Changes in hospital variation in the probability of receiving treatment with curative intent for esophageal and gastric cancer

Josianne C.H.B.M. Luijten [a], Pauline A.J. Vissers [a], Hester Lingsma [b], Nikki van Leeuwen [b], Tom Rozema [c], Peter D. Siersema [d], Camiel Rosman [e], Hanneke W.M. van Laarhoven [f], Valery E. P. Lemmens [a,b], Grard A.P. Nieuwenhuijzen [g], Rob H.A. Verhoeven [a,e,*]

[a] Department of Research & Development, Netherlands Comprehensive Cancer Organization (IKNL), Utrecht, the Netherlands
[b] Department of Public Health, Erasmus University Medical Centre, Rotterdam, the Netherlands
[c] Department of Radiotherapy, Institute Verbeeten, Tilburg, the Netherlands
[d] Department of Gastroenterology and Hepatology, Radboud University Medical Center, Nijmegen, the Netherlands
[e] Department of Surgery, Radboud University Medical Center, Nijmegen, the Netherlands
[f] Department of Medical Oncology, Cancer Centre Amsterdam, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, the Netherlands
[g] Department of Surgery, Catharina Hospital, Eindhoven, the Netherlands

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ABSTRACT

Background: Previous studies describe a large variation in the proportion of patients undergoing treatment with curative intent for esophageal (EC) and gastric cancer (GC). Since centralization of surgical care was initiated and more awareness regarding hospital practice variation was potentially present, we hypothesized that hospital practice variation for potentially curable EC and GC patients changed over time.

Methods: Patients with potentially curable EC (n = 10,115) or GC (n = 3988) diagnosed between 2012–2017 were selected from the Netherlands Cancer Registry. Multilevel multivariable logistic regression was used to analyze the differences in the probability of treatment with curative intent between hospitals of diagnosis over time, comparing 2012−2014 with 2015−2017. Relative survival (RS) between hospitals with different probabilities of treatment with curative intent were compared.

Results: The range of proportions of patients undergoing treatment with curative intent per hospital of diagnosis for EC was 45–95 % in 2012−2014 and 54–89 % in 2015−2017, and for GC 52–100 % and 45–100 %. The adjusted variation declined for EC with Odds Ratios ranging from 0.50 to 1.72 between centers in the first period to 0.70–1.44 in the second period *(p < 0.001)* and did not change for GC (Odds Ratios ranging from 0.78 to 1.23 to 0.82–1.23, *(p = 1.00)*). A higher probability of treatment with curative intent was associated with a better survival for both malignancies.

Conclusion: Although substantial variation between hospitals of diagnosis in the probability in receiving treatment with curative intent still exists for both malignancies, it has decreased for EC. A low probability of receiving curative treatment remained associated with worse survival.

1. Introduction

Geographical variation in cancer care has been observed between and within countries. [1–6] Variation in receiving treatment may occur at any point along the cancer care continuum attributing to potentially avoidable disparities in patient outcomes [3,4]. Earlier studies have shown that the probability of undergoing treatment with curative intent according to the hospital of diagnosis varied significantly for esophageal (EC) and gastric cancer (GC) between hospitals in the Netherlands in the period 2005–2013 [3,4,7]. Furthermore, in hospitals in which the probability of receiving treatment with curative intent was low, survival was also lower [3,4]. Regional variation in the use of (non-)surgical oncologic treatment modalities has also been observed internationally [2,5,8,9].

The cornerstone of curative treatment for patients with these malignancies is surgery with or without (neo)adjuvant chemo(radiation) therapy. [10,11] Other treatment options with curative intent include endoscopic resection for early stage disease. For patients with locally unresectable EC or with EC who are too frail to undergo surgery, definitive chemoradiotherapy is an alternative [12,13].

As EC and GC surgery is associated with a high morbidity and mortality [14], surgery for these malignancies is centralized in the Netherlands [15,16]. Centralization of esophageal surgery was initiated in 2006 by mandating an annual volume of at least 10 esophagectomies per hospital. Since 2011 this increased to 20 esophagectomies and since 2013 a minimum of 20 gastrectomies per hospital were mandated. However, the diagnostic process, including the decision on operability or curability is mainly made in non-expert centers and consultation with and referral to an expert center might not always follow. In 2014 results were published on the regional variation in the Southeast Netherlands. [7] Simultaneously, the Dutch Comprehensive Cancer Organization facilitated regional meetings showing regional variation based on data of the Netherlands Cancer Registry (NCR). As a result of these developments, regional clinical pathways and tumor specific multidisciplinary team meetings (MDTM) were setup in almost all Dutch regions. Previous studies on this topic did not compare time periods before and after centralization [3,4]. Moreover, they do not describe the period after the publication of studies investigating hospital practice variation. We hypothesized that due to created awareness regarding hospital practice variation, variation would change over time. We aimed, to assess whether variation between hospitals in the probability of undergoing treatment with curative intent in patients with potentially curable EC or GC changed over time and to assess the effect of variation on survival.

2. Methods

In this study data of the NCR, a nationwide population-based cancer registry comprising all patients with cancer in the Netherlands, was used. The NCR is primarily based on the notification of all newly diagnosed malignancies by the pathological national automated archive. Additionally, non-pathologically verified cases are identified through the national registry of hospital care and discharge. Trained data managers of the NCR routinely extract information on patient, tumor and treatment characteristics from medical records. Information on vital status is obtained through annual linkage with the Municipal Administrative Database, in which all deceased and emigrated persons in the Netherlands are registered, which is up to date until January 1st 2020.

All patients newly diagnosed with potentially curable EC or GC (cT1−4A,X, any cN, cM0) in 2012–2017 were included in this study. Gastro-esophageal junction (GEJ) and cardia carcinomas were included in the EC-group. Tumor location and morphology were coded according to the third edition of the International Classification of Diseases for Oncology. [17] For EC tumor location was categorized as proximal (C150/C153), mid (C154), distal (C155), GEJ/Cardia (C160), unknown/overlapping (C158/C159). The following categories were used for GC: proximal/middle (fundus/corpus/lesser- and greater curvature) (C16.1/C16.2/C16.5/C16.6), pyloric/antrum (C16.3/C16.4), and unknown/overlapping (C16.8/C16.9).

Tumors were staged using the International Union Against Cancer TNM classification. The seventh edition was used for the 2012–2016 and the eighth for 2017. [18,19] There were no changes in the T, N and M category definitions comparing the 7th to 8th edition of the TNM. However, the definition on when to use esophageal or gastric TNM

staging did change, and as a result, a tumor of which the epicenter was located within 2−5 cm from the GEJ was staged as EC in TNM-7 and as GC in TNM-8. In this study no corrections for the TNM-stages were applied, however GEJ tumors were all classified as EC. For 2015−2017, information on comorbidity (modified Charlson Comorbidity Index) and ECOG performance status (ECOG) was available.

No ethics approval was required according to the Central Committee on Research involving Human Subjects.

2.1. Treatment with curative intent

Treatment with curative intent was defined as the initiation of treatment with the aim of cure, which did not always imply that the patient ultimately would undergo the full treatment plan. This included the initiation of neoadjuvant treatment, surgery (with/without resection) with/without (neo)adjuvant chemo(radiation)therapy, endoscopic resection (cT1N0M0) and definitive chemoradiation (for EC). In some patients surgery with the aim of cure was initiated and the decision not to pursue resection, due to too severe disease, was taken during exploration (surgery without resection).

2.2. Hospital of diagnosis

Hospital of diagnosis was defined as the hospital in which the histological diagnosis was confirmed. Patients were excluded if the diagnosis was determined abroad (n = 7). Hospitals were excluded if <10 patients were diagnosed in a three-year time period (N = 2, N = 2 for EC, N = 8, N = 12 for GC in 2012−2014 and 2015−2017, respectively) (Appendix A). For EC 94 hospitals of diagnosis were included in 2012−2014 and 80 in 2015−2017. For GC 87 hospitals of diagnosis were included in 2012−2014 and 69 in 2015−2017.

2.3. Outcomes and analysis

The proportion of potentially curable EC or GC patients treated with curative intent was calculated per hospital of diagnosis. Differences in baseline patient characteristics between the two time periods were analyzed with the chi-square test. The probability of treatment with curative intent was defined as the proportion of patients diagnosed in a hospital, who underwent treatment with the aim of cure. Multivariable multilevel logistic regression models with random intercepts were constructed to analyze the hierarchically structured data. Undergoing treatment with curative intent or not, was used as dependent variable. Sex, age, histology, cT and cN classification were added to adjust for case mix differences. Missing data were coded as unknown and included in multivariable analyses. Results were expressed in odds ratios (ORs) with 95 % confidence intervals (95 %CI). For each hospital of diagnosis, the OR with 95 %CI for treatment with curative intent was calculated. To assess the difference in hospital variation between the two time periods (2012−2014 versus 2015−2017), we compared a model with only a random intercept per hospital to a model with a random slope for period per hospital. Both models were adjusted for case mix differences (i.e., sex, age, histology, cT and cN). We tested the difference in −2log likelihood between these models with a Chi-square test. A subgroup analysis was conducted for patients diagnosed in 2015−2017 for whom data on ECOG and comorbidity was available. In this model additional adjustments for comorbidities and ECOG were made, to assess whether these variables explain the variation between hospitals of diagnosis.

Relative survival (RS) was defined as the ratio of overall survival for cancer patients to the expected survival based on the Dutch population

with the same age, sex and calendar year as patients with these malignancies. RS analyses with 95 % CI were calculated from date of diagnosis and according to the Pohar Perme method. [20] To assess the effect of the probability of undergoing treatment with curative intent on RS, we divided the hospitals in three groups based on tertiles of the adjusted ORs on the probability of undergoing treatment with curative intent. Since the groups were based on the tertiles of the multivariable model, no further adjustments for the survival analyses were necessary. Difference in RS between these groups was calculated using a two-sample proportion test. Relative excess risk of death (RER) was calculated for EC and GC, respectively. RS was calculated for all (EC n = 16,427 and GC n = 7124), potentially curable and palliative patients, in both time periods to provide a baseline description of RS in the Netherlands. For all analyses a p-value<0.05 was considered statistically significant.

Statistical analyses were performed using SAS® version 9.4 (SAS Institute, Cary, North Carolina, USA). RS and the RER were analyzed using STATA/SE (version 14.1; STATA CORP., College Station, Texas, USA).

3. Results

In total, 10,115 patients with EC and 3988 patients with GC were selected. In 2012−2014, 4796 (62 %) EC patients were according to the aforementioned definition potentially curable and in 2015−2017 this

Table 1
Patient characteristics esophageal cancer for the period 2012-2014 and 2015-2017.

	Total		2012−2014		2015−2017		
	N	%	N	%	N	%	p-value
All included patients	10115	100 %	4796	100 %	5319	100 %	
Sex							0.043
Female	2742	27 %	1255	26%	1487	28 %	
Male	7373	73 %	3541	74%	3832	72 %	
Age							<.001
< 60	1769	17 %	905	19 %	864	16%	
60 to 74	5057	50 %	2327	49%	2730	51%	
75 and higher	3289	33 %	1564	33 %	1725	32%	
Histology							0.445
Adenocarcinoma	2681	27 %	1299	27 %	1382	26%	
Squamous cell carcinoma	7143	71%	3362	70%	3781	71%	
Other	291	3%	135	3%	156	3%	
cT Classification							<.0001
cT1	269	3%	131	3%	138	3%	
cT1A	183	2%	116	2%	67	1%	
cT1B	156	2%	72	2%	84	2%	
cT2	2773	27 %	1213	25 %	1560	29 %	
cT3	4641	46 %	2087	44%	2554	48 %	
cT4A	207	2%	124	3%	83	2%	
cT4Bˆ	24	0%	18	<1%	6	<1%	
cTX	1862	18%	1035	22%	827	16%	
cN Classification							<.0001
cN0	4002	40 %	1812	38 %	2190	41 %	
cN1	3178	31%	1492	31%	1686	32%	
cN2	1611	16%	778	16%	833	16%	
cN3	268	3%	131	3%	137	3%	
cNX	1056	10 %	583	12 %	473	9%	
Tumor location							0.019
Proximal	518	5%	261	5%	257	5%	
Middle	1395	14%	636	13 %	759	14%	
Distal	6259	62 %	2934	61 %	3325	63 %	
Overlapping/unknown	464	5%	213	4%	251	5%	
GEJ	1479	15 %	752	16%	727	14%	
Comorbidities							
No comorbidities					1526	29 %	
1 Comorbidity					1537	29 %	
>2 Comorbidities					1852	35 %	
Unknown					404	8%	
Patients clinical condition							
ECOG 0					1683	32%	
ECOG 1					1535	29 %	
ECOG 2					418	8%	
ECOG 3 and 4					166	3%	
Unknown					1517	28 %	
Type of treatment received							<.001
Surgical resection	4858	48 %	2272	47 %	2586	49%	
Endoscopic resection	338	3%	163	3%	175	3%	
Only chemoradiation*	1938	19 %	866	18%	1072	20 %	
Other or no treatment	2981	29 %	1495	31%	1486	28 %	
Treatment with curative intent							<0.001
No	2981	29 %	1495	31%	1486	28 %	
Yes	7134	71%	3301	69%	3833	72%	

x2 was used to calculate statistical differences between both periods in all analyses presented in this table.
Column percentage, *For the period 2012−2014 no differentiation between definitive chemoradiation and neoadjuvant chemoradiation not followed by resection could be made, ˆ Prior to surgery (without resection) the cT stage was below cT4b. During surgery the team decided to refrain from resection due to the extensiveness of the tumor and staged the tumor as cT4b.

was 5319 (62 %, *p = 0.80,* Appendix B). For GC, 2218 patients (60 %) in 2012−2014 and 1770 patients (56 %) in 2015−2017, were potentially curable, which decreased over time (*p < 0.001,* Appendix B).

3.1. Characteristics

As shown in Table 1, most patients with EC in 2012–2017 were between 60–74 years old (50 %), followed by patients that were ≥75 years (33 %). A cT3 (46 %) and cN+ (50 %) tumor stage was observed in most patients. The percentage of EC patients in which treatment with curative intent was initiated increased from 69 % in 2012−2014 to 72 % in 2015−2017 (*p < 0.001*).

Most GC patients were ≥75 years (48 %), followed by 60–74 years (37 %, Table 2). A cT2 (33 %) and a cN0 (56 %) tumor stage was seen in

most of the patients. Treatment with curative intent was initiated in 73 %, which was the same in both periods (*p = 0.111)*.

3.2. Hospital variation

The proportion of patients with EC that was treated with curative intent showed variation between hospitals in both periods (45–95 % in 2012−2014 *vs.* 54–89 % in 2015−2017). For GC the variation was 52–100 % and 45–100 %, respectively.

Adjusted ORs (Fig. 1) for undergoing treatment with curative intent varied from 0.50 to 1.72 between hospitals in 2012−2014 and from 0.70 to 1.44 in 2015−2017 for EC. The total variation between the hospitals decreased significantly over time (*p < 0.01*). Over time, decision making behavior of hospitals changed: 46 % of the hospitals remained in the

Table 2
Patient characteristics gastric cancer for the period 2012-2014 and 2015-2017.

	Total		2012−2014		2015−2017		
	N	%	N	%	N	%	p-value
All included patients	3988	100 %	2218	100 %	1770	100 %	
Sex							0.519
Female	1571	39 %	864	39 %	707	40 %	
Male	2417	61 %	1354	61 %	1063	60 %	
Age							0.026
< 60	599	15 %	347	16%	252	14%	
60 to 74	1481	37 %	852	38 %	629	35 %	
75 and higher	1908	48 %	1019	46 %	881	50 %	
Histology							0.918
Adenocarcinoma	3881	97%	2159	97%	1722	97%	
Other	107	3%	59	3%	48	3%	
cT Classification							<.0001
cT1	114	3%	71	3%	44	2%	
cT1A	61	2%	43	2%	19	1%	
cT1B	42	1%	19	<1%	23	1%	
cT2	1307	33 %	662	30 %	644	36 %	
cT3	744	19 %	355	16%	388	22%	
cT4A	139	3%	60	3%	79	4%	
cT4Bˆ	118	3%	81	4%	37	2%	
cTX	1463	37 %	927	42 %	536	30 %	
cN Classification							<.001
cN0	2250	56 %	1250	56 %	1000	57%	
cN1	700	18 %	349	16%	351	20 %	
cN2	377	9%	212	10 %	165	9%	
cN3A	33	1%	15	<1%	18	1%	
cN3B	6	0.15 %	2	<1%	4	<1%	
cN X	622	16%	390	18%	232	13 %	
Tumor location							<.001
Proximal/Middle	1254	31%	708	32%	549	31%	
Pyloric and antrum	1672	42 %	882	40 %	790	45 %	
Overlapping/unknown	1059	27 %	628	28 %	431	24%	
Comorbidities							
No comorbidities					449	25 %	
1 Comorbidity					484	27 %	
>2 Comorbidities					686	39 %	
Unknown					150	8%	
Patients clinical condition							
ECOG 0					420	24%	
ECOG 1					436	25 %	
ECOG 2					125	7%	
ECOG 3 and 4					57	3%	
Unknown					732	41 %	
Type of treatment received							0.315
Surgical resection	2711	40 %	1532	69 %	1179	67%	
Endoscopic resection	43	30 %	21	<1%	22	1%	
Only neoadjuvant chemoradiotherapy	155	3%	87	4%	68	4%	
Other or no treatment	1079	27 %	578	26%	501	28 %	
Curative treatment received							0.111
No	1079	27 %	578	26%	501	28 %	
Yes	2909	73 %	1640	74%	1269	72 %	

x2 was used to calculate statistical differences between both periods in all analyses presented in this table.
Column percentage.
ˆPrior to surgery (without resection) the cT stage was below cT4b. During surgerythe team decided to refrain from resection due to the extensiveness of the tumor and staged the tumor as cT4b.
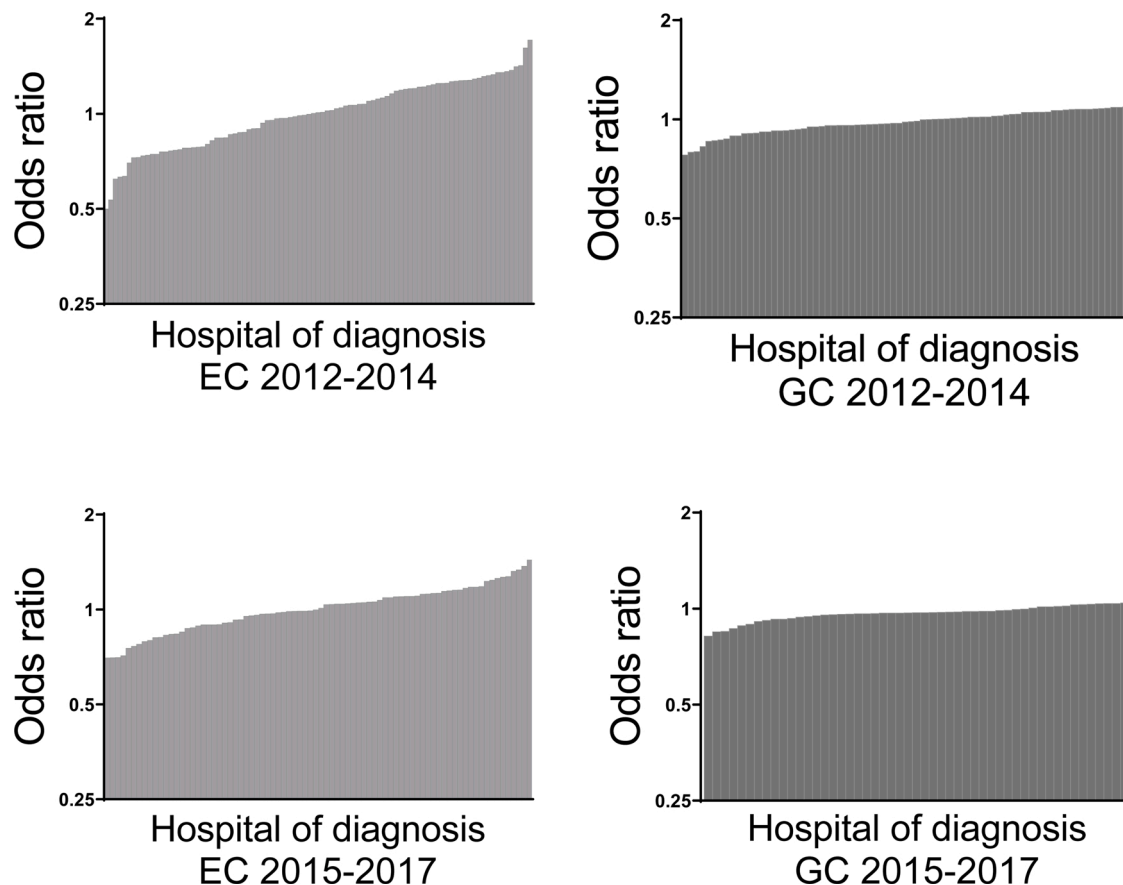
Fig. 1. adjusted odds ratios on the probability of receiving treatment with curative intent according to the hospital of diagnosis for esophageal and gastric cancer on a logarithmic scale. Adjusted for: age, sex, cT and cN stage and histology. Esophageal cancer (EC), Gastric cancer (GC).

same probability group, 25 % were grouped in a higher probability group and 29 % in a lower probability group (Appendix C).

For GC, the adjusted ORs remained stable ($p = 1.00$) and ranged from 0.78 to 1.23 in 2012−2014 and from 0.82 to 1.22 in 2015−2017 (Fig. 1). Over time decision making behavior of hospitals changed: 47 % of the hospitals remained in the same probability group, 25 % were grouped in a higher probability group and 28 % in a lower probability group (Appendix C).

Sensitivity analysis for the period 2015−2017 showed after adjustment for comorbidities and ECOG, that variation in the probability of undergoing treatment with curative intent between hospitals increased or remained stable. For EC, the OR ranged from 0.64 to 1.54 and for GC the OR ranged from 0.82 to 1.18, implying that variation in treatment with curative intent between hospital of diagnosis in both malignancies could not be explained by comorbidities or ECOG.

3.3. Survival

Three-year RS for *all* patients diagnosed with EC increased significantly over time (25 % – 27 %, *p = 0.027) and increased non significantly in potentially curable and palliative patients.* For GC no significant differences in RS were observed (23 % - 23 %, *p = 0.278*) (Appendix D).

For EC (2015−2017), 3-year RS was 35 % (95 % CI 33–37), 38 % (95 % CI 36–40), 41 % (95 % CI 38–43) in the low, medium and high probability of undergoing treatment with curative intent group respectively. Similar results were observed for 2012−2014 (Table 3.). Patients diagnosed in a hospital with a high probability of undergoing treatment for EC with curative intent had a higher RS compared to those in hospitals with a low probability (*p < 0.0001*) in both periods. The RER also was lower when diagnosed in a hospital with a high versus low

probability in 2012−2014 (0.84, 95 % CI, 0.77−0.91, *p < 0.0001*) and in 2015−2017 (0.84, 95 % CI, 0.77−0.91, *p < 0.0001*) (Table 4).

For GC (2015−2017), 3-year RS was 34 % (95 % CI 30–38), 36 % (95 % CI 31–40), and 39 % (95 % CI 36–43) in the low, medium and high probability of undergoing treatment with curative intent group respectively (*p < 0.037*). Similar results were observed for 2012−2014 (Table 3). Patients diagnosed in a hospital with a high probability of undergoing treatment with curative intent for GC had a higher RS in both periods compared to those with a low probability. The RER also was lower when diagnosed in a hospital with a high probability in 2012−2014 (0.81 (95 %CI, 0.72−0.91, *p < 0.0001*)) and in 2015−2017 (0.86 (95 % CI, 0.75−0.99, *p < 0.037*)) (Table4).

4. Discussion

In this study, variation in the probability of receiving treatment with curative intent for EC and GC according to hospital of diagnosis was assessed for two successive periods in the Netherlands. Significantly more patients with EC underwent treatment with curative intent in the second period (69 % – 72 %, *p < 0.001*), meaning more patients could undergo a potentially curative treatment. In our study, variation between hospitals of diagnosis decreased over time for EC (*p < 0.01*) but remained the same for GC (*p = 1.00*). Moreover, comparing the two times periods, overall RS increased for all EC patients and remained stable for all GC patients. Importantly, in both malignancies being diagnosed in a hospital with a high probability of being treated with curative intent was associated with an improved survival.

The cause of practice variation remains to be elucidated and is likely due to a variety of factors. Variation in cancer care typically occurs when accepted standards of care do not exist for a disease or when resources

Table 3

Probability of undergoing treatment with curative intent and relative survival across calendar periods in patients with EC or GC, stratified by probability of undergoing treatment with curative intent per initial hospital of diagnosis in 2012-2017.

	Esophageal cancer					
		Probability of undergoing treatment with curative intent in %	1 yr RS in % (95 % CI)	3 yr RS in % (95 % CI)	5 yr RS in % (95 % CI)	P
2012−2014	Low	45–66 (n = 1413)	61 (59–64)	34 (31–36)	26 (24–29)	ref
	Middle	67–72 (n = 1590)	65 (62–67)	36 (34–39)	28 (26–30)	0.097
	High	73–95 (n = 1793)	67 (65–69)	41 (38–43)	32 (30–34)	<0.0001
2015−2017	Low	54–66 (n = 1557)	63 (61−66)	35 (33–37)		ref
	Middle	67–74 (n = 1833)	65 (63−67)	38 (36–40)		0.094
	High	75–89 (n = 1929)	70 (68−72)	41 (38–43)		<0.0001

Gastric cancer				
Probability of undergoing treatment with curative intent in %	1 yr RS in % (95 % CI)	3 yr RS in % (95 % CI)	5 yr RS in % (95 % CI)	P
52–68 (n = 782)	56 (52–59)	32 (29–36)	25 (22–28)	ref
69–80(n = 664)	60 (56–64)	34 (30–38)	26 (23–30)	0.315
81–100 (n = 772)	63 (60–67)	39 (36–42)	32 (28–35)	<0.0001
45–68 (n = 594)	57 (53–61)	34 (30–38)		ref
69–74 (n = 483)	60 (56–64)	36 (31–40)		0.648
75–100 (n = 690)	64 (60–67)	39 (36–43)		0.037

Patients were divided in 3 groups with a similar number of hospitals according to the adjusted probability to undergo curative treatment of the hospital in which they were diagnosed. P value was calculated using a two sample proportion test.
Esophageal cancer (EC) gastric cancer (GC) Relative survival (RS).

are limited or unavailable. [1,21,22] The latter was not the case in the Netherlands and accepted guidelines were universally available [7,10, 11]. Guidelines may be interpreted differently especially when evidence is equivocal or lacking, which may lead to variation [22–26]. Furthermore, variation might be influenced by hospital based factors such as hospital type, physician's preferences [26,27] and experience [28], and the organization of MDTMs [29,30]. Nevertheless, variation slightly decreased in EC, which might partially be explained by the implementation of regional clinical pathways, regional MDTMs or changes in attitude towards surgery [31]. However, these are mere speculations and robust evidence regarding factors explaining hospital variation is lacking and further research is needed to elucidate these factors. Moreover, a national process improvement program, with continuous monitoring effectiveness and quality of diagnostics and referral with subsequent improving actions, should be undertaken to reduce variability and achieve changes in treatment [32].

Comorbidities and ECOG are important patient characteristics influencing treatment decision-making. [33] Based on the described subgroup analyses, difference in comorbidities and ECOG could not explain the observed variation in the latter period. Hence, other factors are more likely related to the observed variation. Possible associated factors could be the different organizational structure of the hospitals regarding clinical pathways, MDTM, physician's preference and experience and culture within a hospital and treatment team [34–36]. Physicians may well have different perception of the benefits and harms [35] and expected quality of life after treatment, which in turn will affect the decisional processes. Nevertheless, these perceptions are hard to quantify and are certainly not registered in patient's medical files. Moreover, it is unlikely that the variation according to hospital of

diagnosis is influenced by patients' preferences. Because in the Netherlands the general practitioner generally refers the patient to the hospital which is close to the patient's home address. For a further understanding and elucidation of reasons explaining variation, a more qualitative research approach is needed, which is currently undertaken by our group.

Patient specific parameters, such as a patient's preference to undergo surgery or another treatment, patient's social economic status (SES) and the influence of a patient's relatives, will also play an important role. [7, 37] Lux et al. concluded in breast cancer patients that satisfaction with treatment benefits differed to some extent between patients and this was influenced by educational level and previous experiences with other types of therapy [35]. In the Netherlands SES and educational level differ per region [38] and this might at least partly affects the observed variation. Moreover, one third of the group of breast cancer patients delegate the responsibility of the treatment decision to their physician [39]. This implies that, the probability of receiving treatment with curative intent is also determined by preferences of the treating physician. Hence, the ultimate treatment decision is influenced by the shared decisional processes of physician's and patient's preferences. In this study, solely the conclusion of this decision-making process could be assessed.

While variation in undergoing treatment with curative intent for EC decreased, no major adjustments in the Dutch guidelines were made [24]. In this study an unchanged variation in the probability of receiving treatment with curative intent in GC was observed. A Dutch study found in the period in which centralization of esophagectomies was initiated, hospital surgery volume was associated with the probability of undergoing treatment with curative intent. These associations were only

Table 4

Relative Excess Risks of death for esophageal and gastric cancer.

	Probability of undergoing treatment with curative intent	Esophageal cancer				Gastric cancer			
		RER	95 %CI		p-value	RER	95 %CI		p- value
2012−2014	Low probability	1.00				1.00			
	Middle probability	0.93	0.86	1.01	0.097	0.94	0.83	1.06	0.315
	High probability	0.84	0.77	0.91	<0.0001	0.81	0.72	0.91	<0.0001
2015−2017	Low probability	1.00				1.00			
	Middle probability	0.94	0.86	1.02	0.119	0.97	0.83	1.12	0.648
	High probability	0.84	0.77	0.91	<0.0001	0.86	0.75	0.99	0.037

Relative Excess Risks of death (RER).

found in the period in which centralization of surgery was initiated and did not remain in later time periods [3]. A study in patients diagnosed with ovarian cancer found that variation between hospitals decreased due to centralization of surgical care [31]. Since centralization of gastrectomies was initiated later than centralization for esophagectomies, this could at least partly explain the unchanged variation in GC. Other potential explanations for differences in variation between EC and GC might be more treatment options for EC (e.g. definitive chemoradiation and more palliative options) as opposed to surgery (with or without perioperative treatment) and less palliative options in GC. More importantly, since 2016, the Dutch guidelines included PET and staging laparoscopy in the staging algorithm of locally advanced (cT3–4) gastric tumors, which could affect the proportion of patients being potentially curable and receiving curative treatment [23].

Strengths of this study include the population-based design. Moreover, we were able to correct for ECOG and comorbidities in a subset of patients in the multivariable analyses. Since ECOG and comorbidities play an essential role in treatment decision-making and are not registered for the complete time period in the NCR, this can also be seen as a limitation. Especially since findings regarding the influence of ECOG and comorbidities may have differed for early pre-centralization years. Other limitations of this study are that the initial intention of the chosen therapy was not registered but assumed. As only potentially curable EC or GC patients were included in this study, it was assumed that they received neoadjuvant chemo(radiation) or underwent definitive chemoradiation with curative intent. However, this could lead to a potential overestimation of the number of patients that underwent treatment with curative intent. One could argue that the larger proportion of missing T stages in 2012−2014, (42 % GC) when compared with 2015−2017 (30 %), might be due to a more frequent use of diagnostic application of endoscopic ultrasound which could explain the observed variation. However, treatment choices in this patient group depend more on N and M stage, than on the T stage, apart from the T4b-status, which was not included in this study. Additionally, since MDTMs facilitate adherence to clinical practice guidelines, [40,41] it would have been interesting to investigate the effect of discussing cases in a low versus high volume or local versus regional MDTM. Nevertheless, this data was not registered in the NCR for the whole study period and thus further research is needed in order to assess the impact of discussing patients in a tumor specific Upper-GI MDTM incorporating expert centers and assess the effect of the implementation of regional clinical pathways.

In conclusion, our study has shown that in 2012–2017 period, variation in probability of undergoing treatment with curative intent between the different hospitals of diagnosis in the Netherlands decreased for EC but remained stable for GC. Survival was better for patients diagnosed in a hospital in which the probability of undergoing treatment with curative intent was high. Decisive factors associated with the variability are still unclear. Further research is needed to elucidate these factors explaining variation, which may improve care for patients diagnosed with these malignancies.

Authorship justification

Josianne C.H.B.M. Luijten: Authors make substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data; 2) Authors participate in drafting the article or revising it critically for important intellectual content; and 3) Authors give final approval of the version to be published.

Pauline AJ Vissers: Authors make substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data; 2) Authors participate in drafting the article or revising it critically for important intellectual content; and 3) Authors give final approval of the version to be published.

Hester Lingsma: Authors make substantial contributions to conception and design, and/or analysis and interpretation of data; 2) revising it critically for important intellectual content; and 3) Authors give final approval of the version to be published.

Nikki van Leeuwen: Authors make substantial contributions to conception and design, and/or analysis and interpretation of data; 2) revising it critically for important intellectual content; and 3) Authors give final approval of the version to be published.

Tom Rozema: Authors make substantial contributions to analysis and interpretation of data; 2) revising it critically for important intellectual content; and 3) Authors give final approval of the version to be published.

Peter D. Siersema: Authors make substantial contributions to analysis and interpretation of data; 2) revising it critically for important intellectual content; and 3) Authors give final approval of the version to be published.

Camiel Rosman: Authors make substantial contributions to analysis and interpretation of data; 2) revising it critically for important intellectual content; and 3) Authors give final approval of the version to be published.

Hanneke W.M. van Laarhoven: Authors make substantial contributions to analysis and interpretation of data; 2) revising it critically for important intellectual content; and 3) Authors give final approval of the version to be published.

Valery EP Lemmens: Authors make substantial contributions to analysis and interpretation of data; 2) revising it critically for important intellectual content; and 3) Authors give final approval of the version to be published.

Grard AP Nieuwenhuijzen: Authors make substantial contributions to conception and design, and/or analysis and interpretation of data; 2) Authors participate in drafting the article or revising it critically for important intellectual content; and 3) Authors give final approval of the version to be published.

Rob HA Verhoeven: Authors make substantial contributions to conception and design, and/or analysis and interpretation of data; 2) Authors participate in drafting the article or revising it critically for important intellectual content; and 3) Authors give final approval of the version to be published.

CRediT authorship contribution statement

Josianne C.H.B.M. Luijten: Conceptualization, Methodology, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Pauline A.J. Vissers:** Supervision, Conceptualization, Methodology, Data curation, Formal analysis, Writing - review & editing. **Hester Lingsma:** Methodology, Writing - review & editing. **Nikki van Leeuwen:** Methodology, Writing - review & editing. **Tom Rozema:** Conceptualization, Writing - review & editing. **Peter D. Siersema:** Conceptualization, Writing - review & editing. **Camiel Rosman:** Conceptualization, Writing - review & editing. **Hanneke W.M. van Laarhoven:** Conceptualization, Writing - review & editing. **Valery E.P. Lemmens:** Supervision, Writing - review & editing, Conceptualization. **Grard A.P. Nieuwenhuijzen:** Supervision, Methodology, Conceptualization, Writing - review & editing. **Rob H.A. Verhoeven:** Supervision, Conceptualization, Methodology, Writing - review & editing.

Appendix A. Treatment with curative intent in hospital of diagnosis <10 versus >10

Esophageal cancer			Gastric cancer		
Year of diagnosis	<10	>10	Year of diagnosis	<10	>10
2012−2014	0.06% (n = 3)	99 % (n = 4795)	2012−2014	2% (n = 52)	98 % (n = 2218)
2015−2017	0.1% (n = 6)	99.9 %(n = 5319)	2015−2017	4% (n = 72)	96 %(n = 1770)
	N = 9	N = 10,114		N = 124	N = 3988

Appendix B. Distribution of all potentially curable and palliative esophageal and gastric cancer according to year of diagnosis

Esophageal cancer					Gastric cancer				
Year of diagnosis	Potentially curable	Palliative	Total	P value	Year of diagnosis	Potentially curable	Palliative	Total	P value
2012	1610 (63 %)	937 (37 %)	2564	0.60	2012	777 (59 %)	538 (41 %)	1315	<0.01
2013	1597 (63 %)	942 (37 %)	2567		2013	759 (60 %)	504 (40 %)	1263	
2014	1592 (61 %)	1009 (39 %)	2633		2014	734 (61 %)	468 (39 %)	1202	
2015	1737 (62 %)	1057 (38 %)	2841		2015	616 (55 %)	500 (45 %)	1116	
2016	1796 (62 %)	1087 (38 %)	2937		2016	682 (55 %)	491 (45 %)	1173	
2017	1792 (63 %)	1033 (37 %)	2873		2017	544 (53 %)	471 (47 %)	1015	
Total	10,124	6291	16,415		**Total**	4112	2968	7080	

Treatment with curative intent in hospital of diagnosis <10 were excluded from analyses.

Appendix C. Changes in probability of curative treatment between 2012−2014 and 2015−2017 per hospital

	Number of hospitals EC	Number of hospitals GC
No change in probability of curative treatment	34 (46 %)	28 (47 %)
Low – low probability	11 (15 %)	10 (17 %)
Medium – medium probability	9 (12 %)	6 (10 %)
High – high probability	14 (19 %)	12 (20 %)
Decrease in probability of curative treatment	21 (29 %)	17 (28 %)
Medium – low probability	11 (15 %)	6 (10 %)
High – low probability	3 (4%)	5 (8%)
High – medium probability	7 (9.6 %)	6 (10 %)
Increase in probability of curative treatment	18 (25 %)	15 (25 %)
Low – medium probability	7 (9.6 %)	8 (13 %)
Low – High probability	5 (6.9 %)	6 (10 %)
Medium – high probability	6 (8%)	1 (2%)

Esophageal cancer (EC) gastric cancer (GC),
Due to fusions of hospitals and bankruptcies not all hospitals are represented in both periods, therefore numbers might not add up.

Appendix D. 3-year relative survival in all patients, potentially curable patients and 1 year relative survival in palliative patients in the period 2012−2014 and 2015−2017 in the Netherlands

	Esophageal cancer					Gastric cancer				
	2012−2014 RS in % (95 % CI)	Number of patients	2015−2017 RS in % (95 % CI)	Number of patients	P value	2012−2014 RS in % (95 % CI)	Number of patients	2015−2017 RS in % (95 % CI)	Number of patients	P value
3-year RS All patients	25 % (24−26)	7764	27 % (26−28)	8663	0.027	23 % (22−24)	3795	23 % (21−25)	3329	0.278
3-year RS Potentially curable	38 % (37−40)	4845	40 % (38−41)	5461	0.117	36 % (34−38)	2279	38 % (35−40)	1859	0.299
1-year RS Palliative	21 % (20−23)	2919	22% (21−24)	3202	0.248	18% (17−20)	1516	17 % (15−19)	1470	0.81

P value was calculated using a two sample proportion test.
Relative survival (RS).

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