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The Dutch Nationwide Ivory Study

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Marianne C. Kalff: Study conception and design, acquisition of data, statistical analysis and interpretation of data. Drafting and revising the manuscript.

MarkI. vanBerge Henegouwen, Suzanne S. Gisbertz: Study conception and design, acquisition of data, and interpretation of data. Drafting and revising the manuscript.

Objective: This study evaluated the nationwide trends in care and accompanied postoperative outcomes for patients with distal esophageal and gastro-esophageal junction cancer.

Summary of Background Data: The introduction of transthoracic esophagectomy, minimally invasive surgery, and neo-adjuvant chemo (radio)therapy changed care for patients with esophageal cancer.

Methods: Patients after elective transthoracic and transhiatal esophagectomy for distal esophageal or gastroesophageal junction carcinoma in the Netherlands between 2007–2016 were included. The primary aim was to evaluate trends in both care and postoperative outcomes for the included patients. Additionally, postoperative outcomes after transthoracic and tran-shiatal esophagectomy were compared, stratified by time periods.

Results: Among 4712 patients included, 74% had distal esophageal tumors and 87% had adenocarcinomas. Between 2007 and 2016, the proportion of transthoracic esophagectomy increased from 41% to 81%, and neo-adjuvant treatment and minimally invasive esophagectomy increased from 31% to 96%, and from 7% to 80%, respectively. Over this 10-year period, postoperative outcomes improved: postoperative morbidity decreased from 66.6% to 61.8% ($P = 0.001$), R0 resection rate increased from 90.0% to 96.5% ($P < 0.001$), median lymph node harvest increased from 15 to 19 ($P < 0.001$), and median survival increased from 35 to 41 months ($P = 0.027$).

Conclusion: In this nationwide cohort, a transition towards more neo-adju-vant treatment, transthoracic esophagectomy and minimally invasive surgery was observed over a 10-year period, accompanied by decreased postoperative morbidity, improved surgical radicality and lymph node harvest, and improved survival.

Keywords: complications, esophageal cancer, esophagectomy, minimally invasive surgery, neo-adjuvant treatment, survival

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Worldwide, esophageal cancer is the 7th most common cancer and one of the leading causes of cancer death, with over half million new cases in 2020 and accounting for 5.5% of all cancer deaths.[1] Traditionally, curative treatment solely consisted of an esophagectomy, with a 5-year overall survival of 29% to 39%.[2] However, esophageal cancer surgery was associated with considerable postoperative morbidity and mortality, with incidences up to 60% and 5%, respectively.[3,4]

To improve postoperative outcomes, multiple modifications have been made in the treatment of esophageal cancer over the last decade. After the MAGIC, JCOG9907 and CROSS trials, and the subsequent implementation of multimodal treatment regimens, 5-year survival rates after esophageal cancer surgery improved up to 55%.[5–7] In addition, the implementation of minimally invasive surgery has decreased postoperative (pulmonary) morbidity, length of ICU and hospital stay, while maintaining oncological quality.[8,9] This led to a general consensus on the benefit of neo-adjuvant treatment and minimally invasive surgery. However, for other treatment options, consensus is not yet reached. For esophageal tumors located in the distal esophagus or at the gastroesophageal junction, both a transthoracic and a transhiatal esophagectomy are viable treatment options. Whereas a complete sharp dissection and more extensive lymphadenectomy can be performed via a transthoracic resection, a transhiatal esophagectomy generally results in lower postoperative morbidity.[2,10] Both high lymph node yield and limited postoperative morbidity are prognostically favorable outcomes of esophagectomy.[11,12] A Dutch multicenter randomized controlled trial showed improved survival after transthoracic versus transhiatal esophagectomy, although not statistically significant.[2] Parallel to the implementation of multimodal treatment regimens and minimally invasive surgery, the transhiatal approach lost popularity across the Netherlands,[13] although its inferiority has never been proven.

This study evaluated nationwide trends in care and accompanied trends in postoperative outcomes of surgically treated patients with distal esophageal and gastroesophageal junction cancer during a 10-year period in the Netherlands. Additionally, postoperative morbidity and long-term overall survival after transthoracic and transhiatal esophagectomy were compared over the decade of the study.

METHODS

Study Design

The IVORY study (**Iv**or Lewis, McKeown and **Or**ringer esophagectom**y** for cancer of the distal esophagus or gastroesophageal junction) is a nationwide cohort study with participation of all 23 Dutch hospitals performing esophagectomies between January 1, 2007 and December 31, 2016. As data registration was not standardized in every participating center in the early years (2007–2010), data collection was limited to 18 centers for that period. As a result of the Dutch Upper-GI Cancer Audit,[14] an obligatory national gastroesophageal cancer surgery audit, structured data collection was performed in all centers from 2011 onwards. Audit data and hospital datasets were complemented with data extracted from the individual patients' records by surgeons and / or surgical residents of the participating centers. After completion, data were provided anonymously to the coordinating IVORY investigators. Follow-up data on survival were collected until January 2020.

This study obtained approval from the Institutional Review Boards of all participating centers. Formal informed consent was waived by these boards, although some required an opt-out procedure. In those centers, patients were provided the opportunity to optout if they did not agree with anonymous use of their medical data for research purposes. This paper adheres to the STROBE guidelines for observational studies.[15]

Martijn G.H. van Oijen: Study conception and design, statistical analysis and interpretation of data. Drafting and revising the manuscript.

Grard A.P. Nieuwenhuijzen: Study conception and design, acquisition of data, and interpretation of data. Revising the manuscript.

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B. Feike Kingma, Daan M. Voeten: Acquisition and interpretation of data. Revising the manuscript.

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TABLE 1. Baseline and Treatment Characteristics oIncluded Patients With Distal Esophageal and Gastroesophageal Junction Cancer, Stratified by Time Period

		Total n = 4712		2007-2010* n = 1171		2011–2013 n = 1679		2014–2016 n = 1862		
Characteristics		**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	***P***
Sex	Male	3803	80.7	936	79.9	1342	80.0	1525	81.9	0.239
Age, mean	Years (SD)	64.7	9.2	64.6	9.5	64.2	9.3	65.1	8.9	0.014
BMI, mean	Kg/m^2 (SD)	26.0	4.2	25.6	4.1	26.1	4.3	26.2	4.3	0.001
ASA-score	I	849	18.7	237	23.1	289	17.5	323	17.4	0.003
	II	2724	60.0	580	56.6	1027	62.2	1117	60.0	
	III	941	20.7	202	19.7	327	19.8	412	22.1	
	IV	24	0.5	6	0.6	9	0.5	9	0.5	
Comorbidities	Pulmonary	801	17.1	150	13.0	266	15.9	385	20.7	<0.001
	Cardiac	965	20.6	234	20.3	353	21.0	378	20.3	0.841
	Vascular	1745	37.2	390	33.9	629	37.5	726	39.0	0.017
	Diabetes	736	15.7	172	15.0	270	16.1	294	15.8	0.706
Histology	Adenocarcinoma	4105	87.1	998	85.2	1478	88.0	1629	87.5	0.074
	Squamous cell carcinoma	607	12.9	173	14.8	201	12.0	233	12.5	
cT stage	T1	249	5.5	64	5.8	99	6.1	86	4.8	0.003
	T2	818	18.1	174	15.8	295	18.2	349	19.4	
	T3	3328	73.6	828	75.3	1170	72.0	1330	73.9	
	T4	129	2.9	34	3.1	61	3.8	34	1.9	
cN stage	N0	1702	37.0	423	37.7	555	33.9	724	39.3	<0.001
	N1	2100	45.6	667	59.4	703	42.9	730	39.6	
	N2	667	14.5	26	2.3	313	19.1	328	17.8	
	N3	112	2.4	6	0.5	60	3.7	46	2.5	
	N+	23	0.5	-	-	8	0.5	15	0.8	
Clinical tumor location	Distal	3489	74.0	828	70.7	1198	71.4	1463	78.6	<0.001
	GEJ	1223	26.0	343	29.3	481	28.6	399	21.4	
Neo-adjuvant treatment	Yes	3901	84.2	653	59.1	1523	91.0	1725	93.0	<0.001
	Chemo	426	9.2	207	18.8	152	9.1	67	3.6	<0.001
	Chemoradiotherapy	3467	74.9	445	40.3	1368	81.7	1654	89.3	<0.001
	> 80% completed	3702	96.6	565	93.9	1457	96.2	1680	97.9	<0.001
Adjuvant treatment	Yes	211	4.7	77	6.9	76	4.7	58	3.2	<0.001
Approach	Open	2334	49.7	937	80.6	933	55.6	464	25.0	<0.001
	MIS	2260	48.1	198	17.0	720	42.9	1342	72.3	
	Hybrid	103	2.2	28	2.4	24	1.4	51	2.7	
Procedure	Transthoracic	2275	58.9	507	43.3	898	53.5	1370	73.6	<0.001
	Transhiatal	1937	41.1	664	56.7	781	46.5	492	26.4	

*Data collection between 2007 and 2010 included 18 centers and from 2011 onwards 23 centers.

Percentages for the variables are calculated out of the total number of actual results available, excluding the missing values. ASA American Society of Anesthesiologists, BMI Body Mass Index, cN clinical N stage, cT clinical T stage, GEJ gastroesophageal junction, SD standard deviation.

Patients

The study population involved patients with a primary resectable adenocarcinoma or squamous cell carcinoma of the distal esophagus or gastroesophageal junction, excluding the gastric cardia. Included patients underwent curatively intended transhiatal esoph-agectomy with gastric conduit reconstruction and cervical anastomosis, or right transthoracic esophagectomy with gastric conduit reconstruction and cervical or intrathoracic anastomosis in the Netherlands over a 10-year period (2007–2016). Patients who underwent a nonelective or salvage procedure, and patients who applied for opt-out were excluded.

Study Aims

The primary aim was to evaluate nationwide trends in care and accompanied trends in postoperative outcomes of surgically treated patients with distal esophageal and gastroesophageal junction cancer during a 10-year period in the Netherlands. The investigated trends in care were the use of neo-adjuvant therapy, the surgical approach and procedure, and the annual center volume. The investigated trends in postoperative outcomes included lymph node harvest, pathologically complete resection (R0) rates, postoperative morbidity and survival. Secondly, postoperative morbidity and long-term overall survival after transthoracic and transhiatal esophagectomy were compared stratified by time periods. Overall survival was analyzed under the condition of surviving the first 30 days postoperative (i.e. conditional survival). Subgroup analyses were performed to compare survival after transthoracic and transhiatal esoph-agectomy according to approach (minimally invasive and open surgery according to intention to treat), severity of postoperative morbidity [limited: Clavien-Dindo (CD) $\leq$2 and severe: CD $\geq$3] and histology (adeno-carcinoma and squamous cell carcinoma).

Parameters and Definitions

Clinical and pathological stages were defined using the eighth TNM staging edition for cancers of the esophagus and gastroesophageal junction.[16] The Clavien-Dindo classification was used to grade severity of postoperative morbidity.[17] Centers with an annual hospital volume of at least 30 esophagectomies based on the years of complete data entry (2011–2016) were defined as high-volume. As a result of the applied in- and exclusion criteria, presented hospital volumes are lower than actual annual hospital volumes.

Statistical Analysis

Baseline characteristics, perioperative outcomes and survival were presented for the whole cohort of included patients, and stratified by time period and by surgical procedure. According to distribution, an independent T test, one-way ANOVA, Mann-Whitney U test, Kruskal-Wallis, or x2 test was used to compare the groups, and outcomes were presented as mean ± standard deviation (SD), median with interquartile range (IQR) or number of patients (%), accordingly. Survival was compared using Kaplan-Meier life-table estimates and log rank tests. Multivariable Cox proportional hazard regression analyses were used to assess the association between time period or surgical procedure and overall survival adjusted for confounders, presented as the hazard ratio (HR) with 95% confidence interval (CI). Potential confounders known to affect long-term survival [age, sex, American Society of Anesthesiologists (ASA) score, body mass index, the presence of cardiac, vascular, pulmonary and diabetic comorbidities, tumor location, pathological T and N-stage, use of neo-adjuvant therapy, tumor histology, surgical approach and year of surgery] were included in the multivariable models. Missing data was less than 5% for the analyzed clinical variables and therefore handled with complete case analyses. A 2-sided P value of < 0.05 was considered statistically significant. Statistical analyses were performed with SPSS 26.0 software (IBM Corp, Armonk, New York).

RESULTS

Study Population

In total, 4712 patients with distal esophageal and gastroesophageal junction cancer were included (Table 1). The included population was predominantly male (80.7%), with a mean age of 64.7 years (SD 9.2). The majority of patients was diagnosed with a clinically staged T3 tumor (73.6%) and with 1 – 2 lymph node metastases (cN1: 45.6%). Most tumors were adenocarcinomas (87.1%) and were localized in the distal esophagus (74.0%). Over time, higher ASA-scores, and the presence of pulmonary and vascular comorbidities became more frequent among the included patients.

Trends in Esophageal Cancer Care

In the first year of the study (i.e. 2007), only 30.9% of the included patients received neo-adjuvant therapy, which increased to 95.8% in 2016 (Fig. 1). Overall, only 9.2% of included patients received chemotherapy, while the use of neo-adjuvant chemoradiotherapy increased from 16.2% to 91.2% during the study period. In 2007, a transhiatal esophagectomy was the most frequently performed procedure. During the study period, the proportion of transthoracic procedures doubled from 40.5% to 80.9%. The use of a hybrid surgical approach remained limited, accounting for 2.2% of all procedures, while the use of total minimally invasive esophagectomy increased from 6.9% to 79.7%. Esophagectomy became more centralized in this period, reflected by increasing numbers of high-volume centers (≥30 annual resections) from 8/23 (34.7%) to 11/22 (50.0%).

Trends in Outcomes of Esophagectomy

Over the 10-year study period, the median lymph node harvest increased from 15 to 19 ($P < 0.001$; Table 2), and increased for both transthoracic and transhiatal procedures from respectively 18 (IQR 13–24) and 13 (IQR 8–18) in 2007–2010, to 21 (IQR 16–28) and 15 (IQR 11–20) in 2014–2016

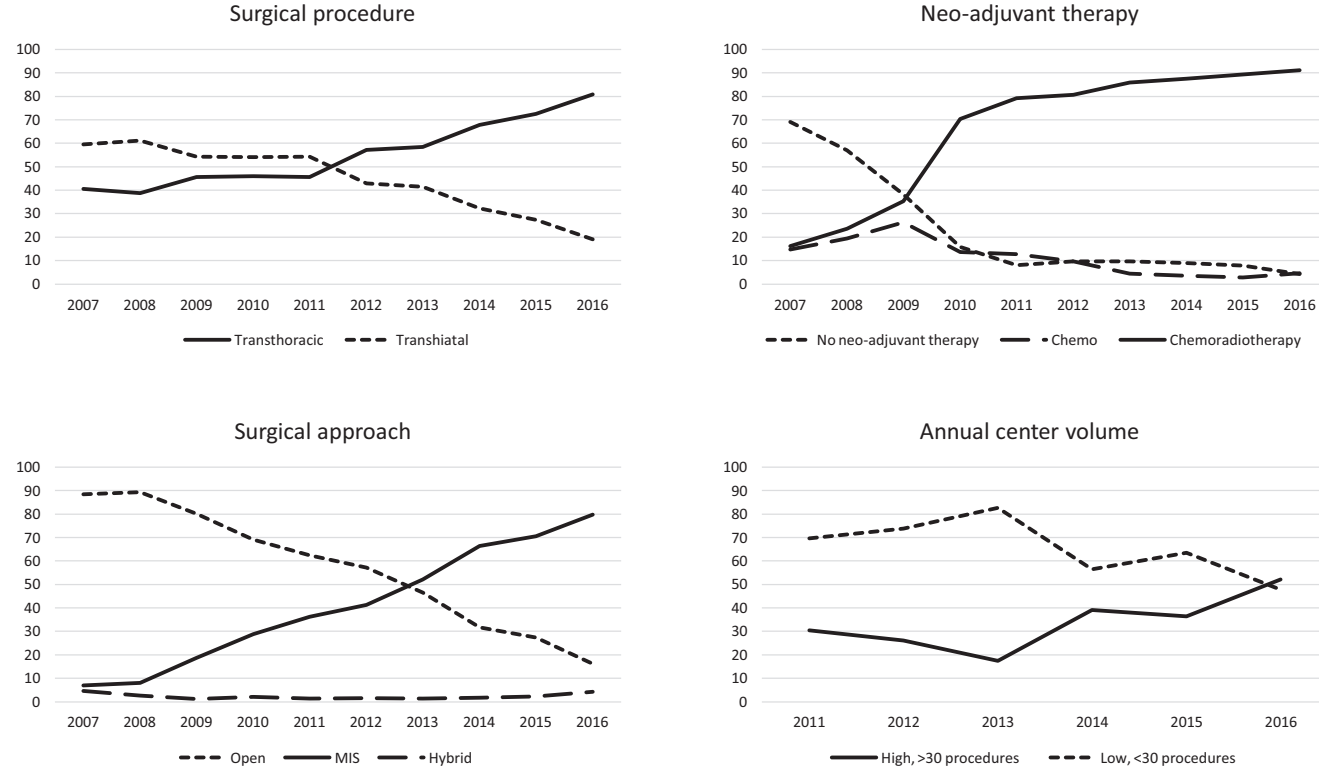


FIGURE 1. Trends in distal esophageal and gastroesophageal junction cancer care in the Netherlands. MIS indicates minimally invasive surgery.

TABLE 2. Surgical and Histopathological Outcomes of Included Patients With Distal Esophageal and Gastroesophageal Junction Cancer, Stratified by Time Period

		Total n = 4712		2007–2010* n = 1171		2011–2013 n = 1679		2014–2016 n = 1862		
Characteristics		**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	***P***
Intraoperative complications	Yes	248	5.3	77	6.6	94	5.6	77	4.1	0.009
Conversion	Yes	120	5.2	20	10.1	43	5.8	57	4.1	0.001
Median lymph nodes	Harvest (IQR)	17	12–23	15	10–21	16	11–23	19	15–26	<0.001
Median positive lymph nodes	Harvest (IQR)	0	0–2	0	0–3	0	0–2	0	0–2	<0.001
(y)pT stage	T0	946	20.2	136	11.7	368	22.1	442	23.8	<0.001
	Tis	18	0.4	8	0.7	7	0.4	3	0.2	
	T1	772	16.5	176	15.2	266	16.0	330	17.8	
	T2	920	19.7	224	19.3	325	19.5	371	20.0	
	T3	1977	42.3	595	51.4	686	41.3	696	37.5	
	T4	45	1.0	19	1.6	11	0.7	15	0.8	
(y)pN stage	N0	2719	57.7	586	50.1	999	59.5	1134	60.9	<0.001
	N1	987	21.0	246	21.0	348	20.7	393	21.1	
	N2	637	13.5	205	17.5	217	12.9	215	11.5	
	N3	366	7.8	132	11.3	114	6.8	120	6.4	
Radicality	R0	4388	94.2	1016	90.0	1578	94.5	1794	96.5	<0.001
Response to neo-adjuvant treatment†	R+	270	5.8	113	10.0	92	5.5	65	3.5	
	TRG 1	864	29.8	120	33.8	330	29.1	414	29.4	<0.001
	TRG 2	597	20.6	60	16.9	200	17.6	337	24.0	
	TRG 3	663	22.9	75	21.1	261	23.0	327	23.3	
	TRG 4	474	16.4	53	14.9	219	19.3	202	14.4	
	TRG 5	297	10.3	47	13.2	124	10.9	126	9.0	
Morbidity	All	2925	62.2	775	66.6	999	59.6	1151	61.8	0.001
	CD ≥ 3	1393	31.4	337	31.2	468	29.7	588	33.1	0.111
	Anastomotic leakage	914	19.5	192	16.5	324	19.3	398	21.4	0.004
	Pneumonia	1070	23.2	319	27.4	374	23.1	377	20.7	<0.001
	Atrial dysrhythmia	603	12.9	142	12.2	221	13.3	240	13.0	0.671
	Chyle leakage	339	7.2	72	6.2	106	6.3	161	8.7	0.009
Re-intervention	Yes	1089	23.5	217	19.5	374	22.5	498	26.8	<0.001
Median ICU stay	Days (IQR)	2	1–5	3	1–6	2	1–5	2	1–5	<0.001
Median hospital stay	Days (IQR)	13	9.25-20	14	11-20	13	10-20	12	9-19	<0.001
Hospital readmission	Yes	562	12.6	96	9.1	207	12.7	259	14.5	<0.001
Mortality	30day	118	2.5	35	3.0	38	2.3	45	2.4	0.450
	90day	258	5.5	77	6.6	88	5.3	90	5.0	0.148
Overall survival‡	Median months (95%CI)	42	39-45	37	32-42	46	41-51	42	37-47	0.020

*Data collection between 2007 and 2010 included 18 centers and from 2011 onwards 23 centers.
†Response to neo-adjuvant treatment was calculated for patients receiving neo-adjuvant treatment.
‡Overall survival was analyzed under the condition of surviving the first 30 days postoperative.
Percentages for the variables are calculated out of the total number of actual results available, excluding the missing values. CD Clavien-Dindo, CI confidence interval, ICU Intensive care unit, IQR interquartile range, pN pathological N stage, pT pathological T stage, TRG tumor regression grade

(Table 3). R0 resection rates also increased for both transthoracic and transhiatal esophagectomy from respectively 91.3% and 88.9% in 2007–2010, to 96.7% and 95.9% in 2014–2016. Postoperative morbidity decreased from 66.6% in 2007–2010 to 61.8% in 2014–2016 ($P = 0.001$), and decreased for both transthoracic and transhiatal procedures from respectively 70.2% and 63.9%, to 62.7% and 59.5%. The median overall survival increased from 35 to 41 months over the study period ($P = 0.027$; Fig. 2), and increased for transthoracic procedures from 34 to 41 months, and for transhiatal procedures from 38 to 56 months.

Patient and Tumor Characteristics in Transthoracic and Transhiatal Esophagectomies

Patients in the transhiatal group were older (65.8 vs. 63.9 years, $P < 0.001$), had a higher ASA score (ASA III: 23.3% vs. 19.1%, $P < 0.001$) and had more cardiac, vascular and diabetic comorbidities compared to the transthoracic group (Supplementary Digital Content Table 1, http://links.lww.com/SLA/D512). Patients operated transhiatally more often had clinically node-negative disease (40.7% vs. 34.4%, $P < 0.001$), adenocarcinomas (89.1% vs. 85.8%, $P = 0.001$), tumors located at the gastroesophageal junction (35.3% vs. 19.4%, $P < 0.001$), and less frequently received neoadjuvant therapy (78.7% vs. 88.0%, $P < 0.001$).

Perioperative Outcomes of Transthoracic and Transhiatal Esophagectomy

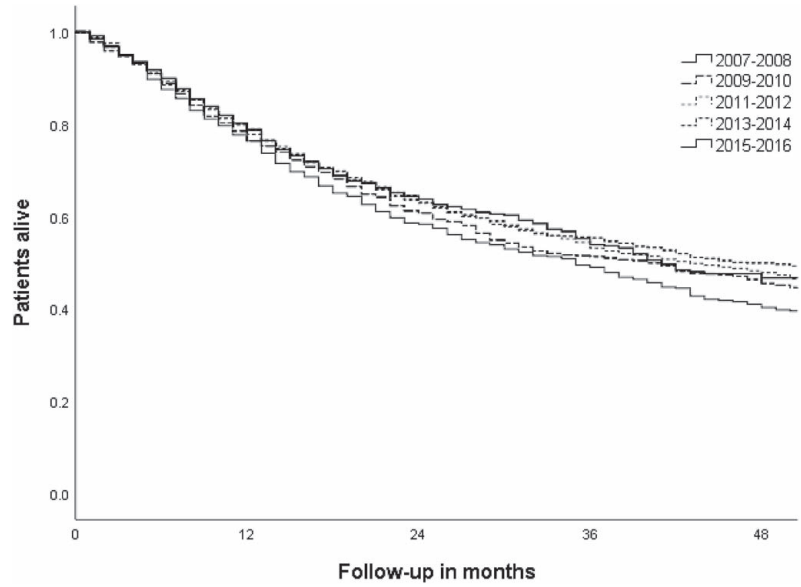
Transhiatal procedures were more frequently performed open compared to transthoracic procedures (74.4% vs. 32.2%, $P < 0.001$), and when performed minimally invasively, were more frequently converted to open (8.3% vs. 4.4%, $P = 0.001$; Table 3). Overall, significantly more lymph nodes were harvested during transthoracic procedures (median 20 vs. 13, $P < 0.001$), and transthoracic procedures more often resulted in R0 resections (95.2% vs. 92.7%, $P < 0.001$).

The majority of patients experienced at least one postoperative complication (62.2%), with pneumonia being the most frequently encountered (23.3%), followed by anastomotic leakage (19.5%; Table 2). Overall, more postoperative morbidity was observed after transthoracic resections (64.6% vs. 58.8%, $P < 0.001$), with more severe complications (CD ≥3: 35.1% vs.

TABLE 3. Surgical, Histopathological and Postoperative Outcomes of Included Patients With Distal Esophageal and Gastroesophageal Junction Cancer, Stratified by Surgical Procedure and Time Period

		2007–2016					2007–2010*					2011–2013					2014–2016				
		Transthoracic n = 2775		Transhiatal n = 1937			Transthoracic n = 507		Transhiatal n = 664			Transthoracic n = 898		Transhiatal n = 781			Transthoracic n = 1370		Transhiatal n = 492		
Characteristics		**n**	**%**	**n**	**%**	***p***	**n**	**%**	**n**	**%**	***p***	**n**	**%**	**n**	**%**	***p***	**n**	**%**	**n**	**%**	***p***
Approach	Open	892	32.2	1442	74.4	<0.001	378	75.3	559	84.6	<0.001	343	38.2	590	75.7	<0.001	171	12.5	293	59.8	<0.001
	MIS	1772	64.0	488	25.3		96	19.1	102	15.4		531	59.1	189	24.3		1145	83.8	197	40.2	
	Hybrid	103	3.7	–	–		28	5.6	–	–		24	2.7	–	–		51	3.7	–	–	
Intraoperative complications	Yes	146	5.3	102	5.3	0.985	37	7.4	40	6.1	0.389	56	6.3	38	4.9	0.221	53	3.9	24	4.9	0.338
Conversion	Yes	81	4.4	39	8.3	0.001	13	11.7	7	8.0	0.381	23	4.2	20	10.6	0.001	45	3.8	12	6.2	0.116
Median lymph nodes	Harvest (IQR)	20	15–26	13	9–18	<0.001	18	13–24	13	8–18	<0.001	20	14–25	12	9–17	<0.001	21	16–28	15	11–20	<0.001
Median positive lymph nodes	Harvest (IQR)	0	0–2	0	0–2	0.627	1	0–3	0	0–3	0.878	0	0–2	0	0–2	0.769	0	0–1.25	0	0–2	0.141
Resection	R0	2636	95.2	1752	92.7	<0.001	461	91.3	555	88.9	0.192	852	95.2	726	93.7	0.175	1323	96.7	471	95.9	0.417
	R+	132	4.8	138	7.3		44	8.7	69	11.1		43	4.8	49	6.3		45	3.3	20	4.1	
Morbidity	All	1793	64.6	1132	58.8	<0.001	355	70.2	420	63.9	0.025	579	64.5	420	54.1	<0.001	859	62.7	292	59.5	0.206
	CD > 3	942	35.1	451	25.8	<0.001	181	37.1	156	26.4	<0.001	301	34.4	167	23.9	<0.001	460	34.9	128	27.9	0.007
	Anastomotic leakage	514	18.5	400	20.8	0.056	66	13.0	126	19.2	0.005	166	18.5	158	20.3	0.339	282	20.6	116	23.6	0.161
	Pneumonia	721	26.5	349	18.5	<0.001	169	33.4	150	22.8	<0.001	255	29.2	119	15.9	<0.001	297	22.1	80	16.6	0.011
	Atrial dysrhythmia	428	15.5	175	9.2	<0.001	83	16.4	59	9.0	<0.001	153	17.2	68	8.9	<0.001	192	14.1	48	9.9	0.018
	Chyle leakage	274	9.9	65	3.4	<0.001	46	9.1	26	4.0	<0.001	83	9.2	23	3.0	<0.001	145	10.6	16	3.3	<0.001
Reintervention	Yes	757	27.4	332	17.7	<0.001	105	21.2	112	18.1	0.202	243	27.1	131	17.1	<0.001	409	29.9	89	18.1	<0.001
Median ICU stay	Days (IQR)	2	1–6	2	1–4	<0.001	3	1–7	2	1–5	0.002	3	1 –6	2	1–4	<0.001	2	1–5	1	1–3.75	<0.001
Median hospital stay	Days (IQR)	13	10–22	12	9–17	<0.001	15	12–23	13	10–18	<0.001	14	10–23	11	9–16	<0.001	12	9–21	10	8–16	<0.001
Hospital readmission	Yes	379	14.0	183	10.4	<0.001	45	9.4	51	8.9	0.789	113	12.6	94	12.7	0.948	221	16.5	38	8.4	<0.001
Mortality	30day	67	2.4	51	2.6	0.635	14	2.8	21	3.2	0.686	21	2.3	17	2.2	0.824	32	2.3	13	2.6	0.704
	90day	158	5.7	100	5.2	0.461	33	6.5	44	6.7	0.887	51	5.7	37	4.8	0.408	74	5.4	19	3.9	0.179
Overall survival†	Median months (95%CI)	39	35–43	48	43–53	0.004	34	26–42	38	32–44	0.554	37	31–43	55	47–63	0.006	41	36–46	56	53–59	0.019

*Data collection between 2007 and 2010 included 18 centers and from 2011 onwards 23 centers.
†Overall survival was analyzed under the condition of surviving the first 30 days postoperative.
CD Clavien-Dindo, CI Confidence Interval, ICU Intensive care unit, IQR interquartile range



Numbers at risk					
2007-2008	474	353	261	213	165
2009-2010	640	486	369	302	267
2011-2012	1119	863	675	550	468
2013-2014	1088	831	631	526	390
2015-2016	1222	910	615	289	55

Survival	Months, median	95% CI	p-value
2007-2008	35	28.9-41.1	0.027
2009-2010	40	32.6-47.4	
2011-2012	43	37.1-48.9	
2013-2014	47	39.7-54.3	
2015-2016	41	36.8-45.2	

FIGURE 2. Overall survival† of surgically treated patients with distal esophageal and gastroesophageal junction cancer in the Netherlands stratified by time periods. †Overall survival was analyzed under the condition of surviving the first 30 days postoperative.

25.8%, $p < 0.001$) and more pneumonias (26.5% vs. 18.5%, $P < 0.001$), but comparable anastomotic leakage rates (18.5% vs. 20.8%, $P = 0.056$). The overall 90-day mortality rate was 5.5%, which was comparable for the two procedures.

Survival after Transthoracic and Transhiatal Esophagectomy

The median follow-up was 29 months; 27 months after transthoracic and 31 months after transhiatal procedures. With a

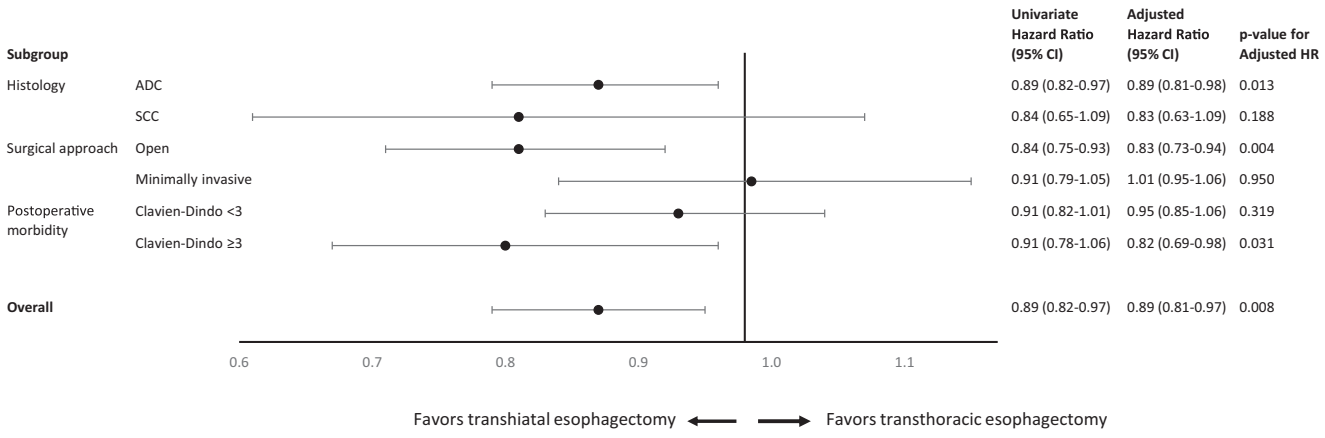


FIGURE 3. Forrest plot of subgroup survival analyses for surgically treated patients with distal esophageal and gastroesophageal junction cancer in the Netherlands. †Overall survival was analyzed under the condition of surviving the first 30 days postoperative. This forest plot shows the adjusted hazard ratios for death with 95% confidence intervals. ADC indicates adenocarcinoma; CI, confidence interval; HR, hazard ratio; SCC, squamous cell carcinoma.

median survival of 48 months, patients who underwent a transhiatal esoph-agectomy had a better overall survival compared to patients who underwent a transthoracic esophagectomy (39 months; HR 0.89, 95%CI 0.81–0.97). Survival after transthoracic and transhiatal esophagectomy was comparable in the minimally invasive surgery subgroup (HR 1.01, 95%CI 0.86–1.17), for patients with squamous cell carcinomas (HR 0.83, 95% CI 0.63–1.09), and for patients with limited postoperative morbidity (HR 0.95, 95%CI 0.85–1.06) as illustrated in Fig. 3.

DISCUSSION

In this study, nationwide trends in care and accompanied trends in postoperative outcomes of surgically treated patients with distal esophageal and gastroesophageal junction cancer over a 10-year period were investigated. In this large population-based cohort, an increase in multimodal treatment, transthoracic procedures and minimally invasive surgery was observed, accompanied by decreased postoperative morbidity, improved surgical radicality and lymph node harvest, and improved survival.

During the study period, an increasing proportion of esoph-agectomies was performed by a transthoracic procedure. In 2007, Omloo et al. showed improved overall survival after transthoracic versus transhiatal esophagectomy for a subgroup of patients with distal esophageal cancer.[18] Combined with studies reporting increased lymph node harvest after transthoracic esophagectomies,[10] and others showing the prognostic benefit of an increased lymph node harvest,[19] these findings can be considered as contributors to the observed trend towards more transthoracic procedures. A more selective application of transhiatal procedures for patients with node-negative disease and higher perioperative risk, as has been previously described,[20] seems to be a resultant of the decreased postoperative morbidity of a transhiatal resection, in which the burden of a thoracotomy or thoracoscopy is circumvented.[10] In the present study, patients in the transhiatal group were indeed older, had higher ASA-class, more comorbidities and more clinical node-negative disease, which is in line with selective application of transhiatal procedures.

The increase in neo-adjuvant therapy followed the incorporation of multimodal treatment regimens in the national and international guidelines after the results of the MAGIC[6], JCOG9907[7], and CROSS trial[5] became available. In total, six centers included in the IVORY study participated in the CROSS trial, possibly explaining the rapid adaption of neo-adjuvant chemoradiotherapy even before the trial results were published. After publication, the CROSS-scheme continuously gained a more prominent role in the treatment of esophageal cancer in the Netherlands, although until now, no clear oncological superiority of the CROSS-regimen over perioperative chemotherapy has been proven.[21,22] While the value of a radical lymphadenectomy, as can be executed through a transthoracic procedure, after neo-adjuvant treatment is debated,[23] a recent meta-analysis showed a higher lymph node yield to be associated with improved survival after neo-adjuvant therapy.[19] The increasing use of neo-adjuvant therapy largely explains the increase in long-term survival observed over the study period.

While the majority of patients was operated via an open approach at the beginning of the IVORY study period, the minimally invasive approach steadily gained more popularity. Although the short-term benefits of minimally invasive surgery were acknowledged during the study,[8,24] most studies demonstrating the long-term oncological safety of minimally invasive esophagectomy were not published until more recent years.[25] In minimally invasive transthoracic esophagectomy, the burden of a thoracotomy is avoided, resulting in decreased postoperative morbidity as compared to open, which is known to be prognostically beneficial.[26,27] A recent meta-analysis showed superior overall survival for minimally invasive esophagectomy as compared to open,[25] and the current study showed overall survival to be comparable after minimally invasive transthoracic and transhiatal esophagectomy.

Despite its inherent less aggressive oncological radicality, this study observed an overall survival benefit for patients selected for transhiatal esophagectomy, even though they had more prognostic unfavorable characteristics, as they were older, had a higher ASA-class, more comorbidities, and less frequently received neo-adjuvant treatment.[28,29] On the contrary, a significantly higher proportion of cN+ patients underwent transthoracic esophagectomy. The actual reasoning for procedure selection for included patients was not registered and the survival of transthoracic procedures might be influenced by 'confounding by indication'.[30] For example, the presence of mediastinal lymph node metastases was not registered, although their presence demands a transthoracic procedure, and they are known to negatively impact prognosis.[31] Although this selective application of both transthoracic and transhiatal esophagectomy influences their comparability in the current study, an individualized use of transhiatal esophagectomy seems justified, and should remain in the repertoire of the upper GI surgeon.

The most recent meta-analysis including survival after transthoracic and transhiatal esophagectomies did not report a survival difference between the two procedures,[32] even though the transthoracic esophagectomy harvests more lymph nodes, and more often results in a microscopically radical resection, both known as important predictors for improved survival.[19,33] As the current study observed comparable survival after transthoracic and transhiatal esophagectomy in patients without severe postoperative morbidity, these favorable short-term oncological outcomes of transthoracic esophagectomy could be overruled by a prognostic negative effect of its increased severe postoperative morbidity.[27,34] The increased severe postoperative morbidity could be a resultant from the observed transition to predominantly transthoracic surgery, which is associated with a proficiency gain curve as described for the implementation of new surgical procedures.[35] During this transition, an imbalance in surgical experience favoring the transhiatal esophagectomy can be expected. In parallel, minimally invasive surgery was introduced, which was predominantly used for transthoracic procedures, and is also associated with a proficiency gain curve and subsequent increased learning-associated postoperative morbidity.[36,37] Furthermore, due to the simultaneously increasing national tendency to preoperatively treat patients with chemoradiotherapy, patients became more prone for postoperative (pulmonary) morbidity inherent to the more aggressive transthoracic resections.[38]

This study has some limitations. First, data collection for 2007-2010 was limited to 18 participating centers. As patient inclusion after 2010 was based on the national obligatory Dutch Upper-GI Cancer Audit, all eligible patients were included from 2011 onwards. Second, important confounders in patient selection and their outcomes, such as surgeon experience and the presence of mediastinal lymph nodes, were not registered within the IVORY study. As such, we were not able to account for these and other (unknown) confounders, retaining possible confounding (by indication). Third, important factors contributing to survival, such as the application of neo-adjuvant

treatment and minimally invasive surgery, changed substantially over the course of the IVORY study. To increase generalizability, population-based studies after complete implementation of neo-adjuvant treatment and minimally invasive surgery, with its subsequent proficiency gain curve, should investigate if the expected decrease in postoperative morbidity after minimally invasive transthoracic esophagectomy will further increase survival, preferably in comparison with minimally invasive transhiatal esophagectomy. Moreover, new modifications holding promise to increase survival include robotic (assisted) surgery,[39] fluorescence guided surgery,[40] and adjuvant treatment strategies.[41] Whilst the implementation of new advancements is encouraged, the need to confirm their effect in population-based studies after a guided implementation should be emphasized.

In conclusion, this large nationwide cohort study of surgically treated patients with cancer of the distal esophagus and gastroesoph-ageal junction showed an increase in transthoracic procedures, neoadjuvant treatment and minimally invasive surgery over a 10-year period, accompanied by decreased postoperative morbidity, improved surgical radicality and lymphadenectomy, and improved survival. In this cohort, in which the transhiatal esophagectomy was increasingly selectively applied, less postoperative morbidity and a survival benefit was observed for transhiatal procedures. However, comparative effectiveness research is hazardous in a retrospective study design due to numerous biases, and the proficiency gain curves associated with the transition towards more transthoracic and more minimally invasive surgery are thought to be of major influence. Future studies will have to elucidate on this. Until then, both the transhiatal and the transthoracic esophagectomy are surgical procedures which may be selected based on patient and tumor characteristics, selecting the appropriate procedure for the individual patient.

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