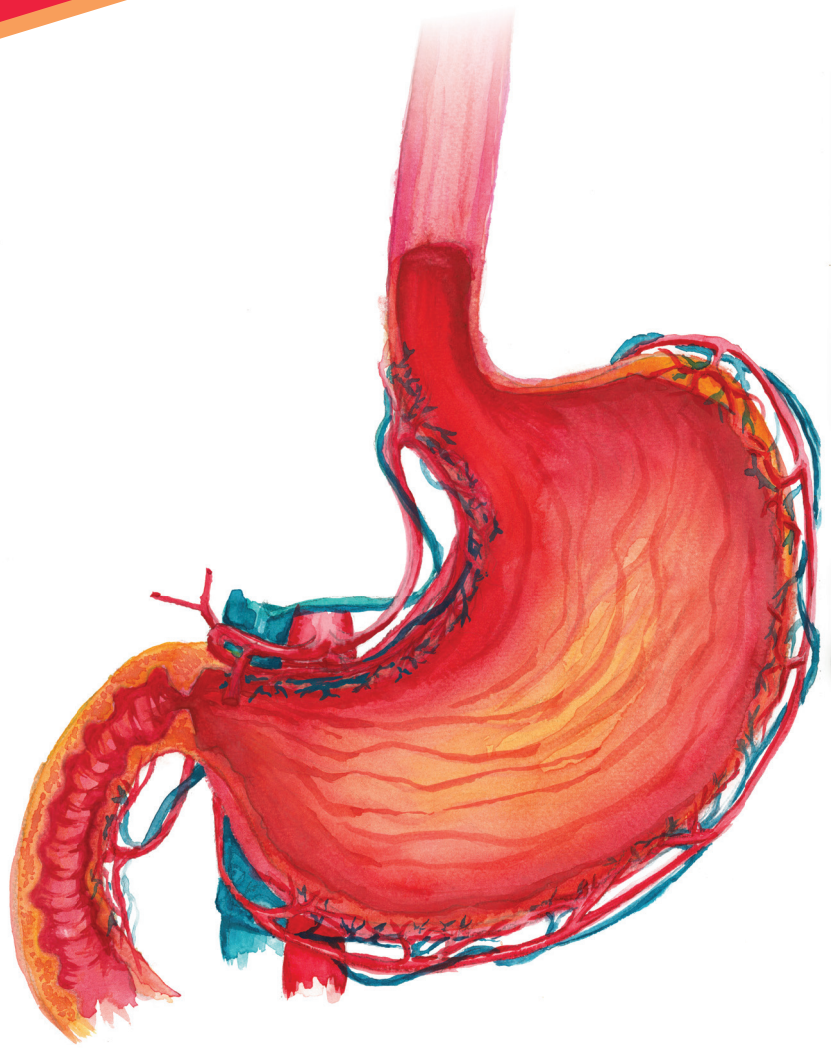
Quality Measurement in Oesophagogastric Cancer Surgery

Leonie Rosanne van der Werf



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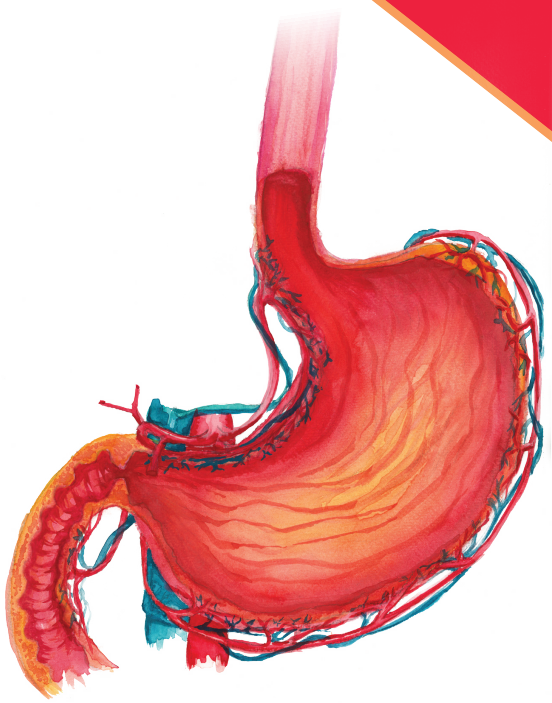

CHAPTER 1

General introduction and thesis outline

GENERAL INTRODUCTION

OESOPHAGEAL CANCER AND GASTRIC CANCER

In the Netherlands, the incidence of oesophageal cancer increased during the past decades, while the incidence of gastric cancer has been stable.[1]

In 2018, the incidence of oesophageal cancer was approximately 2.500 and the incidence of gastric cancer was 1.300.

The percentage of oesophageal cancer patients with potentially curable disease at diagnosis is around 60%.[2] However, the percentage of patients that underwent a curative treatment increased in the past years. Between 2005-2009, 57% of patients underwent curative treatment versus 68% of patients in the period 2011-2013.[2]

The percentage of gastric cancer patients with potentially curable disease according to tumour stage at diagnosis was around 50%.[3] In contrast to oesophageal cancer, the percentage of patients that underwent a curative treatment has decreased. Between 2005-2009, 73% of patients underwent curative treatment versus 65% of patients in the period 2010-2013.[3]

Despite significant improvements in both diagnosis and (multimodality) treatment, prognosis of patients with oesophagogastric cancer remains dismal with 5-year survival rates of 24% and 23%.[1]

MULTIMODALITY TREATMENT OF OESOPHAGEAL CANCER

Multimodality treatment has become the standard of care for locally advanced oesophageal and junctional cancer. The CROSS (Chemo Radiotherapy for Oesophageal cancer followed by Surgery Study) trial showed improved disease-free and overall survival for patients treated with the combination of neoadjuvant chemoradiotherapy and surgery versus surgery alone.[4] The median overall survival was 24.0 months in patients that underwent surgery only and 49.4 months for patients treated with neoadjuvant chemoradiotherapy and surgery. Nowadays, almost 90% of patients receive neoadjuvant chemoradiotherapy followed by oesophagectomy in the Netherlands.[5]

In the past years, also non-surgical treatments have been introduced as an alternative to surgery. Endoscopic resection was introduced for early-stage

tumours and definitive chemoradiotherapy for locally advanced cancer (especially squamous cell cancers) are widely applied now.[6-8]

The most recent development in the treatment of oesophageal cancer is the potential application of active surveillance after neoadjuvant chemoradiotherapy. In the phase-III-multi-centre SANO (Surgery As Needed approach in Oesophageal cancer patients) trial, the (cost-) effectiveness of active surveillance versus standard oesophagectomy after neoadjuvant chemoradiotherapy is assessed.[9] When active surveillance with surgery as needed leads to non-inferior overall survival compared to standard oesophagectomy, this organ-sparing approach may be implemented as a novel treatment strategy.

MULTIMODALITY TREATMENT OF GASTRIC CANCER

Perioperative chemotherapy is nowadays recommended for patients with non-metastasized resectable gastric cancer (excluding stage I). A significant survival benefit of perioperative treatment compared to surgery alone was shown in both the MAGIC trial and the French FNCLCC/FFCD trial.[10, 11] In the perioperative chemotherapy group, the 5-year survival rate was 36%, versus 23% in the surgery only group. Also, a decrease in tumour size, tumour stage, and curative resection rate were seen in the perioperative chemotherapy group. Since the publication of these trials, the administration of perioperative treatment in the Netherlands increased over time. In 2006, 3% of patients received perioperative chemotherapy and in 2014 this percentage increased to 26% of patients.[12] The most recent study for perioperative chemotherapy was the FLOT trial.[13] This trial showed that in locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma, perioperative FLOT improved overall survival compared with perioperative ECF/ECX (median survival 50 months versus 35 months).

SURGICAL MANAGEMENT

Although the treatment of oesophagogastric cancer requires a multimodality approach, surgical resection remains the cornerstone of curative treatment for the majority of patients. The main goals of surgery are a pathologically complete

tumour resection with an adequate lymphadenectomy and reliable reconstruction of the gastrointestinal tract.

ORGANISATION OF OESOPHAGOGASTRIC CANCER CARE IN THE NETHERLANDS

Oesophagectomy and gastrectomy are complex procedures associated with considerable postoperative morbidity and mortality.[14] To minimize morbidity and mortality, several multimodal aspects are essential. Careful patient selection is a requisite which demands accurate staging and risk assessment. Postoperatively, early recognition and timely management of potentially serious complications are needed.[15] Exemplary, skilled surgeons, an experienced multidisciplinary team, excellent hospital facilities, appropriate consultative and critical care staff, experienced nursing staff, and structured perioperative clinical pathways are needed.

To increase the experience and expertise of surgical teams, minimum volume standards for oesophagectomy and gastrectomy were introduced by the Association of Surgeons in the Netherlands.[14] From 2011 onwards, a minimum of 20 resections per hospital is required. For other medical disciplines involved with oesophageal and gastric cancer, no minimum volume standards have been set.[16] In 2016, oesophagogastric surgery was performed in 25 hospitals, this number decreased to 20 in 2018.[17]

DUTCH UPPER GASTROINTESTINAL CANCER AUDIT

Nationwide clinical audits are used to evaluate the quality of care between hospitals. The Dutch Institute for Clinical Auditing (DICA) was founded to facilitate and organise the initiation of nationwide audits in a uniform format.[18] In 2011, the Dutch Upper gastrointestinal Cancer Group initiated the Dutch Upper gastrointestinal Cancer Audit (DUCA).[14] All hospitals need to enter data on all patients undergoing surgery with the intention of resection for oesophageal or gastric cancer. Outcomes are collected and analysed by DICA and on a weekly basis case-mix corrected and benchmarked outcome data are reported to the participating hospitals.

HISTORY OF CLINICAL AUDITING AND THE CLINICAL AUDIT CYCLE

One of the first clinical audits was undertaken by Florence Nightingale during the Crimean War of 1853-1855. Nightingale was appalled by the high mortality rates among injured or ill soldiers. By applying sanitary routines and standards of hygiene to the hospital, the mortality rates fell from 40% to 2%.[19] Her methodical approach is recognised as one of the earliest programmes of outcomes management.[20] Another famous advocate of clinical audits was the surgeon Ernest Amory Codman (1869-1940). He was recognised as the first medical auditor following his work on monitoring outcomes of surgery.[21]

For control and continuous improvement of processes, the clinical audit cycle has been described (Figure 1).[22] This cycle is related to change management methodology and uses the technique of the Plan-Do-Check-Act method.[23] Within this clinical audit cycle there are stages that follow a systematic process: identify an audit topic, set a standard, collect and analyse data, and if needed: act to improve outcomes. Repeating the cycle can be necessary to sustain continuous improvement. By going through this audit cycle, each cycle aspires to a higher level of quality.

QUALITY INDICATORS IN THE DUCA

In the DUCA, the scientific committee determined several audit topics and quality indicators are set. These quality indicators contain results regarding the process of care, pathological outcomes, and postoperative outcomes until 30 days after surgery. The results on these quality indicators are used not only by health care professionals themselves but also by policy makers, health care insurance companies and patient federations.

Therefore, the main focus of this thesis was to determine the *reliability*, *validity* and *value* of these currently used quality indicators.

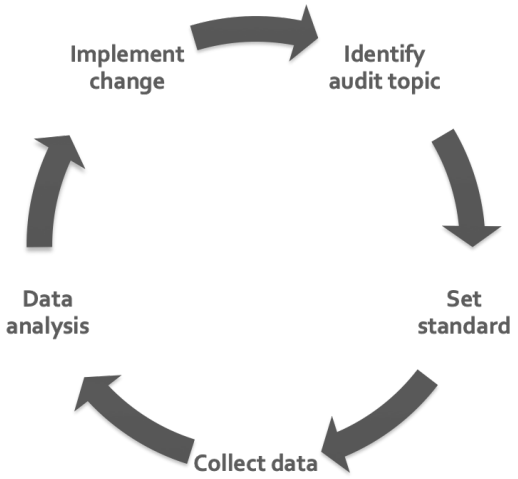

Figure 1. The clinical audit cycle

THESIS OUTLINE

PART I. NATIONAL OUTCOMES ON POSTOPERATIVE MORBIDITY QUALITY INDICATORS

It is known that postoperative complications can affect patient's quality of life, are associated with higher costs, and may affect long term outcomes.[24, 25] Therefore, postoperative morbidity is one of the main topics in the DUCA.

To compare the prevalence of complications between hospitals or countries, it is essential that everyone uses the same definitions. To facilitate these comparisons, an international standardized outcomes set was implemented in the DUCA. The Dutch results on these outcomes are reported in Chapter 2.[26] In most audits and clinical trials, complications are graded using the Clavien Dindo classification. Often, the most severe complication is only recorded. The total number of complications is not taken into account whilst in oesophagogastric cancer surgery, it is common that patients suffer from more than one complication. The Comprehensive Complication Index (CCI) was recently launched as a novel measure to evaluate the total burden of complications for

patients. In Chapter 3, the added value of this CCI measure in a national audit is assessed.[27]

In the new era where active surveillance for oesophageal cancer may gain popularity, postponed surgery is expected to take place more often. While some patients do not need surgery at all due to a complete clinical response to neoadjuvant chemoradiation, delayed surgery (>12 weeks after chemoradiation) may be associated with more complications e.g. due to radiation-induced mediastinal fibrosis. The association between delayed surgery and postoperative complications in oesophageal cancer is evaluated in Chapter 4.[28] Also, additional organ resections are suggested to be associated with higher morbidity. For advanced gastric cancer, segmental pancreatic or colonic resections or splenectomy may be indicated to achieve a complete tumour resection. In Chapter 5, the postoperative outcomes of gastrectomy including partial resection of the pancreas are analyzed.[29]

When using data for comparison, it is essential that the data are robust and reliable. DICA uses a standardized data verification process; this process is described in Chapter 6.[30]

PART II. QUALITY INDICATORS AS A PROXY FOR LONG-TERM OUTCOMES

In addition to quality indicators for postoperative morbidity, quality indicators on short-term outcomes potentially associated with long-term outcomes are included in the DUCA. In Chapter 7, the association of 'complete tumour resection', 'textbook outcome', and 'a complicated postoperative course' with long-term survival is evaluated.[31] Other examples of short-term indicators that may be associated with long-term outcomes are the number of lymph nodes and the percentage of patients with a complete tumour resection.

LYMPH NODES

An extensive lymph node dissection is an integral part of surgery for oesophagogastric cancer. It is felt that a lymph node dissection improves locoregional tumour control. Also, a lymphadenectomy leads to more accurate staging. In Chapter 8, differences in surgical approach and lymph node dissection

for the transhiatal and transthoracic technique of oesophagectomy are discussed. Since 2013, the number of retrieved lymph nodes is used as a quality indicator in the DUCA. In Chapter 9, data on the number of retrieved lymph nodes in the first years after the introduction of this quality indicator and the association with hospital volume are evaluated.[32] In Chapter 10, the association of the quality indicator 'retrieval of at least 15 lymph nodes' with overall survival and accuracy of pathological staging is assessed.[33, 34]

COMPLETE TUMOUR RESECTION

The percentage of patients with a complete tumour resection is another quality indicator because an incomplete tumour resection is associated with worse survival. For gastric cancer, the percentage of patients with an incomplete tumour resection is relatively high (8-11%).[5] In Chapter 11, risk factors associated with an incomplete tumour resection are identified.[35] Another aim of this study is to evaluate whether low hospital volume is associated with incomplete tumour resection.

In Chapter 12, a national improvement project using data of the DUCA is described.

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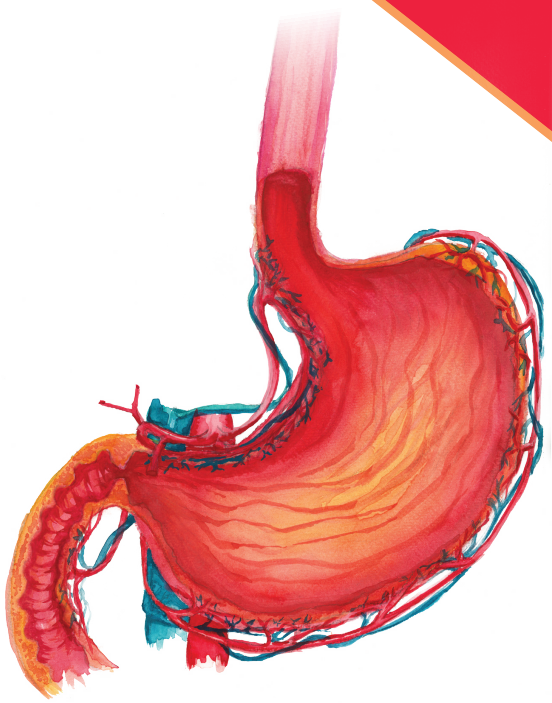
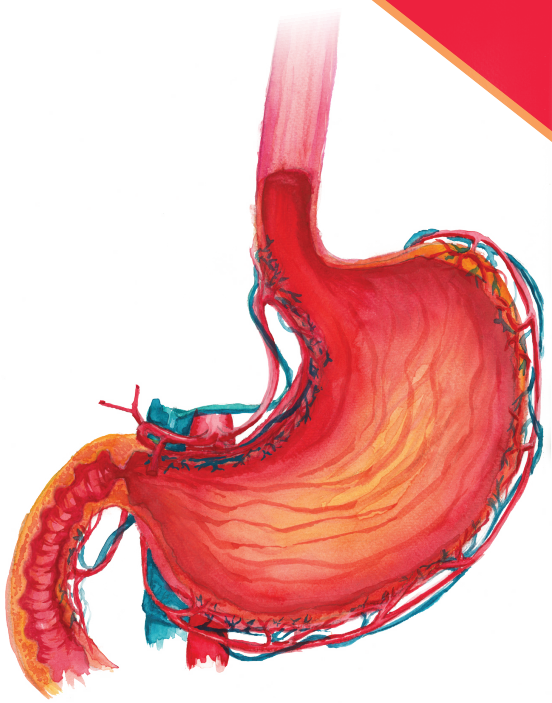


PART I

NATIONAL OUTCOMES ON POSTOPERATIVE MORBIDITY QUALITY INDICATORS



CHAPTER 2

Reporting national outcomes after oesophagectomy and gastrectomy according to the Esophageal Complications Consensus Group (ECCG)

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ABSTRACT

OBJECTIVE

This nation-wide population-based study aimed to report postoperative morbidity and mortality after oesophagectomy and gastrectomy in the Netherlands according to the definitions of the Esophagectomy Complications Consensus Group (ECCG).

BACKGROUND

To standardize international outcome reporting in oesophageal surgery, the ECCG developed a standardized outcomes set.

METHODS

For this national cohort study, all patients undergoing oesophagectomy or gastrectomy for cancer between 2016-2017 were selected from the Dutch Upper gastrointestinal Cancer Audit (DUCA). In a random sample of hospitals, data completeness and accuracy were validated by re-abstraction of the data. The investigated outcomes in the present study were postoperative complications, major complications (Clavien-Dindo grade ≥III), and 30-day mortality, according to definitions of the ECCG.

RESULTS

A total of 2545 patients from 22 hospitals were included. The completeness of the DUCA was estimated at 99.8%. Data accuracy on different items was 94-100%. After oesophagectomy, 1046 of 1617 patients (65%) had a postoperative complication including 468 patients (29%) with a major complication. Most common complications were pneumonia (21%), oesophago-enteric leak from anastomosis, staple line or localized conduit necrosis (19%), and atrial dysrhythmia (15%). The 30-day mortality was 1.7%. After gastrectomy, 397 of 928 patients (42%) had a postoperative complication including 180 patients (19%) with a major complication. Most common complications were pneumonia (12%), oesophago-enteric leak from anastomosis, staple line or localized conduit necrosis (9%), and acute delirium (5%). The 30-day mortality was 4.4%.

CONCLUSIONS

Reporting complications according to the ECCG platform is feasible in the Netherlands and facilitates international benchmarking.

INTRODUCTION

For resectable non-metastatic oesophageal and gastric cancer, resection is as yet the cornerstone of treatment. Both oesophagectomy and gastrectomy are associated with high postoperative morbidity rates. To evaluate quality of care, in several European countries clinical audits are used.[1-3] Feedback of audit data to the specialist may improve outcomes by stimulating best practices and the initiation of improvement programs for health care pathways. For a reliable comparison of outcomes between hospitals on a national level and to compare patterns of care and outcomes between countries, it is important to use uniform definitions.
To standardize outcome reporting in oesophageal surgery, the Esophagectomy Complications Consensus Group (ECCG) developed a standardized outcomes-set.[4] In 2017, in 24 hospitals in different countries the outcomes after oesophagectomy were collected according to the definitions of the ECCG.[5]

In January 2016, the definitions of the ECCG were introduced in the Dutch Upper gastrointestinal Cancer Audit (DUCA).[1] The outcomes including postoperative complications, re-admission and 30-day mortality were registered according to the definitions of the ECCG platform for both oesophagectomy and gastrectomy. At that time, an international standardized outcomes-set for gastrectomy was lacking. Hence, the ECCG outcomes-set was applied for patients that underwent oesophagectomy and gastrectomy also because the type and severity of complications that occur after both procedures is somewhat comparable.

The primary aim of this study was to report postoperative morbidity and mortality after oesophagectomy and gastrectomy in the Netherlands according to the ECCG definitions and to report the completeness and accuracy of the DUCA data. Secondly, the outcomes after oesophagectomy in the DUCA were compared with the reported outcomes of the initial ECCG dataset.[5]

METHODS

STUDY DESIGN

For this national cohort study, patient data were retrieved from the DUCA database. Dutch hospitals are mandated to register all oesophageal (including gastro-oesophageal junction) or gastric cancer patients undergoing surgery with the intent of a resection.

DATA VERIFICATION

Before evaluation of the DUCA data, it is important to test whether the outcomes are valid. The reliability of data of the data was verified in 2016. Participation of hospitals in this data verification process was voluntary. Outcomes of this data verification were the completeness and accuracy of registered data. A random sample of 15 participating hospitals was visited by an external data verification employee and a random sample of operated patients with oesophageal or gastric cancer was checked for inclusion in the DUCA database. Per hospital, 30 patients operated in 2016 were selected. If less than 30 patients were operated, all available patients were selected. Re-abstraction of data from the electronic patient dossier took place for all selected patients. The original data was compared to data registered in the DUCA.[6] In the present study, the accuracy with regard to registration of postoperative complications, 30-day mortality, reinterventions, readmissions, number of lymph nodes, resections margin and ASA score (the physical status classification according to the American Society of Anesthesiologists) was tested. The accuracy was estimated by the number of discrepancies found against the total number of patients in the sample.

PATIENTS

All patients undergoing an oesophagectomy of gastrectomy in the Netherlands between January 2016 and December 2017 for oesophageal or gastric cancer were included in this study. Patients with a palliative bypass procedure were excluded. Also, patients with missing data regarding complications or other essential elements of the registration including date of birth, survival status at 30 days after surgery or date of discharge (in case of a hospital stay of >30 days) were excluded.

OUTCOMES

The primary outcome was frequency of postoperative complications. The severity of the complications was defined according to Clavien-Dindo.[7] Complications grade IIIa or higher were defined as major complications. The secondary outcomes were hospital stay, duration of stay at the Intensive Care Unit (ICU), the frequency of reinterventions, 30-day and/or in-hospital mortality, readmissions, the number of retrieved lymph nodes, surgical resection margins and the ASA score. For all patients who underwent an oesophagectomy, the outcomes were compared to the outcomes of the ECCG as recently reported.[5]

STATISTICAL METHODS

Patient and tumour characteristics of all included patients were reported according to the type of resection (oesophagectomy or gastrectomy) using frequencies and percentages. Also, all postoperative outcomes were described using frequencies and percentages. The outcomes after oesophagectomy in the DUCA were compared with the reported outcomes of the ECCG dataset[5] using $\chi 2$ analyses. Statistical analyses of the present study were performed using Microsoft Excel® for Mac (version 15.41). Statistical significance was defined as $P<0.05$.

RESULTS

DATA VERIFICATION

The completeness of the DUCA was estimated at 99.8% (Table 1). In a sample of 408 patients, one patient who should have been registered according to the inclusion criteria of the DUCA was not registered. Complications were accurately registered in 382 of 407 patients (94%). In 25 patients (6%) no complication was registered in the DUCA, whereas in the electronical patient file a complication was reported. Thirty-day and/or in-hospital mortality was accurately registered in 406 of 407 patients (98.8%). In 13 of 407 patients (3%), a complicated postoperative course (defined as a complication leading to prolonged hospital stay (>21 days), reintervention or death) was not registered in the DUCA

database but was extracted from the electronic patient files. All verified variables are shown in Table 1.

Table 1. Results of external data verification

Completeness of data **Sample size: 408**	**Registered** *n*	**Wrongly not registered** *n*	**Completeness** %
Included in DUCA	407	1	99.8%

Accuracy of data **Sample size: 407**	**Correctly registered** *n*	**Wrongly registered** *n*	**Missing** *n*	**Accuracy** %
Complications	382	25	0	94%
30-day/in-hospital mortality	406	1	0	99.8%
Reinterventions	394	13	0	97%
Complications leading to prolonged hospital stay (>21 days), reintervention or death	394	13	0	97%
Readmission	390	12	5	97%
Number of lymph nodes	394	13	0	97%
Resection margins	394	11	2	97%
ASA score	379	28	0	93%

PATIENTS

From January 2016 to December 2017, a total of 1617 patients undergoing an oesophagectomy and 928 patients undergoing a gastrectomy were registered in the DUCA. Eight patients were excluded due to missing data. Patient, disease and treatment characteristics are summarized in Table 2 and Table 3. Minimally invasive techniques were used in 86% of patients undergoing an oesophagectomy and in 58% of patients undergoing a gastrectomy. Fifty-two percent of oesophagectomies was performed via a transthoracic approach. In 43% percent of all gastrectomies, a total gastrectomy was performed.

Table 2. Patient-, and disease characteristics.

		ECCG Oesophagectomy[5]		DUCA Oesophagectomy		DUCA Gastrectomy	
		n	%	*n*	%	*n*	%
Total		2704		1617		928	
Sex	Male	2096	78%	1228	76%	561	61%
	Female	607	22%	388	24%	367	40%
	Unknown			1	0%	0	0%
Age (in years)	40 or less	66	2%	6	0%	25	3%
	41-50	217	8%	76	5%	53	6%
	51-60	721	27%	316	20%	129	14%
	61-70	1100	41%	739	46%	227	25%
	71-80	532	20%	451	28%	355	38%
	more than 80	67	3%	29	2%	139	15%
Body Mass Index	<18.5	184	7%	47	3%	34	4%
	18.5-25	1085	40%	657	41%	420	45%
	25-30	908	34%	642	40%	329	36%
	30+	526	20%	265	16%	136	15%
	Unknown			6	0%	9	1%
ASA score	I	412	15%	255	16%	113	12%
	II	1249	46%	1012	63%	526	57%
	III	992	37%	340	21%	273	29%
	IV	49	2%	7	0%	15	2%
	V	1	0%	0	0%	0	0%
	Unknown			3	0%	1	0%
Charlson Comorbidity score	0			754	47%	411	44%
	1			385	24%	191	21%
	2+			478	30%	326	35%
Comorbidities	Myocardial infarction	146	5%	86	5%	66	7%
	Congestive heart failure	124	5%	12	1%	19	2%
	Chronic Pulmonary Disease	285	11%	326	20%	155	17%
	Peripheral Vascular Disease	185	7%	73	5%	53	6%
	Diabetes Mellitus (uncomplicated)	348	13%	221	14%	160	17%
	Diabetes Mellitus (end-organ damage)	16	1%	13	6%	5	3%
	Moderate to Severe Renal Disease	35	1%	21	1%	29	3%
Pathology (indication for surgery)	Benign	97	4%				
	Malignant	2585	96%				
	Other, including perforations	21	1%				
Location (ECCG)	At the GE junction	762	28%				
	Proximal 1/2 of oesophagus	304	11%				
	Distal 1/2 of oesophagus	1519	56%				
Location (DUCA)	Cervical (C15.0)			1	0%	0	0%
	Proximal (C15.3)			14	1%	0	0%
	Mid (C15.4)			226	14%	0	0%
	Distal (C15.5)			1087	67%	3	0%
	Gastro-oesophageal junction(C16.0)			261	16%	32	3%
	Fundus (C16.1)			18	1%	69	7%
	Corpus (C16.2)			1	0%	281	30%
	Antrum (C16.3)			0	0%	365	39%
	Pylorus (C16.4)			0	0%	80	9%
	Total stomach			0	0%	44	5%
	Rest stomach / anastomosis			0	0%	34	4%
	Unknown (stomach)			6	0%	1	0%
	Missing			3	0%	19	2%
	Unknown			2	0%	2	0%

Table 3. Pathological- and treatment characteristics, according to type or resection: oesophagectomy (for ECCG[5] and DUCA) and gastrectomy are shown.

		ECCG Oesophagectomy[5]		DUCA Oesophagectomy		DUCA Gastrectomy	
		n	%	*n*	%	*n*	%
Total		2704		1617		928	
Pathological Tumour stage	pT0-2	1242	65%	966	60%	341	37%
	pT3	1075	42%	592	37%	327	35%
	pT4	78	3%	21	1%	236	25%
	Missing	0	0%	38	2%	24	3%
Pathological Node stage	pN-	1477	57%	957	59%	421	45%
	pN+	1101	42%	622	39%	485	52%
	pNx	7	0%	4	0%	7	1%
	Missing			34	2%	15	2%
Pathological Metastases stage	pM-	2170	84%	1528	95%	796	86%
	pM+	46	2%	23	1%	61	7%
	Not applicable	0	0%	48	3%	54	6%
	pMx	369	14%	18	1%	17	2%
Timing of surgery	Elective	2680	99%	1610	100%	895	96%
	Urgent			3	0%	25	3%
	Emergency	23	1%	3	0%	8	1%
	Unknown			1	0%	0	0%
Neoadjuvant therapy	No	545	21%	105	7%	379	42%
	Chemotherapy	763	30%	86	5%	502	55%
	Chemoradiotherapy	1192	46%	1417	88%	28	3%
	Radiotherapy	5	0%	6	0%	0	0%
	Unknown			0	0%	1	0%
	Definitive chemoradiotherapy	80	3%				
Surgical approach	Open	1407	52%	229	14%	394	43%
	MI	1296	48%	1388	86%	534	58%
Esophagectomy (open)	Transhiatal	283	20%	109	48%		
	Transthoracic	1124	80%	120	52%		
Esophagectomy (MI)	Abdomen only	521	40%	222	16%		
	Chest only	144	11%	60	4%		
	Abdomen and chest	631	49%	1106	80%		
Gastrectomy (open and MI)	Total					402	43%
	Partial					526	57%
Site of anastomosis	Chest	1641	61%	876	54%	65	7%
	Neck	1025	38%	696	43%	2	0%
	Abdomen			7	0%	807	87%
	Other/none	37	1%	38	2%	54	6%
Conduit/reconstruction	Stomach	2564	95%	1567	99%	4	0%
	Colon	34	1%	4	0%	1	0%
	Small bowel	72	3%	0	0%	2	0%
	Oesophagojejunostomy (Roux-Y)			5	0%	394	44%
	Gastroenterostomy (BII or Roux-Y)			0	0%	483	54%
	Other/none	33	1%	9	1%	12	1%
Resection margins	R0 Microscopic radical	2414	93%	1532	95%	820	89%
	R1 Microscopic irradical	157	6%	65	4%	83	9%
	R2 Locoregional residual tumour	14	1%	1	0%	4	0%
	Not applicable			8	1%	8	1%
	Unknown			2	0%	2	0%

OUTCOMES AFTER OESOPHAGECTOMY

Sixty-five percent of patients who underwent an oesophagectomy had a postoperative complication (Table 4). Clavien Dindo grade III or higher complications occurred in 29% of all patients (Table 5). Most common complications were pneumonia (21%), leak from the anastomosis, staple line or localized conduit necrosis (19%), and atrial dysrhythmia (15%). All complications are presented in Supplementary Table 1. The median stay at the intensive care unit was 2 days (interquartile range: 1-4), and median hospital stay was 11 days (interquartile range: 9-18). The 30-day mortality rate was 1.7% and the 30-day/in-hospital mortality rate was 2.4%.

In comparison with the reported outcomes of the ECCG[5], the overall complication rate was significantly higher in the DUCA (65% versus 59%, p<0.001). Also, pneumonia and leak from anastomosis, staple line or localized conduit necrosis, occurred more often (respectively, 21% versus 15%, p<0.001 and 19% versus 11%, p<0.001) (Figure 1). Hospital readmission within 30 days after discharge occurred in 15% of patients, significantly more often compared to the ECCG cohort (11%, p<0.001). The 30-day mortality rate was 1.7% versus 2.4% in the ECCG cohort (p=0.10).

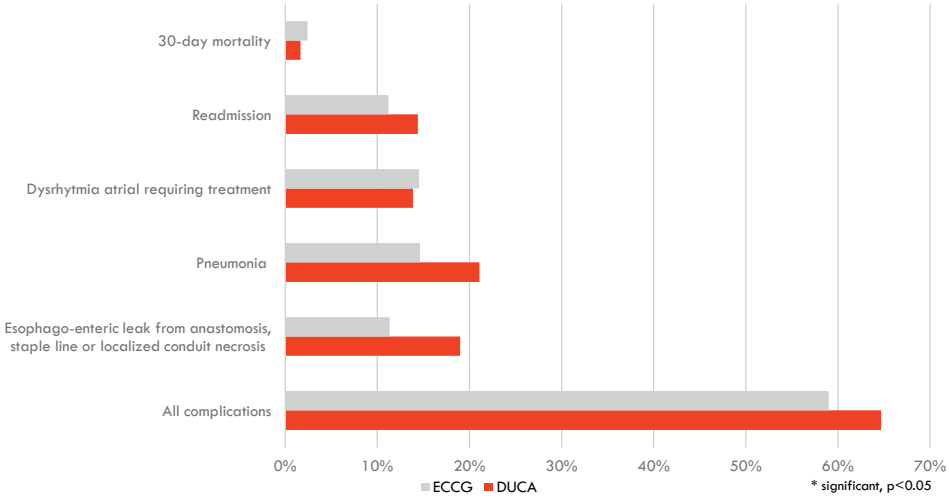

Figure 1. Comparison of outcomes after oesophagectomies, DUCA versus ECCG.

Table 4. Outcomes of the DUCA according to type of resection

Complications	**DUCA Oesophagectomy**		**DUCA Gastrectomy**	
Total (n=)	**1617**		**928**	
	Median	*[IQR]*	*Median*	*[IQR]*
Hospital stay (days)	11	[9-18]	8	[6-13]
ICU stay (days)	2	[1-4]	0	[0-1]
	n	*%*	*n*	*%*
Intra-operative complication	89	5.5%	34	3.7%
Postoperative complication	1046	65%	397	43%
Reintervention	420	26%	186	20%
Radiological	170		51	
Endoscopic	187		54	
Re-operation	208		121	
In-hospital/30-day mortality	38	2.4%	49	5.3%
30-day mortality	27	1.7%	41	4.4%
Readmission	233	15%	123	14%
Postoperative complication Clavien Dindo grade III or more	468	29%	180	19%

ICU: intensive Care Unit

OUTCOMES AFTER GASTRECTOMY

Forty-three percent of patients who underwent a gastrectomy experienced a postoperative complication (Table 4). Clavien Dindo grade III or higher complications occurred in 19% of patients (Table 5). Most common complications were pneumonia (12%), oesophago-enteric leak from anastomosis, staple line or localized conduit necrosis (9%), and acute delirium (5%). All complications are presented in Supplementary Table 1. The severity of four outcome measures according to the ECCG[4] are presented in Supplementary table 2. The median stay at the intensive care unit stay was 0 days (interquartile range: 0-1), and median hospital stay was 8 days (interquartile range: 6-13). Hospital readmission within 30 days after discharge occurred in 14% of patients. The 30-day mortality rate was 4.4%, and the 30-day/in-hospital mortality was 5.3%.

Table 5. Severity of complications in the DUCA according to type of resection

Complication Severity	Esophagectomy				Gastrectomy			
	n	%	*95% CI*		*n*	%	*95% CI*	
No complications	605	37%	35%	40%	562	61%	57%	64%
Grade I	150	9%	8%	11%	39	4%	3%	6%
Grade II	379	23%	21%	26%	130	14%	12%	16%
Grade IIIa	192	12%	10%	14%	51	6%	4%	7%
Grade IIIb	128	8%	7%	9%	66	7%	6%	9%
Grade IVa	110	7%	6%	8%	23	3%	2%	4%
Grade IVb	11	1%	0%	1%	5	1%	0%	1%
Grade V	27	2%	1%	2%	35	4%	3%	5%
Grade unknown	15	1%	1%	2%	17	2%	1%	3%

DISCUSSION

This study with DUCA data shows that reporting complications according to the ECCG definitions can be achieved on a national level. Data verification showed that the completeness and accuracy of data in the DUCA were high. Overall, complications after oesophagectomy and gastrectomy occurred in 65% and 43% of patients, respectively. Major complications (Clavien Dindo grade III or higher) occurred in 29% and 19% of patients, respectively. The most common complications after oesophagectomy were pneumonia, oesophago-enteric leak, and dysrhythmia atrial. After gastrectomy, pneumonia, oesophago-enteric leak, and acute delirium were the most common complications.

Recently, the outcomes of 24 high volume hospitals participating in the ECCG were published[5]. Compared to these data, overall complication rates, pneumonia rates, and oesophago-enteric leakage rates were significantly higher in the DUCA. Different explanations may exist for these discrepancies.
First, differences in patient and treatment characteristics exist between the ECCG cohort and DUCA cohort which might have influenced the occurrence of complications. From previous studies with DUCA data, it is known that higher age, ASA score, body mass index, N+ status, proximal-mid oesophageal tumour-location, and open transthoracic procedures are associated with an increased risk for postoperative complications.[8,9] Some of these factors were more frequently present in the DUCA, e.g., 30% of patients were older than 70 years

old (versus 23% in the ECCG cohort). However, in the ECCG cohort, patients with ASA III or higher were more frequently present then in the DUCA (39% versus 21%).

The second difference was the percentage of patients that was treated with neoadjuvant chemoradiotherapy. In the DUCA, 88% of patients was treated with neoadjuvant chemoradiotherapy, versus 46% in the ECCG cohort. In the literature, some studies regarding neoadjuvant chemoradiotherapy have reported no significant differences in complication rates between neoadjuvant chemoradiotherapy and neoadjuvant chemotherapy alone or no neoadjuvant therapy.[10-12] However, Klevebro et al. reported a higher frequency of severe complications after neoadjuvant chemoradiotherapy in comparison with neoadjuvant chemotherapy alone.[12] It has been suggested that radiotherapy affects the lung tissue and may increase pulmonary complications.[13] The difference in type and frequency of neoadjuvant therapy could be an explanation of the higher pneumonia rate in the DUCA versus the ECCG cohort. A study with combined datasets and correction for differences in case-mix could potentially answer this issue.

Another difference between both cohorts was the type of oesophagectomy. In the DUCA 86% of patients underwent a minimally invasive oesophagectomy versus 48% in the ECCG. The TIME trial, a randomized trial evaluating minimally invasive versus open transthoracic oesophagectomy, showed that in-hospital pulmonary infections occurred significantly less frequent after minimally invasive oesophagectomy (12% versus 34%).[14] A previous Dutch study showed that during the implementation of minimally invasive oesophagectomies in the Netherlands there was no differences in pulmonary complications and 30-day/in-hospital mortality between minimally invasive versus open gastrectomy. However, the same study showed higher anastomotic leakage rates and reintervention rates after minimally invasive gastrectomy.[15] The introduction of minimally invasive surgery and the associated learning curve that goes with it[16], might have influenced the complication rate. Nonetheless, in 2015, 84% of the registered oesophagectomies in the DUCA was performed with minimally invasive techniques and, since the current study only reports data of 2016 and 2017, it could be that most surgeons might already have completed their learning curve in this period. However, it is important to keep in mind that that learning curve until proficiency might be much longer that initially was

expected.[16] Future studies are needed to evaluate the 'real' length of the learning curve.

Also, the approach of oesophagectomy differed between the DUCA and ECCG cohorts. The transhiatal approach was more favourite in the DUCA cohort than in the ECCG cohort: 48% *versus* 20%, respectively. As reported in a meta-analysis of Hulscher *et al*., the transhiatal approach and cervical anastomosis is associated with a higher frequency of anastomotic leakage and vocal cord paralysis.[17] In the transthoracic group in this meta-analysis, there was more perioperative blood loss, pulmonary complications, chyle leak, and wound infections. Thus, the difference in favoured approaches between the DUCA and ECCG might explain the higher anastomotic leakage rate in the DUCA database. Nonetheless, the higher pneumonia rate in the DUCA could not be explained by the differences in surgical approach.

The annual hospital volume of the participating hospitals in the ECCG has been described as all 'high volume'. In the DUCA, in 2016, the annual hospital volume varied each year. In 2016, 9 of 22 hospitals performed 40 or more resections and 5 hospitals performed less than 20 resections.[18] Differences in annual hospital volume may influence outcomes. However, further studies are needed to evaluate whether these differences can explain the variation in outcomes between the cohorts.

Due to the use of a standardized outcomes set, the DUCA outcomes after oesophagectomies could be compared with the ECCG outcomes fairly. For outcomes after gastrectomies, at the time of the implementation of the ECCG outcomes, there was no standardized international consensus set and the ECCG outcomes were also incorporated for patients after gastrectomy. To our knowledge, the ECCG outcomes set has not been used for reporting outcomes after gastrectomy in other cohorts. Recently, a specific standardized outcomes set for gastric cancer surgery was published with the intent to facilitate international comparison.[19] The intent is to implement this standardized set of definitions in the DUCA because it potentially facilitates international comparison.

An international comparison of Dutch results after oesophagectomy and gastrectomy has been done previously. The results of the DUCA were compared to the results of the Swedish NREV (Nationellt Kvalitetsregister matstrups- och

magsäckscancer).[20] However, the results of the registries at that time were not standardized, which makes comparison not really reliable.

The 30-day mortality in the DUCA database was 1.7% after oesophagectomy and 4.4% after gastrectomy. In comparison with the outcomes of the ECCG cohort, the mortality after oesophagectomies was not significantly different. The 30-day mortality after gastrectomy and oesophagectomy was also reported in the annual report of the British 'National Oesophago Gastric Cancer Audit (NOGCA)'. Between 2007-2009 and between 2013-2015, the 30-day mortality after oesophagectomies was 3.8% (95% confidence interval: 3.1%-4.7%) and 1.6% (95% confidence interval: 1.2%-2.1%), respectively. After gastrectomy it was 4.5% (95% confidence interval: 3.4%-5.7%) and 1.9% (95% confidence interval 1.3%-2.7%), respectively. In the annual report of the NOGCA, no clarification was given for this improvement in 30-day mortality after oesophagectomy and gastrectomy. It would be interesting to evaluate the underlying processes; in order to direct a strategy to also improve 30-day mortality after gastrectomy in the Netherlands.

In conclusion, evaluation of quality of care is important, especially for high complex, low-volume procedures such as oesophagectomy and gastrectomy. Reporting outcomes using standardized definitions is an essential step towards reliable results. Furthermore, it enables international comparisons that could help to reveal significant differences in outcomes and to identify factors which could be improved. A more widespread adoption of the ECCG platform could be recommended to improve international benchmarking in oesophageal surgery.

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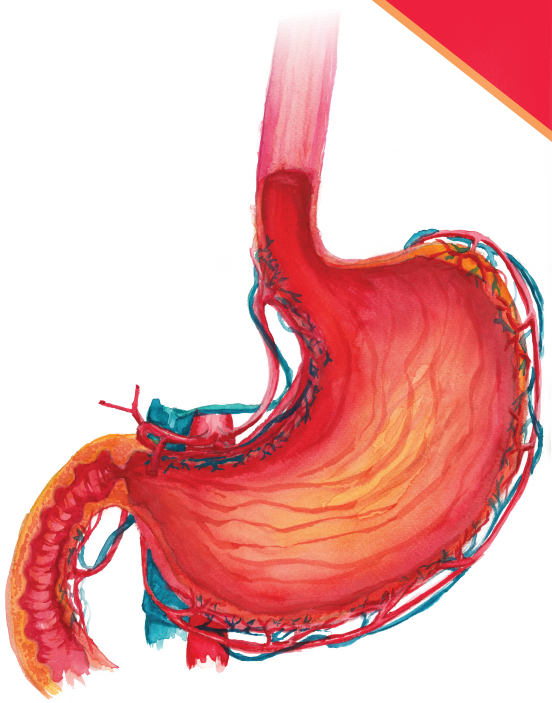


CHAPTER 2

Supplementary data

Supplementary table 1. Complications according to type of resection of the DUCA and comparison with the ECCG[5]

Complications	ECCG oesophagectomy		DUCA oesophagectomy		DUCA gastrectomy	
	n	%	*n*	%	*n*	%
Total	2704		1617		928	
All complications	1595	59%	1046	65%	397	43%
Pulmonary	752	28%	529	33%	154	17%
Pneumonia*	396	15%	341	21%	111	12%
Pleura effusion requiring additional drainage procedure	267	10%	124	8%	28	3%
Pneumothorax requiring treatment	91	3%	68	4%	7	1%
Atelectasis mucous plugging requiring bronchoscopy	85	3%	18	1%	5	1%
Respiratory failure requiring reintubation	189	7%	84	5%	23	3%
Acute aspiration	50	2%	25	2%	15	2%
Acute respiratory distress syndrome **	27	1%	24	2%	3	0%
Tracheobronchial injury	11	0%	11	1%	1	0%
Chest tube maintenance for air leak for >10 days postoperatively	13	1%	11	1%	1	0%
Cardiac	455	17%	276	17%	46	5%
Myocardial infarction***	28	1%	5	0%	5	1%
Dysrhythmia atrial requiring treatment	393	15%	224	14%	25	3%
Dysrhythmia ventricular requiring treatment	15	1%	23	1%	8	1%
Congestion heart failure requiring treatment	25	1%	17	1%	9	1%
Pericarditis requiring treatment	12	0%	3	0%	1	0%
Cardiac arrest requiring CPR	2	0%	9	1%	4	0%
Gastrointestinal	606	22%	392	24%	171	18%
Oesophagoenteric leak from anastomosis, staple line or localized conduit necrosis	307	11%	307	19%	85	9%
Conduit necrosis/failure	34	1%	13	1%	1	0%
Ileus defined as small bowel dysfunction preventing or delaying enteral feeding	46	2%	12	1%	42	5%
Small bowel obstruction	12	0%	4	0%	10	1%
Feeding J-tube complication	27	1%	55	3%	12	1%
Pyloromyotomy/pyloroplasty complication	5	0%	6	0%	0	0%
Clostridium difficile Infection	23	1%	2	0%	2	0%
Gastrointestinal bleeding requiring intervention or transfusion	21	1%	1	0%	24	3%
Delayed conduit emptying requiring intervention or delaying discharge or requiring maintenance of NG drainage >7days postoperatively	180	7%	27	2%	7	1%
Pancreatitis	8	0%	3	0%	6	1%
Liver dysfunction	6	0%	5	0%	2	0%
Urologic	224	8%	66	4%	46	5%
Acute renal insufficiency (defined as doubling of baseline creatinine)	39	1%	11	1%	10	1%
Acute renal failure requiring dialysis	24	1%	5	0%	3	0%
Urinary tract infection	68	3%	20	1%	16	2%
Urinary retention requiring reinsertion of urinary catheter, delaying discharge, or discharge with urinary catheter	104	4%	32	2%	16	2%

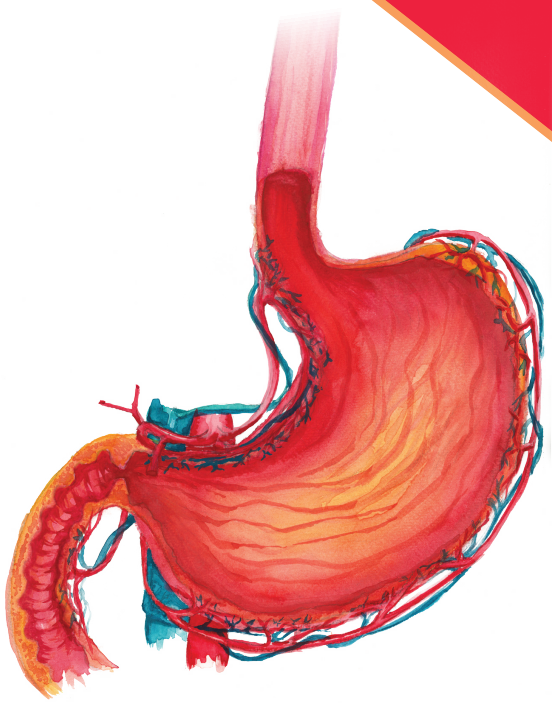
Supplementary table 1. (continued)

Complications	ECCG oesophagectomy		DUCA oesophagectomy		DUCA gastrectomy	
	n	%	*n*	%	*n*	%
Thromboembolic	141	5%	45	3%	18	2%
Deep venous thrombosis	25	1%	4	0%	6	1%
Pulmonary embolus	33	1%	35	2%	10	1%
Stroke (CVA)	4	0%	1	0%	1	0%
Peripheral thrombophlebitis	79	3%	4	0%	1	0%
Neurologic/psychiatric	254	9%	172	11%	53	6%
Recurrent nerve injury	114	4%	70	4%	0	0%
Other neurologic injury	33	2%	10	1%	8	1%
Acute delirium ****	105	4%	97	6%	46	5%
Delirium tremens	16	1%	2	0%	1	0%
Infection	383	14%	120	7%	87	9%
Wound infection requiring opening wound or antibiotics	20	1%	37	2%	20	2%
Central IV-line infection requiring removal or antibiotics	55	2%	10	1%	5	1%
Intrathoracic/intra-abdominal abscess	65	2%	37	2%	34	4%
Generalized sepsis *****	52	2%	17	1%	20	2%
Other infections requiring antibiotics	227	8%	20	1%	21	2%
Wound/diaphragm	78	3%	30	2%	21	2%
Wound dehiscence	40	2%	16	1%	8	1%
Fasciedehiscence/Platzbauch/hernia (acute)	33	1%	7	0%	12	1%
Hernia diafragmatica (acute)	8	0%	7	0%	0	0%
Chyle leak	128	5%	139	9%	15	2%
Other			138	9%	70	8%
Reoperation for reasons other than bleeding, anastomotic leak or conduit necrosis	39	1%	17	1%	7	1%
Multiple organ dysfunction syndrome******	27	1%	2	0%	5	1%
Postoperative bleeding requiring transfusion or reoperation			7	0%	7	1%
Complications of epidural catheter			4	0%	3	0%

* Definition Thoracic Society and Infectious Diseases Society of America
** Berlin definition
*** Definition World Health Organization
**** Definition Diagnostic and Statistical Manual of Mental Disorders, 5th
***** Definition CDC
****** Definition American college of chest physicians/society of critical care medicine consensus conference committee

Supplementary Table 2. Severity of complications in the DUCA in comparison with the ECCG[5]

		ECCG oesophagectomy		DUCA oesophagectomy	
		n	%	*n*	%
Anastomotic leak	No Leak	2403	88.9%	1310	81.0%
	Type I	90	3.3%	92	5.7%
	Type II	131	4.8%	131	8.1%
	Type III	80	3.0%	83	5.1%
	Unknown			1	0.1%
Conduit necrosis/failure	No conduit necrosis	2672	98.8%	1604	99.2%
	Type I	2	0.1%	1	0.1%
	Type II	7	0.3%	3	0.2%
	Type III	23	0.9%	9	0.6%
Recurrent laryngeal nerve injury involvement	No recurrent laryngeal nerve injury	2595	96.0%	1547	95.7%
	Type Ia	81	3.0%	55	3.4%
	Type Ib	6	0.2%	6	0.4%
	Type Iia	12	0.4%	4	0.2%
	Type Iib	4	0.1%	1	0.1%
	Type IIIa	2	0.1%	0	0.0%
	Type IIIb	4	0.1%	1	0.1%
	Unknown			3	0.2%
Chyle leak	No Chyle leak	2578	95.3%	1478	91.4%
	Type Ia	67	2.5%	68	4.2%
	Type Ib	10	0.4%	3	0.2%
	Type Iia	11	0.4%	14	0.9%
	Type Iib	6	0.2%	8	0.5%
	Type IIIa	12	0.4%	2	0.1%
	Type IIIb	20	0.7%	19	1.2%



CHAPTER 3

The Comprehensive Complication Index for quality monitoring of oesophagogastric cancer surgery

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B.P.L. Wijnhoven

SUBMITTED

ABSTRACT

OBJECTIVE

Assessment of postoperative morbidity is crucial to monitor the quality of surgery and perioperative care. The Comprehensive Complication Index (CCI) is a novel composite measure for the total burden of postoperative morbidity. This study aimed to calculate the CCI for hospitals participating in a nationwide audit and to compare the CCI with existing quality indicators.

DESIGN, SETTING, PARTICIPANTS

For this nationwide observational study, data was retrieved from the Dutch Upper Gastrointestinal Cancer Audit (DUCA). Patients with oesophagogastric cancer who underwent an oesophagectomy or gastrectomy between 2016 and 2018 were included.

MAIN OUTCOMES

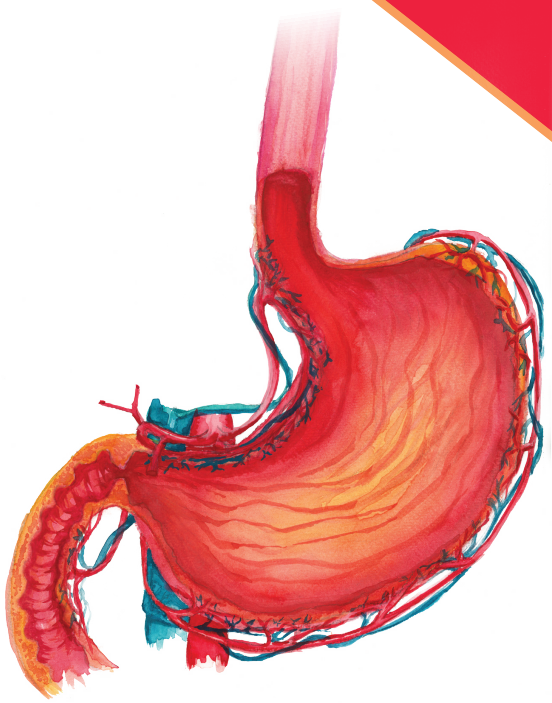
The main outcome was the median CCI per hospital and the percentage of patients per hospital (1) within the 75th percentile of CCI, (2) with a complicated postoperative course (defined as any complication in combination with a hospital stay >21 days, reintervention or in-hospital/30-day mortality, and (3) with a Clavien Dindo Classification grade >II complication, all adjusted for differences in case-mix.

RESULTS

In total, 2396 patients who underwent oesophagectomy and 1373 patients who underwent gastrectomy were included. In the oesophagectomy group, the median CCI was 20.9 (interquartile range: 0.0-33.5) with at least one postoperative complication occurring in 1578 of 2396 patients (66%). In the gastrectomy group, the median CCI was 0.0 (interquartile range: 0.0-20.9) and at least one postoperative complication occurring in 573 of 1373 patients (42%). On hospital level, the percentage of patients within the 75th percentile of CCI was strongly correlated with a complicated postoperative course for both oesophagectomies and gastrectomies but was not correlated with a Clavien Dindo Classification grade >II complication.

CONCLUSION AND RELEVANCE

The CCI can be applied in a national clinical audit to report outcomes. Hospital outcomes on the CCI are strongly correlated with a complicated postoperative course.



CHAPTER 4

Time interval between neoadjuvant chemoradiotherapy and surgery for oesophageal or junctional cancer: a nationwide study

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ABSTRACT

INTRODUCTION

The optimal time between end of neoadjuvant chemoradiotherapy (nCRT) and oesophagectomy is unknown. The aim of this study was to assess the association between this interval and pathologic complete response rate (pCR), morbidity, and 30-day/in-hospital mortality.

METHODS

Patients with oesophageal cancer treated with nCRT and surgery between 2011 and 2016 were selected from a national database. The interval between end of nCRT and surgery was divided into six periods: 0-5 weeks(n=*157*;A), 6-7 weeks(n=*878*;B), 8-9 weeks(n=*972*;C), 10-12 weeks(n=*720*;D), 13-14 weeks(n=*195*;E) and 15 or more weeks(n=*180*;F). The association between these interval groups and outcomes was investigated using univariable and multivariable analysis with group C (8-9 weeks) as reference.

RESULTS

In total 3102 patients were included. The pCR rate for the groups A to F was 31%, 28%, 26%, 31%, 40%, and 37%, respectively. A longer interval was associated with a higher probability of pCR (≥10 weeks for adenocarcinoma: odds ratio[confidence interval]: 1.35[1.00-1.83], 1.95[1.24-3.07], 1.64[0.99-2.71] and ≥13 weeks for squamous cell carcinoma: 2.86[1.23-6.65], 2.67[1.29-5.55]. Patients operated ≥10 weeks after nCRT had the same probability for intraoperative/postoperative complications. Patients from groups D and F had a higher 30-day/in-hospital mortality (1.80[1.08-3.00], 3.19[1.66-6.14]).

CONCLUSION

An interval of ≥10 weeks for adenocarcinoma and ≥13 weeks for squamous cell carcinoma between nCRT and oesophagectomy was associated with a higher probability of having a pCR. Longer intervals were not associated with intraoperative/postoperative complications. The 30-day/in-hospital mortality was higher in patients with extended intervals (10-12 and ≥15 weeks), however this might have been due to residual confounding.

INTRODUCTION

Oesophageal cancer is the eighth most common cancer in the world and the incidence is increasing.[1] Randomized clinical trials have shown that neoadjuvant chemoradiotherapy (nCRT) or chemotherapy improves survival after oesophagectomy. Multimodality treatment for resectable oesophageal cancer has now become standard in the Netherlands.[2] NCRT induces tumour regression and a pathological complete response (pCR) is observed in 25-30% of patients.[3] A pCR is associated with an improved survival compared to patients who have an incomplete pathological response.[3,4]

A longer interval between nCRT and surgery has been suggested to increase the probability of a pCR.[5] In pancreatic and rectal cancer, there is some evidence that a longer interval between end of neoadjuvant treatment and surgery is associated with higher pCR rates and also improved (disease-free) survival.[6-8] However, extended intervals might also lead to residual tumour growth or increased radiation fibrosis resulting in technically more challenging operations with higher postoperative complication rates, resulting in a worse survival. For oesophageal cancer, conflicting data have been published. Most studies modelled the time interval as a dichotomous variable or included only a small number of patients.[9-12]

The aim of this population-based study was to assess the association between the time after nCRT and pCR, complications and postoperative mortality in a large national cohort. It was hypothesized that a longer time interval is associated with a higher pCR, but also with a higher complication rate.

METHODS

STUDY DESIGN

We conducted a retrospective study using data from the Dutch Upper Gastrointestinal Cancer Audit (DUCA), a large prospective national audit facilitated by the Dutch Institute for Clinical Auditing (DICA). All patients undergoing surgery for gastric or oesophageal cancer in the Netherlands are

registered in this database.[13] Patient-, tumour-, treatment characteristics, pathological information and postoperative outcome (until 30 days postoperative) were extracted from this database.

PATIENT SELECTION

Patients who underwent an elective oesophagectomy with curative intent for oesophageal or junctional cancer after nCRT between 2011 and 2016 were included. Criteria for exclusion were: cervical oesophageal tumours, non-completion of the nCRT regimen, cT1N0 tumours (according to the 7th edition of the Union for International Cancer Control-American Joint Committee on Cancer (UICC-AJCC) tumour, node, metastasis (TNM) staging system [14]), unknown date of birth, unknown curability status of resection (curative/palliative), or unknown 30-day/in-hospital survival status.

Since 2010, nCRT followed by surgery has been the standard treatment according to the Dutch guideline for oesophageal carcinoma (with the exception for T1N0 tumours). Furthermore, in 2014, the guideline specified the nCRT regimen based on the CROSS trial[15]: Carboplatin (AUC 2 mg/ml/min) and paclitaxel (50 mg/m^2) is administered on days 1, 8, 15, 22 and 29. Concurrent radiotherapy 41.4 Gray is administered in 23 fractions, 5 days a week starting on the day of first chemotherapy administration.[15,16] Although the exact regimen used was not specified in the database, it was assumed that all patients in this study were treated with this regimen.

TIME INTERVAL

In the DUCA the start of nCRT and the date of surgery are registered. The date of the end of nCRT is not registered. To estimate the interval between the end of nCRT and surgery, 30 days (duration of CROSS schedule) were subtracted from the calculated interval between start of nCRT and operation. In this manuscript 'interval' always refers to the time interval between the end of nCRT and resection.

OUTCOMES

The primary outcome was pCR, defined as no vital tumour cells at the location of the primary tumour and in the lymph nodes. Secondary endpoints were the number of resected lymph nodes, intraoperative complications, postoperative complications (within 30 days postoperative), severe postoperative complications and 30-day/in-hospital mortality. Severe complications were defined as postoperative complications leading to a prolonged hospital stay (>21 days), (surgical, endoscopic or radiological) re-intervention or death. From 2016, the severity of complications was scored according to Clavien Dindo[17].

Patients were grouped in six interval categories: group A: 0-5 weeks, B: 6-7 weeks, C: 8-9 weeks, D: 10-12 weeks, E: 13-14 weeks and F: 15 or more weeks. The upper and lower boundaries of the second and third group were chosen to analyse differences between the most common intervals and the other groups.

POTENTIAL DELAY-RELATED CONFOUNDERS

To adjust for the possibility that variations in interval were not only caused by structure and process difficulties, but also by patient-related characteristics (i.e. intentionally extended interval in e.g. less fit patients), the effects of the interval on the outcomes were adjusted for confounders. These factors were the Charlson comorbidity index (calculated using the registered information regarding comorbidities in the DUCA, the current oesophageal tumour was not included as malignancy)[18], American Society of Anesthesiologists (ASA) score, body mass index (BMI, kg/m^2) at the time of diagnosis, gender, and age. Also, the tumour specific characteristics: tumour location, T-, N- and M- category and histological tumour type were used. Finally, treatment characteristics including type of surgical approach, annual hospital volume and year of surgery were used. [13,19]

In this study, informed consent or ethical approval were not required under Dutch law.

STATISTICAL ANALYSIS

To compare characteristics and outcome parameters between the different interval groups, χ^2 tests were used. To identify associated factors for pCR and the secondary outcomes, univariable logistic regression analysis was performed. Multivariable logistic regression analysis was used to test the association of interval with the outcomes, adjusted for factors identified with univariable analysis. The median time interval was used as reference. For all multivariable logistic regression models, variables were added to the model if the P-value in univariable analysis was ≤*0.10*. In all other analyses, statistical significance was defined as P≤*0.05*. SPSS® version 24 was used for statistical analysis (IBM, Armonk, New York, USA).

RESULTS

Some 3 091 patients underwent oesophagectomy for cT1N1 or T2-3N0-1 oesophageal or junctional cancer. All patients received and completed nCRT and there were no missing data (Figure 1). The median time interval was 8 [interquartile range (IQR): 7-10] weeks (Figure 2). The median time interval increased from 8 weeks (years 2011-2013) to 9 weeks (years 2014-2016).

PRIMARY OUTCOME

Overall, *906* of *3091* of patients (29%) had a pCR. The pCR rate for adenocarcinoma and squamous cell carcinoma is shown in Figure 3. The percentage of patients with a pCR increased with length of time interval and was 31%, 28%, 26%, 31%, 40%, and 37% for group A to F was respectively (Table 2). This difference across the groups was statistically significant (p<*0.01*). For adenocarcinomas, the interval, cT category and year of resection were associated with pathological response. An interval of 10 or more weeks was independently associated with a higher probability of a pCR (reference group: 8-9 weeks): odds ratios(ORs) for group D, E and F [95% confidence interval (CI)]: 1.35[1.00-1.83], 1.95[1.24-3.07] and 1.64[0.99-2.71] (Table 3).

For squamous cell carcinomas both increased interval and cN category were associated with pathological response. Intervals of 13 or more weeks were independently associated with a higher probability of a pCR (reference group: 8-9 weeks): ORs [95%CI] for group E and F: 2.86[1.23-6.65], 2.67[1.29-5.55] (Table 3).

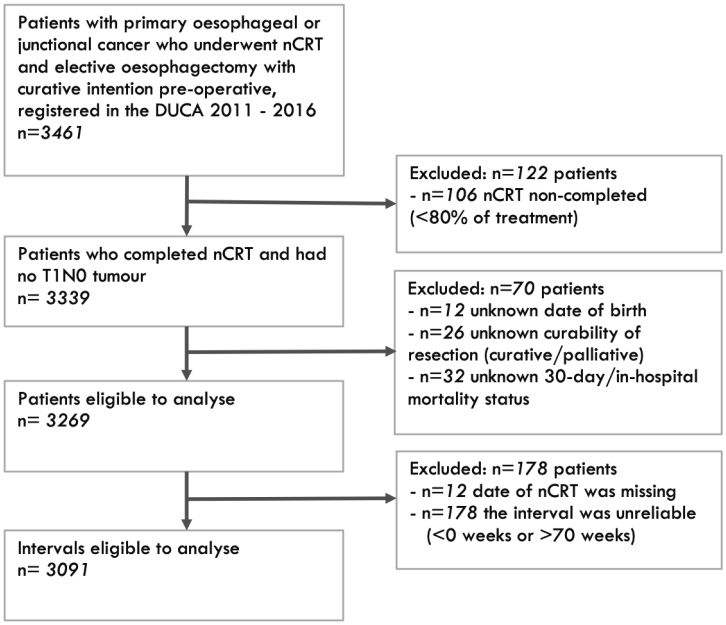

Figure 1. Flowchart included patients

DEMOGRAPHICS AND SURGICAL OUTCOMES

The median age of the study population was 65 [IQR: 59-61] years, and *690* of *3091* patients were female (22%). Patient-, tumour- and treatment characteristics, according to time interval are shown in Table 1.

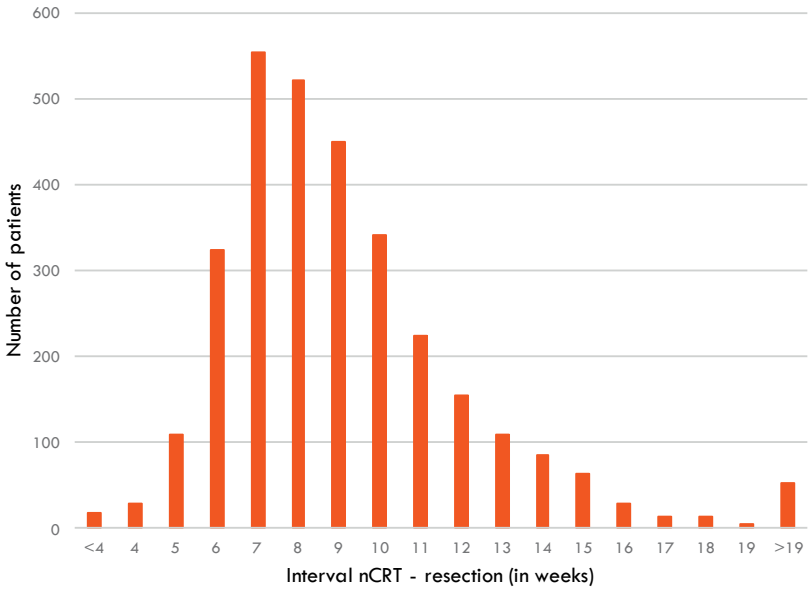

Figure 2. Number of patients treated in different time intervals between neoadjuvant chemo radiotherapy.

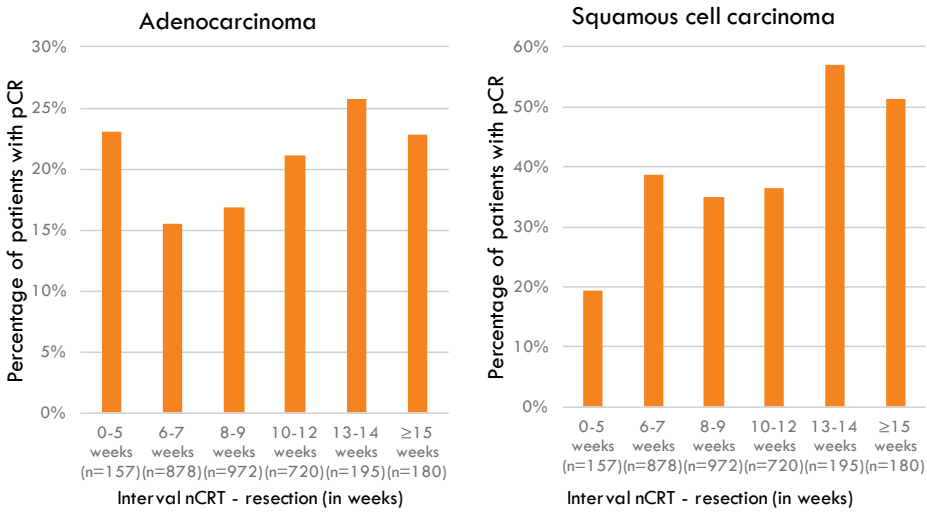

Figure 3a and 3b. Percentage pathological complete response in patients with an adenocarcinoma (a) and a squamous cell carcinoma (b) for the time interval subgroups.

Table 1. Patient, tumour, and treatment characteristics for six groups based on the time interval between the end of neoadjuvant chemo radiotherapy and surgery.

	A		B		C		D		E		F		
Patient characteristics	**0-5 weeks** *n=157*		**6-7 weeks** *n=878*		**8-9 weeks** *n=972*		**10-12 weeks** *n=720*		**13-14 weeks** *n=195*		**≥15 weeks** *n=180*		P value
Age (in years)													0.84
0-64	80	51%	405	46%	428	44%	328	46%	87	45%	75	42%	
65-74	59	38%	364	42%	416	43%	288	40%	83	43%	83	46%	
75+	18	12%	108	12%	126	13%	99	14%	23	12%	21	12%	
Female	31	20%	202	23%	219	23%	153	21%	43	22%	42	23%	0.92
Underweight (BMI<20)	9	6%	61	7%	55	6%	49	7%	15	8%	15	8%	0.69
ASA score													<0.001
ASA I-II	126	80%	707	81%	782	81%	548	77%	142	73%	127	71%	
ASA III+	31	20%	169	19%	184	19%	165	23%	52	27%	53	29%	
Charlson score													0.09
0	91	58%	464	53%	498	51%	342	48%	102	52%	75	42%	
1	37	24%	212	24%	248	26%	186	26%	44	23%	50	28%	
2+	29	19%	202	23%	226	23%	192	27%	49	25%	55	31%	
	A		**B**		**C**		**D**		**E**		**F**		
Tumour characteristics	**0-5 weeks** *n=157*		**6-7 weeks** *n=878*		**8-9 weeks** *n=972*		**10-12 weeks** *n=720*		**13-14 weeks** *n=195*		**≥15 weeks** *n=180*		**P value**
Clinical T category													0.07
cT0-2	42	27%	196	22%	184	19%	143	20%	35	18%	33	18%	
cT3	109	69%	634	72%	722	74%	532	74%	146	75%	127	71%	
cT4	3	2%	19	2%	31	3%	24	3%	9	5%	15	8%	
Unknown	3	2%	29	3%	35	4%	21	3%	5	3%	5	3%	
Clinical N category													0.78
cN0	51	33%	285	33%	318	33%	237	33%	58	30%	54	30%	
cN1	63	40%	371	42%	427	44%	312	43%	80	41%	69	38%	
cN2	34	22%	171	20%	174	18%	131	18%	41	21%	46	26%	
Unknown	9	6%	51	6%	53	6%	40	6%	16	8%	11	6%	
Clinical M category													0.17
cM0	153	98%	860	98%	952	98%	695	97%	190	97%	171	95%	
cM1	1	1%	2	0%	8	1%	4	1%	1	1%	3	2%	
Unknown	3	2%	16	2%	12	1%	21	3%	4	2%	6	3%	
Tumour location													0.04
Proximal-mid oesophagus	22	14%	114	13%	139	14%	101	14%	27	14%	39	22%	
Distal oesophagus	102	65%	618	70%	622	64%	474	66%	131	67%	109	61%	
Gastro-oesophageal junction	33	21%	146	17%	211	22%	145	20%	37	19%	32	18%	
Histologic tumour type													0.29
Adenocarcinoma	104	67%	612	71%	684	70%	498	69%	136	70%	114	63%	
Squamous cell carcinoma	31	20%	155	18%	175	18%	132	18%	28	14%	43	24%	
Other	0	0%	23	3%	21	2%	13	2%	2	1%	3	2%	
Not applicable	17	11%	64	7%	70	7%	59	8%	20	10%	18	10%	
Unknown	3	2%	13	2%	21	2%	16	2%	9	5%	2	1%	

Table 1. Continued

Treatment characteristics	0-5 weeks *n=157*		6-7 weeks *n=878*		8-9 weeks *n=972*		10-12 weeks *n=720*		13-14 weeks *n=195*		≥15 weeks *n=180*		P value
Curability of procedure													n.a.
Curative resection	156	99%	876	100%	972	100%	718	100%	195	100%	180	100%	
Palliative resection (tumour left behind or no resection)	1	1%	1	0%	0	0%	2	0%	0	0%	0	0%	
Surgical approach													<0.001
TTO thoracic part open	38	24%	191	22%	165	17%	72	10%	23	12%	31	17%	
TTO thoracic part MI	42	27%	384	44%	539	56%	488	68%	130	67%	95	53%	
THO open	71	45%	253	29%	174	18%	97	14%	28	14%	34	19%	
THO MI	6	4%	50	6%	90	9%	60	8%	13	7%	19	11%	
Unknown	0	0%	0	0%	4	0%	3	0%	1	1%	1	1%	
Additional resection(s)	3	2%	18	2%	24	3%	15	2%	1	1%	4	2%	0.68

BMI = Body Mass Index, ASA = American Society of Anaesthesiologists, THO = Transhiatal oesophagectomy, TTO = Transthoracic oesophagectomy, MI = Minimally invasive

SECONDARY OUTCOMES

The median number of retrieved lymph nodes was significantly different between the groups; the longer the interval, the higher the number of lymph nodes retrieved (Table 2; p<0.01). In a multivariable logistic regression model, there was no association between the lymph node retrieval and the interval (Table 3). The percentage of patients with an intraoperative complication was not statistically significant different between the groups. The postoperative complication rate was higher for longer intervals: A-F: 52%, 56%, 60%, 62%, 69%, 70%, (p<*0.01*). In a multivariable logistic regression model however, extended intervals were not associated with postoperative complications (reference: 8-9 weeks) (Table 3). The occurrence of severe postoperative complications (defined as postoperative complications that lead to a prolonged hospital stay (>21 days), re-intervention or death) was also not significantly different between the groups (28%, 27%, 28%, 33%, 30% and 34% for respectively group A-F, p=*0.13*). The 30-day/in-hospital mortality was significantly different between the groups (Table 2). In the multivariable analysis, intervals of 10-12 weeks and 15 or more weeks were associated with a significantly higher 30-day/in-hospital mortality (Table 3). The results of all univariable and multivariable analyses are shown in Supplementary Tables 1-6.

Table 2. Outcome characteristics for six groups based on the time interval between the end of neoadjuvant chemo radiotherapy and surgery.

	A		B		C		D		E		F		
Outcome characteristics	**0-5 weeks** *n=157*		**6-7 weeks** *n=878*		**8-9 weeks** *n=972*		**10-12 weeks** *n=720*		**13-14 weeks** *n=195*		**≥15 weeks** *n=180*		**P value**
Pathologic yT stage													0.16
ypT0 (incl. T0N0-2M0)	42	27%	223	25%	213	22%	179	25%	54	28%	53	29%	
ypT1	20	13%	125	14%	155	16%	123	17%	24	12%	34	19%	
ypT2	32	20%	190	22%	207	21%	127	18%	34	17%	32	18%	
ypT3	53	34%	301	34%	357	37%	253	35%	71	36%	56	31%	
ypT4	2	1%	1	0%	8	1%	2	0%	1	1%	1	1%	
Unknown	8	5%	38	4%	32	3%	36	5%	11	6%	4	2%	
Pathologic yN stage													0.3
pN0	90	57%	519	59%	586	60%	444	62%	127	65%	121	67%	
pN1	38	24%	190	22%	199	21%	138	19%	35	18%	39	22%	
pN2	13	8%	95	11%	113	12%	68	9%	18	9%	11	6%	
Unknown	16	10%	74	8%	74	8%	70	10%	15	8%	9	5%	
Pathologic yM stage													0.63
pM0	154	98%	851	97%	943	97%	685	95%	192	99%	174	97%	
pM1	1	1%	9	1%	9	1%	10	1%	0	0%	2	1%	
Unknown	2	1%	18	2%	20	2%	25	4%	3	2%	4	2%	
Pathological response													<0.01
No response	14	9%	56	6%	74	8%	65	9%	16	8%	14	8%	
Complete response	49	31%	244	28%	249	26%	220	31%	77	40%	67	37%	
Partial response	87	55%	526	60%	619	64%	417	58%	95	49%	87	48%	
Unknown	7	5%	52	6%	30	3%	18	3%	7	4%	12	7%	
Resection margins													0.36
Not free of tumour cells	11	7%	29	3%	42	4%	31	4%	8	4%	6	3%	
Free of tumour cells	143	93%	842	97%	922	96%	681	96%	186	96%	174	97%	
Unknown	1	1%	1	0%	3	0%	2	0%	0	0%	0	0%	
Number of LNs													<0.01
Median [IQR]	16 [11-20]		18 [13-23]		18 [13-25]		19 [14-26]		20 [14-29]		20 [14-26]		
≥ 15 LNs	92	59%	599	68%	680	70%	526	73%	143	73%	134	74%	<0.01

	A		B		C		D		E		F		
Outcome characteristics	**0-5 weeks** *n=157*		**6-7 weeks** *n=878*		**8-9 weeks** *n=972*		**10-12 weeks** *n=720*		**13-14 weeks** *n=195*		**≥15 weeks** *n=180*		**P value**
Intraoperative complications	8	5%	48	6%	48	5%	34	5%	8	4%	10	6%	0.97
Postoperative complications (within 30 days)	81	52%	486	56%	582	60%	442	62%	134	69%	126	70%	<0.01
Clavien-Dindo classification complications*													0.34
No complication	6	40%	60	43%	73	38%	74	41%	24	36%	9	20%	
Clavien-Dindo I-II	5	33%	33	23%	65	34%	54	30%	22	33%	17	38%	
Clavien-Dindo III+	4	27%	46	33%	51	26%	48	27%	20	30%	16	36%	
Classification unknown	0	0%	2	1%	4	2%	4	2%	1	2%	3	7%	
Anastomotic leakage/leakage due to necrosis	18	12%	90	10%	92	10%	97	14%	17	9%	27	15%	0.05
Severe complications**	44	28%	241	27%	274	28%	238	33%	59	30%	61	34%	0.13
Mortality (30-day/in-hospital)	5	3%	17	2%	27	3%	35	5%	7	4%	15	8%	<0.01
Length of hospital stay (days)													
Median [IQR]	12 [9-12]		12 [9-18]		12 [9-21]		12 [9-21]		12 [9-18]		15 [10-22.5]		0.16
Length of IC stay (days)													
Median [IQR]	2 [1-4]		2 [1-5]		2 [1-4]		2 [1-4]		1 [1-3]		2 [1-5]		0.98

*LNs = lymph nodes IQR = inter quartal range * Only information of 2016 ** Postoperative complications leading to reintervention, prolonged hospital stay (>21 days) or dead*

Table 3. Multivariable logistic analyses for several outcomes.

Outcomes		**Multivariable analyses n=1982**				
	Interval nCRT - resection (in weeks)	*n*	*OR*	*95% CI*		*P-value*
Pathological Complete Response (pCR) Adenocarcinoma						0.003
Adjusted for: cT category year of resection ^	0-5	97	1.41	0.84	2.37	0.20
	6-7	557	0.90	0.66	1.22	0.50
	8-9	633	ref			
	10-12	466	1.35	1.00	1.83	0.05
	13-14	126	1.95	1.24	3.07	0.004
	15 and more	103	1.64	0.99	2.71	0.05
Pathological Complete Response (pCR) Squamous cell carcinoma						0.006
Adjusted for: cN category ^	0-5	29	0.45	0.17	1.17	0.10
	6-7	143	1.33	0.84	2.11	0.23
	8-9	169	ref			
	10-12	126	1.22	0.75	1.98	0.43
	13-14	27	2.86	1.23	6.65	0.014
	15 and more	38	2.67	1.29	5.55	0.01
Intraoperative complications						1.00
Adjusted for: ASA score, Charlson score, histological type of tumour, surgical approach, year of resection ^	0-5	151	ref			
	6-7	849	0.94	0.42	2.08	0.87
	8-9	934	1.08	0.70	1.66	0.72
	10-12	686	1.00	0.62	1.60	0.99
	13-14	182	0.92	0.42	2.02	0.84
	15 and more	176	1.03	0.50	2.11	0.94
Retrieval of ≥15 LNs						0.93
Adjusted for: age, ASA score, Charlson score, cN category, cT category, location tumour, surgical approach, annual hospital volume, year of resection ^	0-5	154	1.04	0.70	1.55	0.83
	6-7	845	1.07	0.85	1.33	0.58
	8-9	917	ref			
	10-12	677	1.01	0.79	1.29	0.94
	13-14	186	0.96	0.65	1.44	0.85
	15 and more	171	1.23	0.82	1.87	0.32
Postoperative complications						0.05
Adjusted for: age, Charlson score, ASA score, BMI, cN category, histological type of tumour, surgical approach, annual hospital volume ^	0-5	149	0.78	0.54	1.12	0.18
	6-7	839	0.85	0.70	1.04	0.11
	8-9	919	ref			
	10-12	670	0.98	0.79	1.21	0.83
	13-14	180	1.30	0.92	1.84	0.14
	15 and more	172	1.31	0.91	1.87	0.14
Severe postoperative complications*						0.74
Adjusted for: age, Charlson score, ASA score, BMI, histological type of tumour, surgical approach, annual hospital volume	0-5	149	1.32	0.88	1.97	0.18
	6-7	835	1.07	0.87	1.33	0.52
	8-9	919	ref			
	10-12	669	1.12	0.90	1.40	0.32
	13-14	180	0.97	0.68	1.40	0.89
	15 and more	172	1.14	0.80	1.64	0.47
30-day/in-hospital mortality						0.01
Adjusted for: age, Charlson score, ASA score, BMI, cT category, cN category, histological type of tumour	0-5	148	1.42	0.53	3.85	0.49
	6-7	814	0.75	0.39	1.43	0.38
	8-9	900	ref			
	10-12	660	1.87	1.08	3.23	0.03
	13-14	176	1.32	0.55	3.18	0.54
	15 and more	170	2.45	1.20	4.97	0.01

*BMI = Body Mass Index, ASA = American Society of Anaesthesiologists *Postoperative complications leading to reintervention, prolonged hospital stay (>21 days) or dead, ^Based on univariable logistic regression analysis, variables with p≤0.10 are added to the multivariable logistic regression model*

DISCUSSION

This study shows that an interval of ≥10 weeks (adenocarcinoma) and ≥13 weeks (squamous cell carcinoma) is associated with a higher probability of pCR. The percentage of a retrieval of more than 15 lymph nodes, intraoperative and postoperative complications is comparable between the intervals. However, an interval of 10-12 and 15 or more weeks is associated with a higher 30-day/in-hospital mortality.

Some studies also observed a trend towards a higher pCR in patients with longer time intervals[5,12,20-23], while other studies did not find such an association.[10,24] Most studies used a modelled dichotomous variable for interval and used 6-8 weeks as a cut-off point. Because of the rather small sample size in most studies, the interval beyond 10 weeks was not divided into subgroups. Haisley et al. [9] included six time intervals (0-42, 43-56, 57-70, 71-84, 85-98, and 99 or more days). They showed an increased probability of pCR for the group 85-98 days compared with other groups (OR: 5.46 [95% CI: 1.16-25.68]). These results are in line with the results of the present study.

Previous studies also reported conflicting results on complications for the extended interval groups: some showed higher complication rates [12], but other did not.[9,10,21] The higher 30-day/in-hospital mortality rates for patients operated after 10-12 and 15 or more weeks in the present study have not been reported before. The observed higher complication rate and 30-day/in-hospital mortality may be due to selection bias, since more frail patients (higher ASA score and Charlson comorbidity score of 2 or higher) were represented in the extended interval groups. This may reflect that logistic reasons (patient planning) played a role but the delay of the resection may also be due to the time taken to recover from the toxicity of nCRT before undergoing surgery. Despite a longer recovery period after nCRT these patients are still at higher risk for postoperative mortality. In a single-centre Dutch study, an increased risk for postoperative complications in patients treated with extended intervals was reported (OR: 1.20 per additional week). However, after adjustment for potential delay-related confounders and surgical approach this effect was reduced (OR 1.10 per

additional week) and became statistically nonsignificant. Covariates in the multivariate model were Charlson comorbidity index at diagnosis, Karnofsky performance score during the last week of nCRT, and weight loss during nCRT.[12] In our study, we adjusted only for Charlson comorbidity score at diagnosis. When adjusting for the available factors, there was no association of the extended intervals with postoperative complications. However, the association of the extended intervals with 30-day/in-hospital mortality was still present. We assume that there was residual confounding because of missing potential delay-related factors like performance score in the last week of nCRT and weight loss during nCRT. Besides more frail patients in the extended interval group (>15 weeks), there were also more patients with a proximal or mid-oesophageal tumour. Theoretically, these patients may have been enrolled in a wait-and-see strategy with definitive CRT (50 Gray, versus 41.4 Gray as used in the nCRT regimen) to avoid a resection. However, when these patients eventually undergo (salvage) oesophagectomy there may be an increased risk for complications and mortality. Unfortunately, because the CRT dose was not registered in the audit, it was not possible to distinguish between patients treated with definitive CRT and 'salvage' resections, and patients treated with extended intervals after nCRT. When there is indeed residual confounding in the patient- and treatment characteristics as mentioned, we might underestimate the potential benefit of longer waiting time.

Our study has an important strength. Because of the large patient cohort, it was possible to compare small interval groups and to adjust for potential delay related factors. The national and prospective set-up of the audit reduced selection bias and the national pathological guidelines led to uniform registration of pCR.

A limitation is however that we are not informed on the exact reason why surgery was delayed. Furthermore, the exact details of nCRT are not registered in the database (to distinguish between definitive CRT from nCRT). From 2018 onwards, details on the type of nCRT will be registered in the audit. Lastly, previous studies showed a comparable survival for different intervals. This might be due to the small sample size of these studies. Unfortunately, because mortality beyond 30 days/after hospital discharge is not registered in the DUCA,

more accurate analysis of survival of the extended interval groups was not possible in this study.

In conclusion, this study showed that an interval of more than 12 weeks between end of neoadjuvant chemoradiotherapy and oesophagectomy for cancer is associated with higher pathological complete response rate, but not with increased intraoperative and postoperative complications. Higher 30-day/in-hospital mortality was observed for intervals of 10-12 and 15 or more weeks but this might be due to selection bias.

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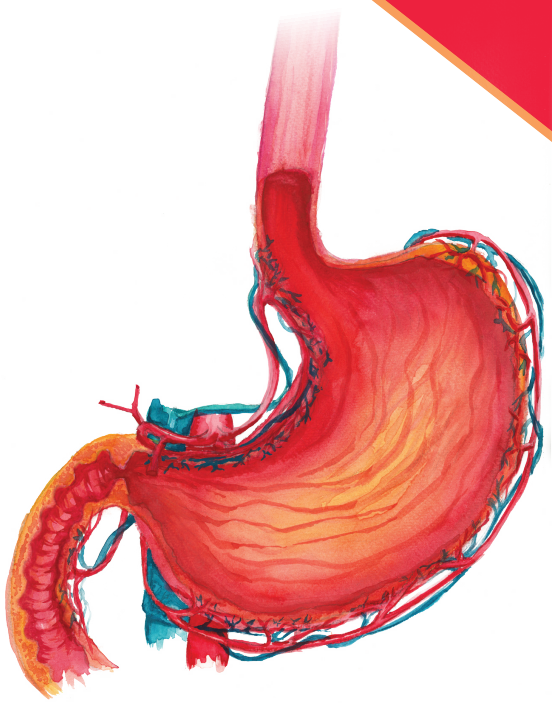


CHAPTER 4

Supplementary data

Supplementary table 1. Univariable and multivariable logistic regression analysis on factors associated with pathological complete response, stratified for adenocarcinoma and squamous cell carcinoma

Pathological Complete Response (pCR) Adenocarcinoma	**Univariable analysis Total Study population n=2139**					**Multivariable analysis n=1982**				
Variables	*n*	*OR*	*95% CI*		*P-value*	*n*	*OR*	*95% CI*		*P-value*
Interval nCRT - resection (in weeks)					0.03					0.003
0-5	99	1.51	0.92	2.50	0.11	97	1.41	0.84	2.37	0.20
6-7	574	0.94	0.70	1.26	0.67	557	0.90	0.66	1.22	0.50
8-9	658	ref				633	ref			
10-12	481	1.27	0.94	1.71	0.11	466	1.35	1.00	1.83	0.05
13-14	128	1.71	1.10	2.65	0.02	126	1.95	1.24	3.07	0.004
15 and more	106	1.46	0.89	2.38	0.13	103	1.64	0.99	2.71	0.05
Gender					1.00					
Male	1718	ref								
Female	327	1.00	0.74	1.35						
Age (in years)					0.40					
0-64	932	ref								
65-74	842	1.18	0.93	1.49	0.18					
75+	272	1.07	0.76	1.51	0.71					
Clinical T category					0.10					0.08
cT0-2	397	ref				397	ref			
cT3	1531	1.05	0.79	1.38	0.75	1531	1.04	0.78	1.38	0.79
cT4	54	0.34	0.12	0.96	0.04	54	0.32	0.11	0.91	0.03
Clinical N category					0.78					
cN0	668	ref								
cN1	862	0.93	0.72	1.20	0.55					
cN2	402	1.06	0.78	1.44	0.73					
Unknown	114	0.86	0.51	1.45	0.58					
Clinical M category					0.23					
cM0	2003	ref								
cM1	12	2.10	0.63	6.99						
Tumour location					0.24					
Proximal-mid oesophagus	88	ref								
Distal oesophagus	1469	1.11	0.63	1.97	0.72					
Gastro-oesophageal junction	489	1.36	0.75	2.47	0.31					
Charlson score					0.98					
0	1054	ref								
1	528	1.00	0.77	1.30	0.99					
2	276	1.07	0.77	1.50	0.67					
3+	188	1.00	0.67	1.48	1.00					
ASA score					0.69					
I/II	1628	ref								
III+	407	0.95	0.72	1.25						
BMI					0.62					
<20	72	ref								
20-24	725	0.87	0.46	1.67	0.68					
25-29	858	1.14	0.89	1.47	0.29					
>30	366	1.00	0.72	1.38	0.99					
Year of resection					0.02					0.003
2011	222	ref				219	ref			
2012	261	1.19	0.75	1.87	0.46	253	1.23	0.78	1.96	0.37
2013	317	1.41	0.92	2.17	0.12	306	1.43	0.93	2.21	0.11
2014	387	1.20	0.79	1.84	0.39	372	1.15	0.75	1.77	0.52
2015	441	1.13	0.75	1.72	0.55	425	1.06	0.69	1.62	0.79
2016	418	0.72	0.46	1.12	0.14	407	0.64	0.41	1.01	0.06

Pathological Complete Response (pCR) Squamous Cell Carcinoma	**Univariable analysis Total Study population n= 562**					**Multivariable analysis n= 532**				
Variables	*n*	*OR*	*95% CI*		*P-value*	*n*	*OR*	*95% CI*		*P-value*
Interval nCRT - resection (in weeks)					0.01					0.006
0-5	29	0.46	0.18	1.20	0.11	29	0.45	0.17	1.17	0.10
6-7	143	1.28	0.81	2.02	0.29	143	1.33	0.84	2.11	0.23
8-9	169	ref				169	ref			
10-12	126	1.09	0.68	1.76	0.73	126	1.22	0.75	1.98	0.43
13-14	27	2.58	1.12	5.90	0.03	27	2.86	1.23	6.65	0.014
15 and more	38	2.43	1.19	4.98	0.02	38	2.67	1.29	5.55	0.01
Gender					0.28					
Male	285									
Female	247	1.21	0.86	1.72						
Age (in years)					0.26					
0-64	228	ref								
65-74	237	0.83	0.57	1.20	0.31					
75+	67	0.64	0.36	1.13	0.12					
Charlson score					0.88					
0	243	ref								
1	121	1.20	0.77	1.86	0.43					
2	106	1.08	0.68	1.72	0.74					
3+	62	1.00	0.57	1.78	1.00					
ASA score					0.72					
I/II	389	ref								
III+	139	0.93	0.63	1.38						
BMI					0.21					
<20	89	1.33	0.81	2.17	0.26					
20-24	250	ref								
25-29	149	1.53	1.02	2.32	0.04					
>30	40	1.07	0.54	2.13	0.86					
Clinical T category					0.10					
cT0-2	106	ref								
cT3	366	0.66	0.42	1.01	0.06					
cT4	38	1.01	0.48	2.12	0.98					
Clinical N category					0.01					0.004
cN0	163	ref				163	ref			
cN1	228	0.51	0.34	0.77	0.001	228	0.49	0.32	0.74	0.001
cN2	106	0.56	0.34	0.93	0.02	106	0.50	0.30	0.83	0.01
Unknown	35	0.50	0.24	1.08	0.08	35	0.45	0.21	0.98	0.04
Clinical M category					n.a.					
cM0	517									
cM1	3									
Tumour location					0.14					
Proximal-mid oesophagus	261	ref								
Distal oesophagus	240	0.98	0.69	1.40	0.90					
Gastro-oesophageal junction	31	0.41	0.17	0.99	0.05					
Year of resection					0.55					
2011	53	ref								
2012	72	0.83	0.39	1.73	0.61					
2013	81	0.97	0.48	1.99	0.94					
2014	91	1.03	0.51	2.07	0.93					
2015	130	1.41	0.74	2.72	0.30					
2016	105	1.19	0.61	2.34	0.61					

BMI = Body Mass Index, ASA = American Society of Anaesthesiologists, THO = Transhiatal oesophagectomy, THO = Transthoracic oesophagectomy, MI = Minimally invasive, nCRT = neoadjuvant Chemo radio Therapy

Supplementary table 2. Univariable and multivariable logistic regression analysis on factors associated with intraoperative complications

Intraoperative complications	**Univariable analysis Total Study population n=3091**					**Multivariable analysis n=2978**				
Variables	*n*	*OR*	*95% CI*		*P-value*	*n*	*OR*	*95% CI*		*P-value*
Interval nCRT - resection (in weeks)					0.96					1.00
0-5	156	1.03	0.48	2.23	0.93	151	ref			
6-7	875	1.11	0.74	1.67	0.62	849	0.94	0.42	2.08	0.87
8-9	966	ref				934	1.08	0.70	1.66	0.72
10-12	714	0.93	0.59	1.46	0.74	686	1.00	0.62	1.60	0.99
13-14	193	0.83	0.39	1.78	0.63	182	0.92	0.42	2.02	0.84
15 and more	179	1.13	0.56	2.28	0.73	176	1.03	0.50	2.11	0.94
Gender					0.62					
Male	2396	ref								
Female	686	1.10	0.75	1.61						
Age (in years)					1.00					
0-64	1397	ref								
65-74	1292	1.00	0.71	1.42	0.98					
75+	394	1.01	0.61	1.69	0.96					
Charlson score					0.02					0.09
0	1562	ref				1502	ref			
1	773	1.15	0.77	1.72	0.50	755	1.03	0.68	1.58	0.88
2	451	1.06	0.64	1.74	0.83	437	0.91	0.54	1.53	0.71
3+	297	2.08	1.30	3.32	0.002	284	1.80	1.08	3.00	0.02
ASA score					0.002					
I/II	2416	ref				2343	ref			
III+	651	1.75	1.23	2.49	0.15	635	1.56	1.06	2.30	
BMI										
<20	204	1.91	1.08	3.36	0.03					
20-24	1164	ref								
25-29	1199	1.10	0.76	1.61	0.61					
>30	482	1.00	0.60	1.67	0.99					
Clinical T category					0.27					
cT0-2	629	ref								
cT3	2256	1.21	0.79	1.84	0.38					
cT4	101	0.43	0.10	1.85	0.26					
Clinical N category					0.23					
cN0	999	ref								
cN1	1314	1.02	0.69	1.50	0.92					
cN2	593	1.43	0.92	2.21	0.11					
Unknown	177	0.71	0.30	1.69	0.44					
Clinical M category					0.93					
cM0	3002	ref								
cM1	19	1.10	0.15	8.32						
Tumour location					0.26					
Proximal-mid oesophagus	439	ref								
Distal oesophagus	2043	0.71	0.46	1.09	0.12					
Gastro-oesophageal junction	601	0.69	0.41	1.18	0.18					
Histological type					0.002					0.01
Adenocarcinoma	2134	ref				2116	ref			
Squamous cell carcinoma	559	2.01	1.39	2.91	<0.001	555	1.91	1.30	2.80	0.001
Other	62	1.55	0.55	4.36	0.41	61	1.69	0.59	4.82	0.33
Not applicable	248	0.94	0.48	1.84	0.86	246	1.02	0.51	2.00	0.97

Supplementary table 2. Continued

Intraoperative complications	Univariable analysis Total Study population n=3091					Multivariable analysis n=2978				
Variables	*n*	*OR*	*95% CI*		*P-value*	*n*	*OR*	*95% CI*		*P-value*
Surgical approach					0.01					0.13
TTO thoracic part open	515	ref				504	ref			
TTO thoracic part MI	1669	0.54	0.36	0.81	0.003	1617	0.66	0.42	1.03	0.07
THO open	654	0.73	0.46	1.17	0.19	625	0.89	0.55	1.47	0.66
THO MI	236	0.43	0.20	0.93	0.03	232	0.48	0.21	1.06	0.07
Location of anastomosis					0.95					
Neck	1957	ref								
Intrathoracic	1091	0.99	0.70	1.40						
Annual hospital volume					0.36					
0-25	390	ref								
26-50	1767	1.45	0.83	2.53	0.19					
50+	908	1.24	0.68	2.27	0.48					
Year of resection					0.09					0.19
2011	343	ref				330	ref			
2012	438	0.65	0.36	1.16	0.14	420	0.66	0.36	1.21	0.18
2013	456	0.65	0.36	1.16	0.14	432	0.65	0.35	1.20	0.17
2014	545	0.37	0.20	0.70	0.002	540	0.42	0.22	0.82	0.01
2015	660	0.70	0.42	1.19	0.19	634	0.78	0.44	1.37	0.38
2016	641	0.64	0.38	1.09	0.10	622	0.76	0.43	1.37	0.36

BMI = Body Mass Index, ASA = American Society of Anaesthesiologists, THO = Transhiatal oesophagectomy, TTO = Transthoracic oesophagectomy, MI = Minimally invasive, nCRT = neoadjuvant Chemo radio Therapy

Supplementary table 3. Univariable and multivariable logistic regression analysis on factors associated with postoperative complications

Postoperative complications	Univariable analysis Total Study population n=3091					Multivariable analysis n=2929				
Variables	*n*	*OR*	*95% CI*		*P-value*	*n*	*OR*	*95% CI*		*P-value*
Interval nCRT - resection (in weeks)					<0.001					0.05
0-5	155	0.73	0.52	1.03	0.08	149	0.78	0.54	1.12	0.18
6-7	874	0.84	0.70	1.01	0.07	839	0.85	0.70	1.04	0.11
8-9	969	ref				919	ref			
10-12	714	1.06	0.87	1.30	0.54	670	0.98	0.79	1.21	0.83
13-14	193	1.49	1.07	2.07	0.02	180	1.30	0.92	1.84	0.14
15 and more	179	1.55	1.10	2.19	0.01	172	1.31	0.91	1.87	0.14
Gender					0.25					
Male	2397	ref								
Female	686	1.11	0.93	1.32						
Age (in years)					<0.001					0.001
0-64	1400	ref				1328	ref			
65-74	1290	1.30	1.12	1.52	0.001	1229	1.27	1.08	1.50	0.01
75+	394	1.58	1.25	1.99	<0.001	372	1.55	1.20	2.01	0.001
Charlson score					<0.001					<0.001
0	1560	ref				1470	ref			
1	774	1.14	0.96	1.35	0.15	744	0.99	0.82	1.19	0.88
2	453	1.54	1.24	1.92	<0.001	434	1.34	1.06	1.70	0.02
3+	297	2.19	1.66	2.88	<0.001	281	1.72	1.27	2.32	<0.001

Supplementary table 3. Continued

Postoperative complications	Univariable analysis Total Study population n=3091					Multivariable analysis n=2929				
Variables	*n*	*OR*	*95%CI*		*P-value*	*n*	*OR*	*95%CI*		*P-value*
ASA score					<0.001					<0.001
I/II	2416	ref					ref			
III+	652	1.90	1.57	2.29			1.61	1.31	1.98	
BMI					0.001					0.003
<20	203	1.52	1.12	2.08	0.01	195	1.43	1.03	2.00	0.04
20-24	1166	ref				1117	ref			
25-29	1200	1.35	1.15	1.59	<0.001	1154	1.37	1.15	1.63	<0.001
>30	481	1.25	1.01	1.55	0.04	463	1.19	0.95	1.50	0.14
Clinical T category					0.47					
cT0-2	630	ref								
cT3	2255	1.03	0.86	1.24	0.72					
cT4	101	1.32	0.85	2.04	0.22					
Clinical N category					0.04					0.04
cN0	999	ref				940	ref			
cN1	1315	0.86	0.73	1.01	0.07	1245	0.90	0.75	1.07	0.22
cN2	592	1.12	0.91	1.38	0.31	575	1.21	0.97	1.51	0.09
Unknown	178	1.07	0.77	1.49	0.69	169	1.02	0.72	1.45	0.90
Clinical M category					0.53					
cM0	3003	ref								
cM1	19	0.75	0.30	1.85						
Tumour location					0.001					0.04
Proximal-mid oesophagus	440	ref				425	ref			
Distal oesophagus	2047	0.76	0.62	0.95	0.01	1934	0.79	0.61	1.03	0.08
Gastro-oesophageal junction	597	0.62	0.48	0.80	<0.001	570	0.67	0.49	0.91	0.01
Histological type					0.05					0.74
Adenocarcinoma	2134	ref				2078	ref			
Squamous cell carcinoma	562	1.31	1.08	1.59	0.01	552	1.07	0.85	1.36	0.56
Other	61	0.95	0.57	1.58	0.83	59	0.95	0.55	1.62	0.84
Not applicable	248	0.99	0.76	1.29	0.94	240	0.89	0.67	1.18	0.42
Surgical approach					<0.001					0.003
TTO thoracic part open	520	ref				505	ref			
TTO thoracic part MI	1668	0.89	0.73	1.10	0.28	1598	0.90	0.72	1.13	0.38
THO open	649	0.59	0.46	0.75	<0.001	603	0.64	0.49	0.83	0.001
THO MI	238	0.92	0.67	1.27	0.62	223	0.87	0.61	1.24	0.45
Location of anastomosis					0.09					
Neck	1953									
Intrathoracic	1090	0.88	0.76	1.02						
Annual hospital volume					<0.001					0.001
0-25	390	ref				363	ref			
26-50	1767	1.03	0.83	1.30	0.78	1712	0.93	0.72	1.19	0.55
50+	909	0.74	0.58	0.94	0.01	854	0.68	0.52	0.89	0.01
Year of resection					0.27					
2011	342	ref								
2012	436	1.25	0.94	1.67	0.13					
2013	461	1.15	0.87	1.53	0.32					
2014	546	1.30	0.99	1.71	0.06					
2015	658	1.32	1.01	1.72	0.04					
2016	641	1.35	1.03	1.76	0.03					

BMI = Body Mass Index, ASA = American Society of Anaesthesiologists, THO = Transhiatal oesophagectomy, TTO = Transthoracic oesophagectomy, MI = Minimally invasive, nCRT = neoadjuvant Chemo radio Therapy

Supplementary table 4. Univariable and multivariable logistic regression analysis on factors associated with severe postoperative complications*

Severe postoperative complications*	Univariable analysis Total Study population n=3091					Multivariable analysis n=2924				
Variables	*n*	*OR*	*95% CI*		*P-value*	*n*	*OR*	*95% CI*		*P-value*
Interval nCRT - resection (in weeks)					0.12					0.74
0-5	155	1.01	0.69	1.47	0.96	149	1.32	0.88	1.97	0.18
6-7	870	0.98	0.80	1.20	0.81	835	1.07	0.87	1.33	0.52
8-9	968	ref				919	ref			
10-12	713	1.28	1.04	1.57	0.02	669	1.12	0.90	1.40	0.32
13-14	193	1.09	0.78	1.53	0.60	180	0.97	0.68	1.40	0.89
15 and more	179	1.28	0.91	1.80	0.15	172	1.14	0.80	1.64	0.47
Gender					0.34					
Male	2393	ref								
Female	684	1.09	0.91	1.32						
Age (in years)					0.01					0.02
0-64	1396	ref				1324	ref			
65-74	1290	1.14	0.97	1.35	0.12	1230	1.14	0.95	1.36	0.17
75+	392	1.43	1.12	1.81	0.003	370	1.45	1.12	1.88	0.01
Charlson score					<0.001					0.003
0	1559	ref				1469	ref			
1	773	1.13	0.94	1.37	0.21	744	1.01	0.82	1.25	0.91
2	451	1.33	1.06	1.67	0.01	432	1.18	0.93	1.51	0.18
3+	295	2.08	1.61	2.69	<0.001	279	1.68	1.26	2.23	<0.001
ASA score					<0.001					<0.001
I/II	2411	ref				2304	ref			
III+	651	2.10	1.76	2.52		620	1.98	1.62	2.43	
BMI					0.06					0.09
<20	203	1.49	1.09	2.04	0.01	195	1.41	1.01	1.97	0.05
20-24	1167	ref				1118	ref			
25-29	1196	1.11	0.93	1.33	0.23	1151	1.15	0.95	1.38	0.15
>30	478	0.99	0.78	1.26	0.95	460	0.95	0.74	1.22	0.68
Clinical T category					0.28					
cT0-2	627	ref								
cT3	2253	1.03	0.85	1.25	0.75					
cT4	101	1.43	0.92	2.21	0.12					
Clinical N category					0.46					
cN0	996	ref								
cN1	1312	0.99	0.83	1.19	0.91					
cN2	593	1.01	0.81	1.27	0.91					
Unknown	177	1.29	0.92	1.81	0.14					
Clinical M category					0.20					
cM0	2997	ref								
cM1	19	0.44	0.13	1.53						
Tumour location					0.002					0.18
Proximal-mid oesophagus	437	ref				423	ref			
Distal oesophagus	2044	0.69	0.56	0.86	0.001	1931	0.80	0.61	1.04	0.10
Gastro-oesophageal junction	597	0.66	0.50	0.85	0.002	570	0.89	0.64	1.23	0.48
Histological type					0.005					0.43
Adenocarcinoma	2131	ref				2075	ref			
Squamous cell carcinoma	560	1.42	1.17	1.73	<0.001	551	1.12	0.88	1.43	0.373
Other	61	1.23	0.71	2.11	0.46	59	1.20	0.68	2.13	0.52
Not applicable	247	1.00	0.74	1.33	0.97	239	0.85	0.62	1.16	0.30
Surgical approach					<0.001					<0.001
TTO thoracic part open	517	ref				502	ref			
TTO thoracic part MI	1664	1.07	0.87	1.32	0.53	1595	1.11	0.88	1.40	0.38
THO open	650	0.48	0.37	0.63	<0.001	604	0.46	0.34	0.62	<0.001
THO MI	238	0.79	0.57	1.12	0.18	223	0.68	0.47	0.98	0.04

Supplementary table 4. Continued

Severe postoperative complications*	Univariable analysis Total Study population n=3091					Multivariable analysis n=2924				
Variables	*n*	*OR*	*95% CI*		*P-value*	*n*	*OR*	*95% CI*		*P-value*
Location of anastomosis					0.19					
Neck	1949	ref								
Intrathoracic	1088	1.11	0.95	1.31						
Annual hospital volume					0.01					0.24
0-25	390	ref				363	ref			
26-50	1765	1.31	1.03	1.68	0.03	1710	1.05	0.80	1.38	0.74
50+	906	1.05	0.80	1.38	0.71	851	0.89	0.66	1.20	0.44
Year of resection					0.46					
2011	340	ref								
2012	434	0.96	0.70	1.31	0.80					
2013	460	0.88	0.64	1.20	0.41					
2014	545	1.16	0.87	1.56	0.311					
2015	658	1.00	0.75	1.34	0.98					
2016	641	1.05	0.79	1.40	0.74					

BMI = Body Mass Index, ASA = American Society of Anaesthesiologists, THO = Transhiatal oesophagectomy, TTO = Transthoracic oesophagectomy, MI = Minimally invasive, nCRT = neoadjuvant Chemo radio Therapy
**Postoperative complications leading to reintervention, prolonged hospital stay (>21 days) or dead*

Supplementary table 5. Univariable and multivariable logistic regression analysis on factors associated with 30-day and in-hospital mortality

30-day and in-hospital mortality	Univariable analysis Total Study population n=3091					Multivariable analysis n=2868				
Variables	*n*	*OR*	*95% CI*		*P-value*	*n*	*OR*	*95% CI*		*P-value*
Interval nCRT - resection (in weeks)					<0.001					0.01
0-5	157	1.15	0.44	3.03	0.78	148	1.42	0.53	3.85	0.49
6-7	877	0.69	0.37	1.28	0.24	814	0.75	0.39	1.43	0.38
8-9	970	ref				900	ref			
10-12	715	1.80	1.08	3.00	0.03	660	1.87	1.08	3.23	0.03
13-14	193	1.31	0.56	3.06	0.53	176	1.32	0.55	3.18	0.54
15 and more	179	3.19	1.66	6.14	<0.001	170	2.45	1.20	4.97	0.01
Gender					0.30					
Male	2402	ref								
Female	688	1.26	0.81	1.96						
Age (in years)					0.01					0.01
0-64	1403	ref				1303	ref			
65-74	1293	2.01	1.30	3.12	0.002	1207	2.07	1.29	3.34	0.00
75+	395	1.81	0.98	3.33	0.06	358	1.65	0.83	3.27	0.15
Charlson score					<0.001					0.16
0	1565	ref				1449				
1	775	1.32	0.80	2.19	0.27	721	0.83	0.48	1.44	0.50
2	454	1.48	0.83	2.64	0.18	426	0.99	0.53	1.83	0.96
3+	297	3.20	1.89	5.43	<0.001	272	1.70	0.92	3.14	0.09
ASA score					<0.001					<0.001
I/II	2422	ref				2280	ref			
III+	653	2.96	1.99	4.41		588	2.61	1.65	4.12	

Supplementary table 5. Continued

30-day and in-hospital mortality	Univariable analysis Total Study population n=3091					Multivariable analysis n=2868				
Variables	*n*	*OR*	*95% CI*		*P-value*	*n*	*OR*	*95% CI*		*P-value*
BMI					0.01					0.06
<20	204	2.43	1.31	4.51	0.01	189	2.16	1.07	4.36	0.03
20-24	1168	ref				1091	ref			
25-29	1202	1.13	0.73	1.77	0.58	1136	1.16	0.72	1.87	0.53
>30	483	0.71	0.36	1.41	0.33	452	0.65	0.31	1.36	0.25
Clinical T category					0.01					0.11
cT0-2	631	ref				601	ref			
cT3	2261	1.03	0.63	1.71	0.90	2167	0.88	0.52	1.50	0.64
cT4	101	2.99	1.32	6.76	0.01	100	2.02	0.83	4.91	0.12
Clinical N category					0.06					0.10
cN0	1001	ref				915	ref			
cN1	1317	1.16	0.71	1.90	0.56	1242	1.21	0.71	2.04	0.49
cN2	594	1.79	1.04	3.06	0.04	568	1.93	1.07	3.49	0.03
Unknown	179	2.14	1.02	4.49	0.05	143	2.03	0.86	4.80	0.11
Clinical M category					0.67					
cM0	3010	ref								
cM1	19	1.55	0.21	11.74						
Tumour location					0.07					0.50
Proximal-mid oesophagus	441	ref				410	ref			
Distal oesophagus	2048	0.67	0.41	1.10	0.12	1894	0.79	0.42	1.46	0.44
Gastro-oesophageal junction	602	0.45	0.23	0.90	0.02	564	0.62	0.28	1.38	0.24
Histological type					0.04					0.37
Adenocarcinoma	2139	ref				2037				
Squamous cell carcinoma	562	1.82	1.16	2.86	0.01	531	1.06	0.58	1.91	0.86
Other	62	2.31	0.81	6.56	0.12	61	2.67	0.90	7.90	0.08
Not applicable	248	1.26	0.62	2.57	0.52	239	1.01	0.46	2.21	0.99
Surgical approach					0.15					
TTO thoracic part open	520	ref								
TTO thoracic part MI	1670	0.87	0.53	1.43	0.59					
THO open	654	0.64	0.34	1.21	0.17					
THO MI	238	0.29	0.09	0.98	0.05					
Location of anastomosis					0.25					
Neck	1959	ref								
Intrathoracic	1091	0.78	0.51	1.19						
Annual hospital volume					0.69					
0-25	391	ref								
26-50	1773	0.89	0.49	1.62	0.71					
50+	909	1.08	0.57	2.03	0.82					
Year of resection					0.12					
2011	343	ref								
2012	439	1.79	0.77	4.17	0.18					
2013	462	1.80	0.78	4.15	0.17					
2014	546	1.26	0.54	2.99	0.59					
2015	660	2.06	0.94	4.54	0.07					
2016	641	0.94	0.39	2.25	0.88					

BMI = Body Mass Index, ASA = American Society of Anaesthesiologists, THO = Transhiatal oesophagectomy, TTO = Transthoracic oesophagectomy, MI = Minimally invasive, nCRT = neoadjuvant Chemo radio Therapy

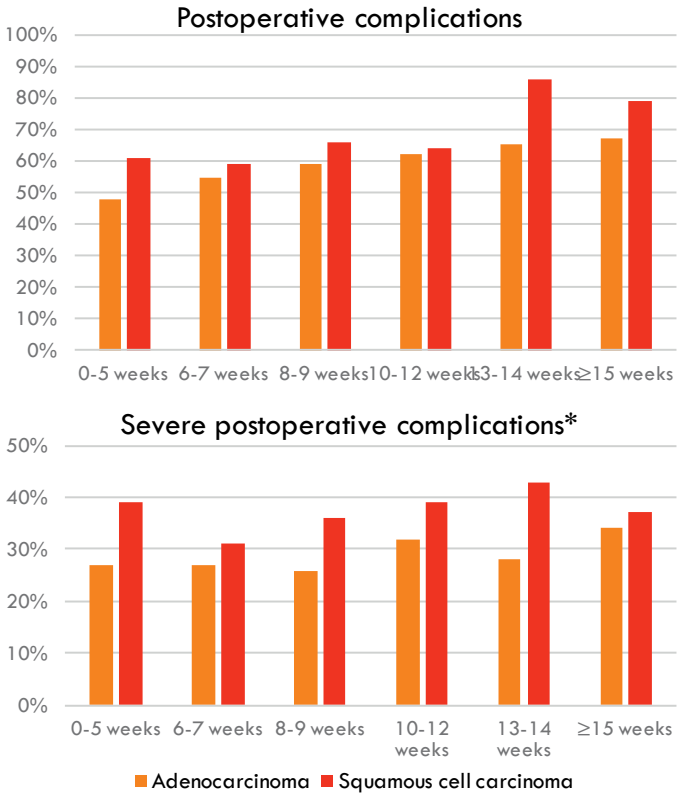
Supplementary table 6. Univariable and multivariable logistic regression analysis on factors associated with retrieval of ≥15 LNs

Retrieval of ≥15 LNs	Univariable analysis Total Study population n=3091					Multivariable analysis n=2950				
Variables	*n*	*OR*	*95% CI*		*P-value*	*n*	*OR*	*95% CI*		*P-value*
Interval nCRT - resection (in weeks)					0.01					0.93
0-5	157	0.61	0.43	0.86	0.01	154	1.04	0.70	1.55	0.83
6-7	877	0.92	0.75	1.12	0.40	845	1.07	0.85	1.33	0.58
8-9	970	ref				917	ref			
10-12	715	1.17	0.94	1.45	0.16	677	1.01	0.79	1.29	0.94
13-14	193	1.19	0.84	1.69	0.32	186	0.96	0.65	1.44	0.85
15 and more	179	1.24	0.86	1.78	0.25	171	1.23	0.82	1.87	0.32
Gender					0.47					
Male	2402	ref								
Female	688	1.07	0.89	1.29						
Age (in years)					<0.001					0.29
0-64	1403	ref				1344	ref			
65-74	1293	0.96	0.81	1.13	0.59	1234	1.01	0.84	1.22	0.91
75+	395	0.65	0.52	0.82	<0.001	372	0.82	0.62	1.08	0.15
Charlson score					0.06					0.24
0	1565	ref				1493	ref			
1	775	0.95	0.78	1.15	0.58	739	1.01	0.81	1.26	0.94
2+	751	0.80	0.66	0.96	0.02	718	0.84	0.67	1.05	0.12
ASA score					0.002					0.32
I/II	2416	ref				2335	ref			
III+	651	1.75	1.23	2.49		615	0.89	0.72	1.12	
BMI					0.75					
<20	204	ref								
20-24	1168	0.99	0.72	1.38	0.97					
25-29	1202	1.01	0.73	1.39	0.97					
>30	483	0.89	0.62	1.27	0.52					
Clinical T category					0.05					0.52
cT0-2	631	ref				619	ref			
cT3	2261	1.25	1.03	1.50	0.02	2231	1.14	0.91	1.41	0.25
cT4	101	1.45	0.90	2.33	0.13	100	1.12	0.65	1.91	0.68
Clinical N category					0.01					0.62
cN0	1001	ref				950	ref			
cN1	1317	1.20	1.00	1.43	0.05	1275	1.10	0.89	1.35	0.37
cN2	594	1.40	1.12	1.75	<0.001	579	1.18	0.91	1.53	0.22
Unknown	179	0.87	0.63	1.22	0.42	146	1.17	0.76	1.79	0.48
Clinical M category					0.86					
cM0	3010	ref								
cM1	19	0.92	0.35	2.42						
Tumour location					<0.001					0.82
Proximal-mid oesophagus	441	ref				421	ref			
Distal oesophagus	2048	0.67	0.53	0.85	<0.001	1956	0.96	0.72	1.26	0.74
Gastro-oesophageal junction	602	0.55	0.42	0.73	<0.001	573	1.02	0.74	1.42	0.90
Histological type					0.26					
Adenocarcinoma	2139	ref								
Squamous cell carcinoma	562	1.26	1.02	1.56	0.03					
Other	62	0.93	0.54	1.60	0.789					
Not applicable	248	1.00	0.75	1.33	0.99					
Unknown	64	1.22	0.70	2.15	0.48					
Surgical approach					<0.001					<0.001
TTO thoracic part open	520	ref				503	ref			
TTO thoracic part MI	1670	1.69	1.34	2.13	<0.001	1611	1.21	0.93	1.57	0.16
THO open	654	0.29	0.22	0.37	<0.001	623	0.27	0.20	0.36	<0.001
THO MI	238	0.43	0.31	0.59	<0.001	213	0.40	0.28	0.58	<0.001
Annual hospital volume					<0.001					<0.001
0-25	391	ref				362	ref			
26-50	1773	2.97	2.38	3.72	<0.001	1713	2.24	1.72	2.92	<0.001
50+	909	4.59	3.55	5.93	<0.001	875	3.637	2.717	4.87	<0.001

Supplementary table 6. Continued

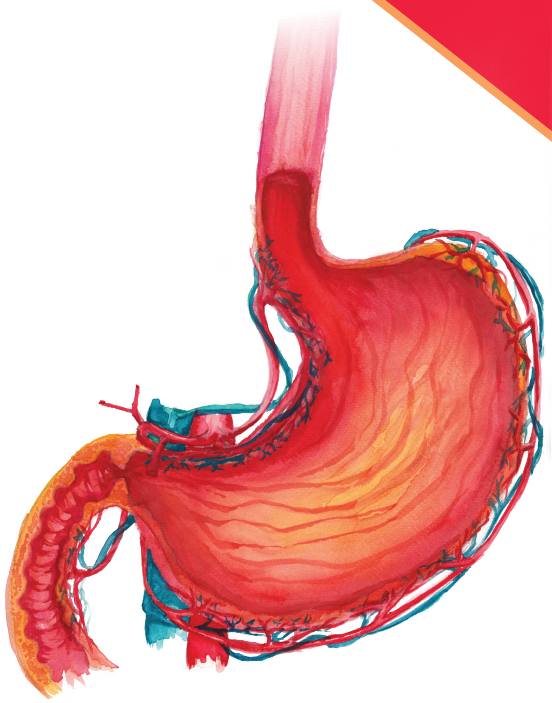
Retrieval of ≥15 LNs	Univariable analysis Total Study population n=3091					Multivariable analysis n=2950				
Variables	*n*	*OR*	*95% CI*		*P-value*	*n*	*OR*	*95% CI*		*P-value*
Year of resection					<0.001					<0.001
2011	343	ref				321	ref			
2012	439	1.61	1.21	2.14	<0.001	413	1.538	1.11	2.13	0.01
2013	462	1.74	1.31	2.32	<0.001	431	1.50	1.08	2.07	0.01
2014	546	2.70	2.03	3.59	<0.001	526	2.17	1.57	2.99	<0.001
2015	660	2.92	2.21	3.85	<0.001	633	2.24	1.63	3.08	<0.001
2016	641	3.84	2.88	5.12	<0.001	626	2.52	1.81	3.50	<0.001

BMI = Body Mass Index, ASA = American Society of Anaesthesiologists, THO = Transhiatal oesophagectomy, TTO = Transthoracic oesophagectomy, MI = Minimally invasive, nCRT = neoadjuvant Chemo radio Therapy



Supplementary figure 1a and 1b: Percentage of postoperative complications (a) and severe postoperative complications (b) for subgroups based on the time interval between neoadjuvant chemo radiotherapy and surgery

*Postoperative complications leading to reintervention, prolonged hospital stay (>21 days) or dead



CHAPTER 5

Nationwide outcome of gastrectomy with enbloc partial pancreatectomy for gastric cancer

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ABSTRACT

BACKGROUND

Radical gastrectomy is the cornerstone of the treatment of gastric cancer. For tumours invading the pancreas, en-bloc partial pancreatectomy may be needed for a radical resection. The aim of this study was to evaluate the outcome of gastrectomies with partial pancreatectomy for gastric cancer.

METHODS

Patients who underwent gastrectomy with or without partial pancreatectomy for gastric or gastro-oesophageal junction cancer between 2011-2015 were selected from the Dutch Upper GI Cancer Audit (DUCA). Outcomes were resection margin (pR0) and Clavien Dindo grade ≥III postoperative complications and survival. The association between partial pancreatectomy and postoperative complications was analysed with multivariable logistic regression. Overall survival of patients with partial pancreatectomy was estimated using the Kaplan Meier method.

RESULTS

Of 1966 patients that underwent gastrectomy, 55 patients (2.8%) underwent en-bloc partial pancreatectomy. A pR0-resection was achieved in 45 of 55 patients (82% versus 85% in the group without additional resection, p=0.82). Clavien Dindo grade ≥III complications occurred in 21 of 55 patients (38% versus 17%, P<0.001). Median overall survival [95% confidence interval] was 15 [6.8-23.2] months. For patients with and without perioperative systemic therapy, median survival was 20 [12.3-27.7] and 10 [5.7-14.3] months, and for patients with pR0 and pR1 resection it was 20 [11.8-28.3] and 5 [2.4-7.6] months, respectively.

CONCLUSIONS

Gastrectomy with partial pancreatectomy is associated with a pR0-resection rate of 82% but also with increased postoperative morbidity. It should only be performed if a pR0-resection is feasible.

INTRODUCTION

The mainstay of curative treatment in gastric cancer is surgery. For patients with resectable gastric cancer of stage II or higher, neoadjuvant or adjuvant chemotherapy is recommended.[1] A radical resection with tumour-negative resection margins (pR0 resection) is the most powerful predictor of survival.[2,3]
In patients with advanced gastric cancer, en-bloc partial pancreatectomy may be needed to obtain a pR0 resection. However, the benefits of en-bloc partial pancreatectomy should be critically evaluated given the potential for increased morbidity. Routine splenectomy in patients who underwent a D2 gastrectomy did not lead to increased survival.[4-6] In the past, a gastrectomy with pancreatosplenectomy was regarded as the standard of care for gastric cancer because it was believed that this would increase lymph node yield and thereby improve oncological outcomes. Since two large trials demonstrated that a D2 lymphadenectomy with pancreatosplenectomy increases postoperative morbidity and mortality without any additional beneficial effects on survival,[7-9] current guidelines recommend a D2 resection without pancreatosplenectomy[1]. Nowadays, an en-bloc partial pancreatectomy is only indicated for tumours that invade the pancreas.[1]
The aim of this study was to evaluate patient characteristics and outcomes of en-bloc partial pancreatectomies in patients undergoing gastrectomy for gastric cancer in the Netherlands between 2011 and 2015.

METHODS

STUDY POPULATION

For this study, the database of the Dutch Upper Gastrointestinal Cancer Audit (DUCA) was used. Participation in this national audit registry is mandatory for all Dutch hospitals that perform oncological upper gastrointestinal surgery. All patients with gastric or oesophageal cancer who are scheduled to undergo resection are included.[10] In this audit, patient, disease, and treatment characteristics are prospectively collected. Outcomes are registered until 30

days postoperatively or during hospitalisation. The completeness of cases registered in the DUCA approached 100% of patients registered in 2013.[10]

Patients who underwent gastrectomy between 2011 and 2015 were selected from the DUCA (Figure 1). Patients with missing 30-day mortality status (n=27), date of birth (n=3) or type of procedure (n=4) were excluded. When a partial pancreatectomy was registered as an additional surgical procedure, details of patient, treatment and (long-term) outcome characteristics were provided by participating centres. Patients in whom the partial pancreatectomy was erroneously registered were excluded. For the comparison of patients with and without partial pancreatectomy, patients with other additional resections than pancreatectomy (e.g. splenectomy) were excluded. A separate analysis was executed to compare the occurrence of complications, in patients with partial pancreatectomy compared to patients with other additional (non-pancreas) resections. Another subgroup analysis was executed for patients with a pT4 tumour, the occurrence of complications in patients with partial pancreatectomy was compared to the occurrence of complications in patients without a partial pancreatectomy.

OUTCOMES

The prevalence of partial pancreatectomy for gastric cancer was analysed for all individual hospitals. Characteristics and short-term outcomes of patients with a partial pancreatectomy were evaluated and compared with patients with no additional resection. Also, short-term outcomes were described for both groups: duration of hospital stay, Intensive Care Unit stay (ICU), resection margins (tumour negative: pR0, microscopically positive: pR1, macroscopically positive: pR2), postoperative complications, postoperative complications Clavien Dindo grade $\geq$III (defined as a complication in combination with a reintervention, readmission to the intensive care unit/medium care unit or death), and 30-day/in-hospital mortality.

Disease-free and overall survival for patients with partial pancreatectomy were evaluated. The following subgroups within the partial pancreatectomy-group were compared: pR0 versus pR1 resections and perioperative systemic therapy versus no perioperative systemic therapy.

STATISTICAL ANALYSIS

Characteristics and short-term outcomes of patients who underwent gastrectomy with and without partial pancreatectomy were compared using Mann-Whitney U test and Chi-square test, when appropriate. The association between partial pancreatectomy and complications was tested with univariable and multivariable logistic regression analysis. In the multivariable analysis, clinically relevant variables were added to the model, as well as the variables that were associated with complications (p-value <0.10 in univariable analyses). The association was tested for sex, age, Charlson comorbidity score[11], American Society of Anaestesiologists (ASA) score, tumour location, cT category, and cN category. Overall survival was estimated using the Kaplan Meier method, and subgroups were compared with log-rank analysis. All analyses were performed using SPSS® version 24 (IBM, Armonk, NY, USA).

RESULTS

PATIENTS

Between 2011 and 2015, 2 192 patients who underwent a gastrectomy for gastric cancer were registered in the DUCA database. Additional resections were performed in 177 of 2 192 patients (8.1%). An additional partial pancreatectomy was performed in 70 of 2 192 patients (3.2%) (Figure 1). The percentage gastrectomies with additional partial pancreatectomy varied between 0% and 10% for the individual hospitals.

Some 55 of 70 patients who underwent additional partial pancreatectomy were included in the analysis because all data could be retrieved from the patient charts. After exclusion of patients with incomplete data, 1 911 patients without additional resections served as the control group.

Patient demographics are shown in Table 1. In 12 of 55 patients who underwent a partial pancreatectomy, the tumour was staged preoperatively as cT4. In all 55 patients a preoperative CT scan was performed. In 15/55 (27%) patients preoperatively EUS was performed.

In the additional pancreatectomy group, total gastrectomy was performed in 31 patients (56%), and 34 patients received perioperative systemic therapy (62%)

(Table 2). Additional resections of adjacent organs/structures were performed in 31 of 55 patients, including the spleen (n=25), mesocolon (n=7), liver (n=4), diaphragm (n=1) and other (n=10). Five of 27 patients with a distal pancreatectomy did not undergo a splenectomy. The remaining patients who underwent a splenectomy, n=3, underwent a wedge resection/pancreatic head resection. Upon pathological examination, 34 (62%) tumours were staged as pT4 (Table 2).

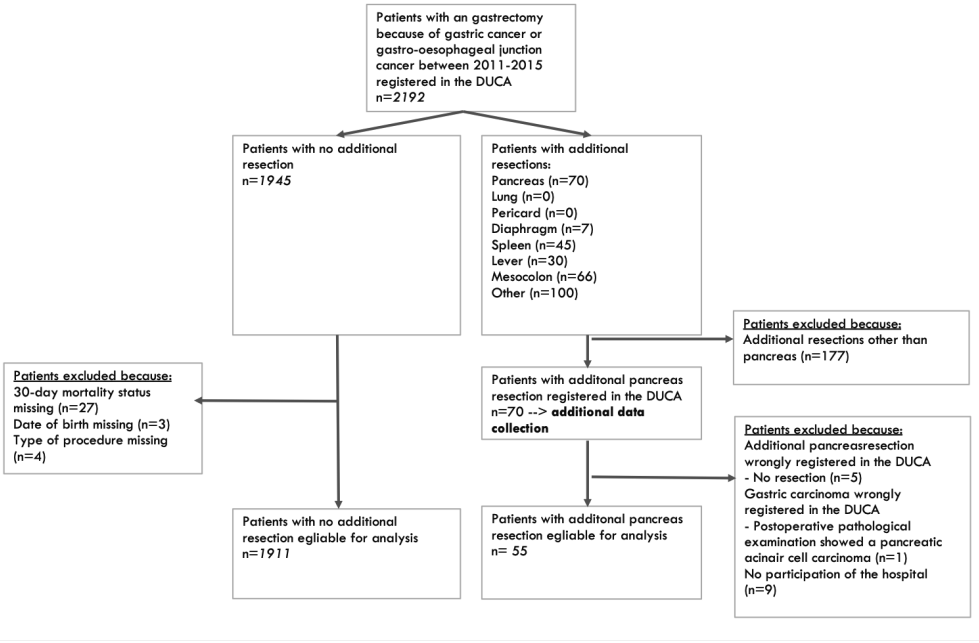

Figure 1. Patients who underwent gastrectomy between 2011 and 2015

Table 1. Patient- and disease characteristics of patients undergoing gastrectomy with no additional resection and with additional partial pancreatectomy

	Gastrectomy alone n=1911 (97%)		Gastrectomy plus partial pancreatectomy n=55 (2.8%)		P value
	n	%	n	%	
Gender					0.53
Man	1207	63%	37	67%	
Women	704	37%	18	33%	
Age (in years, median, IQR)	70	[62-77]	66	[57-73]	
Age (in groups)					0.04
<65 years	605	32%	22	40%	
65-74 years	645	34%	23	42%	
>75 years	661	35%	10	18%	
Charlson score					<0.001
0	835	44%	39	71%	
1	458	24%	7	13%	
2+	618	32%	9	16%	
ASA score					0.71
I-II	1293	68%	39	71%	
III+	600	31%	16	29%	
Unknown	18	0.9%	0	0.0%	
Location of tumour					0.05
Oesophageal-Gastric junction	69	3.6%	1	1.8%	
Fundus	134	7.0%	8	15%	
Corpus	556	29%	16	29%	
Antrum	771	40%	13	24%	
Pylorus	153	8.0%	9	16%	
Entire stomach	95	5.0%	3	5.5%	
Pouch	59	3.1%	3	5.5%	
Unknown	74	3.9%	2	3.6%	
cT-category					<0.001
cT0-2	571	30%	2	3.6%	
cT3	763	40%	27	49%	
cT4	78	4.1%	12	22%	
cTx	457	24%	14	26%	
Missing	42	2.2%	0	0.0%	
cN-category					0.002
cN-0	976	51%	15	27%	
cN+	661	35%	28	51%	
cNx	231	12%	12	22%	
Missing	43	2.3%	0	0.0%	
cM-category					0.001
cM-0	1774	93%	49	89%	
cM+	24	1.3%	4	7.3%	
cMx	113	5.9%	2	3.6%	
TNM stage					n.a.
Stage 0	33	1.8%	0	0.0%	
Stage I	392	21%	1	1.8%	
Stage II	637	35%	17	31%	
Stage III	138	8%	8	15%	
Stage IV	24	1.3%	3	5.5%	
Stage unknown	687	36%	26	47%	

IQR: interquartile range, ASA: American Society Anaesthesiologists, n.a.: not available

Table 2. Treatment characteristics of patients undergoing gastrectomy with no additional resection and with additional partial pancreatectomy

	Gastrectomy alone n=1911 (97%)		Gastrectomy plus partial pancreatectomy n=55 (2.8%)		P value
	n	%	n	%	
(Neo)adjuvant therapy					0.28
None	779	42%	21	38%	
Neoadjuvant and adjuvant	688	37%	17	31%	
Adjuvant	44	2%	3	6%	
Neoadjuvant	358	19%	14	26%	
Urgency of surgery					0.01
Elective	1833	96%	49	89%	
Urgent /Emergency	75	4%	6	11%	
Unknown	3	0%	0	0%	
Curative/Palliative					n.a.
Palliative	52	3%	3	6%	
Curative	1835	96%	51	93%	
Prophylactic resection	13	1%	0	0%	
Unknown	11	1%	1	2%	
Type of resection					0.03
Total gastrectomy	803	42%	31	56%	
Partial gastrectomy	1108	58%	24	44%	
Procedure					n.a.
Open	1331	70%	44	80%	
MI abdomen	489	26%	5	9%	
MI abdomen converted	56	2.9%	6	11%	
MI thorax	1	0.1%	0	0.0%	
MI thorax and abdomen	14	0.7%	0	0.0%	
MI thorax and abdomen converted	3	0.2%	0	0.0%	
Unknown	17	1%	0	0%	
Reconstruction					n.a.
No reconstruction	36	2%	1	2%	
Gastric tube	17	1%	1	2%	
Coloninterponate	2	0%	0	0%	
Jejunuminterponate	39	2.0%	0	0.0%	
Oesophagojejunostomy	776	41%	30	55%	
Gastro-enterostomy	1007	53%	22	40%	
Other	9	1%	1	2%	
Unknown	25	1%	0	0%	
Additional resections other than pancreatic			31	56%	
Spleen (intentional)			25	45%	
Diaphragm			1	1.8%	
Liver			4	7.2%	
Mesocolon			7	13%	
Other			10	19%	
Pathological T-stage					<0.001
pT0-2	728	38%	3	6%	
pT3	753	39%	17	31%	
pT4	371	19%	34	62%	
pTx	29	2%	1	2%	
Unknown	30	2%	0	0%	
Annual volume in the hospital or resection					0.20
0-19 resections	1217	64%	37	67%	
20-39 resections	481	25%	16	29%	
40 or more resections	213	11%	2	4%	

MI: minimally invasive, n.a.: not available

OPERATIONS

Nine of 55 patients (16%) underwent pancreatoduodenectomy, 27 (49%) distal pancreatectomy and 19 (35%) a wedge resection (Table 3). In the vast majority (n=52) the indication for partial pancreatectomy was direct tumour ingrowth into the pancreas. Some 30 of 55 resections were performed by a surgeon with experience in pancreatic surgery. In 6 (11%) procedures, the surgical team was changed for the pancreatectomy.

A pR0 resection was achieved in 45 of 55 patients undergoing gastrectomy with partial pancreatectomy (82%) (Table 4). This was not statistically significant different from the patients who underwent a gastrectomy without additional resection (1 617 of 1 911, 85%, p=0.82).

Table 3. Details of the partial pancreatectomies: treatment characteristics

	Total		Pancreato-duodenectomy		Distal pancrea-tectomy		Minimal/ wedge resection	
			n	%	n	%	n	%
	55		9	16%	27	49%	19	35%
Indication pancreas resection								
Tumour growth in pancreas	52	95%	9	100%	25	93%	18	95%
Intraoperative injury pancreas	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Lymph node dissection	3	5.5%	0	0.0%	2	7.4%	1	5.3%
Other	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Type of surgeon								
Surgeon with expertise in pancreas surgery*	30	55%	7	78%	14	52%	9	47%
Surgeon with expertise in upper GI surgery	25	46%	2	22%	13	48%	10	53%
Change in surgical team								
No	49	89%	8	89%	24	89%	17	90%
Yes, preoperative	2	3.6%	0	0.0%	1	3.7%	1	5.3%
Yes, intraoperative	4	7.3%	1	11%	2	7.4%	1	5.3%
Type of reconstruction								
No	45	82%	3	33%	24	89%	18	95%
Pancreatico-jejunostomy, hepato-jejunostomy and gastro-jejunostomy	8	15%	6	67%	2	7.4%	0	0.0%
Other	2	3.6%	0	0.0%	1	3.7%	1	5.3%
Drain in pancreatic region (intraoperative)								
Yes	16	29%	4	44%	5	19%	7	37%
No	39	71%	5	56%	22	82%	12	63%
Drain in pancreatic region (postoperative, percut.)								
Yes	45	83%	7	78%	23	85%	15	83%
No	9	17%	2	22%	4	15%	3	17%

* in the last year

Table 4. Short-term outcomes of patients with no additional resections versus patients with additional partial pancreatectomies

	Gastrectomy alone n=1911 (97%)		Gastrectomy plus partial pancreatectomy n=55 (2.8%)		P value
	Mean	**Median [IQR]**	**Mean**	**Median [IQR]**	
Hospital stay (days)	14	9 [7-13]	23	14 [10-20]	<0.001
IC stay (days)	1.8	0 [0-1]	1.8	1[0-2]	>0.05
	n	**%**	**n**	**%**	**P value**
Intra-operative complication	73	3.8%	1	1.8%	0.44
Postoperative complication	703	37%	33	60%	<0.001
Reintervention	279	15%	20	36%	<0.001
Radiological	83		11		
Endoscopic	38		3		
Re-operation	211		10		
In-hospital and 30-day mortality	101	5.3%	4	7.3%	0.52
Complications Clavien Dindo ≥III	332	17%	21	38%	<0.001
Resection margins					0.82
R0 Microscopic radical	1617	85%	45	82%	
R1 Microscopic irradical	202	11%	7	13%	
R2 Loco regional residual tumour	25	1.3%	1	1.8%	
Not applicable	21	1.1%	0	0.0%	
Unknown	46	2.4%	2	3.6%	
Multivariable analysis		**OR**		**95% CI**	**P value**
Association with complications Clavien Dindo ≥III *					<0.001
No additional resection		1.00			
Additional partial pancreatectomy		3.13		1.76-5.59	

* Adjusted for age, sex, Charlson comorbidity score[11], ASA score, location tumour, type of resection (partial/total gastrectomy)

IC: Intensive Care, R0: tumour negative resection margins, R1: microscopically tumour positive resection margins, R2: macroscopically tumour positive resection margins, IQR: inter quartile range, CI: confidence interval, ASA: American Society Anaesthesiologists

COMPLICATIONS

In the partial pancreatectomy group, there were relatively more patients with postoperative complications, n=33 (60%) versus n=703 (37%, p=<0.001) (Table 4). Also, Clavien Dindo grade III and higher complications occurred more frequently in the partial pancreatectomy group: in 21 (38%) patients versus 332 (17%) patients (<0.001). An additional partial pancreatectomy was independently associated with a complication with Clavien Dindo grade III or higher (OR [95% CI]: 3.28 [1.85-5.82] (Table 4). Postoperative pancreatic fistulas grade B and C according to the International Study Group on Pancreatic Surgery definition were observed in 9 (16%) and 2 (3.6%) patients, respectively[12] (Table 5). Clavien Dindo grade III or higher occurred in 42/172 (24%) patients with other additional (non-pancreas) resections, this was not significantly different from the partial pancreatectomy group (38%). For the subgroup of patients with a

pT4 tumour, 332/1 911 (17%) patients in the gastrectomy only group had a Clavien Dindo grade III or higher complication versus 4/24 (17%) of patients in the partial pancreatectomy group (p=0.93). Combined in-hospital and 30-day mortality was 7.3% (4 of 53) in patients with partial pancreatectomy versus 5.3% in patients without additional resections (101 of 1 911, p=0.52) (Table 4).

Table 5. Details of the partial pancreatectomies: treatment characteristics

	Total		Pancreato-duodenectomy		Distal pancrea-tectomy		Minimal/ wedge resection	
			n	%	n	%	n	%
	55		9	16%	27	49%	19	35%
Postoperative complications								
No	22	40%	2	22%	10	37%	10	53%
Yes	33	60%	7	78%	17	63%	9	47%
POFP *								
No POPF, no biochemical leakage	39	71%	6	67%	18	67%	15	79%
No POPF, but biochemical leakage	5	9.1%	1	11%	4	15%	0	0.0%
Yes, grade B	9	16%	2	22%	5	19%	2	11%
Yes, grade C	2	3.6%	0	0.0%	0	0.0%	2	11%
Complications Clavien Dindo ≥III								
No	34	62%	3	33%	19	70%	12	63%
Yes	21	38%	6	67%	8	30%	7	37%
30-day/in-hospital mortality								
No	51	93%	8	89%	26	96%	17	90%
Yes	4	7.3%	1	11%	1	3.7%	2	11%

* according to the definition of Bassi&ISGPS, Surgery 2016)
POPF: postoperative pancreatic fistula

SURVIVAL

Median follow up of the patients with partial pancreatectomy was 42 [95% CI: 36.1-47.9] months. Median overall survival was 15 [6.8-23.2] months (Figure 2a), and median disease-free survival was 13 [7.6-18] months (Figure 2b). One-, two-, and three-year survival rates were 56%, 38%, and 31%, respectively. In patients in whom an pR0 resection was obtained, median overall survival was 20 [11.8-28.3] months and for patients with an pR1 resection 5 [2.4-7.6] months (Figure 2c). For patients treated with perioperative systemic therapy, median overall survival was 20 [12.3-27.7] months versus 10 [5.7-14.3] months for patients without perioperative systemic therapy (Supplementary Figure 1).

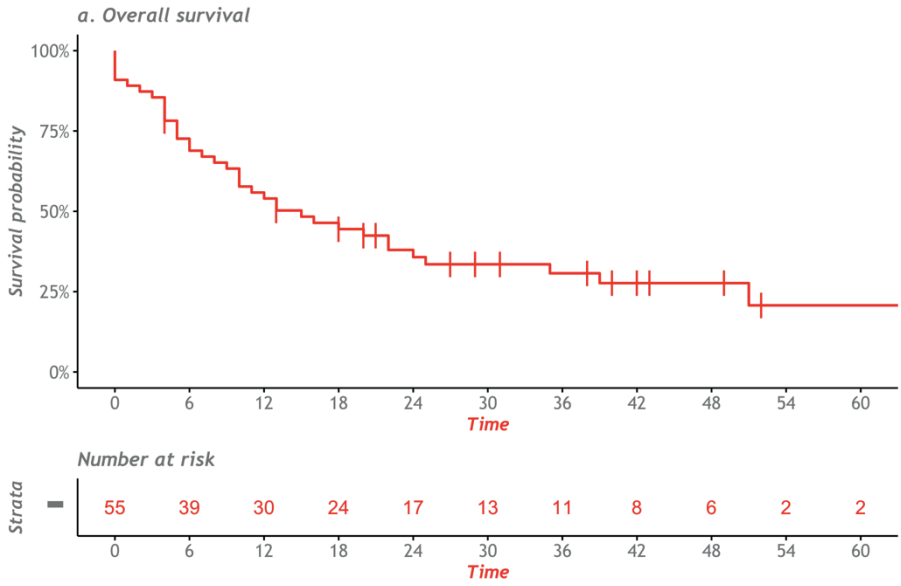

Figure 2a. Overall survival of patients with partial pancreatectomy

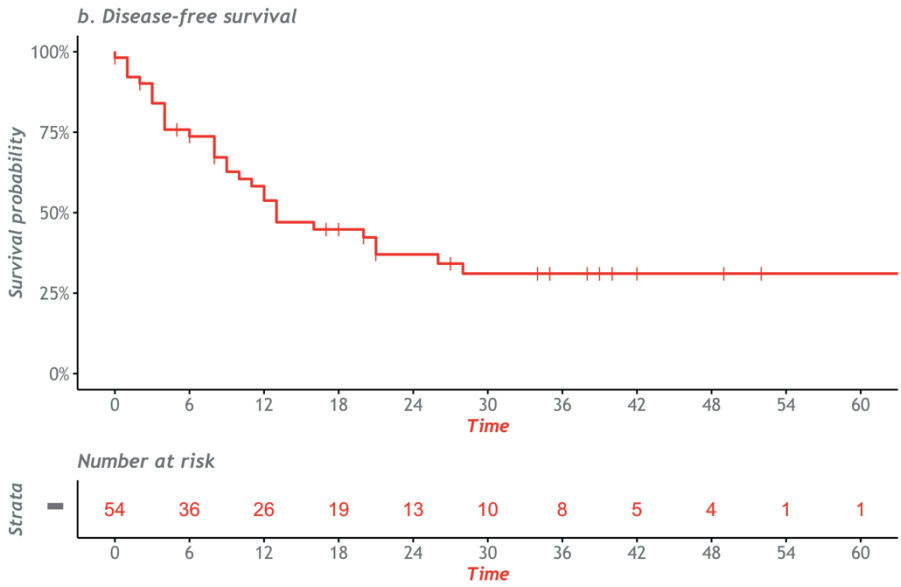

Figure 2b. Disease-free survival of patients with partial pancreatectomy

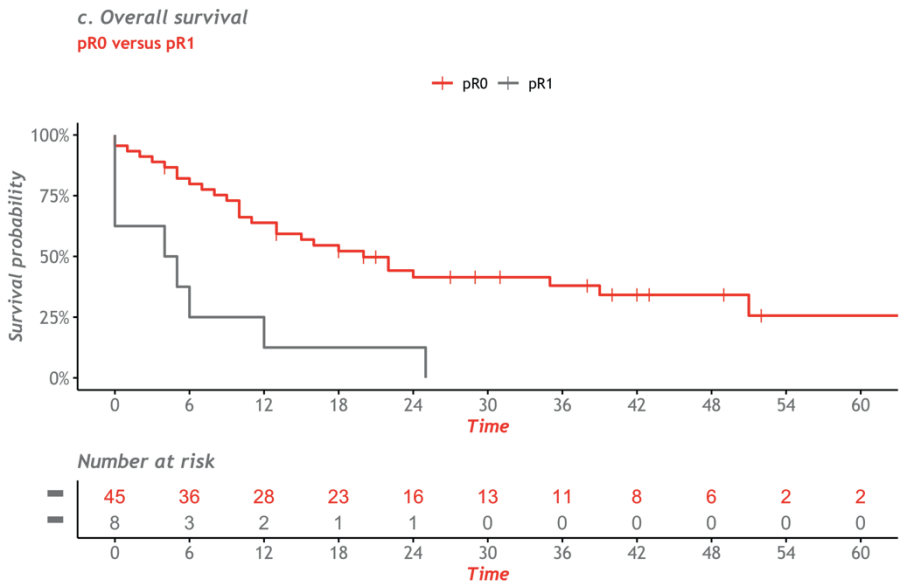

Figure 2c. Overall survival of patients with partial pancreatectomy (pR0 versus pR1).

DISCUSSION

A gastrectomy with en-bloc partial pancreatectomy was rarely performed in the Netherlands between 2011 and 2015. The intra-operative indication for partial pancreatectomy for gastric cancer was usually direct tumour ingrowth in the pancreas. In these patients, additional partial pancreatectomy was associated with an R0-resection rate of 82% but an increased risk for complications.

This study gives a unique overview of the national outcome of patients with gastric cancer for whom an additional partial pancreatectomy was performed during gastrectomy. Most studies on additional resections evaluated different multivisceral resections as one group.[4,13,14] The national audit database enabled the identification of patients who underwent an additional partial pancreatectomy during a gastrectomy. Because multiple centres participated, we could evaluate the outcomes of a reasonable large cohort of patients treated

with gastrectomy with partial pancreatectomy in the Netherlands in the period 2011-2015.

One of the factors associated with improved survival was a radical (pR0) resection. Previous studies also showed a decreased survival in patients in whom an R0 resection could not be achieved.[13-16] In the present study, the percentage of R0 resections was comparable between the group of patients with partial pancreatectomy and without additional resections (82% versus 85%, p=0.82). In the current literature, the percentages R0 resections after multivisceral resections range from 38% to 100%.[17] Tran et al. reported an R0 resection rate of 100% in 34 patients after additional partial pancreatectomy.[18]

In this study, only 22% of patients with an additional partial pancreatectomy had a cT4 tumour, and only 62% had a pT4 tumour at pathological examination. Ideally, a partial pancreatectomy should only be performed in actual T4 tumours. In other cohorts with multivisceral resections, low percentages of pT4 tumours have been reported as well (14-80%).[17] The low percentage of patients with a cT4 tumour shows that there is a discrepancy in the diagnostic assessment of tumour stage with the intraoperative assessment. In order to distinguish a cT3 tumour from a cT4 tumour in the preoperative phase, endoscopic ultrasound (EUS), multidetector row computed tomography (MDCT) and magnetic resonance imaging (MRI) are preferred imaging methods.[19] Also, when it is not known whether there is ingrowth in the pancreas, it may be recommended to perform an EUS, MDCT or MRI. The results of the DUCA showed that in only 27% of patients EUS is used for diagnostics. The use of MDCT and MRI were not registered in the DUCA.
The low percentage of patients with a pT4 tumour shows that there is a discrepancy in the intraoperative assessment of tumour stage with the actual tumour stage as seen in pathological examination. Intraoperatively frozen section biopsy could be used to assess the resection margin and to decide whether an additional pancreatectomy is needed. However, dissecting through the tumour plane violates the principle of surgical oncology i.e. en bloc resection.

In the present study, patients treated with perioperative systemic therapy had better survival. Selection bias might partly explain this difference. A recent study on the use of perioperative therapy in Dutch patients showed that older patients and patients with a higher ASA-score had a lower probability for initiation of perioperative therapy.[20] In the present cohort, the patients who were not treated with preoperative therapy might have been frail patients who were unfit for undergoing preoperative therapy. These patients are probably more likely to die which could have influenced the survival of this group. Furthermore, exclusion for resection of patients that are progressive during perioperative therapy could have occurred. These data are not available in our surgical database. However, based on our results, it may be wise to take the prognosis of patients without perioperative systemic therapy into account. Patients who are not eligible for perioperative systemic therapy may also not benefit from a partial pancreatectomy during gastrectomy.

Since the MAGIC trial, perioperative chemotherapy for gastric cancer gained importance.[21] Since partial pancreatectomies are associated with high complication rates, it is possible that patients who undergo a partial pancreatectomy cannot be treated with adjuvant therapy. In the Dutch guideline perioperative chemotherapy is recommended for patients with stage >1 gastric cancer and are fit enough to undergo chemotherapy.[1] This study showed that 38% of patients in the pancreatectomy group were not treated with neoadjuvant therapy neither adjuvant therapy. A recent Dutch study showed that patients with postoperative complications had a threefold increased likelihood of not receiving adjuvant therapy.[22] It might thus be prudent to focus on a more intense neoadjuvant systemic therapy to patients in whom a partial pancreatectomy is considered. In the future, the results of the CRITICS-II may help in choosing the best neoadjuvant therapy. The CRITICS-II trial aims to optimize preoperative treatment by comparing treatment regimens: (1) chemotherapy, (2) chemotherapy followed by chemoradiotherapy, and (3) chemoradiotherapy.[23]

The performance of additional partial pancreatectomy and splenectomy in order to retrieve more lymph nodes abandoned in the past because of its high postoperative morbidity.[8,9]

The current study showed high postoperative morbidity in gastrectomy patients with partial pancreatectomies. Complications occurred in 60% of patients, and

complications Clavien Dindo grade III and higher in 38% of patients. Tran et al. reported also a significantly higher percentage of complications Clavien Dindo grade III and higher for patients with gastric cancer undergoing a gastrectomy with partial pancreatectomy versus gastrectomy without multivisceral resection (33% versus 17%)18,24. These results are comparable to pancreatic cancer patients: a recent study reported the postoperative outcomes of partial pancreatectomies for pancreatic cancer in the Netherlands; they showed that 30% of patients had a complication Clavien-Dindo grade III of higher.[25]

The survival rates in our study were comparable to those reported in a recent study by Mita et al. evaluating additional partial pancreatectomies for gastric cancer. They reported a 1-year survival rate of 62% and a 3-year survival rate of 35% (versus respectively 56% and 31% in the present cohort).[26] Likewise, the 3-year survival rates of patients with pT4 gastric cancer who underwent multivisceral resections are comparable with the outcomes in our cohort27. Compared to the 2-year survival rate of all potentially curative gastric cancer patients in the Netherlands the survival of this cohort is poor.[28] Van Putten et al. reported national 2-year survival rates varying between 38% and 50%, depending on the variation in surgical treatment probability between hospitals.

A limitation of this study was that a pancreatectomy for gastric cancer was not common and not all hospitals in the Netherlands participated in the data collection for patients with partial pancreatectomy. All hospitals have been contacted to participate. The hospitals that did not participate indicated that the reason was of a logistical nature (no time). A second limitation was that survival information was not available for the patients with gastrectomy only. Another limitation was that it was not possible to determine the independent influence of individual parameters on survival because the number of patients undergoing partial pancreatectomy was relatively limited. Because of this limited number of patients, no conclusions could be drawn regarding the different types of pancreatectomies.

In conclusion, the present study showed that a gastrectomy in combination with a partial pancreatectomy might be considered as a valid curative treatment option for gastric cancer. The reported morbidity and mortality after partial

pancreatectomy for gastric cancer are at least comparable to rates after partial pancreatectomy for pancreatic cancer. Therefore, despite the high morbidity, it may be worthwhile to perform a partial pancreatectomy in patients with gastric cancer when the tumour is directly invading into the pancreas. It should probably be reserved for patients with a T4 tumour in whom an R0 resection is feasible. Preoperative and intraoperative selection of patients for additional partial pancreatectomy might be the key to success.

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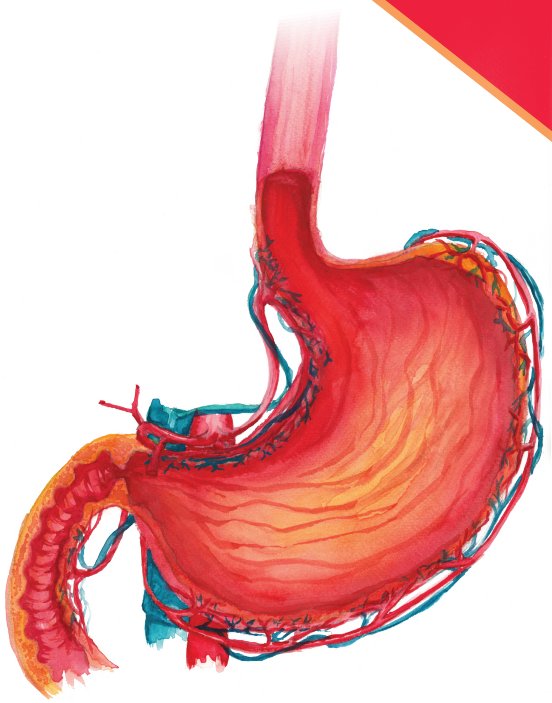
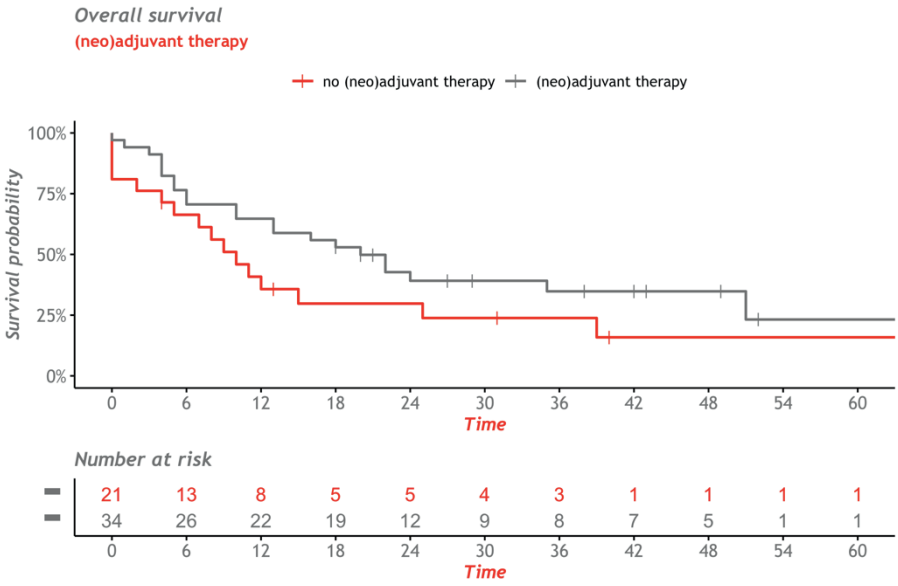
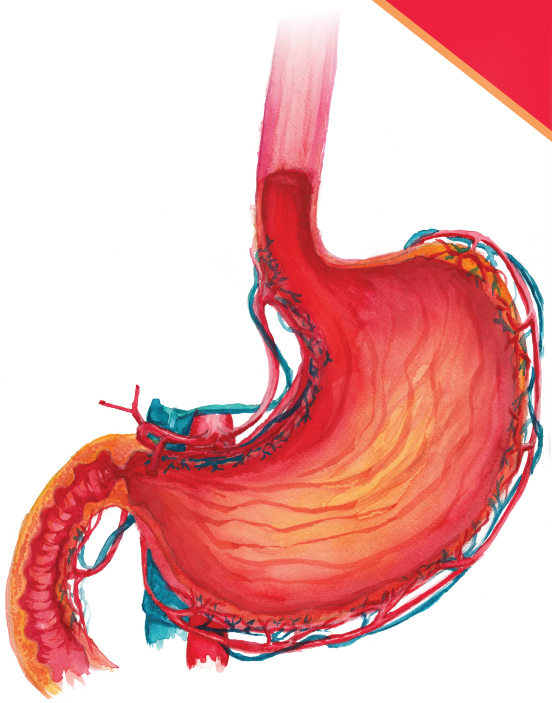


CHAPTER 5

Supplementary data



Supplementary figure 1. Overall survival perioperative systemic therapy versus no perioperative systemic therapy in patients with additional partial pancreatectomy



CHAPTER 6

Data verification of national clinical audits in the Netherlands

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ABSTRACT

BACKGROUND

Clinical auditing is an emerging instrument for quality assessment and improvement. Moreover, clinical registries facilitate medical research as they provide 'real world' data. It is important that entered data is robust and reliable. The aim of this study was to describe the evolving procedure and results of data verification within the Dutch Institute for Clinical Auditing (DICA).

METHODS

Data verification performed on several (disease-specific) clinical registries between 2013-2015 were evaluated. Sign-up, sample size and process of verification were described. For each procedure, hospitals were visited by external data managers to verify registered data. Outcomes of data verification were completeness and accuracy. An assessment of the quality of data was given per registry, for each participating hospital. Using descriptive statistics, analyses were performed for different sections within the individual registries.

RESULTS

Seven of the 21 registries were verified implying 174 visits to hospital departments. A step-by-step description of the data verification process was provided. The completeness of data in the registries varied from 97.3-99.4 per cent. The accuracy of data varied from 86.6-97.0 per cent. Most discrepancies were observed in postoperative complications (0.7-7.5 per cent) and ASA classification (7.5-11 per cent). Data quality was assessed to be 'sufficient' in 145 of 174 (83 per cent) hospital departments.

CONCLUSION

Data verification revealed that the data entered in the observed DICA registries were rather complete and accurate.

INTRODUCTION

Clinical auditing is a predominant instrument for quality assessment and improvement in healthcare which can help to improve patient outcomes[1-4]. Moreover, clinical registries facilitate evidence-based medical research as they provide 'real world' data of patients. In 2009, the nationwide Dutch ColoRectal Audit (DCRA) was initiated by the Association of Surgeons of the Netherlands[5]. Together with the establishment of other clinical registries, this has led to the foundation of the Dutch Institute for Clinical Auditing (DICA) in 2011[4-7]. Nowadays, 21 clinical registries are facilitated by DICA in which already over 500 000 patients had been registered by 2016[8]. The clinical registries are disease-specific. Sixteen of 21 registries are surgical registries. In the Netherlands, all hospitals obligatory participate in these registries. Annually, a set of hospital-specific outcomes are published on a public website, though only after approval of the board of each hospital[9]. These outcomes are used by policymakers, health insurance companies, and patient federations to assess hospital performance.

A prerequisite for using this data for comparison of quality between hospitals is that the entered data is robust and reliable. The validity of the entered data is essential because it is used for medical and epidemiological outcome research. A recent validation study by Cundall-Curry et al.[10] emphasizes the need for checking the uploaded data to a national registry. Another validation of data quality in a national registry has been described by Linder et al.[11], who showed that the database of the registry contained reliable data. A systematic approach for data verification in nationwide clinical registries has not been described. This study aimed to describe the procedure of data verification used by DICA, as well as the results of each procedure of data verification and the lessons learned from each procedure.

METHODS

This was a retrospective, descriptive study on data verification in nationwide registries in the Netherlands. This is a high-income country in Western-Europe with approximately 17 million inhabitants. Healthcare insurance is obligatory. Most secondary health care is provided in public hospitals. Secondary health care was provided in 71 hospitals in 2018. Since 2009 several nationwide registries have been set up by what is now known as Dutch Institute for Clinical Auditing (DICA). In this study data verifications performed between 2013 and 2015 were eligible.

DATA ENTRANCE IN THE REGISTRIES

Medical professionals have been responsible for the correct registration of their data in the registries. At the start of DICA, the majority of surgeons recorded the data themselves. Today, the recording of data is performed by medical specialists, trainees, physician assistants, data managers, research- and administrative nurses. The medical specialist remains the final manager responsible for the quality of the data entered. Data are either uploaded in a web-based system or delivered by the hospitals as a badge, at least once a year but preferably more often to facilitate quality improvements. Hospitals adhere to annual deadlines to deliver all data.

ORGANISATIONAL STRUCTURE OF REGISTRIES IN DICA

Each registry is led by a clinical audit board, consisting of medical professionals mandated by their professional association. The registries also have a scientific committee, consisting of representatives of the participating centres. Together with the scientific bureau of DICA, this scientific committee defines valid quality indicators, coordinates outcomes research and is responsible for the quality of the data.

PROCEDURES TO MAINTAIN THE QUALITY OF REGISTERED DATA

In each clinical registry, the reliability of data is improved and verified in four ways. Verification systems are integrated in the web-based survey. Therewith the registrar receives direct feedback on erroneous, missing or unlikely data items while entering the data.

DICA uses a signalling list which reports the erroneous and missing data of all patients in a hospital. Clinical experts receive a weekly updated report with their outcomes for the use of clinical auditing. This report also provides the number of registered patients and the completeness of the data, which can help to identify errors early. Finally, external data verification can contribute to assess the reliability of the data.

EXTERNAL DATA VERIFICATION

A first pilot project on external data verification was initiated by the Association of Surgeons of the Netherlands in 2014. This initiation has led to the formation of a data verification department at DICA which coordinates the procedures of external verification. An independent data verification committee was assigned, which consists of medical experts, a biostatistician, a deputy of the Dutch Health Care Inspectorate (IGZ) and a deputy from the Dutch patient federation. Since the first procedure in 2014, the procedure of external data verification has been optimised based on experience gained during previous procedures.

The external data verification is done by a third trusted party to guarantee the privacy of patients, Medical Research Data Management (MRDM, Deventer, the Netherlands). MRDM is *NEN 7510:2011* and *ISO 27001:2013* certified and complies to privacy regulations in the Netherlands[12].

PILOT VERIFICATION PROJECT

In the pilot project the longest existing registries of DICA, the colorectal **(**DCRA) and upper gastrointestinal cancer audit (DUCA) were verified. In these verifications, respectively 18 and 20 variables were verified in all hospitals that participated in the registry. Per hospital the data of 20 patients was verified.

With the experiences from the pilot project the data verification procedure has been modified and was continued for other registries.

REGULAR DATA VERIFICATIONS

Patient and variable selection for verification

The scientific committee set selection criteria for the type of patients that should be included in the data verification and selects the variables to be verified.

Sign up

Data verification was performed for each registry individually. All participating hospitals of the registry received an invitation to participate by e-mail. In the invitation letter the procedure, practical requirements, and privacy of data verification were explained. Participation in data verification was voluntary and free of costs for the hospitals, although results were reported to the National Health Care Institute (Zorginstituut Nederland), which was responsible for public transparency of hospital-specific quality information in the Netherlands.

Sample sizes

Since previous studies were lacking, the sample sizes were arbitrarily set in a consensus meeting with the data verification committee including a biostatistician. The preferred number of hospitals to verify for each registry was set at 15. The number of patients to verify in each hospital was based on a percentage of the annual hospital volume or a set number of patients with a minimum of 30 patients.

The process

The process of data verification in hospitals was executed manually by trained employees. They were all trained in both the verification procedure and the medical content by DICA. For each hospital, the completeness of the registration was evaluated, and the accuracy of data was assessed.

Completeness of the registry

For the verification, the dataset of a complete registration year was used. This dataset was used for clinical auditing, to calculate the quality indicators for each hospital. To verify the completeness of the registry, hospitals were asked to provide a patient list derived from their administrative system. A sample of the list was compared with the registered patients in the registry. Patients that were

on the patient list but who were missing in the registry were registered as 'absent'.

Different types of patient lists were used. In the first verified registries, a patient list derived from the nationwide network and registry of histopathology and cytopathology in the Netherlands (PALGA, [13]) or a patient list with specific diagnose-treatment-codes (DBC) as recorded by the hospital administration and insurance companies was used. These DBC codes are used in the Netherlands for reimbursement of all costs of delivered care and are comparable with International Classification of Diseases (ICD) codes.

Not all methods mentioned above, proved to be applicable for every hospital since the PALGA system was not used in all hospitals and the DBC codes in some cases could differ between hospitals. Therefore, it was decided that in the studied verifications hospitals had the opportunity to choose a type of patient list that fit the aim of data verification and matched their system.

Accuracy of the data

To assess the accuracy of the data, the original data derived from the electronic patient records was compared with the data registered in the registry. For the hospitals, it was not possible to revise this data before data verification.

To register the accuracy of data, a web-based survey was used. In this survey, the selected items to be verified were prefilled based on the registered data. Each variable was assessed as 'not discrepant', 'discrepant', missing data was assessed as 'discrepant'. When discrepancies were observed, the correct information from the source data and an additional explanation of discrepancy had to be noted.

At least, the variables needed to calculate two of the quality indicators were verified in all registries, including 'the percentage of patients with severe complications' and 'the percentage of patients who died within 30 days after surgery'. For 'severe complications', different definitions are used among registries. Mostly, the definition was 'complications leading to a prolonged hospital stay, a re-intervention or death'. Another reason to verify a variable was the use of a variable in the case-mix correction of outcome indicators i.e. ASA (American Society of Anesthesiologists)-score, which is a scale of the pre-operative fitness of patients[5].

ANALYSIS OF THE DATA VERIFICATION AND RESULTS

In the process of analysing the data, an assessment of the observed discrepancies was done by an independent data manager and a medical researcher of DICA. Data of different hospitals were analysed separately. Completeness and accuracy of the data were assessed with descriptive statistics for different sections within the registries. Analyses were performed using IBM SPSS Statistics version 23.0® (Armonk, New York, United States of America).
After the evaluation of the discrepancies of each hospital by the data manager and medical researcher, the results of this evaluation were reported to the hospitals. In a hear and rehearse procedure it was possible for each hospital to give a response on the detected discrepancies. The independent verification committee has the final say.

A composite measure was defined for the conclusion of 'sufficient quality' or 'insufficient quality'. Table 1 shows the criteria for the conclusion of 'insufficient quality' in one of the procedures. For some other procedures small adjustments in thresholds were made due to a low number of patients or a low number of events.
The conclusion about the quality of the data and an anonymous summary report were communicated to the hospitals, to learn from the discrepancies and to help them optimising their procedure of registration. The results were also reported to the National Health Care Institute.

Table 1. Criteria

Factors which lead to the label 'insufficient quality'
• Completeness: Of all patients who met the inclusion criteria, more than 2 per cent (at least 2 patients) has not been registered. • Mortality: Of all patients who met the inclusion criteria, one or more patients died but were not registered at all or were not registered as 'death'. • Complications: Of all patients who have had a complication, the complication was not registered in more than 5 per cent (at least 3 patients) of the patients. • Reinterventions: Of all patients who have had a reintervention the reintervention was not registered in more than 5 per cent (at least 3 patients) of the patients. • Readmission: Of all patients who have had a readmission, the readmission was not registered in more than 5 per cent (at least 3 patients) of the patients.

RESULTS

Since 2014, 7 of the 21 registries were verified individually. Information about the different verifications is shown in Table 2 and 3.

PILOT VERIFICATION PROJECT

In the pilot procedure, in all hospitals that signed up (n=77 and n=28), 18-20 variables and all patients eligible in 2013 were verified. This procedure turned out to be very time consuming, which was logistically challenging and financially unfavourable. Therefore, in the following verifications, a more limited set of variables was used. To limit the number of hospitals, a limit of 15 hospitals per registry was set, these hospitals were randomly selected by the third trusted party MRDM.

Table 2. Characteristics and results of the pilot verifications in 2013

	Pilot	
	Dutch Colo Rectal Audit	**Dutch Upper GI Cancer Audit**
Registry year of verification	2013	2013
Validation		
Variables verified (n)	20	18
Hospitals that signed up (n and per cent of total)^	78 (88%)	78 (88%)
Hospitals verified (n)	77	28
Patients verified per hospital (n)	20	20
Completeness		
Missing patients (n and % of total patients following inclusion criteria)*	271 (2.8%)	10 (0.8%)
Missed death patients (n)	24	1
Missed patients with severe complications (n)	55	2
Accuracy		
Total patients in sample (n)	1570	560
Discrepant deaths (n and per cent of sample patients)	5 (0.3%)	0 (0%)
Discrepant complications (n and per cent of sample patients)	117 (7.5%)	17 (3.0%)
Discrepant reinterventions (n and per cent of sample patients)	29 (1.8%)	9 (1.6%)
Discrepant ASA score (n and per cent of sample patients)	134 (8.5%)	64 (11%)
Discrepant radicality (n and per cent of patients in the selected sample)	4 (1.0%)	11 (4.7%)
Objections		
Objections (number of hospitals)	22	16

^ The sign up of the Dutch ColoRectal Audit and Dutch Upper GI Cancer Audit was together.
* Verification of completeness for DSCA and DUCA was done for all registered patients.

REGULAR VERIFICATION PROJECT

Patient and variable selection for verification

The verified variables that were chosen differed between registries, all verified variables are shown in Table 2 and 3.

Sign up

In the included 7 data verification procedures, an average of 71 per cent of hospitals signed up for verification, which varied between registries from 60 to 88 per cent.

In 2 verifications, some hospitals withdrew their sign-in after selection because they were not able to comply with the conditions for verification (no time and priority for preparation). In 2 other verifications, less than 15 hospitals signed up. In 2015, an online survey was held to investigate the reasons to refrain from signing in. The most mentioned reasons included that centres would have signed-in but had forgotten, were too late or miscommunicated (in 8 out of 21 answers), lack of time (in 4 out of 21 answers) and disagree or not comply with the legality of the procedure of verification (in 4 out of 21 answers).

Sample size

The number of patient records that were verified, varied per registry, from 281 to 1570 (median: 388).

Completeness of the registry

The percentage of non-registered patients varied from 0.6 -2.7 per cent between registries. Details on these 'absent patients' are shown in Table 2 and 3.

The accuracy of the data

Discrepancies of the verified items are shown in Table 2 and 3. Most discrepancies were observed in postoperative complications and ASA score. In 3.0 -7.5 per cent of the total number of patients in the sample, the postoperative complication registration was discrepant. The occurrence of a complication was wrongly registered or wrongly not registered, and in 8.5-11.4 per cent of the total number of patients in the sample, an incorrect ASA score was registered or missing.

Results of the procedures

Of 174 data verification processes performed, in 29 the quality of data was assessed as 'insufficient' according to the criteria. The number of hospitals which responded to the results or lodged an objection varied between 5 and 22 per registry (Table 2 and 3).

Table 3. Characteristics and results of the verifications between 2014-2015 (some cells are empty because this information was not available).

	Dutch Lung Cancer Audit	Dutch Audit for Carotid Interventions	Dutch Surgical Aneurysm Audit	Dutch Audit for Treatment of Obesity	Dutch Pancreatic Cancer Audit
Registry year of verification	2014	2015	2015	2015	2015
Validation					
Variables verified (n)	17	6	9	9	13
Hospitals that signed up (n and per cent of total)^	29 (67%)	36 (68%)	39 (65%)	12 (60%)	12 (63%)
Hospitals verified (n)	15	13	14	12	12
Completeness					
Patients verified per hospital (n)	± 26	± 22	± 21	35	30
Missing patients (n and per cent of total patients following inclusion criteria)*	5 (0.6%)	2 (0.7%)	5 (1.7%)	5 (1.2%)	2 (0.6%)
Missed death patients (n)	0	0	0	0	0
Missed patients with severe complications (n)	3	1	2	1	1
Accuracy					
Total patients in sample (n)	388	281	298	420	358
Discrepant deaths (n and per cent of sample patients)	0 (0%)	2 (0.7%)	0 (0%)	0 (0%)	0
Discrepant complications (n and per cent of sample patients)		13 (4.6%)	22 (7.4%)		
Discrepant severe complications (n and per cent of sample patients)**	216 (3.3%)			3 (0.7%)	18 (5.0%)
Discrepant reinterventions (n and per cent of sample patients)		0 (0%)	0 (0%)	3 (0.7%)	
Discrepant readmissions (n and per cent of sample patients)			6 (2.0%)		
Objections					
Objections (number of hospitals)	6		7		

* Verification of completeness for these registries was done for all patients in the sample
** For the Dutch Lung Cancer Audit the percentage is computed as percentage of discrepant registries of the total complications that could be registered for sample patients.

LESSONS LEARNED FROM THE RESULTS OF EACH VERIFICATION

An overview of the derived lessons is shown in Table 4. As concluded from discussions with the registrars, most common discrepancies in the verifications seemed to be caused by unclear definitions and descriptions of variables. This was seen in 6 out of 7 verifications. The variables with the most discrepancies included M-stage of the tumour, ASA score, the urgency of surgery, intra-operative complications, postoperative complications, reinterventions, and the number of days in the Intensive Care Unit. Moreover, incorrect inclusion and incorrect exclusion of patients in the registries was observed.

Table 4. Lessons learned from the verifications

	Dutch Colo Rectal Audit (pilot)	Dutch Upper GI Cancer Audit (pilot)	Dutch Lung Cancer Audit	Dutch Audit for Carotid Interven-tions	Dutch Surgical Aneurysm Audit	Dutch Audit for Treatment of Obesity	Dutch Pancreatic Cancer Audit
Lessons derived for the procedure of data verification							
More extensive training for verification employees needed							x
Patient list not suitable			x	x	x	x	x
Selection of hospitals: too many hospitals verified	x	x					
Selection of variables: too many variables verified	x	x					
Time consuming to evaluate the completeness of all patients instead of a sample			x				
Selection of patients: too little patients verified				x	x	x	
Privacy of patient records at the procedure was complex	x	x					
Criteria for 'sufficient/insufficient' need to be set before start of data verification	x	x					
Criteria for 'sufficient/insufficient' need to be changed	x	x	x				
Criteria for 'sufficient/insufficient' are without nuance			x	x	x	x	x
Data verification has to become a continues process in the audit cycle	x	x	x	x	x	x	x
Lessons derived for registrars							
Need to fill in all variables, also when not required			x				
Complications need to be registered more precise			x	x	x	x	x
ASA score need to be registered as described in the anaesthesia report	x	x					
Date of surgery has to be registered more precise				x		x	
Date of discharge has to be registered more precise							x
Hospitals must adhere the in- and exclusion criteria					x		
Lessons derived for the audits							
Need for clear definitions of variables	x	x	x	x	x	x	x
Error in data structure discovered						x	

DISCUSSION

This study showed that verification of completeness and accuracy of the registry is essential. The strength of the described process is that a dedicated team within the audit organisation initiates and coordinates nationwide data verifications of the registries. By learning from every verification, the process of verification was continuously improved. Data verification may help to improve the survey of the registries and therewith contribute to a higher quality of datasets. The most important lesson derived from the verification is the need for clear definitions of variables.

In the first verification procedures a lot of missing patients had severe complications or died. These discrepancies may have happened because hospitals were afraid to be criticised if they registered all complicated patients. Another explanation might be that hospitals were not capable of following some of their complicated patients, as they are often treated on different wards (e.g. at the intensive care unit) or even transferred to another hospital. Because the registry is used to compare hospitals, it is imperative that all hospitals have a complete registry. Verification of data completeness may stimulate hospitals to adhere to the proposed rules of data entry.

The verification of data accuracy is also important. One of the requirements for accurate data is the use of clear definitions in multi-interpretable variables. Many discrepancies however were seen in simple, uni-interpretable variables, like date of surgery and date of discharge. Because length of stay and waiting times are frequently used as quality indicators, these results indicate that simple variables should also be verified. By detecting common discrepancies, for example, because of unclear description of items, the survey could be improved by the clarification of definitions to prevent incorrect data in the future. Furthermore, by reporting erroneous data, registrars in hospitals can learn lessons and improve the registrations. A side effect of integrated data verification in the cycle of clinical auditing might be that it stimulates hospitals to register correctly because they know their data will be verified. This so-called 'Hawthorne' effect describes improved results which might be caused by

increased awareness for an outcome, in this situation the collection of correct data[14]. All these mechanisms could benefit the quality of the datasets and may lead to more valid registries and more reliable data for outcome research. Valid registries are important because the results of quality indicators are publicly available for policymakers, health insurance companies and patient federations.

The described process also has limitations which can be improved. Hospitals which might intentionally register incorrect or incomplete, were not identified by the current procedure because signing up for data verification was voluntary. Hospitals can influence their published results by intentionally registering incorrect or incomplete data. This might be a problem since the results are used for clinical auditing and comparisons between hospitals. A counter argument for making the verification mandatory is that some medical specialists already feel criticised by clinical auditing as it takes some time. Forcing them to have a data verification may create resistance in the field. For the integrity of verification, however, it is desirable that the National Health Care Institute (Zorginstituut Nederland) declares the process of data verification mandatory. Another possibility could be that details on sign-in and participation in data verification become publicly transparent and can be used to assess the validity of indicator results of individual hospitals.

Another limitation in the current procedure is the struggle to verify the completeness of the registry. At this moment hospitals are free to choose which patient list they will provide. A frequently used patient list is the list extracted from the electronic patient record system. This strategy is unprotected for flaws because this list could be the same list as used to select patients for registration. Another disadvantage of this system is that hospitals could manipulate the patient list if they would like to hide patients with severe complications. The results of the verifications however showed that the use of the current self-provided lists succeeded in identifying unregistered patients.

To further improve registries and provide valuable, verified, benchmark data to all parties involved, DICA aims to develop a system in which data verification becomes a continuous process as part of the registry. For this purpose, data verification is included in the annual budget. This year will be the first time that

data verification is going to be repeated in two registries that have been verified previously, 3 years ago.
Regarding the right sample size for verification, difficulties to find a balance between the cost-aspect and certainty of the verification were experienced in the past. In the near future pilots will be started to verify data of the clinical outcome registry in a more automated process. This pilot aims to select patients with high risk of discrepancies.[15] The hypothesis is that verification of these high-risk patients will lead to a higher sensitivity for discrepancies when the same sample size is used as in the current procedure. As sample size directly influences costs, this procedure will be more cost-effective. This pilot is funded by Stichting Kwaliteitsgelden Medisch Specialisten (SKMS), a Dutch foundation aiming at improvement of quality policy for medical specialists, which is part of the Dutch Federation of Medical Specialists (FMS).

In most verifications, the absence of clear and uniform definitions of items led to the most discrepancies. DICA will make an important improvement by creating uniform, clear and correct definitions for items in all registries. Recently, a project has been launched for this purpose. SKMS also supports this project. In this project, as many items as possible will be defined equally in all registries, and it will be attempted to use existing guidelines, classifications and definitions. For example, definitions of SNOMED CT and the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes.
It is expected that the registration of data will become increasingly automated in the near future. The authors envision that correct data from the electronic patient records are automatically uploaded to the registry without the use of data managers.

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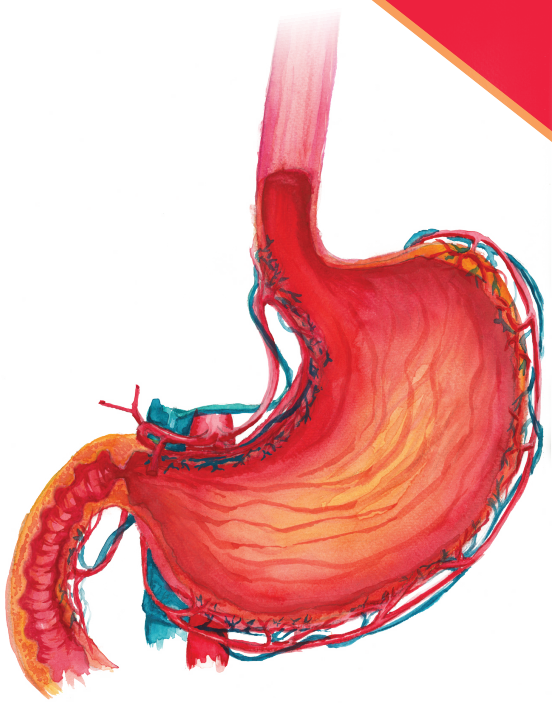
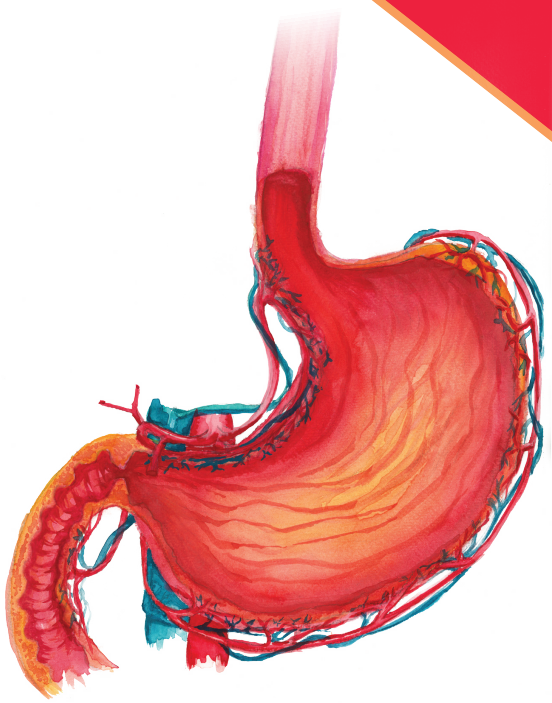


PART II

QUALITY INDICATORS AS PROXY FOR LONG-TERM OUTCOMES



CHAPTER 7

A NATIONAL COHORT STUDY EVALUATING THE ASSOCIATION BETWEEN SHORT-TERM OUTCOMES AND LONG-TERM SURVIVAL AFTER OESOPHAGEAL AND GASTRIC CANCER SURGERY

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ANNALS OF SURGERY 2019

ABSTRACT

OBJECTIVE

The aim of this study was to investigate the association between short-term outcome indicators and long-term survival after oesophagogastric resections.

SUMMARY BACKGROUND DATA

Short-term outcome indicators are often used to compare performance between care providers. Some short-term outcome indicators concern the direct quality of care; i.e., complications, others are used because they are expected to be associated with long-term outcomes.

METHOD

For this national cohort study, all patients that underwent oesophagectomy or gastrectomy for cancer with curative intent between 2011-2016 and were registered in the Dutch Upper gastrointestinal Cancer Audit were included. Primary outcome was conditional survival (under the condition of surviving the first postoperative 30 days and hospital admission). Cox regression modelling was used to study the independent association between 'textbook outcome' with survival. 'Textbook outcome', a composite quality indicator, was defined as a pathological complete resection with at least 15 retrieved lymph nodes, an uneventful postoperative course, and no hospital readmission.

RESULTS

In total, 4414 and 2943 patients with oesophageal or gastric cancer respectively were included. The 1-, 2-, and 3-year overall survival rates were 76%, 62%, and 54% and 71%, 56%, and 49% for oesophageal and gastric cancer, respectively. Textbook outcome was achieved in 33% and 35% of patients respectively. 'Textbook outcome' was independently associated with longer conditional survival (HR: 0.75 [95%CI: 0.68-0.84] and 0.69 [0.60-0.79]), respectively.

CONCLUSION

This study showed that the short-term outcome indicator textbook outcome is associated with long-term overall survival and therefore may accentuate the importance of using these indicators in clinical audits.

INTRODUCTION

Society increasingly demands information on the quality of care in hospitals. One of the main principles of improving quality of care is monitoring and benchmarking performance of hospitals. To evaluate the quality of care, quality indicators for many diseases have been defined. These indicators can be subdivided into structure, process, and outcome indicators.[1]

To monitor the quality of oesophageal and gastric cancer surgery, the Dutch Upper gastrointestinal Cancer Audit (DUCA) has developed a set of indicators. Benchmarked information on these indicators is weekly reported to all participating hospitals.[2] To limit registration burden, long-term follow-up including survival is not registered in most clinical audits. Short-term outcomes are currently used for feedback to facilitate continuous quality improvement in the hospitals. Some of the used short-term outcome indicators concern direct quality of care, for example complications. Other short-term indicators are used because they are expected to be associated with long-term outcomes, for example: 'complete resection of the tumour'. In clinical auditing, composite measures may help to ease the interpretation of outcomes since it is not needed to evaluate all separate outcomes. In the DUCA, the composite measure 'a complicated postoperative course' is used to evaluate outcomes on complications. This measure is defined as a postoperative complication in combination with a prolonged hospital stay (>21 days), reintervention, or death.[2] Another composite measure that is used in the DUCA is 'Textbook outcome'.[4] 'Textbook outcome' consists of different parameters, all of which are short-term outcomes. It describes the number of patients in whom all desired outcomes are achieved, including a pathological complete tumour resection (pR0), retrieval of at least 15 lymph nodes and no complicated postoperative course.

If outcomes on short-term quality indicators are associated with the ultimate goal of cancer treatment; i.e., long-term survival, this will accentuate the importance of using these outcome indicators in national audits. The aim of this study was to investigate the association of the short-term outcome indicators

with long-term survival in a national cohort of patients with oesophageal or gastric cancer who underwent resection with curative intent.

METHODS

For this national cohort study, data were retrieved from the DUCA. This surgical audit was initiated in 2011. It is mandatory for hospitals performing oesophagogastric cancer surgery to register all patients with oesophageal or gastric cancer undergoing surgery with the intent of resection. All hospitals in the Netherlands register data on the patient, tumour, and treatment characteristics, pathology, and 30-day morbidity and 30-day/in-hospital mortality. Surgeons have the responsibility for completeness and validity of the data collection and registration. To limit the registration burden, registration of postoperative outcomes is limited to 30 days after surgery and/or the duration of hospital stay. Validation of completeness and accuracy of this data registration in the DUCA dataset has been performed by external data verification. The completeness of the DUCA database is estimated at 97.8% and 96.2% for all primary oesophageal and gastric cancer resections, respectively. The accuracy of data was estimated to be 94-99.8% for morbidity and pathological outcomes.[2]

PATIENT SELECTION

Included in this study were all patients with oesophageal or gastric cancer who underwent surgery with the intent of resection registered in the DUCA between January 2011 and December 2016. Patients were excluded if essential elements of the registration were unknown including the intent of surgery (curative/palliative/prophylactic), date of birth, survival status at 30 days after surgery, and date of discharge (in case of a hospital stay >30 days). Also, patients with a reported date of death in the Vektis dataset that lies before the date of surgery as reported in the DUCA dataset were excluded (n=2). To identify best performing hospitals and underperforming hospitals, patients operated between January 2015 and December 2018 were included because this composite measure was introduced in the DUCA in 2015.

COMBINED DATASETS

To provide information regarding overall survival, the data of the DUCA were combined with a dataset provided by Vektis. Vektis is a national health care insurance database including all medical treatments paid for by Dutch insurance companies.[5] Date of death of all deceased patients is included in this database since health care insurance ends when the patient dies. Health care insurance is obligatory in the Netherlands and therefore almost all Dutch inhabitants (99%) are registered in the Vektis database[6].

The combining of datasets was performed by a third trusted party to guarantee the privacy of patients: Medical Research Data Management (MRDM). MRDM is *NEN 7510:2011* and *ISO 27001:2013* certified and complies to privacy regulations in the Netherlands.[7] The combining of data was done in September 2017. As the Vektis dataset contains only deceased patients, it had to be assumed that all patients in the DUCA without a match were alive at the time that data were extracted from the Vektis database (date of the last follow-up: 1st of September 2017). For all patients, the interval (in months) from the date of surgery to the date of death or date of the last follow-up was calculated. The actual date-of-death-variable was deleted in the dataset to guarantee the privacy of all patients. It was not possible to differentiate between patients that did not match because they were not deceased and those that did not match because the matching was technically not possible. Therefore, validation tests of the survival information in the combined dataset were performed.

VALIDATION OF THE COMBINED DATASET

The validation was performed with two patient cohorts. Validation cohort 1: 30-day mortality data: In the DUCA the 30-day mortality status is registered, including date of death if a patient died within 30 days or during hospital admission. All patients that had deceased within 30 days or during hospital admission were included in the primary validation cohort. A comparison was made between the date of death as registered by DUCA and by Vektis.

Validation cohort 2: Snapshot study: From a recent snapshot study with DUCA data, long-term outcomes of patients with additional pancreatic resection for gastric cancer were added to the DUCA dataset.[8] In this study, participating hospitals provided follow-up information regarding recurrence and survival of 54 patients. These data were compared with data registered by Vektis.

The main outcome in the validation was the percentage of patients with a discrepancy in survival status, i.e., patients assumed to be alive in the combined dataset, while those have been registered deceased in the data of the validation cohort.

PRIMARY OUTCOMES AND SUBGROUPS

The primary outcomes were overall survival and conditional survival (under the condition of surviving the first postoperative 30 days). To examine whether short-term outcomes were associated with long-term outcomes, stratified survival analyses were performed according to outcomes used in the DUCA: 'textbook outcome', 'complicated postoperative course' and 'pR0'. For all survival analyses, only patients with curative intent of surgery, as preoperatively defined by the surgeon, were included.

To evaluate variation in hospital outcomes on 'textbook outcome', subgroups of patients treated in hospitals with different annual volumes were compared (0-19, 20-39, and 40 or more resections/year). Also, variation between individual hospitals was evaluated; to identify best performing hospitals and underperforming hospitals, the percentage 'textbook outcome' in every hospital was compared to the national mean. A hospital with a significantly higher percentage on textbook outcome was classified as 'best performer,' and a hospital with a significantly lower percentage on textbook outcome was classified as 'underperformer'.

DEFINITIONS

'Textbook outcome' in the DUCA is defined as a radical resection according to the surgeon at the end of the operation, no intraoperative complications, a pR0 resection with at least 15 lymph nodes retrieved and examined, no severe postoperative complication, no reintervention, no readmission to the intensive care unit or medium-care unit, no prolonged hospital stay (21 days or less), no postoperative mortality and no hospital readmission.[4] A 'complicated postoperative course' in the DUCA is defined as a complication in combination with a hospital stay >21 days, any reintervention or death during hospitalization or within 30 days postoperative.[2] Pathological complete tumour resection (pR0)

was defined as microscopic tumour-negative resection margins as reported by the pathologist. Incomplete resection was defined as tumour-positive resection margins as reported by the pathologist (pR1 or pR2).[9]

STATISTICAL ANALYSIS

In all analyses, patients with oesophageal cancer (including gastroesophageal junction tumours) or gastric cancer were analysed separately. Patient, tumour, and treatment characteristics were analysed using descriptive statistics. Overall survival was reported using 1, 2, and 3-year survival rates and evaluated using the Kaplan Meier method. To evaluate the independent association of 'textbook outcome', 'complicated postoperative course', 'pR0' with overall survival and conditional survival, a multivariable Cox regression model was compiled. To assess confounding, the following factors were analysed (based on the literature): sex, age, pre-operative weight loss, body mass index (BMI), location of the tumour, American Society of Anesthesiologists (ASA) score, Charlson comorbidity score,[10] pathological tumour stage according to the TNM-7 classifications, pathological T- and N-stage, clinical M-category, histological subtype of the tumour, differentiation grade, and, surgical procedure. All factors with a p-value <0.10 in the univariable Cox regression analyses were included in the multivariable model to adjust for confounding.

Missing items were analysed in a separate group if exceeding 5%. For all analyses, statistical significance was defined as $P<0.05$. All analyses were performed with SPSS version 24 (for Mac, IBM, Armonk, New York, USA) and R studio version 1.1.456 (for Mac, RStudio, Inc).

RESULTS

A total of 7357 patients were included, 4414 patients with oesophageal cancer and 2943 patients with gastric cancer (Figure 1).

VALIDATION OF THE DATASET

In the first validation cohort, in 15 of 249 patients (6.0%) a discrepancy in survival status was found between the combined dataset and data of the validation cohort (Figure 1). In the second validation cohort in 2 of 39 patients (5.1%) a discrepancy was found.

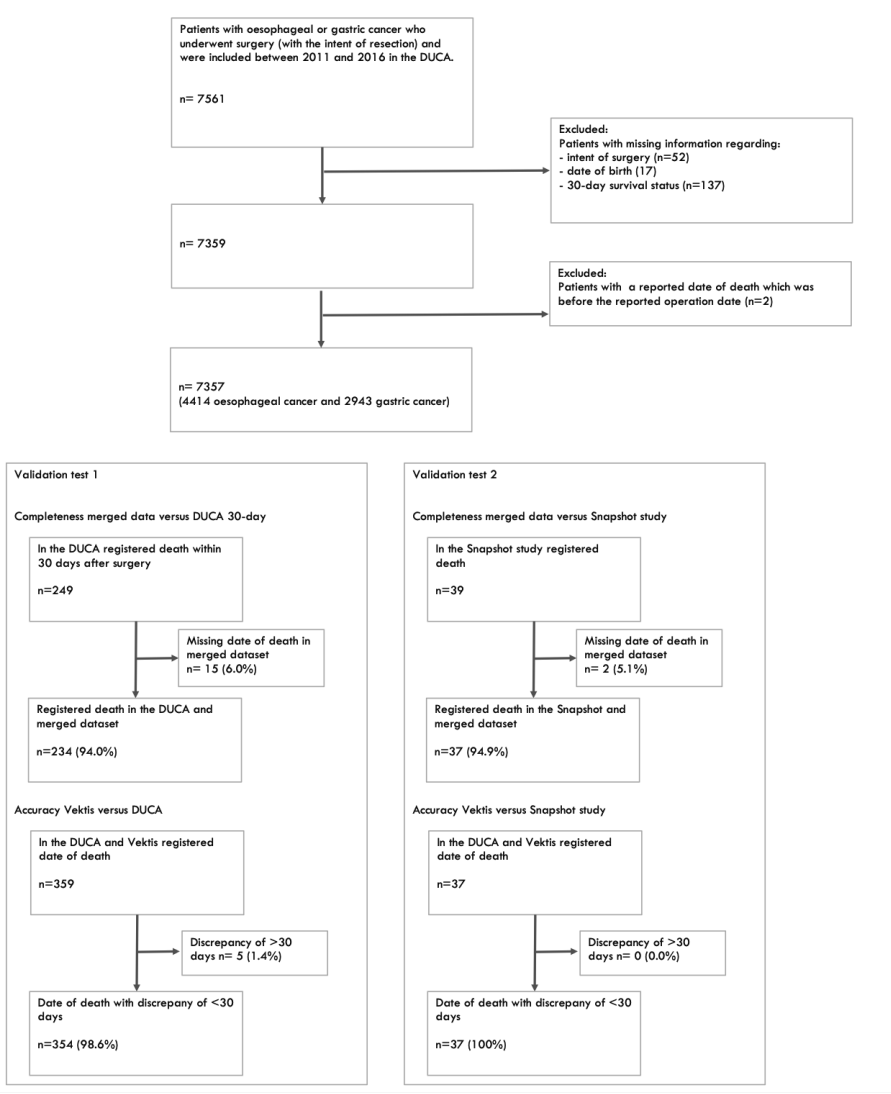

Figure 1. Flowchart inclusion and results validation tests

Table 1. Basic characteristics

		Oesophageal cancer		Gastric cancer	
		n	%	n	%
Total		4414		2943	
Gender	Male	3422	78%	1838	63%
	Female	991	22%	1102	37%
	Unknown	1	0%	3	0%
Age (in years)	40 or less	35	1%	69	2%
	41-50	264	6%	171	6%
	51-60	968	22%	418	14%
	61-70	1927	44%	822	28%
	71-80	1114	25%	1050	36%
	more than 80	106	2%	413	14%
Body Mass Index	<18.5	124	3%	116	4%
	18.5-25	1848	42%	1367	46%
	25-30	1695	38%	992	34%
	30+	697	16%	371	13%
	Unknown	50	1%	97	3%
ASA score	I	737	17%	399	14%
	II	2633	60%	1616	55%
	III	994	23%	863	29%
	IV	20	1%	39	1%
	V	0	0%	1	0%
	Unknown	23	1%	18	1%
Charlson Comorbidity score	0	2098	48%	1282	44%
	1	1124	26%	677	23%
	2+	1192	27%	984	33%
Comorbidities	Myocardial infarction	287	7%	231	8%
	Congestive heart failure	47	1%	70	2%
	Chronic Pulmonary Disease	820	19%	495	17%
	Peripheral Vascular Disease	177	4%	130	4%
	Diabetes Mellitus (uncomplicated)	647	15%	474	16%
	Diabetes Mellitus (end-organ damage)	28	4%	14	3%
	Moderate to Severe Renal Disease	50	1%	103	4%
Timing of surgery	Elective	4388	100%	2789	95%
	Urgent	11	0%	111	4%
	Emergency	9	0%	41	1%
	Unknown	2	0%	1	0%
Neoadjuvant therapy	No	419	10%	1368	47%
	Chemotherapy	359	8%	1509	52%
	Chemoradiotherapy	3612	82%	47	2%
	Radiotherapy	11	0%	2	0%
	Unknown	1	0%	2	0%
Location tumour: Oesophagus	Cervical (C15.0)	9	0%	0	0%
	Proximal (C15.3)	45	1%	0	0%
	Mid (C15.4)	529	12%	0	0%
	Distal (C15.5)	2681	61%	0	0%
	Gastro-oesophageal junction(C16.0)	1120	25%	0	0%
Location tumour: Stomach	Fundus (C16.1)	0	0%	248	8%
	Corpus (C16.2)	0	0%	870	30%
	Antrum (C16.3)	0	0%	1133	39%
	Pylorus (C16.4)	0	0%	260	9%
	Total stomach	0	0%	184	6%
	Rest stomach / anastomosis	0	0%	133	5%
	Unknown (stomach)	28	1%	55	2%
	Missing	2	0%	60	2%

Table 2. Treatment characteristics

		Oesophageal cancer		Gastric cancer	
		n	%	n	%
Total		4414		2943	
Pathological Tumour stage	pT0-2	2452	56%	937	32%
	pT3	1561	35%	1005	34%
	pT4	59	1%	608	21%
	Missing	342	8%	393	13%
Pathological Node stage	pN-	2481	56%	1126	38%
	pN+	1607	36%	1403	48%
	pNx	16	0%	57	2%
	Missing	310	7%	357	12%
Pathological Metastases stage	pM-	4071	97%	2248	88%
	pM+	58	1%	183	7%
	Not applicable	12	0%	46	2%
	pMx	62	2%	66	3%
Surgical approach	Open	1814	41%	1901	65%
	MI	2595	59%	1037	35%
Type of procedure	Transhiatal oesophagectomy	1349	31%	21	1%
	Transthoracic oesophagectomy	2780	63%	19	1%
	Total gastric resection	98	2%	1072	37%
	Partial gastric resection	7	0%	1490	51%
	Bypass (gastro-enterostomy)	2	0%	110	4%
	Exploratory only open	122	3%	192	7%
	Exploratory only MI	38	1%	2	0%
	Other	11	0%	33	1%
Site of anastomosis	Intrathoracic	1401	32%	183	6%
	Neck	2703	61%	23	1%
	Abdomen	57	1%	2294	78%
	Other/none	253	6%	443	15%
Conduit/reconstruction	Stomach	4055	96%	54	2%
	Colon	24	1%	4	0%
	Small bowel	5	0%	40	2%
	Oesophagojejunostomy (Roux-Y)	90	2%	1054	41%
	Gastroenterostomy (BII or Roux-Y)	12	0%	1365	53%
	Other/none	24	1%	76	3%
Intent of resection preoperative	Palliative	5	0%	120	4%
	Prophylactic	5	0%	14	1%
	Unknown	3	0%	39	1%
	Curative	4399	100%	2769	94%
Intent end-of-surgery	No resection	163		246	
	Curative, macroscopic radical	4222		2445	
	Palliative, tumour left behind	12		74	
	Prophylactic	2		4	

PATIENT COHORT

A curative intent of resection was registered for 4399 (99.7%) oesophageal cancer patients and 2769 (94%) gastric cancer patients. Basic and treatment characteristics are shown in Tables 1 and 2. Of all patients with oesophageal cancer who underwent resection with curative intent, 33% had a textbook outcome, 30% had a complicated postoperative course, and 93% had a pR0 resection. Of all patients with gastric cancer who underwent resection with

curative intent, 35% had a textbook outcome, 19% had a complicated postoperative course, and 87% had a pR0 resection (Table 3).

SURVIVAL OF OESOPHAGEAL CANCER PATIENTS

The 1-, 2-, and 3-year overall survival of patients who underwent a curative resection was 76%, 62%, and 54%, respectively (Figure 2a). Patients with a textbook outcome had 1-, 2-, and 3-year overall survival rates of 85%, 70%, and 62%, respectively, versus 72%, 58%, and 50% for patients with no textbook outcome, respectively. The conditional survival curves are shown in Figure 2b. A textbook outcome was independently associated with longer overall survival (hazard ratio (HR): 0.68 [95% confidence interval (CI): 0.61-0.76]) and longer conditional survival (HR: 0.72 [95% CI: 0.65-0.81])(Table 3). The conditional survival curves of patients with a pR0 versus pR1/pR2 resection are shown in Supplementary figure 1a. The association of a complicated postoperative course and pR0 resection with survival are shown in Table 3. A sensitivity analysis including only patients treated with neoadjuvant chemo radio therapy did not significantly change results.

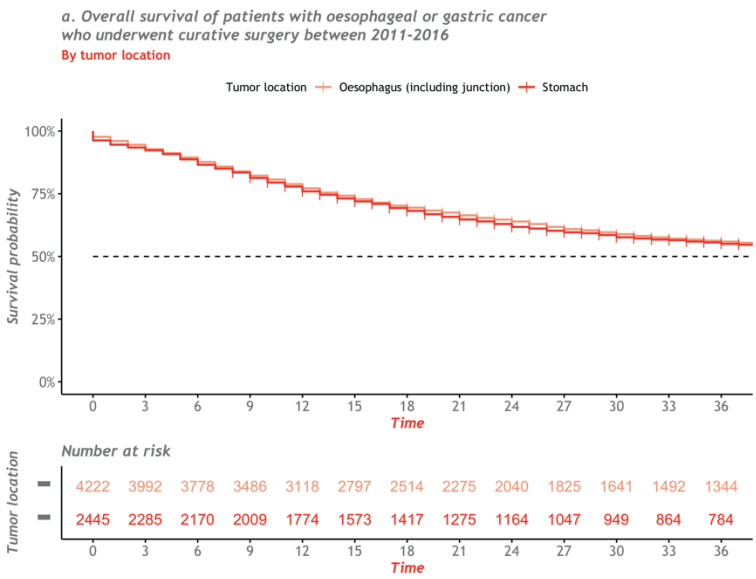

Figure 2a. Overall survival of oesophageal and gastric cancer of patients who underwent curative surgery.

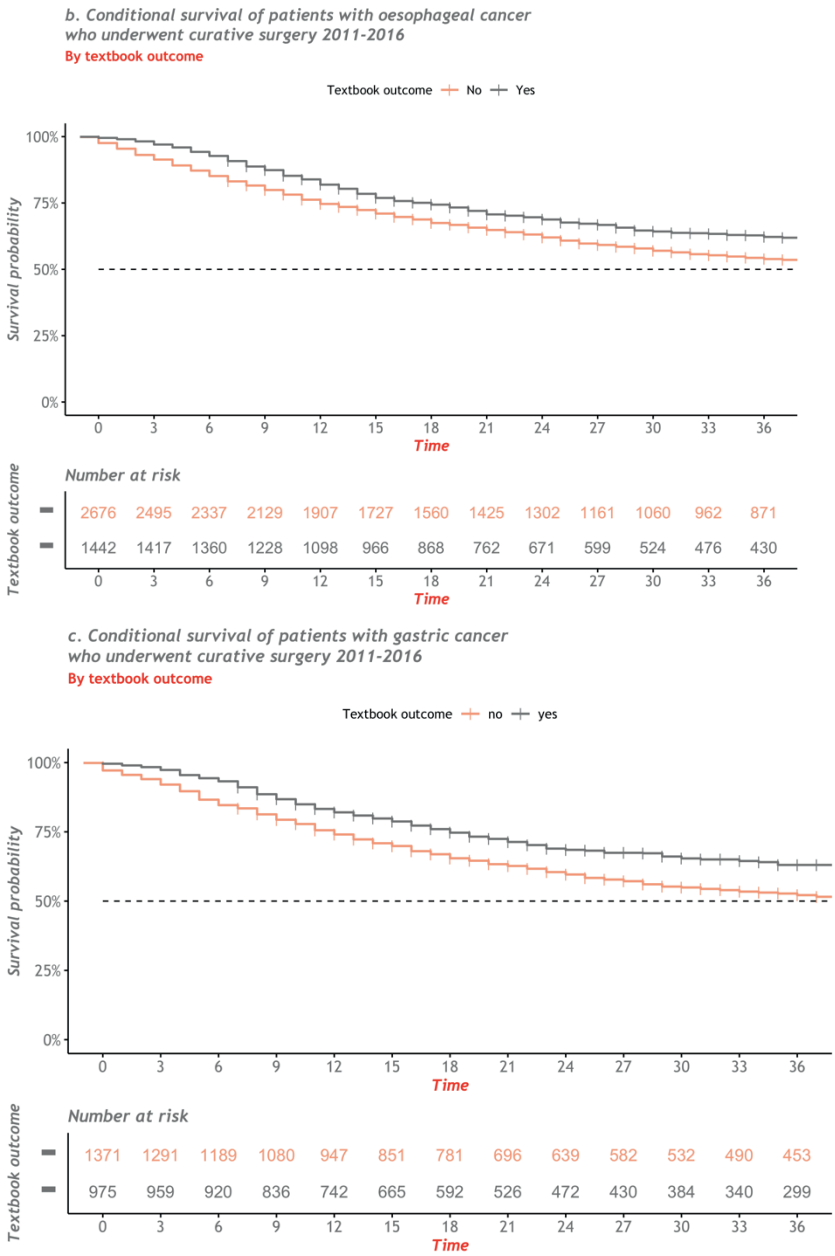

Figure 2b and 2c. (b) Conditional survival (under the condition of surviving the first postoperative 30 days) of patients who underwent curative surgery for oesophageal cancer and whether or not had a 'textbook outcome' and (c) Conditional survival (under the condition of surviving the first postoperative 30 days) of patients who underwent curative surgery for gastric cancer and whether or not had a 'textbook outcome'.

Table 3. Multivariable Cox regression analyses, multiple models evaluating the independent association of short-term outcomes with overall survival and conditional survival (under the condition of surviving the first postoperative 30 days).

Oesophageal cancer

Each outcome is adjusted for: sex, age, Charlson comorbidity score, American Society of Anesthesiologists (ASA), Body Mass Index, weight loss preoperatively, location tumour, pTNM stage, pT-stage, pN-stage, cM-category, histological subtype, differentiation of the tumour and surgical procedure.

	n	P value	HR	CI 95%	
Association short-term outcomes with overall survival	4110				
Textbook outcome	1443 (33%)	<0.001	0.68	0.61	0.76
Complicated postoperative course	1310 (30%)	<0.001	1.54	1.39	1.70
pR0	3933 (93%)	<0.001	0.75	0.63	0.89
Association short-term outcomes with conditional survival	4110				
Textbook outcome		<0.001	0.72	0.65	0.81
Complicated postoperative course		<0.001	1.36	1.22	1.51
pR0		0.003	0.77	0.64	0.92

Gastric cancer

Each outcome is adjusted for: sex, age, Charlson comorbidity score, American Society of Anesthesiologists (ASA), Body Mass Index, weight loss preoperatively, location tumour, pTNM stage, pT-stage, pN-stage, cM-category, histological subtype and differentiation of the tumour.

	n	P value	HR	CI 95%	
Association short-term outcomes with overall survival	2382				
Textbook outcome	975 (35%)	<0.001	0.62	0.54	0.71
Complicated postoperative course	533 (19%)	<0.001	1.91	1.67	2.20
pR0	2169 (87%)	<0.001	0.69	0.58	0.82
Association short-term outcomes with conditional survival	2276				
Textbook outcome		<0.001	0.67	0.59	0.77
Complicated postoperative course		<0.001	1.51	1.29	1.77
pR0		<0.001	0.67	0.56	0.80

SURVIVAL OF GASTRIC CANCER PATIENTS

The 1-, 2-, and 3-year overall survival of the patients who underwent a curative resection was 71%, 56%, and 49%, respectively (Figure 2a). Patients with a textbook outcome had 1-, 2-, and 3-year overall survival rates of 85%, 70%, and 64%, respectively, versus 64%, 49%, and 42% for patients with no textbook outcome, respectively. The conditional survival curves are shown in Figure 2c. A textbook outcome was independently associated with longer overall survival

(HR: 0.62 [95% CI: 0.54-0.71]) and longer conditional survival (HR: 0.69 [95% CI: 0.60-0.79])(Table 3). The conditional survival curves of patients with pR0 versus pR1/pR2 are shown in Supplementary figure 1b. The association of a complicated postoperative course and pR0 resection with survival are shown in Table 3. A sensitivity analysis including only patients not treated with neoadjuvant therapy did not significantly change results.

HOSPITAL VARIATION

'Textbook outcome' was achieved in 15% of patients who underwent surgery in hospitals performing 0-19 oesophagectomies per year (total number of patients (n)=102), in 21% of patients in hospitals performing 20-39 oesophagectomies per year (n=938), and 37% of patients in hospitals performing >40 oesophagectomies per year (n=3374)(p=<0.001). For gastric cancer, 'textbook outcome' was achieved in 23% of patients who underwent surgery in hospitals performing 0-19 gastrectomies per year (n=483), 29% in hospitals performing 20-39 gastrectomies per year (n=567), and 27% in hospitals performing >40 gastrectomies per year (n=1896)(p=<0.001). In the time period 2015-2018, for oesophagectomies, 4 hospitals could be identified as best performers and 4 hospitals as underperformers. Textbook outcome was achieved in 44% and 26% of patients in the best-performing and underperforming hospitals, respectively. For gastrectomies, 3 hospitals could be identified as best performers and 3 hospitals as underperformers. Textbook outcome was achieved in 48% and 32% of patients in the best-performing and underperforming hospitals, respectively.

DISCUSSION

This study was performed to assess the association between short-term outcomes and long-term survival in a national cohort of patients with oesophageal or gastric cancer who underwent resection with curative intent. It was shown that the composite measure 'textbook outcome' was associated with longer overall survival and conditional survival. Separately, an 'uncomplicated postoperative course' and 'complete tumour resection (pR0)' were also associated with longer overall and conditional survival. This study showed that

it was possible to identify best-performing hospitals and underperforming hospitals based on 'textbook outcome'.

The results of this national cohort study are in line with findings of previous research. It is generally known that complete tumour resection (pR0) is associated with longer survival,[11-17] and recently, in a single centre cohort study, 'textbook outcome' was found to be associated with longer survival.[18] This single centre was a tertiary hospital, which might not represent the 'real world' situation. In the current study, the association with long-term outcomes is confirmed with data of a 'real world' cohort.
For patients with postoperative complications it is known that these have worse short-term outcomes; i.e., lower postoperative quality of life and higher costs.[19,20] However, there is inconclusive evidence that postoperative complications are associated with long-term survival. In the current study, the composite measure: 'a postoperative complicated course' was associated with worse long-term outcomes, even after adjustment for several confounding factors.

In the Netherlands, the quality indicators evaluated in this study are currently used in the DUCA. 'Textbook outcome', 'complicated postoperative course', and 'pR0' were already considered valuable by patient federations, healthcare insurance companies, and the scientific committee of the DUCA. The results of this study might accentuate the value of these indicators for use in clinical auditing.
The outcome indicators of the DUCA contain only information on the postoperative period until 30 days and during the initial hospital admission. There are two major reasons not to include long-term outcome indicators in the DUCA. A first reason for not using long-term outcomes in the DUCA is to limit the registration burden. The second reason for not using long-term outcomes may be even more important. For control and continuous improvement of processes, the Plan-Do-Check-Act cycle is often used.[21] For efficient quality improvement, a short feedback loop is essential. For long-term outcomes, the Plan-Do-Check-Act method is less effective and efficient as it may take up to one to two years to evaluate these long term outcomes. For example, when the percentage of patients that experience anastomotic leakage is used as a quality

indicator, a short feedback loop may help surgical teams noticing a high percentage of anastomotic leakage on time. Appropriate measures can be taken (e.g., team evaluation, surgical training, or proctoring). Subsequently, the results of this intervention can then also be analysed in the short term. When using long-term outcomes, deviating outcomes might be noticed too late, interventions might be started too late, and the results after an intervention might be announced too late. The present study provides additional evidence that short-term outcome indicators may be a proxy for long-term outcomes and this result may highlight the importance of the use of these outcomes.

Hospital outcomes on percentage 'complicated postoperative course' and 'complete tumour resection' are open to the public. The primary goal of transparency is to stimulate quality improvement initiatives in underperforming hospitals. Secondly, patients can use this information to choose between hospitals. Selecting good-performing hospitals by patients may improve outcomes on a nationwide basis. The national outcomes on the DUCA indicators suggest that performance on short-term indicators could be improved. This study showed that in patients that are operated on with curative intent, the percentage of patients with a 'textbook outcome' in the DUCA cohort was only 33% for oesophageal cancer and 35% for gastric cancer, respectively. A 'complicated postoperative course' occurred in 30% of oesophageal cancer patients and 19% of gastric cancer patients. Complete tumour resection was achieved in 93% of oesophageal cancer patients and 87% of gastric cancer patients.

Because of the transparency of DUCA indicators, it was already known that the outcomes of 'complicated postoperative course' and 'complete tumour resection' varied between individual hospitals.[22] In this study also variety in hospital outcomes on 'textbook outcome' was shown. High annual volume hospitals had higher percentages of 'textbook outcome' after both oesophagectomy and gastrectomy, and best-performing hospitals and underperforming hospitals could be identified. Taken together the variation between hospitals and the association of these outcomes with survival may underline the importance of the use of these indicators in national audits. These indicators might be an important instrument to improve the quality of care on a national level.

In previous studies, it has been suggested that the relationship between complications and survival may not be causal. Patients with comorbidities or more severe disease may be at higher risk for complications but may also die sooner because of comorbidities or more severe disease. However, some other studies suggest that secondary disturbance of the immune system due to the presence of perioperative complications may lead to an early recurrence.[23-26] In this study, it was attempted to adjust for confounding with multivariable analysis. However, residual confounding could have been present. For more accurate assessment of causality, data on disease-specific survival are needed. Unfortunately, those were lacking in the used datasets.

A limitation of this study was the validity of the combined dataset. The survival information of a nationwide database was combined with the data of the DUCA. Based on the validation tests with two cohorts in this study, the accuracy of survival status in the combined dataset is estimated to be 94-95% based on discrepancies in 5.1-6.0% of patients in the test cohorts. The most likely reason for the discrepancy between test cohort data and the combined dataset is that matching of patients from both datasets failed. The citizen's service number (BSN) was used to match patients. However, when by accident an incorrect BSN was registered in the DUCA dataset, matching was not possible. Another reason for the discrepancy could be that patients were missing in the Vektis dataset, for example because they had no health care insurance or because they have been migrated. In this study, it was assumed that patients with a discrepancy in survival status were randomly divided between the stratified analyses on outcomes executed in this study. However, registration of incorrect BSN might not be randomly divided between hospitals, and therefore it is not excluded that this dataset has influenced the analysis on association of hospital performance and survival.

FUTURE PERSPECTIVES AND CONCLUSIONS

This study showed an association of the composite measure 'a complicated postoperative course' with long-term survival. Further research is needed to assess the association of different kinds of complications with long-term survival and to assess the association of complications with disease-specific survival. The DUCA group aims to create a dataset with fair survival information to also support hospital comparisons and more reliable survival rates.

With these findings, it can be concluded that the achievement of good short-term outcomes such as 'textbook outcome' is valuable for long-term survival after surgery for both oesophageal and gastric cancer. These outcomes should be used in clinical auditing to improve outcomes of clinical care in these patients. With the Plan-Do-Check-Act cycle, the outcomes of every hospital need to be evaluated on a continuous base to improve the quality of care.

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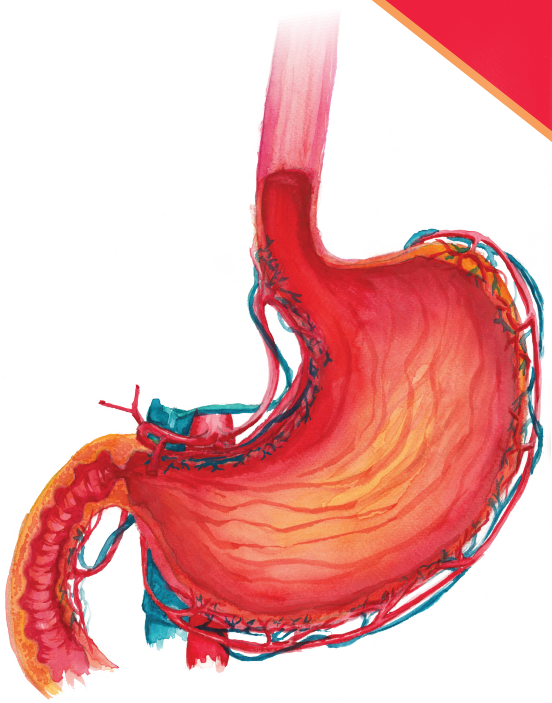
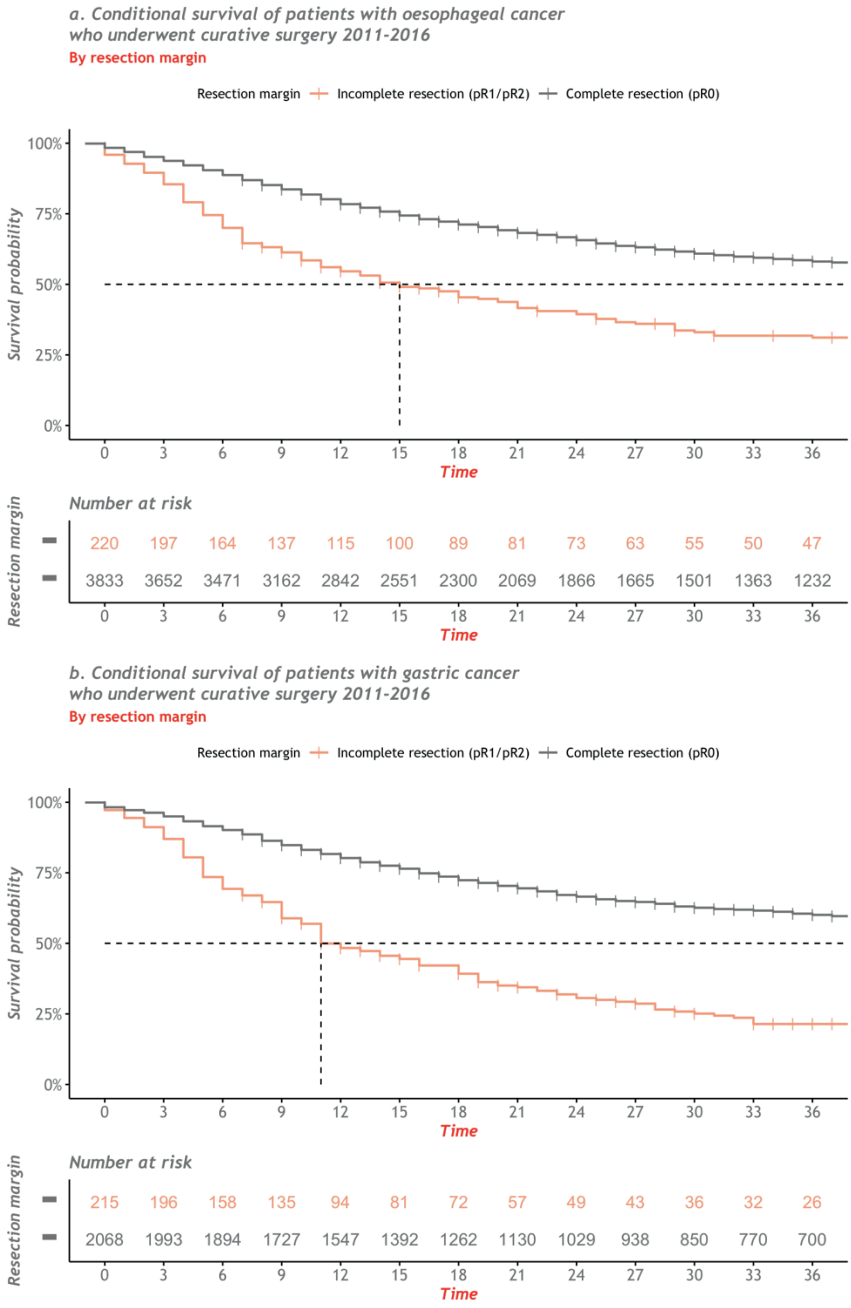
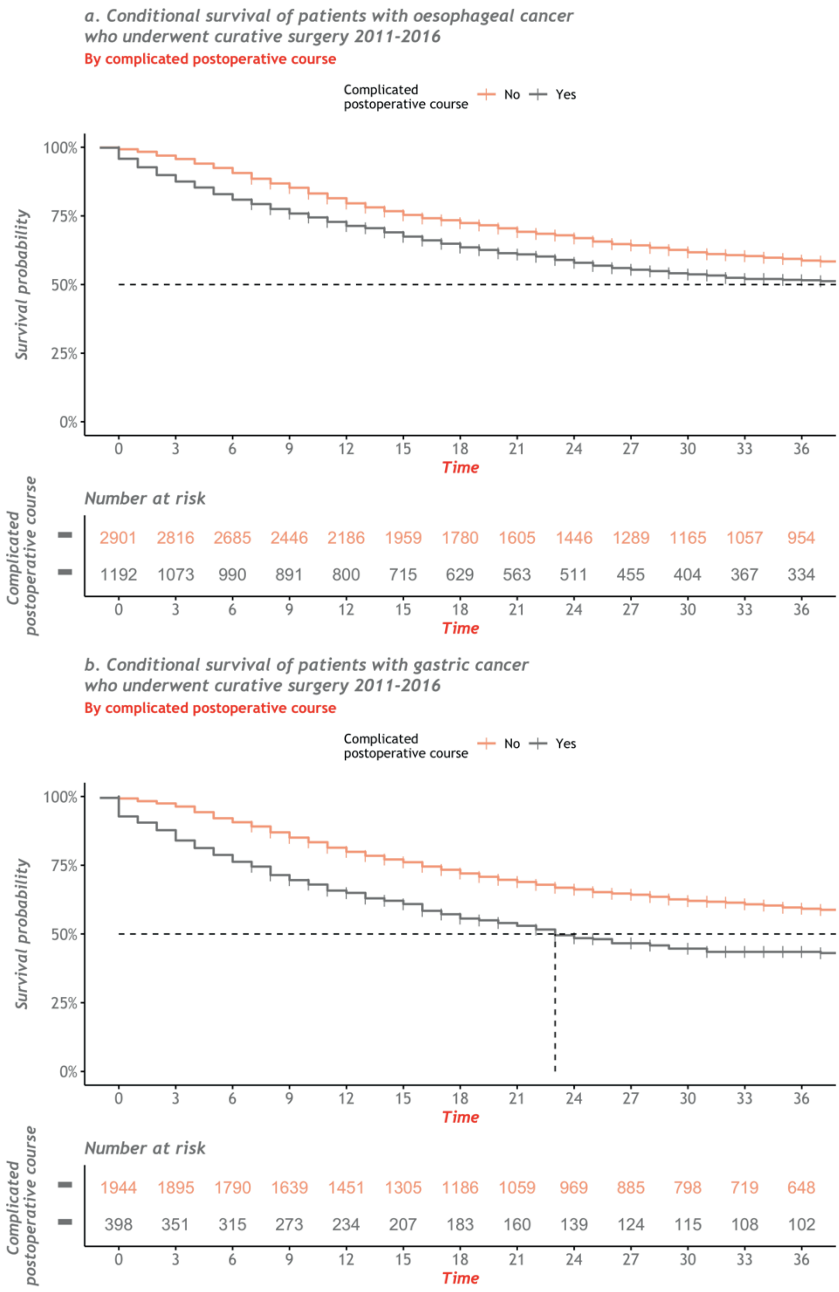


CHAPTER 7

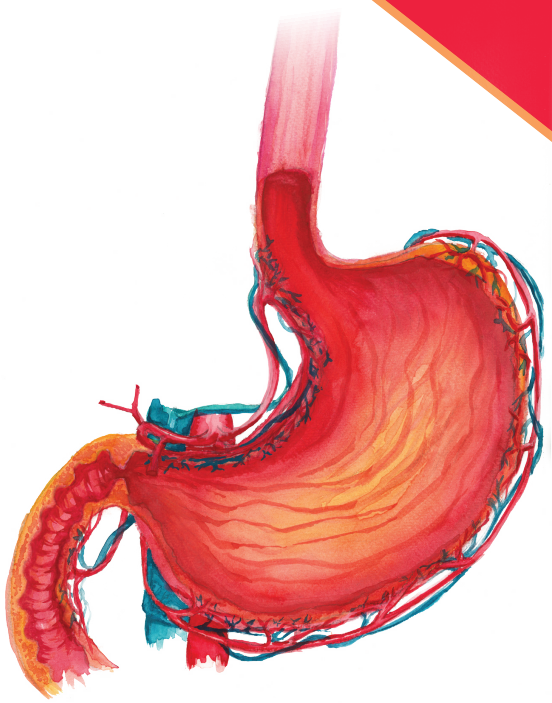
Supplementary data



Supplementary figure 1a and 1b. Conditional survival (under the condition of surviving the first postoperative 30 days) of patients who underwent curative surgery for oesophageal (a) and gastric (b) cancer and had a pR0 versus pR1/2 resection



Supplementary figure 2a and 2b. Overall survival of patients who underwent curative surgery for oesophageal (a) and gastric (b) cancer in best performing hospitals versus underperforming hospitals, identified based on 'textbook outcome'.



CHAPTER 8

Transhiatal or transthoracic oesophagectomy

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ADAPTED BY PERMISSION FROM: SPRINGER NATURE,
MINIMALLY INVASIVE SURGERY FOR
UPPER ABDOMINAL CANCER
BY MIGUEL CUESTA (EDITOR) © 2019

INTRODUCTION

A surgical resection remains the most important treatment modality for the cure of non- metastasized oesophageal cancer. For many years, open oesophagectomy was performed worldwide through two approaches: the transhiatal oesophagectomy (THO) and transthoracic oesophagectomy (TTO). Pertaining in-hospital mortality rates were between 3 and 10%, and the 5-year survival rate after surgery was 20–30%. Resulting contributions to improved patient-care and selection were the improvement of perioperative care, the introduction of neoadjuvant treatments, the centralization of surgery in high volume centres and the better imaging modalities. Hence, short and long-term outcomes of surgical resection have improved substantially.

Minimally invasive oesophagectomy (MIE) was pioneered in the early nineties and popularized in the last decades by many surgeons. Three meta-analyses support the concept that MIE may be associated with less respiratory complications, a reduction of morbidity and a faster postoperative recovery.[1–3] At the same time, the procedure is technically demanding and programs to safely introduce these techniques are warranted. Two randomized trials compared open oesophagectomy with MIE: the total (thoraco-laparoscopic) MIE in the TIME-trial and the hybrid (laparoscopy and thoracotomy) oesophagectomy in the MIRO-trial. Both studies show the short-term advantages of MIE: less blood loss, a lower rate of respiratory infection, a shorter hospital stay and a better quality of life in favour of the MIE. The quality of the specimen resected is similar to the open technique (radicality and number of lymph nodes). Long-term oncological outcome of the TIME trial at 1-year and 3-year showed no differences between the two groups concerning overall and disease-free survival.[4]

In this chapter we review the transhiatal and transthoracic oesophagectomy and discuss the comparison of the outcomes of these two open approaches by a randomized controlled study, the HIVEX trial.

COMPARING THO WITH TTO: THE HIVEX TRIAL

TRANSHIATAL OESOPHAGECTOMY

Via an upper abdominal incision, the distal oesophagus and locoregional lymph nodes in the posterior mediastinum are dissected en bloc through a widened hiatus. The upper abdominal lymph nodes are dissected including the paracardial lymph nodes, the nodes along the lesser curvature and the nodes at the left gastric artery. A standard D1 plus or D2 lymphadenectomy of the celiac trunk is performed. The cervical oesophagus is dissected via a left (or right) cervical incision and the intrathoracic oesophagus dissected bluntly and stripped with the aid of a vein stripper. Creation of gastric tube and resection of the specimen is then followed by positioning the gastric tube in the prevertebral plane to the neck where the anastomosis is made.[5]

TRANSTHORACIC OESOPHAGEAL RESECTION

Several techniques are used: Ivor Lewis procedure (right thoracotomy and laparotomy), Mc Keown (three-stage with neck incision) and the Sweet procedure (left thoraco-abdominal incision). The three-stage and the two-stage open oesophagectomy involves an oesophageal resection, creation of a gastric tube, a two-field lymphadenectomy (celiac trunk and mediastinal lymphadenectomy) followed by a cervical anastomosis in the three-stage procedure and an intra- thoracic anastomosis in the case of an Ivor Lewis procedure. The extent of the mediastinal lymphadenectomy is still debated, but the majority of the patients undergoes a total mediastinal lymphadenectomy.

DIFFERENCES BETWEEN OPEN TTO AND THO

In 2001, Hulscher et al. published a meta- analysis on transthoracic and transhiatal oesophagectomy.[6] Six prospective comparative studies including three control-randomized studies (RCT) and 18 retrospective comparative studies were included (all published between 1990 and 1999). The three RCTs in this meta-analysis were all underpowered and focused on squamous cell carcinoma.[7–9] In 2002, Hulscher et al. published the Dutch HIVEX trial, an RCT

comparing TTO with THO.[10] In 2007, Omloo et al. published a long- term follow-up of this trial (5 years).[11]

The HIVEX trial included 220 patients with adenocarcinoma type I of the distal oesophagus or adenocarcinoma type II of the gastric cardia involving the distal oesophagus. Patients were randomized to THO or TTO with extended en bloc lymphadenectomy. Primary endpoints of this study were overall survival and disease-free survival. Secondary endpoints were the perioperative data and other parameters such as postoperative morbidity and mortality, the quality of the resected specimen, the number of lymph nodes involved and the number of quality-adjusted life-years gained.

Perioperative morbidity was higher after TTO, but there was no statistically significant difference between the groups THO and TTO regarding in-hospital mortality (2% in the transhiatal group and 4% in the transthoracic group, $p = 0.45$). In the TTO group, 57% of patients had pulmonary complications vs. 27% in the THO group ($p < 0.001$). Chyle leakage occurred more in the TTO group, 10% vs. 2% ($p = 0.02$). In the THO group, vocal-cord paralysis was more common but this difference was not significant (21% vs. 13%, $p = 0.15$). Mechanical ventilation time, ICU stay and hospital stay were significantly higher in the TTO group (postoperative ventilation time: 2 days vs. 1 day, $p < 0.001$; ICU stay: 6 days vs. 2 days, $p < 0.001$; and postoperative hospital stay: 19 days vs. 15 days, $p < 0.001$).

After a median follow-up of 4.7 years, 142 patients had died: 74 (70%) after THO and 68 (60%) after TTO ($p = 0.12$). Although the difference in survival was not statistically significant, there was at 5 years a trend toward a survival benefit holding for the extended approach. Disease- free survival was 27% in the THO group, as compared with 39% in the TTO group, whereas overall survival was 29% as compared with 39%.

The conclusion of this HIVEX trial was that THO was associated with a lower morbidity rate than TTO with its extended en bloc lymphadenectomy. Although median overall, disease-free, and quality-adjusted survival did not differ statistically between the groups, there was at 5 years a trend toward improved long-term survival holding for the extended transthoracic approach.

The long-term follow-up of this randomized trial was published in 2007. Omloo et al., analysed a total of 95 patients who underwent a THO and 110 patients who underwent a TTO. After transhiatal and transthoracic resection, 5-years survival was 34% and 36%, respectively ($p = 0.71$).

WHO MAY BENEFIT FROM TTO OR THO?

In a subgroup analysis, based on the location of the primary tumour (classified after pathological examination of the resection specimen), no over- all survival benefit for either surgical approach was seen in 115 patients with a type II tumour (p = 0.81). In 90 patients with a type I tumour, an absolute survival benefit of 14% was observed with the transthoracic approach (51% vs. 37%, p = 0.33). Moreover, there was evidence that depending on the number of positive lymph nodes in the resection specimen, the effect of treatment differed. In patients (n = 55) without positive nodes, the locoregional disease-free survival after THO was comparable to that of TTO (86% and 89%, respectively). A poor outcome was found for patients (n = 46) with more than eight positive lymph nodes in the resection specimen: the survival was 0% in both groups. Regarding patients (n = 104) with one to eight positive lymph nodes in the resection specimen, a 5-year locoregional disease-free survival advantage was seen for those patients operated via the transthoracic approach (64% vs. 23%, p = 0.02). The authors concluded that there is no significant overall survival benefit for either approach. However, when compared with THO, a TTO for type I oesophageal cancer shows an ongoing trend towards a better 5-year survival rate. Moreover, patients with a limited number of positive lymph nodes (between one and eight) in their resection specimen also seem to benefit from TTO. In patients with a limited nodal burden, a more extensive nodal dissection may indeed cure the patient. However, when the number of positive nodes is very high, this reflects systemic disease and then more extensive surgery can not cure the

patient. Moreover, in patients with a very limited nodal spread, the locoregional nodes can be removed by a THO as well as a TTO.

POST-OPERATIVE MORBIDITY

Most studies showed more complications for the TTO as compared to the THO. The meta-analysis of Hulscher et al.[2] showed more perioperative blood loss, pulmonary complications, chyle leakage, and wound infections in the transthoracic group. More anastomotic leakage and vocal cord paralysis were found in the transhiatal group. The in-hospital mortality rates for transthoracic resection in comparison with transhiatal were higher (9.2% vs. 5.7%, RR: 1.60,

95% confidence interval: 1.89–1.35). The question arises whether these differences still are representative because in recent years we see better patient selection, improvement of perioperative care and refinement of surgical techniques. Lacking recent RCTs we note a cohort study in 2014 by Davies et al. including 680 patients operated between 2000 and 2010, showing a shorter median hospital stay for transhiatal surgery (14 days vs. 17 days, $p < 0.001$). The in-hospital mortality rate also favoured THO (1.1% vs. 3.2% for THO and TTO respectively, $p = 0.110$). The results show a median of 20 nodes in the transthoracic group vs. 13 in the transhiatal group ($p < 0.001$).[12]

MINIMALLY INVASIVE OESOPHAGECTOMY (MIE)

Over the last decades, the safe and oncological- proficient operation termed MIE emerged. Ideally, minimally invasive techniques should be as radical as open approaches and not compromise oncological outcome.[13] It may be fair to say that during the early developmental phase of MIE a somewhat different oncological operation was performed—attributable to the enormous technical challenges and search for optimal techniques. More recent studies show, however, that indices of the number of lymph nodes dissected and surgical margins for MIE are similar or perhaps superior to open approaches. Two RCTs have been performed, one total MIE (TIME trial) and the other hybrid, in which laparoscopy and right posterolateral thoracotomy are performed with intrathoracic anastomosis (MIRO trial).[14, 15] The long-term follow-up of the TIME trial up to 3 years posits similar survival outcomes for the open and the MIE groups.[16]

Minimally invasive oesophagectomy may harbour several advantages for the surgeons as well. The developments of high definition and 3D cameras with robotic platforms offer an excellent and detailed view of the operation field. This facilitates a careful dissection along the tissue planes enabling an increased radical nodal dis- section with less blood loss. Also, ergonomics of the instruments has improved and the surgeon may feel more comfortable during MIE than at open surgery. The possible advantages of robotic surgery including

oesophageal cancer resections seems clear but this has yet to be evidenced by the ROBOT trial, which compares the open oesophageal resection vs. the laparoscopy and thoracoscopy as assisted by robot.[17]
Minimally invasive surgery—especially in prone position—is technically challenging and needs careful introduction using a structured program.

INFLUENCE OF NEOADJUVANT THERAPY

The extended use of neoadjuvant therapy changed the prognosis of the resectable oesophageal cancer cure. According to the long-term outcome of the CROSS trial, a better survival after neoadjuvant chemoradiotherapy is seen for both adenocarcinoma and squamous cell cancer (Carboplatin and Paclitaxel for 5 weeks with concurrent radiotherapy, 41.4 Gy given in 23 fractions, 5 days a week). Five-year overall and progression-free survival rates were 47 and 44% in the neo-adjuvant chemoradiotherapy-plus- surgery group while in the surgery-alone group 33% and 27%, respectively. Holding for the squamous cell cancer, it was 61% vs. 30% and 58% vs. 28%; whereas in the adenocarcinomas case it was 43% vs. 33% and 41% vs. 27%, respectively.[18, 19]
The dissection of lymph nodes is important for the staging of oesophageal cancer and the number of dissected lymph nodes is an important predictor of survival in patients with oesophageal cancer.
Based on data from the CROSS study, Talsma et al. found that in the group of patients treated by surgery alone, the number of resected lymph nodes indeed had a prognostic impact on the survival rate.[20] But the therapeutic value of lymphadenectomy is still controversial in this study after CRT because the number of resected nodes was not associated with survival. Also, a cohort study by Lagergren et al. showed no significant influence of the number of resected nodes on the 5-year survival rates (disease specific and overall) in patients with the surgery-alone group.[21]
As described above, an important distinction between the outcomes of transthoracic and of transhiatal oesophagectomies concerns the differences in lymph-node yield and the possible influence on locoregional recurrent disease. Moreover, given the data on the association between the number of nodes

dissected after neoadjuvant chemoradiotherapy, the question arises what the best surgical approach is for Gastro- oesophageal junction tumours: either the transhiatal approach with limiting morbidity and inability to dissect the nodes from the middle and upper mediastinum, or the transthoracic MIE with extended mediastinal nodal dissection. The trend in the Netherlands is to operate distal oesophageal tumours (type I) totally minimally invasive by use of thoracoscopy and laparoscopy after neoadjuvant therapy. For type II tumours (cardia cancers) many Dutch surgeons prefer a thoracoscopic or transhiatal approach by laparoscopy after neoadjuvant therapy.
Discussions concern whether to organize a new trial, one comparable with the HIVEX trial, in which patients will be treated by neoadjuvant therapy and by minimally invasive surgery. This trial is yet to be accomplished.

CONCLUSION

Evidence concerning which approach is the best for distal oesophageal and GEJ cancers was produced by the HIVEX trial that compared the Transhiatal vs. Transthoracic approach without neoadjuvant therapy. Given the current use of neoadjuvant therapy, there is no comparison of cohorts or of randomized studies that compare MIE THO with MIE TTO for distal or GEJ types 1 and 2 tumours after neoadjuvant therapy. Such a study is crucial for improving the treatment of the distal and GEJ cancers.

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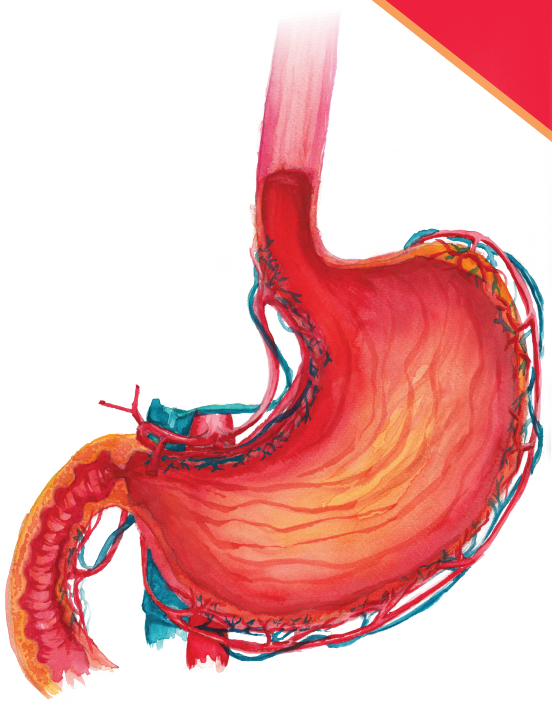

CHAPTER 9

A population-based study on lymph node retrieval in patients with oesophageal cancer: results from the Dutch Upper Gastrointestinal Cancer Audit

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ABSTRACT

BACKGROUND

For oesophageal cancer, the number of retrieved lymph nodes (LNs) is often used as a quality indicator. The aim of this study was to analyse the number of retrieved LNs in the Netherlands, to assess factors associated with LN yield and to explore the association with short-term outcomes.

STUDY DESIGN

For this retrospective national cohort study, patients with an oesophageal carcinoma who underwent oesophagectomy between 2011-2016 were included. Primary outcome was the number of retrieved LNs. Associations were tested with univariable and multivariable regression analysis for the association with ≥15 LNs.

RESULTS

3970 patients were included. Between 2011-2016 the median number of LNs increased from 15 to 20. Factors independently associated with ≥15 LNs were: 0-10 kg preoperative weight loss (versus: unknown weight loss, odds ratio [95% confidence interval]: 0.71[0.57-0.88]), Charlson-score 0 (versus: Charlson-score 2: 0.76[0.63-0.92]), cN2-category (reference: cN0, 1.32[1.05 – 1.65]), no neoadjuvant therapy and neoadjuvant chemotherapy (reference: neoadjuvant chemoradiotherapy, 1.73[1.29-2.32], 2.15[1.54-3.01]), minimally invasive transthoracic (reference: open transthoracic, 1.46[1.15-1.85]), open transthoracic (versus open and minimally invasive transhiatal, 0.29[0.23-0.36] and 0.43[0.32-0.59], hospital volume of 26-50 or >50 resections/year (reference: 0-25, 1.94[1.55-2.42], 3.01[2.36-3.83]) and year of surgery (reference: 2011, ORs: 1.48, 1.53, 2.28, 2.44, 2.54). There was no association of ≥15 LNs with short-term outcomes.

CONCLUSION

The number of LNs retrieved increased between 2011 and 2016. Weight loss, Charlson score, cN-category, neoadjuvant therapy, surgical approach, year of resection and hospital volume were all associated with increased LN yield. The retrieval of ≥15 LNs was not associated with increased postoperative morbidity/mortality.

INTRODUCTION

Since a relationship between the number of retrieved LNs and survival has been shown, the number of retrieved lymph nodes (LNs) is often used as a quality indicator for oesophageal cancer surgery.[1-5]

In 2013, the total number of retrieved LNs has been introduced as one of the quality indicators in the Dutch Upper gastrointestinal Cancer Audit (DUCA).[6] This nationwide audit is to provide insight in the quality of delivered care by reporting reliable and benchmarked information on process and outcome parameters, defined as 'quality indicators'. The 7th edition of the Union for International Cancer Control (UICC) / American Joint Committee on Cancer (AJCC) classification recommended removal of at least 15 LNs for reliable staging of gastric cancer.[7] Hence, the number of 15 nodes was introduced as a quality indicator for oesophageal cancer.

It is unclear whether or not the introduction of this indicator has resulted in a higher LN yield. Furthermore, it is unknown which factors are associated with the number of LNs retrieved and whether or not a higher LN yield is associated with a higher postoperative morbidity or mortality.

The aim of this study was to evaluate trends in the number of retrieved lymph nodes and the proportion of patients with ≥15 LNs in the resection specimen. The second aim was to identify patient, tumour, and treatment factors associated with the number of retrieved LNs, LN yield and thirdly, to evaluate if a higher LN yield is associated with increased morbidity and/or 30-day/in-hospital mortality.

METHODS

STUDY DESIGN

Data were retrieved from the DUCA. This surgical audit was initiated in 2011 and is part of the Dutch Institute for Clinical Auditing (DICA). All patients with oesophageal or gastric cancer undergoing with the intent of resection should be registered. Results on quality indicators are reported to the participating

hospitals. Every year, external quality indicators are transparent for the public, policy makers, insurance companies and patient federations. Validation of completeness and accuracy of data registration is performed.[6] For this study, patient -, tumour -, and treatment characteristics, pathological information, and postoperative outcome (until 30 days after the operation) were retrieved from the DUCA. Because patient- and hospital identity are anonymous in the database, it was not possible to retrieve missing data and additional variables in retrospect.

PATIENT SELECTION

All patients undergoing surgery for oesophageal cancer with curative intention between 2011 and 2016 were included. Patients with an unknown date of birth, unknown survival status at 30 days after surgery or discharge (in case of a hospital stay of >30 days), or with an unknown number of retrieved LNs were excluded.

Since 2010, nCRT followed by surgery has been the standard treatment according to the Dutch guideline for oesophageal carcinoma (with the exception for T1N0 tumours).[8]

OUTCOMES

Primary outcomes were the number of retrieved LNs (as documented by the pathologist based on examination of the resection specimen) and the percentage of patients with ≥15 LNs retrieved (as defined by the number of patients with at least 15 retrieved LNs relative to the total number of patients who underwent a resection).

No informed consent or ethical approval was required under Dutch law.

STATISTICAL ANALYSIS

To compare patient-, tumour-, and treatment characteristics and surgical outcomes between the groups with ≥15 LNs and with <15 LNs, the $\chi 2$ test was used. To identify associated factors, univariable and multivariable logistic regression analyses was performed. Factors with a P value < 0.10 in univariable analyses or clinically relevant were included in the multivariable analyses. For all analyses, statistical significance was defined as $P < 0.05$. All analyses were performed with SPSS® version 24 (IBM, Armonk, New York, USA) and R (R Studio, version 0.99.903, Inc., with package 'ggplot2').

Possible factors associated with LN yield were selected by the scientific committee of the DUCA based on the literature. Consensus was reached for the factors age, pre-operative weight loss, body mass index (BMI), location of the tumour, American Society of Anesthesiologists (ASA) score, Charlson comorbidity score[9], clinical T-, N- and M-category of the tumour, neoadjuvant chemo(radio)therapy, surgical approach (minimally invasive or open, and transhiatal or transthoracic), annual hospital volume, and year of surgery. For evaluation of minimally invasive approaches, a stratified multivariable analysis for transhiatal and transthoracic were used. To assess the relationship between ≥15 LNs and surgical outcomes, a yield of ≥15 LNs was analysed in relation to irradicality of the resections (resection margins not free of tumour cells), intraoperative complications, postoperative complications and 30-day and/or in-hospital mortality was tested. A severe complication was defined as a complication leading to a hospital stay of >21 days, reintervention or death.

RESULTS

A total of 4 076 patients who underwent oesophagectomy for oesophageal carcinoma were registered in the DUCA between 2011 and 2016. Some patients were excluded because date of birth was missing (n=12), survival status after 30 days/at discharge was missing (n=80) or the number of LNs was not documented (n=14). Hence, a total of 3970 patients was included in the study analyses (Supplementary Figure 1).

NUMBER OF RETRIEVED LNS

Since 2011, the median number of retrieved LNs increased from 15 LNs (interquartile range, IQR: 10-21) in 2011 to 20 (IQR: 16-27) in 2016 (Figure 1). Overall, the percentage of patients with ≥15 LNs was 69%. Among patients with ≥15 LNs, the median number of retrieved LNs was 22 (IQR: 18-28), and in the group of patients with <15 LNs, this number was 11 (IQR: 8-13). The percentage of patients with ≥15 retrieved LNs increased from 51% in 2011 to 81% in 2016. In 2011, the percentage of patients with ≥15 retrieved LNs ranged between 0% and 77% among hospitals. In 2016, this hospital variation decreased (Figure 2).

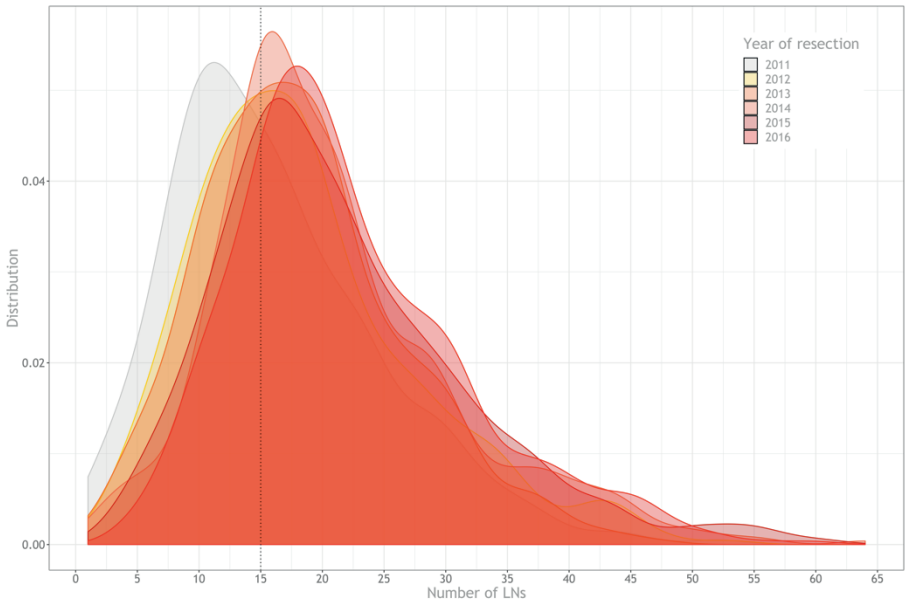

Figure 1. Distribution of the absolute number of LNs retrieved from 2011-2016.

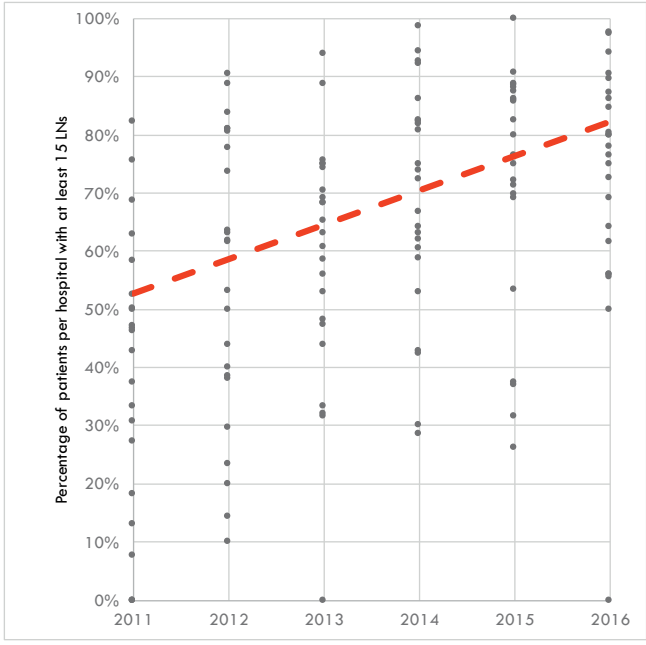

Figure 2. Variation in hospital score on the indicator 'a minimal number of 15 retrieved LNs'.

FACTORS ASSOCIATED WITH ≥15 LNS

Patient, tumour, treatment and hospital characteristics are shown in Table 1. Factors associated with <15 LNs were a Charlson score of 2 (reference: Charlson score 0, 0.76[0.63-0.92]) and unknown preoperative weight loss (reference: 0-10 kg weight loss, odds ratio [95% confidence interval]: 0.71[0.57-0.88]) (Table 2).

Factors associated with ≥15 LNs were clinical N2-category (reference: clinical N0, 1.32[1.05 – 1.65]), no neoadjuvant therapy and neoadjuvant chemotherapy (reference neoadjuvant chemoradiotherapy, 1.73[1.29-2.32] and 2.15[1.54-3.01]), resection in a hospital with 26-50 or >50 resections per year (reference: 0-25 resections, 1.94[1.55-2.42] and 3.01[2.36-3.83]) and resection between 2012-2016 (reference: 2011, ORs: 1.48[1.13-1.94], 1.53[1.17-2.00], 2.28[1.73-3.00], 2.44[1.85-3.21], 2.54[1.91-3.39] for the years 2012 through 2016).

A transthoracic (open or minimal invasive) approach was associated with a higher percentage of patients with ≥15 LNs (versus an open or minimally invasive transhiatal approach, 0.29[0.23-0.36] and 0.43[0.32-0.59]).

A stratified multivariable analysis for transthoracic resections showed a statistically significant association of the minimally invasive approach with a LN yield of ≥15 LNs (reference: open transthoracic approach, 1.46[1.15-1.85]). There was no such association for minimally invasive transhiatal resection with ≥15 LNs (reference: open transhiatal resection, 1.31 [0.97-1.75]).

Table 1. Basic characteristics of study population, including score of percentage of patients with <15 or ≥15 retrieved lymph nodes for each subgroup

Patient characteristics		Total	Results on the quality indicator		
			<15 LNs	≥15 LNs	P value*
		n (%)	%	%	
Total		3970	31%	69%	
Gender	Male	3077 (78%)	31%	69%	0.83
	Female	892 (23%)	31%	69%	
	Unknown	1 (0.0%)	0%	100%	
Age (in years)	0-64	1787 (45%)	29%	71%	0.002
	65-74	1650 (42%)	31%	69%	
	75+	533 (13%)	37%	63%	
Weight loss pre-operative	0-5 kg	2154 (54%)	29%	71%	<0.001
	6-10 kg	835 (21%)	31%	69%	
	10+ kg	443 (11%)	33%	67%	
	Unknown	538 (14%)	38%	62%	
Body mass index	<20	257 (6.5%)	34%	66%	0.48
	20-24	1512 (38%)	31%	70%	
	25-29	1522 (38%)	30%	70%	
	30+	635 (16%)	33%	67%	
	Unknown	44 (1.1%)	41%	59%	

Table 1. Continued

Patient characteristics		Total	Results on the quality indicator		
			<15 LNs	≥15 LNs	P value
		n (%)	%	%	
Location tumour in oesophagus	Cervical	4 (0.1%)	50%	50%	
	Proximal	40 (1.0%)	15%	85%	<0.001
	Mid	486 (12%)	25%	76%	
	Distal	2504 (63%)	31%	69%	
	Gastro-oesophageal junction	936 (24%)	36%	65%	
ASA score	I-II	3070 (77%)	30%	70%	0.08
	III+	880 (22%)	33%	67%	
	Unknown	20 (0.5%)	50%	50%	
Charlson score	0	1939 (49%)	29%	71%	0.002
	1	1012 (26%)	31%	69%	
	2+	1019 (26%)	35%	65%	
Clinical T-category	cT0-1	209 (5.3%)	29%	71%	0.63
	cT2	736 (19%)	33%	67%	
	cT3	2731 (69%)	31%	69%	
	cT4	135 (3.4%)	29%	71%	
	Unknown	159 (4.0%)	31%	69%	
Clinical N-category	cN0	1407 (35%)	33%	67%	0.001
	cN1	1591 (40%)	31%	69%	
	cN2	716 (18%)	26%	74%	
	cN3	100 (2.5%)	25%	75%	
	cN+ (count unknown)	42 (1.1%)	29%	71%	
	Unknown	114 (2.9%)	45%	55%	
Clinical M-category	cM0	3837 (97%)	31%	69%	0.85
	cM1	34 (0.9%)	29%	71%	
	Unknown	99 (2.5%)	34%	66%	
Neoadjuvant therapy	No	324 (8.2%)	28%	73%	0.05
	Chemotherapy	253 (6.4%)	26%	74%	
	Chemoradiotherapy	3373 (85%)	32%	68%	
Surgical approach	TTO thoracic part open	694 (18%)	27%	73%	<0.001
	TTO thoracic part MI	1984 (50%)	18%	82%	
	THO open	935 (24%)	56%	44%	
	THO MI	344 (8.7%)	45%	55%	
	Unknown	13 (0.3%)	69%	31%	
Salvage resection	No	3870 (98%)	31%	69%	0.75
	Yes	55 (1.4%)	29%	71%	
	Unknown	45 (1.1%)	29%	71%	
Hospital volume (in average number of resections/year)	0-25	522 (13%)	53%	47%	<0.001
	26-50	2194 (55%)	29%	71%	
	50+	1229 (31%)	24%	76%	
	Stopped before 2014	25 (0.6%)	76%	24%	
Year of resection	2011	491 (12%)	50%	50%	<0.001
	2012	613 (15%)	39%	62%	
	2013	641 (16%)	37%	63%	
	2014	702 (18%)	26%	74%	
	2015	778 (20%)	24%	76%	
	2016	745 (19%)	20%	80%	

* Chi square analysis, in case of <5% 'unknown' this category is not added in the statistical analysis (exception: cN-category) ASA= American Society of Anesthesiologists, TTO= transthoracic oesophagectomy, THO= transhiatal oesophagectomy, MI= minimally invasive, LNs= Lymph nodes

Table 2. Multivariable logistic regression analysis for factors associated with ≥15 LNs

			Multivariable analysis			
Characteristics		**n**				
Total		**3970**	**P value**	**OR**	**CI 95%**	
Age (in years)			0.29			
	0-64	1756		ref		
	65-74	1615	0.67	0.96	0.82	1.14
	75+	521	0.12	0.83	0.66	1.05
Weight loss pre-operative			0.01			
	0-10 kg	2938		ref		
	10.1-15 kg	261	0.12	0.79	0.59	1.06
	>15 kg	174	0.19	0.78	0.54	1.13
	Unknown	519	<0.001	0.71	0.57	0.88
Location tumour in oesophagus			0.59			
	Cervical	4	0.41	0.4	0.05	3.46
	Proximal	39	0.22	1.8	0.71	4.54
	Mid	480	0.68	0.95	0.74	1.22
	Distal	2451		ref		
	Gastro-oesophageal junction	918	0.59	1.05	0.87	1.27
ASA score			0.77			
	I-II	3020		ref		
	III+	872		1.03	0.85	1.24
Charlson score			0.02			
	0	1897		ref		
	1	998	0.68	0.96	0.8	1.16
	2+	997	0.01	0.76	0.63	0.92
Clinical N-category			0.02			
	cN0	1383		ref		
	cN1	1553	0.37	1.08	0.91	1.29
	cN2	707	0.02	1.32	1.05	1.65
	cN3	99	0.15	1.47	0.87	2.48
	cN+ (count unknown)	41	0.3	1.5	0.7	3.19
	Unknown	109	0.07	0.67	0.43	1.03
Neoadjuvant therapy			<0.001			
	No	322	<0.001	1.73	1.29	2.32
	Chemotherapy	249	<0.001	2.15	1.54	3.01
	Chemoradiotherapy	3321		ref		
Surgical approach			<0.001			
	TTO thoracic part open (incl. MI abdomen)	686		ref		
	TTO thoracic part MI	1968	0.004	1.38	1.11	1.73
	THO open	912	<0.001	0.29	0.23	0.36
	THO MI	326	<0.001	0.43	0.32	0.59
Hospital volume (in average number of resections/year)			<0.001			
	0-25	506		ref		
	26-50	2174	<0.001	1.94	1.55	2.42
	50+	1212	<0.001	3.01	2.36	3.83
Year of resection			<0.001			
	2011	462		ref		
	2012	599	0.01	1.48	1.13	1.94
	2013	616	0	1.53	1.17	2
	2014	699	<0.001	2.28	1.73	3
	2015	774	<0.001	2.44	1.85	3.21
	2016	742	<0.001	2.54	1.91	3.39

ASA= American Society of Anesthesiologists, TTO= transthoracic oesophagectomy, THO= transhiatal oesophagectomy, MI= minimally invasive, OR= Odds Ratio, CI= confidence interval

LN YIELD IN RELATING TO SHORT TERM SURGICAL OUTCOMES

In Table 3 the association of ≥15 LNs with short term outcomes (with <15 LNs as reference group) are shown. A LN yield with ≥15 LNs was independently associated with fewer intraoperative complications (4.5% versus 6.8%, OR: 0.69[0.50-0.95]). Postoperative complications were more frequent in patients with ≥15 LNs than in patients with <15 LN, but in multivariable analysis there was no statistically significant association (Table 3).

Table 3. Surgical outcomes associated with ≥15 LNs

Outcomes	<15 LNs	≥15 LNs	Univariable analysis (with outcomes as dependent variable)		Multivariable analysis (with outcomes as dependent variable)	
	% (n)	% (n)	OR [95% CI] ≥15 LNs	P value	OR [95% CI] ≥15 LNs	P value
Positive resection margins	5.6% (68)	4.9% (132)	1.16 [0.86-1.57]	0.33		
Intraoperative complications	6.8% (83)	4.5% (122)	0.64 [0.48-0.86]	0.003	0.69 [0.50-0.95] ^	0.02
Bleeding (with transfusion)	22% (18)	16% (20)				
Intestinal injury	9.6% (8)	5.8% (7)				
Spleen injury	13% (11)	17% (20)				
Other	55% (46)	61% (75)				
Postoperative complications	57% (702)	61% (1667)	1.17 [1.02-1.34]	0.02	1.01 [0.93-1.27] *	0.28
Pulmonary	29% (356)	32% (879)				
Cardiac	12% (150)	15% (401)				
Anastomosis leakage/local necrosis conduit	20% (241)	18% (503)				
Chyle leakage	5% (58)	8% (240)				
Severe postoperative complications	28% (339)	31% (847)	1.18 [1.01-1.37]	0.03	1.00 [0.85-1.19] *	0.98
30-day/in-hospital mortality	4.2% (52)	3.5% (95)	0.82 [0.58-1.15]	0.24		

^ Adjusted for: body mass index, ASA score, surgical approach, year of resection. * Adjusted for: age, body mass index, Charlson score, ASA score, histological type, tumour location, surgical approach, hospital volume. ASA= American Surgical Association, LNs= Lymph nodes, OR= Odds Ratio, CI= Confidence Interval

DISCUSSION

Between 2011-2016, the percentage of patients with at least 15 retrieved LNs in oesophageal cancer surgery increased on a national level as well as for the individual hospitals. Our results show an association of ≥15 LNs with a higher clinical N-category. It may be possible that in patients with clinical suspicious positive lymph nodes the surgeon is particularly focused on a more complete LN dissection. Also, tumour positive LNs are often increased in size and therefore easier to identify during the operation and during pathological examination of the resection specimen. This could result in a higher number of retrieved LNs.

Another explanation is that the immune response against the tumour influences the number of retrieved LNs. It has been suggested that larger tumours may cause a more intense immune response, leading to hyperplasia of local LNs, which could increase the LN detectability.[10] However, this hypothesis is not proven yet.

It is well known that the type of surgical approach in oesophageal resection influences the number of retrieved LNs; i.e., a transthoracic as compared to a transhiatal approach is associated with a higher number of LNs retrieved, as was also seen in the current study.[11,12] Regarding the impact of a minimally invasive approach on LN yield, conflicting results have been published. A systematic review showed no differences between open and minimally invasive surgery while another meta-analysis showed a significant higher LN retrieval in minimally invasive surgery (16 vs. 10, P = 0.03).[13,14] In the present study, a higher LN retrieval was seen especially in minimally invasive transthoracic procedures, which is in accordance with a recent propensity score matched analysis also with the data of the DUCA (20 LNs (2-59) versus 18 (0-53); p<0.001).[15] It is possible that minimally invasive surgery offers benefits in terms of magnification and visibility of surgical structures and planes which may translate into a higher LN yield.

Busweiler et al. recently showed that in patients undergoing gastrectomy, the percentage of patients with ≥15 retrieved LNs was higher in hospitals with a higher composite hospital volume (gastrectomies, oesophagectomies and pancreatectomies).[16] In our study, a similar association was noticed for oesophageal cancer surgery. It is suggested that hospitals performing this type of surgery, may benefit from the in-hospital experience.[16] More intensive cooperation of a multidisciplinary team could be important for quality improvement initiatives.

This study showed an increase in the number of LNs every year. It is expected that since the introduction of quality indicators in the DUCA, quality improvement initiatives in all hospitals have been initiated because the results of these indicators are transparent for all individual hospitals each year. The national health care inspectorate, the health insurance authorities, and different federations use the outcomes of this indicator to assess the quality of upper

gastrointestinal surgical care in the hospitals in the Netherlands. The increased numbers of retrieved LNs over the years could be the result of an increased awareness for the importance of LN dissection by the surgeon. On the other hand, back table dissection of the specimen and more extensive pathological assessment as a result of dedication of the pathologist, could be major explanations as well. All explanations have likely contributed to improving quality of care. The role of the pathologists in identifying the nodes in the resection specimen is very important as the time spent doing this makes a great difference.[17] In this study the role of the pathologist could not be studied but dedicated pathologists or technicians are associated with increased number of nodes detected.[18,19]

A more extensive LN dissection may lead to better loco-regional tumour control. However, the importance of LN dissection for loco-regional tumour control is debated since the introduction of neoadjuvant chemoradiotherapy. It is known that neoadjuvant chemoradiotherapy leads to tumour and lymph node down staging, resulting in more resections with negative margins and lymph nodes.[20] The study of Talsma et al. showed that the number of retrieved LNs had a prognostic impact for patients who underwent surgery without neoadjuvant chemoradiotherapy, but not in the group of patients who underwent neoadjuvant chemoradiotherapy.[21] For patients treated with neoadjuvant chemotherapy, Markar et al. also showed for patients with a higher lymph node yield, a lower recurrence rate and improved survival. Similarly, the effects of a higher lymph node yield on survival or recurrence was not observed in patients treated with neoadjuvant chemoradiotherapy.[22] In the current study, we observed an inverse correlation between neoadjuvant chemoradiotherapy and retrieved LNs which has been reported before.[11,21,23,24] An explanation for this phenomenon could be that the use of neoadjuvant chemoradiotherapy leads to less priority for an extended LN dissection by Dutch surgeons, or that neoadjuvant treatment, especially neoadjuvant chemoradiotherapy may induce regression of LNs as reported before.[10] So, despite a radical resection, fewer LNs are retrieved or detected by the pathologist. Unfortunately, the DUCA registry has no long-term follow-up. Hence, from the results of this study it cannot be concluded whether or not the number of retrieved LNs is a valid indicator for the quality of loco regional tumour treatment. Nonetheless, this indicator may be

meaningful as an indicator for overall quality of oesophageal cancer care. A higher number of retrieved LNs may lead to an improved tumour staging and complete pathological staging is essential to predict the prognosis of patients. Furthermore, in patients treated with neoadjuvant chemoradiotherapy, signs of tumour regression in LNs (instead of positive LNs) are a better predictor of prognosis than clinical N-category which is not always easy to assess preoperatively.

CONCLUSION

Pro and contra arguments can be provided for the use of a minimal number of retrieved LNs as a quality indicator in clinical auditing. An argument to use this indicator in clinical auditing is that the use of this indicator shows relevant variation in outcomes of hospitals, which seems to distinguish hospitals. Another advantage could be that this indicator may lead to better quality of oesophageal cancer because of quality improvement initiatives. However, the validity of this indicator as a direct measure for the quality of LN dissection is questionable, and the effect of more retrieved LNs on tumour control is debatable since the introduction of neoadjuvant chemoradiotherapy. Nevertheless, a higher lymph node retrieval does not seem to lead to higher morbidity or mortality, so the number of retrieved LNs could be used safely as an indicator for quality of care.

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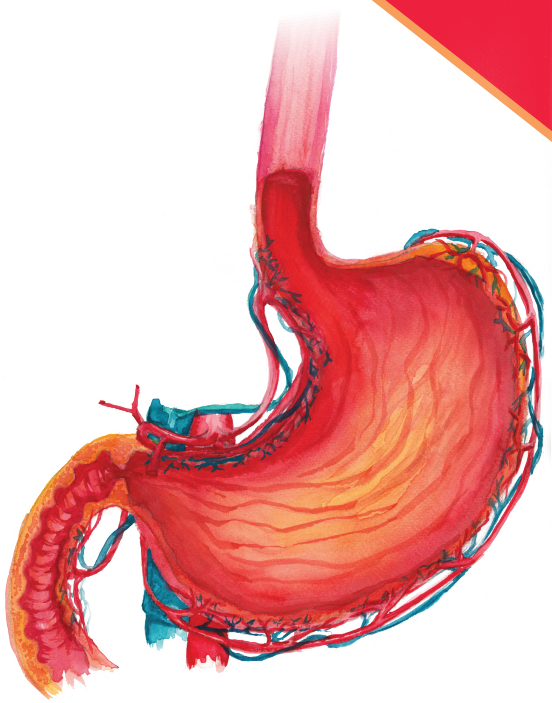
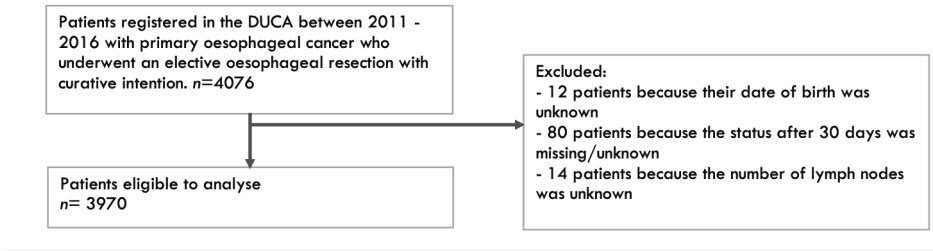
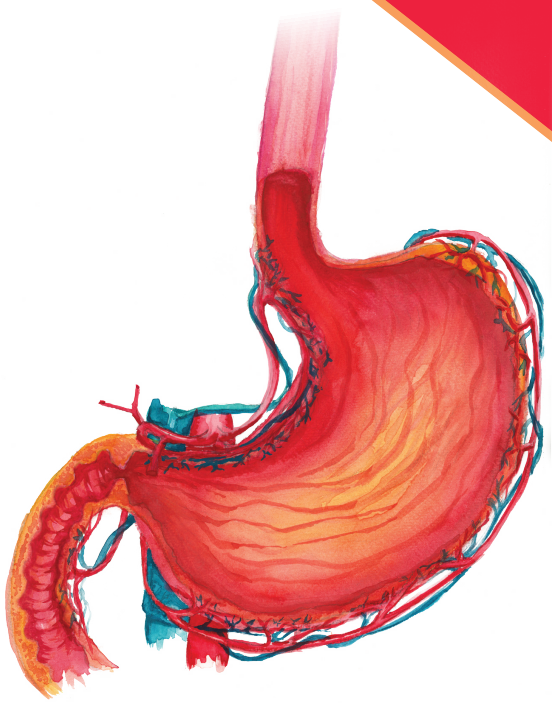


CHAPTER 9

Supplementary data



Supplementary figure 1. Flowchart for inclusion



CHAPTER 10

A PROPENSITY SCORE MATCHED COHORT STUDY TO EVALUATE THE ASSOCIATION OF LYMPH NODE RETRIEVAL WITH LONG-TERM OVERALL SURVIVAL IN PATIENTS WITH OESOPHAGEAL CANCER

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SUBMITTED

ABSTRACT

OBJECTIVE

This study aimed to evaluate whether the quality indicator 'retrieval of at least 15 lymph nodes (LNs)' is associated with better long-term survival and more accurate pathological staging in patients with oesophageal cancer treated with neoadjuvant chemoradiotherapy and resection.

SUMMARY BACKGROUND DATA

Previous studies evaluating the association of LN yield and survival presented conflicting results and many may be influenced by confounding and stage migration.

METHODS

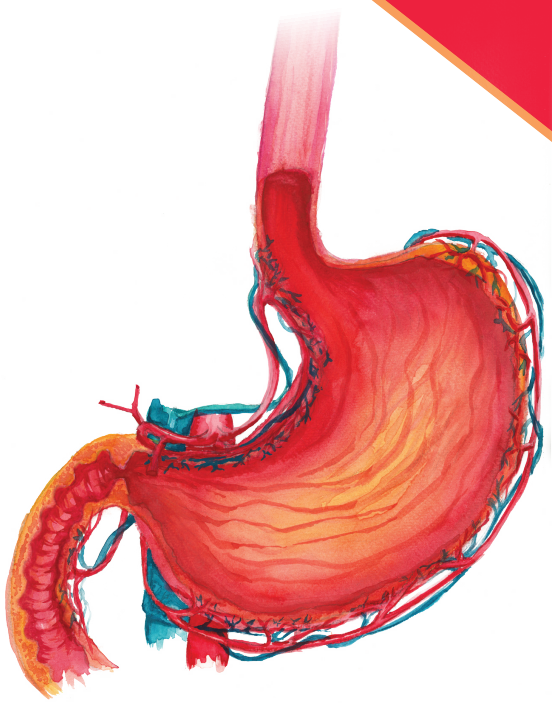
Data of oesophageal cancer patients who underwent neoadjuvant chemoradiotherapy and surgery between 2011-2016 was retrieved from the Dutch Upper Gastrointestinal Cancer Audit. Patients with <15 LNs and ≥15 LNs were compared after propensity score matching based on patient and tumour characteristics. The primary endpoint was 3-year survival. To evaluate the effect of LN yield on the accuracy of pathological staging, pathological N-stage was evaluated and 3-year survival was analysed in a subgroup of patients with node-negative disease.

RESULTS

In 2260 of 3281 patients (67%) ≥15 LNs were retrieved. In total, 992 patients with ≥15 LNs were matched to 992 patients with <15 LNs. The 3-year survival did not differ between the two groups (57% versus 54%, p=0.28). pN+ was scored in 41% of patients with ≥15 LNs versus 35% of patients with <15 LNs. For node-negative patients, the 3-year survival was significantly better for patients with ≥15 LNs (69% versus 61%, p=0.01).

CONCLUSIONS

In this propensity score matched cohort, 3-year survival was comparable for patients with ≥15 LNs, although increasing nodal yield was associated with more accurate staging. In node-negative patients, 3-year survival was higher for patients with ≥15 LNs.



CHAPTER 11

Population-based study on risk factors for tumour-positive resection margins in patients with gastric cancer

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ABSTRACT

BACKGROUND

Radical gastrectomy is the cornerstone of the treatment of locally advanced gastric cancer. This study aimed to evaluate factors associated with a tumour-positive resection margin after gastrectomy and to evaluate the influence of hospital volume.

METHODS

In this Dutch cohort study, patients with junctional or gastric cancer who underwent curative gastrectomy between 2011-2017 were included. The primary outcome was incomplete tumour removal after the operation defined as the microscopic presence of tumour cells at the resection margin. The association of patient and disease characteristics with incomplete tumour removal was tested with multivariable regression analysis. The association of annual hospital volume with incomplete tumour removal was tested and adjusted for the patient- and disease characteristics.

RESULTS

In total, 2 799 patients were included. Incomplete tumour removal was seen in 265 (9.5%) patients. Factors associated with incomplete tumour removal were: tumour located in the entire stomach (OR[95%CI]: 3.38[1.91-5.96] reference: gastro-oesophageal junction), cT3, cT4, cTx (1.75[1.20-2.56], 2.63[1.47-4.70], 1.60[1.03-2.48], reference: cT0-2), pN+ (2.73[1.96-3.80], reference: pN-), and diffuse and unknown histological subtype (3.15[2.14-4.46] and 2.05[1.34-3.13], reference: intestinal). Unknown differentiation grade was associated with complete tumour removal (0.50[0.30-0.83], reference: poor/undifferentiated). Compared to a hospital volume of <20 resections/year, 20-39 and >39 resections were associated with lower probability for incomplete tumour removal (OR 0.56[0.42-0.76] and 0.34[0.18-0.64]).

CONCLUSIONS

Tumour location, cT, pN, histological subtype and tumour differentiation are associated with incomplete tumour removal. The association of incomplete tumour removal with an annual hospital volume of <20 resections may underline the need for further centralization of gastric cancer care in the Netherlands.

INTRODUCTION

A radical gastrectomy is one of the most important predictors of survival in patients with gastric cancer.[1] An non-radical resection, i.e. gastrectomy with a tumour-positive resection margin (incomplete tumour removal), is seen in approximately 1.8-8.4% of patients.[2] In the Netherlands, the percentage of incomplete tumour removal is used as one of the quality indicators of gastrectomies. Between 2011 and 2016, of all gastrectomies for gastric cancer with curative intent, in 9 to 13% the tumours were incompletely removed.[3] This number corresponds with other European outcome registries.[4,5] The British National Oesophago-Gastric Cancer Audit (NOGCA) reported that up to 29% of the gastrectomies performed in individual hospitals had tumour-positive margins.[5] In the Swedish Register for Oesophageal and Gastric Cancer (NREV) the percentage of incomplete tumour removal/unknown resection status was 17%.[4]
Gastric cancer surgery might involve tumour-positive margins on the distal side (duodenum), proximal (gastric remnant or oesophagus) or circumferential. With the current literature, it is unknown which side is most involved. The Dutch national guideline, nevertheless, recommends a proximal and distal resection margin of 60 millimeter.[6]

Awareness of increased risk for incomplete tumour removal may prevent this undesirable outcome. However, data on factors associated with incomplete tumour removal, including preoperative risk assessment models, are scarce. So far, retrospective studies have reported on cohorts from single centres and only few patients were included.[2,7] Also, surgical expertise and quality assurance may play an important role. As individual surgical volume data are difficult to retrieve, annual hospital volume is a widely accepted proxy for surgical experience. For complex surgery including upper gastrointestinal surgery, there is evidence that higher hospital volume and individual surgeon volume are associated with improved surgical quality and outcome.[8-11] However, the relation between hospital volume and incomplete tumour removal has never been investigated.

This study aimed to evaluate the factors associated with incomplete tumour removal in a Dutch cohort. Furthermore, we sought the association between hospital volume and incomplete tumour removal.

METHODS

STUDY DESIGN

Patient data were retrieved from the Dutch Upper Gastrointestinal Cancer Audit. This surgical audit was initiated in 2011. Hospitals are mandated to register all patients with oesophageal or gastric cancer undergoing surgery with curative intent. The DUCA provides insight into the quality of care by reporting validated process and outcome parameters, defined as 'quality indicators'.

Because the radicality of an operation is used as one of the quality indicators, the resection status (R0, R1, R2, not applicable, or unknown), as well as the site of the resection margin (proximal, distal, circumferential) in millimeters is registered. For the reporting of the pathological examination of oesophageal and gastric cancer, a standardized report is used.[12] For this study, data on pathology of the resection specimen, patient -, tumour -, and treatment characteristics were used. Validation of completeness and accuracy of data registration in the DUCA dataset has been performed.[13] Patient- and hospital identity is anonymous in this database. The study protocol was approved by the DUCA scientific committee.

PATIENT SELECTION

Included were all patients with gastric cancer or cancer of the oesophagogastric junction (Siewert type I-III) [14] who underwent gastrectomy between 2011 and 2017 defined as curative by the surgeon at the end of the operation. Patients were excluded if the resection status or essential elements of the registration were unknown including date of birth, survival status at 30 days after surgery or date of discharge (in case of a hospital stay of >30 days).

OUTCOMES

The primary outcome was complete tumour removal as documented by the pathologist based on examination of the resection specimen. The definition of the College of American Pathologists is used in the DUCA to define the completeness of the tumour removal.[15] Removal of the tumour is considered complete (R0) if no microscopical tumour cells are visible in the margin and incomplete (R1 or R2) if microscopically or macroscopically tumour cells are visible in the margin (Patients of who the surgeon defined the resection as complete and curative at the end of the operation, but where the pathological examination showed an R2 resection, were included because this study focuses on the surgeon's estimation of the resection margins.)

STATISTICAL ANALYSIS

To compare patient, and tumour characteristics between the groups with an R0 and R1/R2 resection, the $\chi 2$ test was used. Univariable and multivariable logistic regression analyses were performed to identify factors associated with incomplete tumour removal. Factors with a P value <0.10 in univariable analyses or with clinical relevance were included in the multivariable analyses. To test whether the explanatory variables are useful in predicting the outcome, the Nagelkerke R2 and an area under the receiver operating characteristic curve (ROC) was used. By expert opinion, possible factors for the preoperative associated risk model were selected. At the selection of factors for this model, it was decided to choose only patient- and tumour characteristics. Treatment characteristics such as neo-adjuvant chemotherapy and surgical approach were not selected because this could potentially lead to bias, these factors were analysed with descriptive statistics. The factors age, Charlson comorbidity score16, American Society of Anesthesiologists (ASA) score, tumour location, TNM stage, histological subtype, differentiation grade, and year of surgery were used. To determine factors which can be used preoperatively to identify patients who are at risk for incomplete tumour removal, the clinical TNM-category was preferred for this analysis. However, for N-status of the tumour it was chosen to use pN-stage. The first reason was because an unknown clinical N-stage (cNx) was registered in 13% of patients.[1]. Also, cN-stage and pN-stage do often not correspond and pN-stage is more reliable.

To test the association of annual hospital volume with the resection status, logistic regression models were used with and without adjustment for case-mix variety. Because centralization has taken place in the Netherlands, analyses were executed in the total cohort of 2011-2017 and stratified for the most recent years 2014-2017. Between 2014-2017 hospital volumes were more constant. To address possible confounding caused by differences in treatment strategy between high and low volume hospitals, stratified analyses for patients treated with or without neoadjuvant therapy was performed.

The annual hospital volume in the year of surgery was assigned to each patient. Because the minimum annual hospital volume in the Netherlands is 20 resections per year, and to draw clinically relevant conclusions, subsequently, the volume was grouped into three groups: <20, 20-39 and ≥40 resections per year. Missing items were analysed in a separate group if exceeding 5 per cent.

For all analyses, statistical significance was defined as $P<0.05$. All analyses were performed with SPSS® version 24 (IBM, Armonk, New York, USA).

RESULTS

A total of 2 799 patients had undergone a curative gastrectomy according to the surgeon at the end of the operation and met the inclusion criteria (Figure 1). The majority of patients were male (63%), and the median age was 70 years [interquartile range: 62-77]. In 265 patients (9.5%) the tumour was not completely removed. Patient- and tumour characteristics according to resection status are shown in Table 1.

Tumour location, histological subtype, and, differentiation grade were statistically significant different between patient with complete or incomplete tumour removal. Clinical and pathological T-, N-, and M- stage was more advanced in patients with incomplete tumour removal.

RISK FACTORS FOR INCOMPLETE TUMOR REMOVAL

A tumour located in the entire stomach (versus gastroesophageal junction/fundus), higher cT-categories (cT3, cT4 and cTx category versus cT0-2),

a pN+-category and pNx-category (versus pN-), and diffuse or unknown type adenocarcinoma (versus intestinal type) were associated with incomplete tumour removal (Table 2). Unknown differentiation grade was associated with a complete tumour removal (in comparison with poor differentiation grade/undifferentiated). The area under the ROC of the multivariate model was 0.76.

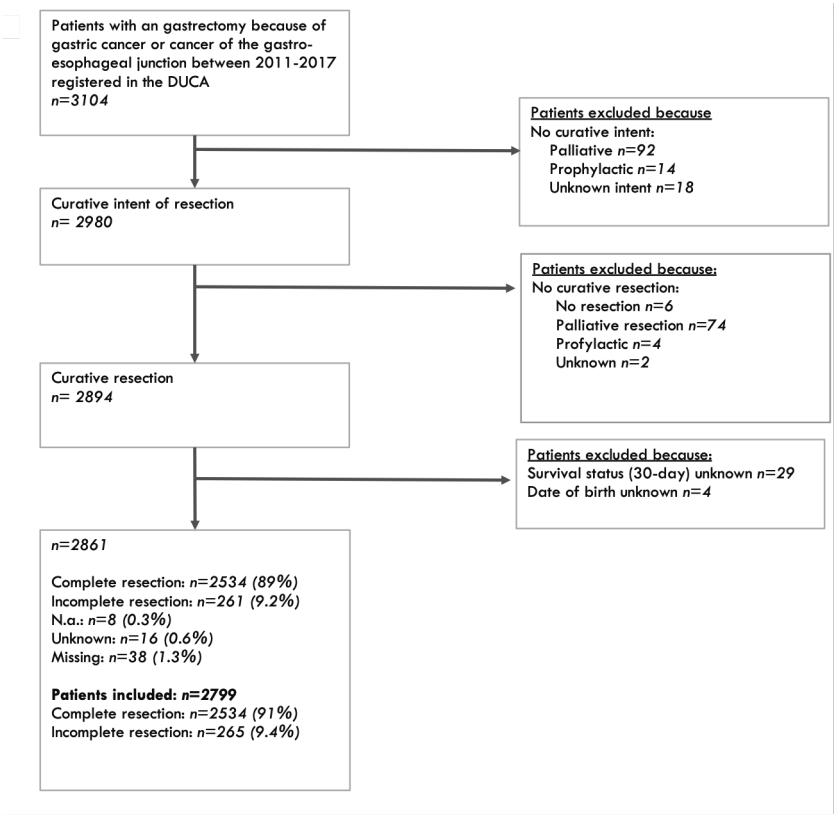

Figure 1. Flowchart inclusion

HOSPITAL VOLUME

In Figure 2, the centralization of gastric surgery in the Netherlands is shown. Compared to 2011, the hospital volumes were higher in 2017, and the number of hospitals performing gastric surgery decreased.

In all logistic regression models, annual hospital volume of <20 was associated with a higher percentage of incomplete tumour removal compared to annual hospital volumes of 20-39 and ≥40 resections per year (Table 3). There was no statistically significant difference between 20-39 and ≥40 resections per year. In a sensitivity analysis including data from the period 2014-2017, similar results were found (data not shown). In stratified analyses according to neoadjuvant therapy, similar results were found. Patients not treated with neoadjuvant therapy, with a volume of <20 resections/year had a higher probability for incomplete tumour resection compared to 20-39 resections/year and 40 or more resections/year ((OR: 0.60 [0.37-0.98] and 0.19 [0.05-0.69], respectively). In patients treated with neoadjuvant therapy, the probability for incomplete tumour resection was also higher for low hospital volume (<20 resections/year) compared to 20-39 resections/year (OR: 0.65 [0.43-0.98]) and for 40 or more resections/year (OR: 0.50 [0.23-1.09]).

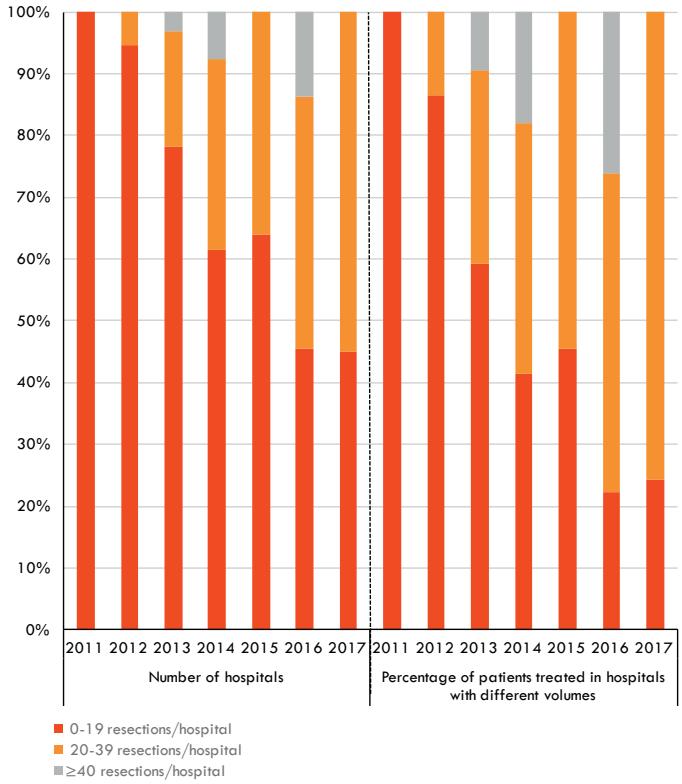

Figure 2. Centralization gastric cancer surgery

Table 1. Patient and tumour characteristics

Patient characteristics	Total n=2799		Complete tumour removal n=2534 (90.5%)		Incomplete tumour removal n=265 (9.5%)		P value
	n	%	n	%	n	%	
Gender							0.044
Man	1754	63%	1603	63%	151	57%	
Women	1045	37%	931	37%	114	43%	
Age (in groups)							0.142
<65 years	888	32%	791	31%	97	37%	
65-74 years	959	34%	880	35%	79	30%	
>75 years	952	34%	863	34%	89	34%	
Charlson score							0.119
0	1243	44%	1121	44%	122	46%	
1	634	23%	587	23%	47	18%	
2+	922	33%	826	33%	96	36%	
ASA score							0.17
I-II	1942	70%	1768	70%	174	66%	
III+	838	30%	749	30%	89	34%	
Unknown							
Location of tumour							<0.001
Oesophageal-Gastric junction/Fundus	313	12%	286	12%	27	11%	
Corpus	833	31%	775	31%	58	23%	
Antrum/Pylorus	1330	49%	1214	49%	116	45%	
Entire stomach	141	5%	94	4%	47	18%	
Pouch/anastomosis	109	4%	99	4%	10	4%	
Unknown	0	0%	0	0%	0	0%	
Clinical Tumour category							<0.001
cT0-2	825	30%	781	31%	44	17%	
cT3	1177	43%	1041	42%	136	52%	
cT4	152	6%	128	5%	24	9%	
cTx	602	22%	542	22%	60	23%	
Missing	0	0%	0	0%	0	0%	
Clinical Node category							0.007
cN0	1433	52%	1319	53%	114	43%	
cN+	1038	38%	925	37%	113	43%	
cNx	288	10%	251	10%	37	14%	
Missing	0	0%	0	0%	0	0%	
Clinical Metastases category							0.043
cM-0	2618	94%	2375	94%	243	92%	
cM+	44	2%	35	1%	9	3%	
cMx	137	5%	124	5%	13	5%	
Tumour histology							0.092
Adenocarcinoma	2633	95%	2379	95%	254	97%	
Squamous carcinoma	5	0%	5	0%	0	0%	
Other	133	5%	127	5%	6	2%	
Not applicable	3	0%	2	0%	1	0%	
Unknown	0	0%	0	0%	0	0%	
Histological subtype							<0.001
Intestinal adenocarcinoma	1149	41%	1097	43%	52	20%	
Diffuse adenocarcinoma	823	29%	676	27%	147	56%	
Mixed type	164	6%	153	6%	11	4%	
Unknown	663	24%	608	24%	55	21%	

Table 1. Continued

Patient characteristics	Total n=2799		Complete tumour removal n=2534 (90.5%)		Incomplete tumour removal n=265 (9.5%)		P value
	n	%	n	%	n	%	
Differentiation grade							<0.001
Well/moderate	881	32%	835	33%	46	17%	
Poor/undifferentiated	1471	53%	1273	50%	198	75%	
not available	93	3%	91	4%	2	1%	
Unknown	354	13%	335	13%	19	7%	
Pathological Tumour stage							<0.001
pT0-2	1030	37%	1010	40%	20	8%	
pT3	1094	40%	977	39%	117	45%	
pT4	614	22%	490	20%	124	47%	
pTx	32	1%	30	1%	2	1%	
Missing	0	0%	0	0%	0	0%	
Pathological Node stage							<0.001
pN0	1254	45%	1198	48%	56	21%	
pN+	1481	53%	1277	51%	204	78%	
pNx	36	1%	33	1%	3	1%	
Missing	0	0%	0	0%	0	0%	
Pathological Metastases stage							<0.001
pM0	2490	89%	2272	90%	218	82%	
pM1	118	4%	89	4%	29	11%	
pMx	54	2%	47	2%	7	3%	
Not applicable	137	5%	126	5%	11	4%	
cT vs. pT staging							0.019
Correct estimated	549	20%	509	20%	40	15%	
Underestimated T stage	256	9%	218	9%	38	14%	
Overestimated T stage	72	3%	68	3%	4	2%	
cTx	283	10%	256	10%	27	10%	
pTx	21	1%	20	1%	1	0%	
cT or pT missing	0	0%	0	0%	0	0%	
Not applicable (neo-adjuvant therapy)	1585	57%	1431	57%	154	58%	

ASA: American Society of Anesthesiologists

SITE OF TUMOR-POSITIVE MARGIN

In 175 of 265 patients with incomplete tumour removal, the site of the tumour-positive resection margin was reported in the DUCA (Supplementary table 1). When the resection of the tumour was incomplete, the proximal resection margin was mostly involved in patients with proximal gastric cancer (junctional/fundus 86% and corpus 80%). Gastrectomy for distal tumours (antrum/pylorus) was most often incomplete at the distal margin (68%). When the tumour was located in the entire stomach, the resection was incomplete at the distal margin in 17%, the proximal margin in 42%, and involvement of both margins was seen in 42% of patients (Supplementary table 2).

Table 2. Probability for incomplete tumour removal, results of uni- and multivariable analyses

Probability for incomplete tumour removal	Univariable analysis			Multivariable analysis		
Variables	**n**	**OR [95% CI]**	**P-value**	**n**	**OR [95% CI]**	**P-value**
Total	2799			2671		
Age (in years)			0.143			
0-64	888	1				
65-74	959	0.73 [0.54-1]	0.050			
75+	952	0.84 [0.62-1.14]	0.263			
Charlson score			0.121			
0	1243	1				
1	634	0.74 [0.52-1.05]	0.087			
2+	922	1.07 [0.81-1.42]	0.648			
ASA score			0.170			
I/II	1942	1				
III+	838	1.21 [0.92-1.58]				
Tumour location			<0.001			<0.001
GEJ/Fundus	313	1		304	1	
Corpus	833	0.79 [0.49-1.28]	0.339	813	0.70 [0.43-1.16]	0.167
Antrum/Pylorus	1330	1.01 [0.65-1.57]	0.957	1308	0.95 [0.60-1.50]	0.828
Entire stomach	141	5.30 [3.13-8.98]	<0.001	138	3.38 [1.91-5.96]	<0.001
Pouch/residual stomach	109	5.30 [3.13-8.98]	0.862	108	1.14 [0.51-2.57]	0.749
Clinical Tumour category			<0.001			0.005
cT0-2	825	1		808	1	
cT3	1177	2.32 [1.63-3.30]	<0.001	1137	1.75 [1.20-2.56]	0.004
cT4	152	3.33 [1.96-5.66]	<0.001	146	2.63 [1.47-4.70]	0.001
cTx	602	1.97 [1.31-2.94]	0.001	580	1.60 [1.03-2.48]	0.036
Pathological Node category			<0.001			<0.001
pN-	1254	1		1207	1	
pN+	1481	3.42 [2.52-4.64]	<0.001	1433	2.73 [1.96-3.80]	<0.001
pNx	36	1.95 [0.58-6.53]	0.282	31	3.17 [0.86-11.61]	0.082
Clinical Metastases category			0.053			0.984
cM0	2618	1		2517	1	
cM1	44	2.51 [1.19-5.29]	0.015	43	1.08 [0.46-2.51]	0.867
cMx	137	1.03 [0.57-1.84]	0.935	111	1.02 [0.53-1.99]	0.948
Histological subtype			<0.001			<0.001
Intestinal adenocarcinoma	1149	1		1112	1	
Diffuse adenocarcinoma	823	4.59 [3.30-6.38]	<0.001	797	3.15 [2.14-4.64]	<0.001
Mixed type	164	1.52 [0.77-2.97]	0.224	160	1.02 [0.50-2.06]	0.963
Unknown	663	1.91 [1.29-2.82]	0.001	602	2.05 [1.34-3.13]	0.001
Differentiation grade			<0.001			0.017
Well/moderate	881	0.35 [0.25-0.49]		839	0.72 [0.48-1.06]	
Poor/undifferentiated	1471	1	<0.001	1417	1	0.096
Not applicable	93	0.14 [0.04-0.58]	0.006	89	0.33 [0.08-1.38]	0.129
Unknown	354	0.37 [0.22-0.59]	<0.001	326	0.50 [0.30-0.83]	0.008
Year of resection			0.562			
2011	250	1				
2012	319	0.71 [0.42-1.20]	0.199			
2013	448	0.71 [0.43-1.15]	0.160			
2014	498	0.78 [0.49-1.25]	0.294			
2015	419	0.66 [0.40-1.09]	0.104			
2016	475	0.64 [0.39-1.05]	0.078			
2017	390	0.61 [0.36-1.02]	0.061			

ASA = American Society of Anesthesiologists

Table 3. Multiple regression models to test the association of hospital volume with incomplete tumour removal

Probability for incomplete tumour removal		Association with hospital volume					
2011-2017		n	OR	95% CI	P-value	Nagelkerke R2	ROC
Probability model based on patient and tumour characteristics *Added to the model: location tumour, cT category, pN stage, cM category, histological subtype, differentiation grade		2671				0.17	0.76
Hospital volume *Not adjusted	<20 resections/year	1388	1		0.001		
	20-39 resections/year	1155	0.68	[0.52-0.89]	0.004		
	40 or more resections/year	256	0.41	[0.23-0.74]	0.003		
Hospital volume *Adjusted for: location tumour, cT category, pN stage, cM category, histological subtype, differentiation grade					<0.001		
	<20 resections/year	1308	1				
	20-39 resections/year	1134	0.56	[0.42-0.76]	<0.001		
	40 or more resections/year	229	0.34	[0.18-0.64]	0.001		
Hospital volume (OTHER REFERENCE) *Adjusted for: location tumour, cT category, pN stage, cM category, histological subtype, differentiation grade					<0.001		
	<20 resections/year	1308	2.95	[1.57-5.55]	0.001		
	20-39 resections/year	1134	1.66	[0.88-3.13]	0.120		
	40 or more resections/year	229	1				

DISCUSSION

This Dutch cohort study shows that patients with advanced gastric cancers (i.e. involving the entire stomach, advanced TNM-stage and diffuse-type gastric cancer) are at risk for incomplete tumour removal. Furthermore, low annual hospital volume (<20 resections per year) is also associated with a higher risk for incomplete tumour removal than middle and high-volume hospitals. The present study is the first population-based study reporting patient-related and tumour-related factors associated with incomplete tumour removal for gastric cancer. The risk factors that were identified in this national cohort study are similar to earlier studies: Songun et al. reported the association between incomplete tumour removal with tumour location and size of the tumor.[18] Other studies

reported the association between incomplete tumour removal and diffuse type carcinoma.[19,20] The risk factors identified in the present study appear to be related to more advanced stomach cancer, and this in itself might be a risk factor for an incomplete tumour removal.
In addition to patient and tumour factors, Bissolati et al. studied the association between the distance from the tumour to the margin of resection and incomplete tumour removal. They showed that resection margins of <20 millimeters in T1 tumours resection and resection margins of <30 millimeters in and T2-4 tumours were associated with incomplete tumour removal.[7] In the present study, the association of resection margin with incomplete tumour removal could not be assessed. Based on the study by Bissolati et al., it could be argued that an extra wide resection margin may prevent incomplete tumour removal. The Dutch guideline recommends a minimum resection margin of 60 milimeters.[6] The German guideline recommends a resection margin of 50 millimeters for intestinal type and 80 millimeters for diffuse-type gastric cancer.[21]

Choosing an appropriate surgical margin can be challenging. The margin should be wide enough to prevent incomplete tumour removal but at the same time a technically feasible and reliable reconstruction should be created. To achieve a safe proximal resection margin for middle gastric tumours, a total gastrectomy may be indicated. Although postoperative mortality and 5-year survival after total and subtotal gastrectomy is comparably,[22] a subtotal gastrectomy is associated with less nutritional side effects and a better quality of life.
For proximal gastric tumours that invade the oesophagus, a more technically challenging anastomosis in the lower mediastinum or a total gastrectomy with subtotal oesophagectomy and colonic interposition may be indicated. This procedures have a higher risk for anastomotic leakage or other postoperative complications.[23,24]
Bissolati et al. also showed that there was an association between incomplete tumour removal at the oesophagogastric junction. However, the surgeon may be confronted intra-operatively with a difficult decision as how to deal with suspicious extension of the tumour beyond what was anticipated. Proximal gastric cancers may invade the oesophagus and the proximal resection margin is at risk.

In the present study, tumour location was not associated with incomplete tumour removal. Distal gastric cancers may invade the duodenum and a Whipple's operation for patients who can tolerate this should be considered. Hence, in the Netherlands the foundation for oncological cooperation (SONCOS) recommends that gastric and oesophageal resections should be performed in the same hospital.[25] However, there are no recommendations regarding the combination of gastric and hepatobiliary surgery.[26] Therefore, when it is anticipated that the proximal margin at the oesophagus or the duodenum is at risk, it is probably advisable to refer patients to hospitals where oesophageal and/or hepatobiliary surgery is performed.

To facilitate a radical resection without unnecessarily wide resection margins, intraoperative frozen section analysis could be used. However, this technique is time-consuming, and the clinical value can be dubious since results can be false negative.[27,28] Squires et al. evaluated outcomes of patients with gastric cancer with a positive intraoperative proximal frozen section converted to an R0 resection in the same procedure. The local recurrence was significantly lower in the converted-to-R0-group than in patients with a positive final frozen section. This study showed that overall survival and progression-free survival was not improved.[29] If time is a concern of hospitals, a frozen section could be considered to achieve a R0 resection in high-risk patients as identified in this study rather than in all patients.
Additionally, intraoperative endoscopic ultrasonography may help in determining the extent of infiltration in the oesophagus or duodenum.[30] Kawakatsu et al. described the combination of preoperative placement of marking clips and intraoperative endoscopy as being helpful in determining a surgical margin in patients who undergo laparoscopic gastrectomy. However, this is the only study that describes the systematically use of endoscopy during gastrectomy. Further studies are therefore needed to evaluate the benefits of this technique.

Besides tumour-related factors, the surgeon's experience with oesophageal and gastric cancer surgery and the number of operations per year performed (hospital volume) may be important to reduce the number of incomplete resections. In the present study, a hospital volume of <20 gastric resections per

year was associated with a higher chance of incomplete tumour removal compared to 20-50, and >50 resections per year. In the past, the association between hospital volume and postoperative morbidity/mortality and overall survival has been studied.[8-10,31-34] For overall survival, conflicting results were published. However, for postoperative morbidity and mortality, several studies reported improved outcomes in high-volume centres. More recently, low hospital volume (<25 resections per year) was associated with fewer retrieved lymph nodes.[35] Between 2012 and 2014, the Association of Surgeons of the Netherlands introduced volume standards for complex surgery. In particular for gastric surgery, a minimum volume of 10 gastric cancer resections in 2012, and from 2013 onwards a minimum of 20 resections per year was required. Currently, some Dutch hospitals have not met this standard yet, and centralization in gastric surgery is still ongoing (Figure 2). It may be possible that hospitals with a relatively low number of patients with gastric cancer use more liberal criteria to select patients for gastrectomy to comply with the minimum required target. This may result in worse outcomes; e.g. higher rates of incomplete tumour removal. At present, we are performing a more in-depth examination in several hospitals to identify if organizational, human or technical factors contribute to unfavourable outcomes after gastrectomy. Nevertheless, the current study endorses the need for centralization of gastric cancer surgery. Another strategy could involve discussing complex patients in a multicentre multidisciplinary team.[36]

In the case of postoperative determination of tumour-positive resection margins, some studies describe that adjuvant chemoradiotherapy is associated with improved survival,[37,38] especially for patients who had no neoadjuvant therapy.[39] Another option which may of benefit is to perform a reoperation with resection of the tumour-positive resection margins.[40,41] The largest cohort of reoperations was 122 patients and a reoperation was successfully performed in 41% of these patients. The authors of the study describe a survival benefit especially for stage N2 or lower tumors.[42] However, evidence for an optimal treatment after an incomplete tumour removal is based on non-randomized studies with small patient groups.

The main strength of this study is the nationwide coverage of the dataset allowing national performance to be assessed. Outcomes of studies using

population-based data reflect daily clinical practice. Prospective (randomized) trials are usually conducted under strict quality control and only with selected patients and thus may not reflect the real world. A national registry might do reflect the real world. However, a database from a national registry may also have its disadvantages; the accuracy and completeness of data may be questioned. Nevertheless, we believe that the DUCA database is accurate to answer our research question. The case ascertainment of the DUCA database is estimated at 97.8%[13] and the resection status is reported with high completeness (1.6% missing, Figure 1). Because in the Netherlands, the information regarding resection margins must be reported according to a standardized pathology report, we assume that the accuracy of the registered resection status is also high.[12]

Another limitation is the retrospective nature of this study. In this study, we could not evaluate the influence of treatment-related factors on resection status such as neoadjuvant chemotherapy and the surgical approach. The reason for this is that bias in the selection of patients for specific treatments may have occurred (treatment by indication bias). Therefore, this study could not evaluate much-discussed treatment-related factors such as the approach of surgery. However, recently, a study with data of the DUCA compared minimally invasive gastrectomy with open gastrectomy in a propensity-matched cohort. This study showed no differences in resection status between the two groups (R0 in 88% versus 85%, p=0.189).[17] Another potential treatment-related factor that could not be evaluated in this study is inadequate diagnostic staging. From the present dataset it was not possible to compare the diagnostic work up between patients that underwent a complete and incomplete tumour removal, because both patient identity and hospital identity are anonymous.

Finally, data on survival were not available. Therefore, evaluation of the (independent) association of complete resection with survival was not possible. A gastrectomy with tumour-positive margins may reflect an aggressive biology of the tumour and as a consequence have a poor prognosis. Even after gastrectomy with negative resection margins, large poorly differentiated tumours will likely spread beyond the surgical field and surgery can not cure these patients. Future studies may be needed to evaluate the independent association of incomplete resections with survival.

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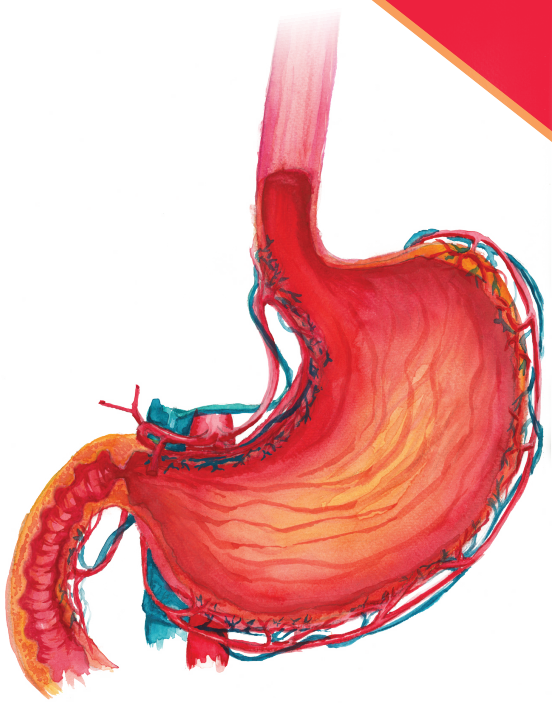


CHAPTER 11

Supplementary data

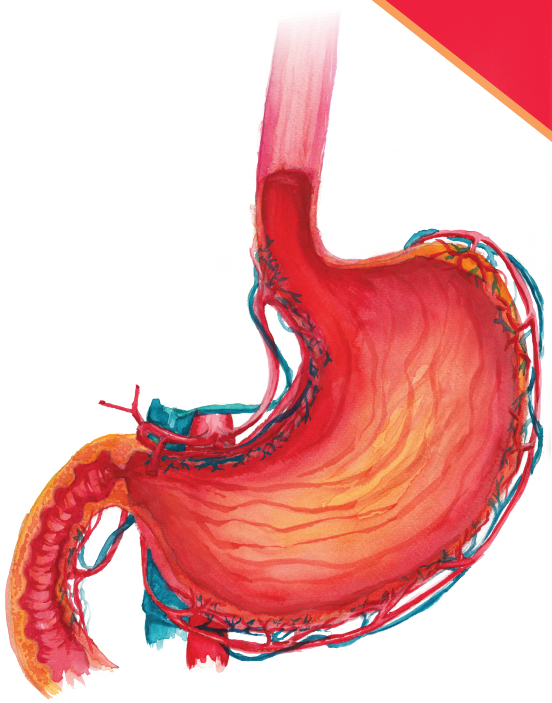
Supplementary table 1. Location tumor-positive resection margin

Location tumor-positive resection margin		
	n	%
Distal	68	26%
Proximal	78	29%
Circumferential	1	0.4%
Distal and proximal	29	11%
Unknown	90	34%
Reported 'unknown'	37	41%
Both margins reported >0mm	43	48%
Missing	6	6.7%
Reported 'not applicable'	3	0.3%
Total	265	

Supplementary table 2. Location tumor-positive resection margin for each tumor location

			Location tumor-positive resection margin							
	Total	**No information**	**Distal**		**Proximal**		**Distal and proximal**		**Circumferential**	
	n	**n**	**n**	%	**n**	%	**n**	%		
Location of tumor										
GEJ	14	6	0	0%	7	88%	0	0%	1	13%
Fundus	13	6	1	14%	5	71%	1	14%		
Corpus	58	18	6	15%	32	80%	2	5%		
Antrum/Pylorus	116	38	53	68%	16	21%	9	12%		
Entire stomach	47	11	6	17%	15	42%	15	42%		
Pouch/anastomosis	10	5	2	40%	2	40%	1	20%		

GEJ: Gastro-esophageal junction



CHAPTER 12

Improving outcomes by safe sharing of outcomes of oesophagogastric cancer surgery

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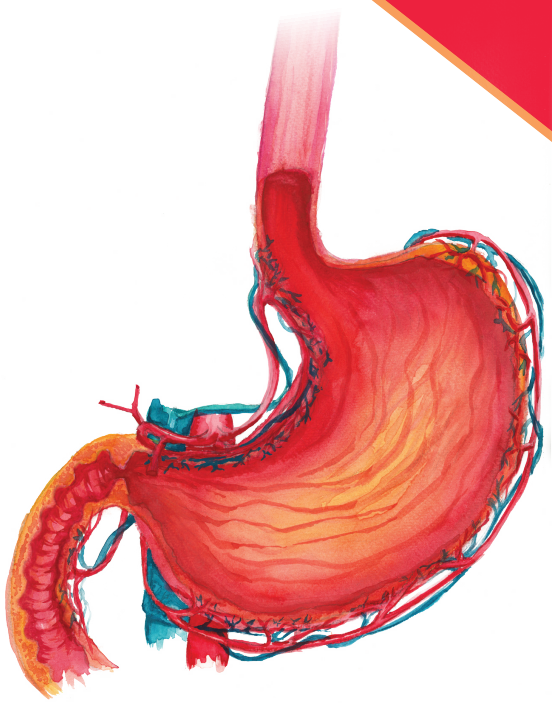
SUBMITTED

ENGLISH SUMMARY

Since the introduction of the Dutch Upper Gastrointestinal Cancer Audit, some outcomes in oesophagogastric cancer surgery has been improved (30-day mortality, lymph node retrieval). However, outcomes on a complicated postoperative course (a complication in combination with reintervention, prolonged hospital stay or death) are stable. Therefore, a nationwide improvement project was initiated. In this project, two meetings were organized. In these meetings, all Dutch upper gastrointestinal surgeons participated, and all presented their results regarding anastomotic leakage and lymph node retrieval. All results were compared and discussed. Also, experiences with different anastomosis techniques were shared. During these meetings, the atmosphere was safe, which seem to be essential for sharing results and experiences. One of the conclusions during these meetings was that the Dutch upper gastrointestinal surgeons feel joint responsibility for national outcomes and are willing to work together for the improvement of these national outcomes. Future data is needed to show whether these meetings are effective in improving quality of oesophagogastric cancer surgery.



CHAPTER 13

General discussion and future perspectives

GENERAL DISCUSSION

Quality of care can be monitored in clinical audits and can be improved with improvement initiatives. Both are of absolute necessity in the current health care system. To define the quality of care, reliable and valid quality indicators are essential. In this thesis, the *reliability* and *validity* of different quality indicators in the Dutch Upper Gastrointestinal Cancer Audit (DUCA) were evaluated. Additionally, the *value* of the use of different indicators for oesophagogastric cancer care was evaluated.

RELIABILITY OF THE DUCA INDICATORS

Quality indicators can be considered *reliable* if the indicator would produce similar outcomes in the same conditions if used again. When doctors themselves register data in a national audit, it is important that this registered data is verified to check whether it is complete and accurate. Therefore, in Chapter 6, the procedure for data verification was described,[1] as well as the results of this data verification in the DUCA, showing that the data are highly complete and accurate (Chapter 2).[2] The use of an outcomes set with uniform definitions is essential for fair comparisons between different hospitals and different countries. In 2016, the international uniform standardized outcomes set of the Oesophagectomy Complication Consensus Group (ECCG) Platform was successfully implemented in the DUCA (Chapter 2).[2]

With the outcomes of data verification and the recent implementation of the international uniform standardized outcomes set, it can be concluded that the data and results in the DUCA are reliable.

VALIDITY OF THE DUCA INDICATORS

Indicators can be considered *valid* to monitor the quality of care if they actually measure aspects of the quality of care. The quality of care for oesophagogastric cancer patients can be determined by two pillars; quality of life and long-term survival outcomes.

Quality of life

To evaluate quality of life, patient-reported outcomes are essential. In this thesis, it was not possible to evaluate indicators with data on Patient-Reported Outcome Measures (PROMs) because data on PROMs were not yet available in the DUCA. However, it is described that postoperative morbidity has a significant effect on the quality of life postoperatively,[3] and some quality indicators on postoperative morbidity were evaluated on validity. In the DUCA, one of the existing quality indicators regarding postoperative morbidity is a complicated postoperative course, defined as the percentage of patients with a complication in combination with a prolonged hospital stay, reintervention or death.[4] Another existing quality indicator regarding postoperative morbidity is the percentage of patients with 'a complication Clavien Dindo grade III or higher'.

In recent literature, a new parameter on postoperative morbidity was described; the Comprehensive Complication Index (CCI). Because the CCI is the first morbidity outcome that is partly based on patients' opinion, it was evaluated in Chapter 5 whether the CCI could be applied in a clinical audit. 'The percentage of patients in the 75th percentile of the CCI' was defined as a new quality indicator. With this new quality indicator, it was possible to identify hospitals with significantly better performance or significantly worse performance. It was also shown that hospital outcomes on this new quality indicator were highly correlated to hospital outcomes on the existing indicator 'a complicated postoperative course' but not to hospital outcomes on 'a complication Clavien Dindo grade III or higher'. Although future studies are needed to determine whether CCI is associated with quality of life, results of this study suggest that the new indicator on CCI and the existing indicator 'a complicated postoperative course' are valid to measure the quality of care.

Long-term survival

The validity of quality indicators regarding association with long-term survival outcome was evaluated in the second part of this thesis.

Because monitoring long-term outcomes is important, in the DUCA some short-term outcome indicators are used as a proxy for long-term outcomes. In this thesis, four DUCA outcomes were evaluated on the association with long-term survival. In Chapter 7, it was found that three of these outcomes; 'Textbook outcome', 'Complicated postoperative course', and 'Complete tumour

resection', were associated with long-term survival.[5] In Chapter 10, a fourth indicator was evaluated on the association with long-term survival; 'retrieval of at least 15 lymph nodes'. The importance of lymph node retrieval has been re-discussed since the introduction of neoadjuvant chemo- and radiotherapy (Chapter 8). In these studies, it was found that there was no association of retrieval of at least 15 lymph nodes with survival, however, in patients with at least 15 retrieved lymph nodes, the pathological staging appeared to be more accurate.

VALUE OF THE DUCA INDICATORS

Variation

The *value* of the use of indicators in a national audit can be determined by analysing whether these indicators demonstrate variation between hospitals or international cohorts. The comparison of the DUCA outcomes with outcomes of an international cohort of the Oesophagectomy Complication Consensus Group (ECCG) Platform, showed that significantly more complications and anastomotic leakage exist in the DUCA (Chapter 2). These differences underlined the value of indicators on morbidity outcomes.

For other outcomes, significant differences were found between different types of hospitals. Low volume hospitals failed more often in the retrieval of at least 15 lymph nodes in the treatment of patients with oesophageal cancer (Chapter 9). In patients with gastric cancer, low volume hospitals failed more often in achieving a complete tumour resection (Chapter 11).

Trends

Not only differences between hospitals or international cohorts are important to determine the *value* of indicators, but also the ability to demonstrate trends in outcomes after introduction of an indicator may emphasize the *value* of indicators. In Chapter 9, a significant improvement of national outcomes on lymph node retrieval was shown since the introduction of the DUCA. This improvement may be an effect of the use of the indicator regarding lymph node retrieval and therefore, may strengthen the *value* of the DUCA and its indicators.

FUTURE PERSPECTIVE

BEST QUALITY INDICATORS FOR OESOPHAGOGASTRIC CANCER SURGERY

Short-term outcomes

All indicators of the DUCA contain only information on short-term outcomes. There are two reasons for this. Firstly, because limiting the number of outcomes and the follow-up period reduces the registration burden. Secondly, because the use of short-term outcomes facilitates a short feedback loop. For continuous control and improvement of processes, the Plan-Do-Check-Act cycle is often used.[6] For efficient quality improvement, a short feedback loop in this cycle is essential and therefore, the use of short-term outcomes in a clinical audit such as the DUCA is recommended. Since it has been shown that the short-term outcomes 'Textbook outcome', 'a complicated postoperative course' and 'complete tumour resection' are a proxy for long-term survival, these specific short-term indicators seem valid (Chapter 7**).**[5]

Composite measures

Another type of indicators that may be important for quality monitoring are composite measures. Because composite measures simplify the interpretation of outcomes, these are preferable for use by external parties including patient organisations and health insurance companies. An example is the composite measure 'Textbook outcome'. It should be noted that outcomes on the individual elements/parameters are essential for health care providers to monitor and improve quality of care. Future studies are needed to evaluate which method is the best to improve outcomes on these specified parameters.

Morbidity

Postoperative morbidity after oesophagogastric surgery has a serious impact on the quality of life and costs and may be associated with long-term survival. Therefore, it can be argued to use morbidity as a main outcome in a clinical audit.[3, 5, 7] The CCI may reflect the most complete outcome on complications because it considers all complications and the outcome is partly based on

patients' opinion. In this thesis, it was shown that the CCI and a complicated postoperative course are highly correlated. Therefore, both outcomes can be recommended to use in the DUCA (Chapter 3).

Patient-reported outcomes and patient-reported experience

For the future, it might be of great value to include patient-reported outcomes and patient-reported experience in the DUCA.

In the Netherlands, patient-reported outcomes are collected on a national base in the Prospective Observational Cohort Study of Oesophageal-gastric cancer Patients (POCOP) project. Because it is not desirable to target the patient with overlapping questionnaires, the DUCA is working on a link between the POCOP database and the DUCA database to give hospitals benchmarked information regarding the quality of life of patients treated in their hospital. Patient-reported outcomes can be used to validate currently used clinical outcomes by evaluating the association of these factors with quality of life. Also, a quality indicator regarding the percentage of patients that completed a patient-reported outcome questionnaire may help to increase the use of these questionnaires in clinical contact.

Patient-reported experience questionnaires are not yet included in the DUCA. Because patient-reported experience may be a promising outcome to use as a quality measure for hospital performance, implementation of this outcome in the DUCA should be considered in the future.

ULTIMATE GOAL OF CLINICAL AUDITING: QUALITY IMPROVEMENT

Quality improvement based on monitoring of outcomes has been described in the past.[8] Also, making outcomes transparent may help to improve outcomes.[9-11] In the first 8 years after initiation of the DUCA, some of the outcomes have improved over time including the number of retrieved lymph nodes,[9] and the 30-day mortality after gastrectomy.[4]

On the other hand, some other important outcomes in the DUCA did not improve; especially morbidity remained stable.[12] This in itself is not a problem as these outcomes might be just the best that is achievable at the moment. However, for morbidity, it was shown that morbidity reported by the DUCA was significantly worse than that in an international cohort containing data of several

high-volume hospitals.[2] These results emphasize the need for critical evaluation of morbidity outcomes after 8 years of clinical auditing. Moreover, it underlined the need for an alternative method of outcome evaluation in addition to the standard method of evaluation.[13] (see below)

In the standard method, outcomes on quality indicators are reported online to the hospital. In this report, the outcome of a particular hospital is shown among the outcomes of all other hospitals that remain anonymous. Hospital outcomes are compared to the national mean and 95% confidence intervals are used to identify outliers, defined as hospitals performing significantly better or significantly worse than the national mean. To improve quality of care, this method falls short on some points. First, hospitals with outcomes that are at the same level of the national mean may not be stimulated to start improvement initiatives. This may lead to a lack of improvement over time. Secondly, in the Netherlands, oesophagogastric cancer surgery is still performed in rather low volumes (20-40 resections per year). A small number of patients leads to broad confidence intervals. With broad confidence intervals, a type II error may occur; underperforming or overperforming hospitals may not be identified as a significant outlier. Thirdly, most quality indicators are composite quality indicators.[4, 14] For example, the quality indicators regarding morbidity evaluate all complications together. With these indicators, hospitals obtain no insight in specific complications while focusing on specific complications is needed for effective improvement initiatives. Lastly, outcomes are reported anonymously. Individual hospitals are notified, but cannot be helped by offering quality improvement programs as long as they remain anonymous. The initiative to do so completely lies within the hospital itself.

In this thesis, it was shown that outcomes on morbidity and especially anastomotic leakage within the DUCA cohort were significantly worse compared with an international cohort.[2] Since introduction of the DUCA these outcomes were stable.[12] To improve the outcomes after oesophagogastric cancer surgery, an alternative evaluation of national outcomes was introduced in the DUCA (Chapter 12). In 2018, a two-day meeting was organized for upper gastrointestinal surgeons of all hospitals performing oesophagogastric cancer surgery in the Netherlands. This meeting was repeated in 2019. The purpose of this meeting was to evaluate outcomes, and with an expert group to discuss how

national outcomes might be improved. All hospitals were asked to present their results and to discuss why they thought these outcomes were better or worse than other outcomes (no matter if they were an outlier or not). Since the goal of these meetings was to improve outcomes, the choice was to focus on two specific outcomes; anastomotic leakage and lymph node retrieval.

In the future, more of these meetings are needed to bring joint responsibility for outcomes after oesophagogastric surgery in the Netherlands. Future evaluation of outcomes in the DUCA cohort are needed to evaluate whether these meetings lead to an improvement in outcomes.

THE SAFETY-I VERSUS THE SAFETY-II APPROACH

Another idea that has penetrated into the world of clinical auditing is focusing on a desired outcome rather than an undesired outcome. The first indicators for oesophagogastric cancer surgery mainly reflected undesired outcomes including a complicated postoperative course. To improve this outcome, hospitals must ensure that as little as possible goes wrong. In the example of a complicated postoperative course, to prevent a high score on complicated postoperative course, physicians have to ensure that complications will not lead to a reintervention, prolonged hospital stay or death. This reactive management is described in the literature as the 'Safety-I' approach.[15] In contrast, the newer indicator 'Textbook outcome' focusses on a desired outcome. 'Textbook outcome' is defined as a perioperative process following the textbook; a curative treatment with no undesired events. To improve this outcome, hospitals have to ensure that many key attributes in the care for the patient are well performed. For 'Textbook outcome', this means that hospitals are motivated to monitor and improve the whole perioperative pathway. This proactive management is described as the 'Safety-II' approach.[15] It has been described that Safety-I is inadequate in the long run, while the Safety-II approach provides flexible solutions to many potential problems.[16]

Another application of the Safety-II approach in the DUCA would be to identify the three best performing hospitals and to explore if and where these hospitals differ in the perioperative management of the patient and to set a blueprint for all other hospitals. It has been suggested that in clinical practice, the way ahead lies in the combination of the Safety-I and Safety-II approach.[16]

BETTER INSIGHT IN RESULTS

Another development which may lead to quality improvement is a new dynamic dashboard (CODMAN dashboard) that shows trends in hospital's outcomes at a glance. This dashboard may help to monitor hospital's quality and may stimulate improvement projects. In 2019, this new dynamic dashboard was introduced for all hospitals participating in the DUCA. Besides the fact that it is easier to gain insight into trends with this new dashboard, it enables doctors also to focus on subgroups of patients, which allows in-depth evaluation of outcomes. This information may facilitate the evaluation of results during morbidity and mortality conferences held in individual hospitals.

CENTRALISATION

With the currently used annual volume standard of at least 20 resections per year, centralisation has taken place in the past years. Several studies in this thesis underlined the need for better organization of oesophagogastric cancer surgery in the Netherlands. Further centralization may be needed, but also setting up networks with multicentre multidisciplinary team meetings may help. However, an annual volume of 20 may be still be considered as 'low volume'. Additionally, a higher number of patients per year in the individual hospitals enable short-cycle auditing with higher distinctiveness.

Another consideration in the organization of oesophagogastric cancer surgery is the introduction of a composite volume-outcome. The current guideline describes that oesophageal and gastric cancer surgery is preferably performed in the same hospitals because it shares many similarities. However, this is not yet set as a standard. In addition, also quality of oesophagogastric cancer surgery may benefit from shared experience with other complex upper gastrointestinal cancer resections such as pancreatectomies.

MULTIDISCIPLINARY AUDIT

In previous studies with national data on patients with oesophagogastric cancer, considerable variation between hospitals was shown in the percentage of patients treated with curative intent.[17, 18] This underlines the need for a

multidisciplinary clinical audit. At this moment, full data on all oesophagogastric cancer patients are collected in the Dutch Cancer Registry. In the DUCA, only information regarding the (peri)operative treatment in patients that underwent surgery is registered. The DUCA is working on a link between the Dutch Cancer Registry database and the DUCA database to create a multidisciplinary audit without extra registration burden. In the future, it is essential to monitor the entire treatment process and the outcomes of all multimodality treatments to give a complete overview of the quality of care between hospitals. This will be of imminent importance for the quality of care of all oesophagogastric cancer patients in the Netherlands

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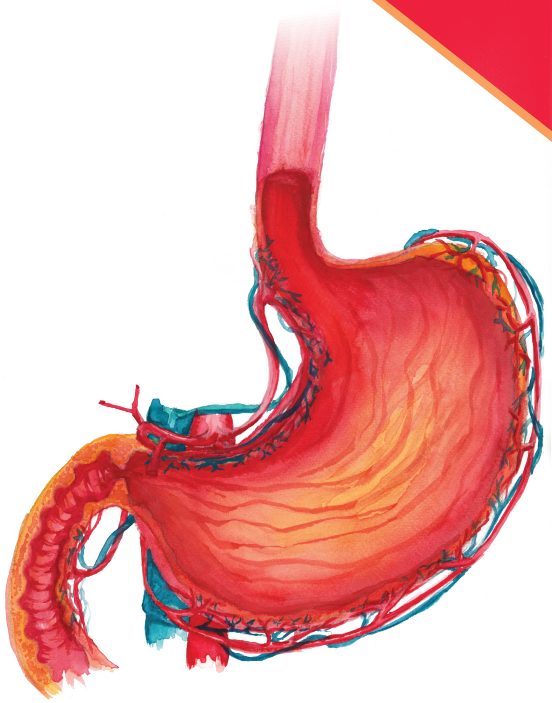


CHAPTER 14

Summary

QUALITY MEASUREMENT IN OESOPHAGOGASTRIC CANCER SURGERY

The research described in this thesis focuses on the *reliability* and *validity* of different quality indicators in the Dutch Upper Gastrointestinal Cancer Audit (DUCA). Additionally, the *value* of the use of different indicators for oesophagogastric cancer care was evaluated.

PART I. NATIONAL OUTCOMES ON POSTOPERATIVE MORBIDITY QUALITY INDICATORS

CHAPTER 2. INTERNATIONAL STANDARDISED OUTCOMES SET

In this national cohort study, morbidity and mortality after oesophagogastric cancer in the Netherlands is reported. The outcomes are reported according to the definitions of an international standardised outcomes set. The results showed that the data of the DUCA are complete and accurate. In the Netherlands, the most common complications were pneumonia and anastomotic leakage. The DUCA outcomes were compared to previously reported outcomes of an international cohort. Complications occurred more often in the DUCA and the percentage of anastomotic leakage was higher. The conclusion of this study was that using an international standardised outcomes set facilitates international comparison.

CHAPTER 3. COMPREHENSIVE COMPLICATION INDEX

Because oesophageal and gastric surgery is associated with high morbidity, monitoring complications is important. The purpose of this study was to investigate whether a new measure of morbidity can be applied in a national

audit. This new measure was the Comprehensive Complication Index (CCI). In this measure, recorded complications are combined and weighted by the severity of each complication. In the study was seen that the CCI outcomes varied between hospitals in the Netherlands. In addition, it was seen that the CCI outcomes per hospital were strongly correlated with an existing DUCA quality indicator that describes the percentage of patients with a complicated course. From this study it was concluded that the CCI can be applied in a national audit. In the future, the CCI outcome can possibly contribute to accurate trend monitoring of outcomes per hospital.

CHAPTER 4. TIME INTERVAL BETWEEN NEOADJUVANTE CHEMORADIOTHERAPY AND SURGERY

Because the optimal time interval between neoadjuvant chemoradiotherapy and surgery for oesophageal cancer is unknown, in this study the difference in pathological outcomes and complications between patients operated on after varying time intervals was evaluated. The research showed that a longer time interval (>10-13 weeks) was associated with a higher percentage pathologically complete response. For the different time intervals, the lymph node yield and the percentage of intraoperative and postoperative complications were comparable. From these results it can be concluded that postponed surgery after neoadjuvant chemoradiation does not appear to be associated with morbidity and may have a positive effect on the response to neoadjuvant therapy.

CHAPTER 5. GASTRIC RESECTIONS WITH ADDITIONAL PANCREAS RESECTION

In this study the outcomes of patients undergoing gastric resection with additional pancreatic resection were investigated. The purpose of this additional resection usually is to achieve a complete resection in case the tumour has grown into the pancreas. A complete resection was shown to be achieved in 82% of patients. However, it was seen that there were more serious complications in these patients compared to those without an additional resection. These results emphasize that a gastric resection with additional pancreatic resection may be

a curative treatment strategy, but that it should only be done when it is expected that the tumour can be completely removed.

CHAPTER 6. DATA VERIFICATION

When using national data for hospital comparison, it is important that the entered data are robust and reliable. The Dutch Institute for Clinical Auditing has developed a data verification procedure for the national audits in the Netherlands. This chapter describes the procedure of the data verification. The results of different data verification procedures are described together with the lessons learned from these different procedures.

PART II. QUALITY INDICATORS AS A PROXY FOR LONG-TERM OUTCOMES

To monitor and improve outcomes in a short-cycle, it is important that outcomes can be determined in the short term. However, in cancer operations, survival is often seen as the ultimate outcome measure.

CHAPTER 7. ASSOCIATION SHORT-TERM OUTCOMES WITH LONG-TERM OUTCOMES

This study investigated whether different short-term outcomes used in the DUCA were associated with long-term outcomes. A significant association was found with three short-term outcomes. It concerned "Textbook outcome", a composite outcome measure which describes a postoperative period "as described in the textbook", "complicated course" and "complete resection of the tumour". The use of these outcomes facilitates monitoring and improvement of outcomes in the short term, whereby this study showed that these short term outcomes also function as a proxy for long-term outcomes as overall survival.

CHAPTER 8. TRANSHIATAL RESECTION OR TRANSTHORACAL RESECTION

In this chapter the differences between a transhiatal or transthoracic resection for oesophageal cancer were described based on existing literature. In an early study, less morbidity after open transhiatal resections was described. In contrast, a trend towards better survival after open transthoracic resections was described. It is suggested that more extensive lymph node dissection with transthoracic resections had a part in this. It is also described that, since the introduction of neoadjuvant chemoradiotherapy, the value of lymph node dissection is re-discussed. The differences between the two approaches in minimally invasive surgery are unclear.

CHAPTER 9. QUALITY INDICATOR LYMPH NODE RETRIEVAL

Another short-term outcome indicator concerns the "percentage of patients in whom at least 15 lymph nodes have been examined in the resection preparation". In this study, the results on this quality indicator in the first years of DUCA were evaluated. The results showed that the lymph node retrieval has been increased in recent years but that there is still variation between hospitals. Hospitals with a high annual hospital volume achieved the quality indicator more often. These findings may indicate that using a quality indicator can lead to an improvement of outcomes.

CHAPTER 10. EFFECT OF LYMPH NODE RETRIEVAL ON SURVIVAL AFTER OESOPHAGEAL CANCER

As described in Chapter 8, the value of lymph node dissection after neoadjuvant chemoradiation has been discussed which also questions the value of the quality indicator regarding lymph node retrieval. Therefore, in this study the association of this quality indicator with survival was evaluated for oesophageal cancer. It was found that oesophageal cancer patients with <15 lymph nodes and ≥15 lymph nodes had a similar survival. However, it was found that patients with <15 lymph nodes may have had positive lymph nodes left behind (in the resection specimen or in the body), resulting in a lower tumour stage. The conclusion of this study is that patients in which ≥15 lymph nodes have been examined are

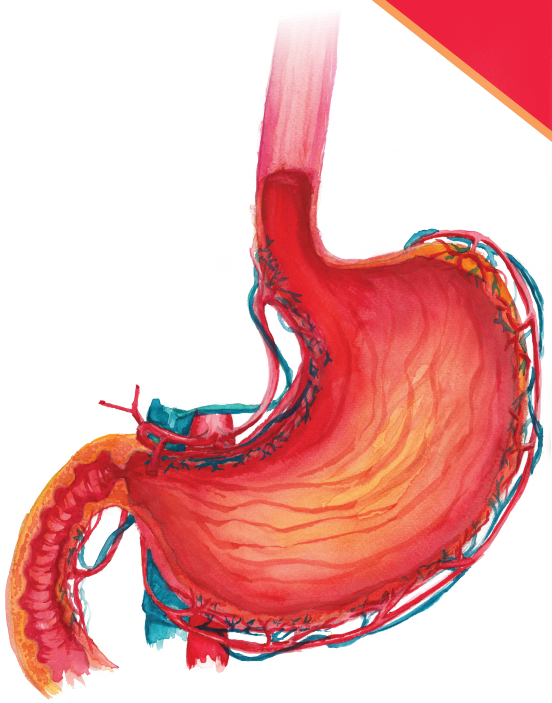
better staged and that this quality indicator is therefore important for measuring quality of care.

CHAPTER 11. RISK FACTORS FOR INCOMPLETE RESECTIONS FOR GASTRIC CANCER

In this study, risk factors for incomplete resections for gastric cancer have been identified. An incomplete resection is associated with poor survival and therefore the percentage of complete resections is one of the quality indicators within the DUCA. In this chapter, it was seen that various tumour-specific factors are associated with incomplete resections, but also that in high volume hospitals, incomplete resections are less common. The results of this study show that re-organization of gastric cancer surgery in the Netherlands may help to improve outcomes. High-risk patients might be better off in a hospital with a higher annual hospital volume.

CHAPTER 12. NATIONAL IMPROVEMENT PROJECT WITH DUCA DATA

Because morbidity outcomes in the DUCA are stable in the first 8 years after the introduction of the DUCA and because there is a wide variation between hospitals on specific outcomes, a national improvement project has been started. National meetings were organized. In these meetings the results were compared and discussed. Joint plans were made to improve outcomes on national level. In this chapter, the complete process of this project was described.



CHAPTER 15

Summary in Dutch (Nederlandse samenvatting)

KWALITEITSMETING BINNEN DE SLOKDARM- EN MAAGKANKERCHIRURGIE

INTRODUCTIE

In Nederland stijgt de incidentie van slokdarmkanker terwijl de incidentie van maagkanker stabiel is.[1] In 2018 was de incidentie van slokdarmkanker 2.500 en van maagkanker 1.300. Het percentage patiënten dat in aanmerking komt voor een curatieve behandeling is 60% voor slokdarmkanker en 50% voor maagkanker.[23]
Multimodale therapie wordt in de behandeling van slokdarm- en maagkanker steeds belangrijker.[3-6] Voor slokdarmkanker wordt het overgrote merendeel van de patiënten behandeld met neoadjuvante chemoradiatie gevolgd door een operatie. Ook niet-chirurgische behandelingen zoals endoscopische resectie en definitieve chemoradiatie worden tegenwoordig als curatieve behandeling gezien.[7-9] De meest recente ontwikkeling is de potentiele toepassing van actieve surveillance na neoadjuvante chemoradiatie in plaats van een operatie.[10]
Voor maagkanker is de combinatie van chemotherapie met een operatie de standaardbehandeling als patiënten fit genoeg zijn om chemotherapie te ondergaan.

Bij de operatieve behandeling staat het verkrijgen van een complete resectie van de tumor, een lymfeklier dissectie en een reconstructie van het maag-darm kanaal centraal. Slokdarm- en maagresecties zijn complexe operaties welke gepaard gaan met een hoge morbiditeit en mortaliteit.[14] Om te zorgen voor voldoende ervaring in de operatie en de postoperatieve zorg is er een volumenorm ingesteld. In Nederland is een minimumaantal van 20 resecties per jaar per ziekenhuis verplicht voor zowel slokdarmresecties als maagresecties.[14] In 2016 werden in 25 ziekenhuizen slokdarm- en maagresecties uitgevoerd, dit is gedaald naar 20 ziekenhuizen in 2018.[17] De kwaliteit van slokdarm- en maagresecties wordt gemonitord met behulp van een clinical audit: de Dutch Upper gastrointestinal Cancer Audit (DUCA).[14] Door middel van kwaliteitsindicatoren wordt de kwaliteit van de slokdarm- en maagchirurgie in

Nederland in kaart gebracht. De uitkomsten op deze indicatoren worden teruggekoppeld aan de ziekenhuizen en eens per jaar transparant gemaakt zodat iedereen (patiënten, zorgverzekeraars en overheidsinstellingen) deze kunnen inzien. Met inzicht in deze uitkomsten kunnen ziekenhuizen volgens de plan-do-check-act methode streven naar het verbeteren van uitkomsten.
In dit proefschrift ligt de focus op het vaststellen van de betrouwbaarheid, validiteit en waarde van kwaliteitsindicatoren binnen de slokdarm- en maagchirurgie.

DEEL I. LANDELIJKE UITKOMSTEN VAN POSTOPERATIEVE MORBIDITEIT KWALITEITSINDICATOREN

HOOFDSTUK 2. INTERNATIONALE GESTANDAARDISEERDE UITKOMST SET

In dit landelijke cohortonderzoek is gerapporteerd wat de morbiditeit en mortaliteit na slokdarm- en maagresecties in Nederland was. De uitkomsten zijn gerapporteerd volgens de definities van een eerder beschreven internationale gestandaardiseerde uitkomst set. Er bleek in dit onderzoek dat de data in de DUCA zeer compleet en accuraat geregistreerd zijn. In Nederland bleken pneumonie en naadlekkage de meest voorkomende complicaties te zijn. De Nederlandse uitkomsten werden vergeleken met eerder gepubliceerde uitkomsten van een internationaal cohort. In de DUCA kwamen vaker complicaties voor en het percentage naadlekkage was hoger. Een van de conclusies uit dit onderzoek was dat er gemakkelijk een goede internationale vergelijking plaats kan vinden wanneer uitkomsten volgens een gestandaardiseerde uitkomst set geregistreerd zijn.

HOOFDSTUK 3. COMPREHENSIVE COMPLICATION INDEX

Doordat slokdarm- en maagoperaties gepaard gaan met een hoge morbiditeit is het monitoren van complicaties belangrijk. Het doel van deze studie was om te onderzoeken of een nieuwe maat betreffende morbiditeit toegepast kan worden in een landelijke audit. Het betreft de nieuwe samengestelde

complicatie maat: de Comprehensive Complication Index (CCI). Bij deze maat worden eventueel meerdere geregistreerde complicaties gecombineerd en gewogen aan de hand van de ernst van iedere complicatie. In het onderzoek werd gezien dat de CCI-uitkomsten tussen ziekenhuizen in Nederland varieerde. Daarnaast werd gezien dat de CCI-uitkomsten per ziekenhuis sterk gecorreleerd waren aan een bestaande DUCA-kwaliteitsindicator welke het percentage patiënten beschrijft met een gecompliceerd beloop. De conclusie van dit onderzoek was dat het haalbaar is om de CCI toe te passen in een landelijke audit. Mogelijk kan de CCI in de toekomst bijdragen aan nauwkeurige trend-monitoring van uitkomsten per ziekenhuis.

HOOFDSTUK 4. TIJDSINTERVAL TUSSEN NEOADJUVANTE CHEMORADIOTHERAPIE EN CHIRURGIE

Omdat het optimale tijdsinterval tussen neoadjuvante chemoradiotherapie en chirurgie bij slokdarmkanker onbekend is, is in dit onderzoek gekeken naar het verschil in pathologische uitkomsten en complicaties tussen patiënten geopereerd na variërende tijdsintervallen. Het onderzoek liet zien dat er vaker sprake was van een pathologisch complete respons bij een langer tijdsinterval (>10-13 weken). De lymfeklier opbrengst en het percentage intra-operatieve en postoperatieve complicaties waren vergelijkbaar voor de verschillende tijdsintervallen. Uit deze resultaten is te concluderen dat langer wachten na neoadjuvante chemoradiatie niet geassocieerd te zijn met meer complicaties en mogelijk zelfs een positief effect kan hebben door een hogere kans op een pathologisch complete respons.

HOOFDSTUK 5. MAAGRESECTIES MET AANVULLENDE PANCREASRESECTIE

In deze studie is onderzocht wat de uitkomsten zijn van patiënten die een maagresectie met aanvullende pancreasresectie hebben ondergaan. Het doel van deze aanvullende resectie is meestal om een complete resectie van de tumor te verkrijgen wanneer deze is doorgegroeid in het pancreas. Er werd aangetoond dat in 82% van de patiënten een complete resectie werd behaald.

Wel werd er gezien dat er vaker sprake was van ernstige complicaties in vergelijking met patiënten zonder een aanvullende resectie. Deze resultaten benadrukken dat een maagresectie met aanvullende pancreasresectie mogelijk een curatieve behandeling kan zijn, maar dat het alleen moet worden gedaan wanneer er wordt verwacht dat de tumor compleet kan worden verwijderd.

HOOFDSTUK 6. DATA VERIFICATIE

Om op een goede en eerlijke manier uitkomsten te vergelijken in een landelijke registratie is het van belang dat data compleet en accuraat worden ingevoerd. Bij het Dutch Institute for Clincial Auditing is een dataverificatie procedure ontwikkeld. Met deze dataverificatie wordt de data van landelijke audits extern geverifieerd. In dit hoofdstuk wordt in detail beschreven hoe deze procedure in zijn werk gaat. De resultaten van verschillende data verificatie procedures worden beschreven samen met de lessen die geleerd zijn uit deze verschillende procedures.

DEEL 2. KWALITEITSINDICATOREN ALS PROXY VOOR LANGE TERMIJNSUITKOMSTEN

Om kort-cyclisch uitkomsten te monitoren en verbeteren is het van belang dat uitkomsten op korte termijn kunnen worden vastgesteld. Bij oncologische operaties is het echter zo dat overleving vaak wordt gezien als ultieme uitkomstmaat.

HOOFDSTUK 7. ASSOCIATIE KORTE TERMIJNSUITKOMSTEN MET LANGE TERMIJNSUITKOMSTEN

In deze studie werd onderzocht in hoeverre verschillende korte-termijn uitkomsten welke worden gebruikt in de DUCA geassocieerd waren met lange-termijn uitkomsten. Er werd een significante associatie gevonden bij drie korte-termijn uitkomsten. Het ging om ‘Textbook outcome’, een samengestelde

uitkomstmaat waarbij alles ‘volgens het boekje’ verloopt, ‘gecompliceerd beloop’ en ‘complete resectie van de tumor’. Het gebruik van deze uitkomsten zorgt voor monitoring en verbetering van uitkomsten op korte termijn, waarbij dit ook effect heeft op de kwaliteit van zorg op lange termijn; namelijk betere lange termijn overleving.

HOOFDSTUK 8. TRANSHIATALE RESECTIE OF TRANSTHORACALE RESECTIE

In dit hoofdstuk zijn de verschillen tussen een transhiatale of transthoracale resectie voor slokdarmkanker beschreven op basis van bestaande literatuur. In de gerandomiseerde HIVEX-trial werd minder morbiditeit beschreven bij open transhiatale resecties. Daarentegen werd een trend naar betere overleving bij open transthoracale resecties beschreven. Er wordt beschreven dat het idee bestaat dat uitgebreidere lymfeklierdissectie bij transthoracale resecties hierin een aandeel heeft gehad. Daarbij wordt ook beschreven dat sinds de introductie van neoadjuvante chemoradiotherapie, de waarde van lymfeklierdissectie in twijfel wordt getrokken. Daarnaast zijn de verschillen tussen beide benaderingen bij minimaal invasieve chirurgie onduidelijk.

HOOFDSTUK 9. KWALITEITSINDICATOR LYMEKLIERENOPBRENGST SLOKDARMKANKER

Een andere korte-termijn uitkomst indicator betreft het ‘percentage patiënten waarbij tenminste 15 lymfeklieren zijn aangetoond in het resectiepreparaat’. In deze studie is onderzocht wat de uitkomsten waren van deze kwaliteitsindicator in de Nederlandse ziekenhuizen in de eerste jaren van de DUCA. Er werd gezien dat de uitkomsten toegenomen zijn in de afgelopen jaren maar dat er nog steeds variatie bestaat tussen ziekenhuizen. Ziekenhuizen met een hoog aantal slokdarmoperaties per jaar behaalden vaker deze kwaliteitsindicator. Deze bevindingen wijzen er mogelijk op dat het gebruiken van een kwaliteitsindicator kan leiden tot een toename van uitkomsten.

HOOFDSTUK 10. EFFECT VAN LYMFEKLIEROPBRENGT OP OVERLEVING NA SLOKDARMKANKER

Zoals beschreven in Hoofdstuk 9 bestaat er twijfel over de waarde van lymfeklierdissectie na neoadjuvante chemoradiatie waardoor ook de waarde van de kwaliteitsindicator betreffende lymfeklieropbrengt in twijfel getrokken wordt. Dat was de reden waarom in deze studie is onderzocht of het behalen van deze kwaliteitsindicator geassocieerd was met een betere overleving. Er werd in deze studie gevonden dat slokdarmkankerpatiënten met <15 lymfeklieren en ≥15 lymfeklieren een vergelijkbare overleving hadden. Wel werden er aanwijzingen gevonden dat bij patiënten met <15 lymfeklieren mogelijk positieve lymfeklieren zijn achtergebleven (in het resectie preparaat of in het lichaam) waardoor een te laag tumor stadium is afgegeven. De conclusie van deze studie is dat patiënten waarbij ≥15 lymfeklieren zijn onderzocht betere gestadieerd zijn en dat deze kwaliteitsindicator daardoor valide is voor het meten van kwaliteit van zorg.

HOOFDSTUK 11. RISICOFACTOREN VOOR IRRADICALE MAAGRESECTIES

Deze studie beschrijft een analyse waarbij risico factoren voor irradicale maagresecties zijn geïdentificeerd. Een irradicale maagresectie is geassocieerd met een slechte overleving en daarom is het percentage radicale maagresecties ook een van de kwaliteitsindicatoren binnen de DUCA. In dit hoofdstuk werd gezien dat er verschillende tumor-specifieke factoren geassocieerd zijn met irradicale maagresecties, maar ook dat in hoog volume ziekenhuizen minder vaak irradicale maagresecties voorkomen. De resultaten van deze studie laten zien dat de organisatie van maagchirurgie in Nederland mogelijk kan helpen om uitkomsten te verbeteren. Hoog-risicopatiënten zijn daarom wellicht beter af zijn in een ziekenhuis met een hoger volume.

HOOFDSTUK 12. LANDELIJK VERBETERPROJECT MET DATA UIT DE DUCA

Omdat de morbiditeit uitkomsten in de DUCA in de eerste 8 jaar na de introductie van de DUCA stabiel zijn en er grote variatie in sommige uitkomsten is tussen ziekenhuizen, is een landelijk verbeterproject gestart. Er zijn landelijke meetings georganiseerd. In deze meetings zijn uitkomsten vergeleken en

bediscussieerd. Gezamenlijk werden er plannen gemaakt om de landelijke uitkomsten te verbeteren. In dit hoofdstuk is het complete proces van dit project beschreven.

CONCLUSIE

In dit proefschrift zijn verschillende kwaliteitsindicatoren voor de slokdarm- en maagchirurgie geëvalueerd op betrouwbaarheid, validiteit en waarde.
Allereerst is aangetoond dat de data en resultaten in de DUCA betrouwbaar zijn. Wat betreft de validiteit is er gevonden dat de indicatoren over 'gecompliceerd beloop' en 'CCI' mogelijk iets zeggen over de postoperatieve kwaliteit van leven. Er kon geconcludeerd worden dat de indicatoren 'Textbook outcome', 'gecompliceerd beloop' en 'complete resectie van de tumor' valide waren omdat zij geassocieerd zijn met lange termijn uitkomsten. De waarde van de verschillende indicatoren werd onderschreven doordat er in verschillende studies variatie aangetoond werd. Er werd gevonden dat de uitkomsten in de DUCA significant afwijken van internationale uitkomsten. Ook werd er variatie gevonden tussen laag- en hoog volume ziekenhuizen. Daarnaast werd de waarde van de DUCA-indicatoren bevestigd doordat er een toename van lymfeklier opbrengst werd gezien na introductie van een indicator betreffende het aantal lymfeklieren.

DISCUSSIE EN TOEKOMSTPERSPECTIEF

Met de verschillende onderzoeken in dit proefschrift is te concluderen dat de geteste uitkomstindicatoren welke worden gebruikt in de DUCA bijna allemaal als betrouwbaar, valide en waardevol kunnen worden beschouwd.
Het doel van de DUCA is monitoren en verbeteren van de kwaliteit van de slokdarm- en maag oncologische zorg. In de eerste 8 jaar van de DUCA zijn sommige uitkomsten verbeterd. Echter, de uitkomsten betreffende morbiditeit stabiel gebleven. In de toekomst is het van belang dat resultaten van de DUCA

naast de gebruikelijke manier ook op een alternatieve manier worden geëvalueerd. Een voorbeeld hiervan kan zijn het bespreken van specifieke complicatie uitkomsten in een georganiseerde bijeenkomst. Daarnaast is het belangrijk dat in de toekomst door de patiënt gerapporteerde uitkomsten over kwaliteit van leven worden geïmplementeerd in de DUCA. Als laatste is het van belang dat ook de niet-chirurgische zorg voor slokdarm- en maagkanker patiënten in kaart wordt gebracht door de audit multidisciplinair te maken.

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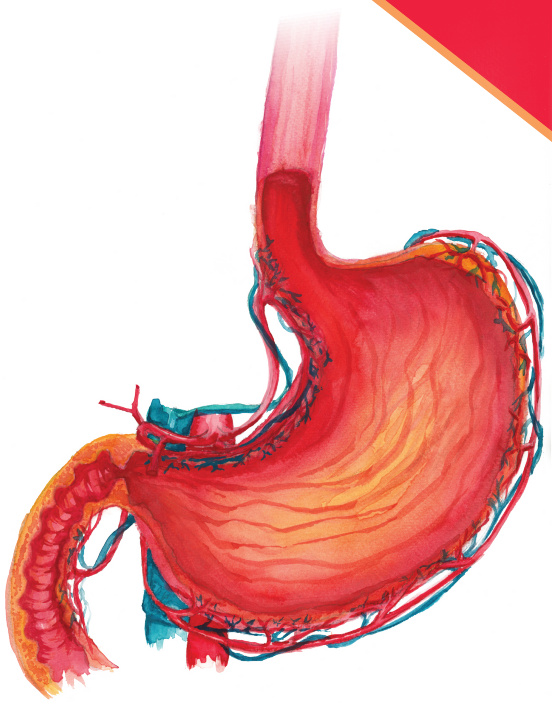

APPENDICES

LIST OF PUBLICATIONS

LIST OF PUBLICATIONS

2017

L.R. van der Werf and B.P.L. Wijnhoven. **Chapter 5: Transhiatal or transthoracic Esophagectomy.** *Minimally Invasive Surgery for Upper Abdominal Cancer - Miguel A. Cuesta ISBN 978-3-319-54300-0 (2017)*

L.R. van der Werf en B.P.L. Wijnhoven. **Laparoscopie direct vergeleken met open maagresectie.** *Ned Tijdschr Geneeskd.161:D2177 (2017)*

2018

L.R. van der Werf, J.L. Dikken, E.M. van der Willik, M.I. van Berge Henegouwen, G.A.P. Nieuwenhuijzen, B.P.L. Wijnhoven. On behalf of the Dutch Upper Gastrointestinal Cancer Audit (DUCA) group. **Time interval between neoadjuvant chemoradiotherapy and surgery for oesophageal or junctional cancer: A nationwide study.** *European Journal of Cancer 91 (2018) 76e85*

L. R. van der Werf, J. L. Dikken, M. I. van Berge Henegouwen, V. E. P. P. Lemmens, G. A. P. Nieuwenhuijzen, B. P. L. Wijnhoven. On behalf of the Dutch Upper GI Cancer Audit group. **A Population-based Study on Lymph Node Retrieval in Patients with Oesophageal Cancer: Results from the Dutch Upper Gastrointestinal Cancer Audit**. *Annals of Surgical Oncology 25 (2018) 1211-1220*

E.G. Karthaus, A. Vahl, **L.R. van der Werf**, B.H.P. Elsman, J.A. van Herwaarden, M.W.J.M. Wouters, J.F. Hamming. **Variation in Surgical Treatment of Abdominal Aortic Aneurysms With Small Aortic Diameters in the Netherlands.** *Annals of Surgery (2018)*

L.R. van der Werf and B.P.L. Wijnhoven. **ASO Author Reflections: A population-based study on lymph node retrieval in patients with oesophageal cancer.** *Annals of Surgical oncology (2018)*

L.R. van der Werf, E. Wassenaar, A. de Niet, F. Lalezari, H.J. Braam, B. van Ramshorst, J. Nederend, I.H.J.T. de Hingh, N.F.M. Kok, A.G.J. Aalbers. **The impact of radiological retroperitoneal lymphadenopathy on survival after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for colorectal peritoneal metastases.** *European Journal of Surgical Oncology (2018)*

2019

L.R. van der Werf, L.A.D. Busweiler, J.W. van Sandick, M.I. van Berge Henegouwen, B.P.L. Wijnhoven. **Reporting national outcomes after esophagectomy and gastrectomy according to the Esophageal Complications Consensus Group (ECCG).** *Annals of Surgery (2019)*

L.R. van der Werf and B.P.L. Wijnhoven. **Comment on: Prognostic Value of Lymph Node Yield on Overall Survival in Esophageal Cancer Patients: A Systematic Review and Meta-analysis.** *Annals of Surgery (2019)*

L.R. van der Werf, W.J. Eshuis, W.A. Draaisma, B. van Etten, S.S. Gisbertz, E. van der Harst, M.S.L. Liem, V.E.P.P. Lemmens, B.P.L. Wijnhoven, M.G. Besselink, M.I. van Berge Henegouwen. **Nationwide outcome of gastrectomy with en-bloc partial pancreatectomy for gastric cancer.** *Journal of Gastrointestinal Surgery (2019)*

L.R. van der Werf, N.F.M. Kok, C.I. Buis, D.J. Grünhagen, F.J.H. Hoogwater, R.J. Swijnenburg, M. den Dulk, C.H.C. Dejong, J.M. Klaase. On behalf of the Dutch Hepato Biliary Audit Group. **Implementation and first results of a mandatory, nationwide audit on liver surgery**. *Oxford HPB (2019)*

L.R. van der Werf, S.C. Voeten, C.M.M. van Loe, E.G. Karthaus, M.W.J.M. Wouters, H.A. Prins. **Data verification of national clinical audits in the Netherlands.** *BJS open (2019)*

L.R. van der Werf, C. Cords, I. Arntz, E.J.T. Belt, I.M. Cherepanin, P.P.L.O. Coene, E. van der Harst, J. Heisterkamp, B.S. Langenhoff, B. Lamme, M.I. van Berge Henegouwen, S.M. Lagarde, B.P.L. Wijnhoven. **Population-based study on risk factors for tumor-positive resection margins in patients with gastric cancer.** *Annals of Surgical Oncology (2019)*

L.R. van der Werf, B.P.L. Wijnhoven. **ASO Author Reflections: Increasing National Performance on Complete Tumor Resection in Patients with Gastric Cancer by Awareness of Risk Factors and Network Organization for Gastric Cancer Surgery**. *Annals of Surgical Oncology (2019)*

L.R. van der Werf, B.P.L. Wijnhoven, L.F.C. Fransen, J.W. van Sandick, G.A.P. Nieuwenhuijzen, L.A.D. Busweiler, R. van Hillegersberg, M.W.J.M. Wouters, M.D.P. Luyer*, M.I. van Berge Henegouwen*. **A national cohort study evaluating the association between short-term outcomes and long-term survival after esophageal and gastric cancer surgery**. *Annals of Surgery (2019)*

PHD PORTFOLIO

PHD PORTFOLIO

Name PhD student: Leonie Rosanne van der Werf
Erasmus MC Department: Surgery
PhD Period: September 2016 – July 2019

COURSES		ECTS
2016	R-course	1.8
2017	eBROK	1.5
2017	Basic statistics (NIHES)	2.0
2017	Integrity in science	0.3
2017	Survival Analysis	0.5
2018	Scientific writing	3.0
2018	BJS writing course	1.0
2018	R-course at DICA	1.8

ORAL PRESENTATIONS		ECTS
2018	Wetenschapsdag Chirurgie ErasmusMC	
	Time interval between neoadjuvant chemoradiotherapy and surgery for oesophageal or junctional cancer: A nationwide study	1.0
2018	Chirurgendagen	
	Morbiditeit en mortaliteit na slokdarmresecties in Nederland volgens de 'Esophagectomy Complications Consensus Group'	1.0
	De nationale uitkomsten van aanvullende pancreasresecties bij maagresecties voor maagkanker	1.0
2018	United European Gastroenterology week	
	Time interval between neoadjuvant chemoradiotherapy and surgery for oesophageal or junctional cancer: A nationwide study	1.0
2018	European Society of Diseases of the Esophagus Conference	
	Time interval between neoadjuvant chemoradiotherapy and surgery for oesophageal or junctional cancer: A nationwide study	1.0
	A Population-based Study on Lymph Node Retrieval in Patients with Esophageal Cancer: Results from the Dutch Upper Gastrointestinal Cancer Audit	1.0

2018	Digestive Disease Days	
	Reporting national outcomes after oesophagectomy and gastrectomy according to the Esophageal Complications Consensus Group (ECCG)	1.0
	Population-based study on risk factors for tumor-positive resection margins in patients with gastric cancer	1.0
2018	International Society of Diseases of the Esophagus	
	A Population-based Study on Lymph Node Retrieval in Patients with Oesophageal Cancer: Results from the Dutch Upper Gastrointestinal Cancer Audit	1.0
2018	United European Gastroenterology week	
	Reporting national outcomes after oesophagectomy and gastrectomy according to the Esophageal Complications Consensus Group (ECCG)	1.0
2019	Digestive Disease Days	
	A national cohort study evaluating the association between short-term outcomes and long-term survival after oesophageal and gastric cancer surgery	1.0
2019	International Gastric Cancer Congress	
	A national cohort study evaluating the association between short-term outcomes and long-term survival after oesophageal and gastric cancer surgery	1.0
2019	Annual meeting of the European Surgical Association	
	A national cohort study evaluating the association between short-term outcomes and long-term survival after oesophageal and gastric cancer surgery	1.0
2019	International Audit and Feedback Conference	
	Composite quality measures; long-term outcomes and improvement	1.0
2019	Digestive Disease Days	
	A propensity score matched cohort study to evaluate the association of lymph node retrieval with long-term overall survival in patients with oesophageal cancer	1.0
2019	European Society of Diseases of the Esophagus Conference	
	The Comprehensive Complication Index for quality monitoring of oesophagogastric cancer surgery	1.0

CONFERENCES AND SEMINARS

		ECTS
2016	European Society of Surgical Oncology	1.0
2017	Chirurgendagen	1.0
	Dutch Upper Gastrointestinal Cancer Group symposium	1.0
2018	Wetenschapsdag Chirurgie ErasmusMC	0.3
	Chirurgendagen	1.0
	United European Gastroenterology week	1.0
	European Society of Diseases of the Esophagus Conference	1.0
	European Gastric Cancer Congress	1.0
	Digestive Disease Days	1.0
	International Society of Diseases of the Esophagus	1.0
	United European Gastroenterology week	1.0
	Dutch Upper Gastrointestinal Cancer Group Studieavond (4x)	1.2
2019	Digestive Disease Days (2x)	2.0
	International Gastric Cancer Congress	1.0
	Annual meeting of the European Surgical Association	1.0
	International Audit and Feedback Conference	0.5
	Dutch Upper Gastrointestinal Cancer Group Studieavond (3x)	0.9

TEACHING

		ECTS
2017	Supervision Master thesis	2.0
2018	Supervision Master thesis	2.0
2018	EHBO courses	0.25
2016-2018	Education methodology and surgery at DICA	4.0

ABOUT THE AUTHOR

CURRICULUM VITAE

Leonie Rosanne van der Werf was born on 13 April, 1990. She has two younger siblings, a sister and a brother. Until the age of 18, she lived in Drachten where she graduated secondary school at Scholengemeenschap Liudger. After graduation, she moved to Groningen. She studied Pharmacy for one year, and in 2009 she was selected for Medicine by a decentral selection procedure. During her study, she spent many weekends and summers in Friesland, where she was a sailing instructor as well as a trainer for sailing instructors.

In the last two years of her studies, she developed a specific interest in gastrointestinal oncological surgery. She moved to Amsterdam to finish her last year in the Antoni van Leeuwenhoek Hospital – Netherlands Cancer Institute where she started research in gastrointestinal oncological surgery.

In 2016, she started working as a resident not in training at the surgical department of the Onze Lieve Vrouwe Gasthuis in Amsterdam. At the end of 2016, she started a PhD program at the Erasmus University Medical Center and the Dutch Institute for Clinical Auditing focusing on nationwide quality monitoring of oesophagogastric cancer surgery leading to this thesis. Her supervisors in this research were dr. B.P.L. Wijnhoven (Erasmus University Medical Center), prof. dr. M.I. van Berge Henegouwen (Amsterdam University Medical Center) and prof. dr. J.J.B. van Lanschot (Erasmus University Medical Center). During her PhD program, she coordinated the Dutch Upper Gastrointestinal Cancer Audit and the Dutch HepatoBiliary Audit. For that purpose, she collaborated with many surgeons and other medical specialists in gastrointestinal and hepatobiliary oncology. In the last period of her PhD program, at the Dutch Institute for Clinical Auditing, she was responsible for aligning all oncological-gastrointestinal cancer audits and she represented the interests of her colleague PhD-students in management team meetings.
Currently, Leonie still lives in Amsterdam and is working as a resident not in training at the surgical department in the Amsterdam University Medical Center.