UiT The Arctic University of Norway

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Gastric Cancer surgery at the University Hospital of Northern Norway from 2007 to 2017, from open to minimal invasive surgery

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Preface

The surgical fields have always piqued an interest in me and thus have driven a significant part of my academic efforts. Gastroenterological surgery, being one of the major surgical specialties has brought me both frustration and joy. Complex and life-saving procedures, being at the front lines of both elective and emergency surgery world-wide.
Cancer being a major cause of death, is no exception to the daily objectives of a GI-surgical team.

The purpose of this study was to determine whether the introduction of a minimally invasive, more modern technique would lead to improvement for patients with gastric adenocarcinoma.

The question raised in this study was primarily directed at survival and post-operative complications between the two different surgical approaches. It was also interesting to determine if the degree of resection made a difference, as well as the time periods themselves.

My undivided gratitude and many thanks to my mentor Eirik Kjus Aahlin, for sharing his valuable time. Between being a consultant GI-surgeon and spending his few vacant hours with his family, he has guided me through the complexity of the field. Had it not been for his expertise on the subject, one would drown in the ocean of information and surely struggle.

As a final addendum to the preface I would like to thank the sensors for reading my thesis carefully and critically during the first evaluation. The work of pointing out both the qualities and especially the areas in need of improvement, has not gone unnoticed. I have made effort to refine my work and undoubtedly profited by learning even more about the topic.

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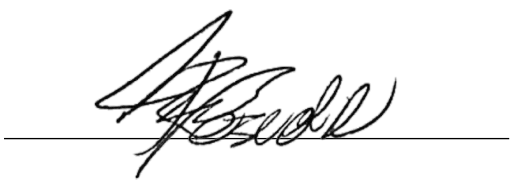

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Content

List of abbreviations

MIS	Minimally invasive surgery
NGICG	Norwegian Gastrointestinal Cancer Group
KLASS	Korean Laparoendoscopic gastrointestinal surgery study
LADG	Laparoscopy assisted distal gastrectomy
ODG	Open distal gastrectomy
JCOG	Japanese Clinical Oncology Group
JAMA	Journal of the American Medical Association
UNN	University hospital of Northern Norway
ECF	Epirubicin, Cisplatin and 5-FU
FLOT	Fluorouracil plus leucovorin, oxaliplatin and docetaxel
NET	Neuro Endocrine Tumor
GIST	Gastrointestinal Stromal Tumor
EPJ	Electronic Patient Journal
CD	Clavien-Dindo surgical complication score
TNM	Tumor Node Metastasis
RCT	Randomized controlled trial
EGC	Early Gastric Cancer
GEJ/EGJ	Gastro Esophageal junction/Esophago-gastric junction

Abstract

Background: Gastric cancer is one of the leading causes of cancer related death, world-wide. The most common type is adenocarcinoma, which account for 95% of all gastric tube cancers. Curative treatment always includes surgery and, with few exceptions, neoadjuvant and adjuvant chemotherapy. The surgical treatment of gastric cancer has changed from open to minimally invasive surgery in many centers around the world. Minimal invasive surgery has been associated with decreased length of stay and fewer complications compared to open surgery.

Our study aimed to investigate whether the introduction of minimally invasive gastrectomy for adenocarcinoma in the gastric tube was associated with similar benefits, as well as better survival rates at the University hospital of Northern Norway.

Methods: Minimal invasive gastric cancer surgery was introduced at the University Hospital of Northern Norway in 2012. 170 patients admitted for curative treatment of gastric adenocarcinoma, with either minimally invasive surgery or open surgery, in the period of 2007 to 2017 were included and studied retrospectively using SPSS 26 (IBM).

Results: Statistical analysis did not show a significant difference in survival using minimally invasive surgery compared to open surgery (p=0.45), nor a significant difference in survival between the two time periods (p=0.50). There was however a significant association between minimally invasive surgery and a decreased length of stay (p=0.009). Subtotal gastrectomy was associated with decreased length of stay (LOS) compared to total gastrectomy (Average LOS 8 vs. 13 days, p=0.005). There was no significant difference in severe complications between open and minimal invasive surgery (p=0.12), but significantly fewer severe complications were observed in the 2012-2017 period (p=0.007).

Conclusion: This study does not show increased survival, nor a reduction in postoperative complications using minimally invasive surgery to treat gastric adenocarcinoma, compared to open surgery. A significant reduction in length of stay and postoperative complications was observed in the recent years. Some of this might be associated with the introduction of minimal invasive surgery. Further research at the University hospital of Northern Norway is warranted.

Background

Gastric cancer is a malignant disease with decreasing incidence worldwide and especially in Europe and North America. The prognosis is gradually improving, yet poor compared to colorectal cancer. In 2012, Gastric cancer was the fifth most prevalent cancer, and the third leading cause of cancer-related death (1).

There are many risk factors for developing gastric cancer. One of the significant risk factors for gastric cancer is Helicobacter Pylori. Eradication of this bacteria is known to reduce the risk of developing gastric neoplasms, but even after eradication patients can develop gastric cancer (2). The decreasing prevalence of Helicobacter Pylori around the world is thought to be one of the reasons for the astonishing global decrease in gastric cancer. Mapping out the risk factors in a population where Helicobacter Pylori is far less prevalent is a complex task, but necessary to further reduce incidence. Thus, identifying modifiable risk factors is a key part in the prevention of gastric cancer. The reduction in salt-preservation of foods and the introduction of the electrically cooled refrigerator and freezer is discussed as partly responsible for reducing the incidence in the west (3). Although the northernmost region in Norway have had access to modern kitchen appliances for decades, a cultural culinary heritage, with salt as a preservative for both fish and meat, still yields a high salt intake. Another challenge is that the region has for a long time been on the top of national statistics on tobacco-use and alcohol consumption (4). Convincing data from Buckland et al., with results from the EPIC-cohort, showed that nearly 20% of all gastric cancer could be prevented if the participants had followed the healthy life style behaviors of their index (5). Buckland described non-smoking, no/low-alcohol consumption and adherence to the Mediterranean diet as key constructs in reducing chance of gastric cancer. The revised Mediterranean diet score coarsely consists of tertile scores 1-3 based on intake of fruit, vegetables, fresh fish and olive oil, as well as few other variables (6).

When preventative measures have come too short, and cancer has developed; the prognosis of gastric cancer is poor. In the period 2011-2015 the five-year relative survival rates in Norway were only 24.3% and 24.6% in men and women, respectively (7). The latest publication from the cancer registry of Norway (2018) shows an increase in five-year

survival; 27.8% in men and 26.7% in women (8). There are multiple modifiable and unmodifiable disease related factors associated with a worsened outcome. Examples being male gender, high age, cancer in an advanced stage, the lack of adherence to chemotherapy and major treatment related complications (9-15).

Another unmodifiable risk factor for developing gastric cancer is heritage and familial gastric cancers. The diseases are rare, but about 1-3% of gastric cancers are of the hereditary diffuse gastric cancer type with mutation in the tumor suppressor gene CDH1 (16). There are several other genes related to the development of gastrointestinal cancer, gastric cancer included (17). Gene-analysis is recommended if the patient is diagnosed with a diffuse stomach cancer before the age of 40 or there is a familial pattern, as well as annual screening in high risk population (16).

Minimally invasive surgery (MIS) is in general known to cause less post-operative immune suppression, shorter hospital stay and less pain (11). Complications both perioperatively and postoperatively along with prolonged hospital stays are in turn associated with worsened outcomes and increased mortality and morbidity (7, 18, 19). This is true for most types of surgical intervention, including gastric cancer (5).

There is a difference in incidence between the west and the east (20). Eastern countries have a higher incidence, thus a vast number of strong studies come from the Asian countries. Large randomized controlled trials (RCTs) from Asia have previously documented the non-inferiority of MIS when compared to open surgery. The Korean laparoendoscopic gastrointestinal surgery study (KLASS) with authors Kim, Kim, and Han et. al. published a phase 3 multicenter study in 2016, comparing laparoscopy-assisted distal gastrectomy (LADG) to open distal gastrectomy (ODG). The authors conclude that LADG is safe, and has the benefit of fewer wound complications compared to ODG (21). A year later a publication by the Japanese Clinical Oncology Group (JCOG) concluded that LADG was non-inferior compared to ODG regarding adverse events and short time survival. In the conclusion, they also stated the need for studies proving that the relapse free survival is better or non-inferior (22) with LADG in order to consider it an alternative to ODG. A recent study from the Chinese Laparoscopic surgery study (CLASS) published in the Journal of American Medical

Association (JAMA) by authors Yu, Huang, Sun et al. has relapse as a secondary outcome. The CLASS-01 study concludes that open surgery and MIS was equally safe and that there was no significant difference in recurrence between the two arms (23).

Prior to the fifth edition (2018) of the Norwegian national guidelines (NGICG), there were no recommendation of minimally invasive versus open surgery. The department of gastrointestinal surgery at the University Hospital of Northern Norway (UNN) introduced a change in surgical modality in 2012. Going from open surgery to minimally invasive surgery, when possible.

Gastrectomies were complimented with resection of at least 16 lymph nodes, using a modified D2-resection, in accordance with national guidelines since the first edition. A modified D2 is described in the nation guidelines as an extended lymph node dissection, entailing removal of nodes in station 1 to 12a, except for station 10 and without the removal of spleen and pancreas. The level of evidence to support this choice of lymph node resection changed from grade D (low level) in the first four editions, to grade A (high level) in the fifth and most recent guideline(16).

The MAGIC study from 2006 influenced the preferred oncological treatment of resectable gastric cancer in Norway. Perioperative chemotherapy with epirubicin, cisplatin and 5-FU (ECF) was inaugurated for stages II to III in 2007 as a result of the study. The study itself has been criticized, and several studies have shown a lack of long term benefit of the aforementioned chemotherapy-treatment (24, 25). The choice of chemotherapy has more recently been modified, with the FLOT-study by Al-Batran et. al. showing improved results for docetaxel-based triplet FLOT (fluorouracil plus leucovorin, oxaliplatin and docetaxel) (26).

Staging

Tumor, node, and metastasis

The Tumor-node-metastasis (TNM) classification is a method of categorizing neoplasms based on depth of invasion (see figure 1), lymph node involvement (figure 2) and metastasis.

Tis, the least invasive tumor category, only involves the epithelium - above the lamina propria. This T-status never constitutes advanced cancer and is along with T1 (without lymph node involvement or metastasis) the tumor stage with the highest survival rate (27).
T1 is characterized by infiltration through the lamina propria or through the submucosa. As the tumor progresses further and breaches through the muscularis propria or the subserosa it develops into T2. T3 involves the visceral peritoneum, but not further. As it invades deeper and involves organs and structures outside the serosa (visceral peritoneum) it is called T4; the highest T-status.

Lymph node involvement is determined by resection of at least 15 nodes surrounding the stomach and includes microscope examination of the nodes to evaluate the spread of tumor cells. The more lymph nodes that are affected, the higher the N-status becomes. N0 - zero lymph nodes, N1 involves 1-6 nodes. N2 is 7-15 and all above 15 is N3.

Metastasis is a dichotomized category with a M0 for no metastasis and M1 for confirmed distant metastasis.

Staging is a result of these three variables, as shown in Table 1. Higher stage involves a worsened prognosis (27).

Another term frequently used is early gastric cancer (EGC) and is defined by Murakami as "Carcinoma limited to the gastric mucosa and/or submucosa regardless of lymph node status." (28).

Siewert classification

The Siewert classification is a classification system based on the anatomical location of a tumor in the junction between the esophagus and the stomach (figure 3). This area is called the gastro-esophageal junction or the esophago-gastric junction (GEJ/EGJ) in the literature and is based upon the area proximal and distal to the anatomical cardia. (16).

Type I - tumor center is located between 5 and 1 cm proximal to the anatomical cardia.

Type II – tumor center is located between 1 cm proximal and 2 cm distal to the anatomical cardia. Type III – Tumor center is located between 2 and 5 cm distal to the anatomical cardia.

Clavien-dindo

The Clavien-dindo (CD) classification system for postoperative complications is considered a reliable tool for classifying complications in surgery regardless of borders and specialty (29). The classification system was developed to report complications in a similar manner across the world and different fields of surgery. The Clavien-Dindo group proposed a system that focuses on the level of treatment necessary to correct the complication.

The lowest grade (Grade I) of complication is defined as any deviation from the postoperative course, without the need for intervention. Grade II is defined as pharmacological treatment with drugs, blood transfusion and total parenteral nutrition. Grade III is surgical, endoscopic, or radiological intervention, and is divided into two separate subgroups depending on the need for general anesthesia or not. Grade IV is a life-threatening organ dysfunction/complication requiring intensive care management. This grade is also divided in two subgroups, depending on it being a single organ dysfunction or multiorgan dysfunction. Grade V is postoperative death.

The main objectives of this thesis were to analyze gastric cancer surgery at the University Hospital of Northern Norway, in a decade (2007-2017) when both perioperative chemotherapy and minimally invasive surgery were introduced. This in order to evaluate the efficacy of the new technique and most importantly determine if it is as safe as the open approach. Furthermore, we aimed to compare two patient cohorts: The period with mainly open surgery, 2007-2011, with the period with mainly minimally invasive surgery, 2012-2017. The primary outcomes were post-operative complications, length of stay and overall survival.

Method

Data collection

A total of 212 patients which underwent surgery for gastric cancer between March 2007 and December 2017 at the University hospital of Northern Norway (UNN) were included. Inclusion criteria were curative surgery for gastric cancer (adenocarcinoma) performed in the period 2007-2017 at UNN. 170 of the 212 resected tumors were adenocarcinoma, the remaining 42 being mostly neuroendocrine tumors (NET) and gastrointestinal stromal tumors (GIST) and thus excluded from the study. Thus, 170 adenocarcinoma gastric cancers were included in the study.

Our study is a retrospective cohort study, based on information gathered from electronic patient journal (EPJ) from a single center (UNN). Registration of death was done using passive follow-up in January of 2020, making the shortest follow up time two years.

The collected data was entered in a dataset and all data was collected through DIPS electronic patient journal (EPJ). The thesis protocol was presented to the hospital's PVO (Data protection officer at UNN) 16.10.18 through their internal reporting system.

Groups

Operative strategy for gastric cancer at UNN was determined according to tumor location and depth of invasion and were based on current recommendations from the Norwegian guidelines. Patients with gastric cancer should be evaluated and treatment planned by a multidisciplinary team consisting of radiologist, surgeon, oncologist, gastroenterologist and preferably a pathologist (16, 30-33).

Patients were dichotomized into male vs. female, elderly (≥60 years) vs. younger, open vs. minimal invasive surgery (MIS), total vs. subtotal gastrectomy, neoadjuvant chemotherapy vs. direct surgery, adjuvant vs. no adjuvant chemotherapy, Clavien-Dindo ≥ 3a vs. Clavien-Dindo 0-3 complications, anastomotic leak vs. no leak, deceased vs. living.

Ordinal variables, such as clinical stage, pathological stage, number of lymph nodes were also gathered. As well as other cancer specific variables, like histological classification.

Analysis

Statistical analyses were performed using SPSS version 26.0 (SPSS Inc, Chicago, IL). Variables were grouped into: Preoperative clinic, Surgical factors, complications, pathology studies, chemotherapy, metastases, and survival (table 2).

Statistical significance is defined as a p-value of 5% (0.05) or lower.

Descriptive analyses were performed using mean and median. Normality was tested using the Kolmogorov-Smirnov test.

Median survival to describe survival time was chosen. Distribution of survival time is often skewed to the right, because a large proportion of patients die relatively soon after diagnosis, whereas some survive for much longer. The median may thus present a more accurate estimate of survival time than mean.

Absolute frequencies (n) and the relative frequencies (%) were studied where relevant. 17 variables were grouped to non-modifiable factors, treatment related factors, complications and pathological factors as shown in tables 1 to 4.

Independent T-test was used to compare independent and normally distributed samples from the studied binominal variables. Mann-Whitney U test was applied where there was a small sample ($n<50$) and non-gaussian distribution (17). General linear model was used to adjust for covariates in univariate measurements.

Fischer exact test was used to measure difference between two unpaired groups with a binominal outcome (death within 1-year, major complication e.g.). Spearman correlation was used to test the strength of the association between to ordinal variables.

Kaplan-Meier was used as a descriptive survival analysis of all patients, as well as comparative between groups. Mantel-Cox/Log-rank was used to measure whether there was a significant difference in survival.

Simple linear regression was used to predict value from another measured variable. Multiple linear regression was then used to predict value from multiple measured or binominal variables.

Results

Descriptive statistics

Patient characteristics

In the period 2007-2017, 170 patients underwent resection for gastric adenocarcinomas at the University Hospital of Northern Norway. Distribution of gender was approximately 2:1 with 111 male patients (65%) and 59 female patients (35%) (table 3). The mean age for all patients were 69 years (35-88), with no difference between genders (p=0.54).

More patients were treated after 2011, with 95 cases in the 2012-2017 period (56%) vs. 75 resections between 2007 and 2011 (44%).

Surgical factors

Surgical approach in this study was categorized into laparotomy or laparoscopy. In total 170 resections were included and 101 (59%) were planned laparotomies. Of the 69 performed laparoscopies, a total of 16 (23%) were converted to open. Thus, the total number of laparoscopic gastrectomies were 53 (table 4). There was no statistically significant difference in TNM stage between the open vs. MIS group (p=0.94).

Type of resection was grouped into total and subtotal gastric resection in this study. 104 (61%) resections were categorized as a total resection. There was no statistically significant difference in pTNM stage between the subtotal and total group (p=0.56) (table 5).

Cancer stage and histology

The most prevalent stages were 2a and 2b (19% and 19%) using pathological TNM (pTNM) and staging. Most tumors affected the sub-serosa or deeper (T>2 = 55%). Signet ring cell carcinoma, which is considered a highly malignant subtype, was found in 32 (19%) of the resected specimens (table 6). There was no statistically significant difference stage between the signet vs no-signet group (p=0.30). 84 (49%) patients had no lymph node involvement on pathological examination. 156 (92%) had no metastasis on examination.

Chemotherapy

Approximately half of the population received neoadjuvant chemotherapy (49%) and about two fifths (41%) received adjuvant chemotherapy. There was significant difference between pathological stage for those who received neoadjuvant and those who did not (p=0.018). Those with advanced stage cancer received perioperative chemotherapy more often. There was a similar association between high pathological stage and concurrent adjuvant therapy (p=0.007).

Complications

Severe complications, categorized in this study as Clavien-Dindo (CD) greater than or equal to 3a, occurred in 42 (25%) patients (table 7).

Postoperative complications and length of stay

There was no significant difference in complication rates between the total vs. subtotal group (p=0.12) or the open vs. laparoscopic group (p=0.12). There was no change in significance when adjusted for age and gender using logistic regression. However, the period cohorts had a significant difference in the amount of severe complications with 26 cases in the first period vs. 16 in the later years (p=0.007).

Hospital stay was shortened from ≈13 days in the open group to ≈7 days in the MIS group (p=0.009). Similar results were shown with type of resection, subtotal gastrectomy had ≈8 days and total gastrectomy had ≈13 days on average (p=0.005). Length of stay also changed between the time periods, with longer in hospital stay for the earlier period (p=0.034).

Anastomotic leak

Anastomotic leak occurred in 16 patients (9%). There was no significant difference between the two surgical methods (p=0.43) or between the two time periods (p=0.98).

90-day mortality

A total of 5 patients died within the first month. 30-day mortality was ≈3%. Within the next 60 days; 2 more patients succumbed, giving a 90-day mortality of 4% (table 7). Cumulative 90-day survival is 96% in our population. In the period 2007-2011 93% survived, while in 2012-2017 there was a 98% survival. There was no significant difference between the periods (p=0.14).

Death within 1 year

31 patients (18%) died within one year. There was no significant difference in one-year mortality between the time periods (p=0.09) or open vs minimal invasive resection (p=0.07). There was however a significant association between subtotal vs. total gastrectomy and death within one year (p=0.004). There were fewer cases of death within one year in the subtotal-group (5 vs. 26).

Survival analysis

Actual 1-year survival for the entire population was 82% and estimated 5-year survival was 44% (Figure 4). Median survival for all groups was 3 years and 11 months.

Minimally invasive surgery vs. open surgery

MIS had a median survival time of 4 years and 4 months, and open surgery had 3 years and 2 weeks. The difference was not statistically significant (p=0.45). 1- and 5-year survival for MIS was 88% and 49%, respectively. Open surgery had 79% and 41%, respectively (Figure 5).

Total vs. subtotal gastrectomy

Total gastrectomy had a median survival time of 2 and a half years. While the subtotal group had a median survival time of 7 years and 4 months. The statistical difference was significant

(p=0.012). After five years the total resection group had 38% survival, while the sub-total group had 54% survival (Figure 6).

Time periods

In the 2007-2011 cohort the median survival time was just short of 3 years. The 2012-2017 cohort on the other hand had approximately 4 years and 4 months. There was however no significant difference (p=0.50). After five years the 2007-2011 cohort had 41% survival, while the 2012-2017 cohort had about 47% (Figure 7).

Discussion

During these ten years of Gastric cancer treatment at the University Hospital of Northern Norway there were 170 gastrectomies due to adenocarcinoma of the gastric tube. The goal of studying the implementation of a new surgical modality is to evaluate potential benefits of the new technique and equally important check for potential inferior results. MIS has become an important supplement to the modern surgical approach. MIS was significantly associated with decreased length of stay, but there was no statistically significant difference in severe complications or overall survival compared to open surgery in this study. These results do not differ from the general consensus currently.

Significantly shorter length of stay was observed after subtotal vs total gastrectomy. There was no significant difference in complications between subtotal and total gastrectomy. However, there was a difference in 5-year survival, survival after total gastrectomy was approximately 15% lower compared to subtotal gastrectomy (p=0.012). This might be indicative of several things. Gastroesophageal junction (GEJ) cancer is a known location for increasing incidence and a worse prognosis (34-36). A sub-total resection is the treatment of choice for distal-third and middle gastric cancer, as it provides similar rates of survival and better post-operative organ function. This is especially true in early stage disease (37). The use of subtotal resection is also related to a less advanced cancer (with less chance of micro-metastases (38)) and a smaller tumor size. In our study there was no significant difference in pathological stage between the total gastrectomy and subtotal group. See figure 1 and 3 for tumor growth and distribution, as well as Table 1 for staging.

Due to a higher incidence of gastric cancer in the east compared to the west, there has been an adoption of screening programs in countries like Japan and Korea. This allows for detection of early gastric cancer, and early surgical treatment. Cancer survival rates can be described as inversely proportional to cancer stage. Early gastric cancer has more than 90% five-year survival rate (39). One can theorize that this, at least in part, is a reason for the discrepancy between eastern and western survival. It is not the complete truth as there are studies showing a difference in survival even when stratified by stage (40). The implementation of a similar national screening program with the relatively low incidence in the Norwegian population might not be cost-effective, but there are certain indications for

annual screening with gastroscopy and multiple biopsies. Surveillance of hereditary gastric cancer is an example of this. Screening in hopes of early recognition and curative treatment might be the key to minimizing mortality and morbidity in patients with high risk for developing gastric cancer.

Overall, 5-year survival in Norway is expected to be between 35-50% in curatively treated gastric cancer, with a tendency towards large volume centers having the highest survival (16, 41). The numbers nationwide are slowly, but steadily improving. In our study UNN had an estimated 5-year survival of 44%, regardless of surgical modality and other factors such as stage. An important consideration in the population is the potentially increased risk of advanced cancer. This due to reduced accessibility to specialist health care (42) combined with a high prevalence of modifiable risk factors.

A total of 25% of treated patients had a severe complication. This is less than the national average of 28% in gastrectomies during the period 2016-2018, but it is considerably higher than optimal (43). Anastomotic leak was prevalent in 16 patients (9%). This is above the national treatment goal of <5% and the acceptable level of <8% (16, 43). There was no significant difference in anastomotic leak between the surgical techniques ($p=0.43$) or the time periods ($p=0.98$). Although complication rates are declining in the fields of surgery, increased operator experience, as well as more research on complication reducing factors and safe surgery should prompt better results for patients, as shown in several studies (44, 45).

2- year passive follow up/censor is an acceptable length of follow up, although actual five-year survival would be preferable. 170 patients make for a good number of cases in total. Adjusted for different variables some analyses are prone to become weaker due to a small number of cases, and in some instances cause type II statistical error. Passive follow-up might give an overestimation of the true survival rate: the error is due both to the reliability of the national registration process and to emigration of registered cases abroad**.** The results of this study are based on retrospective analyses, and therefore only associations. They are comparable with the latest numbers published by the national cancer registry and recent RCTs.

Conclusion

Outcome after treatment for gastric cancer are steadily improving nationwide, both in terms of mortality and morbidity (41). At the University Hospital of Northern Norway there has been a similar pattern. In this study there was no statistically significant difference in survival, as well as no significant difference in frequency of complications, between open and minimally invasive technique. A significant reduction in length of stay was observed in the recent years. Although many factors are at play, some of this might be associated with the introduction of minimal invasive surgery. There was a trend towards better survival in the latest period, but the difference was not statistically significant. This might be caused by the small size of the cohort. Further research at the gastrointestinal surgical ward at UNN, with longer follow up and a larger study population, as well as continued efforts to maximize patient outcome is warranted.

Ethics and disclosure

The patient data has been collected after treatment and all patients received the procedural course of treatment for their time of admission. The study has caused no change in treatment or outcome, on the contrary may be used to improve patient outcome in the future.

The project had no need for an external budget. All software licenses are paid for by the University of Tromsø.

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Figures

Figure 1(46):

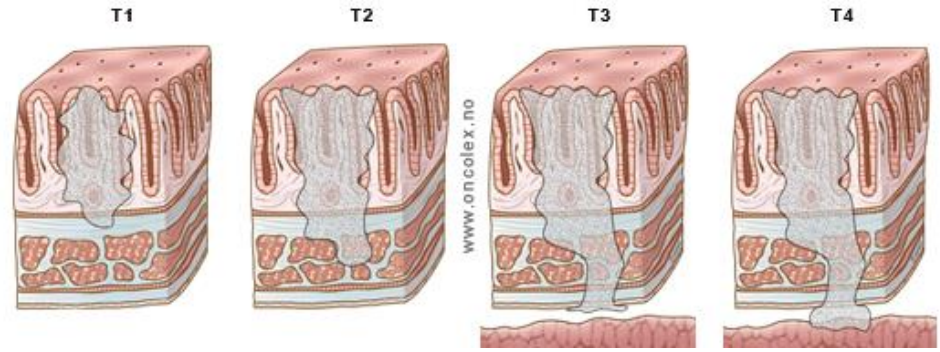


Figure 1: Tumor distribution and classification according to invasion through mucosal layers.

Figure 2(47):

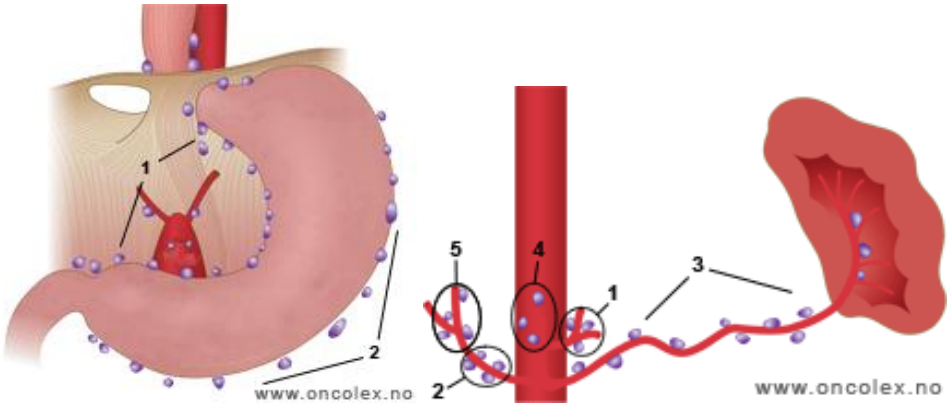


Figure 2: Perigastric lymph nodes along the minor and major curvature, as well as lymph nodes along the arteries supplying and surrounding the stomach. The left image shows lymph nodes in the minor curvature (1) and the major curvature (2). The right image shows lymph nodes next to the left gastric artery (1), the common hepatic artery (2), the splenic artery (3), around the coeliac axis (4), and the duodenum as well as the liver (5).

Figure 3(48):

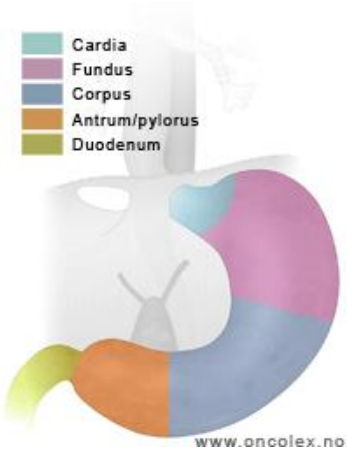


Figure 3: Anatomical description of the stomach. Commonly used to describe tumor location.

Figure 4: Overall survival in the entire population

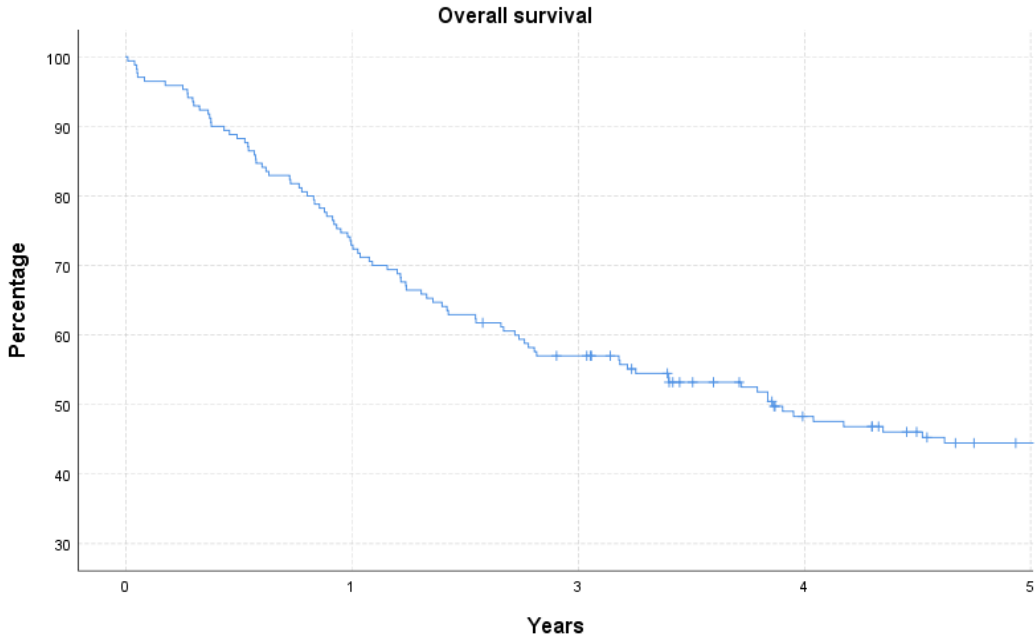
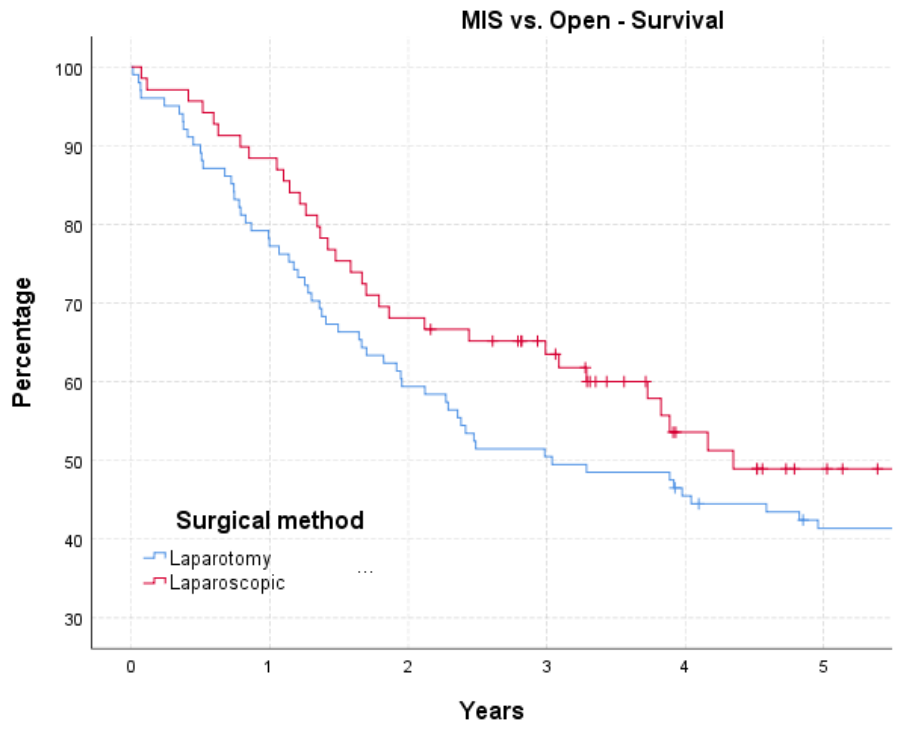


Figure 4: This figure shows up to five-year survival for the entire population.

Figure 5: Survival according to minimally invasive surgery (MIS) or open approach.



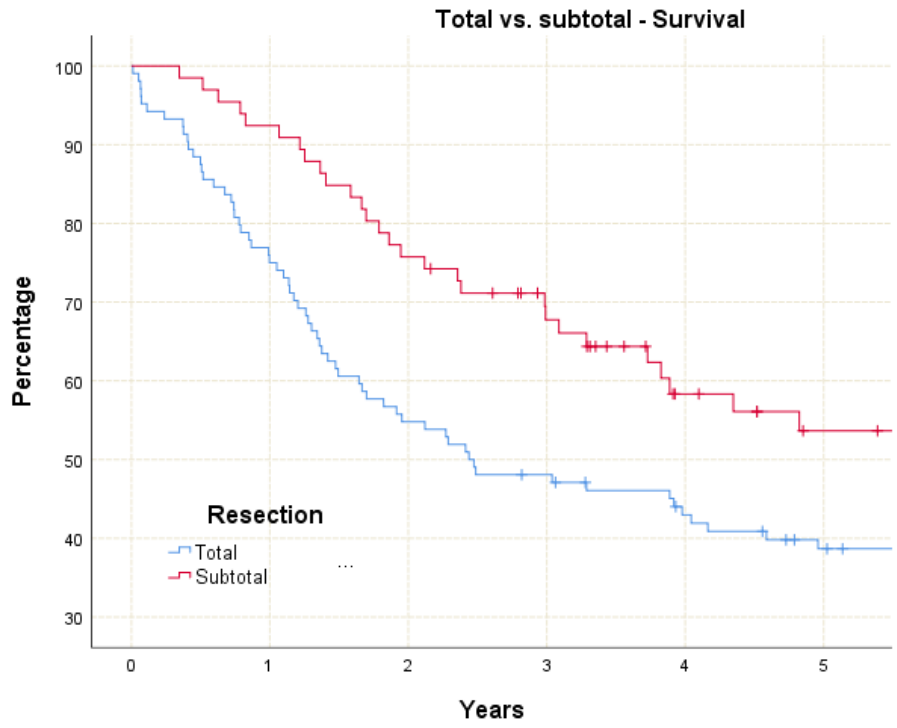
Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	,571	1	,450

Test of equality of survival distributions for the different levels of Surgical method.

Figure 5: This figure shows survival according to the two surgical methods, open vs. minimally invasive surgery. There was no statistically significant difference between the arms (p=0.45).

Figure 6: Survival according to total or subtotal approach



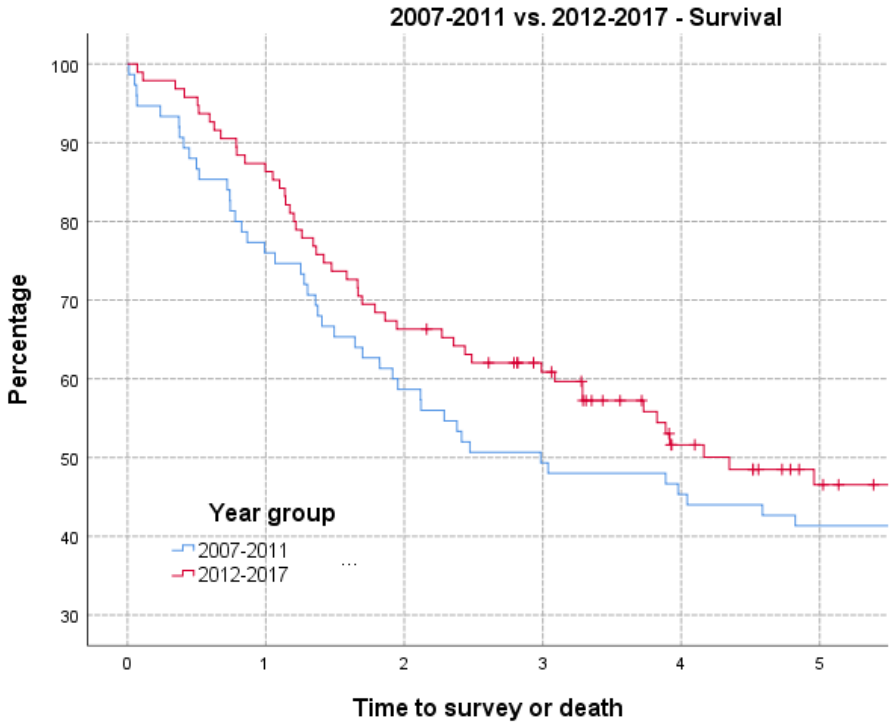
Overall Comparisons

	Chi-Square	Df	Sig.
Log Rank (Mantel-Cox)	6,299	1	,012

Test of equality of survival distributions for the different levels of Resection.

Figure 6: This figure shows survival according to grade of resection total vs. subtotal. There was a statistically significant difference in survival between the two resection types (p=0.012).

Figure 7: Survival according to time periods the surgery took place.



Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	,449	1	,503

Test of equality of survival distributions for the different levels of Year group.

Figure 7: This figure shows survival according to time periods the surgery took place. There was no statistically significant difference in survival between the time-periods (p=0,50).

Tables

Table 1: Tumor-Node-Metastasis (TNM) classification for determining cancer stage (49)

Stage TNM			
Stage	**T**	**N**	**M**
0/IA	Tis, T1	N0	M0
IA/IB	T1	N0, N1	M0
II	T1, T2, T3	N2, N1, N0	M0
IIIA	T2, T3, T4	N2, N1, N0	M0
IIIB	T3	N2	M0
IV	T1, T2, T3, T4	N0, N1	M1

Stage 1

Stage – the combined variables "depth of invasion, lymph node involvement and metastasis" determine the stage of cancer.

Table 2: All included variables	
Patient related factors	• Gender • Age • Time period
Preoperative clinic	- Preoperative histology - Preoperative CT; cTNM
Surgical	1. Resection type a. Subtotal b. Total 2. Surgical approach a. Minimally invasive b. Open
Complications	- Severe complication (Clavien-Dindo > 3) - Anastomotic leak - Mortality (90 days) - Treatment failure (1. year mortality)
Pathology	- Signet - Adenocarcinoma type - Stage - pTNM - Tumor (t) - Lymph nodes (n) - Metastasis(m) - Resection- status (R-status)
Chemotherapy	- Neoadjuvant or Directly to surgery - Adjuvant
All-cause mortality	- Number of years

Table 2: This table shows the variable list used for collecting data prior to analysis.

Table 3. Non-modifiable factors

Variable		Frequency (n)	Percent (%)
Gender	Male	111	65
	Female	59	35
Age	30-44	4	2
	45-59	24	14
	60-74	83	49
	75+	59	35
Year	2007-2011	75	44
	2012-2017	95	56

Table 3: This table shows the variable list of non-modifiable risk factors.

Table 4. Treatment related factors

Variable		Frequency (n)	Percent (%)
Adjuvant	Yes	69	41
	No	101	59
Neoadjuvant	Yes	84	49
	No	86	51
Surgical method	Laparotomy	101	59
	Laparoscopic	69	41
Type of resection	Total	104	61
	Subtotal	66	39

Table 4: This table shows the variable list of treatment related factors, such as chemotherapy and choice of modality.

Table 5. Distribution of pathological stage between the two arms

Stage	Open (n)	Minimally invasive (n)	Total (n)	Percent (%)
Stage 0	1	0	1	1
1a	13	9	22	13
1b	18	8	26	15
2a	17	16	33	19
2b	17	15	32	19
3a	15	9	24	14
3b	9	5	14	8
3c	2	2	4	2
4	5	0	5	3
CPR	4	5	9	5

Table 5. This table shows the distribution of stage between the two arms. Complete pathological response (CPR) is defined as disappearance of all invasive cancer after chemotherapy.

Table 6. Pathological factors

Variable		**Frequency (n)**	**Percent (%)**
Signet	No	138	81
	Yes	32	19
Stage			
	Stage 0	1	1
	1a	22	13
	1b	26	15
	2a	33	19
	2b	32	19
	3a	24	14
	3b	14	8
	3c	4	2
	4	5	3
	CPR	9	5

Variable		Frequency (n)	Percent (%)
Resection	R0	151	89
	R1	12	7
	CPR	7	4
Tumor	T1 or T2	68	40
	T3 or T4	93	55
	CPR	9	5
Node	No	84	49
	Yes	77	45
	CPR	9	5
Metastasis	No	156	92
	Yes	5	3
	CPR	9	5

Table 6. Complete pathological response (CPR) is defined as disappearance of all invasive cancer after chemotherapy.

Table 7. Complications

Variable		**Frequency (n)**	**Percent (%)**
Anastomotic leak	No	154	91
	Yes	16	9
Significant complication	CD > 3	128	75
	CD ≥ 3a	42	25

Variable		Frequency (n)	Percent (%)
Alive after one year	Yes	139	82
	No	31	18
90-day mortality	2007-2011	5	7
	2012-2017	2	2

Table 7. Clavien-dindo (CD) is a system of determining post-operative complication from I to V

Appendix

Contract with the supervisor/mentor

Vedlegg 1: VEILEDNINGSKONTRAKT FOR MASTEROPPGAVE MEDISIN VED DET HELSEVITENSKAPELIGE FAKULTET

Kontrakten leveres Seksjon for utdanningstjenester, Det helsevitenskapelige fakultet.

1 STUDENTENS PERSONALIA

Etternavn: ROSVOLD
Fornavn: SONDRE
Studieadresse: SKIPPERGATA 14G
Postnummer/-sted: 9008, TROMSØ
Telefon: 90365061

2 AVTALEPERIODE

Avtalen gjelder fra 27.9.18 til 27.9.20

3 VEILEDNING

Angi hovedveileder og biveileder(e). En av veilederne må være fast vitenskapelig ansatt ved Det helsevitenskapelige fakultet. Hvis veileder planlegger å ha forskningstermin i kontraktsperioden, skal studenten informeres om dette når prosjektbeskrivelsen utarbeides. Veileder er i samarbeid med enheten ansvarlig for å sikre studenten veiledning i hele kontraktsperioden.

Veileders navn og institutt EIRIK KJUS AAHLIN, IKM
Biveileders navn og institutt
Biveileders navn og institutt
Veileder skal ha forskningstermin i perioden:

Veilederen skal:

- gi råd om formulering og avgrensing av tema og problemstilling
- drøfte og vurdere hypoteser og metoder
- gi hjelp til orientering i faglitteratur og datagrunnlag (bibliotek, arkiv, etc.)
- drøfte opplegg og gjennomføring av fremstillingen (disposisjon, språklig form, dokumentasjon etc.)

- holde seg orientert om progresjonen i masterstudentens arbeid, og vurdere den i forhold til prosjektplanen, drøfte resultater og tolkningen av disse
- gi studenten veiledning i forskningsetiske spørsmål knyttet til forskningsprosjektet

Studenten forplikter seg til å legge fram rapporter eller utkast til deler av oppgaven for veileder, samt i sitt arbeid å etterleve forskningsetiske prinsipper som gjelder for fagområdet.

Begge parter har krav på jevnlig kontakt og orientering under arbeidets gang.

4 MASTEROPPGAVEN

Tittel: GASTRIC CANCER SURGERY AT UNN – BENEFITS FROM MIN. INV. SURG?

5 RESSURSBRUK

Enhet prosjektet skal utføres ved: V.I.T.
Samarbeidspartnere av teknisk eller vitenskapelig art: .....

6 ENDRINGER/BRUDD PÅ KONTRAKTEN

Alle endringer i veiledningskontrakten underveis i studiet (endring av prosjekt, veileder, forlengelse av kontraktsperiode og lignende) skal informeres om til Seksjon for forskningstjenester ved Det helsevitenskapelige fakultet.

Brudd på kontrakten skal behandles av Konfliktrådet ved det Helsevitenskapelige fakultet.

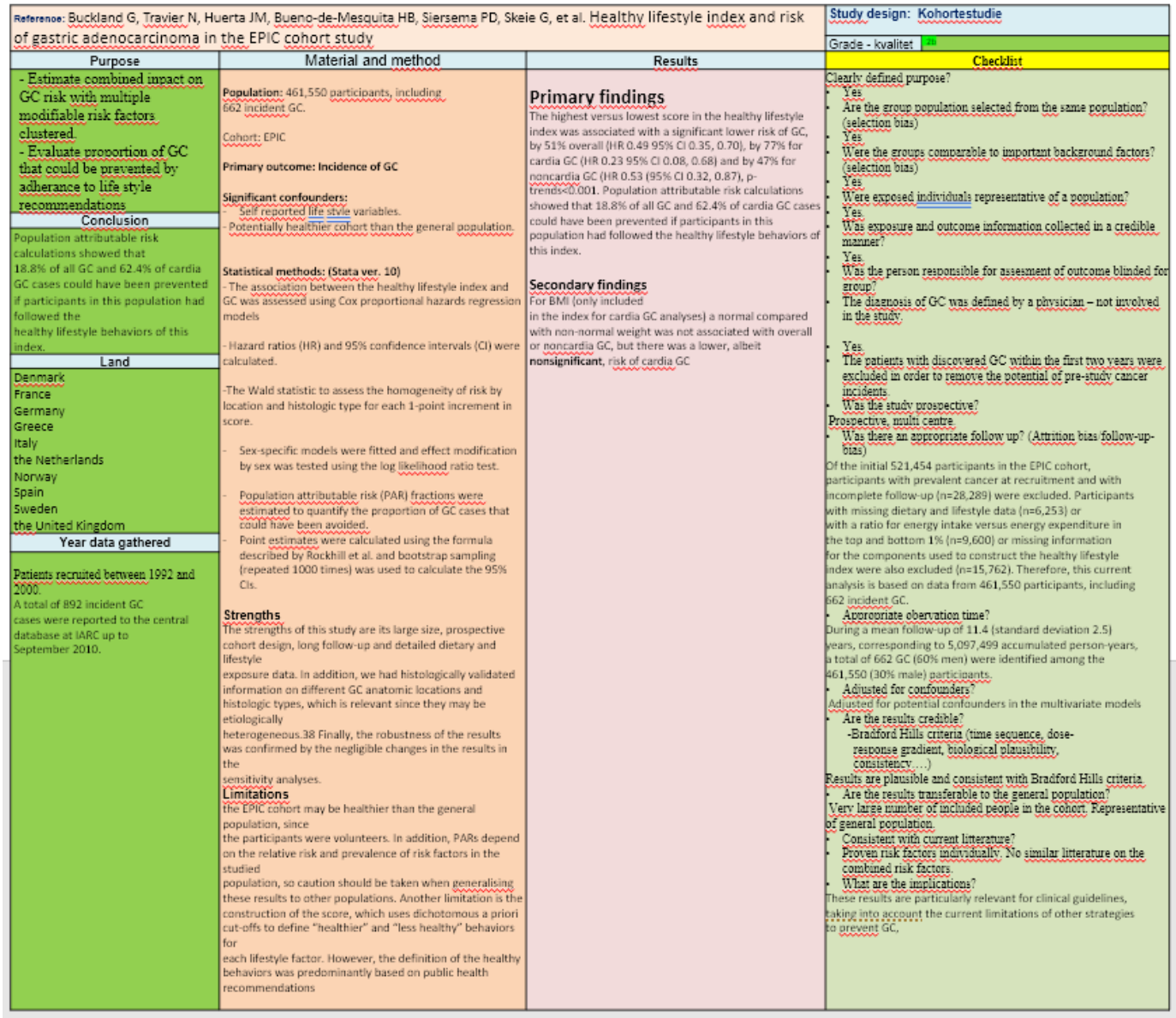
7 UNDERSKRIFTER

Undertegnede er kjent med ovenstående retningslinjer som legges til grunn for samarbeidet i den faglige veiledning. Det er både veileders og studentens ansvar at planen blir fulgt, både innholds- og framdriftsmessig.

	Sted/dato:	Underskrift:
Veileder:	27.9.18	
Biveileder:		
(Biveileder):		
Student:	27.9.18	

Summary of GRADE

(5)



Reference: Buckland G, Travier N, Huerta JM, Bueno-de-Mesquita HB, Siersema PD, Skeie G, et al. Healthy lifestyle index and risk of gastric adenocarcinoma in the EPIC cohort study

Study design: Kohortestudie

Grade - kvalitet 2b

Purpose	Material and method	Results	Checklist
- Estimate combined impact on GC risk with multiple modifiable risk factors clustered. - Evaluate proportion of GC that could be prevented by adherance to life style recommendations **Conclusion** Population attributable risk calculations showed that 18.8% of all GC and 62.4% of cardia GC cases could have been prevented if participants in this population had followed the healthy lifestyle behaviors of this index. **Land** Denmark France Germany Greece Italy the Netherlands Norway Spain Sweden the United Kingdom **Year data gathered** Patients recruited between 1992 and 2000. A total of 892 incident GC cases were reported to the central database at IARC up to September 2010.	**Population:** 461,550 participants, including 662 incident GC. Cohort: EPIC **Primary outcome: Incidence of GC** **Significant confounders:** - Self reported life style variables. - Potentially healthier cohort than the general population. **Statistical methods: (Stata ver. 10)** - The association between the healthy lifestyle index and GC was assessed using Cox proportional hazards regression models - Hazard ratios (HR) and 95% confidence intervals (CI) were calculated. -The Wald statistic to assess the homogeneity of risk by location and histologic type for each 1-point increment in score. - Sex-specific models were fitted and effect modification by sex was tested using the log likelihood ratio test. - Population attributable risk (PAR) fractions were estimated to quantify the proportion of GC cases that could have been avoided. - Point estimates were calculated using the formula described by Rockhill et al. and bootstrap sampling (repeated 1000 times) was used to calculate the 95% CIs. **Strengths** The strengths of this study are its large size, prospective cohort design, long follow-up and detailed dietary and lifestyle exposure data. In addition, we had histologically validated information on different GC anatomic locations and histologic types, which is relevant since they may be etiologically heterogeneous.38 Finally, the robustness of the results was confirmed by the negligible changes in the results in the sensitivity analyses. **Limitations** the EPIC cohort may be healthier than the general population, since the participants were volunteers. In addition, PARs depend on the relative risk and prevalence of risk factors in the studied population, so caution should be taken when generalising these results to other populations. Another limitation is the construction of the score, which uses dichotomous a priori cut-offs to define "healthier" and "less healthy" behaviors for each lifestyle factor. However, the definition of the healthy behaviors was predominantly based on public health recommendations	**Primary findings** The highest versus lowest score in the healthy lifestyle index was associated with a significant lower risk of GC, by 51% overall (HR 0.49 95% CI 0.35, 0.70), by 77% for cardia GC (HR 0.23 95% CI 0.08, 0.68) and by 47% for noncardia GC (HR 0.53 (95% CI 0.32, 0.87), p-trends<0.001. Population attributable risk calculations showed that 18.8% of all GC and 62.4% of cardia GC cases could have been prevented if participants in this population had followed the healthy lifestyle behaviors of this index. **Secondary findings** For BMI (only included in the index for cardia GC analyses) a normal compared with non-normal weight was not associated with overall or noncardia GC, but there was a lower, albeit **nonsignificant**, risk of cardia GC	Clearly defined purpose? • Yes • Are the group population selected from the same population? (selection bias) Yes • Were the groups comparable to important background factors? (selection bias) Yes • Were exposed individuals representative of a population? Yes • Was exposure and outcome information collected in a credible manner? Yes • Was the person responsible for assesment of outcome blinded for group? The diagnosis of GC was defined by a physician – not involved in the study. Yes • The patients with discovered GC within the first two years were excluded in order to remove the potential of pre-study cancer incidents. • Was the study prospective? Prospective, multi centre. • Was there an appropriate follow up? (Attrition bias/follow-up-bias) Of the initial 521,454 participants in the EPIC cohort, participants with prevalent cancer at recruitment and with incomplete follow-up (n=28,289) were excluded. Participants with missing dietary and lifestyle data (n=6,253) or with a ratio for energy intake versus energy expenditure in the top and bottom 1% (n=9,600) or missing information for the components used to construct the healthy lifestyle index were also excluded (n=15,762). Therefore, this current analysis is based on data from 461,550 participants, including 662 incident GC. • Appropriate observation time? During a mean follow-up of 11.4 (standard deviation 2.5) years, corresponding to 5,097,499 accumulated person-years, a total of 662 GC (60% men) were identified among the 461,550 (30% male) participants. • Adjusted for confounders? Adjusted for potential confounders in the multivariate models • Are the results credible? -Bradford Hills criteria (time sequence, dose-response gradient, biological plausibility, consistency…) Results are plausible and consistent with Bradford Hills criteria. • Are the results transferable to the general population? Very large number of included people in the cohort. Representative of general population. • Consistent with current litterature? • Proven risk factors individually. No similar litterature on the combined risk factors. • What are the implications? These results are particularly relevant for clinical guidelines, taking into account the current limitations of other strategies to prevent GC.

C

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Reference: Cook et al. Sex Disparities in Cancer Mortality and Survival Cancer Epidemiol Biomarkers Prev. 2011 August ;20(8): 1629–1637. doi: 10.1158/1055-9965.EPI-11-0246.			**Study design: Cohort** Grade 2a
Purpose	Material and method	**Results**	**Checklist**
Systematic comparisons of cancer mortailty and survival between males and females. **Conclusion** Male-to-female MRRs differed markedly while cancer survival disparities were much less pronounced. This suggests that sex-related cancer disparities are more strongly related to etiology than prognosis. **Land** United states of America **Year data gathering** Data were restricted to individuals with a single primary diagnosis of malignant cancer diagnosed during 1973–2006.	**Population: SEER – among 400.000 cancer cases** - 76687 stomach cancer patients. Cohort: NCHS – National Center for Health Statistics SEER – Surveillance Epidemiology and End Results **Primary outcome:** Death **Significant confounders** Not adjusted for most variables related to mortality. **Statistical methods** Cox proportional hazards models, adjusted for age, stage, and grade, were used to test for sex differences in survival in the five years following cancer diagnosis. All analyses were adjusted for age at diagnosis (ten-year age groups to 80+) and stratified by year of cancer diagnosis. • **Strengths** Strengths of this study include the use of a large, population-based cancer registry database. In addition, SEER has extensive quality control procedures • **Limitations** use of cause of death extracted from death certificates which is known to have problems and imperfections. However, inaccuracies are likely to be nondifferential by sex. Lack of information on co-morbidities and only having adjusted for stage and grade, which may be suboptimal for certain cancers. The results are not perfectly generalizable to the total US population due to the fact that the data are restricted to the 17 cancer registries currently in SEER.	**Primary findings** For the vast majority of cancers, age-adjusted mortality rates were higher among males than females with the highest male-to-female MRR for lip (5.51), larynx (5.37), hypopharynx (4.47), esophagus (4.08) and urinary bladder (3.36). Cancer-specific survival was, for most cancers, worse for males than females, but such disparities were drastically less than corresponding MRRs; e.g., lip (HR = 0.93), larynx (1.09), hypopharynx (0.98), esophagus (1.05), and urinary bladder (0.83). **Secondary findings** Stomach adjusted for age - HZ 1.04 (CI 1.02–1.06) P<0.001	• Is the purpose of the study clearly presented? Yes • Are the the groups recruited from the same population • The patients were all recruited from the general population of USA at the time of diagnosis. SEER cohort. • Were the groups comparable according to important background factors? • Yes. • Was exposure and outcomes measured appropriately? (Classification bias) ** • Yes. • Was the registrar of primary outcomes properly blinded for group status? • Not relevant. Death as an outcome is not affected by groups. • Was the study prospective? • No. • Was there an appropriate follow up time? • Yes. • Are the results credible? -Yes, according to the Bradford Hills criteria (time sequence, dose-response gradient, biological plausibility, consistency….) Plausible data • Are the results transferable to the general population? • Not directly. • Consistent with other studies? • Most studies on the subject. • What are the implications? • Not much, potentially useful for screening and public information.

(12)

Referanse: Sun F, Sun H, Mo X, et al. Increased survival rates in gastric cancer, with a narrowing gender gap and widening socioeconomic status gap: a period analysis from 1984 to 2013. J Gastroenterol Hepatol 2018; 33: 837-46.75			**Study design: Cohort** Grade IIc – Outcome research with potential confounderss
Purpose	Material og method	**Results**	**Checklist**
explore the change of GC incidence and survival rates by age, gender, race, and socioeconomic status (SES) **Conclusion** The analysis demonstrated the decreased incidence and increased survival rate of GC. In addition, lower SES was associated with lower survival rates. **Land** United States of America **Year – data gathered** Data registered from 1984 to 2013	**Population: 87242 cases of GC** Cohort: SEER program - National Cancer Institute of the United States **Primary outcome: Death** **Statistical methods:** - **Kaplan-Meier to estimate relative survival rates** - **Cox Regression analysis to compare groups and variables**	**Primary findings** **Betweem exposes/unexposed:** During these three decades, the incidence of GC was 7.4, 6.8, and 5.5 per 100 000 individuals in each decade. The 1-year relative survival rates (RSRs) improved from 42.4% to 44.3% to 49.0% (P < 0.0001), with a larger increase seen in the third decade. However, the long-term survival rates remained low (from 17.8% to 20.3% to 22.9% for the 5-year RSRs, P < 0.0001; from 14.1% to 16.4% to 18.6% for the 10-year RSRs, P < 0.0001). **Secondary findings** With respect to the 12-month RSRs in the first decade, females exhibited higher RSRs than males (43.8% vs 41.6%, P < 0.01), but the RSRs of males increased more rapidly; the superiority of females in terms of the RSR disappeared, and instead, the RSR was superior in males over the next two decades (43.9% vs 44.5%; 47.3% vs 50.0%, P < 0.0001). However, none of the differences in the RSRs of the different age groups in the third decade were statistically significant.	• Is the purpose of the study clearly presented? Yes • Are the the groups recruited from the same population • The patients were all recruited from the general population of USA at the time of diagnosis. • Were the groups comparable according to important background factors? • Background factors were used as variables for risk stratification, thus they were carefully evaluated. • Was exposure and outcomes measured appropriately? (Classification bias) ** • All data came from the national registry of cancer. We must assume that this was done correctly, but one can never be certain there was never an erronous filing. • Was the registrar of primary outcomes properly blinded for group status? • Not relevant. Death as an outcome is not affected by groups. • Was the study prospective? • No. Retrospective over 30-years. • Was there an appropriate follow up time? • Yes. • Are the results credible? -Yes, according to the Bradford Hills criteria (time sequence, dose-response gradient, biological plausibility, consistency….) Plausible data • Can the results be transfered to the general population? Multiple risk factors are not modifiable, yet the subjects of the study are equal to those of the gen.pop. Are the results similar to other studies? • Similar results are the general understanding and consensus • Does the study lead to any real world benefit? **Targeted screening is easier when we know the population at risk for developing and suffering from high mortality.**

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Reference: S. D. Nelen et al. Increasing survival gap between young and elderly gastric cancer patients Gastric Cancer (2017) 20:919–928 DOI 10.1007/s10120-017-0708-7

Study design: Cohort

Grade IIb

Purpose	Materials og method	Results	Checklist
This study investigates the treatment and survival of young versus elderly potentially curable gastric cancer patients in the Netherlands. **Conclusion** There was a major increase in the proportion of patients treated with resection and chemotherapy after 2004–2008. Multivariable Cox regression analyses confirmed that overall survival improved for young and elderly patients. **Land** The Netherlands **Year data collection** Data ranging from 1989-1993 and 2009-2013.	**Population:** 8107 young and 13,814 elderly gastric cancer patients were included. Kohorter: population-based Netherlands Cancer Registry (NCR) - the total Dutch population of approximately 17 million inhabitants. **Primary outcome:** Surgical treatment and death **Significant confounders** selection bias, as fitter patients are likelier to be treated more extensively and included in this study. The limitations of this study are the lack of data on comorbidity, performance status, and the possible contributing reasons to forgo surgery or chemotherapy. These factors are known to impact treatment choice and survival. **Statistical methods** Descriptive statistics were used to characterize the patients the young and elderly patients. Univariable and multivariable logistic regression analyses were performed for young and elderly patients to examine the influence of different clinicopathological factors with regard to patients undergoing surgery and Chemotherapy Kaplan–Meier curves were generated to examine the overall survival for young and elderly patients over sequential periods. Multivariable Cox regression analyses were performed for young and elderly patients to investigate the influence of various patient-, tumor-, and treatment-specific variables on overall survival over time.	**Primary findings** In total, 8107 young and 13,814 elderly gastric cancer patients were included. There was a major increase in the proportion of patients treated with resection and chemotherapy after 2004–2008. In young patients the increase was from 2.6% in 1999–2003 to 63% in 2009–2013 (p=0.01). Also an increase was noticed among elderly patients, from 0.1% to 16% (p=0.01). Median survival increased from 2004 to 2008 onward particularly in young patients and to a lesser extent in elderly patients (from 28 to 41 months vs from 11 to 13 months). Multivariable Cox regression analyses confirmed that overall survival improved for young and elderly patients. **Secondary findings** Patients treated with both chemotherapy and resection have the highest survival rate in the study. --- **Strengths** The main strength of the study is the size of the study population and the fact that the study is based on nationwide population-based data, which makes it possible to investigate trends in treatment, survival, and the influence of various clinicopathological factors on treatment and survival, representing daily clinical practice. **Limitations** The limitations of this study are the lack of data on comorbidity, performance status, and the possible contributing reasons to forgo surgery or chemotherapy. These factors are known to impact treatment choice and survival.	Clearly defined purpose? • Yes • Are the group population selected from the same population? (selection bias) • Yes • Were the groups comparable to important background factors? (selection bias) • Yes • Were exposed individuals representative of a population? • Yes, the dutch nation • Was exposure and outcome information collected in a credible manner? • Outcome was defined by the national registry system • Was the person responsible for assesment of outcome blinded for groun? • Yes. • Was there an appropriate follow up? (Attrition bias/follow-up-bias) • Yes • Was the length of follow up appropriately long? • Yes. • Has there been adjustment for confounders? • Yes. • Are the results believable? -Bradford Hills criteria (time sequence, dose-response gradient, biological plausibility, consistency….) Yes. • Are the results transferable to the gen.pop.? • Yes. • IS this study supported by similar papers? • Yes. Most litterature on the topic. • What are the implications of this study? • Older patients with potentially curable non-cardia GC should recieve curative treatment as extensively as possible as long as they are physically fit.

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Reference: Leizhen Zheng, Chunxiao Wu, Pan Xi, Meiling Zhu, Li Zhang, Siyu Chen, Xiaoping Li, Jianchun Gu and Ying Zheng - The survival and the long-term trends of patients with gastric cancer in Shanghai, China BMC Cancer 2014, 14:300 http://www.biomedcentral.com/1471-2407/14/300

Study design: Cohort

Grade IIc

Purpose	Material and method	Results	Checklist
This study aims to describe the trends of long term survival as well as the age, sex, stage and tumor sites specific characteristics. **Conclusion** The survival probability of patients with gastric cancer in Shanghai has improved significantly during the last decades. Age, stage and site of tumor have an impact on prognosis. **Land** China **Year data gathered** obtained the 5-year follow-up data of gastric cancer patients diagnosed in 2002–2003. Last follow-up 31. dec. 2010.	**Population:**10909 newly diagnosed gastric cancer cases reported during 2002–2003 Cohorts: Shanghai Cancer Registry **Primary outcomes:** Death **Significant confounders:** >58% of cases were reported with unknown stages for unknown causes. On plausible reason is that they were not surgically treated, thus lowering the survival rate. **Statistical methods** Both observed and relative survival probabilities were estimated. Life tables were constructed to calculate the cumulative probability of survival at time ti+1 from the conditional probabilities of survival during consecutive intervals of follow-up time up to and including ti+1. Chi-Square test was used to compare the distribution between males and females. Log rank test was used to compare the survival rates with 95% confidence interval (CI). **Strengths** One strength of our study was that the databases were acquired from the Shanghai Cancer Registry, the oldest population based cancer registry in mainland China. Survival data obtained from a population-based cancer registry ideally portrays the average outcome of the disease which avoids the selective bias that commonly appears in hospital sourced cases. **Limitations** One limitation of this study is that there were 58.4% patients reported with unknown stages. It might be attributed to missing information or patients with unresected cancers. Secondly, it has been reported that cancer site-related factors may influence the outcome. However, due to the retrospective nature of the present study, we failed to obtain all the needed information for the sites which could have contributed to the bias in estimating the survival rate and thus the influence on the outcome. Thirdly, in the present study, we chose the "classical" relative survival method for cancer survival estimation which may not correctly estimate the population based net survival(Pohar et al.).	**Primary findings** We observed an increased trend of survival probability during the last decades. Patients diagnosed during 1972–1976 had a 5-years relative survival rate at 12% for males and 11% for females, respectively, which had dramatically increased to 30% for male and 32% for female patients respectively during the period of 2002–2003. Among the patients diagnosed in 2002–2003, the overall survival probability declined with patient's age at the time of diagnosis. The lowest survival rate was observed among the oldest group, with the median survival time of 0.8 years. Patients diagnosed with stage I had a higher relative survival rate. Patients with cardia cancer had the worst prognosis, with the 5-year relative survival rate of 29%. **Secondary findings** SES 47.1% living in the urban and 52.9% living in the suburb. Patients living in the urban had slightly higher survival rate compared with the patients in the suburb. Among them, there were 7038 (64.5%) males and 3871 (35.5%) females. Patients aged 65–84 years accounted for more than 58% of all cases.The proportion of patients being classified as stage I to IV was 5.5%, 9.9%, 12.4%, and 13.8% respectively, while 58.4% of cases were reported with "unknown stage". The gender difference of tumor sites was significant ($\chi 2 = 79.41$, $P < 0.001$). Malignant neoplasm of pyloric antrum account for 22.3% and 4796 (44.0%) cases were reported with unspecified sites.	Clearly defined purpose? • Yes • Are the group population selected from the same population? (selection bias) • Yes • Were the groups comparable to important background factors? (selection bias) • Yes • Were exposed individuals representative of a population? • Yes. • Was exposure and outcome information collected in a credible manner? • Yes. • Was the person responsible for assesment of outcome blinded for group? • Yes. • Ble mange nok personer i kohorten fulgt opp? (Attrition bias/follow-up-bias) • Yes. • Are there consideratoins for lost to follow up? At the time of the last follow-up (December 31, 2010), 8365 (76.7%) patients died, 2312 (21.2%) patients were alive, and 232 (2.1%) cases were lost to follow up. • Was there an appropriate follow up? (Attrition bias/follow-up-bias) • Yes • Was the length of follow up appropriately long? • Yes. • Has there been adjustment for confounders? • Yes. • Are the results believable? -Bradford Hills criteria (time sequence, dose-response gradient, biological plausibility, consistency…) Yes. • Are the results transferable to the gen.pop.? • Yes. • IS this study supported by similar papers? • Yes. Most litterature on the topic. • What are the implications of this study? Comparing to clinical survival study providing information about the treatment, the population-based survival study can evaluate the effectiveness of healthcare systems.

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