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The association between hospital variation in curative treatment for esophagogastric cancer and health-related quality of life and survival

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ABSTRACT

Background: As previous studies showed significant hospital variation in curative treatment of esophagogastric cancer, this study assesses the association between this variation and overall, cancer-specific and recurrence-free survival, and Health-Related Quality of Life (HRQoL).

Methods: Patients diagnosed with potentially curable esophageal or gastric cancer between 2015 and 2018 as registered in the Netherlands Cancer Registry were included. Data on overall survival was available for all patients, data on cancer-specific and recurrence-free survival and HRQoL was available for subgroups. Patients were classified according to diagnosis in hospitals with low, medium or high probability of treatment with curative intent (LP, MP or HP). Multivariable models were used to assess the association between LP, MP and HP hospitals and HRQoL and survival.

Results: This study includes 7,199 patients with esophageal, and 2,407 with gastric cancer. Overall and cancer-specific survival was better for patients diagnosed in HP versus LP hospitals for both esophageal (HR = 0.82, 95% CI:0.77–0.88 and HR = 0.82, 95%CI:0.75–0.91, respectively), and gastric cancer (HR = 0.82, 95%CI:0.73–0.92 and HR = 0.74, 95%CI:0.64–0.87, respectively). These differences disappeared after adjustments for treatment. Recurrence-free survival was worse for gastric cancer patients diagnosed in HP hospitals (HR = 1.50, 95% CI:1.14–1.96), which disappeared after adjustment for radicality of surgery. Minor, but no clinically relevant, differences in HRQoL were observed.

Conclusions: Patients diagnosed in hospitals with a high probability of treatment with curative intent have a better overall and cancer-specific but not recurrence-free survival, while minor differences in HRQoL were observed.

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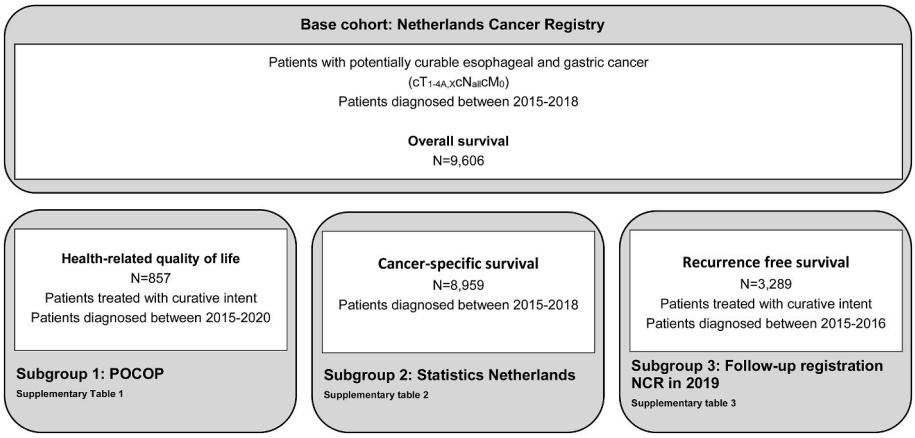

Fig. 1. Available data and data sources.

1. Introduction

For patients with potentially curable esophageal or gastric cancer, treatment with or without (neo)adjuvant chemo(radio)therapy followed by resection or endoscopic resection for early-stage disease, is the preferred treatment [1,2]. Recently, adjuvant nivolumab has been approved for patients with esophageal or gastro-esophageal junction cancer with an incomplete response after neoadjuvant chemoradiotherapy and resection [3]. For patients with esophageal cancer who are unwilling to undergo surgical resection or unfit, definitive chemoradiation is an alternative curative treatment option [4,5]. Although still experimental, active surveillance after a complete clinical response of neoadjuvant chemoradiotherapy is increasingly being used [6].

In the Netherlands, a minimum annual volume of 20 resections was defined in 2011 for esophageal and since 2013 for gastric cancer resections. As esophageal and gastric cancer are often diagnosed in non-resection centers, the decision to treat with curative intent depends on adequate regional collaboration and referral between non-resection and resection centers. Previous studies in the Netherlands demonstrated that the probability of receiving treatment with curative intent for potentially curable esophageal or gastric cancer varies considerably between hospitals of diagnosis [7–9]. In more recent years this variation decreased for esophageal, but not for gastric cancer [10]. Moreover, a higher probability of treatment with curative intent has been associated with an increased overall and relative survival [8–10]. However, whether the probability of treatment with curative intent also influences cancer-specific survival, and recurrence free survival is currently unknown.

Besides survival, the influence of this variation in receiving treatment with curative intent on Health-Related Quality of Life (HRQoL) should be addressed. A recent review and meta-analysis showed that both an esophagectomy and gastrectomy resulted in long-term deterioration of various HRQoL functioning and symptom scales [11], which was also observed in other studies [12–14]. For esophageal cancer no long-term differences in HRQoL were observed between neoadjuvant chemoradiotherapy with surgery and surgery alone or surgery alone and definitive chemoradiotherapy [11]. As, by definition, treatment differs between hospitals with low or high probability of curative treatment we hypothesize that the probability of treatment with curative intent is associated with HRQol. Hospitals with a high probability of curative treatment might be more inclined to treat frail patients possibly resulting in poorer HRQoL. Nevertheless, currently it is unknown whether this variation in curative treatment actually impacts HRQoL.

Therefore, this study aims to assess the association between the probability of treatment with curative intent and overall, cancer-specific and recurrence-free survival, and HRQoL in patients with esophagogastric cancer.

2. Methods

2.1. Study population and data sources

The base cohort includes patients with potentially curable esophageal, including gastro-esophageal junction and cardia carcinomas, or gastric cancer ($cT_{1-4A,X}cN_{all}cM_0$) diagnosed between 2015 and 2018 as selected from the population-based Netherlands Cancer Registry (NCR). All newly diagnosed cancer patients are identified through notification of the national automated pathology archive. Subsequently, trained registrars of the NCR routinely collect data on patient-, tumor-, and treatment characteristics from the medical records of all patients diagnosed with cancer in the Netherlands. Patients diagnosed in hospitals with less than 10 diagnoses over the 4-year study period were excluded (esophageal cancer: n = 0, gastric cancer: n = 15 patients). Three subgroups were defined for which additional data on HRQoL, cancer-specific and recurrence-free survival was available (Fig. 1). For analysis on HRQoL, additional data from diagnosis years 2019 and 2020 was included to obtain sufficient data for multivariable analyses.

Data on overall survival was available for the main cohort through linkage of the NCR with the Dutch municipal personal records database, and follow-up was complete until February 1, 2022. Data on recurrence were available for a subgroup of the main cohort and were collected in the second half of 2019 for patients with a primary diagnosis of esophageal or gastric cancer in 2015 and 2016, and treated with curative intent (i.e., resection (with or without (neo)adjuvant chemotherapy) or for esophageal cancer definitive chemoradiation). Data regarding cancer specific survival was retrieved from the underlying cause of death (coded according to ICD-10) on death certificates, available from non-public microdata from Statistics Netherlands (CBS) and linked with the NCR.

Information regarding HRQoL was retrieved through linkage of the NCR with the Prospective Observational Cohort Study of Esophageal-gastric cancer Patients (POCOP) [15]. POCOP is a nationwide registry which aims to collect clinical data and patient-reported outcomes for patients with esophageal and gastric cancer. Questionnaires are sent out at baseline, and after 3, 6, 9, 12, 18, and 24 months, and thereafter annually. For the current study, patients diagnosed after 2015 who were treated with curative intent, and completed at least 2 questionnaires, including 1 prior to treatment, were included. Patients with a potentially curable tumor stage who did not receive treatment with curative intent were excluded from HRQoL analyses as the numbers were deemed to small (i.e., n < 50 for both esophageal and gastric cancer). Questionnaires were categorized as before treatment (before Tx), during treatment (during Tx), 0–3, 3–6, 6–9 and 9–12 months after treatment (0–3, 3–6, 6–9, 9–12 months after Tx). Patients diagnosed in 2019 and 2020, who were not present in the main cohort, for whom clinical data from

Table 1
Baseline characteristics for the main cohort including all patients diagnosed with potentially curable esophageal or gastric cancer according to the probability of treatment with curative intent.

	Esophageal cancer							Gastric cancer						
	Probability of treatment with curative intent							Probability of treatment with curative intent						
	Low (LP) (N = 2515)		Medium (MP) (n = 2326)		High (HP) (n = 2358)			Low (LP) (n = 823)		Medium (MP) (n = 700)		High (HP) (n = 884)		
	N	%	N	%	N	%	P-value	N	%	N	%	N	%	P-value
Year of incidence							0.66							0.41
2015	610	24.3	554	23.8	578	24.5		225	27.3	163	23.3	219	24.8	
2016	608	24.2	602	25.9	585	24.8		216	26.2	197	28.1	260	29.4	
2017	627	24.9	587	25.2	611	25.9		187	22.7	153	21.9	196	22.2	
2018	670	26.6	583	25.1	584	24.8		195	23.7	187	26.7	209	23.6	
Sex							0.98							0.11
Male	1824	72.5	1684	72.4	1704	72.3		471	57.2	438	62.6	530	60	
Female	691	27.5	642	27.6	654	27.7		352	42.8	262	37.4	354	40	
Age							0.78							0.58
< 60 yrs	410	16.3	355	15.3	371	15.7		106	12.9	109	15.6	132	14.9	
60–74 yrs	1288	51.2	1184	50.9	1218	51.7		298	36.2	249	35.6	305	34.5	
≥75 yrs	817	32.5	787	33.8	769	32.6		419	50.9	342	48.9	447	50.6	
Histology							0.61							0.0006
Squamous cell carcinoma	632	25.1	596	25.6	629	26.7		NA		NA		NA		
Adenocarcinoma - intestinal	807	32.1	763	32.8	729	30.9		290	35.2	304	43.4	313	35.4	
Adenocarcinoma - diffuse	233	9.3	200	8.6	196	8.3		315	38.3	254	36.3	312	35.3	
Adenocarcinoma - other	759	30.2	690	29.7	738	31.3		187	22.7	127	18.1	230	26	
Unknown	84	3.3	77	3.3	66	2.8		31	3.8	15	2.1	29	3.3	
cT							0.0003							0.66
cT1	121	4.8	131	5.6	126	5.3		31	3.8	27	3.9	47	5.3	
cT2	710	28.2	615	26.4	709	30.1		293	35.6	229	32.7	312	35.3	
cT3	1290	51.3	1165	50.1	1064	45.1		205	24.9	171	24.4	212	24	
cT4	44	1.7	50	2.1	45	1.9		51	6.2	45	6.4	55	6.2	
cTX	350	13.9	365	15.7	414	17.6		243	29.5	228	32.6	258	29.2	
cN							<0.0001							0.98
cN0	946	37.6	979	42.1	1043	44.2		465	56.5	402	57.4	510	57.7	
cN+	1365	54.3	1124	48.3	1108	47		247	30	208	29.7	256	29	
cNX	204	8.1	223	9.6	207	8.8		111	13.5	90	12.9	118	13.3	
Treatment							<0.0001							<0.0001
No curative treatment	746	29.7	607	26.1	547	23.2		290	35.2	184	26.3	199	22.5	
Resection with or without (neo)adjuvant treatment	1124	44.7	1139	49	1143	48.5		493	59.9	488	69.7	647	73.2	
Endoscopic resection	103	4.1	124	5.3	159	6.7		9	1.1	6	0.9	11	1.2	
Chemoradiotherapy	542	21.6	456	19.6	509	21.6								
Initiation of neoadjuvant chemotherapy								31	3.8	22	3.1	27	3.1	
Performance status							<0.0001							<0.0001
ECOG/WHO 0	896	35.6	781	33.6	629	26.7		235	28.6	188	26.9	186	21	
ECOG/WHO 1	792	31.5	681	29.3	641	27.2		234	28.4	163	23.3	190	21.5	
ECOG/WHO 2	254	10.1	161	6.9	172	7.3		60	7.3	48	6.9	68	7.7	
ECOG/WHO 3	81	3.2	70	3	63	2.7		41	5	17	2.4	27	3.1	
ECOG/WHO 4	9	0.4	16	0.7	11	0.5		7	0.9	1	0.1	7	0.8	
unknown	483	19.2	617	26.5	842	35.7		246	29.9	283	40.4	406	45.9	
Number of comorbidities							<0.0001							<0.0001
No comorbidity	983	39.1	970	41.7	875	37.1		294	35.7	250	35.7	336	38	
1 comorbdity	824	32.8	751	32.3	706	29.9		259	31.5	249	35.6	270	30.5	
≥2 comorbidities	602	23.9	516	22.2	515	21.8		216	26.2	179	25.6	179	20.2	
unknown	106	4.2	89	3.8	262	11.1		54	6.6	22	3.1	99	11.2	
Body mass index							<0.0001							<0.0001
<18.5 kg/m2	116	4.6	70	3	64	2.7		16	1.9	17	2.4	22	2.5	
18.5–25 kg/m2	734	29.2	658	28.3	514	21.8		263	32	204	29.1	209	23.6	
25–30 kg/m2	610	24.3	591	25.4	471	20		165	20	136	19.4	135	15.3	
≥ 30 kg/m2	265	10.5	233	10	202	8.6		72	8.7	52	7.4	59	6.7	
unknown	790	31.4	774	33.3	1107	46.9		307	37.3	291	41.6	459	51.9	

the NCR was complete were additionally included for HRQoL analyses. Patients provided written informed consent. The POCOP study was not considered as research under the Medical Research Involving Human Subjects Act (WMO) according to the medical ethics committee of the AMC Amsterdam. According to the Central Committee on Research involving Human Subjects, observational research with NCR data does not require approval from an ethics committee in the Netherlands. Based on current Dutch legislation it is not necessary to retrieve informed consent from patients for registration into the NCR. The study was approved by the Privacy Review Board of the NCR, and the scientific committee of the Dutch Upper-GI Cancer Group. This study was performed in accordance with the ethical standards as laid down in the Declaration of Helsinki.

2.2. Patient, tumor and treatment characteristics

Patient- (age, sex, body mass index (BMI), number of comorbidities, and performance status), tumor-, and treatment characteristics were available from the NCR. Tumor location and histology were coded according to the third edition of the International Classification of Diseases for Oncology [16]. Clinical tumor stage was coded according to the TNM classification of the International Union Against Cancer 7th and 8th

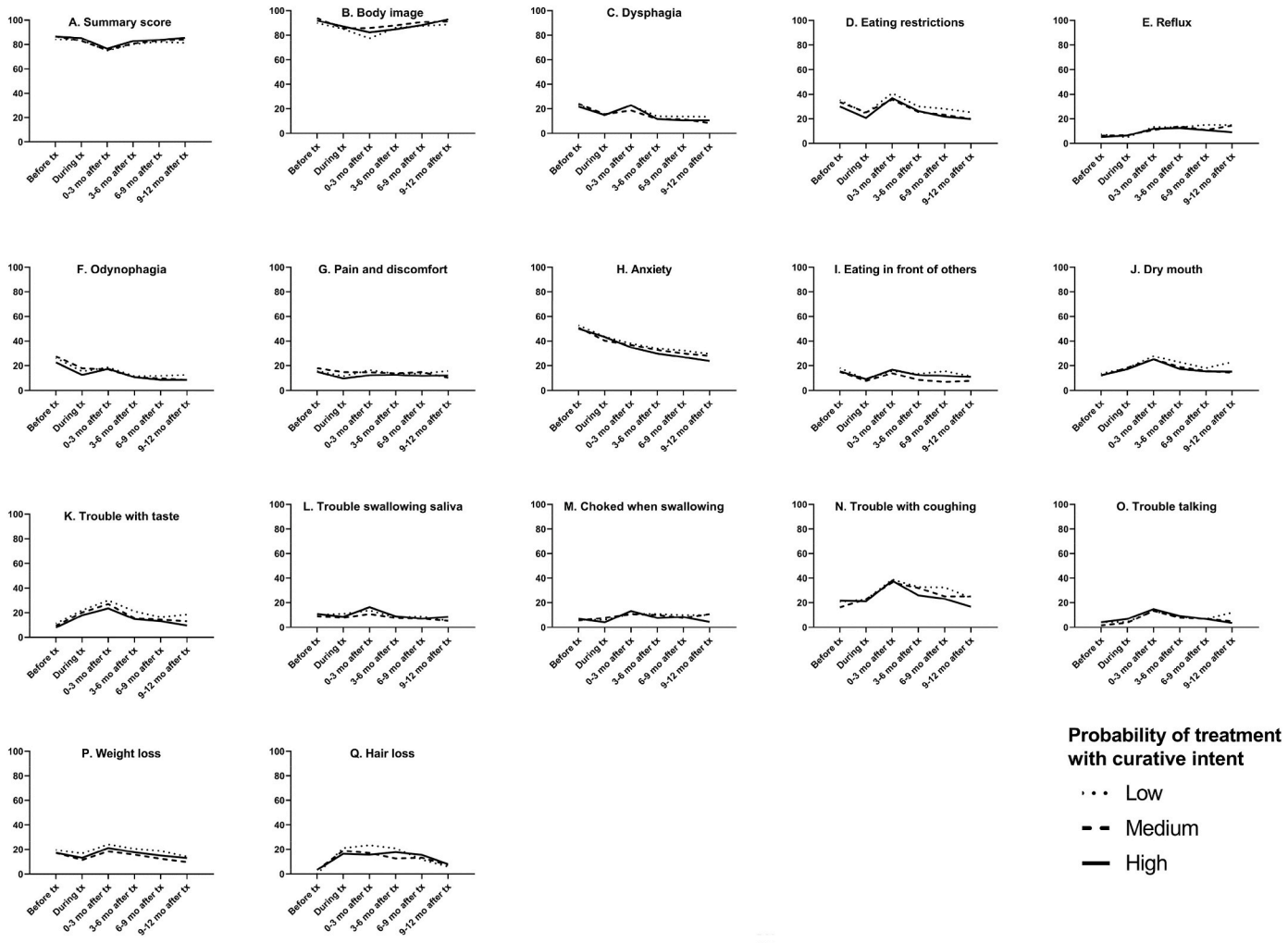

Fig. 2. A–Q Health-related quality of life among patients with esophageal cancer treated with curative intent (N = 729).

edition for diagnosis in 2015–2016, and from 2017 onwards, respectively [17,18]. Treatment with curative intent was defined as initiation of treatment with the aim of curation, and included the initiation of: neoadjuvant chemo(radio)therapy, surgery (with/without resection), endoscopic resection, and definitive chemoradiation (for esophageal cancer only).

2.3. Outcomes - HRQoL

HRQoL was assessed with the Dutch validated version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the Esophageal-Gastric Cancer Module 25 (EORTC-QLQ-OG25) [19,20]. The EORTC QLQ-C30 summary score was used which is calculated as the mean of 13 of the scales from the EORTC QLQ-C30 (i.e. physical, role, cognitive, emotional and social functioning, fatigue, pain, nausea and vomiting, dyspnea, appetite loss, sleep disturbance, constipation and diarrhea) [21]. The EORTC QLQ-OG25, contains one functioning scale (body image), six multi-item symptom scales (dysphagia, eating restrictions, reflux, odynophagia, pain and discomfort, and anxiety) and nine single-item symptom scales (eating in front of others, dry mouth, trouble with taste, trouble swallowing saliva, choked when swallowing, trouble with coughing, trouble talking, weight loss and hair loss). After linear transformation, all scales range in score from 0 to 100. A higher score on the EORTC QLQ-C30 summary score, and body image corresponds to better functioning, while for all other scales from the EORTC-QLQ-OG25 a higher score corresponds to more symptoms. As no standard guidelines for evaluation of clinical relevance for the summary score or QLQ OG-25 exist, a difference of 10 points as defined by Osaba et al., was used to assess medium clinical relevance [22].

2.4. Outcomes - survival

Overall survival was assessed for the main cohort from time of diagnosis to death, or end of follow-up as of February 1st, 2022. Recurrence-free survival was available for all curative treated patients with a primary diagnosis in 2015–2016, and time to recurrence was calculated from end of curative treatment until first recurrence or end of follow-up at December 31st, 2019. Cancer-specific survival was calculated from time to diagnosis until death due to esophageal or gastric cancer or end of follow-up at December 31st, 2018.

2.5. Statistical methods

For all potentially curable patients diagnosed between 2015 and 2018, and included in the main cohort, hospitals of diagnosis were categorized into low, medium and high probability of treatment with curative intent separately for esophageal and gastric cancer, further referred to as LP, MP and HP-hospitals, respectively. The probability was calculated using a multilevel multivariable logistic regression model adjusted for variables that where a priori selected based on literature: sex, age, histology, clinical T stage, clinical N stage, performance status,

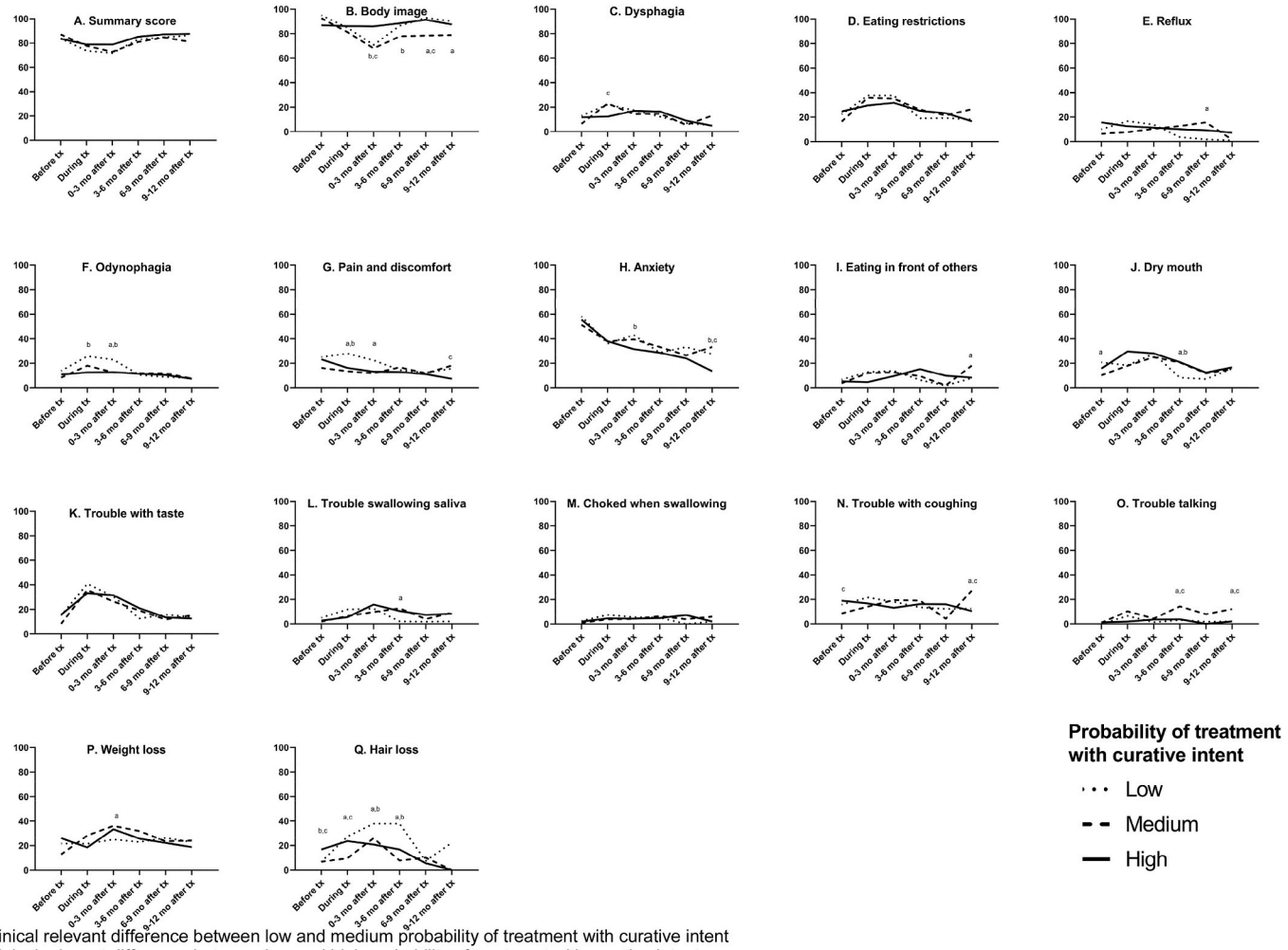

Fig. 3. A –Q Health-related quality of life among patients with gastric cancer treated with curative intent (N = 128).

BMI and comorbidity, with random intercept for hospital of diagnosis. Odds ratios for treatment with curative intent for each hospital of diagnosis were retrieved and divided into tertiles (i.e., low (LP), medium (MP) and high probability (HP)), as has been done previously [10].

All baseline characteristics were presented according to LP, MP or HP hospitals using frequencies with Chi-square or Fishers exact test, and stratified for esophageal and gastric cancer. Univariable longitudinal HRQol scores were presented graphically and multivariable generalized linear mixed models, with an unstructured covariance structure, were used to assess HRQoL according to LP, MP and HP hospitals. Betas with standard errors (SE) were reported.

Overall, cancer-specific and recurrence-free survival were univariably assessed with Kaplan Meier curves and the log-rank test. Cox proportional hazard analysis were conducted to assess the association between the probability of curative treatment and overall, recurrence-free, and cancer-specific survival. For recurrence-free survival death was considered a competing event, whereas for cancer-specific survival, death due to other causes than esophageal or gastric cancer was included as competing event. Hazard ratios (HRs) with 95%CIs were reported.

For analysis regarding HRQoL and survival, confounders were selected a priori based on literature. Model 1 was adjusted for patient- and tumor characteristics, while model 2 was additionally adjusted for treatment.

All analyses were conducted with SAS® version 9.4 (SAS Institute, Cary, North Carolina, USA), or STATA/SE (Version 14.1; STATACorp, College Station, Texas, USA).

3. Results

3.1. Baseline characteristics

In total, 7,199 patients with esophageal cancer were included of whom 34.9%, 32.3%, and 32.8% were diagnosed in LP, MP and HP hospitals, respectively (Table 1). For gastric cancer, of the 2,407 included patients, 34.2%, 29.1%, and 36.7% were diagnosed in LP, MP and HP hospitals, respectively. Patients with esophageal cancer diagnosed in a LP hospital had more often a cT3 tumor (51.3% vs 50.1% and 45.1%), a cN+ tumor (54.3% vs 48.3% and 47%) as compared to patients diagnosed MP or HP hospitals.

For gastric cancer cT and cN were comparable between patients diagnosed LP, MP and HP hospitals. Similar differences were observed for the subgroups for whom data on cancer-specific survival (n = 8,959), recurrence-free survival (n = 3,289) and HRQoL (n = 857) was available (see Supplementary Tables 1–3).

3.2. Health-related quality of life

No clinically relevant differences in HRQoL were observed between patients with esophageal cancer (n = 729) diagnosed in LP, MP or HP

Table 2
Association between probability of treatment with curative intent and HRQoL using multivariable generalized linear mixed models.

	Model 1						Model 2					
	MP vs LP			HP vs LP			MP vs LP			HP vs LP		
	Beta	SE	p-value	Beta	SE	p-value	Beta	SE	p-value	Beta	SE	p-value
Esophageal cancer												
Summary score	1.12	0.95	0.24	1.31	1	0.19	0.97	0.95	0.31	1.26	1	0.2
Body image	2.49	1.45	0.09	0.88	1.52	0.56	2.38	1.45	0.1	0.84	1.52	0.58
Dysphagia	−0.39	1.27	0.76	−1.23	1.33	0.36	−0.15	1.26	0.91	−1.16	1.32	0.38
Eating restrictions	−2.15	1.7	0.21	**−3.89**	**1.79**	**0.029**	−1.78	1.68	0.29	**−3.63**	**1.76**	**0.04**
Reflux	−0.03	1.06	0.98	−0.6	1.12	0.59	0.12	1.06	0.91	−0.56	1.11	0.61
Odynophagia	−0.04	1.28	0.98	−1.52	1.34	0.26	0.1	1.28	0.94	−1.47	1.34	0.27
Pain and discomfort	1.03	1.37	0.45	−1.32	1.44	0.36	1.17	1.37	0.39	−1.27	1.44	0.38
Anxiety	−0.91	1.91	0.63	−1.83	2.01	0.36	−1.03	1.92	0.59	−1.86	2.01	0.35
Eating in front of others	−2.27	1.65	0.17	0.18	1.74	0.92	−2.11	1.65	0.2	0.23	1.74	0.89
Dry mouth	−1.71	1.7	0.31	−2.14	1.79	0.23	−1.53	1.7	0.37	−2.13	1.78	0.23
Trouble with taste	−2.34	1.56	0.13	**−3.78**	**1.63**	**0.02**	−2.17	1.55	0.16	**−3.73**	**1.63**	**0.02**
Trouble swallowing saliva	−1	1.34	0.46	0.56	1.41	0.69	−0.74	1.34	0.58	0.63	1.4	0.65
Choked when swallowing	−0.09	1.06	0.93	−0.74	1.11	0.5	0.07	1.05	0.95	−0.66	1.1	0.55
Trouble with coughing	−2.97	1.57	0.06	−1.54	1.65	0.35	−2.59	1.56	0.1	−1.43	1.63	0.38
Trouble talking	−1.52	0.92	0.1	0.85	0.97	0.38	−1.48	0.92	0.11	0.85	0.97	0.38
Weight loss	−2.88	1.58	0.07	−1.41	1.66	0.39	−2.59	1.57	0.1	−1.33	1.64	0.42
Hairloss[#]	−1.62	2.48	0.51	−1.27	2.65	0.63	1.11	1.89	0.56	1.36	1.84	0.46
Gastric cancer												
Summary score	0.28	2.23	0.9	−1.83	2.16	0.4	−0.09	2.27	0.97	−2.17	2.19	0.32
Body image	−7	4.39	0.11	−3.81	4.21	0.37	−6.92	4.48	0.13	−3.75	4.29	0.39
Dysphagia	0.05	3.29	0.99	1.88	3.17	0.55	0.29	3.34	0.93	1.78	3.21	0.58
Eating restrictions	5.34	4.56	0.24	4.88	4.38	0.27	5.52	4.6	0.23	4.5	4.42	0.31
Reflux	2.09	2.7	0.44	**7.79**	**2.59**	**0.003**	2.52	2.69	0.35	**7.59**	**2.58**	**0.004**
Odynophagia	0.84	3.2	0.79	0.65	3.05	0.83	0.74	3.14	0.81	−0.2	3	0.95
Pain and discomfort	−4.41	3.9	0.26	−3.24	3.78	0.39	−4.61	3.97	0.25	−3.45	3.85	0.37
Anxiety	1.27	4.86	0.79	−0.44	4.66	0.92	1.66	4.94	0.74	−0.46	4.73	0.92
Eating in front of others	1.28	3.24	0.69	3.87	3.12	0.22	1.13	3.27	0.73	3.29	3.15	0.3
Dry mouth	3.91	4.62	0.4	4.66	4.46	0.3	2.86	4.72	0.55	3.66	4.55	0.42
Trouble with taste	0.62	4.29	0.89	1.53	4.13	0.71	−0.1	4.33	0.98	0.85	4.16	0.84
Trouble swallowing saliva	−0.66	2.6	0.8	0.95	2.49	0.7	−0.96	2.6	0.71	1.12	2.49	0.66
Choked when swallowing	−2.07	1.62	0.2	−1.41	1.56	0.37	−2.3	1.63	0.16	−1.46	1.57	0.36
Trouble with coughing	−2.36	3.51	0.5	2.6	3.38	0.44	−1.94	3.54	0.58	3.21	3.41	0.35
Trouble talking[#]	**4.93**	**2.00**	**0.02**	−0.45	1.91	0.82	**4.77**	**2.02**	**0.02**	−0.33	1.93	0.86
Weight loss	1.12	4.44	0.8	−0.65	4.18	0.88	0.95	4.54	0.83	−0.89	4.26	0.83
Hairloss[#]	−5.11	6.30	0.42	−1.25	5.85	0.83	−5.23	6.28	0.41	−0.47	5.84	0.94

Statistically significant results are indicated in bold.
LP: patients diagnosed in hospitals with low probability of curative intent.
MP: patients diagnosed in hospitals with medium probability of curative intent.
HP: patients diagnosed in hospitals with high probability of curative intent.
Model 1: adjusted for sex, age, histology, clinical T stage, clinical N stage, performance status, BMI and comorbidity.
Model 2: Model 1 additionally adjusted for treatment.
#For hair loss (model 1) for esophageal cancer and for trouble talking and hairloss (model 1 and 2) for gastric cancer a compound symmetry covariance structure was used due to limited variation in the model.

hospitals (Fig. 2a-q). For patients with gastric cancer (n = 128) several clinically relevant differences were observed (Fig. 3a-q) with the majority being present during, 0–3 months or 3–6 months after treatment. Mainly, patients diagnosed in MP and/or HP hospitals reported better functioning and less symptoms.

In multivariable analyses, patients with esophageal cancer diagnosed in HP hospitals reported on average 3.89 points lower on eating restrictions (SE: 1.78, p-value = 0.029), and 3.78 points lower on trouble with taste (SE:1.63, p-value = 0.02) as compared to patients diagnosed in LP hospitals (Model 1, Table 2). For gastric cancer significant higher scores for reflux were reported (beta = 7.79, SE = 2.59, p-value = 0.003) in patients diagnosed in HP versus LP hospitals (Model 1, Table 2). More trouble with talking was reported for MP versus LP hospitals (beta = 4.93, SE = 2.00, p-value = 0.02). Similar results were found after additional adjustment for treatment (model 2, Table 2). None of the described significant differences reached the threshold for clinical relevance of 10 points.

3.3. Survival

Among patients with esophageal cancer, overall, cancer-specific, and recurrence-free survival were significantly higher for patients diagnosed in HP hospitals compared to patients diagnosed in MP or LP hospitals respectively (3-year overall survival 36.1% vs 37.6% vs 39.9%, cancer-specific survival: 40.2% vs 42.8% vs 46.6% and recurrence-free survival 34.6% vs 37.6% vs 39%, Fig. 4a). Cox regression analyses adjusted for patient- and tumor characteristic showed a significantly increased overall and cancer specific survival for patients diagnosed in HP hospitals (HR = 0.82 (95% CI:0.77–0.88) and HR = 0.82 (95% CI:0.75–0.91), respectively (Model 1, Table 3)). For recurrence free survival no differences were observed after adjustment for patient- and tumor characteristics (model 1). After additional adjustments for treatment (model 2) no significant differences in overall, cancer-specific or recurrence-free survival were observed between esophageal cancer patients diagnosed in LP, MP and HP hospitals.

For gastric cancer no differences in unadjusted overall or recurrence-free survival were observed (Fig. 4b: p-value = 0.061 and p-value = 0.34, respectively). Cancer-specific survival was significantly better in patients diagnosed in MP hospitals (3-year cancer-specific survival: 38.7 vs 47.4% vs 43.1% for LP, MP and HP, respectively, p-value = 0.02). Multivariable analysis showed increased overall survival for patients diagnosed in HP versus LP hospitals (HR = 0.82; 95%CI: 0.73–0.92,

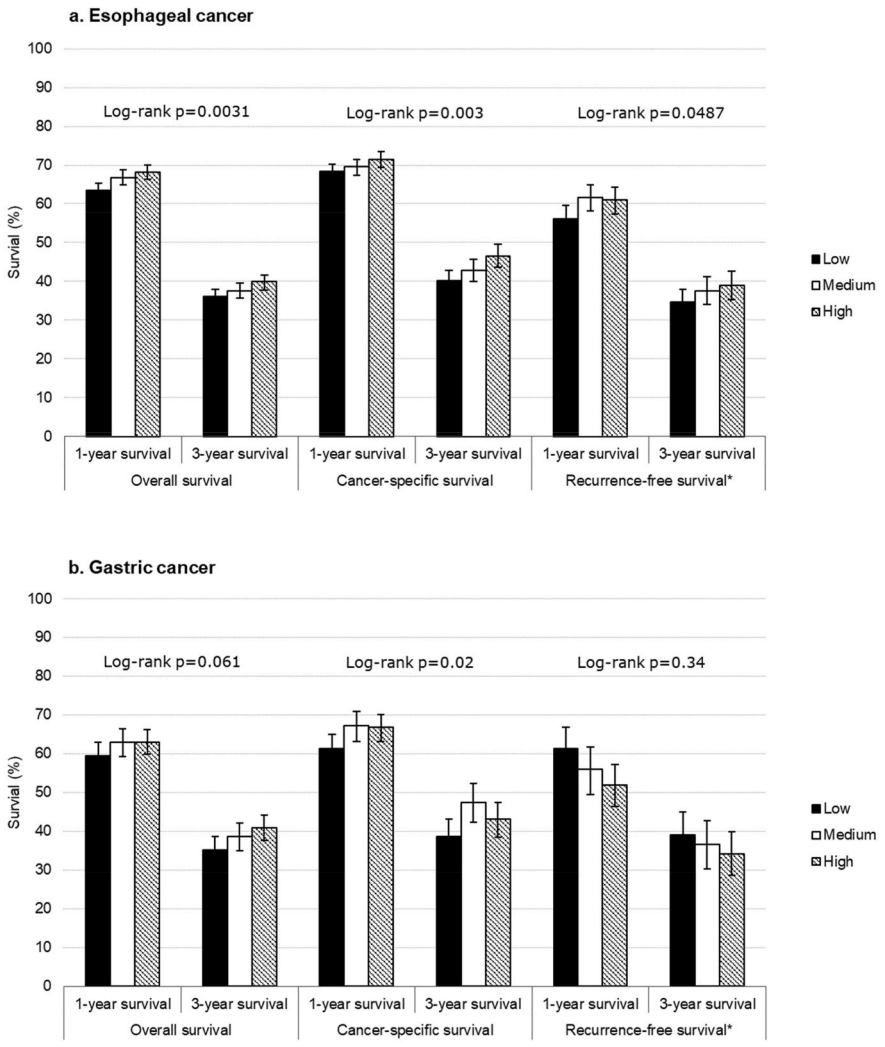

Fig. 4. One and three-year overall, cancer-specific and recurrence free survival among patients with esophageal (2a) and gastric cancer (2b) according to hospital with low, medium or high probability of treatment with curative intent.

Model 1, Table 3). Multivariable adjusted cancer-specific survival for patients diagnosed in both MP (HR = 0.74; 95%CI: 0.63–0.88), and HP hospitals (HR = 0.74; 95%CI: 0.64–0.87) was higher (Model 1, Table 3). Again, after additional adjustment for treatment, the differences for overall and cancer-specific survival disappeared (Model 2, Table 3). Multivariable adjusted recurrence-free survival was lower in patients diagnosed in HP hospitals (model 1: HR:1.51; 95%CI:1.15–1.98), which remained after additional adjustments for treatment (model 2: HR:1.50; 95%CI: 1.14–1.96). A non-radical resection occurred slightly more often among patients in HP hospitals but this was not significant (LP:9.7%, MP:7.5%, HP:12.2%, p-value = 0.21 Supplementary Table 2). After additionally adjusting model 2 for radicality of surgery in a post-hoc analysis the association between the probability of treatment with curative intent and recurrence-free survival disappeared (MP vs LP: HR = 1.19, 95%CI:0.95–1.50, HP vs LP: HR = 1.14, 95%CI:0.92–1.42, data not shown).

4. Discussion

This study assessed the association between the probability of treatment with curative intent and overall, cancer-specific and recurrence-free survival, and HRQoL in patients with esophagogastric cancer. Results showed that there were minor differences in HRQoL between LP, MP and HP hospitals. It is likely that these differences are underestimated because we were not able to include all patients with a potentially curable tumor stage, due to the limited sample size of curable patients without curative treatment. As has been previously shown, elderly patients, patients with multiple comorbidities, lower SES and patients who receive no treatment are less likely to participate in observational research on patient reported outcomes [23]. Probably differences would have been larger if patients without curative treatment were included as these patients are more apparent in hospitals with a low probability. Moreover, we used a cut-off of 10 points for medium clinical relevance, however, this guideline might be too simplistic as it does not take differences between HRQoL scales, nor the direction of the estimates into account. Howevere, as we see no clear direction in our estimates from multivariable analyses and the majority of estimates is low, it is unlikely that using different guidelines might influence the results.

Overall and cancer specific survival was highest in patients

Table 3
The association between low, medium and probability of treatment with curative intent (LP, MP and HP) and overall, cancer-specific and recurrence free survival.

	Esophageal cancer							Gastric cancer						
				Model 1		Model 2					Model 1		Model 2	
	N	N_{events}	Person years	HR	95% CI	HR	95% CI	N	N_{events}	Person years	HR	95% CI	HR	95% CI
Overall survival														
LP	2515	1812	5878.9	Ref.		Ref.		823	596	1897.0	Ref.		Ref.	
MP	2326	1639	5725.2	0.95	(0.89–1.02)	1.01	(0.94–1.08)	700	489	1668.2	0.90	(0.80–1.02)	1.06	(0.94–1.20)
HP	2358	1617	6045.9	**0.82**	**(0.77–0.88)**	0.98	(0.91–1.05)	884	591	2192.4	**0.82**	**(0.73–0.92)**	1.00	(0.88–1.12)
Cancer-specific surival														
LP	2428	1043	3081.3	Ref.		Ref.		775	373	959	Ref.		Ref.	
MP	2153	906	2885.3	0.99	(0.90–1.09)	1.08	(0.98–1.18)	673	264	824	**0.74**	**(0.63–0.88)**	0.84	(0.71–1.00)
HP	2125	823	2868.9	**0.82**	**(0.75–0.91)**	0.97	(0.88–1.07)	797	347	1030	**0.74**	**(0.64–0.87)**	0.91	(0.78–1.08)
Curative treated patients														
Recurrence free survival														
LP	836	413	1358.1	Ref.		Ref.		278	105	492.5	Ref.		Ref.	
MP	818	378	1383.1	0.97	(0.84–1.12)	0.98	(0.85–1.13)	252	105	414.4	1.24	(0.94–1.64)	1.24	(0.93–1.64)
HP	786	327	1321.9	0.89	(0.76–1.03)	0.90	(0.78–1.05)	319	138	484.6	**1.51**	**(1.15–1.98)**	**1.50**	**(1.14–1.96)**

Statistically significant results are indicated in bold.
LP: patients diagnosed in hospitals with low probability of curative intent.
MP: patients diagnosed in hospitals with medium probability of curative intent.
HP: patients diagnosed in hospitals with high probability of curative intent.
Model 1: adjusted for sex, age, histology, clinical T stage, clinical N stage, performance status, BMI and comorbidity.
Model 2: Model 2 additionally adjusted for treatment.

diagnosed in HP hospitals for both esophageal and gastric cancer. Recurrence-free survival was worse in patients diagnosed in HP hospitals for gastric cancer. The results for overall survival were comparable to previous studies [8–10]. Although not assessed previously, similar results for cancer-specific survival were observed. This is not suprising as patients with esophageal or gastric cancer are more likely to die of their cancer than due to other causes [24]. Differences in treatment seemed to explain the differences in overall and cancer-specific survival, as after adjustment for treatment the differences disappeared. A lower recurrence-free survival for gastric cancer patients diagnosed in HP hospitals was observed which could be explained by radicality of surgery. In patients diagnosed with esophageal cancer no association with recurrence-free survival was observed probably due to the alternative curative treatment option: definitive chemoradiation. For gastric cancer the only curative option is surgery. This might imply that treating physicians of HP hospitals are more inclined to proceed with surgery, possibly even in less favorable patients, risking a non-radical resection.

Outcomes for potentially curable patients could possibly be improved if all patients with esophageal or gastric cancer were to be discussed during a multidisciplinary team meeting in which a resection centre is involved (expert MDTM). In the Netherlands in 2015 and 2016, 80–97% of patients stage I-III upper-GI cancer were discussed during a MDTM. However, this percentage varied between 71 and 91% between hospitals [25]. Moreover another study showed that implementation of a regional expert MDTM resulted in a higher proportion of discussed patients, a higher resection rate and improved survival [26]. Thus increasing the proportion of patients discussed during an expert MDTM might improve adequate patient selection for curative treatement, and subsequently improve survival.

This study has several strenghts and limitations. Strengths of this study include its population-based design and the detailed information on overall, cancer-specifc and recurrence-free survival, as well as HRQoL. Although adjustments were made for performance status, BMI and comorbidity, the proportion of missings was relatively large. We did not use multiple imputation as the missings were most likely not missing at random. Another limitation of the study is that no information on HRQoL and recurrence-free survival was available for patiens with a potentially curable tumor stage who did not receive treatment with curative intent. As patients who do not receive treatment with curative intent are likely to be more frail, the exclusion of this group might have resulted in an underestimation of differences in HRQoL between patients diagnosed in LP, MP and HP hospitals.

In conclusion, for patients with potentially curable esophagogastric cancer, overall and cancer-specific survival is highest in hospitals with a high probability of treatment with curative intent for both esophageal and gastric cancer. Recurrence-free survival is lower in hospitals with high probability of treatment with curative intent for gastric cancer only. Moreover, minor differences in HRQoL were observed between patients who received curative treatment and were diagnosed in a hospital with low, medium, or high probability of treatment with curative intent. This study creates awareness about current variation in daily clinical practice and might decrease variation between hospital of diagnoses in the treatment with curative intent in the future.

5. Data availability

Data regarding the cancer-specific survival are accessible for statistical and scientific research, within the microdata from Statistics Netherlands. Contact microdata@cbs.nl for further information. All other data is available by the corresponding author upon reasonable request.

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CRediT authorship contribution statement

Pauline A.J. Vissers: Conceptualization, Acquisition of data, Formal analysis, Interpretation of data, Methodology, Supervision, Writing – original draft, Writing – review & editing, Final approval of the manuscript. **Josianne C.H.B.M. Luijten:** Conceptualization, Acquisition of data, Formal analysis, Interpretation of data, Methodology, Writing – review & editing, Final approval of the manuscript. **Valery E.P.P. Lemmens:** Conceptualization, Interpretation of data, Writing – review

& editing, Final approval of the manuscript. **Hanneke W.M. van Laarhoven:** Acquisition of data, Interpretation of data, Writing – review & editing, Final approval of the manuscript. **Marije Slingerland:** Interpretation of data, Writing – review & editing, Final approval of the manuscript. **BasP.L. Wijnhoven:** Interpretation of data, Writing – review & editing. **C. Rosman:** Interpretation of data, Writing – review & editing, Final approval of the manuscript. **Stella Mook:** Interpretation of data, Writing – review & editing, Final approval of the manuscript. **Joos Heisterkamp:** Interpretation of data, Writing – review & editing, Final approval of the manuscript. **Ellen M. Hendriksen:** Interpretation of data, Writing – review & editing, Final approval of the manuscript. **Suzanne S. Gisbertz:** Interpretation of data, Writing – review & editing, Final approval of the manuscript. **Grard A.P. Nieuwenhuijzen:** Conceptualization, Interpretation of data, Methodology, Supervision, Writing – review & editing, Final approval of the manuscript. **Rob H.A. Verhoeven:** Conceptualization, Acquisition of data, Formal analysis, Interpretation of data, Methodology, Supervision, Writing – review & editing, Final approval of the manuscript.

Declaration of competing interest

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Appendix A. Supplementary data

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