European Journal of Surgical Oncology 45 (2019) 1926–1933

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Poor compliance with perioperative chemotherapy for resectable gastric cancer and its impact on survival

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ARTICLE INFO

Article history:
Received 24 January 2018
Received in revised form
27 January 2019
Accepted 28 March 2019
Available online 6 April 2019

Keywords:
Gastric cancer
Perioperative chemotherapy
Multimodality treatment
Trends
Survival

ABSTRACT

Background: In several Western European countries it is recommended to treat gastric cancer patients with perioperative chemotherapy if they are eligible for surgery. However, little is known about its use in daily clinical practice. This study examines the use of perioperative treatment and its impact on survival in the Netherlands.

Methods: Patients diagnosed with potentially resectable gastric cancer (cT1N+/cT2-T3,X any cN, cM0,X) between 2006 and 2014 were selected from the Netherlands Cancer Registry ($N = 5824$). Treatment trends were examined. Propensity score matching was used to create a subsample to reduce selection bias. Cox regression analysis was used to assess differences in overall survival.

Results: The percentage of patients treated with perioperative treatment increased from 3% in 2006 to 26% in 2014 and the use of only surgery decreased from 60% to 26%. 35% of all patients did not undergo surgery. Of the patients who underwent preoperative chemotherapy and surgery, 43% did not commence postoperative treatment. Cox regression analysis showed a better overall survival for patients who underwent perioperative treatment compared to patients who underwent preoperative treatment only (HR = 0.80 95%CI 0.70–0.93; propensity matched sample: HR = 0.84 95%CI 0.71–0.99), whereas survival was comparable for patients who underwent preoperative chemotherapy versus surgery alone (HR = 0.89 95%CI 0.77–1.02, propensity matched sample: HR = 0.85 95%CI 0.72–1.01).

Conclusion: This population-based study highlights that a significant proportion of the patients did not receive perioperative treatment. More research is necessary to elucidate the importance of the individual components of perioperative treatment.

Introduction

Gastric cancer is one of the leading cancers in incidence and mortality throughout the world. Survival rates are dismal with a 5-year relative survival of 18–33% in Europe[1]. Therefore, during the past decade several randomised trials have been conducted to improve survival of patients with gastric cancer. These studies showed a benefit of multimodality treatment in patients with resectable gastric cancer[2–4].

An international consensus on the best multimodality treatment has not been reached. In Northern America perioperative chemotherapy or postoperative chemoradiotherapy is the preferred treatment for patients with resectable gastric cancer whereas in Japan postoperative chemotherapy is the preferred treatment[3,5,6]. In several Western European countries perioperative chemotherapy is recommended based on the results of the UK MAGIC trial [7]. Results of the MAGIC trial demonstrated that patients with resectable gastric or lower oesophageal adenocarcinoma randomised for perioperative chemotherapy had a 13% improved overall survival compared to surgery alone (35% vs. 23%) [2]. According to the results of this trial perioperative

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https://doi.org/10.1016/j.ejso.2019.03.040
0748-7983/

chemotherapy consisting of epirubicine, cisplatin and 5-FU (ECF) or a similar regime is the recommended treatment as of May 2009 in the Dutch guidelines for patients with resectable gastric cancer unless patients are too frail or have severe comorbidities[2,3,8].

Although perioperative chemotherapy is recommended for resectable gastric cancer in several Western European countries, the actual use seems limited in patients with gastric cancer as only 66% of the gastric cancer patients included in the MAGIC trial allocated to perioperative chemotherapy were able to start postoperative treatment[2,9,10]. However, to our knowledge, no data are available on the utilisation and impact of perioperative treatment on survival in daily clinical practice. Therefore, the aim of this nationwide observational study was to analyse trends in administration of perioperative treatment and its impact on survival among potentially resectable gastric cancer patients in the Netherlands.

Methods

Netherlands cancer registry

Data were obtained from the Netherlands Cancer Registry (NCR). This registry serves the total Dutch population of 16.9 million inhabitants. The NCR is based on notification of all newly diagnosed malignancies by the national automated pathological archive (PALGA). Additional sources are the national registry of hospital discharge and radiotherapy institutions. Specially trained data managers of the NCR extract information on diagnosis, staging and treatment from the medical records. Information on vital status was obtained through an annual linkage with the Municipal Administrative Database, in which all deceased and emigrated persons in the Netherlands are registered. This study was approved by the Privacy Review Board of the Netherlands Cancer Registry and does not require approval from an ethics committee in the Netherlands.

Patients with a potentially resectable non-cardia gastric adenocarcinoma diagnosed in the period 2006–2014 eligible for perioperative treatment (cT1 cN+/cT2-3,X, any cN, cM0,X (TNM-6)) were included in the study. The gastro-oesophageal junction could be involved, but the bulk of the tumour had to be in the stomach. The study period 2006–2014 was chosen as the results of the MAGIC trial were published in 2006 which favoured perioperative chemotherapy for resectable gastric cancer patients instead of surgery alone[2]. Topography and morphology were coded according to the International Classification of Diseases for Oncology (ICD-O-3)[11]. Tumour staging was performed according to the International Union Against Cancer TNM classification that was valid at the time of diagnosis[12,13]. TNM-7 tumour staging was recoded according to TNM-6. Patients were considered potentially resectable if they had no distant metastasis (cM1) and no infiltration into surrounding organs (cT4 according to TNM-6). Patients with a cT1N0 tumour were also excluded as they were not eligible for perioperative chemotherapy according to the Dutch guidelines (A STROBE diagram of the study population is presented in Fig. 1). Patients with unknown clinical distant metastasis (cMX) were considered as having a cM0 and were therefore included in the study. Prior to 2010 coding regulations to register a cM0 or cM1 status into the NCR were strict and patients who were treated as cM0 were sometimes registered as cMX (due to certain coding regulations). As of 2010 the coding regulations were less strict which resulted in almost no cMX patients since 2010 and an increase in cM0 patients (with virtually no increase in cM1 patients). Therefore, to avoid bias due to changing regulations, all patients with cMX were included.

Treatment definitions

Perioperative treatment was defined as preoperative chemotherapy followed by a surgical resection and postoperative chemotherapy or chemoradiotherapy. As information on the number of received cycles was not available in the NCR for the study period, preoperative and postoperative chemotherapy were

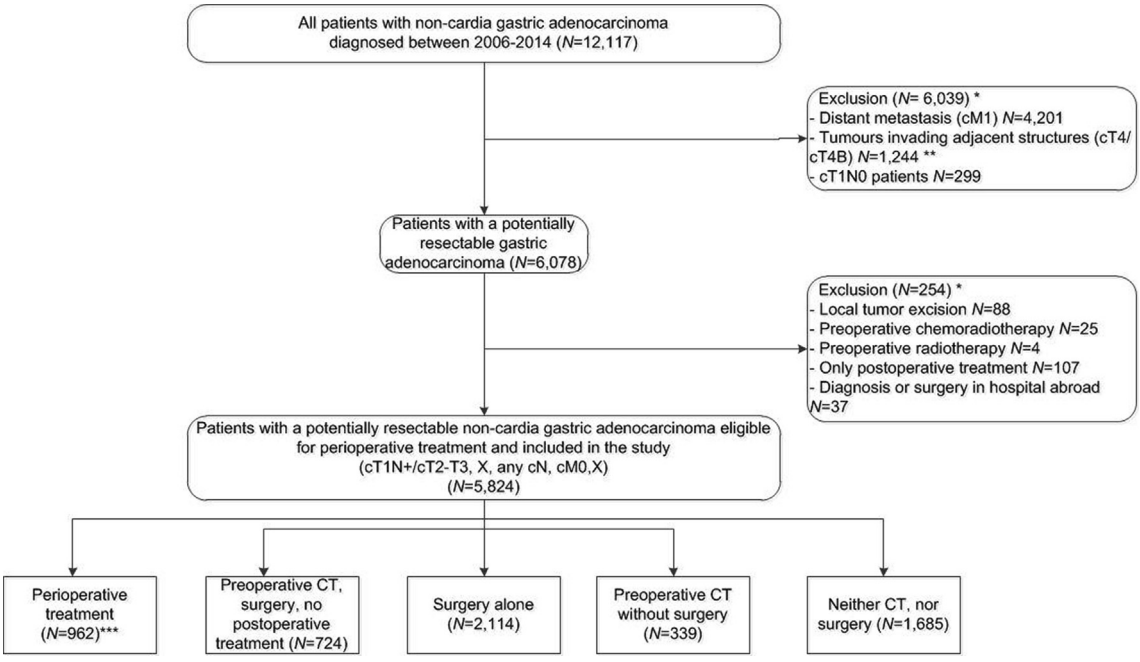

Fig. 1. STROBE diagram of the study population
* The sum of the excluded patients per exclusion criteria is larger than the total number of excluded patients because some patients met two exclusion criteria
** cT4 according to TNM-6 and cT4B according to TNM-7. Patients with a cT4A tumour according to TNM-7 were recoded as having a cT3 tumour according to TNM-6.
***Perioperative treatment was defined as preoperative chemotherapy followed by a surgical resection and postoperative chemotherapy or chemoradiotherapy
CT = chemotherapy.

defined as receiving at least one dose of chemotherapy pre- and/or postoperative. Surgical resection was defined as a subtotal or total gastrectomy. Surgery alone was defined as receiving surgery without preoperative or postoperative treatment. Patients who did not undergo surgery were allocated to the groups 'preoperative chemotherapy without surgery' or 'neither chemotherapy nor surgery', whichever was appropriate. As the intention of chemotherapy (preoperative or palliative) was not registered in the NCR, we assumed that patients who were potentially resectable and received chemotherapy without surgery, had started with preoperative chemotherapy with curative intent and were therefore allocated to the group 'preoperative chemotherapy without surgery'. Subgroup analysis were performed to estimate the number of cycles received for patients diagnosed between 2010 and 2014 based on the number of days between start of chemotherapy and end of chemotherapy. This period was chosen as the date of end of chemotherapy was not routinely registered prior to 2010. Treatment duration of 1–20 days was defined as 1 cycle, 21–41 days as 2 cycles, and 42–70 days as 3 cycles, whereas all other treatment durations were defined as unknown.

Statistical analysis

Descriptive statistics were used to characterise the patients according to type of treatment i.e. perioperative treatment, preoperative chemotherapy with surgery, surgery alone, preoperative chemotherapy without surgery and neither chemotherapy nor surgery. Differences in characteristics between treatment groups were analysed by means of chi-squared tests for nominal data and ANOVA for continuous data.

Kaplan-Meier curves were generated to examine overall survival according to type of treatment for all potentially resectable patients and were compared with the log-rank test. For this analysis, survival time was defined from diagnosis until death or until February 1st, 2017. Survival curves were also generated for patients who underwent surgery with or without pre- and/or postoperative treatment using the Kaplan-Meier method. For this and all other survival analyses survival time was defined as time from four months after surgery to death or until February 1st, 2017 for patients who were still alive. This landmark at four months postoperative addressed immortal time bias of patients receiving postoperative treatment, which starts 6–8 weeks after surgery and takes approximately 9 weeks to complete the three cycles.

Differences in overall survival were compared between patients who underwent perioperative treatment and patients who underwent only preoperative chemotherapy (comparison 1) as well as between patients who underwent only preoperative chemotherapy versus patients who underwent surgery alone using multivariable Cox regression analyses (comparison 2). Furthermore, propensity score matching was performed to minimise confounding due to nonrandomised assignment of treatment. Selection of covariates for matching unrelated to survival was avoided, even though they were associated with the treatment received, as this may increase bias[14,15]. For comparison 1 a logistic regression was used to determine the probability of perioperative treatment, i.e. the propensity score, based on gender, age, period of diagnosis, tumour location, pT classification, pN classification, tumour grade, type of surgery, margin involvement and duration of postoperative hospital stay. For comparison 2 a logistic regression was used to determine the probability of only preoperative chemotherapy, i.e. the propensity score, based on gender, age, period of diagnosis, tumour location, cT classification, cN classification and tumour grade. On the basis of propensity scores patients were then 1:1 matched within tight bound of the propensity scores; predicted probabilities could vary by no more than 0.01 (1%) on a scale of 0–1. Subsequently, Cox regression analyses were also performed for the propensity matched sample to investigate the prognostic impact of the treatment received. Reported p values of <0.05 were considered statistically significant. Analyses were conducted using SAS version 9.4 (Statistical Analysis System).

Results

Patients

Between January 2006 and December 2014, 12,117 patients were diagnosed with non-cardia gastric adenocarcinoma. Based on our inclusion and exclusion criteria a study population of 5824 patients was identified (Fig. 1). Patient characteristics were summarised in Table 1.

Perioperative treatment was administered in 962 patients (17%) and preoperative chemotherapy without postoperative treatment was administered in 724 patients (12%). Surgery alone was performed in 2114 patients (36%). Patients who underwent perioperative treatment were more often younger than patients who underwent only preoperative chemotherapy followed by surgery or surgery alone (Table 1).

Trends in treatment

Administration of perioperative treatment increased over time (Fig. 2). In 2006 3% of the patients underwent perioperative treatment and in 2014 26% underwent perioperative treatment. The number of patients who started with preoperative chemotherapy followed by surgery regardless of receiving postoperative treatment, increased from 6% in 2006 to 42% in 2014. Of the patients who underwent preoperative chemotherapy and surgery, 43% did not commence postoperative treatment in 2014. In line with these findings, the percentage of patients who underwent surgery alone decreased from 60% in 2006 to 26% in 2014. The percentage of patients who started with preoperative chemotherapy and did not undergo surgery remained stable over the study period varying from respectively 4% to 7%. Similarly, the percentage of patients who received neither chemotherapy nor surgery also remained stable over time varying from 28% to 32%.

Subgroup analysis among patients who underwent preoperative chemotherapy with or without postoperative treatment in the period 2010–2014 showed that 89% of the patients who underwent perioperative treatment received 3 cycles of chemotherapy preoperatively, whereas patients who underwent preoperative treatment without postoperative treatment received less often 3 cycles of chemotherapy preoperatively (58%, supplementary Table 1).

Survival

Kaplan Meier survival curves of potentially resectable patients showed that overall survival was worst for patients who received preoperative chemotherapy without surgery and for patients who received neither chemotherapy nor surgery with an almost equal 1-year overall survival rate of 22% and 21%, respectively (Fig. 3). Among patients who underwent surgery and survived the first four months after surgery, univariable overall survival was most favourable for patients who underwent perioperative treatment with a 5-year overall survival rate of 48% ($P < 0.01$). Patients who underwent only preoperative chemotherapy had a 5-year overall survival comparable to patients who underwent surgery alone, respectively 43% and 39% ($P = 0.22$; Fig. 4).

Multivariable Cox regression analysis also showed a favourable survival for patients who underwent perioperative treatment compared to patients who underwent only preoperative

Table 1
Characteristics of patients with potentially resectable non-cardia gastric adenocarcinoma (cT1N+/T2-T3,X, any cN, cM0,X), diagnosed in the period 2006–2014 in the Netherlands ($N = 5824$).

	Perioperative treatment		Preoperative CT, surgery, no postoperative treatment		Surgery alone		Preoperative CT without surgery		Neither CT nor surgery		*P* value	All patients	
	N	%[c]	N	%[c]	N	%[c]	N	%[c]	N	%[c]		N	%[b]
All patients	962	17%	724	12%	2114	36%	339	6%	1685	29%		5824	100%
Gender											<0.01		
Male	620	18%	437	13%	1272	37%	221	6%	927	27%		3477	60%
Female	342	15%	287	12%	842	36%	118	5%	758	32%		2347	40%
Age (median yrs., IQR)	62	54–69	67	60–72	76	69–81	68	60–74	83	77–87	<0.01	74	65–81
Age (yrs.)											<0.01		
< 60	398	46%	162	19%	172	20%	78	9%	59	7%		869	15%
60- 74	502	24%	448	21%	719	34%	188	9%	241	11%		2098	36%
≥ 75	62	2%	114	4%	1223	43%	73	3%	1385	48%		2857	49%
Period of diagnosis											<0.01		
2006–2008	187	9%	167	8%	993	48%	105	5%	599	29%		2051	35%
2009–2011	341	18%	268	14%	608	32%	133	7%	564	29%		1914	33%
2012–2014	434	23%	289	16%	513	28%	101	5%	522	28%		1859	32%
Tumour location											<0.01		
Proximal/middle[a]	331	20%	266	16%	562	33%	90	5%	446	26%		1695	29%
Antrum	319	17%	232	12%	815	43%	72	4%	471	25%		1909	33%
Pyloric	69	15%	46	10%	236	50%	11	2%	106	23%		468	8%
Overlapping, unknown	243	14%	180	10%	501	29%	166	9%	662	38%		1752	30%
cT classification											<0.01		
cT1	11	16%	4	6%	19	28%	3	4%	31	46%		68	1%
cT2	434	25%	316	18%	525	30%	143	8%	328	19%		1746	30%
cT3	55	19%	33	11%	93	32%	32	11%	74	26%		287	5%
cTX	462	12%	371	10%	1477	40%	161	4%	1252	34%		3723	64%
cN classification											<0.01		
cN0	536	19%	395	14%	1274	46%	111	4%	438	16%		2754	47%
cN+	296	21%	218	15%	414	29%	157	11%	327	23%		1412	24%
cNX	130	8%	111	7%	426	26%	71	4%	920	55%		1658	28%
cM classification											<0.01		
cM0	943	98%	700	97%	1952	92%	297	88%	1314	78%		5206	89%
cMX	19	2%	24	3%	162	8%	42	12%	371	22%		618	11%
Tumour grade											<0.01		
Moderate/well differentiated	115	11%	83	8%	599	57%	33	3%	229	22%		1059	18%
Poorly differentiated or anaplastic	430	16%	366	14%	1165	43%	143	5%	604	22%		2708	46%
Unknown	417	20%	275	13%	350	17%	163	8%	852	41%		2057	35%
Type of surgery													
Total gastrectomy	388	33%	296	25%	498	42%	n.a.	n.a.	n.a.	n.a.		1182[d]	31%
Subtotal gastrectomy	544	23%	378	16%	1474	62%	n.a.	n.a.	n.a.	n.a.		2396[d]	63%
Multi-organ surgery	30	14%	50	23%	142	64%	n.a.	n.a.	n.a.	n.a.		222[d]	6%
Margin involvement													
No tumour residue	820	27%	560	18%	1704	55%	n.a.	n.a.	n.a.	n.a.		3084[d]	81%
Microscopic tumour residue	99	20%	123	25%	272	55%	n.a.	n.a.	n.a.	n.a.		494[d]	13%
Macroscopic tumour residue	8	13%	17	27%	39	61%	n.a.	n.a.	n.a.	n.a.		64[d]	2%
Unknown	35	2%	24	1%	99	5%	n.a.	n.a.	n.a.	n.a.		158[d]	4%
Duration of postoperative hospital stay													
<14 days	579	35%	346	21%	721	44%	n.a.	n.a.	n.a.	n.a.		1646[d]	43%
14 days	115	17%	162	24%	400	59%	n.a.	n.a.	n.a.	n.a.		677[d]	18%
Unknown	268	8%	216	6%	993	28%	n.a.	n.a.	n.a.	n.a.		1477[d]	39%

CT = chemotherapy.
[a] Proximal/middle = Fundus, corpus and greater and lesser curvature.
[b] Column percentage.
[c] Row percentage.
[d] This figure is based on patients who underwent surgery (with or without chemotherapy).

chemotherapy (HR = 0.80 95%CI 0.70–0.93; Table 2a). A similar association was investigated among the propensity score matched sample. After adjustment, the Cox regression analysis among the propensity score matched sample showed that perioperative treatment was associated with a better overall survival (HR = 0.84 95%CI 0.71–0.99; Table 2a).

A favourable overall survival was also found by multivariable Cox regression for patients who underwent at least preoperative chemotherapy followed by surgery with or without postoperative treatment compared to patients who underwent surgery alone (HR = 0.85 95%CI 0.76–0.96; Table 2b). Survival analysis in the propensity score matched sample showed a similar association (HR = 0.77 95%CI 0.67–0.89).

Multivariable Cox regression analysis demonstrated no significant difference in overall survival for patients who underwent only preoperative chemotherapy and for patients who underwent surgery alone (HR = 0.89 95%CI 0.77–1.02; Table 2c). Survival analysis for the propensity score matched sample also showed no significant difference in survival (HR = 0.85 95%CI 0.72–1.01 (Table 2b). Characteristics of the matched patient groups were comparable and shown in supplementary table 2, 3 and 4.

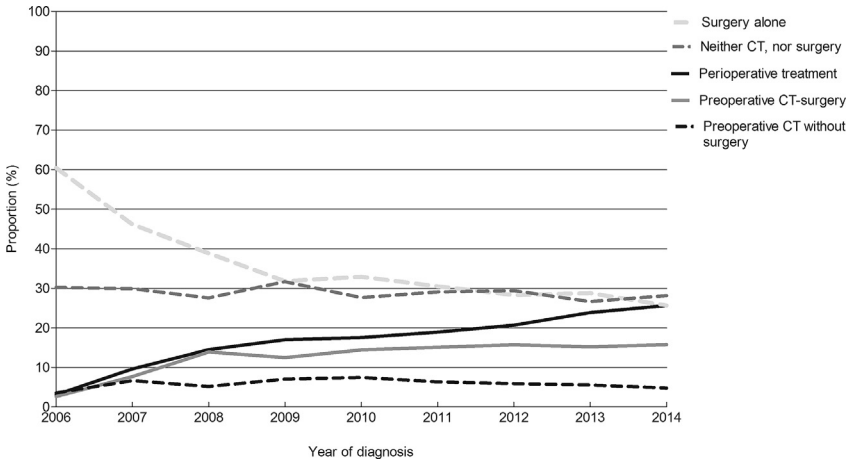

Fig. 2. Trends in multimodality treatment among patients with potentially resectable non-cardia gastric adenocarcinoma (cT1N+/cT2-T3,X, any cN, cM0,X) diagnosed in the period 2006–2014 ($N = 5824$).
CT = chemotherapy.

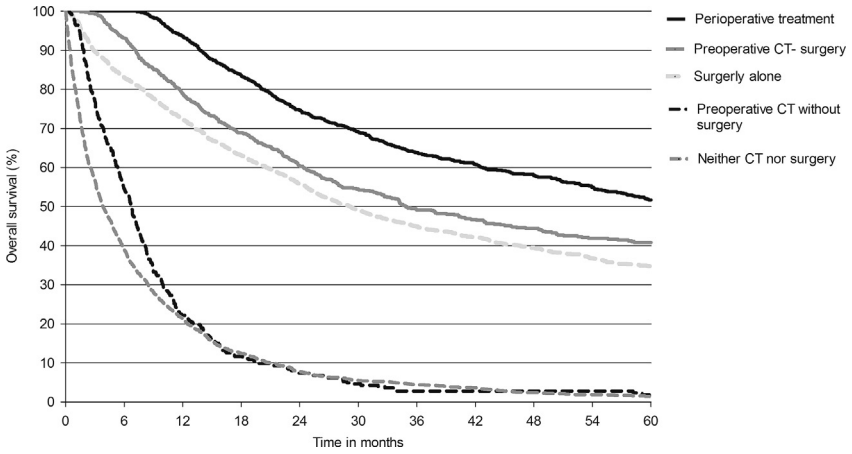

Fig. 3. Overall survival among patients with potentially resectable non-cardia gastric adenocarcinoma (cT1N+/cT2-3,X, any cN, cM0,X) diagnosed in the period 2006–2014 ($N = 5824$). Survival was defined as time from diagnosis to death or 1st of February 2017 for patients who were still alive.
CT = chemotherapy.

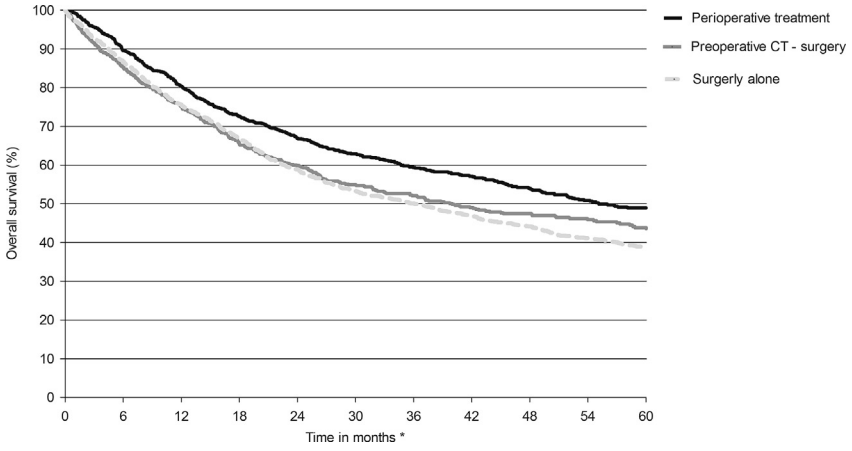

Fig. 4. Overall survival among patients with potentially resectable non-cardia gastric adenocarcinoma (cT1N+/cT2-T3,X, any cN, cM0,X) who underwent surgery with or without pre- and/or postoperative treatment and were diagnosed in the period 2006–2014 ($N = 3389$; $P < 0.01$).
* Survival was defined as time from four months after surgery to death or 1st
of February 2017 for patients who were still alive. Patients who died within 4 months after surgery were excluded from the analysis.
CT = chemotherapy.

Table 2a
Multivariable Cox proportional hazards analyses of overall survival for potentially resectable non-cardia gastric adenocarcinoma patients who underwent preoperative chemotherapy followed by surgery with or without postoperative treatment for all patients and for the propensity score matched sample.

	All patients $N = 1598$			Propensity score matched sample[b] $N = 1062$		
	Crude 2-year OS	Multivariable overall survival [a]		Crude 2-year OS	Multivariable overall survival [a]	
	%	HR	95% CI	%	HR	95% CI
Treatment						
Perioperative treatment	67	0.80	0.70–0.93	67	0.84	0.71–0.99
Preoperative chemotherapy - surgery	60	ref		61	ref	

OS = overall survival. Patients who died within 4 months after surgery were excluded from the analysis.
[a] Adjusted for gender, age, period of diagnosis, tumour location, pT classification, pN classification, tumour grade, type of surgery, margin involvement and duration of postoperative hospital stay.
[b] Characteristics of the propensity score matched sample were demonstrated in supplementary Table 2.

Table 2b
Multivariable Cox proportional hazards analyses of overall survival for potentially resectable non-cardia gastric adenocarcinoma patients who underwent at least preoperative chemotherapy followed by surgery with or without postoperative treatment and for patients who underwent surgery alone; for all patients and for the propensity score matched sample.

	All patients $N = 3389$			Propensity score matched sample [b] $N = 1421$		
	Crude 2-year OS	Multivariable overall survival [a]		Crude 2-year OS	Multivariable overall survival[a]	
	%	HR	95% CI	%	HR	95% CI
Treatment						
Preoperative chemotherapy - surgery – with or without postoperative treatment	64	0.85	0.76–0.96	65	0.77	0.67–0.89
Surgery alone	59	ref		60	ref	

OS = overall survival. Patients who died within 4 months after surgery were excluded from the analysis.
[a] Adjusted for gender, age, period of diagnosis, tumour location, cT classification, cN classification and tumour grade.
[b] Characteristics of the propensity score matched sample were demonstrated in supplementary Table 3.

Table 2c
Multivariable Cox proportional hazards analyses of overall survival for potentially resectable non-cardia gastric adenocarcinoma patients who underwent preoperative chemotherapy followed by surgery without postoperative treatment and for patients who underwent surgery alone; for all patients and for the propensity score matched sample.

	All patients $N = 2429$			Propensity score matched sample[b] $N = 967$		
	Crude 2-year OS	Multivariable overall survival [a]		Crude 2-year OS	Multivariable overall survival [a]	
	%	HR	95% CI	%	HR	95% CI
Treatment						
Preoperative chemotherapy - surgery	60	0.89	0.77–1.02	61	0.85	0.72–1.01
Surgery alone	59	ref		58	ref	

OS = overall survival. Patients who died within 4 months after surgery were excluded from the analysis.
[a] Adjusted for gender, age, period of diagnosis, tumour location, cT classification, cN classification and tumour grade.
[b] Characteristics of the propensity score matched sample were demonstrated in supplementary Table 4.

Discussion

This population-based study of potentially resectable gastric cancer patients has demonstrated an increase in the administration of perioperative treatment of 3%–26% in the course of time which may have led to a survival benefit compared to treatment with only preoperative chemotherapy followed by surgery. Although, 74% of the patients were not treated with perioperative chemotherapy, physicians may have attempted to deliver perioperative chemotherapy to nearly 40% of the patients in 2014, however most patients failed to receive the postoperative component (43%). Some hypotheses might explain the low percentage of resectable gastric cancer patients receiving perioperative treatment (26%), despite the publication of the MAGIC trial and the French FNCLCC/FFCD trial both demonstrating a significant survival benefit of perioperative treatment compared to surgery alone[2,4]. Many patients with gastric cancer have an older age, comorbidities and suffer from malnutrition and weight loss which could preclude them from starting with the perioperative treatment regimen[16]. After preoperative chemotherapy there could be several reasons for not undergoing surgery such as disease progression, toxicity from chemotherapy, patient request and death[2,17]. Moreover, gastric cancer surgery is associated with substantial morbidity and postoperative complications which could interfere with receiving postoperative treatment[2,18–20]. As only a minority of the patients is actually capable of receiving the full regimen, one could argue about the appropriateness of perioperative chemotherapy as a reference regime for patients with resectable gastric cancer.

In this observational study, many patients (43%) did not start postoperative treatment after preoperative chemotherapy followed by surgery. This percentage was somewhat higher compared to the results of the MAGIC trial [2] and CRITICS trial [21] but similar to the FLOT4-AIO trial[22], in which respectively 35%, 38% and 40%, of the patients did not start with postoperative treatment. However, the patients included in the trials were highly selected for trial eligibility and may therefore differ from the general gastric cancer patient population who probably have a worse performance status and are less ideal candidates for perioperative treatment. Another retrospective study found that 35% of the patients did not start with postoperative treatment after preoperative chemotherapy followed

by surgery[23]. Our survival results, based on real world data, support the survival benefits reported by the MAGIC trial and the French FNCLCC/FFCD trial[2,4]. Both trials reported an increase in 5-year overall survival of respectively 13% and 14% in the perioperative chemotherapy group compared to the surgery only group which is similar to the 10% increase found in the present study[2,4]. Multivariable Cox regression analyses, among all patients and the propensity score matched sample, indicated a favourable survival after perioperative treatment compared to only preoperative chemotherapy.

Although, propensity score matching was performed to minimise confounding due to nonrandomised assignment of treatment, groups may not be completely comparable and confounding due to nonrandomised assignment may still exists. For example, the differences in number of preoperative cycles received suggests that patients who underwent only preoperative chemotherapy were less fit than patients who underwent perioperative treatment. Furthermore, propensity score matching may amplify the risk of residual bias by unmeasured confounders as matching is only performed for measured confounders forcing balance of these confounders[24]. In addition, there could still be bias due to incomplete matching as 58% of the patients who received perioperative treatment, 77% of the patients who underwent only preoperative treatment and 26% of the patients who underwent surgery alone were excluded from the propensity score matched samples. Full matching instead of 1 to 1 matching seems a more appropriate method when performing survival analysis, however after full matching imbalance remained in characteristics between the treatment groups[25]. Although propensity score matching has uses and limitations, the authors decided to present the results of both the unmatched and propensity score matched analyses to facilitate the ongoing debate about the added value of propensity score matching to estimate causal effects.

Compliance to perioperative treatment in patients with resectable gastric cancer is poor, even in selected trial patients. Only 36% to 47% of all trial patients completed the entire treatment protocol [2,4,22,26]. As a substantial number of patients do not receive postoperative treatment, preoperative approaches may be particularly attractive[27]. Therefore, the CRITICS II trial which is a future Dutch multi-centre randomised phase II study that aims to assess the feasibility and safety of three preoperative treatment approaches (chemotherapy vs chemoradiotherapy vs chemotherapy plus chemoradiotherapy) will include no additional postoperative treatment. On the other hand, the Asians were successful in the adjuvant chemotherapy regime after gastrectomy without prior chemotherapy. Maybe S-1 based regimes, which seem effective according to Asian trials, may be more appropriate than postoperative chemotherapy regimes using triplets consisting of cisplatin and 5-FU[28,29]. However, results from trials based on Asian populations seem difficult to extrapolate to Western populations.

This study has some limitations. First, information was not available about performance status, comorbidities and postoperative complications. However, age and duration of postoperative hospital stay may be proxies for comorbidities and postoperative complications, respectively. Reasons for noncompliance with perioperative chemotherapy were also not available. Second, because endoscopic ultrasonography is not always performed in patients with gastric cancer, clinical stage was unknown in a relatively high percentage of patients (64% cTX stage and 28% cNX stage; Table 1). Missing data for cT and cN might have led to an underestimation of the proportion of patients who underwent perioperative chemotherapy as inclusion of patients is based on clinical stage. However, the underestimation may only be to a small extent as most patients who were not eligible for perioperative chemotherapy were excluded from the study based on cM stage (67%) which is less often missing compared to cT and cN stage (Fig. 1). Moreover, the missing values for cT and cN stage provide information on care in daily clinical practice. Third, the number of cycles of preoperative or postoperative chemotherapy received was unknown for the total study period and was therefore not included in the analysis. Finally, if patients were treated with preoperative intent but failed to undergo surgery, these patients were assigned to preoperative chemotherapy without surgery, and as a consequence patients treated with preoperative intent followed by surgery may represent a selection of the fittest patients. To conclude, this study, based on real world data, highlights that a significant proportion of the patients did not receive perioperative treatment, which may, at least partially, explain the poor survival rates for gastric cancer. More research is necessary to elucidate the importance of the individual components of perioperative treatment.

Conflict of interest

H. W. M. van Laarhoven has served as a consultant for Celgene, Lilly, and Nordic, and has received unrestricted research funding from Bayer, BMS, Celgene, Lilly, Merck Serono, MSD, Nordic, Philips and Roche. All other authors declare that they have no financial or non-financial conflict of interest.

Acknowledgements

We would like to thank the registration team of the Netherlands Comprehensive Cancer Organisation (IKNL) for the collection of data for the Netherlands Cancer Registry. Furthermore, we thank all participating hospitals in the Netherlands.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.03.040.

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