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OUTCOME OF GASTRIC CANCER SURGERY IN SWEDEN

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To Axel and Karl

To Charlotte, for helping me through everything and made this possible.

ABSTRACT

Gastric cancer worldwide is the fifth most common cancer and has the third highest cancer related mortality. Curative treatment includes surgical resection but comes with risk of complications and the optimal surgery including extent of lymphadenectomy has evolved over time. This thesis aims to assess the impact of surgical treatment and lymphadenectomy in gastric cancer and its postoperative short-term outcomes and long-term survival effects. It also examines the decision-making process and impact of the variation of different proportion of the population that is offered curative treatment for gastric cancer.

Paper I is a single center retrospective study examining the incidence of postoperative pancreatic fistula following gastrectomy with D2 lymphadenectomy and bursectomy. The results show that there is an acceptable general complication rate and the risk of postoperative pancreatic fistula is low when no concomitant pancreatic resection is carried out.

Paper II and III are national register-based studies using the National Register of Oesophageal and Gastric Cancer (NREV) quality register. The studies examine the impact of different extent of lymphadenectomy on postoperative morbidity, mortality and long-term survival. The results show that extensive lymphadenectomy, D1+/D2, can be performed with acceptable and low postoperative complication rate and mortality and offers a survival advantage compared to limited, D0/D1, lymphadenectomy.

Paper IV is a NREV study examining the different rates of curative gastric cancer resection across geographical regions in Sweden and its impact on survival. The results show that the rate of resection varies greatly across different regions and years in Sweden indicative of room for improvement in the decision-making process. A higher rate of curative resection is accompanied with improved survival for the entire population of gastric cancer.

LIST OF SCIENTIFIC PAPERS

I. **Postoperative pancreatic fistula formation according to ISGPF criteria after D2 gastrectomy in Western patients.**
Kung CH, Lindblad M, Nilsson M, Rouvelas I, Kumagai K, Lundell L, Tsai JA.
Gastric Cancer. 2014;17(3):571-7. doi: 10.1007/s10120-013-0307-1. Epub 2013 Oct 9

II. **Extent of lymphadenectomy has no impact on postoperative complications after gastric cancer surgery in Sweden**
Kung CH, Song H, Ye W, Nilsson M, Johansson J, Rouvelas I, Irino T, Lundell L, Tsai JA, Lindblad M.
Chin J Cancer Res. 2017 Aug;29(4):313-322. doi: 10.21147/j.issn.1000-9604.2017.04.04

III. **Nationwide study of the impact of D2 lymphadenectomy on survival after gastric cancer surgery**.
Kung CH, Tsai JA, Lundell L, Johansson J, Nilsson M, Lindblad M
BJS Open. 2020 Mar 4. doi: 10.1002/bjs5.50270

IV. **Impact of rate of surgical resection on survival in gastric cancer patients. Nationwide register study from the Swedish National Register of Oesophageal and Gastric Cancer – NREV**
Kung CH, Jestin C, Linder G, Johansson J, Nilsson M, Hedberg J, Lindblad M
Manuscript

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LIST OF ABBREVIATIONS

AJCC	American Joint Committee on Cancer
ASA	America Society of Anaesthesiologists
BMI	Body Mass Index
CI	Confidence interval
CRS	Cytoreductive Surgery
CRT	Chemoradiotherapy
CT	Computed Tomography
D0	Less than D1 lymphadenectomy
D1	Lymphadenectomy of perigastric nodes (stations 1-7)
D1+	D1 lymphadenectomy plus station 8a and 9 (also 11p for total gastrectomy)
D2	Extended lymphadenectomy
DGE	Delayed gastric emptying
ECF	Epirubicin, Cisplatin, 5-Fluorouracil
ECX	Epirubicin, Cisplatin, Capecitabine
EOX	Epirubicin, Oxaliplatin, Capecitabine
EPIC	Early Postoperative Intraperitoneal Chemotherapy
ERP	Enhanced Recovery Program
FLOT	5-Fluorouracil, Leucovorin, Oxaliplatin, Docetaxel
FU	5-Fluorouracil
GIST	Gastrointestinal Stromal Cell Tumour
GOO	Gastric outled obstruction
Gy	Gray (Joule/Kg)
HIPEC	Hyperthermic Intraperitoneal Chemotherapy
H. Pylori	Helicobacter Pylori
HR	Hazard Ratio
IQR	Interquartile range
ISGPF	International Study Group of Pancreatic Fistula
JGCA	Japanese Gastric Cancer Association
MALT	Mucosa Associtated Lymphoid Tissue

MDT	Multidisciplinary therapy conference
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
MSI	Microsatellite instability
MVR	Multivisceral resection
NET	Neuroendocrine Tumour
NREV	National Register for Oesophageal and Gastric Cancer
OR	Odds Ratio
OS	Overall Survival
POPF	Postoperative Pancreatic Fistula
RCT	Randomized Controlled Trial
S-1	Chemotherapy regimen of 5-FU prodrug, 5-FU degradation inhibitor and 5-FU phosphorylation inhibitor
TNM	Tumor Node Metastasis
UICC	Union for International Cancer Control

1 INTRODUCTION

1.1 EPIDEMIOLOGY

Gastric cancer has historically been one of the most common forms of cancer worldwide with the second highest disease related mortality [1, 2]. However, over the last decades the incidence rates have substantially decreased, particularly in Europe and in Northern America [3]. The incidence is still high in other regions and globally gastric cancer is the fifth most common malignancy and accounts for a substantial morbidity and mortality burden and it is the third leading cause of cancer mortality [4-6].

The majority of gastric cancer cases comprises adenocarcinoma as classified in the WHO classification from 2010. Infection by *Helicobacter pylori* (*H. Pylori*) is regarded as a group 1 carcinogen by the International Agency for Research on Cancer (IARC). *H. Pylori* is estimated to double the risk of gastric cancer [7, 8] and a high dietary intake of salt is associated with a similar risk increase [9, 10]. Other risk factors include smoking and male gender [11, 12]. Some forms are also hereditary and constitutes around 10% of all gastric cancers [13, 14]. The incidence rate of gastric cancer per 100.000 people in Sweden for 2018 is for male 8.74 and for female 4.64 [15]. It has been steadily declining over the last decades and a similar pattern has been observed also in other European countries [5]. This decrease is believed to be driven by changes in diet [16, 17] and a lower prevalence of *H. Pylori* infection. A decrease in the age adjusted incidence of gastric cancer has also been observed in the Far East, possibly due to similar changes in the exposure to risk factors [5].

Symptoms of gastric cancer can be diffuse and are often recognized late why many cases are advanced at the time of diagnosis, which contributes to the poor prognosis of gastric cancer. A review of historical data from three decades up to 1990 showed that only around 35% of patients with gastric cancer in non-Japanese series underwent tumour resection, with a curative resection rate of only around 18%. Due to several factors, including earlier detection by screening, the corresponding resection rate in Japanese series were 93% and 59% respectively. Of those undergoing curative resection the mean 5-year survival rate was 39% and 61% for non-Japanese and for Japanese series [18]. Similar results have also been reported in Korea, where a single institution demonstrated an overall 5-year survival rate of 64% for the period 1986-1990 [19]. The large difference in survival of patients with gastric cancer between the East and West is multi factorial. First, there is a difference in which tumour stage patients are diagnosed, with more early gastric cancer in the East, but the prognosis per stage is still superior in the East [20, 21]. Improvements have been achieved in the treatment of gastric cancer in the past decades, but the prognosis is still dire. If there is an actual difference in terms of tumour biology in East Asian carcinomas, a difference in tolerability to treatment or better care and treatment of gastric cancer in the East is still not clear [22].

1.2 DIAGNOSTIC WORK UP

The diagnosis of gastric cancer is achieved by endoscopy with biopsy and histopathological assessment of suspicious macroscopic lesions. Gross classification is divided into categories depending on the endoscopic assessment. Superficial tumours are classified according to Paris classification and larger tumours are classified according to Borrman [23]. The TNM classification is according to American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) 8th edition [24].

The mainstay diagnostic procedures for accurate staging is abdominal/thoracic CT-scan. For assessment of tumour depth in early lesions endoscopic ultrasound can be applied [25] and for advanced disease staging laparoscopy and peritoneal cytology is used to more accurately determine possible peritoneal spread [26]. In cases where assessment of distant metastasis is inconclusive the use of MRI or FDG-PET-CT may complement the work-up, but no single modality has been shown to be superior [27-29]. A more stringent investigation protocol has been implemented to an increasing extent during the last decade in order to provide an optimal and personalized treatment regimen. Regardless of these diagnostic procedures the diagnostic accuracy is still only around 60-80% [30] and it has been reported that a change in management was made due to too advanced local disease or distant metastases in 8,5-59,6%, as discovered during diagnostic laparoscopy [26]. The advancements of imaging modalities have most likely improved the accuracy of preoperative staging. It has however also made staging assessment more complex and difficult to interpret.

1.2.1 Screening and early detection

In countries with a high incidence of gastric cancer nationwide screening might have a positive effect. There are currently national screening programs in South Korea and Japan. Studies show that since the introduction of screening the proportion of early gastric cancers has increased and the mortality rate has decreased [19, 31-34]. These screening programs might however not yield the same effect if introduced in western countries due to differences in incidence rate, diagnostic availability and treatment traditions [35]. Randomized trials of screening for gastric cancer are however lacking.

1.2.2 Histologic classification

The term gastric cancer refers to adenocarcinoma of the stomach that is the most common type malignancy of the stomach that constitutes around 95 % of all malignant gastric lesions [36]. Gastric cancer with signet ring cells or linitis plastica, a diffuse gastric cancer with poorly differentiated tumour cells characterised by a thick rigid gastric wall, is associated with a worse prognosis [37]. The Lauren classification of histological subtypes consists of the diffuse (undifferentiated) and intestinal type [38]. The prognosis for these subtypes is debatable and there are studies that imply that prognosis is better for the intestinal type but this difference may not necessarily be only related to the histology, but could also be related to more advanced stage for the diffuse type compared to the intestinal type [39-42]. Less common malignancies in the stomach that are not a part of this thesis and therefore not discussed further include

Gastrointestinal Stromal Cell Tumours (GIST), Mucosa Associated Lymphoid Tissue (MALT) lymphoma, Neuroendocrine Tumours (NET).

1.2.3 Molecular classification

With the improvement of next generation sequencing methods, the understanding and knowledge of tumour biology and its importance has progressed [43, 44]. The genome for gastric cancer and molecular characterization has been published in a trial in 2014 [45]. This study characterized gastric cancer molecular profile in four distinct subgroups. Chromosomal instability is the most frequent subgroup with around half of all patients and characterized with TP53 mutation. Other groups are those with microsatellite instability (MSI), genomically stable group and those with tumours with Epstein-Barr virus infection.

1.3 TREATMENT

A profound change in the management of cancer patients during the last decade is multidisciplinary therapy conferences (MDT). The conference gathers all relevant specialties and aims to accurately classify the stage and extent of disease, determine if the disease is resectable and along with risk factors asses if the patient is operable. The MDT also aims to recommend an individual-based multimodal evidence-based treatment. The ultimate decision is however made by the responsible physician together with the patient [46].

1.3.1 Endoscopic resection

Early gastric cancer (T1) is defined as tumours confined to the mucosa. If possible, early gastric cancer should be resected using endoscopic techniques provided that a radical resection can be performed with an adequate margin and with low risk for lymph node metastasis, since this does not interfere with the function of the alimentary tract. In a large study of 5265 patients with gastric cancer in Japan, 1230 cases had well differentiated intramucosal cancers of a size less than 30 mm, none had lymph node metastasis. There were 929 tumours without ulceration regardless of tumour size, and those were also without lymph node metastasis [47]. This is corroborated by another study from Japan examining 1196 patients with early gastric cancer with an overall lymph node metastatic rate of only 3,5% [48]. In multivariate analysis, lymphatic vessel invasion, histologic ulceration and tumour size of more than 30 mm were independent risk factors of lymph node metastasis and the prevalence of lymph node metastasis in cases without these independent risk factors was only 0,36%. Based on these and similar studies, the Japanese Gastric Cancer Association guidelines for endoscopic treatment of early gastric cancer criteria consist of: absolute indication: differentiated adenocarcinoma with a depth of cT1a and without ulceration (with ulceration up to 3 cm in tumour diameter) and expanded indication: un-differentiated adenocarcinoma without ulcerative findings, depth of cT1a and diameter < 2 cm[49]. After endoscopic resection a careful histopathological assessment of the specimen to determine the exact tumour size, the depth of growth, radicality and lymphovascular invasion is essential for the following decision if complementary surgery with

lymphadenectomy is indicated or if the endoscopic treatment is to be regarded as curative. The 5-year survival rate after applying this strategy of organ preserving treatment for early gastric cancer is as high as 83% to 97.5% [50-52].

1.3.2 Surgical resection

In cases where organ preserving endoscopic treatment is not possible, surgical resection is standard of care in the treatment of gastric cancer. The two most common types of resections are total gastrectomy involving removal of the entire stomach and distal gastrectomy which involves removal of the distal part of the stomach including the pylorus. The decision on what extent of the stomach that needs to be removed is dependent on tumour location, size and the histopathological characteristics since the diffuse type cancer has a more infiltrative growth pattern where more extensive surgery may be mandated. A French prospective controlled study [53], performed before neoadjuvant/adjuvant oncological treatment became standard of care, comparing total versus subtotal gastrectomy for cancer in the gastric antrum showed no difference in postoperative mortality 1,3% and 3,2 % respectively and an equal 5-year survival rate, 48% in both groups. Reconstruction of the alimentary tract after gastrectomy can be performed in many ways. For total gastrectomy Roux en-Y oesophagojejunostomy and jejunojejunostomy is the standard and most prevalent reconstruction method [54]. An alternative reconstruction consists of functional jejunal interposition (Henley´s reconstruction) and there is low grade evidence suggesting an improved functional outcome, but this procedure is performed very seldom due to the increased complexity [55]. For distal gastrectomy, reconstruction can be performed with Billroth 1 gastroduodenostomy, Billroth 2 with omega loop gastrojejunostomy with or without Braun jejunojejunostomy or Roux-en-Y gastrojejunostomy with jejunojejunostomy. With the evolution of gastric surgery from ulcer surgery to cancer surgery, there has been a shift towards reconstruction with a Roux-en-Y limb following distal gastrectomy, however there are no clear evidence to which is superior in terms of postoperative complications and long term quality of life [56-59]. In the scarcer proximal gastrectomy, reconstruction is typically performed with a jejunal pouch interposition. In superficial, small and well defined centrally located tumours a pylorus preserving central gastrectomy has been shown to give a better functional outcome, probably because of the preserved duodenal passage of nutrients. These less common methods of reconstruction seem to have a better functional outcome compared to standard gastrectomy according to some trials [60-62].

1.3.2.1 Lymphadenectomy

The extent of lymphadenectomy in gastric cancer surgery has been developed over several decades and studied extensively [63]. The lymph node stations in the upper abdomen have been assigned numbers which are based on the lymphatic flow at different tumour sites of the stomach and the associated long-term survival depending on the presence of metastasis in each specific lymph node station. The stations most adjacent to the stomach are called the gastric lymph nodes and numbered 1-6. The stations around the celiac artery and branches of the artery and splenic hilum are numbered 7-11. The lymph node station in the hepatoduodenal ligament

is numbered 12 and is subdivided according to proximity to the artery, bile duct or portal vein. Stations around the superior mesenteric vessels and the middle colic branch are numbered 14a, 14v and 15. The peripancreatic lymph node stations are numbered 13 and 17-18. Para-aortic stations are numbered 16. Stations around the diaphragm are numbered 19-20. The associated lymph nodes in the lower thorax associated to gastric cancer surgery and lymphadenectomy are numbered 110-112.

Originally the lymph node stations were grouped together into tiers depending on the tumour location. This system corresponded to similar frequency and pattern of metastasis in each lymph node station for the respective tier depending on the location of the primary tumour [20, 64, 65]. This nomenclature generated three tiers of lymph node groups and thus three corresponding extents of lymphadenectomy, assigned D1 involving dissection of tier 1 nodes, D2 involving tier 1 and 2 nodes, D3 tier 1, 2 and 3 nodes and D0, lymphadenectomy not sufficient for D1, D2 or D3. This system was not entirely adopted in the West because of its complexity and difficult to understand since the lymph node stations included in each tier differed depending on the location of the tumour and not on the type of gastrectomy that was performed. This grouping of tiers has been simplified and reclassified in the 3rd English edition of Japanese gastric cancer treatment guidelines [66]. The lymphadenectomy extents are now classified as D0, D1, D1+ and D2 and the respective stations required for adequate lymphadenectomy for each extent is specified depending on what type of surgical procedure rather than tumour location. The lymphadenectomy that should be performed is specified for total gastrectomy, distal gastrectomy, pylorus-preserving gastrectomy and proximal gastrectomy now according to the 5th English version of Japanese gastric cancer treatment guidelines [49] (Figure 1).

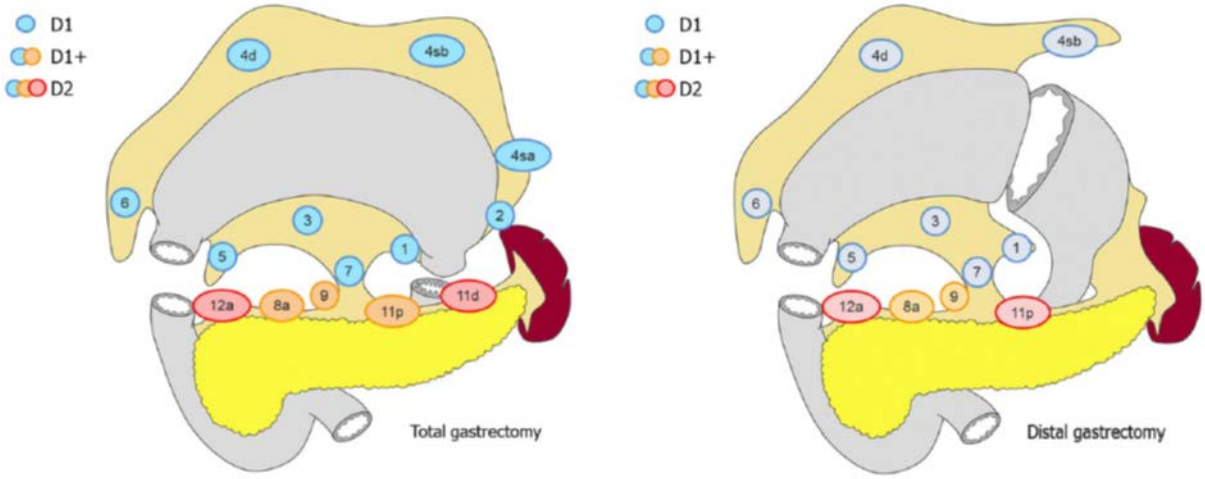


Figure 1. *Extent of lymphadenectomy for total and distal gastrectomy. Number refer to lymphnode stations as specified above and complete dissection of blue nodes are necessary for D1 lymphadenectomy, addition of orange nodes for D1+ lymphadenectomy and addition of red nodes for D2 lymphadenectomy. Reprinted with permission from the publisher. Japanese gastric cancer treatment guidelines 2018 (5th edition). Gastric Cancer (2020).* *https://doi.org/10.1007/s10120-020-01042-y*.

Early non-randomized studies regarding the oncological outcome depending on extent of lymphadenectomy in Japan show that more extensive lymphadenectomy resulted in improved long-term survival and acceptable morbidity [20, 67, 68]. Based on this experience, D2 gastrectomy became standard of care in Japan for advanced gastric cancer already in the 1980's. Early small non-Japanese trials found conflicting results regarding lymphadenectomy extent showing no favour for extensive lymphadenectomy and some showing a slight possible advantage but not definitive results [69-71].

In the 1990's two large European randomized controlled trials were conducted comparing D1 versus D2. The initial reports of short-term data showed a substantial increased amount of postoperative complications, morbidity and mortality [72, 73]. The analysis of those data attributed the high complication rate to a high rate of concomitant pancreatic tail resection and splenectomy as an integral part of D2 dissection. Long-term follow-up therefore failed to show any benefit for D2 dissection [74, 75] and the initial conclusions did not favour D2 dissection. However, the 15-year follow up [76] has shown a survival benefit of D2 after exclusion of postoperative mortalities. The overall conclusions from these trials were that the high postoperative morbidity and mortality cancelled the proposed oncological benefit of D2 dissection. Other concerns from these studies were that pancreatic tail resection and splenectomy as an integral part of D2 was attributed in the high complication rate and during the 2000's these procedures have only been performed in locally advanced tumours or in cases with signs of lymph node metastases in the splenic hilum. A majority of the surgery in the European studies were performed in low volume centers, raising questions about the quality of surgery. This aspect has certainly changed over the last decade with the implementation of centralization of surgery.

Due to the implementation of D2 gastrectomy as a standard procedure another European randomized controlled trial [77] was conducted between 1998 and 2006. This study showed substantially lower rates of postoperative morbidity in D2 vs D1 and no differences in mortality compared to the two previous European trials [78], but still no difference in overall 5-year survival between D1 and D2[77]. It was suggested that the failure to show a benefit of D2 occurred due to "contamination", which means that the D1 group underwent more lymphadenectomy than should have been done, as well as a high share of T1 cancers that probably did not benefit from D2. It was also concluded that D2 lymphadenectomy might be of benefit in a subgroup of patients with more advanced T2-T4 and N+ disease.

A single center randomized controlled trial that earlier had been performed in Taiwan comparing D1 to D3 (in principle very similar to D2) [79, 80] showed a survival benefit for D3 and low complication rates. The possible value of an even more extensive lymphadenectomy was evaluated in a large study from Japan comparing D2 gastrectomy with or without para-aortal lymphadenectomy. The data showed an increase in postoperative morbidity without any improvement in long term survival after para-aortal lymphadenectomy [81].

It can be argued that there is still no large scale European RCT showing a survival benefit for D2 versus D1. The previous Japanese non RCT studies show good results for D2 and the

current results of D2 surgery in clinical practice in Far East are far superior compared to European centers, making an RCT in the Far East comparing D1 vs D2 impossible to conduct due to ethical considerations. A recent meta-analysis [82] however concludes that there are still questions regarding lymphadenectomy extent that should be answered through a randomized clinical trial and another large scale multicenter RCT was recommended. It should be noted that all studies of D1 vs. D2, both RCTs and cohort studies were performed before the introduction of neoadjuvant and or adjuvant treatment as standard of care. Therefore, there is limited data in the literature showing benefit of D2 in patients that also receive oncological therapy.

1.3.2.2 Bursectomy

Bursectomy in gastric cancer involves the removal of the peritoneal leaf comprising the lesser sac. In Japan, previously it has been routinely performed for tumours invading the serosa but avoided in early T1/T2 tumours [66]. A randomized clinical trial from Japan [83] comparing bursectomy vs non bursectomy in patients with T2 or T3 tumours showed similar morbidity and mortality rates and concluded that bursectomy could be performed safely by experienced surgeons. Long term follow-up of that study [84] show that 5-year overall survival was 77,5% for the bursectomy group and 71,3% for the non-bursectomy group. The difference was not significant, but trial design was set up for noninferiority of the omission of bursectomy and they conclude that bursectomy should not be regarded as a completely redundant procedure. A meta-analysis [85] of both RCT and non RCT show no overall survival benefit for bursectomy versus non-bursectomy. In subgroup analysis of serosa-positive patients, bursectomy might improve survival but the difference was not statistically significant. In a recent RCT of 1204 patients, half were randomized to bursectomy and the other half to non-bursectomy. The results did not reveal any survival advantage for bursectomy. The bursectomy group however had more incidence of postoperative pancreatic fistula. Conclusions from this trial recommend that bursectomy should not be performed as standard surgery for patients with cT3/T4a resectable gastric cancer [86].

1.3.2.3 Laparoscopic surgery

Laparoscopic gastrectomy has been introduced to an increasing degree during the last years. There is no clear indication for when laparoscopic gastrectomy may be applied. In the Far East T1b-T2 N0-1 has been the most common indication. There are numerous case series and cohort studies of laparoscopic gastrectomy, but randomized trials comparing this approach vs open gastrectomy are less common. In an early randomized controlled trial comparing laparoscopic versus open subtotal gastrectomy for distal cancer performed between 1992-1996 showed no significant difference in postoperative mortality which was in the range of 3,3% to 6,7 %, postoperative morbidity was 27% for both groups, or 5-year overall survival that was around 55% for both groups [87]. A randomized study performed between 2008 and 2009 comparing laparoscopy-assisted gastrectomy versus open gastrectomy in clinical T2-T3 cancer showed a 3-year overall survival of 67% and 54%, no significant difference, for the laparoscopic and open approach respectively [88]. Similarly, a study comparing early distal T1 tumours that were

resected with laparoscopy-assisted or open distal gastrectomy showed similar 5-year overall survival of 97,6% and 96,3% respectively with no significant differences in postoperative complications [89]. The increasing amount of evidence for laparoscopic surgery in gastric cancer show that laparoscopic gastrectomy in non-advanced gastric cancer cases is non-inferior to open surgery regarding overall survival in the hands of experienced surgeons. In terms of postoperative complications there might be slight advantages for laparoscopic surgery [90]. Most studies are however conducted in Korea and Japan and are single center trials. There are two recently published large scale multicenter randomized controlled trials investigating long term survival after laparoscopic and open distal gastrectomy for clinical stage I disease. The results show that laparoscopic distal gastrectomy seems to be non-inferior to open surgery in regard to overall survival and diseases free survival [91, 92].

1.3.2.4 Multivisceral resection

Curative intended treatment for gastric cancer consists of resection of the tumour with radical margins and a microscopically radical (R0) resection is a positive prognostic factor for survival [93, 94]. In cases with locally advanced cancer with suspected or confirmed growth into adjacent organs a question is raised regarding resectability. A systematic review of multivisceral resection show perioperative mortality ranging from 1,9% to 15% and a 5-year survival of 0% to 40%. The rate of successful R0 resection following multivisceral resection was 38%-100% in the studies examined. The authors conclude that the postoperative morbidity and mortality might be higher after multivisceral resection but the potential benefit of achieving radical resection should outweigh the increased perioperative risks. Adequate identification of suitable patients that will benefit from this extensive procedure is essential [95, 96].

1.3.2.5 HIPEC and metastatic surgery

Around 5-20 % of patients with gastric cancer planned for curative resection are found to have peritoneal dissemination during laparotomy [97, 98]. The results of peritonectomy and hyperthermic intraperitoneal chemotherapy (HIPEC) in selected cases of other neoplastic abdominal malignancies than gastric cancer, in particular pseudomyxoma and colorectal cancer, have been encouraging [99, 100] but the few studies [101, 102] on peritonectomy and HIPEC or early postoperative intraperitoneal chemotherapy (EPIC) in advanced gastric cancer with peritoneal carcinomatosis has shown high morbidity rates. In certain subgroups of gastric cancer patients that are treated with peritonectomy and HIPEC, where macroscopic radicality can be achieved, the initial results may be promising [102], but the long-term results are very uncertain. A Spanish multicenter retrospective trial showed that in selected patients, especially with peritoneal carcinomatosis index less than 7, cytoreductive surgery (CRS) and HIPEC could be of benefit but conclusions from that trial still warrant more studies [103]. There is one published randomized clinical trial from China studying CRS alone versus CRS and HIPEC that showed a median survival of 6.5 months and 11 months respectively [104]. Sample size was only 68 patients and no widespread general conclusions can be drawn. There is an ongoing

French randomized multicenter study investigating the role of perioperative HIPEC without CRS in patients with high risk gastric cancer but with no macroscopic peritoneal carcinomatosis [105]and a German randomized study comparing the effect of CRS with or without HIPEC for peritoneal carcinomatosis (NCT02158988). In a few years more information and data will be available regarding the treatment of peritoneal carcinomatosis and the role of CRS and HIPEC but presently it is not recommended outside clinical trials.

There is a current randomized trial comparing the effect of surgery in gastric cancer patients with limited metastatic disease where resection is possible. The trial compares chemotherapy alone versus chemotherapy plus surgical resection and results are highly anticipated[106].

Series of carefully selected patients with liver metastases from gastric cancer have shown a 5-year survival of up to 30% after multimodal treatment including liver resection [107-109]. Given the very limited experience, curatively intended treatment for gastric cancer liver metastases is regarded as treatment that should not be performed outside clinical trials.

1.3.2.6 Sentinel node navigation surgery

Sentinel node surgery for early gastric cancer has been attempted and there are ongoing trials investigating this further. Although for gastric cancer the concept of sentinel node surgery has not come as far as for breast cancer the results are promising. A multicenter trial of sentinel node surgery for early gastric cancer [110] with dual tracer technique show a sentinel node detection rate of 97.5% and an accuracy of 99% to evaluate nodal metastasis. There were however four (1%) false negative sentinel node biopsies. A large multicenter phase III trial is currently ongoing studying sentinel basin dissection with stomach preserving surgery versus standard D1+ lymphadenectomy for early gastric cancer [111]. A quality control study from the RCT examining safety of the procedure show that laparoscopic sentinel basin dissection can be performed safely. There were only eight postoperative complications out of 108 patients and only one patient with Clavien-Dindo grade IIIa [112]. The trial might come with promising results. However, the patients included are early gastric cancers with cT1N0M0 and the proportion of patients in western population with clinical early gastric cancer at presentation is much less than in Japan and South Korea. The possible implementation of this in Sweden must be done with caution and more trials are needed.

1.3.3 Postoperative complications

Surgery for gastric cancer encompasses a vast variety of complications that may arise, and surgery is often carried out in frail and elderly patients with comorbidities. Complication rates and the severity of these vary substantially in the literature and depend on how complications are defined, patient selection and the extent of surgery. A single center retrospective study of D2 gastrectomy in Sweden [113] showed that the total complication rate of Clavien 3b or higher amounts to around 24 %. When compared to the previous large European randomized trials the postoperative morbidity and complication rate where lower in the Italian D2 trial [78] with 18%

overall morbidity rate in the D2 group. This is a substantial difference when compared to the British MRC and Dutch trial [72, 73] with overall morbidity of 43-46% in the D2 group and a mortality of 10-13%. This evolution and improvement of complication rate should be expected as many different components in the management of gastric cancer has improved over the years and the Italian D2 trial was conducted nearly a decade later than the two former. The key factor for reducing the postoperative complication is probably the omission of routine pancreaticosplenectomy as part of D2. Centralization and increasing hospital volume has most likely also reduced complication rate as the Taiwanese single center trial with high volume shows no postoperative mortality and a complication rate of merely 17% in the D3 group [80].

Another key step in reducing postoperative complications, shown mostly after colorectal surgery, has been the implementation of enhanced recovery programs (ERP) [114, 115]. There is a consensus guideline for ERP gastric cancer program [116]. An Italian study has evaluated the implementation of the program at several institutions showing a wide range of adherence to the program and that further improvements can be made [117].

1.3.3.1 Postgastrectomy syndromes

Dumping is a common syndrome after gastrectomy which can include symptoms such as abdominal pain, diarrhea, nausea, bloating as well as palpitations, flush, tachycardia and diaphoresis. It can occur early within 30 minutes from meal intake or late, a few hours after meal. Symptoms can be alleviated with dietary modifications.

There are also numerous nutritional deficiencies that can occur after gastric cancer surgery. Among the more common are vitamin B12 that occur due to loss of Intrinsic Factor. Iron deficiency as well as Vitamin D and calcium deficiency can also occur and depends somewhat on extent of resection and reconstruction methods after gastrectomy [118].

1.3.4 Oncological therapy

1.3.4.1 Perioperative therapy

The introduction of chemotherapy and/or radiotherapy has changed the general treatment paradigm for gastric cancer. There are basically three principally different treatments that are practiced in the United States, Europe and Far East respectively, based on three different pivotal clinical trials. A trial performed in the USA [119] on patients with adenocarcinoma of the stomach or gastroesophageal junction found an increase in median overall survival from 27 months to 36 months in patients who had adjuvant chemoradiotherapy compared to surgery alone. The treatment arm consisted of postoperative fluorouracil and leucovorin and a total of 45 Gy administered at 1.8 Gy for 25 days. Around 64% of patients could receive the treatment as planned.

A British trial that included both gastric cancer and cancer of the gastroesophageal junction [120] showed a survival benefit of 13% for neoadjuvant and adjuvant chemotherapy (perioperative)

consisting of epirubicin, cisplatin and 5-fluorouracil. Treatment consisted of 3 preoperative and 3 postoperative cycles. Each cycle lasting for 3 weeks with epirubicin and cisplatin infusion at first day of cycle and 5-fluorouracil infusion daily for 21 days. Postoperative morbidity rates were similar in both treatment arms but only around 40 percent of the assigned patients could receive all cycles of perioperative chemotherapy.

A Japanese trial comparing adjuvant S-1 (a combination of an oral prodrug to fluorouracil, an inhibitor of fluorouracil degradation, and an inhibitor of fluorouracil phosphorylation to reduce the gastrointestinal toxicity) to surgery showed a 3-year survival rate of 80,1% with S-1 compared to 70,1% in patients that had D2 gastrectomy [121]. The treatment arm received daily oral S1 for four weeks in a six-week cycle, and treatment continued for 1 year after surgery. In total around 66% received treatment for 1 year after surgery. However, amongst these patients, dosage had to be decreased for roughly half of the patients. These three trials have had a major impact on treatment guidelines in the regions where the trials were performed.

Another subsequent multicenter trial in China, South-Korea and Taiwan studied adjuvant treatment following surgery compared to surgery alone. The treatment consisted of capecitabine and oxaliplatin for two weeks in a three-week cycle for six months. The estimated overall 5-year survival was 78% and 69% for adjuvant chemotherapy and surgery alone respectively [122]. The ARTIST trial [123] compared adjuvant chemotherapy with capecitabine and cisplatin to adjuvant chemoradiotherapy with capecitabine and cisplatin and a total radiation of 45 Gy fractionated to 1.8 Gy 5 days a week for 5 weeks. Long term results show similar disease-free survival and overall survival for both treatment arms, but a subgroup analysis show that chemoradiotherapy improved disease-free survival in patients with N+ disease and intestinal type cancer. The recent CRITICS trial [124] comparing perioperative chemotherapy versus perioperative chemotherapy with the addition of radiotherapy in the postoperative phase did not show any survival benefit with the addition of radiotherapy. Results from a French trial [125] comparing perioperative chemotherapy with cisplatin and fluorouracil to surgery alone show an overall survival advantage in favour for the perioperative chemotherapy group with a 5-year survival of 38% and 24% for the surgery alone group. A recent published randomized trial comparing standard ECF/ECX perioperative treatment compared to perioperative 5-Fluorouracil, Leucovorin, Oxaliplatin, Docetaxel (FLOT) showed an increased median overall survival from 35 months to 50 months[126]. The treatment arm was administered for four preoperative and four postoperative cycles and each cycle lasted for 2 weeks as compared to the control arm which consisted of three preoperative and postoperative cycles. A total of 46% of patients completed all cycles in the treatment arm (FLOT) and only 37% completed all cycles in the control arm. A pathological complete response was achieved in 16% of cases in the treatment arm as compared to 6% in the control arm [127].

These trials of perioperative and adjuvant oncological therapy have shown a benefit of oncological therapy in addition to surgery. However, it has been discussed if chemotherapy adds any oncological advantage or if it merely complements inadequate lymphadenectomy, in particular because the dominant lymphadenectomy extent in the US trial was D0 [128, 129]. These new insights examined further in more ongoing trials but the trial settings for these large RCT still do not necessarily reflect clinical reality. Real life data on neoadjuvant and adjuvant therapy in gastric cancer are however scarce. A recent Norwegian population-based study comparing no perioperative oncological therapy in one time period to another with perioperative chemotherapy showed no benefit for chemotherapy [130]. However, this study was hampered by a low adherence, since only 44% of the patients tolerated the full treatment regimen, thus questioning to what extent the results from clinical trials translate into similar results in real life. A table summarizing selected studies on oncological therapy can be seen in Table 1.

1.3.4.2 Antibody therapy/Immunotherapy

There is an ongoing RCT studying the effect of addition of Trastuzumab or Trastuzumab and Pertuzumab to perioperative chemotherapy in HER2 positive gastric cancer patients [131]. The recently published preliminary results of the MAGIC-b trial investigating the effect of bevacizumab in addition to perioperative chemotherapy showed no evidence of benefit for the use of bevacizumab. This trial however also includes adenocarcinoma of the lower oesophagus and not strictly gastric cancer [132].

Immunotherapy has gained strong positive evidence in the treatment of melanoma and renal cell carcinoma but for gastric cancer there is still no shown advantages. There are multiple studies showing the prognostic importance of PD-L1, PD1/PD-L2 and MSI status as summarized in a recent review [133]. But interventional trials are not yet up to speed. A phase III trial conducted in Japan, South-Korea and Taiwan included 493 patients with advanced gastric cancer that were refractory or intolerable to two previous chemotherapy regimens and randomly assigned them to nivolumab or placebo in a 2:1 fashion. The results show a significantly improved median overall survival for nivolumab group, but the efficacy was modest as the survival improved from 4.14 months to 5.26 months in the nivolumab group [134]. The results at this moment has little clinical implementation importance in western patients but might be the start of a future new therapeutic adjunct in the treatment of gastric cancer.

Table 1. *Selected studies on oncological therapy in curative treatment of gastric cancer.*

Study	Patients	Treatment arms	Results
Macdonald, NEJM 2001 [119]	556 patients with gastric cancer or GEJ cancer	Surgery alone vs Adjuvant 5-Fu + Leucovorin + 45 Gy radiotherapy	Median survival 27 vs 36 months. HR 1.35 (95% CI 1.09-1.66) p = 0.005
Cunningham, NEJM 2006 [120]	503 patients with gastric cancer, GEJ cancer or cancer to lower oesophagus.	Perioperative ECF vs surgery alone	5-year OS 36% vs 23 %. HR 0.75 (95% CI 0.60-0.93) p = 0.009
Sakuramoto, NEJM 2007 [121]	1059 patients with gastric cancer	Adjuvant S-1 vs surgery alone	3-year OS 80.1% vs 70.1%. HR 0.68 (95% CI 0.52-0.87) p = 0.003
Ychou, JCO 2011 [125]	224 patients with gastric cancer, GEJ cancer or cancer to lower oesophagus	Perioperative 5-FU and cisplatin vs surgery alone	5-year OS 38% vs 24%. HR 0.69 (95% CI 0.50-0.95) p = 0.02
Noh, Lancet oncology 2014 [122]	1035 patients with gastric cancer	Adjuvant oxaliplatin and capecitabine vs surgery alone	5-year OS 78% vs 69%. HR 0.66 (95% CI 0.51-0.85) p = 0.0015
Park, JCO 2015 [123]	458 patients with gastric cancer	Adjuvant cisplatin and capecitabine vs Adjuvant cisplatin, capecitabine and 45 Gy radiotherapy	5-year OS 73% vs 75%. HR 1.13 (95% CI 0.78-1.65) p = 0.527
Cats, Lancet oncology 2018 [124]	788 patients with gastric cancer or GEJ cancer	Perioperative ECX/EOX vs preop ECX/EOX and postop CX and 45 Gy radiotherapy	5-year OS 42% vs 40%. HR 1.01 (95% CI 0.84-1.22) p = 0.90
Al-Batran, Lancet 2019 [126]	716 patients with gastric cancer or GEJ cancer	Perioperative FLOT vs perioperative ECF/ECX	5-year OS 45% vs 36% HR 0.77 (95% CI 0.63-0.94) p = 0.012

1.3.5 Palliative therapy

1.3.5.1 Palliative surgery

For patients with specific tumour related symptoms surgery can be an option. In patients with gastric outlet obstruction (GOO) both duodenal stenting and by-pass with gastrojejunostomy are possible alternatives. A systematic review comparing the two methods show that stenting is preferable in cases with relatively short life expectancy and more favourable with gastrojejunostomy in patients with longer life expectancy [135]. However, the frequency of gastrojejunostomy has been decreasing with the introduction of stenting and both techniques still have failure of treatment. A retrospective study comparing partial stomach-partitioning gastrojejunostomy to gastrojejunostomy showed improved oral intake and lower frequency of postoperative delayed gastric emptying (DGE) [136]. The result of this study is also in line with a meta-analysis of seven studies with 207 patients showing improved outcomes of partial stomach-partitioning gastrojejunostomy compared to conventional gastrojejunostomy in terms of improving DGE [137].

Palliative resection can also be of value in the occurrence of bleeding or perforation. Bleeding can be controlled with radiotherapy or endoscopic therapy but in refractory bleeding there might be need for resection [138]. For perforation, resection can also be warranted either in the setting of curative intention or palliation depending on the stage of disease[139, 140].

The value of palliative resection in terms of survival has been studied in a subgroup of patients in the large Dutch gastric cancer trial and show that for subgroup of patients younger than 70 years of age and metastatic disease localized to one metastatic site, palliative resection increased median survival time with around 4 months [141]. A study randomizing 86 patients to chemotherapy alone versus 89 patients to gastrectomy plus chemotherapy in the presence of one non-curable factor showed no advantage for gastrectomy plus chemotherapy [142]. Two case series from Taiwan investigating the effects of palliative resection show some results of slightly better survival of palliative resection compared to no resection on palliative patients. But these are case series from single institutions and non-randomized [143, 144].

1.3.5.2 Palliative oncological treatment

Amongst newly diagnosed gastric cancer patients around 30 % are assessed as primarily with distant metastatic disease and only around 45-60% can undergo potentially curative resection [145, 146]. The high number of cases ineligible for curatively intended treatment warrants efficient palliative therapy. If tolerable, palliative chemotherapy may have a small survival advantage compared to best supportive care and increases overall median survival time with approximately 3 - 9 months [147-149]. A randomised phase 3 study comparing a combination of trastuzumab and first line chemotherapy of capecitabine plus cisplatin or fluorouracil plus cisplatin versus chemotherapy alone for HER2 positive tumours showed a significant increased median overall survival of 13,8 months for the trastuzumab group versus 11,1 months for the chemotherapy alone group [150].

Another multicenter trial investigated for HER2 positive metastatic gastric cancer and gastroesophageal junction cancer patients the added effect of dual HER2 targeted therapy. The trial compared the addition of Pertuzumab to Trastuzumab and chemotherapy compared to Trastuzumab and chemotherapy alone. The results do not show any improved overall survival for the Pertuzumab group [151].

A study on second line treatment compared Regorafenib to placebo and studied progression-free survival as primary endpoint showed significant difference in favour for Regorafenib. However, the effect was very modest showing median progression free survival of 2.6 months compared to 0.9 months for Regorafenib and placebo respectively [152].

Second line treatment with Irinotecan compared to best supportive care on patients that had progressed on first line treatment had a median survival of 4 months compared to 2,4 months respectively, the hazard ratio for death was reduced to 0.48 [153]. Although statistically significant, the actual clinical relevance and value of second-line therapy with those modest results can be questioned.

1.4 FOLLOW UP

There are no clear recommendations concerning follow-up after gastrectomy for cancer. Most Swedish centers will typically have 2-3 follow-up visits during the first year after gastrectomy to follow and manage weight-loss and different types of post-gastrectomy symptoms, such as early satiety and dumping. Thereafter yearly follow-up is common for up to five years after surgery but there is no evidence that it improves oncological outcomes because recurrences are very seldom possible to cure [154-156]and early detection and treatment has not been shown to be beneficial. For patients with early gastric cancer that have undergone endoscopic resection, recurrences are possible to cure, and such patients are therefore subjected to regular re-endoscopy. Eradication of *H. Pylori* infection is also important because this decreases the risk of developing metachronous gastric cancer [157]. For patients that have undergone resection for gastric cancer, vitamin B12 supplementation should be initiated following total gastrectomy [158]. There are other studies correlating nutritional deficiencies to gastric surgery, however there are no clear recommendations on supplementation except for vitamin B12 [159-161].

2 AIMS

The aims of this thesis were:

To evaluate the risk of Postoperative pancreatic fistula (POPF) and other postoperative complications after D2 gastrectomy with bursectomy for cancer in a high-volume tertiary unit.

To investigate time trends and changes in some aspects of surgical treatment of gastric cancer in Sweden.

To investigate the impact of extended lymphadenectomy during gastrectomy for cancer on postoperative morbidity and long-term survival.

To investigate the effect of gastric cancer resection rates on survival for the entire gastric cancer population.

3 PATIENTS AND METHODS

3.1 NATIONAL REGISTERS

3.1.1 NREV

The National Register for Oesophageal and Gastric Cancer (NREV) was started in 2006. The register aims to have complete coverage of all patients in Sweden diagnosed with oesophageal and gastric cancer. The register is run by a board of multidisciplinary health-care professionals with representatives from all of Sweden's six health care regions and from the regional cancer centers. There are additional support staff maintaining the integrity of the register and it is also monitored by the six regional cancer centers. The register is developed from a national goal from the National Board of Health and Welfare to implement diagnose specific quality registers in order to monitor and evaluate as well as do research on the results and quality of the healthcare given in Sweden.

Patients in the NREV are cross referenced with the Swedish Cancer Register continuously to maximize the coverage of NREV. A validation study has shown the validity of the data in the register to be 91% [162]. The register has been updated during the last years and from 2018 now comprises five sections. The first section covers diagnostic data. The second section covers the surgical details of treatment. The third covers postoperative complications. The fourth has a subset of sections detailing oncological treatment from neoadjuvant, perioperative, adjuvant and palliative treatment and follow up. The fifth section covers quality of life details.

The NREV publishes an annual report based on data from the previous year in the register to monitor changes in treatment pattern over the years and highlight regional differences in the care of gastric cancer patients [163].

The board of NREV have regular meetings to improve the register and develop the register so that the data it contains are of highest possible quality.

The register has a research committee that are responsible for assessing applications to perform research on the data in the register.

To date, in the spring of 2020 there has been published thirteen peer-reviewed scientific reports based on data from the register [162, 164-175] and a fourteenth article in press.

3.1.2 Swedish Cancer register

A national register run by the National Board of Health and Welfare. There are roughly 60,000 cases reported to the register each year. The cases refer to reported tumours and not individuals. The register was founded in 1958 with the purpose of creating a register to map and follow the incidence and prevalence of malignant diseases and change over time as well as a foundation for clinical and epidemiologic research. All pathologically verified tumours are mandated to be reported to the register separately by the pathologist and clinician and this is monitored in Sweden's six regional cancer centers. There is near complete coverage of diagnosed cases [176].

3.1.3 National Patient register

The register was established in 1964 and is administered by the National Board of Health and Welfare. It has complete coverage of inpatient data from 1987 and for specialized outpatient data from 2001. The register does not contain data on primary care outpatient data[177]. The register contains the ICD codes of main diagnosis and secondary diagnosis. The register has been used to obtain and determine the Charlson co-morbidity Index.

3.1.4 National Register of Education

The register (also integrated with Longitudinell integrationsdatabas för sjukförsäkrings- och arbetsmarknadsstudier (LISA)) is administered by Statistics Sweden. The first version of the register was from 1985. The register has since then been updated. The register has information on individuals highest completed degree. The register also has details on year of obtaining the degree. The data is obtained from the countries schools in the primary education system as well as from higher education system [178, 179].

3.1.5 Total population Register and Cause of Death register

These registers contain information on emigration, date of death and cause of death on all of Sweden's population since 1968. The data is retrieved from the Swedish Tax Agency and based on the Swedish Census[180].

3.1.6 Swedish Prescribed Drug Register

The register was started in 2005 and includes all prescribed drugs that are dispensed at Swedish pharmacies[181, 182].

3.2 PAPER I

3.2.1 Study design

Retrospective single center cohort study.

3.2.2 Data retrieval

Data was retrieved from the county's electronic patient chart system. Data covers extensive detail on patient baseline characteristics, treatment details and postoperative course and survival. The data were stored on institutional servers with censored patient information.

3.2.3 Study population

All gastric cancer patients that had a gastrectomy with D2 lymphadenectomy at Karolinska University Hospital between 2006 and June 2012.

3.2.4 Main outcome measure

The incidence and risk of postoperative pancreatic fistula (POPF) as defined by the International Study Group of Pancreatic Fistula (ISGPF) [183].

3.2.5 Statistical analysis

Data are presented as median with interquartile range. The Fisher exact test and Mann-Whitney U test were used for categorical and continuous variables. Multivariable analysis of risk factors was conducted with multivariable logistics regression. Statistical analysis was done with STATA/IC 12.1 software (StataCorp. LP, College Station, Texas, USA).

3.2.6 Ethical approval

The study has been approved by the Regional Ethics Committee (EPN Stockholm Dnr: 2013/596-31/3).

3.3 PAPER II

3.3.1 Study design

National quality register study cross matched with other national healthcare registers.

3.3.2 Study population

All patients in Sweden with gastric cancer that had curative intended surgery (based on responsible surgeons' opinion on treatment intent) from 2006-2013.

3.3.3 Main outcome measure

The main outcome was 30-day postoperative mortality and 30-day overall morbidity after surgery for gastric cancer as defined below.

3.3.4 Secondary outcome measure

90-day postoperative mortality: Mortality within 90 days of surgery.

Postoperative complications as defined by

Surgical complications

Anastomotic insufficiency: Clinically significant leakage, pure radiologic signs without clinical correlation were not included.

Bleeding: More than 2 L or need of reoperation.

Abscess: Radiological or surgically proven collection of pus of at least 3 cm × 3 cm with clinical symptoms such as fever or pain.

Other: Other complications prolonging hospital length of stay for at least 7 days.

General complications

Pneumonia: Radiological consolidations or opacities with clinical correlation with fever, dyspnoea or cough.

Sepsis: Fever, chills and positive blood culture.

Serious cardiovascular complications: New onset arrhythmia, myocardial infarction and stroke

Pulmonary embolism: Radiologically proven and needing treatment

Other: Other complications prolonging hospital length of stay for at least 7 days.

3.3.5 Definition of exposure

Patients were categorized and classified to different extent of lymphadenectomy based on which stations had been reported as resected in NREV. The categorization and definition was based upon JGCA 3rd English version treatment guidelines [66] for gastric cancer and categorized to D0, D1 or D1+/D2. Modifications were made to D2 in total gastrectomy where omission of station 10 node still was categorized as D2. And D1 distal gastrectomy where omission of station 1 and 7 nodes still was classified as D1.

3.3.6 Statistical analysis

Data are presented as mean ± SD and actual count and percentage in parenthesis. Data are analysed with chi square test and Fisher exact test for categorical parametric and non-parametric variables and ANOVA and Kruskall-Wallis for continuous parametric and non-parametric variables. Risk factor analysis was performed with logistics regression and multivariable analysis with multivariable logistics regression. Variables used in the multivariable model were age, gender, BMI, ASA class, Charlson comorbidity index, tumour stage (TNM 7), surgical procedure, multivisceral resection, hospital volume and calendar year. Associations was presented as Odds ratio (OR) with 95% confidence interval (95% CI). All analyses were done using IBM SPSS Statistics (Version 22.0; IBM Corp., New York, USA).

3.3.7 Ethical approval

The study has been approved by the Regional Ethics Committee (EPN Stockholm Dnr: 2013/596-31/3).

3.4 PAPER III

3.4.1 Study design

National quality register study cross matched with other national healthcare registers.

3.4.2 Study population

All patients in Sweden with gastric cancer which had curative intended surgery (based on responsible surgeons' opinion on treatment intent) from 2006-2017.

3.4.3 Main outcome measure

The main outcome was overall survival after surgery.

3.4.4 Definition of exposure

Patients were categorized and classified to different extent of lymphadenectomy based on the reported lymph node stations in NREV. The categorization and definition were based upon JGCA 4th English version treatment guidelines [184] for gastric cancer and categorized to D0, D1, D1+ and D2. The exposure was grouped to D0/D1 and D1+/D2.

3.4.5 Statistical analysis

Data are presented as mean ± SD and actual count and percentage in parenthesis. Data are analysed with chi square test and Fisher exact test for categorical variables. Student *t* test was used for continuous variables. Overall survival was estimated using the Kaplan-Meier method with Log Rank test. Analysis in a multivariable model to estimate Hazard Ratio (HR) and 95% confidence interval (95% CI) was done using cox proportional hazard method. Variables used in the multivariable model were age, gender, ASA class, Charlson comorbidity index, tumour stage (TNM 8), surgical procedure, multivisceral resection, preoperative chemotherapy, education level and calendar year. All analyses were done using IBM SPSS Statistics (Version 25.0; IBM Corp., New York, USA).

3.4.6 Ethical approval

The study has been approved by the Regional Ethics Committee (EPN Stockholm Dnr: 2016/1486-32 and 2013/596-31/3)

3.5 PAPER IV

3.5.1 Study design

National quality register study cross matched with other national healthcare registers.

3.5.2 Study population

All patients in Sweden diagnosed with clinical M0 gastric cancer from 2006-2017.

3.5.3 Main outcome measure

The main outcome was overall survival from time of diagnosis in the entire cohort of gastric cancer patients.

3.5.4 Definition of exposure

Main exposure was the resection rate for the particular county of residence and year when the diagnosis was set for that patient regardless if the patient had a resection or not. This annual county resection rate was calculated by dividing the number of resected gastric cancers by the total number of gastric cancer cases diagnosed that year. Resection rate was stratified to three equal groups and compared and analysed for association with the main outcome measure.

3.5.5 Statistical analysis

Data are presented as mean ± SD and actual count and percentage in parenthesis. Analysis with chi square test and ANOVA was used for categorical and continuous variables respectively. Overall survival was estimated using the Kaplan-Meier method with Log Rank test. Multivariable analysis of risk factors and association to survival was done with Cox proportional hazard model to estimate Hazard Ratio (HR) and 95% confidence interval (95% CI). Variables used in multivariable model were resection rate, age, gender, clinical tumour stage, ASA class, Charlson comorbidity index, education level and multidisciplinary conference. All analyses were done using IBM SPSS Statistics (Version 26.0; IBM Corp., New York, USA).

3.5.6 Ethical approval

The study has been approved by the Regional Ethics Committee (EPN Stockholm Dnr: 2016/1486-32 and 2013/596-31/3)

4 RESULTS

4.1 PAPER I

Identification through electronic hospital records yielded a total of 93 patients during the six-and-a-half-year study period that had a D2 gastrectomy. One patient underwent concomitant total pancreatectomy and was excluded for analysis of risk to develop postoperative pancreatic fistula (POPF). This resulted in a population of 92 patients eligible for analysis. The complete flow chart for patient selection can be seen from Figure 2.

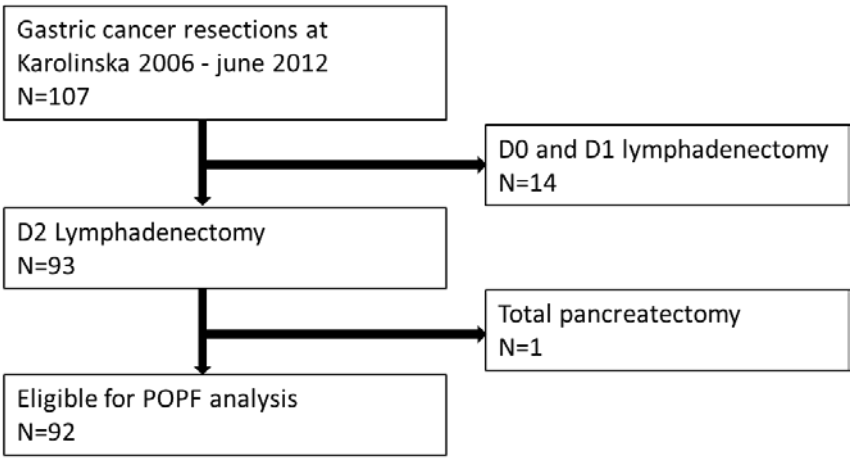


***Figure 2**. Patient selection for Paper I.*

4.1.1 Patient demographics and treatment details

In general patients were quite young and close to normal BMI. Their physical status as classified by ASA class was assessed as quite moderate as 84 patients (91%) were of ASA class 2-3. Neoadjuvant chemotherapy was given in roughly half of the patients and 31 patients (34%) had additional organ resection other than gastrectomy. Complete details of the patient demographics and baseline characteristics are presented in Table 2 and treatment details presented in Table 3.

4.1.2 Postoperative complications

In total the 30-day mortality was low (2 patients). General complication rate of Clavien 3b or higher occurred in 22 (24%) cases. Postoperative abscess occurred in 22 (24%) patients of which ten cases could be attributed to POPF. The overall POPF grade B or C occurred in 11 (12%) cases. Details of complications are presented in Table 4.

Table 2. *Patient demographics and baseline characteristics.*

	N = 92
Age median (IQR)	66.5 (57–77)
Gender	
Male	48 (52%)
Female	44 (48%)
BMI median (IQR)	25.2 (22.2–27.7)
ASA class	
ASA I	4 (4.3%)
ASA II	45 (48.9%)
ASA III	39 (42.4%)
ASA IV	2 (2.2%)
Missing	2 (2.2%)
Tumour stage	
Stage 0	4 (4.3%)
Stage I	29 (31.5%)
Stage II	34 (37.0%)
Stage III	19 (20.7%)
Stage IV	6 (6.5%)

BMI body mass index, ASA American Society of Anaesthesiologists. Tumour stage according to TNM7. IQR Interquartile range. Values refer to actual count and percentage in parenthesis.

Table 4. *Postoperative complications.*

	n = 92
30-day mortality	2 (2%)
90-day mortality	9 (10%)
POPF grade B/C	11 (12%)
Anastomotic leakage [a]	11 (12%)
Reoperation	18 (20%)
Abscess	22 (24%)
Pneumonia	7 (8%)
Sepsis	13 (14%)
Cardiovascular	10 (11%)
Pulmonary embolism	6 (7%)
Clavien score	
Clavien 0/1	31 (34%)
Clavien 2	25 (27%)
Clavien 3a	14 (15%)
Clavien 3b	9 (10%)
Clavien 4a	3 (3%)
Clavien 4b	8 (9%)
Clavien 5	2 (2%)

Values refer to actual counts and percentage in parenthesis. [a] *includes oesophagojejunal, gastrojejunal and duodenal bulb leakage.*

Table 3. *Treatment details.*

	N = 92
Surgical procedure	
Total gastrectomy	57 (62%)
Distal gastrectomy	28 (30%)
Pylorus-preserving gastrectomy	7 (8%)
Neoadjuvant therapy	
Perioperative chemotherapy	45 (49%)
No perioperative chemotherapy	47 (51%)
Completeness of resection	
R0	72 (78%)
R1	16 (17%)
R2	4 (4%)
Operation time [a] **n = 91**	263 (228-338)
Bleeding [b] **n = 78**	500 (331-888)
Lymphnode yield (median IQR)	21 (15-29)
bursectomy n = 91	83 (90%)
Additional organ resection [c]	31 (34%)
Pancreaticoduodenectomy	4 (4%)
Distal pancreaticosplenectomy	4 (4%)
local pancreatic resection	2 (2%)
Splenectomy	21 (23%)
Other [d]	5 (7%)

Values refer to actual counts and percentage in parenthesis. [a] *median time in minutes and interquartile range in parenthesis.* [b] *bleeding in ml and interquartile range in parenthesis.* [c] *Some patients appear in more than one group.* [d] *includes colectomy, liver resection, cholecystectomy, adrenalectomy and small bowel resection.*

4.1.3 Postoperative pancreatic fistula

Age (p = 0.051), pancreatic resection (p < 0.01) and splenectomy (p = 0.016) were associated and identified as risk factors for developing POPF grade B or C. Although the occurrence of splenectomy was also associated with distal pancreatectomy in 4 cases. Multivariable analysis with multivariable logistics regression revealed that pancreatic resection with OR 156 (95% CI 8-3047) and age with OR 1.2 (95% CI 1.0-1.3) remained as independent risk factors for development of POPF grade B or C and that splenectomy was not independently associated, OR 2.9 (95% 0.5-19.1) Table 5.

Table 5. *Univariable and multivariable risk factors for developing POPF grad B or C.*

Risk factor	Univariable		Multivariable	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (year increment)	1.07 (1.0-1.1)	0.042	1.2 (1.0-1.3)	0.023
Pancreatectomy				
No pancreatic resection	ref		ref	
Pancreatic resection	45.5 (8.4-245.3)	<0.01	156 (8-3047)	<0.01
Splenectomy				
No splenectomy	ref		ref	
Splenectomy	5.3 (1.4-19.6)	0.013	2.9 (0.5-19.1)	0.260
BMI	0.99 (0.8-1.2)	0.901		
Operative time (10 min increment)	1.0 (0.9-1.1)	0.881		
Bleeding (cl)	1.0 (1.0-1.0)	0.832		
Gender				
Female	ref			
Male	0.7 (0.2-2.6)	0.635		
ASA class				
ASA I-II	ref			
ASA III-IV	2.3 (0.6-8.6)	0.208		
Neoadjuvant chemotherapy				
No chemotherapy	ref			
Chemotherapy	0.9 (0.2-3.0)	0.807		
Surgical procedure				
Distal gastrectomy	ref			
Total gastrectomy	1.1 (0.3-4.0)	0.903		
T-stage				
T0-T2	ref			
T3-T4	1.1 (0.3-3.9)	0.888		
N-stage				
N0	ref			
N1-N3	2.3 (0.6-9.3)	0.244		

Univariable and multivariable logistics regression for risk factors associated for POPF grade B or C.

4.2 PAPER II

During the study period from 2006-2013 a total of 1,101 patients were identified for analysis of lymphadenectomy and postoperative morbidity and mortality. Complete flow chart of patient selection can be seen from Figure 3.

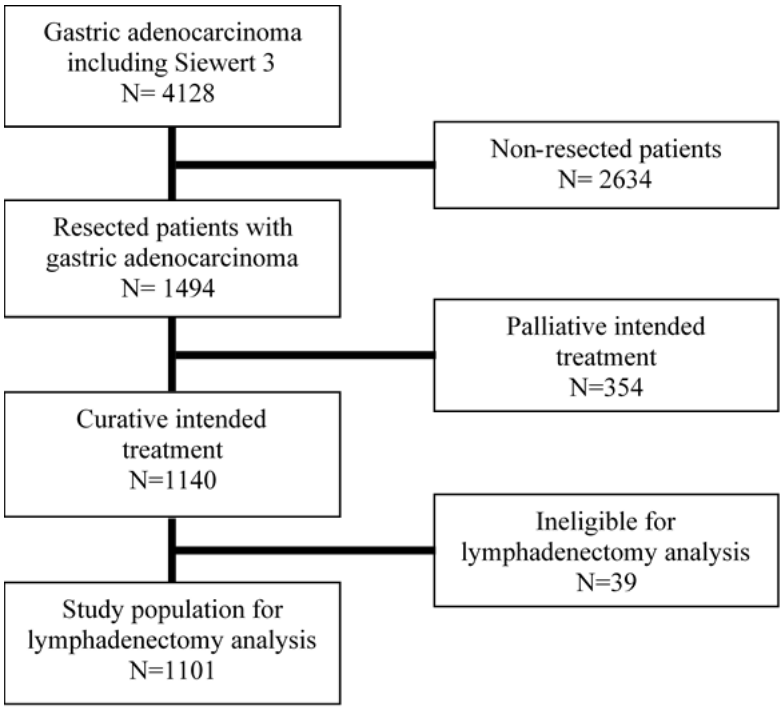


Figure 3. *Patient selection for Paper II. Ineligible for lymphadenectomy analysis include local excisions, previous gastric resection, proximal or pylorus-preserving central gastrectomy, or unknown surgical procedure.*

4.2.1 Patient demographics and baseline characteristics

There were in total 349 (31.7%) D0, 494 (44.9%) D1 and 258 (23.4%) D1+/D2 respectively and their baseline characteristics are found in Table 6. There were in general more D1+/D2 performed later in the study period. It was more frequently performed in high volume hospitals and University hospitals. The tumour stage distribution was slightly unproportioned towards more advanced stage in the D1+/D2 group. The opposite can be seen in ASA class where there is slightly lower ASA class in the D1+/D2 group.

Table 6. *Baseline characteristics of patients in Paper II.*

	All cases	Extent of lymphadenectomy			
	(n=1101)	D0 (n=349)	D1 (n=494)	D1+/D2 (n=258)	p-value
Age	69 ± 12	72 ± 11	70 ± 11	65 ± 12	<0.001
Gender					0.013
Female	473 (43.0%)	129 (37.0%)	233 (47.2%)	111 (43.0%)	
Male	628 (57.0%)	220 (63.0%)	261 (52.8%)	147 (57.0%)	
BMI	25.1 ± 4.5	24.7 ± 4.6	25.4 ± 4.5	25.2 ± 4.4	0.044
Tumour stage					0.032
Stage 0-I	323 (29.3%)	104 (29.8%)	158 (32.0%)	61 (23.6%)	
Stage II	386 (35.1%)	129 (37.0%)	175 (35.4%)	82 (31.8%)	
Stage III	198 (18.0%)	51 (14.6%)	88 (17.8%)	59 (22.9%)	
Stage IV	48 (4.4%)	15 (4.3%)	21 (4.3%)	12 (4.7%)	
Missing	146 (13.3%)	50 (14.3%)	52 (10.5%)	44 (17.1%)	
ASA class					0.033
I	290 (26.3%)	87 (24.9%)	122 (24.7%)	81 (31.4%)	
II	540 (49.0%)	181 (51.9%)	232 (47.0%)	127 (49.2%)	
III	231 (21.0%)	66 (18.9%)	123 (24.9%)	42 (16.3%)	
IV	15 (1.4%)	6 (1.7%)	8 (1.6%)	1 (0.4%)	
Missing	25 (2.3%)	9 (2.6%)	9 (1.8%)	7 (2.7%)	
CCI					0.171
0-2	590 (53.6%)	199 (57.0%)	250 (50.6%)	141 (54.7%)	
3 or higher	511 (46.4%)	150 (43.0%)	244 (49.4%)	117 (45.3%)	
Neoadjuvant chemotherapy					<0.001
No	768 (69.8%)	288 (82.5%)	359 (72.7%)	121 (46.9%)	
Yes	327 (29.7%)	58 (16.6%)	132 (26.7%)	137 (53.1%)	
Missing	6 (0.5%)	3 (0.9%)	3 (0.6%)	0 (0.0%)	
Education level					0.123
Less or equal to 9 years	458 (41.6%)	155 (44.4%)	206 (41.7%)	97 (37.6%)	
10-12 years	434 (39.4%)	142 (40.7%)	194 (39.3%)	98 (38.0%)	
More than 12 years	184 (16.7%)	45 (12.9%)	85 (17.2%)	54 (20.9%)	
Missing	25 (2.3%)	7 (2.0%)	9 (1.8%)	9 (3.5%)	
Hospital type					<0.001
University hospital	496 (45.0%)	94 (26.9%)	203 (41.1%)	199 (77.1%)	
County hospital	492 (44.7%)	199 (57.0%)	245 (49.6%)	48 (18.6%)	
Small local hospital	113 (10.3%)	56 (16.0%)	46 (9.3%)	11 (4.3%)	
Hospital volume					<0.001
Low volume (0-<5)	370 (33.6%)	184 (52.7%)	152 (30.8%)	34 (13.2%)	
Intermediate volume (5-<10)	527 (47.9%)	134 (38.4%)	303 (61.3%)	90 (34.9%)	
Moderately high (10-<15)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
High volume (15 or more)	204 (18.5%)	31 (8.9%)	39 (7.9%)	134 (51.9%)	
Operation year					<0.001
2006-2007	231 (21.0%)	98 (42.4%)	98 (42.4%)	35 (15.2%)	
2008-2009	323 (29.3%)	113 (35.0%)	145 (44.9%)	65 (20.1%)	
2010-2011	282 (25.6%)	75 (26.6%)	142 (50.4%)	65 (23.0%)	
2012-2013	265 (24.1%)	63 (23.8%)	109 (41.1%)	93 (35.1%)	

Values show actual numbers and percentage in parenthesis. BMI Body Mass Index, ASA American Society of Anaesthesiologists, CCI Charlson Comorbidity Index. Categorical variables analysed with the Chi-square test. Continuous variables analysed by Kruskall-Wallis test. P-values refer to any significant difference between all three groups.

4.2.2 Operative details

There was a discrepancy regarding the surgical details between the groups. There was more multivisceral resection, bursectomy and longer operative time in the D1+/D2 group as would be expected. There was not an increase in perioperative bleeding for total gastrectomy patients regardless of extent of lymphadenectomy but however significantly more bleeding for distal gastrectomy in D1+/D2 lymphadenectomy. Complete operative details can be seen from Table 7.

Table 7. *Details of surgical procedure in Paper II.*

	All cases (n=1101)	Extent of lymphadenectomy			
		D0 (n=349)	D1 (n=494)	D1+/D2 (n=258)	p-value
Surgical procedure					<0.001
Total gastrectomy	518 (47.0%)	145 (41.5%)	169 (34.2%)	204 (79.1%)	
Distal gastrectomy	583 (53.0%)	204 (58.5%)	325 (65.8%)	54 (20.9%)	
Number of lymphnodes					
Total gastrectomy	22±15 (n=471)	16±12 (n=136)	19±12 (n=159)	29±17 (n=176)	<0.001
Distal gastrectomy	15±12 (n=530)	12±11 (n=190)	15±11 (n=293)	24±14 (n=47)	<0.001
Operative time (min)					
Total gastrectomy	303±125 (n=401)	284±117 (n=104)	260±89 (n=140)	355±139 (n=157)	<0.001
Distal gastrectomy	212±86 (n=464)	208±110 (n=155)	207±71 (n=259)	245±63 (n=50)	<0.001
Bleeding (millilitre)					
Total gastrectomy	713±596 (n=506)	755±745 (n=139)	687±513 (n=168)	706±543 (n=199)	0.731
Distal gastrectomy	414±401 (n=566)	368±400 (n=192)	433±417 (n=320)	463±284 (n=54)	<0.001
Bursectomy					
Total gastrectomy	181 (35.2%) (n=514)	38 (26.4%) (n=144)	34 (20.4%) (n=167)	109 (53.7%) (n=203)	<0.001
Distal gastrectomy	104 (18.1%) (n=574)	19 (9.5%) (n=200)	50 (15.6%) (n=321)	35 (66.0%) (n=53)	<0.001
Multivisceral resection					
Total gastrectomy	191 (37.1%) (n=515)	47 (32.9%) (n=143)	39 (23.1%) (n=169)	105 (51.7%) (n=203)	<0.001
Distal gastrectomy	48 (8.2%) (n=582)	15 (7.4%) (n=203)	28 (8.6%) (n=325)	5 (9.3%) (n=54)	0.831*

Values show actual numbers and percentage in parentheses. Continuous variables analysed by Kruskall-Wallis test. Categorical variables analysed with the Chi-square test. P-values refer to any significant difference between all three groups. Multivisceral resections included concomitant resection of either colon, diaphragm, oesophagus and thoracic duct, liver segment, spleen, pancreas, gallbladder, small bowel, adrenal gland or other organs. Fisher's exact test due to low expected counts.*

4.2.3 Lymphnode yield

There was a significant difference in the lymphnode yield between the three groups. The lymphnode yield was highest 29 ± 17 for D1+/D2 total gastrectomy as expected and lowest for D0 distal gastrectomy 12 ± 11. Distribution of lymphnode yield for each procedure can be seen from Figure 4.

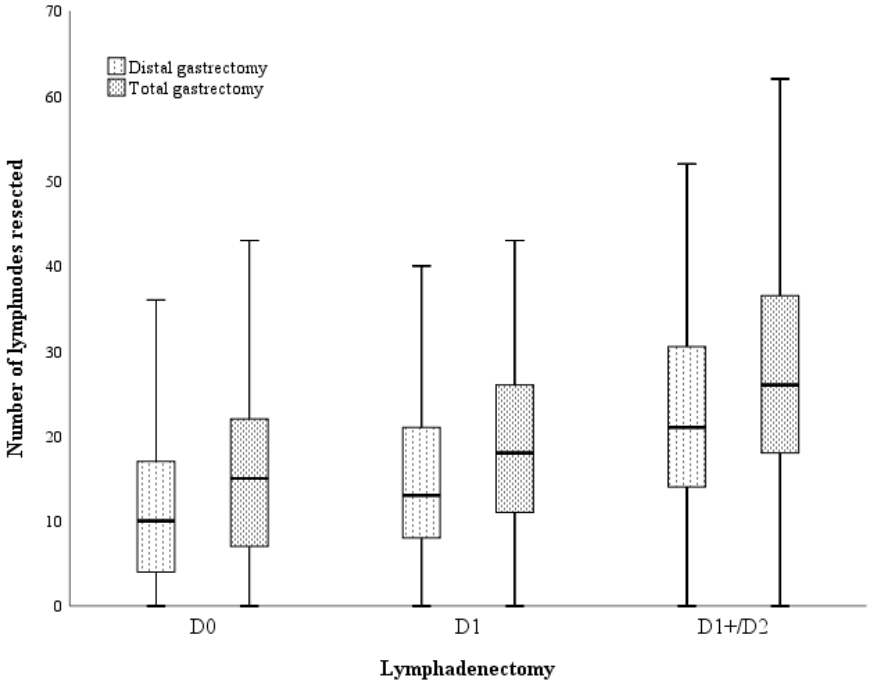


Figure 4. *Boxplot of number of lymphnodes resected. Presented for lymphadenectomy and surgical procedure. Line represents median and box represents IQR. Whiskers represents 1.5 times the IQR. Outliers are not shown in the graph. Statistical inference with Kruskall-Wallis test between all groups, $p < 0.001$.*

4.2.4 Postoperative complications

The overall 30-day mortality was 2.8% and 90-day mortality was 5.9%. The highest postoperative mortality occurred in D0 lymphadenectomy. The overall morbidity rate was 26.9% and there was a significant difference and higher morbidity for D1+/D2 lymphadenectomy. For specific complications there was significantly higher pulmonary embolism rates in D1+/D2 lymphadenectomy as well as reintervention with endoscopic stent placement in D1+/D2 lymphadenectomy. Details of postoperative complications can be seen from Table 8.

Table 8. *Association between postoperative mortality or complications and different extent of gastric cancer lymphadenectomy in Paper II.*

	All cases	Extent of lymphadenectomy			
	(n = 1101)	D0 (n = 349)	D1 (n = 494)	D1+/D2 (n = 258)	p-value
30-day mortality	31 (2.8%)	20 (5.7%)	4 (0.8%)	7 (2.7%)	<0.001
90-day mortality	65 (5.9%)	29 (8.3%)	21 (4.3%)	15 (5.8%)	0.048
Overall complication	296 (26.9%)	89 (25.5%)	124 (25.1%)	83 (32.2%)	0.017
General complication	178 (16.2%)	57 (16.3%)	74 (15.0%)	47 (18.2%)	0.304
Pneumonia	52 (4.7%)	17 (4.9%)	28 (5.7%)	7 (2.8%)	0.250
Sepsis	45 (4.1%)	10 (2.9%)	24 (4.9%)	11 (4.3%)	0.319
Cardiovascular complication	36 (3.3%)	12 (3.4%)	17 (3.4%)	7 (2.8%)	0.919
Pulmonary embolism	12 (1.1%)	0 (0.0%)	5 (1.0%)	7 (2.8%)	0.003*
Other general complication	73 (6.6%)	25 (7.2%)	28 (5.7%)	20 (7.8%)	0.393
Missing	84 (7.6%)	19 (5.4%)	33 (6.7%)	32 (12.4%)	
Surgical complication	190 (17.3%)	52 (14.9%)	86 (17.4%)	52 (20.2%)	0.096
Bleeding	34 (3.1%)	13 (3.7%)	14 (2.8%)	7 (2.8%)	0.761
Anastomotic insufficiency	41 (3.7%)	10 (2.9%)	16 (3.2%)	15 (5.8%)	0.073
Abscess	60 (5.4%)	13 (3.7%)	29 (5.9%)	18 (7.0%)	0.125
Other surgical complication	88 (8.0%)	23 (6.6%)	45 (9.1%)	20 (7.8%)	0.391
Missing	86 (7.8%)	20 (5.7%)	33 (6.7%)	33 (12.8%)	
Reintervention					
Reoperation	107 (9.7%)	32 (9.2%)	48 (9.7%)	27 (10.5%)	0.688
Stent	15 (1.4%)	2 (0.6%)	5 (1.0%)	8 (3.1%)	0.017*

Values show actual numbers and percentage in parentheses. Variables analysed with Chi-square test. P-values refer to any significant difference between all three groups. * *Fisher's exact test due to low expected counts.*

4.2.5 Risk factors for mortality and complications

To assess the risk of overall 30-day complication and 90-day mortality logistics regression was performed. The results of univariable and multivariable analysis can be seen from Table 9 and 10. For both 30-day overall complication and 90-day mortality there is no increased risk of D1+/D2 lymphadenectomy in multivariable analysis. The analysis also reveals that age, male gender, total gastrectomy, MVR, high hospital volume, calendar year (2012-2013 vs 2006-2007) is independently associated with higher risk of 30-day complication, Table 9. High hospital volume along with surgery late in the study period is somewhat conflicting to be associated with higher risk of complication. They are both associated with more D1+/D2 being performed and more MVR. There are some colinearity for these variables and despite analysis in multivariable model there could be some residual confounding left.

For 90-day mortality higher ASA class and MVR were other risk factors independently associated with increased risk, Table 10.

Table 9*. Univariable and multivariable risk factor analysis for overall 30-day complication*

Risk factor	Univariable		Multivariable	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Extent of lymphadenectomy				
D0	ref		ref	
D1	1.0 (0.73-1.37)	0.982	1.08 (0.77-1.52)	0.657
D1+/D2	1.57 (1.09-2.26)	0.015	1.04 (0.66-1.63)	0.871
Age				
≤ 60	ref		ref	
61-70	1.42 (0.94-2.16)	0.099	1.71 (1.09-2.67)	0.019
71-80	1.98 (1.34-2.94)	<0.001	2.48 (1.60-3.85)	<0.001
> 80	1.60 (1.01-2.53)	0.046	2.22 (1.31-3.75)	0.003
BMI				
1st quartile	ref		ref	
2nd quartile	0.83 (0.55-1.26)	0.383	0.76 (0.49-1.19)	0.229
3rd quartile	1.07 (0.72-1.61)	0.727	1.05 (0.69-1.62)	0.818
4th quartile	1.05 (0.70-1.58)	0.805	1.04 (0.67-1.60)	0.868
Missing	0.95 (0.58-1.56)	0.845	1.10 (0.65-1.87)	0.712
Gender				
Female	ref		ref	
Male	1.44 (1.09-1.90)	0.010	1.42 (1.05-1.90)	0.021
ASA class				
ASA 1-2	ref		ref	
ASA 3-4	1.60 (1.17-2.19)	0.004	1.36 (0.96-1.94)	0.083
Missing	1.57 (0.65-3.80)	0.315	1.40 (0.54-3.65)	0.492
CCI				
0-2	ref		ref	
3 or higher	1.18 (0.90-1.54)	0.242	1.12 (0.84-1.51)	0.443
Tumour stage				
Stage 0-I	ref		ref	
Stage II	1.26 (0.90-1.77)	0.174	1.15 (0.81-1.63)	0.451
Stage III	1.62 (1.10-2.38)	0.015	1.16 (0.76-1.77)	0.487
Stage IV	1.54 (0.81-2.96)	0.191	1.23 (0.60-2.52)	0.574
Missing	1.58 (0.88-2.84)	0.124	1.35 (0.72-2.53)	0.348
Surgical procedure				
Total gastrectomy	ref		ref	
Distal gastrectomy	0.58 (0.44-0.77)	<0.001	0.60 (0.43-0.83)	0.002
MVR				
No	ref		ref	
Yes	1.86 (1.36-2.55)	<0.001	1.56 (1.09-2.24)	0.016
Hospital volume				
<15	ref		ref	
≥15	1.79 (1.28-2.51)	0.001	1.62 (1.08-2.44)	0.020
Calendar year				
2006-2007	ref		ref	
2008-2009	0.91 (0.61-1.35)	0.638	0.95 (0.63-1.45)	0.828
2010-2011	1.13 (.075-1.68)	0.565	1.16 (0.75-1.79)	0.496
2012-2013	1.71 (1.14-2.55)	0.009	1.74 (1.12-2.72)	0.014

BMI Body Mass Index, ASA American Society of Anaesthesiologists. CCI Charlson comorbidity index. MVR multivisceral resection. Multivariable model includes all variables in the univariable list.

Table 10. Univariable and multivariable risk factor analysis for 90-day mortality.

Risk factor	Univariable		Multivariable	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Extent of lymphadenectomy				
D0	ref		ref	
D1	0.49 (0.28-0.87)	0.016	0.46 (0.24-0.86)	0.015
D1+/D2	0.68 (0.36-1.30)	0.243	0.50 (0.21-1.19)	0.116
Age				
≤ 60	ref		ref	
61-70	1.21 (0.46-3.16)	0.701	1.14 (0.42-3.12)	0.798
71-80	2.56 (1.10-5.98)	0.030	1.86 (0.73-4.72)	0.192
> 80	3.99 (1.65-9.66)	0.002	2.92 (1.07-7.99)	0.037
BMI				
1st quartile	ref		ref	
2nd quartile	0.54 (0.24-1.19)	0.127	0.64 (0.28-1.49)	0.299
3rd quartile	0.97 (0.49-1.93)	0.931	1.16 (0.54-2.48)	0.702
4th quartile	0.48 (0.21-1.10)	0.082	0.57 (0.24-1.38)	0.215
Missing	1.17 (0.53-2.55)	0.701	1.36 (0.58-3.17)	0.480
Gender				
Female	ref		ref	
Male	0.87 (0.53-1.44)	0.592	0.79 (0.45-1.36)	0.390
ASA class				
ASA 1-2	ref		ref	
ASA 3-4	3.48 (2.09-5.82)	<0.001	3.45 (1.89-6.30)	<0.001
Missing	1.01 (0.13-7.67)	0.995	1.05 (0.13-8.62)	0.968
CCI				
0-2	ref		ref	
3 or higher	1.68 (1.01-2.79)	0.047	1.60 (0.91-2.83)	0.104
Tumour stage				
Stage 0-I	ref		ref	
Stage II	1.30 (0.64-2.66)	0.468	1.29 (0.60-2.76)	0.519
Stage III	2.83 (1.38-5.79)	0.004	3.28 (1.46-7.39)	0.004
Stage IV	2.17 (0.68-6.95)	0.193	3.00 (0.84-10.78)	0.092
Missing	1.20 (0.47-3.08)	0.703	1.57 (0.56-4.40)	0.392
Surgical procedure				
Total gastrectomy	ref		ref	
Distal gastrectomy	0.75 (0.45-1.24)	0.259	0.94 (0.50-1.78)	0.848
MVR				
No	ref		ref	
Yes	2.28 (1.35-3.87)	0.002	2.35 (1.24-4.45)	0.009
Hospital volume				
<15	ref		ref	
≥15	1.34 (0.74-2.45)	0.332	1.63 (0.76-3.50)	0.212
Calendar year				
2006-2007	ref		ref	
2008-2009	0.97 (0.50-1.85)	0.915	0.97 (0.48-1.99)	0.943
2010-2011	0.66 (0.32-1.36)	0.260	0.66 (0.29-1.47)	0.304
2012-2013	0.55 (0.25-1.19)	0.127	0.48 (0.20-1.16)	0.104

BMI Body Mass Index, ASA American Society of Anaesthesiologists. CCI Charlson comorbidity index. MVR multivisceral resection. Multivariable model includes all variables in the univariable list.

4.3 PAPER III

During the study period of 2006-2017 a total of 6154 patients were identified as having gastric cancer. 1677 (27%) of which were eligible for lymphadenectomy analysis on survival. Flow chart for patient selection can be seen from Figure 5.

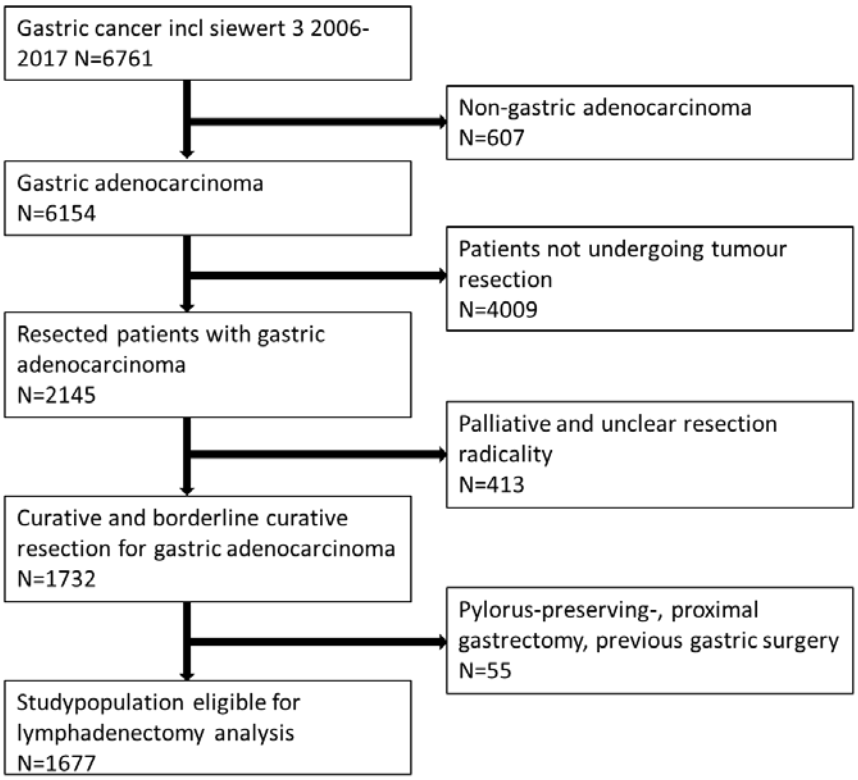


Figure 5. *Patient selection for paper III.*

4.3.1 Trends in surgery

Traditionally surgery for gastric cancer has been done in almost all hospitals during the last decade, centralization has taken place and number of hospitals performing gastric cancer surgery is decreasing. In 2007 the number of hospitals performing curative intended resections for gastric cancer were as high as 45 and has been decreasing to 12 in 2017. The number of resections performed have been around 150 annually and then decreased to around 120 for 2014 to 2016. The data for 2017 is incomplete as all registrations are not yet in the register as of the time of data withdrawal, Figure 6. The centralization process has also shifted the procedures to university hospitals over the study period and the frequency of D1+/D2 procedures have increased later in the period as seen in Figure 7.

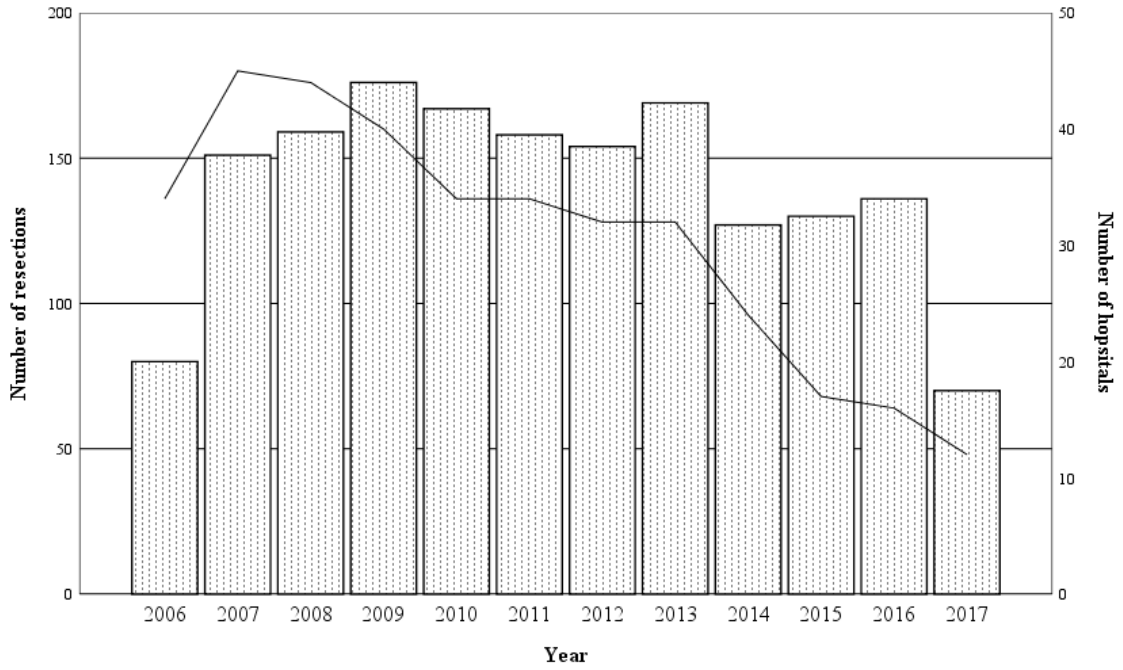


Figure 6. *Number of cases and number of hospitals performing surgery during the study period. Bar represent number of resections for respective year and follows y-axis on left side. Line represents number of hospitals performing curative intended resection for respective year and follows y-axis on right side.*

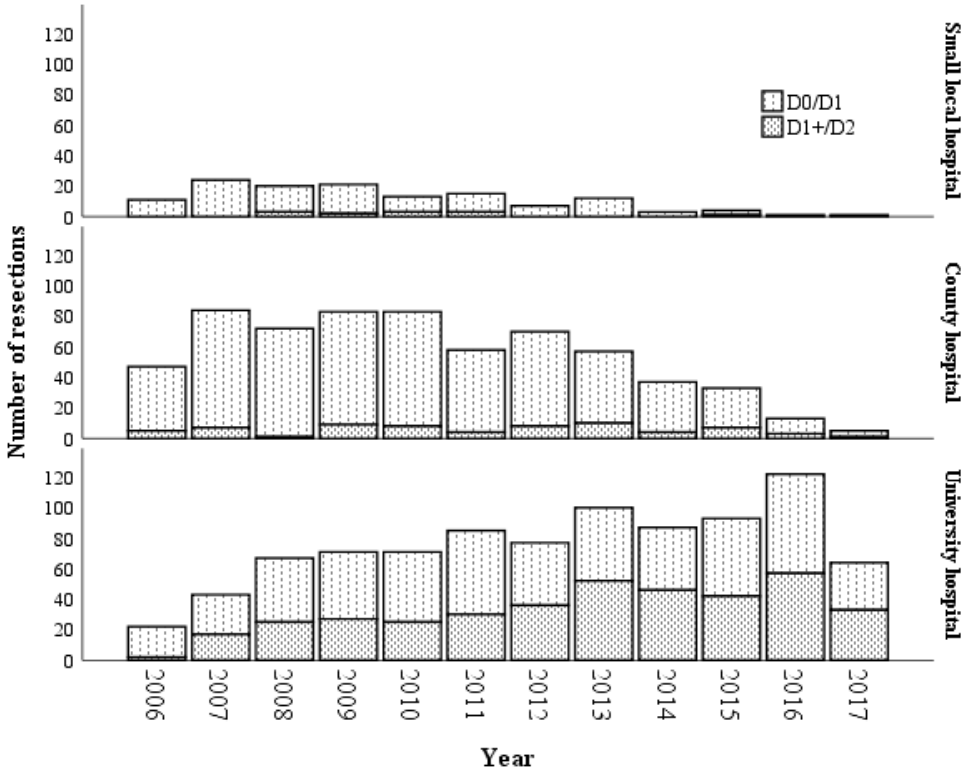


Figure 7. *Distribution of resections in hospital type and extent of lymphadenectomy during the study period.*

4.3.2 Patient demographics

During the study period there was 1206 (72%) D0/D1 and 471 (28%) D1+/D2 performed. Complete baseline characteristics of the patients are presented in Table 11. The D1+/D2 cases are generally younger, have a higher level of education, a slightly lower ASA class and had a more advanced tumour stage.

Table 11. *Baseline characteristics of patients in Paper III.*

	D0/D1 (n=1206)	D1+/D2 (n=471)	Total (n=1677)	p-value
Age (mean ± SD)	70 ± 11	65 ± 12	69 ± 12	<0.001
BMI (mean ± SD)	25.1 ± 4.45	25.2 ± 4.43	25.2 ± 4.44	0.682
Gender				0.602
Male	698 (57.9%)	266 (56.5%)	964 (57.5%)	
Female	508 (42.1%)	205 (43.5%)	713 (42.5%)	
ASA class				<0.001*
ASA I	310 (25.7%)	168 (35.7%)	478 (28.5%)	
ASA II	591 (49.0%)	223 (47.3%)	814 (48.5%)	
ASA III	252 (20.9%)	66 (14.0%)	318 (19.0%)	
ASA IV	24 (2.0%)	3 (0.6%)	27 (1.6%)	
Missing	29 (2.4%)	11 (2.3%)	40 (2.4%)	
Clinical tumour stage				<0.001
Stage I	402 (33.3%)	120 (25.5%)	522 (31.1%)	
Stage II	312 (25.9%)	167 (35.5%)	479 (28.6%)	
Stage III	149 (12.4%)	100 (21.2%)	249 (14.8%)	
Stage IV	27 (2.2%)	17 (3.6%)	44 (2.6%)	
Missing	316 (26.2%)	67 (14.2%)	383 (22.8%)	
CCI				0.655
0-1	400 (33.2%)	147 (31.2%)	547 (32.6%)	
2	195 (16.2%)	83 (17.6%)	278 (16.6%)	
3 or higher	611 (50.7%)	241 (51.2%)	852 (50.8%)	
Education level				<0.001
Less or equal to 9 years	474 (39.3%)	149 (31.6%)	623 (37.1%)	
10 to 12 years	455 (37.7%)	193 (41.0%)	648 (38.6%)	
More than 12 years	186 (15.4%)	111 (23.6%)	297 (17.7%)	
Missing	91 (7.5%)	18 (3.8%)	109 (6.5%)	
Tumour location				<0.001
GOJ Siewert III	37 (3.1%)	52 (11.0%)	89 (5.3%)	
Upper	39 (3.2%)	34 (7.2%)	73 (4.4%)	
Middle	386 (32.0%)	205 (43.5%)	591 (35.2%)	
Lower	625 (51.8%)	123 (26.1%)	748 (44.6%)	
Whole	25 (2.1%)	23 (4.9%)	48 (2.9%)	
Missing	94 (7.8%)	34 (7.2%)	128 (7.6%)	
Calendar year of surgery				<0.001
2006-2009	468 (38.8%)	98 (20.8%)	566 (33.8%)	
2010-2013	469 (38.9%)	179 (38.0%)	648 (38.6%)	
2014-2017	269 (22.3%)	194 (41.2%)	463 (27.6%)	

*Values show actual numbers and percentage in parenthesis. BMI Body Mass Index, ASA American Society of Anaesthesiologists, CCI Charlson comorbidity index. Continuous variables analysed with student t test and categorical variables analysed with the Chi-square test except for cases marked with * where Fisher's Exact test was used.*

4.3.3 Surgical treatment details and complications

The treatment details for the two groups are presented in Table 12. The D1+/D2 group had a higher proportion of total gastrectomy, preoperative chemotherapy and multivisceral resection (including pancreaticosplenectomy and splenectomy). The 30- and 90-day postoperative mortality did not differ between the groups but D1+/D2 lymphadenectomy yielded more lymphnodes and also carried a higher postoperative complication rate, Table 13.

Table 12. *Surgical details of patients submitted to either a limited D0/D1 lymphadenectomy or a more extensive D1+/D2 dissection.*

	D0/D1 (n=1206)	D1+/D2 (n=471)	Total (n=1677)	p-value
Surgical procedure				<0.001
Distal gastrectomy	770 (63.8%)	120 (25.5%)	890 (53.1%)	
Total gastrectomy	436 (36.2%)	351 (74.5%)	787 (46.9%)	
Laparoscopic surgery				0.111
No	1171 (97.1%)	450 (95.5%)	1621 (96.7%)	
Yes	35 (2.9%)	21 (4.5%)	56 (3.3%)	
Preoperative chemotherapy				<0.001
No	870 (72.1%)	191 (40.6%)	1061 (63.3%)	
Yes	322 (26.7%)	280 (59.4%)	602 (35.9%)	
Missing	14 (1.2%)	0 (0.0%)	14 (0.8%)	
Multivisceral resection				<0.001
No	1004 (83.9%)	312 (66.5%)	1316 (79.0%)	
Yes	193 (16.1%)	157 (33.5%)	350 (21.0%)	
Pancreaticosplenectomy				<0.001
No	1178 (98.4%)	446 (95.1%)	1624 (97.5%)	
Yes	19 (1.6%)	23 (4.9%)	42 (2.5%)	
Splenectomy				<0.001
No	1118 (93.4%)	369 (78.7%)	1487 (89.3%)	
Yes	79 (6.6%)	100 (21.3%)	179 (10.7%)	
Emergency operation				0.457
No	1162 (97.0%)	460 (97.7%)	1622 (97.2%)	
Yes	36 (3.0%)	11 (2.3%)	47 (2.8%)	

Values show actual numbers and percentage in parenthesis. Variables analysed with the Chi-square test.

Table 13. *Lymph node yield and postoperative complications in patients submitted to either a limited D0/D1 lymphadenectomy or a more extensive D1+/D2 dissection.*

	D0/D1 (n=1206)	D1+/D2 (n=471)	Total (n=1677)	p-value
Number of lymphnodes (mean ± SD)				
Distal gastrectomy	16 ± 12 (n=693)	25 ± 15 (n=106)	17 ± 13 (n=799)	<0.001
Total gastrectomy	19 ± 13 (n=398)	31 ± 18 (n=301)	24 ± 16 (n=699)	<0.001
30-day postop mortality				
No	1179 (97.8%)	460 (97.7%)	1639 (97.7%)	0.905
Yes	27 (2.2%)	11 (2.3%)	38 (2.3%)	
90-day postop mortality				
No	1143 (94.8%)	451 (95.8%)	1594 (95.1%)	0.407
Yes	63 (5.2%)	20 (4.2%)	83 (4.9%)	
Overall complication				
No	811 (73.4%)	264 (64.4%)	1075 (71.0%)	0.001
Yes	294 (26.6%)	146 (35.6%)	440 (29.0%)	

Values show actual numbers and percentage in parenthesis. Continuous variables analysed with student t test and categorical variables analysed with the Chi-square test.

4.3.4 Survival

Overall stage specific survival can be seen from Figure 8A. The total overall median survival for all patients subjected to curative intended surgery is 39 months (95% CI 35-43). Regional differences in survival is presented in Figure 8B with the highest median overall survival in one region of 51 months (95% CI 23-79) and the lowest median overall survival in another region of 29 months (95% CI 24-35) log rank test $p = 0.001$.

Survival in respect to hospital volume is presented in Figure 8C. The results show incremental increase in survival curve for higher annual hospital volume. Where patients operated on in high volume hospitals (more than 15 cases per year) had a median overall survival of 49 months (95% CI 35-62) and patients in low volume hospitals (less than 5 cases per year) had a median overall survival of 37 months (95% CI 31-42) log rank test $p = 0.095$.

Preoperative chemotherapy in crude survival analysis increased overall survival and is presented in Figure 8D. The overall median survival is 52 months (95% CI 39-65) for preoperative chemotherapy and 34 months (95% CI 30-38) for no preoperative chemotherapy, log rank test $p < 0.001$.

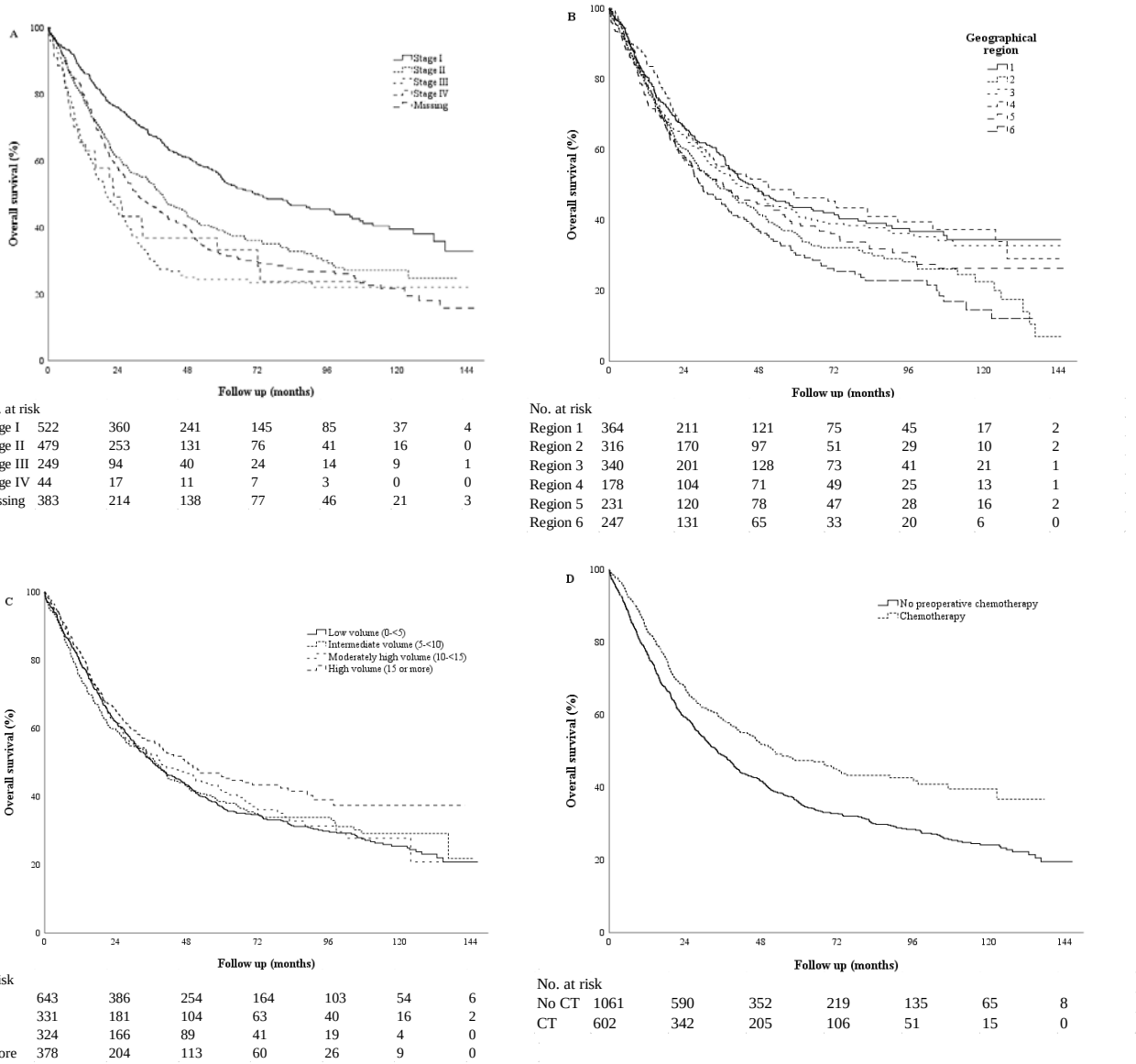
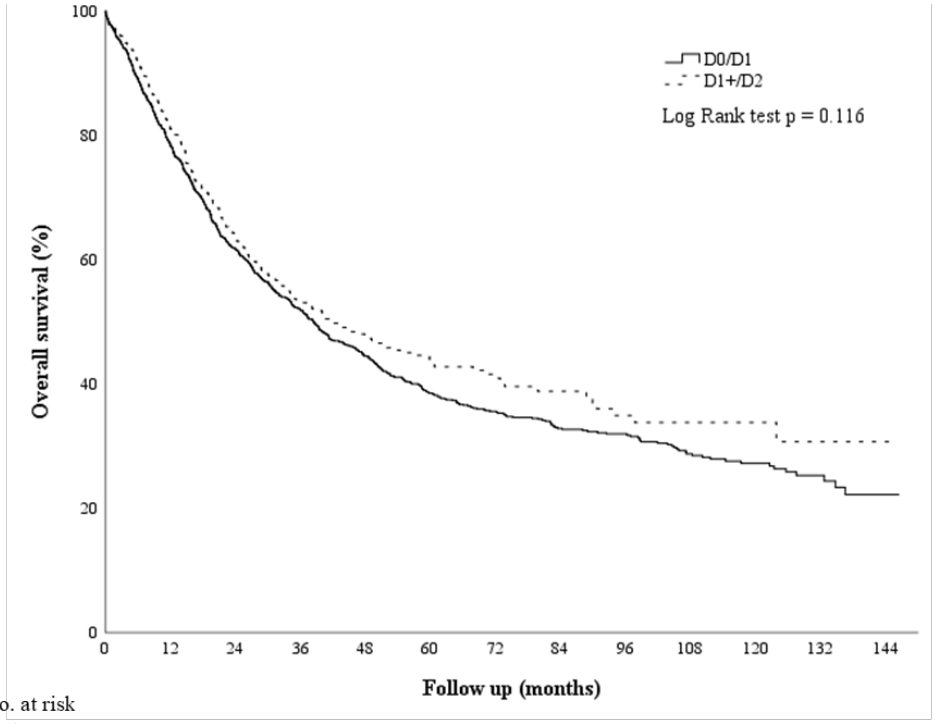


Figure 8. *Overall survival for curatively resected patients presented in various patient specific and treatment specific details.* ***A.*** *Clinical stage specific survival with TNM8 definition, Log rank test p < 0.001* ***B.*** *According to geographical region of treatment in Sweden, Log rank test p = 0.001.* ***C.*** *Annual hospital volume, Log rank test p = 0.095.* ***D.*** *With and without preoperative chemotherapy, Log rank test p < 0.001.*

4.3.5 Lymphadenectomy and survival

Overall median survival was 41 months (95% CI 30-53) and 5-year survival was 44% for D1+/D2 lymphadenectomy. The median survival was 38 months (95% CI 34-43) and 5-year survival was 39% for D0/D1 respectively, log rank test p = 0.116, Figure 9. Multivariable Cox proportional hazard revealed D1+/D2 was associated with lower risk of death with hazard ratio of 0.81 (95% CI 0.68-0.95) p = 0.012, Table 14.



No. at risk

D0/D1	1206	929	693	541	430	334	265	197	158	107	69	30	7
D1+/D2	471	363	245	168	131	95	64	46	31	20	14	4	1

Figure 9. *Overall survival for curatively resected patients for different extent of lymphadenectomy.*

Table 14. *Cox proportional hazard analysis of the impact of lymphadenectomy on survival.*

	D1+/D2 vs D0/D1 (HR, 95 % CI)			
	Crude	p-value	Adjusted	p-value
All cases	0.89 (95% CI 0.77-1.03)	0.107	0.81 (95% CI 0.68-0.95)	0.012
Distal gastrectomy	0.61 (95% CI 0.44-0.84)	0.003	0.75 (95% CI 0.54-1.06)	0.100
Total gastrectomy	0.86 (95% CI 0.72-1.03)	0.108	0.85 (95% CI 0.70-1.04)	0.111

Adjusted for age, gender, Charlson comorbidity index, ASA class, clinical tumour stage, surgical procedure (in analysis with all cases), multivisceral resection, preoperative chemotherapy, education level and calendar year of surgery.

4.4 PAPER IV

During the study period of 2006-2017 a total of 6154 patients were identified as having gastric cancer. Clinical M1 and Mx cases were excluded resulting in 3465 cases left for analysis. Flow chart for patient selection can be seen from Figure 10.

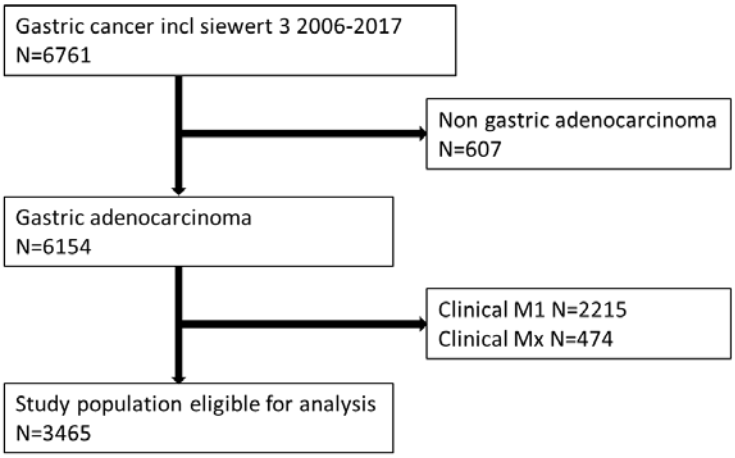


Figure 10. *Patient selection for paper IV.*

The total number of patients resected were 1934 (55.8%). There was a large geographical variation in between counties regarding their annual county specific resection rate which varied from 0% - 100%. The 5th to 95th percentile ranged from 22% - 80% and the IQR was 41% - 63%.

4.4.1 Patient demographics and resection rate

The patients assigned resection rate were grouped to tertiles resulting in low, intermediate and high group. The distribution of patients for these groups were 1261, 1141 and 1063 patients respectively. The resection rate ranged from 0% – 50.0%, 50.1% - 62.5% and 62.6% - 100% respectively. The complete details of baseline characteristics of patients are presented in Table 15.

***Table 15**. Baseline characteristics of patients.*

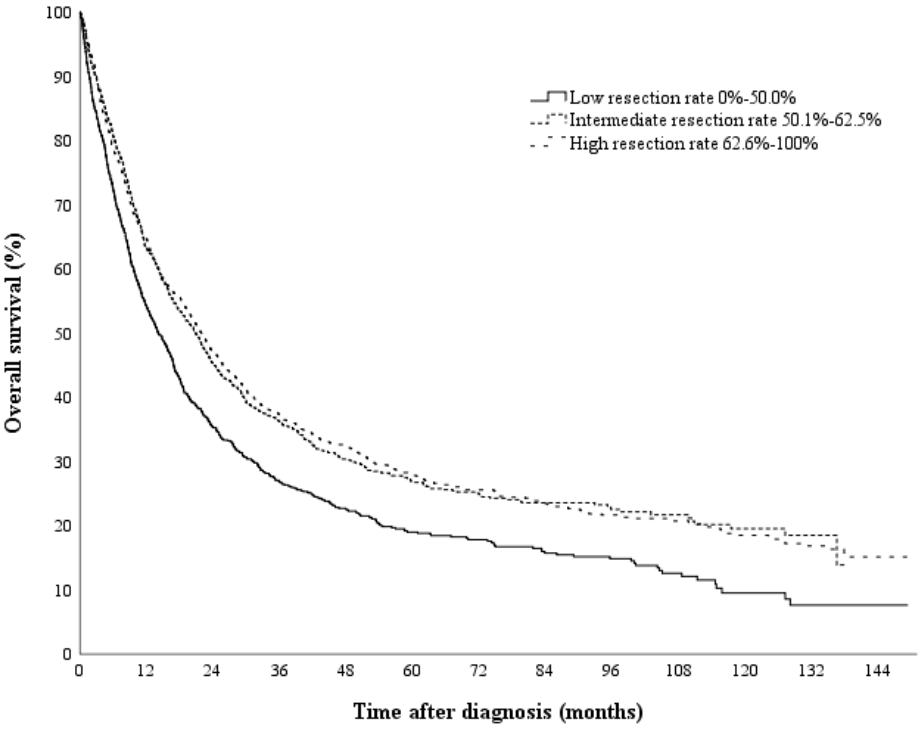
	Resection rate				
	Low (0%-50.0%) (n=1261)	Intermediate (50.1%-62.5%) (n=1141)	High (62.6%-100%) (n=1063)	All patients (n=3465)	p-value
Age [a]	73 ± 12	72 ± 12	72 ± 12	72 ± 12	0.064[b]
Gender					
Male	747 (59.2%)	652 (57.1%)	613 (57.7%)	2012 (58.1%)	0.554
Female	514 (40.8%)	489 (42.9%)	450 (42.3%)	1453 (41.9%)	
ASA class					
ASA I-II	729 (57.9%)	741 (65.0%)	676 (63.6%)	2146 (62.0%)	<0.001
ASA III-IV	382 (30.3%)	371 (32.5%)	322 (30.3%)	1075 (31.0%)	
Missing	149 (11.8%)	28 (2.5%)	65 (6.1%)	242 (7.0%)	
Clinical tumour stage					
Stage I	237 (18.8%)	289 (25.3%)	304 (28.6%)	830 (24.0%)	<0.001
Stage II	356 (28.2%)	329 (28.8%)	283 (26.6%)	968 (27.9%)	
Stage III	242 (19.2%)	234 (20.5%)	182 (17.1%)	658 (19.0%)	
Stage IVa	18 (1.4%)	7 (0.6%)	3 (0.3%)	28 (0.8%)	
Missing	408 (32.4%)	282 (24.7%)	291 (27.4%)	981 (28.3%)	
CCI					0.003
0-1	424 (33.6%)	362 (31.7%)	385 (36.2%)	1171 (33.8%)	
2	177 (14.0%)	202 (17.7%)	192 (18.1%)	571 (16.5%)	
3 or more	660 (52.3%)	577 (50.6%)	486 (45.7%)	1723 (49.7%)	
Education level					
Less or equal to 9 years	519 (41.2%)	430 (37.7%)	414 (38.9%)	1363 (39.3%)	<0.001
10 to 12 years	465 (36.9%)	431 (37.8%)	341 (32.1%)	1237 (35.7%)	
More than 12 years	188 (14.9%)	186 (16.3%)	139 (13.1%)	513 (14.8%)	
Missing	89 (7.1%)	94 (8.2%)	169 (15.9%)	352 (10.2%)	
MDT					
No	487 (38.6%)	295 (25.9%)	439 (41.3%)	1221 (35.2%)	<0.001
Yes	764 (60.6%)	828 (72.6%)	570 (53.6%)	2162 (62.4%)	
Missing	10 (0.8%)	18 (1.6%)	54 (5.1%)	82 (2.4%)	
Resected patients					
No resection	773 (61.3%)	482 (42.2%)	276 (26.0%)	1531 (44.2%)	<0.001
Resection	488 (38.7%)	659 (57.8%)	787 (74.0%)	1934 (55.8%)	

ASA American society of Anaesthesiologists, CCI Charlson comorbidity index, MDT multidisciplinary therapy conference. Values show actual count and percentage. [a] Mean ± SD. Statistical inference with chi-square test, [b] ANOVA.

4.4.2 Survival

Overall median survival was 14.2, 20.9 and 21.9 months respectively for low, intermediate and high actual resection rate, Log Rank test $p < 0.001$. The survival graph can be seen in Figure 11.

In multivariable analysis with cox proportional hazard intermediate and high tertiles compared to low tertiles has better survival. The complete analysis can be seen in Table 16 revealing other independently associated factors related to survival.



No. at risk													
Low	1260	599	333	220	156	109	82	63	57	25	12	8	3
Intermediate	1140	716	471	343	245	178	130	87	64	48	28	12	0
High	1062	688	485	364	307	253	214	160	122	100	66	38	13

Figure 11. *Overall survival from diagnosis according to actual resection rate tertiles, Log rank test $p < 0.001$.*

Table 16. *Cox proportional hazard on overall survival.*

	Univariable analysis			Multivariable analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Resection rate						
Low (0%-50.0%)	ref	-	-	ref	-	-
Intermediate (50.1%-62.5%)	0.75	0.68-0.83	<0.001	0.81	0.74-0.90	<0.001
High (62.6%-100%)	0.74	0.68-0.82	<0.001	0.80	0.73-0.88	<0.001
Age						
per year increment	1.04	1.03-1.04	<0.001	1.03	1.02-1.03	<0.001
Gender						
Male	ref	-	-	ref	-	-
Female	0.98	0.91-1.06	0.624	1.02	0.94-1.10	0.683
ASA						
I-II	ref	-	-	ref	-	-
III-IV	1.93	1.78-2.10	<0.001	1.52	1.39-1.66	<0.001
Missing	1.20	1.00-1.46	0.055	1.12	0.91-1.37	0.289
Clinical tumour stage						
Stage I	ref	-	-	ref	-	-
Stage II	1.79	1.59-2.01	<0.001	1.92	1.71-2.17	<0.001
Stage III	2.54	2.24-2.88	<0.001	2.96	2.60-3.36	<0.001
Stage IVa	4.50	2.96-6.85	<0.001	4.95	3.22-7.63	<0.001
Missing	2.28	2.04-2.56	<0.001	1.98	1.76-2.22	<0.001
CCI						
0-1	ref	-	-	ref	-	-
2	1.01	0.90-1.14	0.821	0.98	0.87-1.10	0.709
3 or more	1.21	1.11-1.32	<0.001	1.04	0.95-1.14	0.353
Education level						
Less or equal to 9 years	ref	-	-	ref	-	-
10 to 12 years	0.84	0.77-0.92	<0.001	0.98	0.90-1.08	0.720
More than 12 years	0.71	0.63-0.81	<0.001	0.96	0.84-1.09	0.511
Missing	1.44	1.27-1.63	<0.001	1.20	1.05-1.37	0.006
MDT						
No	ref	-	-	ref	-	-
Yes	0.66	0.61-0.71	<0.001	0.77	0.71-0.84	<0.001
Missing	0.66	0.51-0.84	0.001	0.90	0.69-1.17	0.425

ASA American society of Anaesthesiologists, CCI Charlson comorbidity index, MDT multidisciplinary therapy conference. Multivariable Cox proportional hazard regression model include all variables in univariable list.

5 DISCUSSION

5.1 RETROSPECTIVE SINGLE CENTER STUDIES

Paper I is a single center retrospective study. Like all single center retrospective studies it has its inherent limits with selection bias and poor generalizability. However, it has a strong internal validity and also show the true results of that particular center. Regarding the outcome of postoperative pancreatic fistula, there are no missing cases.

5.2 REGISTER BASED STUDIES

As in all register-based studies the quality of the research is dependent on the validity and accuracy of the data. Sweden has a long history of national registers and register based studies. What these studies may lack in specific detail, is compensated by volume of patients and follow up time. The NREV is a fairly "young" register but a validation study [162] has shown a coverage of over 95% and a validity of data of over 91%. In addition to this register, additional data needed for patients can be obtained through other national registers such as the Cancer-, Patient-, Total population-, Cause of death-, Prescribed drug register, and LISA, the national register of education, all of which have been validated to have high quality data and completeness[176, 177, 182, 185, 186] and have been operational during a long time.

Since NREV has near complete coverage over the whole population of Sweden, selection bias should be minimal and allows us to study these patients in the routine clinical care as they are not highly selected as in a RCT. Thus, a major strength of the population-based register-based study is its high external validity and generalizability.

Limitations in the data itself due to it being a national register is the poor detail on important confounding variables such as smoking and alcohol use.

However, a large limitation in especially Paper II and Paper III studying short term outcomes and long-term outcomes after different extents of lymphadenectomy is selection bias. The decision to perform a certain lymphadenectomy lies under the responsible surgeon. Patient clinical functional level, comorbidities and stage of disease all are factors influencing survival and also might influence the surgeon's decision on what extent of lymphadenectomy performed. Since the nature of the studies are register-based there is always an uncertainty that cannot be controlled as for an RCT [187]. An issue of stage migration can also occur due to extended lymphadenectomy, but in paper III where we analyse long term survival, we have chosen to stage the disease according to clinical tumour stage instead of pathological tumour stage. However, an issue of different quality of preoperative work-up and classification across different regions still remain. In the studies we have tried to adjust for confounding factors between the different study groups of extent of lymphadenectomy with multivariable logistics regression and cox proportional hazard. The models include known factors that influence survival and are adjusted for. The database has a large study population and a long follow up

time thus we have the possibility to include several covariates and still have robustness in the model with a high number of events per variable. There might still be residual confounding and unknown important confounding factors might be missed. Therefore, the implications and conclusions drawn from Paper II and Paper III are more reserved.

A strength of the register-based study design and its completeness is exemplified in Paper IV where we have the possibility to study all patients, especially patients that are not operated on. Since most RCT and also many retrospective case studies focus primarily on resected patients and study a single research question, far too little is known concerning the patients that are not operated on. In Paper IV we have the possibility to investigate how the resection rate influences survival in the entire population, and the variation of which across different geographical regions and years, which would be truly difficult to study with a different study design.

5.3 ONCOLOGICAL THERAPY

A substantial limitation in the current NREV is lack of details of oncological therapy. The last decades of improvement in gastric cancer care are in large due to the introduction of more oncological therapeutic alternatives. The pivotal MAGIC study [120] showed a survival benefit for perioperative chemotherapy versus surgery alone for gastroesophageal cancer. The 5-year survival rate was 36% versus 23% respectively. Along with the MAGIC study are also study comparing adjuvant chemoradiotherapy and more recent perioperative chemotherapy [119, 122, 125, 126] all showing survival advantage.

Most gastric cancer patients included in NREV during the study period 2006-2018 have been evaluated to receive oncological therapy. In our studies we have adjusted for the presence of oncological therapy in our multivariable analyses as this is important factor affecting survival. However, in our studies we have labelled it as preoperative chemotherapy. The different oncological studies mentioned previously have somewhat different regimens and either perioperative or adjuvant and some also have addition of radiotherapy. The NREV register has been updated regularly and there is from 2017 a prospective detailed robust section on oncological therapy. During the study periods in this thesis' papers the detail of oncological therapy was not that specific, and we therefore only have reliable data on the preoperative part of perioperative chemotherapy, and unfortunately not the specific regimen nor if it was completed or fulfilled with reduced doses. Most patients have however received MAGIC regimen with ECF or modified version with EOX. Some have received treatment as part of the CRITICS trial [124] but very few have had addition of radiotherapy in the oncological treatment. Even though we do not have fully detailed data we still have valuable information in the register. In the MAGIC study as well as a Norwegian study [120, 130] show that only around half of the patients go on to receive the postoperative course of chemotherapy. And the CRITICS study [124] also show poor compliance to the postoperative treatment regimen and recommend further studies to optimize the preoperative part of treatment. The FLOT trial [126] which showed improved overall survival for the investigation arm (FLOT), also show that 60 % of patients

started the postoperative course and 46 % of patients finished all allocated cycles as compared to 52 % and 37 % respectively for the ECF/ECX treatment arm. Even in these RCT settings the postoperative compliance is low and in routine clinical care the estimated compliance of postoperative part of chemotherapy should be even lower. The use in our studies of preoperative chemotherapy as a confounding variable and adjusting for it should be fairly representative and not detrimental that we do not have complete detail of all cycles and the postoperative part. The survival effect of preoperative chemotherapy from the register data, Figure 11, are in similar numbers as the studies mentioned above comparing perioperative chemotherapy to surgery alone.

5.4 LYMPHADENECTOMY

The study of different extent of lymphadenectomy has been under great debate. Trials on surgical procedure or technique is always difficult and has been especially so in the studies on lymphadenectomy in gastric cancer. Our register studies show strength in its generalizability to everyday clinical practice but are lacking in detail.

The first major concern in lymphadenectomy studies is that the terminology, definitions and procedure itself have changed over the years [20, 49, 64, 66, 184, 188, 189] thus making it difficult to compare different studies to each other. This is essential to interpreting the high postoperative morbidity and mortality in the Dutch RCT [72] where at the time pancreaticosplenectomy was routine in D2 for proximal cancers. The high postoperative morbidity and mortality was not seen in the later Italian trial [78] where routine pancreaticosplenectomy was not performed for D2.

Another important factor is accuracy of the procedure. As described in the follow up analysis of lymphadenectomy in the Dutch trial [190] there was in the D1 group 80.5 % non-compliance and 25.8 % contamination. For the D2 group there was 81.6 % non-compliance and 28.7 % contamination. These factors warrant more careful interpretation of the register data. The time period for the register studies cover 2006-2017 and include clinical routine practice that follow and with some implementation delay the classification of lymphadenectomy of the JGCA treatment guidelines from English ver. 2 to ver. 4 [66, 184, 188] where substantial changes were from ver. 2 to ver. 3. Our paper II uses the classification according to JGCA treatment guidelines ver. 3 which was the most recent one at the time. And Paper III uses the 4th English version. In our material we see non-compliance especially in station 1 and station 7 nodes for D1 lymphadenectomy. This might be due to that the 2nd English version classified station 1 as tier 2 node for lower (distal) gastric cancers and not necessary for D1, but in the 3rd and 4th version it is included to be mandatory for D1. Station 7 was classified as tier 2 node irrespective of location of cancer in the 2nd version but in the 3rd and 4th as mandatory for D1 lymphadenectomy. This confusion together with the two first European RCT [74, 75] showing no improved results for D2 might have delayed the implementation of proper D2 lymphadenectomy in clinical routine in Sweden. A consequence that we can see in our data is

that choosing to perform D1 on the basis that D2 was not superior at the time actually resulted in a large number of D0 lymphadenectomy in a lot of distal gastrectomy cases because of the omission of station 1 and station 7 nodes. This is the reason for why in paper II we have accepted D1 lymphadenectomy even if missing station 1 and 7 in distal gastrectomy and in paper III we have combined D0 and D1 patients together in the analysis.

The registration of dissected lymphnode stations in NREV are typically performed by the responsible surgeon directly after surgery. Misclassification can occur, but data from paper II Figure 4, show that there is significantly increased amount of retrieved lymphnodes in the specimen for more extensive lymphadenectomy.

For our register-based studies there are possibilities of patients classified as D2 to have not received the same adequate extent of lymphadenectomy. But this is also true for randomized trials as exemplified by the Dutch follow up study [190]. This is the nature of studying outcomes of surgical intervention and surgical technique and in our best efforts to adjust, and account for those possible errors we feel that the results of our studies regarding D1+/D2 lymphadenectomy stands and that it is truly superior to D0/D1 lymphadenectomy when performed in routine clinical care that is offered to all patients in Sweden.

6 CONCLUSION

Our studies show that the treatment for gastric cancer in Sweden varies across different regions of Sweden. There has been a substantial centralization over the last decade and treatment patterns of lymphadenectomy are changing.

D2 lymphadenectomy during gastrectomy for cancer does not entail a high risk for postoperative pancreatic fistula in cases where direct pancreatic resection can be omitted.

D1+/D2 lymphadenectomy during gastrectomy for cancer has over the last decades only been offered to a minority of patients

D1+/D2 lymphadenectomy during gastrectomy for cancer can be performed safely with acceptable postoperative complication rate and low postoperative mortality in routine clinical healthcare

D1+/D2 lymphadenectomy during gastrectomy for cancer is superior to D0/D1 lymphadenectomy in regard to long term survival.

The decision-making in gastric cancer treatment has room for standardisation and improvement in Sweden.

The curative resection rate offered to patients varies greatly across different healthcare regions.

A high resection rate is of survival benefit for the entire population with gastric cancer.

7 FUTURE RESEARCH

The results of this thesis leave many more questions unanswered. Future perspectives would be to analyse in more depth the possible reasons for geographical differences of treatment principles. Also, to study the effects on postoperative morbidity and mortality as well as long-term survival the effects of the last decade's centralization of care and more recent shift to more minimally invasive approach.

More detailed studies on the effects of perioperative chemotherapy and its' effect on surgical outcomes. Especially concerning perioperative chemotherapy and future emerging immunotherapy and its role in different molecular subtypes of gastric cancer. Larger databases and the emerging infrastructure with biobanking and next generation sequencing allows very interesting trials on the efficacy of oncological therapy in the molecular subtypes of gastric cancer.

8 POPULÄRVETENSKAPLIG SAMMANFATTNING

Magsäckscancer är den femte vanligaste cancersjukdomen i världen och den cancerform som orsakar tredje flest dödsfall i världen. Historiskt sett har det varit den vanligaste cancerformen i världen men har senaste decennierna blivit mer ovanlig. I Sverige drabbas cirka 800 personer årligen. Prognosen för magsäckscancer är dyster med en 5 års överlevnad på endast ca 30 % av de som behandlas. Det finns dock geografiska skillnader och i östasiatiska länder som Japan och Sydkorea är magsäckscancer en mycket vanligare sjukdom och överlevnaden där också avsevärt bättre. Det finns skillnader i hur långt gången sjukdomen är när man upptäcker och behandlar den men det är inte den enda förklaringen till de bättre resultaten i de länderna. Möjligen beror det också på en kvalitetsskillnad i hur vi behandlar patienter med magsäckscancer. Kirurgi är grunden för botande behandling av magsäckscancer utan alltför stor spridning och syftar till att med marginal operera bort alla cancerceller i magsäcken och i de närliggande lymfkörtlarna. Kirurgin är dock behäftad med betydande risk för komplikationer. För att få bästa möjliga resultat vid kirurgi är det också viktigt att en stor andel av de lymfkörtlar som finns i närheten av tumören också opereras bort. Det brukar benämnas som omfattande lymfkörtelutrymning. För att studera behandlingen och vården av personer med magsäckscancer i Sverige har det inrättats ett nationellt kvalitetsregister. Det startades 2006 och organiseras av Sveriges regionala cancercentrum och heter Nationella Registret för Esofagus och Ventrikelcancer (NREV).

Våra studier baserade på NREV har visat på att optimal kirurgisk behandling med omfattande lymfkörtelutrymning för att kirurgisk avlägsna all cancervävnad sker i varierande grad i Sverige. Det finns regionala skillnader, men överlag över tid så är det fler och fler patienter som opereras med omfattande lymfkörtelutrymning.

Våra resultat visar också att långtidsöverlevnaden för magsäckscancer förbättras om man opereras med omfattande lymfkörtelutrymning. Detta har tidigare varit känt i studier från Östasien men det har ej tidigare visats på europeiska studier på hela populationer. Här ser vi också att komplikationer efter operation för magsäckscancer inte förekommer avsevärt oftare vid omfattande lymfkörtelutrymning.

En stor fördel med vårt nationella kvalitetsregister är att vi dessutom kan studera de personer med magsäckscancer som inte opereras. Mycket studier runtom i världen studerar endast de personer som går vidare till operation. Men majoriteten av de som får magsäckscancer kan inte opereras för sin sjukdom. Här har våra resultat visat att överlevnaden överlag är dålig om man inte opereras och att om man diagnosticeras i ett län med hög andel som opereras så ger det effekt och visar på att överlevnaden för hela gruppen förbättras.

Sammanfattningsvis visar avhandlingen att för att ge hela populationen bästa behandling skall man sträva efter att erbjuda operation av magsäckscancer med syfte att bota och utföra operationen med omfattande lymfkörtelutrymning till så många patienter som möjligt. Det verkar finnas stora regionala skillnader i Sverige och mer arbete behöver göras för att så många som möjligt i Sverige skall erbjudas den mest optimala vården.

9 ACKNOWLEDGEMENTS

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10 REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. *International journal of cancer Journal international du cancer* 2001;**94**(2): 153-156.

2. Parkin DM, Stjernsward J, Muir CS. Estimates of the worldwide frequency of twelve major cancers. *Bulletin of the World Health Organization* 1984;**62**(2): 163-182.

3. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *International journal of cancer Journal international du cancer* 2010;**127**(12): 2893-2917.

4. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;**68**(6): 394-424.

5. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *International journal of cancer Journal international du cancer* 2015;**136**(5): E359-386.

6. Soerjomataram I, Lortet-Tieulent J, Parkin DM, Ferlay J, Mathers C, Forman D, et al. Global burden of cancer in 2008: a systematic analysis of disability-adjusted life-years in 12 world regions. *Lancet* 2012;**380**(9856): 1840-1850.

7. Infection with Helicobacter pylori. *IARC monographs on the evaluation of carcinogenic risks to humans / World Health Organization, International Agency for Research on Cancer* 1994;**61**: 177-240.

8. Helicobacter, Cancer Collaborative G. Gastric cancer and Helicobacter pylori: a combined analysis of 12 case control studies nested within prospective cohorts. *Gut* 2001;**49**(3): 347-353.

9. Joossens JV, Hill MJ, Elliott P, Stamler R, Lesaffre E, Dyer A, et al. Dietary salt, nitrate and stomach cancer mortality in 24 countries. European Cancer Prevention (ECP) and the INTERSALT Cooperative Research Group. *Int J Epidemiol* 1996;**25**(3): 494-504.

10. Shikata K, Kiyohara Y, Kubo M, Yonemoto K, Ninomiya T, Shirota T, et al. A prospective study of dietary salt intake and gastric cancer incidence in a defined Japanese population: the Hisayama study. *International journal of cancer Journal international du cancer* 2006;**119**(1): 196-201.

11. Gonzalez CA, Pera G, Agudo A, Palli D, Krogh V, Vineis P, et al. Smoking and the risk of gastric cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). *International journal of cancer Journal international du cancer* 2003;**107**(4): 629-634.

12. Sipponen P, Correa P. Delayed rise in incidence of gastric cancer in females results in unique sex ratio (M/F) pattern: etiologic hypothesis. *Gastric Cancer* 2002;**5**(4): 213-219.

13. La Vecchia C, Negri E, Franceschi S, Gentile A. Family history and the risk of stomach and colorectal cancer. *Cancer* 1992;**70**(1): 50-55.

14. Zanghieri G, Di Gregorio C, Sacchetti C, Fante R, Sassatelli R, Cannizzo G, et al. Familial occurrence of gastric cancer in the 2-year experience of a population-based registry. *Cancer* 1990;**66**(9): 2047-2051.

15. National Board of Health and Welfare, Statistics database for cancer. https://sdb.socialstyrelsen.se/if_can/resultat.aspx.

16. Tsugane S, Sasazuki S, Kobayashi M, Sasaki S. Salt and salted food intake and subsequent risk of gastric cancer among middle-aged Japanese men and women. *Br J Cancer* 2004;**90**(1): 128-134.

17. Zamora-Ros R, Agudo A, Lujan-Barroso L, Romieu I, Ferrari P, Knaze V, et al. Dietary flavonoid and lignan intake and gastric adenocarcinoma risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *The American journal of clinical nutrition* 2012;**96**(6): 1398-1408.

18. Akoh JA, Macintyre IM. Improving survival in gastric cancer: review of 5-year survival rates in English language publications from 1970. *Br J Surg* 1992;**79**(4): 293-299.

19. Ahn HS, Lee HJ, Yoo MW, Jeong SH, Park DJ, Kim HH, et al. Changes in clinicopathological features and survival after gastrectomy for gastric cancer over a 20-year period. *Br J Surg* 2011;**98**(2): 255-260.

20. Maruyama K, Okabayashi K, Kinoshita T. Progress in gastric cancer surgery in Japan and its limits of radicality. *World J Surg* 1987;**11**(4): 418-425.

21. Wanebo HJ, Kennedy BJ, Chmiel J, Steele G, Jr., Winchester D, Osteen R. Cancer of the stomach. A patient care study by the American College of Surgeons. *Ann Surg* 1993;**218**(5): 583-592.

22. Markar SR, Karthikesalingam A, Jackson D, Hanna GB. Long-term survival after gastrectomy for cancer in randomized, controlled oncological trials: comparison between West and East. *Ann Surg Oncol* 2013;**20**(7): 2328-2338.

23. Japanese Gastric Cancer A. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011;**14**(2): 101-112.

24. Brierley JD GM, Wittekind C, editor. *TNM Classification of Malignant Tumours. 8th ed.* Wiley Blackwell: New Jersey, 2017.

25. Hassan H, Vilmann P, Sharma V. Impact of EUS-guided FNA on management of gastric carcinoma. *Gastrointestinal endoscopy* 2010;**71**(3): 500-504.

26. Leake PA, Cardoso R, Seevaratnam R, Lourenco L, Helyer L, Mahar A, et al. A systematic review of the accuracy and indications for diagnostic laparoscopy prior to curative-intent resection of gastric cancer. *Gastric Cancer* 2012;**15 Suppl 1**: S38-47.

27. Chen J, Cheong JH, Yun MJ, Kim J, Lim JS, Hyung WJ, et al. Improvement in preoperative staging of gastric adenocarcinoma with positron emission tomography. *Cancer* 2005;**103**(11): 2383-2390.

28. Dassen AE, Lips DJ, Hoekstra CJ, Pruijt JF, Bosscha K. FDG-PET has no definite role in preoperative imaging in gastric cancer. *Eur J Surg Oncol* 2009;**35**(5): 449-455.

29. Kinkel K, Lu Y, Both M, Warren RS, Thoeni RF. Detection of hepatic metastases from cancers of the gastrointestinal tract by using noninvasive imaging methods (US, CT, MR imaging, PET): a meta-analysis. *Radiology* 2002;**224**(3): 748-756.

30. Seevaratnam R, Cardoso R, McGregor C, Lourenco L, Mahar A, Sutradhar R, et al. How useful is preoperative imaging for tumor, node, metastasis (TNM) staging of gastric cancer? A meta-analysis. *Gastric Cancer* 2012;**15 Suppl 1**: S3-18.

31. Jeong O, Park YK. Clinicopathological features and surgical treatment of gastric cancer in South Korea: the results of 2009 nationwide survey on surgically treated gastric cancer patients. *Journal of gastric cancer* 2011;**11**(2): 69-77.

32. Kim YG, Kong SH, Oh SY, Lee KG, Suh YS, Yang JY, et al. Effects of screening on gastric cancer management: comparative analysis of the results in 2006 and in 2011. *Journal of gastric cancer* 2014;**14**(2): 129-134.

33. Lee KJ, Inoue M, Otani T, Iwasaki M, Sasazuki S, Tsugane S, et al. Gastric cancer screening and subsequent risk of gastric cancer: a large-scale population-based cohort study, with a 13-year follow-up in Japan. *International journal of cancer Journal international du cancer* 2006;**118**(9): 2315-2321.

34. Miyamoto A, Kuriyama S, Nishino Y, Tsubono Y, Nakaya N, Ohmori K, et al. Lower risk of death from gastric cancer among participants of gastric cancer screening in Japan: a population-based cohort study. *Prev Med* 2007;**44**(1): 12-19.

35. Suh YS, Yang HK. Screening and Early Detection of Gastric Cancer: East Versus West. *Surg Clin North Am* 2015;**95**(5): 1053-1066.

36. Adami H-O, Hunter DJ, Trichopoulos D, Oxford University Press. Textbook of cancer epidemiology. In. 2nd ed. New York ; Oxford: Oxford University Press,; 2008. p. 1 online resource (xxxiii, 748 p.

37. Li C, Oh SJ, Kim S, Hyung WJ, Yan M, Zhu ZG, et al. Macroscopic Borrmann type as a simple prognostic indicator in patients with advanced gastric cancer. *Oncology* 2009;**77**(3-4): 197-204.

38. Lauren P. The Two Histological Main Types of Gastric Carcinoma: Diffuse and So-Called Intestinal-Type Carcinoma. An Attempt at a Histo-Clinical Classification. *Acta pathologica et microbiologica Scandinavica* 1965;**64**: 31-49.

39. Miyahara R, Niwa Y, Matsuura T, Maeda O, Ando T, Ohmiya N, et al. Prevalence and prognosis of gastric cancer detected by screening in a large Japanese population: data from a single institute over 30 years. *Journal of gastroenterology and hepatology* 2007;**22**(9): 1435-1442.

40. Qiu MZ, Cai MY, Zhang DS, Wang ZQ, Wang DS, Li YH, et al. Clinicopathological characteristics and prognostic analysis of Lauren classification in gastric adenocarcinoma in China. *Journal of translational medicine* 2013;**11**: 58.

41. Yamashita K, Sakuramoto S, Katada N, Futawatari N, Moriya H, Hirai K, et al. Diffuse type advanced gastric cancer showing dismal prognosis is characterized by deeper invasion and emerging peritoneal cancer cell: the latest comparative study to intestinal advanced gastric cancer. *Hepatogastroenterology* 2009;**56**(89): 276-281.

42. Zheng H, Takahashi H, Murai Y, Cui Z, Nomoto K, Miwa S, et al. Pathobiological characteristics of intestinal and diffuse-type gastric carcinoma in Japan: an immunostaining study on the tissue microarray. *Journal of clinical pathology* 2007;**60**(3): 273-277.

43. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell* 2000;**100**(1): 57-70.

44. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011;**144**(5): 646-674.

45. Cancer Genome Atlas Research N. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature* 2014;**513**(7517): 202-209.

46. Palser TR, Cromwell DA, Hardwick RH, Riley SA, Greenaway K, Allum W, et al. Re-organisation of oesophago-gastric cancer care in England: progress and remaining challenges. *BMC health services research* 2009;**9**: 204.

47. Gotoda T, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, et al. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer* 2000;**3**(4): 219-225.

48. Yamao T, Shirao K, Ono H, Kondo H, Saito D, Yamaguchi H, et al. Risk factors for lymph node metastasis from intramucosal gastric carcinoma. *Cancer* 1996;**77**(4): 602-606.

49. Japanese Gastric Cancer A. Japanese gastric cancer treatment guidelines 2018 (5th edition). *Gastric Cancer* 2020.

50. Kim HS, Lee DK, Baik SK, Kim JM, Kwon SO, Kim DS, et al. Endoscopic mucosal resection with a ligation device for early gastric cancer and precancerous lesions: comparison of its therapeutic efficacy with surgical resection. *Yonsei medical journal* 2000;**41**(5): 577-583.

51. Kim YI, Kim YW, Choi IJ, Kim CG, Lee JY, Cho SJ, et al. Long-term survival after endoscopic resection versus surgery in early gastric cancers. *Endoscopy* 2015;**47**(4): 293-301.

52. Kosaka T, Endo M, Toya Y, Abiko Y, Kudara N, Inomata M, et al. Long-term outcomes of endoscopic submucosal dissection for early gastric cancer: a single-center retrospective study. *Digestive endoscopy : official journal of the Japan Gastroenterological Endoscopy Society* 2014;**26**(2): 183-191.

53. Gouzi JL, Huguier M, Fagniez PL, Launois B, Flamant Y, Lacaine F, et al. Total versus subtotal gastrectomy for adenocarcinoma of the gastric antrum. A French prospective controlled study. *Ann Surg* 1989;**209**(2): 162-166.

54. Lawrence W, Jr. Reconstruction after total gastrectomy: what is preferred technique? *Journal of surgical oncology* 1996;**63**(4): 215-220.

55. Ding X, Yan F, Liang H, Xue Q, Zhang K, Li H, et al. Functional jejunal interposition, a reconstruction procedure, promotes functional outcomes after total gastrectomy. *BMC Surg* 2015;**15**: 43.

56. Hirao M, Takiguchi S, Imamura H, Yamamoto K, Kurokawa Y, Fujita J, et al. Comparison of Billroth I and Roux-en-Y reconstruction after distal gastrectomy for gastric cancer: one-year postoperative effects assessed by a multi-institutional RCT. *Ann Surg Oncol* 2013;**20**(5): 1591-1597.

57. Kojima K, Yamada H, Inokuchi M, Kawano T, Sugihara K. A comparison of Roux-en-Y and Billroth-I reconstruction after laparoscopy-assisted distal gastrectomy. *Ann Surg* 2008;**247**(6): 962-967.

58. Lee MS, Ahn SH, Lee JH, Park do J, Lee HJ, Kim HH, et al. What is the best reconstruction method after distal gastrectomy for gastric cancer? *Surg Endosc* 2012;**26**(6): 1539-1547.

59. Tran TB, Worhunsky DJ, Squires MH, Jin LX, Spolverato G, Votanopoulos KI, et al. To Roux or not to Roux: a comparison between Roux-en-Y and Billroth II reconstruction following partial gastrectomy for gastric cancer. *Gastric Cancer* 2015.

60. Chen W, Jiang X, Huang H, Ding Z, Li C. Jejunal pouch reconstruction after total gastrectomy is associated with better short-term absorption capacity and quality of life in early-stage gastric cancer patients. *BMC Surg* 2018;**18**(1): 63.

61. Namikawa T, Munekage E, Munekage M, Maeda H, Kitagawa H, Nagata Y, et al. Reconstruction with Jejunal Pouch after Gastrectomy for Gastric Cancer. *The American surgeon* 2016;**82**(6): 510-517.

62. Yun L, Zhiwei J, Junsheng P, Xiaobin W, Cancan X, Jieshou L. Comparison of Functional Outcomes between Functional Jejunal Interposition and Conventional Roux-en-Y Esophagojejunostomy after Total Gastrectomy for Gastric Cancer. *Dig Surg* 2019: 1-9.

63. Kajitani T. The general rules for the gastric cancer study in surgery and pathology. Part I. Clinical classification. *The Japanese journal of surgery* 1981;**11**(2): 127-139.

64. Maruyama K, Gunven P, Okabayashi K, Sasako M, Kinoshita T. Lymph node metastases of gastric cancer. General pattern in 1931 patients. *Ann Surg* 1989;**210**(5): 596-602.

65. Tokunaga M, Ohyama S, Hiki N, Fukunaga T, Yamada K, Sano T, et al. Investigation of the lymphatic stream of the stomach in gastric cancer with solitary lymph node metastasis. *World J Surg* 2009;**33**(6): 1235-1239.

66. Japanese Gastric Cancer A. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer* 2011;**14**(2): 113-123.

67. Mine M, Majima S, Harada M, Etani S. End results of gastrectomy for gastric cancer: effect of extensive lymph node dissection. *Surgery* 1970;**68**(5): 753-758.

68. Nakajima T, Nishi M. Surgery and adjuvant chemotherapy for gastric cancer. *Hepatogastroenterology* 1989;**36**(2): 79-85.

69. Dent DM, Madden MV, Price SK. Randomized comparison of R1 and R2 gastrectomy for gastric carcinoma. *Br J Surg* 1988;**75**(2): 110-112.

70. Pacelli F, Doglietto GB, Bellantone R, Alfieri S, Sgadari A, Crucitti F. Extensive versus limited lymph node dissection for gastric cancer: a comparative study of 320 patients. *Br J Surg* 1993;**80**(9): 1153-1156.

71. Viste A, Svanes K, Janssen CW, Jr., Maartmann-Moe H, Soreide O. Prognostic importance of radical lymphadenectomy in curative resections for gastric cancer. *The European journal of surgery = Acta chirurgica* 1994;**160**(9): 497-502.

72. Bonenkamp JJ, Songun I, Hermans J, Sasako M, Welvaart K, Plukker JT, et al. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. *Lancet* 1995;**345**(8952): 745-748.

73. Cuschieri A, Fayers P, Fielding J, Craven J, Bancewicz J, Joypaul V, et al. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. The Surgical Cooperative Group. *Lancet* 1996;**347**(9007): 995-999.

74. Bonenkamp JJ, Hermans J, Sasako M, van de Velde CJ, Welvaart K, Songun I, et al. Extended lymph-node dissection for gastric cancer. *N Engl J Med* 1999;**340**(12): 908-914.

75. Cuschieri A, Weeden S, Fielding J, Bancewicz J, Craven J, Joypaul V, et al. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. *Br J Cancer* 1999;**79**(9-10): 1522-1530.

76. Songun I, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol* 2010;**11**(5): 439-449.

77. Degiuli M, Sasako M, Ponti A, Vendrame A, Tomatis M, Mazza C, et al. Randomized clinical trial comparing survival after D1 or D2 gastrectomy for gastric cancer. *Br J Surg* 2014;**101**(2): 23-31.

78. Degiuli M, Sasako M, Ponti A. Morbidity and mortality in the Italian Gastric Cancer Study Group randomized clinical trial of D1 versus D2 resection for gastric cancer. *Br J Surg* 2010;**97**(5): 643-649.

79. Wu CW, Hsiung CA, Lo SS, Hsieh MC, Chen JH, Li AF, et al. Nodal dissection for patients with gastric cancer: a randomised controlled trial. *Lancet Oncol* 2006;**7**(4): 309-315.

80. Wu CW, Hsiung CA, Lo SS, Hsieh MC, Shia LT, Whang-Peng J. Randomized clinical trial of morbidity after D1 and D3 surgery for gastric cancer. *Br J Surg* 2004;**91**(3): 283-287.

81. Sasako M, Sano T, Yamamoto S, Kurokawa Y, Nashimoto A, Kurita A, et al. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. *N Engl J Med* 2008;**359**(5): 453-462.

82. Seevaratnam R, Bocicariu A, Cardoso R, Mahar A, Kiss A, Helyer L, et al. A meta-analysis of D1 versus D2 lymph node dissection. *Gastric Cancer* 2012;**15 Suppl 1**: S60-69.

83. Imamura H, Kurokawa Y, Kawada J, Tsujinaka T, Takiguchi S, Fujiwara Y, et al. Influence of bursectomy on operative morbidity and mortality after radical gastrectomy for gastric cancer: results of a randomized controlled trial. *World J Surg* 2011;**35**(3): 625-630.

84. Hirao M, Kurokawa Y, Fujita J, Imamura H, Fujiwara Y, Kimura Y, et al. Long-term outcomes after prophylactic bursectomy in patients with resectable gastric cancer: Final analysis of a multicenter randomized controlled trial. *Surgery* 2015;**157**(6): 1099-1105.

85. Shen WS, Xi HQ, Wei B, Chen L. Effect of gastrectomy with bursectomy on prognosis of gastric cancer: a meta-analysis. *World J Gastroenterol* 2014;**20**(40): 14986-14991.

86. Kurokawa Y, Doki Y, Mizusawa J, Terashima M, Katai H, Yoshikawa T, et al. Bursectomy versus omentectomy alone for resectable gastric cancer (JCOG1001): a phase 3, open-label, randomised controlled trial. *Lancet Gastroenterol Hepatol* 2018;**3**(7): 460-468.

87. Huscher CG, Mingoli A, Sgarzini G, Sansonetti A, Di Paola M, Recher A, et al. Laparoscopic versus open subtotal gastrectomy for distal gastric cancer: five-year results of a randomized prospective trial. *Ann Surg* 2005;**241**(2): 232-237.

88. Cai J, Wei D, Gao CF, Zhang CS, Zhang H, Zhao T. A prospective randomized study comparing open versus laparoscopy-assisted D2 radical gastrectomy in advanced gastric cancer. *Dig Surg* 2011;**28**(5-6): 331-337.

89. Kim YW, Yoon HM, Yun YH, Nam BH, Eom BW, Baik YH, et al. Long-term outcomes of laparoscopy-assisted distal gastrectomy for early gastric cancer: result of a randomized controlled trial (COACT 0301). *Surg Endosc* 2013;**27**(11): 4267-4276.

90. Zhang CD, Chen SC, Feng ZF, Zhao ZM, Wang JN, Dai DQ. Laparoscopic versus open gastrectomy for early gastric cancer in Asia: a meta-analysis. *Surgical laparoscopy, endoscopy & percutaneous techniques* 2013;**23**(4): 365-377.

91. Kim HH, Han SU, Kim MC, Kim W, Lee HJ, Ryu SW, et al. Effect of Laparoscopic Distal Gastrectomy vs Open Distal Gastrectomy on Long-term Survival Among Patients With Stage I Gastric Cancer: The KLASS-01 Randomized Clinical Trial. *JAMA Oncol* 2019;**5**(4): 506-513.

92. Katai H, Mizusawa J, Katayama H, Morita S, Yamada T, Bando E, et al. Survival outcomes after laparoscopy-assisted distal gastrectomy versus open distal gastrectomy with nodal dissection for clinical stage IA or IB gastric cancer (JCOG0912): a multicentre, non-inferiority, phase 3 randomised controlled trial. *Lancet Gastroenterol Hepatol* 2020;**5**(2): 142-151.

93. Martin RC, 2nd, Jaques DP, Brennan MF, Karpeh M. Extended local resection for advanced gastric cancer: increased survival versus increased morbidity. *Ann Surg* 2002;**236**(2): 159-165.

94. Martin RC, 2nd, Jaques DP, Brennan MF, Karpeh M. Achieving RO resection for locally advanced gastric cancer: is it worth the risk of multiorgan resection? *Journal of the American College of Surgeons* 2002;**194**(5): 568-577.

95. Brar SS, Seevaratnam R, Cardoso R, Yohanathan L, Law C, Helyer L, et al. Multivisceral resection for gastric cancer: a systematic review. *Gastric Cancer* 2012;**15 Suppl 1**: S100-107.

96. Roberts P, Seevaratnam R, Cardoso R, Law C, Helyer L, Coburn N. Systematic review of pancreaticoduodenectomy for locally advanced gastric cancer. *Gastric Cancer* 2012;**15 Suppl 1**: S108-115.

97. Ikeguchi M, Oka A, Tsujitani S, Maeta M, Kaibara N. Relationship between area of serosal invasion and intraperitoneal free cancer cells in patients with gastric cancer. *Anticancer research* 1994;**14**(5B): 2131-2134.

98. Kuramoto M, Shimada S, Ikeshima S, Matsuo A, Yagi Y, Matsuda M, et al. Extensive intraoperative peritoneal lavage as a standard prophylactic strategy for peritoneal recurrence in patients with gastric carcinoma. *Ann Surg* 2009;**250**(2): 242-246.

99. Cashin PH, Dranichnikov F, Mahteme H. Cytoreductive surgery and hyperthermic intra-peritoneal chemotherapy treatment of colorectal peritoneal metastases: cohort analysis of high volume disease and cure rate. *Journal of surgical oncology* 2014;**110**(2): 203-206.

100. van Leeuwen BL, Graf W, Pahlman L, Mahteme H. Swedish experience with peritonectomy and HIPEC. HIPEC in peritoneal carcinomatosis. *Ann Surg Oncol* 2008;**15**(3): 745-753.

101. Glehen O, Gilly FN, Arvieux C, Cotte E, Boutitie F, Mansvelt B, et al. Peritoneal carcinomatosis from gastric cancer: a multi-institutional study of 159 patients treated by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy. *Ann Surg Oncol* 2010;**17**(9): 2370-2377.

102. Hultman B, Lind P, Glimelius B, Sundbom M, Nygren P, Haglund U, et al. Phase II study of patients with peritoneal carcinomatosis from gastric cancer treated with preoperative systemic chemotherapy followed by peritonectomy and intraperitoneal chemotherapy. *Acta Oncol* 2013;**52**(4): 824-830.

103. Manzanedo I, Pereira F, Rihuete Caro C, Perez-Viejo E, Serrano A, Gutierrez Calvo A, et al. Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Gastric Cancer with Peritoneal Carcinomatosis: Multicenter Study of Spanish Group of Peritoneal Oncologic Surgery (GECOP). *Ann Surg Oncol* 2019;**26**(8): 2615-2621.

104. Yang XJ, Huang CQ, Suo T, Mei LJ, Yang GL, Cheng FL, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric cancer: final results of a phase III randomized clinical trial. *Ann Surg Oncol* 2011;**18**(6): 1575-1581.

105. Glehen O, Passot G, Villeneuve L, Vaudoyer D, Bin-Dorel S, Boschetti G, et al. GASTRICHIP: D2 resection and hyperthermic intraperitoneal chemotherapy in locally advanced gastric carcinoma: a randomized and multicenter phase III study. *BMC cancer* 2014;**14**: 183.

106. Al-Batran SE, Goetze TO, Mueller DW, Vogel A, Winkler M, Lorenzen S, et al. The RENAISSANCE (AIO-FLOT5) trial: effect of chemotherapy alone vs. chemotherapy followed by surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction - a phase III trial of the German AIO/CAO-V/CAOGI. *BMC cancer* 2017;**17**(1): 893.

107. Gadde R, Tamariz L, Hanna M, Avisar E, Livingstone A, Franceschi D, et al. Metastatic gastric cancer (MGC) patients: Can we improve survival by metastasectomy? A systematic review and meta-analysis. *Journal of surgical oncology* 2015;**112**(1): 38-45.

108. Ohkura Y, Shinohara H, Haruta S, Ueno M, Hashimoto M, Sakai Y, et al. Hepatectomy Offers Superior Survival Compared with Non-surgical Treatment for </=3 Metastatic Tumors with Diameters <3 cm from Gastric Cancer: A Retrospective Study. *World J Surg* 2015.

109. Petrelli F, Coinu A, Cabiddu M, Ghilardi M, Borgonovo K, Lonati V, et al. Hepatic resection for gastric cancer liver metastases: A systematic review and meta-analysis. *Journal of surgical oncology* 2015;**111**(8): 1021-1027.

110. Kitagawa Y, Takeuchi H, Takagi Y, Natsugoe S, Terashima M, Murakami N, et al. Sentinel node mapping for gastric cancer: a prospective multicenter trial in Japan. *J Clin Oncol* 2013;**31**(29): 3704-3710.

111. Park JY, Kim YW, Ryu KW, Nam BH, Lee YJ, Jeong SH, et al. Assessment of laparoscopic stomach preserving surgery with sentinel basin dissection versus standard gastrectomy with lymphadenectomy in early gastric cancer-A multicenter randomized phase III clinical trial (SENORITA trial) protocol. *BMC cancer* 2016;**16**: 340.

112. An JY, Min JS, Lee YJ, Jeong SH, Hur H, Han SU, et al. Safety of Laparoscopic Sentinel Basin Dissection in Patients with Gastric Cancer: an Analysis from the SENORITA Prospective Multicenter Quality Control Trial. *Journal of gastric cancer* 2018;**18**(1): 30-36.

113. Kung CH, Lindblad M, Nilsson M, Rouvelas I, Kumagai K, Lundell L, et al. Postoperative pancreatic fistula formation according to ISGPF criteria after D2 gastrectomy in Western patients. *Gastric Cancer* 2014;**17**(3): 571-577.

114. Lassen K, Soop M, Nygren J, Cox PB, Hendry PO, Spies C, et al. Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) Group recommendations. *Archives of surgery* 2009;**144**(10): 961-969.

115. Rawlinson A, Kang P, Evans J, Khanna A. A systematic review of enhanced recovery protocols in colorectal surgery. *Ann R Coll Surg Engl* 2011;**93**(8): 583-588.

116. Mortensen K, Nilsson M, Slim K, Schafer M, Mariette C, Braga M, et al. Consensus guidelines for enhanced recovery after gastrectomy: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations. *Br J Surg* 2014;**101**(10): 1209-1229.

117. Fumagalli Romario U, Weindelmayer J, Coratti A, Cossu A, Gianotti L, Rausei S, et al. Enhanced recovery after surgery in gastric cancer: which are the main achievements from the Italian experience? *Updates Surg* 2018;**70**(2): 257-264.

118. Davis JL, Ripley RT. Postgastrectomy Syndromes and Nutritional Considerations Following Gastric Surgery. *Surg Clin North Am* 2017;**97**(2): 277-293.

119. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med* 2001;**345**(10): 725-730.

120. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006;**355**(1): 11-20.

121. Sakuramoto S, Sasako M, Yamaguchi T, Kinoshita T, Fujii M, Nashimoto A, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med* 2007;**357**(18): 1810-1820.

122. Noh SH, Park SR, Yang HK, Chung HC, Chung IJ, Kim SW, et al. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. *Lancet Oncol* 2014;**15**(12): 1389-1396.

123. Park SH, Sohn TS, Lee J, Lim do H, Hong ME, Kim KM, et al. Phase III Trial to Compare Adjuvant Chemotherapy With Capecitabine and Cisplatin Versus Concurrent Chemoradiotherapy in Gastric Cancer: Final Report of the Adjuvant Chemoradiotherapy in Stomach Tumors Trial, Including Survival and Subset Analyses. *J Clin Oncol* 2015;**33**(28): 3130-3136.

124. Cats A, Jansen EPM, van Grieken NCT, Sikorska K, Lind P, Nordsmark M, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. *Lancet Oncol* 2018;**19**(5): 616-628.

125. Ychou M, Boige V, Pignon JP, Conroy T, Bouche O, Lebreton G, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. *J Clin Oncol* 2011;**29**(13): 1715-1721.

126. Al-Batran SE, Homann N, Pauligk C, Goetze TO, Meiler J, Kasper S, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. *Lancet* 2019;**393**(10184): 1948-1957.

127. Al-Batran SE, Hofheinz RD, Pauligk C, Kopp HG, Haag GM, Luley KB, et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. *Lancet Oncol* 2016;**17**(12): 1697-1708.

128. Hundahl SA, Macdonald JS, Benedetti J, Fitzsimmons T, Southwest Oncology G, the Gastric I. Surgical treatment variation in a prospective, randomized trial of chemoradiotherapy in gastric cancer: the effect of undertreatment. *Ann Surg Oncol* 2002;**9**(3): 278-286.

129. Nakajima T, Fujii M. What make differences in the outcome of adjuvant treatments for resected gastric cancer? *World J Gastroenterol* 2014;**20**(33): 11567-11573.

130. Bringeland EA, Wasmuth HH, Fougner R, Mjones P, Gronbech JE. Impact of perioperative chemotherapy on oncological outcomes after gastric cancer surgery. *Br J Surg* 2014;**101**(13): 1712-1720.

131. Wagner AD, Grabsch HI, Mauer M, Marreaud S, Caballero C, Thuss-Patience P, et al. EORTC-1203-GITCG - the "INNOVATION"-trial: Effect of chemotherapy alone versus chemotherapy plus trastuzumab, versus chemotherapy plus trastuzumab plus pertuzumab, in the perioperative treatment of HER2 positive, gastric and gastroesophageal junction adenocarcinoma on pathologic response rate: a randomized phase II-intergroup trial of the EORTC-Gastrointestinal Tract Cancer Group, Korean Cancer Study Group and Dutch Upper GI-Cancer group. *BMC cancer* 2019;**19**(1): 494.

132. Cunningham D, Stenning SP, Smyth EC, Okines AF, Allum WH, Rowley S, et al. Peri-operative chemotherapy with or without bevacizumab in operable oesophagogastric adenocarcinoma (UK Medical Research Council ST03): primary analysis results of a multicentre, open-label, randomised phase 2-3 trial. *Lancet Oncol* 2017;**18**(3): 357-370.

133. Vrana D, Matzenauer M, Neoral C, Aujesky R, Vrba R, Melichar B, et al. From Tumor Immunology to Immunotherapy in Gastric and Esophageal Cancer. *International journal of molecular sciences* 2018;**20**(1).

134. Kang YK, Boku N, Satoh T, Ryu MH, Chao Y, Kato K, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017;**390**(10111): 2461-2471.

135. Jeurnink SM, van Eijck CH, Steyerberg EW, Kuipers EJ, Siersema PD. Stent versus gastrojejunostomy for the palliation of gastric outlet obstruction: a systematic review. *BMC gastroenterology* 2007;**7**: 18.

136. Ernberg A, Kumagai K, Analatos A, Rouvelas I, Swahn F, Lindblad M, et al. The Added Value of Partial Stomach-partitioning to a Conventional Gastrojejunostomy in the Treatment of Gastric Outlet Obstruction. *J Gastrointest Surg* 2015;**19**(6): 1029-1035.

137. Kumagai K, Rouvelas I, Ernberg A, Persson S, Analatos A, Mariosa D, et al. A systematic review and meta-analysis comparing partial stomach partitioning gastrojejunostomy versus conventional gastrojejunostomy for malignant gastroduodenal obstruction. *Langenbeck's archives of surgery / Deutsche Gesellschaft fur Chirurgie* 2016;**401**(6): 777-785.

138. Matsumoto S, Takayama T, Wakatsuki K, Tanaka T, Migita K, Ito M, et al. Palliative Surgery for Gastric Cancer with Gastric Outlet Obstruction or Anemia due to Tumor Bleeding. *Hepatogastroenterology* 2015;**62**(140): 1041-1046.

139. Jwo SC, Chien RN, Chao TC, Chen HY, Lin CY. Clinicopathological features, surgical management, and disease outcome of perforated gastric cancer. *Journal of surgical oncology* 2005;**91**(4): 219-225.

140. Hata T, Sakata N, Kudoh K, Shibata C, Unno M. The best surgical approach for perforated gastric cancer: one-stage vs. two-stage gastrectomy. *Gastric Cancer* 2014;**17**(3): 578-587.

141. Hartgrink HH, Putter H, Klein Kranenbarg E, Bonenkamp JJ, van de Velde CJ, Dutch Gastric Cancer G. Value of palliative resection in gastric cancer. *Br J Surg* 2002;**89**(11): 1438-1443.

142. Fujitani K, Yang HK, Mizusawa J, Kim YW, Terashima M, Han SU, et al. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial. *Lancet Oncol* 2016;**17**(3): 309-318.

143. Huang KH, Wu CW, Fang WL, Chen JH, Lo SS, Wang RF, et al. Palliative resection in noncurative gastric cancer patients. *World J Surg* 2010;**34**(5): 1015-1021.

144. Wang CS, Chao TC, Jan YY, Jeng LB, Hwang TL, Chen MF. Benefits of palliative surgery for far-advanced gastric cancer. *Chang Gung Med J* 2002;**25**(12): 792-802.

145. Coburn NG, Lourenco LG, Rossi SE, Gunraj N, Mahar AL, Helyer LK, et al. Management of gastric cancer in Ontario. *Journal of surgical oncology* 2010;**102**(1): 54-63.

146. Le A, Berger D, Lau M, El-Serag HB. Secular trends in the use, quality, and outcomes of gastrectomy for noncardia gastric cancer in the United States. *Ann Surg Oncol* 2007;**14**(9): 2519-2527.

147. Glimelius B, Ekstrom K, Hoffman K, Graf W, Sjoden PO, Haglund U, et al. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 1997;**8**(2): 163-168.

148. Murad AM, Santiago FF, Petroianu A, Rocha PR, Rodrigues MA, Rausch M. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. *Cancer* 1993;**72**(1): 37-41.

149. Pyrhonen S, Kuitunen T, Nyandoto P, Kouri M. Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. *Br J Cancer* 1995;**71**(3): 587-591.

150. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. *Lancet* 2010;**376**(9742): 687-697.

151. Tabernero J, Hoff PM, Shen L, Ohtsu A, Shah MA, Cheng K, et al. Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (JACOB): final analysis of a double-blind, randomised, placebo-controlled phase 3 study. *Lancet Oncol* 2018;**19**(10): 1372-1384.

152. Pavlakis N, Sjoquist KM, Martin AJ, Tsobanis E, Yip S, Kang YK, et al. Regorafenib for the Treatment of Advanced Gastric Cancer (INTEGRATE): A Multinational Placebo-Controlled Phase II Trial. *J Clin Oncol* 2016;**34**(23): 2728-2735.

153. Thuss-Patience PC, Kretzschmar A, Bichev D, Deist T, Hinke A, Breithaupt K, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer--a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *European journal of cancer* 2011;**47**(15): 2306-2314.

154. Bohner H, Zimmer T, Hopfenmuller W, Berger G, Buhr HJ. Detection and prognosis of recurrent gastric cancer--is routine follow-up after gastrectomy worthwhile? *Hepatogastroenterology* 2000;**47**(35): 1489-1494.

155. Eom BW, Ryu KW, Lee JH, Choi IJ, Kook MC, Cho SJ, et al. Oncologic effectiveness of regular follow-up to detect recurrence after curative resection of gastric cancer. *Ann Surg Oncol* 2011;**18**(2): 358-364.

156. Kodera Y, Ito S, Yamamura Y, Mochizuki Y, Fujiwara M, Hibi K, et al. Follow-up surveillance for recurrence after curative gastric cancer surgery lacks survival benefit. *Ann Surg Oncol* 2003;**10**(8): 898-902.

157. Fukase K, Kato M, Kikuchi S, Inoue K, Uemura N, Okamoto S, et al. Effect of eradication of Helicobacter pylori on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. *Lancet* 2008;**372**(9636): 392-397.

158. Adachi S, Kawamoto T, Otsuka M, Todoroki T, Fukao K. Enteral vitamin B12 supplements reverse postgastrectomy B12 deficiency. *Ann Surg* 2000;**232**(2): 199-201.

159. Prodan CI, Bottomley SS, Vincent AS, Cowan LD, Greenwood-Van Meerveld B, Holland NR, et al. Copper deficiency after gastric surgery: a reason for caution. *The American journal of the medical sciences* 2009;**337**(4): 256-258.

160. Rino Y, Yamamoto Y, Wada N, Yukawa N, Murakami H, Tamagawa H, et al. Changes in vitamin D after gastrectomy. *Gastric Cancer* 2007;**10**(4): 228-233.

161. Ueda N, Suzuki Y, Rino Y, Takahashi T, Imada T, Takanashi Y, et al. Correlation between neurological dysfunction with vitamin E deficiency and gastrectomy. *Journal of the neurological sciences* 2009;**287**(1-2): 216-220.

162. Linder G, Lindblad M, Djerf P, Elbe P, Johansson J, Lundell L, et al. Validation of data quality in the Swedish National Register for Oesophageal and Gastric Cancer. *Br J Surg* 2016.

163. NREV, Kvalitetsregisterrapporter matstrups- och magsäckscancer. https://www.cancercentrum.se/samverkan/cancerdiagnoser/matstrupe-och-magsack/kvalitetsregister/rapporter/.

164. Busweiler LAD, Jeremiasen M, Wijnhoven BPL, Lindblad M, Lundell L, van de Velde CJH, et al. International benchmarking in oesophageal and gastric cancer surgery. *BJS Open* 2019;**3**(1): 62-73.

165. Claassen YHM, Bastiaannet E, Hartgrink HH, Dikken JL, de Steur WO, Slingerland M, et al. International comparison of treatment strategy and survival in metastatic gastric cancer. *BJS Open* 2019;**3**(1): 56-61.

166. de Steur WO, Henneman D, Allum WH, Dikken JL, van Sandick JW, Reynolds J, et al. Common data items in seven European oesophagogastric cancer surgery registries: towards a European upper GI cancer audit (EURECCA Upper GI). *Eur J Surg Oncol* 2014;**40**(3): 325-329.

167. Dikken JL, van Sandick JW, Allum WH, Johansson J, Jensen LS, Putter H, et al. Differences in outcomes of oesophageal and gastric cancer surgery across Europe. *Br J Surg* 2013;**100**(1): 83-94.

168. Jeremiasen M, Linder G, Hedberg J, Lundell L, Bjor O, Lindblad M, et al. Improvements in esophageal and gastric cancer care in Sweden-population-based results 2007-2016 from a national quality register. *Dis Esophagus* 2019.

169. Klevebro F, Lindblad M, Johansson J, Lundell L, Nilsson M. Outcome of neoadjuvant therapies for cancer of the oesophagus or gastro-oesophageal junction based on a national data registry. *Br J Surg* 2016;**103**(13): 1864-1873.

170. Klevebro F, Nilsson K, Lindblad M, Ekman S, Johansson J, Lundell L, et al. Association between time interval from neoadjuvant chemoradiotherapy to surgery and complete histological tumor response in esophageal and gastroesophageal junction cancer: a national cohort study. *Dis Esophagus* 2019.

171. Kung CH, Song H, Ye W, Nilsson M, Johansson J, Rouvelas I, et al. Extent of lymphadenectomy has no impact on postoperative complications after gastric cancer surgery in Sweden. *Chinese journal of cancer research = Chung-kuo yen cheng yen chiu* 2017;**29**(4): 313-322.

172. Kung CH, Tsai JA, Lundell L, Johansson J, Nilsson M, Lindblad M. Nationwide study of the impact of D2 lymphadenectomy on survival after gastric cancer surgery. *BJS Open* 2020.

173. Linder G, Sandin F, Johansson J, Lindblad M, Lundell L, Hedberg J. Patient education-level affects treatment allocation and prognosis in esophageal- and gastroesophageal junctional cancer in Sweden. *Cancer epidemiology* 2018;**52**: 91-98.

174. Song H, Fang F, Valdimarsdottir U, Lu D, Andersson TM, Hultman C, et al. Waiting time for cancer treatment and mental health among patients with newly diagnosed esophageal or gastric cancer: a nationwide cohort study. *BMC cancer* 2017;**17**(1): 2.

175. Song H, Zhu J, Lu D, Fang F, Ye W, Lundell L, et al. Psychiatric morbidity and its impact on surgical outcomes for esophageal and gastric cancer patients: A nationwide cohort study. *Oncotarget* 2017;**8**(46): 81305-81314.

176. Barlow L, Westergren K, Holmberg L, Talback M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. *Acta Oncol* 2009;**48**(1): 27-33.

177. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011;**11**: 450.

178. Statistics Sweden, Register of Education. https://www.scb.se/vara-tjanster/bestalla-mikrodata/vilka-mikrodata-finns/individregister/registret-over-befolkningens-utbildning/.

179. Statistics Sweden, LISA. https://www.scb.se/vara-tjanster/bestalla-mikrodata/vilka-mikrodata-finns/longitudinella-register/longitudinell-integrationsdatabas-for-sjukforsakrings--och-arbetsmarknadsstudier-lisa/.

180. Statistics Sweden, Total Population Register. https://www.scb.se/vara-tjanster/bestalla-mikrodata/vilka-mikrodata-finns/individregister/registret-over-totalbefolkningen-rtb/.

181. National Board of Health and Welfare, Swedish Prescribed Drug Register. https://www.socialstyrelsen.se/statistik-och-data/register/alla-register/lakemedelsregistret/.

182. Wallerstedt SM, Wettermark B, Hoffmann M. The First Decade with the Swedish Prescribed Drug Register - A Systematic Review of the Output in the Scientific Literature. *Basic Clin Pharmacol Toxicol* 2016;**119**(5): 464-469.

183. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, et al. Postoperative pancreatic fistula: an international study group (ISGPF) definition. *Surgery* 2005;**138**(1): 8-13.

184. Japanese Gastric Cancer A. Japanese gastric cancer treatment guidelines 2014 (ver. 4). *Gastric Cancer* 2017;**20**(1): 1-19.

185. Brooke HL, Talback M, Hornblad J, Johansson LA, Ludvigsson JF, Druid H, et al. The Swedish cause of death register. *Eur J Epidemiol* 2017;**32**(9): 765-773.

186. Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad Olausson P, Bergman U, et al. The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf* 2007;**16**(7): 726-735.

187. Norgaard M, Ehrenstein V, Vandenbroucke JP. Confounding in observational studies based on large health care databases: problems and potential solutions - a primer for the clinician. *Clin Epidemiol* 2017;**9**: 185-193.

188. Japanese Gastric Cancer A. Japanese Classification of Gastric Carcinoma - 2nd English Edition. *Gastric Cancer* 1998;**1**(1): 10-24.

189. Maruyama K, Sasako M, Kinoshita T, Sano T, Katai H, Okajima K. Pancreas-preserving total gastrectomy for proximal gastric cancer. *World J Surg* 1995;**19**(4): 532-536.

190. de Steur WO, Hartgrink HH, Dikken JL, Putter H, van de Velde CJ. Quality control of lymph node dissection in the Dutch Gastric Cancer Trial. *Br J Surg* 2015;**102**(11): 1388-1393.