatively high proportion of patients was documented to have a primary tumor without serosal involvement (< T4). However, it should be noted that stage grouping in this study was almost invariably based on clinical staging, which is known for its inaccuracy in gastric cancer [15]. In addition, T-stage was often unknown (Table 2). From other studies, it is known that advanced tumor stage is associated with the presence of peritoneal metastases [16].

Recently, a shift in the distribution of histological subtypes of gastric adenocarcinoma was described with the diffuse type now being the predominant subtype [9, 17]. This might partially explain the increase in patients with peritoneal metastases, as the diffuse type gastric cancer is more prone to metastasize to the peritoneum than the intestinal type [18, 19]. Additional explanations for the increased frequency of detecting peritoneal metastases can be found in the diagnostic workup of gastric cancer. The accuracy of Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) has improved over the years [20, 21]. Furthermore, the diagnostic laparoscopy has been added to the Dutch national guideline for staging gastric cancer patients with locally advanced disease in 2016 [13]. The diagnostic laparoscopy is essential for the evaluation of the peritoneum in gastric cancer and it avoids unnecessary laparotomies [22]. The efficacy of the diagnostic laparoscopy in gastric cancer staging is currently under investigation [23].

With the introduction of new systemic therapies, such as taxanes, trastuzumab, ramucirumab, and trifluoride/tipiracil, the armamentarium of the medical oncologist expanded during the last decades [24–26]. Over the years, the proportion of patients with gastric cancer and synchronous peritoneal metastases who were treated with systemic treatment increased from 15% in 1999–2002 to 42% in 2008–2012 and remained stable thereafter. Nevertheless, the overall survival of all gastric cancer patients with peritoneal metastases did not improve in this time period. This finding questions the benefit of systemic therapy in this patient group. The survival increase in patients treated with systemic therapy is most likely the result of lead time bias. That is, by improved diagnostic modalities and more use of the diagnostic laparoscopy, peritoneal metastases have been diagnosed at an earlier stage, leading to an apparently longer survival time. Furthermore, the poor prognosis of patients not treated with systemic therapy can in part be explained by immortal-time bias.

Thus, systemic therapy alone is not the optimal palliative treatment strategy for peritoneal metastases. Intra-abdominal chemotherapy might be a better option as it has a few advantages over systemic therapy. First, it provides superior penetration into the peritoneal lesions; second, the peritoneum-blood barrier allows for a higher intra-abdominal concentration of cytostatic drugs without systemic toxicity; and lastly, the chemotherapeutic agents can be heated which potentially improves the cytotoxic effects [27–29]. The combination of CRS and HIPEC has been used to treat patients with peritoneal metastases of colorectal and ovarian origin [30, 31]. Similarly, recent nationwide cohort data have suggested a survival benefit for gastric cancer patients with synchronous peritoneal metastases treated with CRS and HIPEC

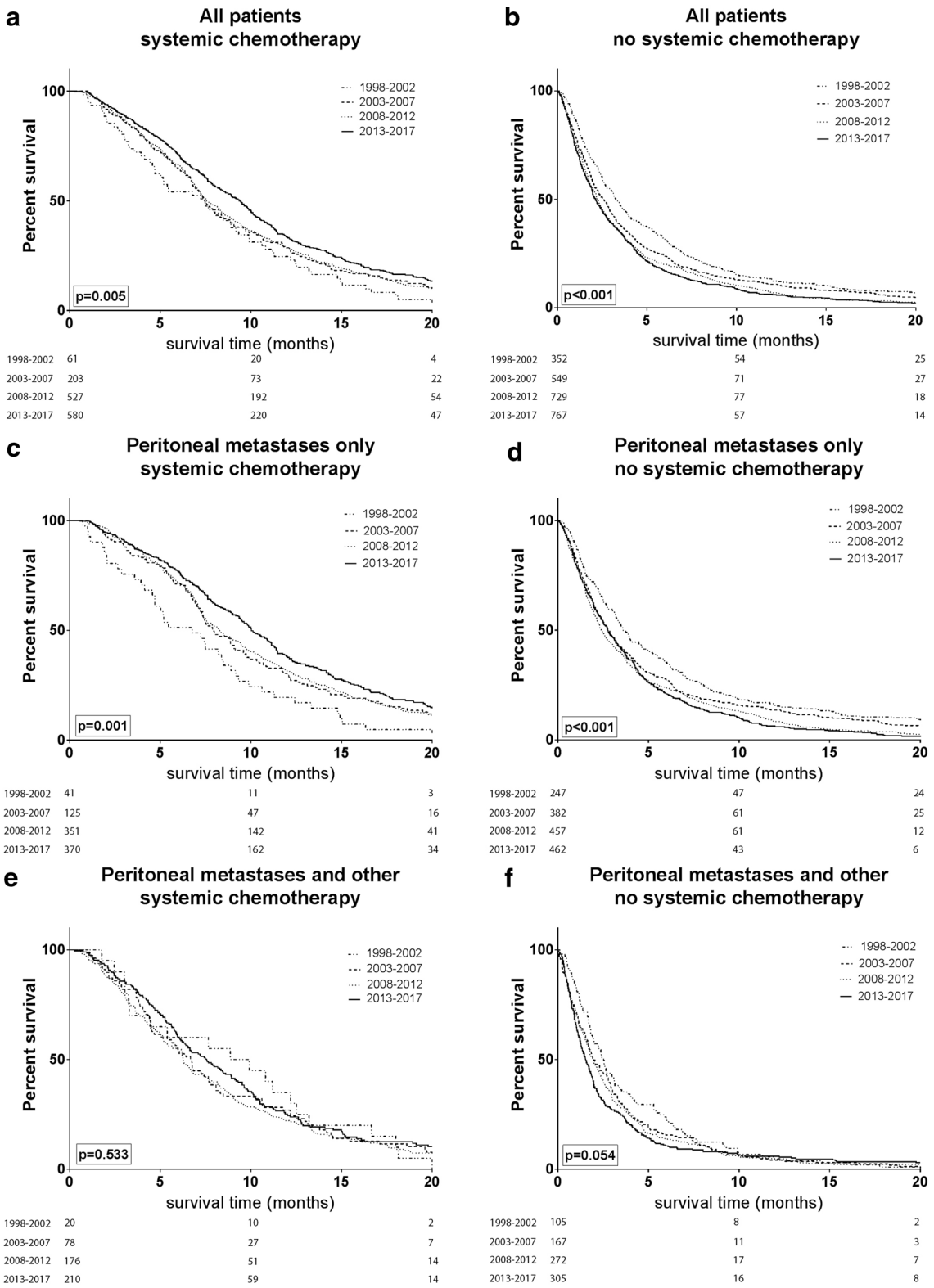

Fig. 1 Kaplan–Meier survival curves by time period for **a** all patients treated with systemic chemotherapy, **b** all patients not treated with systemic chemotherapy, **c** patients with peritoneal metastases only treated with systemic chemotherapy, **d** patients with peritoneal metastases only not treated with systemic chemotherapy, **e** patients with peritoneal metastases and metastases at other locations treated with systemic chemotherapy, **f** patients with peritoneal metastases and metastases at other locations not treated with systemic chemotherapy

[32–34]. At current times, in the Netherlands, a HIPEC procedure for gastric cancer is only performed within the context of the PERISCOPE II trial [35]. There are other ways to apply intra-abdominal chemotherapy with palliative intent. A few studies showed effect of a catheter-based approach in gastric cancer patients with peritoneal metastases [36]. In addition, pressurized intraperitoneal aerosol chemotherapy (PIPAC) was recently introduced as a new technique, and is practiced in a growing amount of hospitals worldwide [37]. A feasibility study showed that PIPAC is safe and well tolerated in gastric cancer patients with peritoneal metastases [38]. Nevertheless, PIPAC is not yet practiced for gastric cancer in the Netherlands. Although catheter-based intra-abdominal chemotherapy and PIPAC have theoretical advantages over systemic therapy, their efficacy has not yet been proven. Therefore, these techniques should only be used in a study setting.

The median overall survival in our nationwide cohort (3.6–4.4 months) was lower than in other studies, with median overall survival rates ranging from 4.8 to 17.0 months [39–43]. This can be explained by the fact that we reported on the entire population of patients with peritoneal metastases from gastric origin, including 47% of patients who did not receive any anti-cancer treatment at all. All other studies reported on patients who underwent treatment, such as palliative systemic therapy or a primary tumor resection. Although the effects of these treatments on overall survival are unclear, patients selected for treatment are likely to have a more favorable prognosis than patients considered unsuitable for treatment. Furthermore, selecting a patient for treatment inevitably creates immortal-time bias.

The strengths of this study are the nationwide population-based study design and the large number of included patients. Before 2008, the NCR consisted of several regional databases, which all registered the presence of metastatic disease, but not invariably its location. This led to an underestimation of the proportion of patients with synchronous peritoneal metastases in the years 1999–2007. Therefore, the incidence rates in these years were not reported in this study. Even nowadays, peritoneal metastases may be missed during the initial staging process, thus there still is an underestimation of the actual number of patients with synchronous peritoneal metastases [44, 45]. Another limitation of the study is the lack of information on the extent of peritoneal disease. The peritoneal carcinomatosis index is known to affect overall survival, but was not registered by the NCR during the study years [46]. The peritoneal carcinomatosis index has been integrated in the NCR nowadays, but still for many patients with (widespread) peritoneal metastases, its exact extent is irrelevant. Finally, another limitation of the study is the high proportion of unknown clinical tumor and clinical nodal stage which may have impeded the interpretation of these factors in multivariate analyses.

In conclusion, this population-based study showed that the absolute and relative incidence of gastric cancer patients with synchronous peritoneal metastases increased in the Netherlands. Although the use of systemic treatment increased significantly, there was no improvement of overall survival for the total group of patients. Therefore, it is important to study alternative treatment strategies, such as CRS and HIPEC, catheter-based intra-abdominal chemotherapy or repetitive PIPAC to treat peritoneal metastases of gastric cancer origin.

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