Student thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Clinical and Molecular Medicine

Ann Amelia Savage Ubøe, Christina Våge

Gastric remnant cancer and long-term survival in Central Norway 2001 to 2016 – a population-based study

Student thesis in Medicine Programme of Professional Study
Supervisor: Reidar Fossmark
Co-supervisor: Erling A. Bringeland
June 2023

NTNU
Norwegian University of Science and Technology

Ann Amelia Savage Ubøe, Christina Våge

Gastric remnant cancer and long-term survival in Central Norway 2001 to 2016 – a population-based study

Student thesis in Medicine Programme of Professional Study
Supervisor: Reidar Fossmark
Co-supervisor: Erling A. Bringeland
June 2023

Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Clinical and Molecular Medicine

NTNU
Norwegian University of
Science and Technology

Gastric remnant cancer and long-term survival in Central Norway 2001 to 2016 – a population-based study

Ann Amelia Savage Ubøe[1*], Christina Våge[1*], Patricia Mjønes [1,2], Erling A. Bringeland[1,3], Reidar Fossmark[1,4]

[1]Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology (NTNU), Trondheim, Norway

[2]Department of Pathology, St. Olav's hospital, Trondheim University Hospital, N-7006 Trondheim, Norway

[3] Department of Gastrointestinal Surgery, St Olav´s Hospital, Trondheim, Norway

[4]Department of Gastroenterology, St Olav´s Hospital, Trondheim, Norway

*Shared first co-authorship.

Keywords: gastric remnant cancer, survival, distal gastrectomy

Abstract

Introduction: Gastric remnant cancer (GRC) has been defined as a distinct clinical entity and is reported to account for 1-8% of all gastric cancers. In the current study we aimed to characterize patients with GRC and their survival in a large Western population-based cohort.

Materials and methods: Retrospective population-based cohort study including 1217 patients diagnosed with gastric adenocarcinoma in Central Norway 2001–2016. GRCs (n=78) were defined as adenocarcinomas arising in the residual stomach after distal gastrectomy and were compared to non-GRC overall (n=1139) and to proximal non-GRC (n=595). Minimum follow-up time was 6 years and 7 months.

Results: 78 (6.4 %) of gastric cancers were GRC. The annual number and proportion of GRC declined during the study period (p=0.003). Median latency from distal gastrectomy to GRC diagnosis was 37.6 years, and Billroth 2 reconstruction was most common (87.7%). Compared to control groups, GRC patients were more frequently males (83.3%), were diagnosed in earlier TNM stages and were older at diagnosis. A smaller proportion of GRC patients received perioperative or palliative chemotherapy. Overall median survival for GRC was 7.8 months, which did not differ from non-GRCs or proximal non-GRC. TNM stage and age were independently associated with mortality, whereas GRC was not.

Conclusions: GRCs declined during the study period, but the latency between distal gastrectomy and GRC diagnosis was long. GRC patients were more often male and older than other gastric cancer patients, but GRC was not independently associated with survival also after adjusting for TNM stage and tumour location.

1. Introduction

One hundred years ago it was noted that patients previously operated with partial gastrectomy had a high risk of gastric cancer in the remaining stomach (Balfour, 1922). Gastric remnant cancer (GRC) or stump cancer has later been defined as an adenocarcinoma arising in the residual stomach at least five years after partial gastrectomy for benign ulcer disease (Schaefer et al., 2007) and this has been considered a distinct clinical entity (Kondo, 2002). However, cancers diagnosed after distal gastrectomy for malignant disease has by others also been included in the definition of GRC (Ohira et al., 2016).

GRC has been reported to account for 1-8% of all gastric cancers (Mezhir et al., 2011; Sinning et al., 2007) and the incidence of GRC seems higher in Western compared to Asian populations (Mak et al., 2021). After the advent of proton pump inhibitors in the 1980s and the discovery of H. pylori as a main etiological factor of peptic ulcer disease, markedly fewer patients have been operated with distal gastrectomy for benign disease. There is a long latency period between surgery for benign ulcer disease and development of GRC (Lagergren et al., 2012; Viste et al., 1986). The mean time between distal gastrectomy and diagnosis of GRC has been reported to be from 6.8 years (Ahn et al., 2008) to 18.8 years (An et al., 2007) for malignant disease and from 22.0 years (Ojima et al., 2010) to 34.6 years (Di Leo et al., 2014) for benign disease.

The etiology of GRC is unknown. Proposed pathogenetic factors include duodenogastric reflux, which exposes the gastric mucosa for bile acids perceived to have a carcinogenic effect (Kondo, 2002; Tatsugami et al., 2012). The reconstruction methods after distal gastrectomy cause a varying degree of gastric bile acid reflux and although some studies have found higher risk of GRC after Billroth II compared to Billroth I reconstruction, the importance of the reconstruction method is uncertain (Lagergren et al., 2012; Ohira et al., 2016; Tersmette et al., 1990). H pylori infection increases the risk of GRC and the relatively rapid carcinogenesis in the remnant stomach after resection of cancer has been attributed to pre-existing corpus gastritis and premalignant changes (Ohira et al., 2016).

The prognosis of patients with GRC does neither seem to differ from the prognosis of primary gastric cancers overall (Galata et al., 2020) nor from primary proximal gastric cancers (Schaefer et al., 2007). This has been observed although GRCs often have been diagnosed in a more advanced stage (Dhir, 2020).

The aim of the present study was to characterize patients with GRC and assess long-term survival in a large population-based cohort.

2. Materials and Methods

2.1 Study design and data source

Patients diagnosed with gastric adenocarcinoma in Central Norway between 2001 and 2016 (n=1217) have previously been identified and described in previous publications (25-27). The catchment area of approximately 700,000 persons comprised 15 % of the Norwegian population. Patients were identified from searches in the Norwegian Cancer Registry (NCR) and Norwegian Patient Registry (NPR) databases using ICD-10 codes C16.0 to C16.9, C15.5 and C15.9. The files were merged based on a unique 11-digit identification number for each citizen in Norway. Patients with tumours other than gastric adenocarcinoma were excluded by manual assessment of all patient records. Patients with Siewert type I cardia cancer were excluded. The censoring date was February 4th, 2023, and the minimum follow-up time was 6 years and 7 months.

2.2 Gastric remnant cancer and control groups

GRCs were defined as gastric adenocarcinomas in patients previously operated with a distal gastrectomy for either benign or malignant disease and these constituted 78 patients. In the main analyses the 78 GRC patients were compared to the remaining 1139 patients with non-GRC. In a sub-analysis, a control group of patients with primary proximal non-GRC was defined that included corpus and cardia Siewert type II and III cancers, totalling 595 proximal non-GRC. The date of diagnosis of gastric cancer was defined as the date of the upper endoscopy where the tumour was described as suspicious of cancer and biopsied the first time.

2.3 Data collection and variables

Data on patient and tumour characteristics were used to describe the entire cohort, including age, sex, TNM stage and Lauren histological type (Bringeland, Wasmuth, Mjones, et al., 2017). For the purpose of the present study the digital medical records of patients with GRC (n=78) were reviewed manually and the following information extracted: indication for distal gastrectomy (benign or malignant disease), time of distal gastrectomy and reconstruction method (Billroth I, Billroth II or Roux-en-Y). The time interval between distal gastrectomy and GRC diagnosis, and the time interval between upper endoscopy at the time

of diagnosis and the previous upper endoscopy were calculated. Surgical treatment, perioperative and palliative chemotherapy was recorded.

2.4 Statistical analysis

Continuous variables were presented as median (range) or mean (standard deviation (SD) as depending on distribution. Analyses of GRC number and proportions over the study period was done by univariable linear regression. Categorical variables were cross tabulated and analysed by Chi-Square test. Continuous variables were analysed using the Mann–Whitney or Student's t-test depending on distribution. Survival was calculated and presented by the Kaplan-Meier method. The Cox proportional hazard method was used in a multivariable analysis to identify factors independently associated with survival. P values <0.05 were considered significant. Statistical analyses were performed using SPSS version 29 (IBM, Armonk, NY, USA).

2.6 Ethics approval

The gastric cancer projects have been approved by the Regional Committee for Medical and Health Research Ethics (2011/1436 and 2016/2173).

3. Results

3.1 Characteristics of patients with GRC (n=78) vs. all primary gastric cancers (non-GRC) (n=1139) and proximal non-GRC (n=595).

The proportion of gastric remnant cancer (GRC) was 6.4 % (78 of a total of 1217 patients, Table 1). Median age at diagnosis was 78.7 years for GRC vs. 74.9 years for non-GRC patients (p<0.001) and 72.8 years for proximal non-GRC patients (p<0.001). The proportion of males was higher among GRC than among non-GRC (p<0.001) and proximal non-GRC patients (p=0.014), 83.3 % vs. 62.9 % and 71.3 %, respectively. The annual number of non-GRC (p=0.032), the number of GRC (p=0.002) and proportion of GRC (GRC / all gastric cancers) (p=0.003) all declined during the study period (Figure 1).

Figure 1. *The annual number of gastric adenocarcinomas and GRC in Central Norway 2001-2016.*

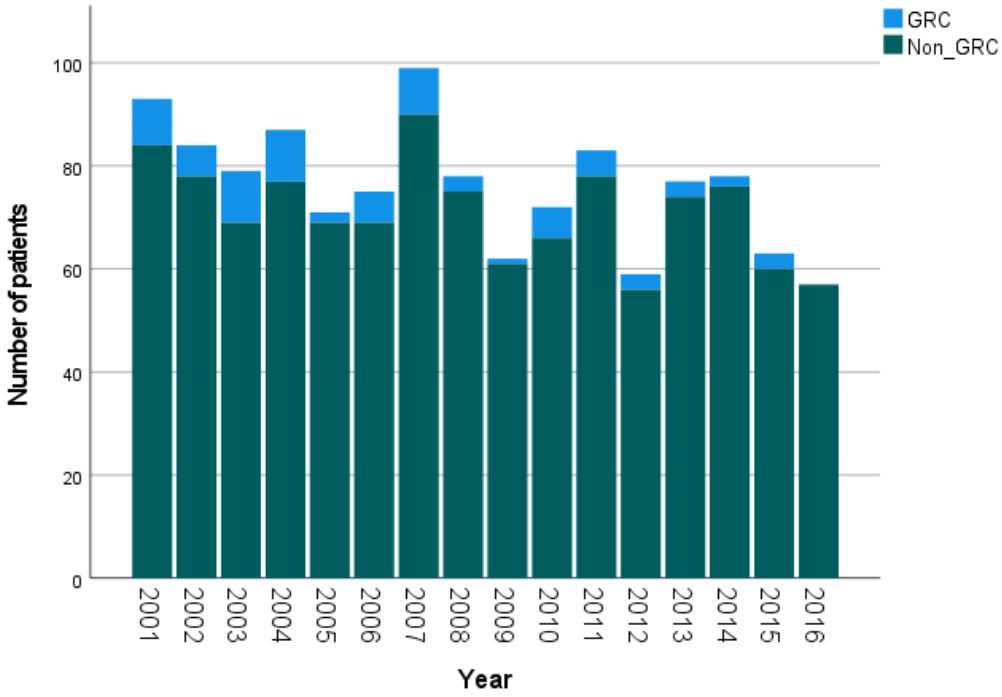


Table 1. Patient demographics and disease characteristics of gastric remnant cancers (GRC) (n=78) vs. all other gastric adenocarcinomas (non-GRC) (n=1139) and proximal non-GRC (n=595).

Variable	GRC	Non-GRC	Proximal non-GRC	Entire cohort
Patients, *n* (%)	78 (6.4)	1139 (93.6)	595 (48.9)	1217
Age at diagnosis, years				
Median (range)	78.7 (52.5-94.9)	74.9 (21.1-99.4)	72.8 (33.0-99.0)	75.3 (21.1-99.4)
Male sex, *n* (%)	65 (83.3)	717 (62.9)**	424 (71.3)*	782 (64.3)
Tumour localization, *n* (%)				
Proximal	78 (100.0)	595 (52.2)	595 (100.0)	673 (55.3)
Distal	0 (0.0)	397 (34.9)	0 (0.0)	397 (32.6)
Diffuse	0 (0.0)	141 (12.4)	0 (0.0)	141 (11.6)
Not recorded	0 (0.0)	6 (0.5)	0 (0.0)	6 (0.5)
TNM stage, *n* (%)				
St 0+I	18 (23.1)	146 (12.8)**	65 (10.9)**	164 (13.5)
St II	5 (6.4)	155 (13.6)	88 (14.8)*	160 (13.1)
St III	7 (9.0)	198 (17.4)	103 (17.3)	205 (16.8)
St IV + X	48 (61.5))	640 (56.2)	339 (57.0)	688 (56.5)
Lauren classification, *n* (%)				
Diffuse	18 (23.1)	347 (30.5)	127 (21.3)	356 (30.0)
Intestinal	44 (56.4)	516 (45.3)	306 (51.4)	560 (46.0)
Mixed diff/intest.	9 (11.5)	125 (11.0)	71 (11.9)	134 (11.0)
Cancer NUD	6 (7.7)	110 (9.7)	74 (12.4)	116 (9.5)
No malignant biopsy	0 (0.0)	25 (2.2)	11 (1.8)	25 (2.1)
No biopsy	1 (1.3)	16 (1.4)	6 (1.0)	17 (1.4)
Chemotherapy				
Neoadjuvant/adjuvant	2 (2.5)	196 (17.2)**	122 (20.5)**	198 (16.3)
Palliative	12 (15.4)	319 (28.0)*	196 (32.9)**	331 (27.2)
Treatment method, *n* (%)				
Formal resection	36 (46.1)	519 (45.5)	242 (40.6)	555 (45.9)
Local resection	0 (0.0)	11 (0.9)	7 (1.2)	11 (0.9)
Non-resective intervention	9 (10.3)	143 (12.6)	58 (6.8)	151 (12.3)
No surgical intervention	34 (43.6)	466 (40.9)	288 (48.4)	500 (41.1)

SD: standard deviation; NUD: non-numerical unstructured data; *: $p<0.05$ and ** $p<0.01$ for comparison between GRC and non-GRC or proximal non-GRC; Formal resection: total, subtotal and proximal resection; Local resection: included wedge resection and endoscopic resection; Non-resective intervention: gastrojejunostomy, explorative laparoscopy, primary stent placement.

3.2 TNM-stage

GRC-patients were diagnosed at an earlier TNM-stage compared to non-GRC ($p<0.001$) and proximal non-GRC ($p<0.001$) (Table 1). In particular, a higher proportion of GRC than

non-GRC and proximal non-GRC were diagnosed in stages 0+I (23.1 % vs. 12.8 % (p=0.01) vs. 10.9% (p=0.002)), while the proportions diagnosed in stages II-IV did not differ significantly.

3.3 Lauren classification

The Lauren histological classification was not significantly different between GRC and non-GRC (p=0.38) and proximal non-GRC (p=0.66) (Table 1). In patients with GRC vs. non-GRC and vs. proximal non-GRC, the proportion of patients with diffuse type were 23.1 % vs. 30.5 % vs. 21.3% and intestinal type 56.4 % vs. 45.3 % vs. 51.4%, respectively.

3.4 Perioperative and palliative chemotherapy

A significantly smaller proportion of GRC patients received perioperative chemotherapy compared to non-GRC patients and proximal non-GRC patients (2.5% of GRC vs. 17.2% of non-GRC (p<0.001) vs. 20.5% of proximal non-GRC (p<0.001) (Table 1). Similarly, fewer GRC patients received palliative chemotherapy compared with non-GRC patients and proximal non-GRC patients (15.4% vs. 28.0% (p=0.025) vs. 32.9% (p=0.002), respectively).

3.5 Surgical cancer treatment and reconstruction method

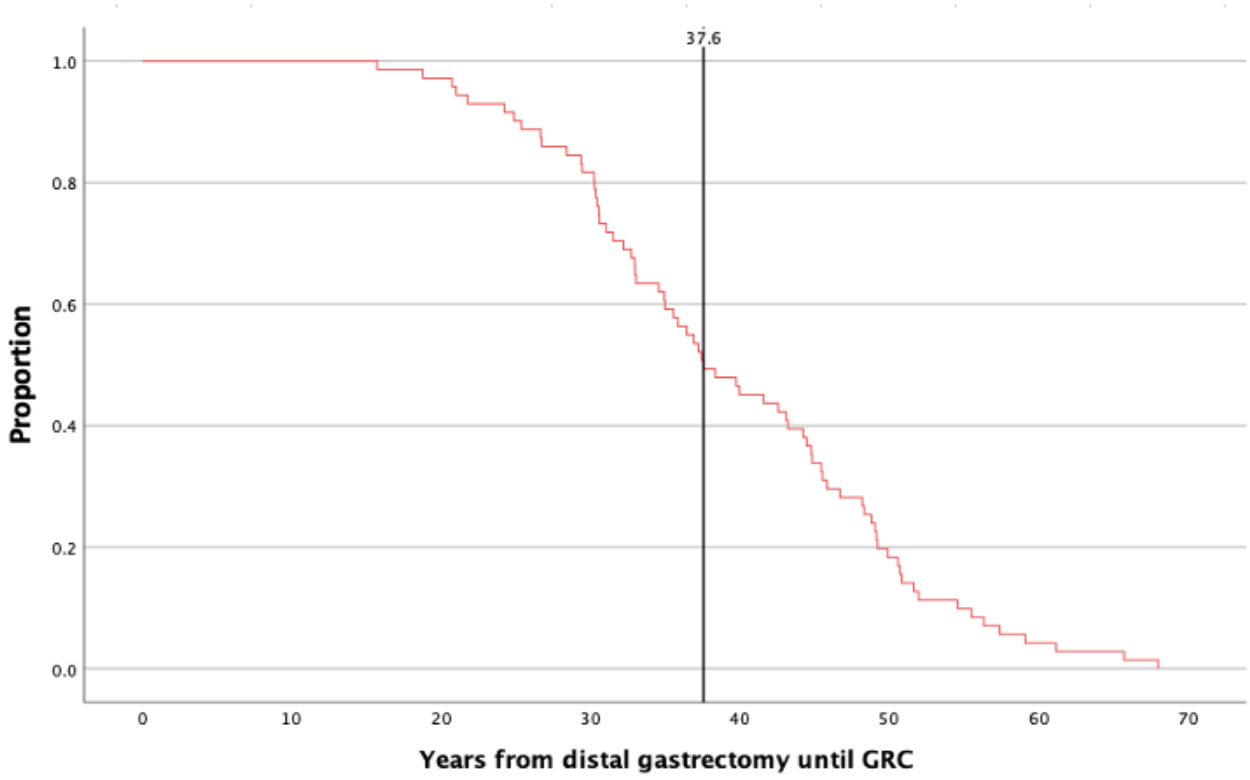
In all three patient groups, GRC, non-GRC and proximal non-GRC, the largest portions of patients were treated by a gastrectomy, either total, subtotal or proximal (46.1% of GRC vs. 45.5% of non-GRC vs. 40.6% of proximal non-GRC) (Table 1). All three groups also had a high and similar proportion of patients who did not undergo surgical cancer treatment (43.6 % vs. 40.9 % vs. 48.4%, respectively).

3.6 Indication for initial distal gastrectomy, reconstruction method and time to GRC diagnosis

Out of 78 GRC patients, two patients (2.6%) had an initial distal gastrectomy due to malignant disease, and the remaining 76 (97.4%) were operated for benign peptic ulcer disease. The majority constituting 64 patients (87.7%) had a Billroth 2, eight patients (11%) had a Billroth 1, and one patient (1.4%) had undergone a Roux-en-Y reconstruction after distal gastrectomy. The time of the distal gastrectomy preceding GRC was found in 71 of 78 GRC patients allowing the latency to GRC diagnosis to be calculated (Figure 2). The median time from distal gastrectomy until GRC diagnosis was 37.6 years, ranging from 15.7 to 68.0

years. The median age at distal gastrectomy was 34.6 years, ranging from 18.1 to 70.3 years of age.

Figure 2. There was a median of 37.6 years from distal gastrectomy until gastric remnant cancer (GRC) diagnosis.



3.7 Overall survival in patients with GRC (n=78) vs. non-GRC (n=1139) and vs. proximal non-GRC (n=595)

The survival in patients with GRC and non-GRC did not differ significantly, p=0.368 (Figure 3a), neither did the survival between GRC and proximal non-GRC (p=0.056) (Figure 3b). The median survival in patients with GRC, non-GRC and proximal non-GRC, was 7.8 months (95% CI 4.3-18.2 months), 10.4 months (95% CI 9.3-11.5 months) and 10.3 months (95% CI 9.1-12.2 months), respectively.

The five-year survival rates were found to be 23.1% among GRC patients, 18.5% among non-GRC patients and 18.8% among proximal non-GRC.

Figure 3a. Survival in patients with gastric remnant cancers (GRC) (n=78) vs. non-GRC (n=1139).

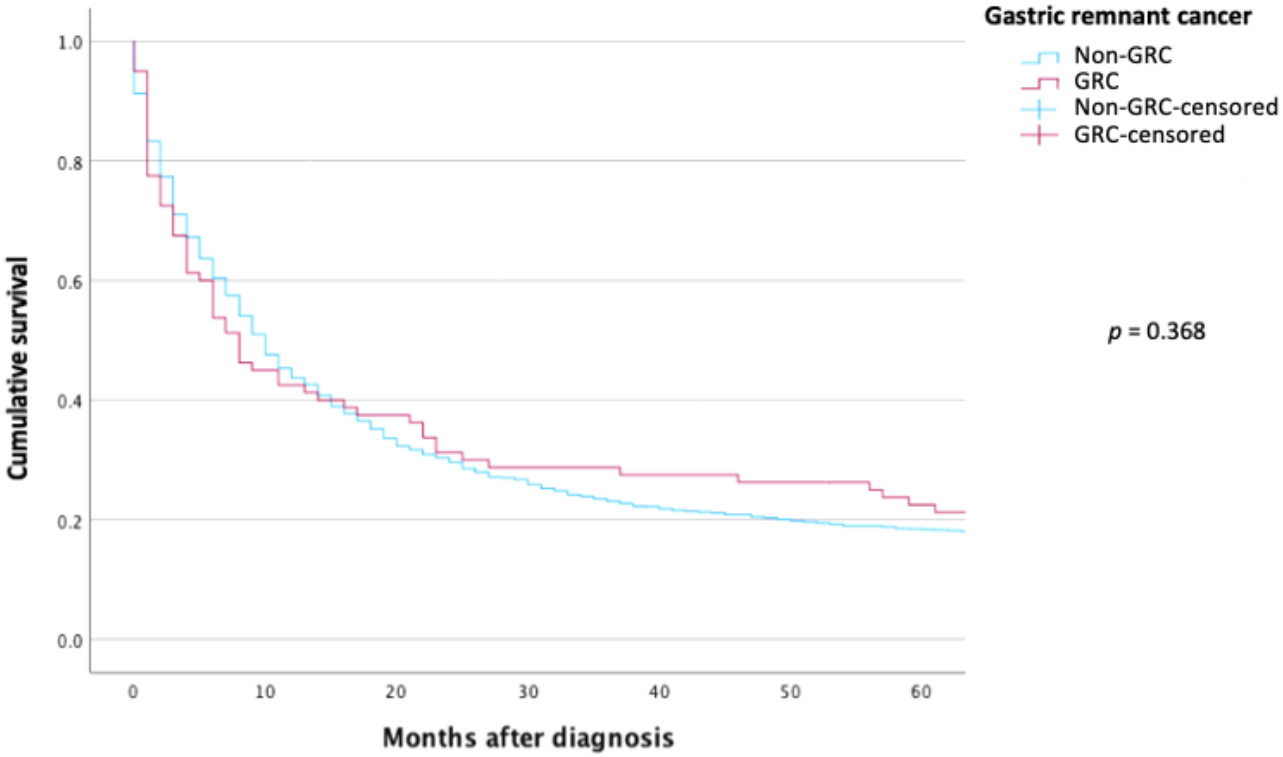
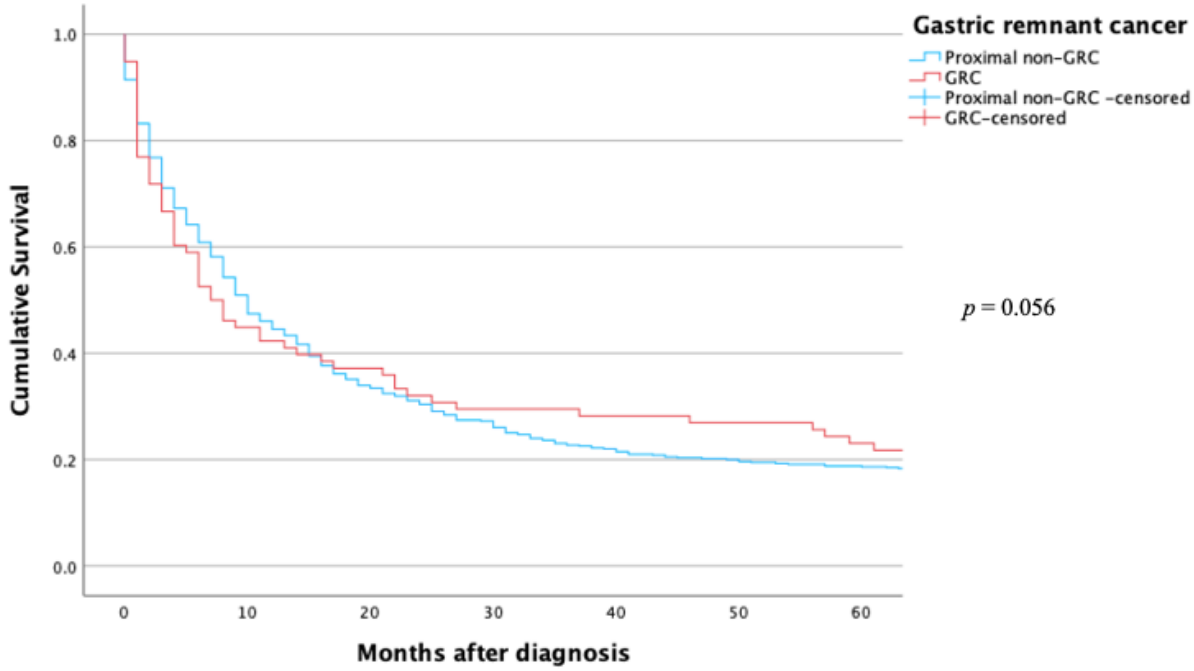


Figure 3b. Survival in patients with gastric remnant cancers (GRC) (n=78) vs. proximal non-GRC (n=595).



3.8 Cox proportional hazard analysis for survival in GRC compared with all gastric adenocarcinomas (non-GRC)

In analyses of Cox proportional hazards, a higher age and more advanced TNM stage at diagnosis were independently associated with survival (p<0.001) (Table 2). The hazard ratio (HR) for age at diagnosis was 1.012 (95% CI 1.007-1.017), whereas for TNM stage the HR was 1.911 (95% CI 1.809-2.019). Tumour localization was also associated with survival with a HR 1.085 (95% CI 1.019-1.156).

Table 2a. Cox proportional hazard analysis for survival in GRC compared with all gastric adenocarcinomas (non-GRC)

Variable	HR	95% CI	*p*-value
Male sex	0.889	0.781-1.012	0.076
Tumour localization	1.085	1.019-1.156	0.011
Lauren classification	1.015	0.953-1.081	0.64
Age at diagnosis	1.012	1.007-1.017	<0.001
TNM	1.911	1.809-2.019	<0.001
GRC	0.963	0.755-1.229	0.76

HR: hazard ratio; CI: confidence interval; GRC: gastric remnant cancer

Table 2b. Cox proportional hazard analysis for survival in GRC compared with proximal non-GRC.

Variable	HR	95% CI	*p*-value
Male sex	0.959	0.795-1.157	0.665
Lauren classification	0.919	0.844-1.001	0.052
Age at diagnosis	1.023	1.015-1.030	<0.001
TNM	2.576	2.321-2.858	<0.001
GRC	1.046	0.812-1.348	0.727

HR: hazard ratio; CI: confidence interval; GRC: gastric remnant cancer

4. Discussion

In the current study, GRCs were found to account for 6.4% of all gastric adenocarcinomas in Central Norway between 2001 and 2016. The proportion of GRC in other cohorts has been reported to be within the range 1-8% of all gastric cancers (Sinning et al., 2007; Mezhir et al.,

2011), and was in 2007 reported to increase due to a long latency time from distal gastrectomy until GRC arises (Sinning et al., 2007). During the years 2001-2016, however, the annual number of GRC in Central Norway decreased. This could be due to a decrease in distal gastrectomies performed for peptic ulcer disease from the 1980s when efficient proton pump inhibitors (Sharma et al., 1984) replaced H2-receptor blockers and operation with proximal selective vagotomy (Sagatun et al., 2014) in the treatment of such patients.

We found that the proportion of males was more than 80% in GRC patients and significantly higher than in non-GRC and proximal non-GRC patients. The marked male predominance has been found in several other studies (Ohira et al., 2016). The main reasons for this finding seem to be that men are more likely to develop both gastroduodenal ulcers as well as gastric cancer (Ohira et al., 2016).

In the current study, there was a higher proportion of GRCs diagnosed in stages 0+I compared to both non-GRCs and proximal non-GRCs. While we in our cohort found a tendency of GRCs being detected at an early stage, others have observed that GRC were more often diagnosed at an advanced stage (Ohira et al., 2016; Takeno et al., 2014).

We found a median time between the distal gastrectomy and GRC diagnosis of 37.6 years, which was similar to the latency observed in other cohorts (Viste et al., 1986; Lagergren et al., 2012; Di Leo et al., 2014). Previous studies have reported relatively longer latency in patients operated for benign compared to malignant disease. In the current study only two GRC patients (2.6%) had initially undergone distal gastrectomy due to malignant disease and while these two patients had a shorter median latency of 22.6 years, they affected the overall latency only little. Due to the long latency, and the fact that distal gastrectomies for benign ulcer disease were performed relatively often into the 1980s, it is likely that GRCs will continue to be encountered (Mezhir et al., 2011). However, a few patients had a latency time exceeding 60 years and a minor proportion of GRCs may not have been caused by the distal gastrectomy but developed independently of the operation.

Previous and current (Helsedirektoratet, 2021) Norwegian guidelines have not recommended regular surveillance endoscopies after curative surgical treatment for stomach cancer, stating that surveillance has not been documented to affect survival (Helsedirektoratet, 2021). Similarly, there are no guidelines covering follow-up or surveillance after distal gastrectomy for benign disease. However, due to the long latency after distal gastrectomy until GRC arises it is still important that physicians are aware of this increased risk and have a low threshold for referring symptomatic patients despite the lack of guidelines. In absence of formal recommendations experts have suggested that surveillance

endoscopy after distal gastrectomy for benign disease should start 15-20 years after surgery (Tersmette et al., 1990), which also seemed sufficient for our cohort. After distal gastrectomy for malignant disease surveillance endoscopies should start earlier and Japanese institutions have performed annual surveillance endoscopies for at least ten years after surgery (Ohashi et al., 2007).

The large majority (87.7%) of our GRC patients had undergone a previous Billroth 2 reconstruction. The reconstruction methods after distal gastrectomy cause varying degree of gastric bile acid reflux and some studies have suggested a higher risk of GRC after Billroth 2 reconstruction which could be attributed to continuous duodenogastric reflux (Murphy et al., 2009; Nishikawa et al., 2002). The bile reflux hypothesis has support from animal models as gastrojejunostomy without removal of the antrum is carcinogenic in rat models, moreover the carcinogenesis may be enhanced by proton pump inhibitor-induced hypoacidity and hypergastrinemia (Viste et al., 2004). However, others have found that in patients operated for benign disease the risk of GRC did not differ between Billroth 1 and Billroth 2 anastomoses (Stalsberg & Taksdal, 1971). Similarly, in a large population-based study the reconstruction method was not found to affect the incidence of GRC (Lagergren et al., 2012).

The survival in GRC patients has been studied and five-year survival rates have been reported to be between 7 % and 20 % (Sinning et al., 2007). A meta-analysis found a five-year survival rate ranging from 19.4 % to 49.0 % for GRC with benign primary gastric disease, and from 30.6% to 59.3 % for those with malignant primary gastric disease (Mak et al., 2021). In our GRC-cohort the five-year overall survival was 23.1 %, and the overall survival did not differ from non-GRC patients. We found a median survival time of 7.8 months (95% CI 4.3-18.2 months). We also compared survival of GRCs to proximal gastric cancers including cardia type II and III cancers, which were classified as gastric cancers in the study period. Cardia cancers have shorter median survival than non-cardia cancers (Bringeland, Wasmuth, Mjønes, et al., 2017), we did not find that survival in patients with GRC differed from patients with proximal non-GRCs. Similarly, previous studies have not found differences in five-year survival rates when comparing GRC and proximal primary gastric cancer (Shimada et al., 2016).

Factors associated with survival in GRC patients has been a subject to many studies. A meta-analysis of 20 studies with a pooled GRC prevalence of only 2.2%, but higher rates in Western populations (Mak et al., 2021), found that lower TNM-stage was associated with a better five-year survival. However, five-year survival in GRC-patients with benign primary gastric diseases vs. malignant primary gastric disease did not differ, even though the patients

with malignant disease as indication for distal gastrectomy had higher TNM-stage at diagnosis (Mak et al., 2021).

To further explore whether GRC *per se* seemed to affect survival we performed a multivariable Cox proportional hazard analyses that included first the entire cohort of patients with gastric cancer and then as second analysis after excluding patients with distal cancers. In both analyses, which included age, sex, TNM stage and Lauren histological classification, GRC as a variable was not independently associated with overall survival. However, as expected we found that a more advanced TNM stage and higher age were associated with shorter survival.

5. Conclusions

GRC constituted a significant proportion of gastric adenocarcinomas in Central Norway, but the number and proportion declined during the study period. The latency between distal gastrectomy and GRC was 37 years. The survival of GRC patients did neither differ from non-GRC overall nor from proximal non-GRC patients.

Acknowledgements

We thank Biobank1 and Department of Pathology, St.Olavs Hospital, Trondheim, for contribution to the project.

Institutional Review Board Statement: The project was approved by the Regional Committee for Medical and Health Research Ethics (2011/1436 and 2016/2173).

Data Availability Statement

The project data cannot be shared according to regulations given by the Regional Committee for Medical and Health Research Ethics

Conflicts of Interest: none

References

Ahn, H. S., Kim, J. W., Yoo, M. W., Park, D. J., Lee, H. J., Lee, K. U., & Yang, H. K. (2008). Clinicopathological features and surgical outcomes of patients with remnant gastric cancer after a distal gastrectomy. *Ann Surg Oncol*, *15*(6), 1632-1639. https://doi.org/10.1245/s10434-008-9871-8

An, J. Y., Choi, M. G., Noh, J. H., Sohn, T. S., & Kim, S. (2007). The outcome of patients with remnant primary gastric cancer compared with those having upper one-third gastric cancer. *Am J Surg*, *194*(2), 143-147. https://doi.org/10.1016/j.amjsurg.2006.10.034

Balfour, D. C. (1922). FACTORS INFLUENCING THE LIFE EXPECTANCY OF PATIENTS OPERATED ON FOR GASTRIC ULCER. *Ann Surg*, *76*(3), 405-408. https://doi.org/10.1097/00000658-192209000-00014

Bringeland, E. A., Wasmuth, H. H., Mjones, P., Myklebust, T. A., & Gronbech, J. E. (2017). A population-based study on incidence rates, Lauren distribution, stage distribution, treatment, and long-term outcomes for gastric adenocarcinoma in Central Norway 2001-2011. *Acta Oncologica*, *56*(1), 39-45. https://doi.org/10.1080/0284186x.2016.1227086

Bringeland, E. A., Wasmuth, H. H., Mjønes, P., Myklebust, T., & Grønbech, J. E. (2017). A population-based study on incidence rates, Lauren distribution, stage distribution, treatment, and long-term outcomes for gastric adenocarcinoma in Central Norway 2001-2011. *Acta Oncol*, *56*(1), 39-45. https://doi.org/10.1080/0284186x.2016.1227086

Dhir, M. (2020). Gastric Remnant Cancer: Is it different From Primary Gastric Cancer? Insights Into a Unique Clinical Entity. *Ann Surg Oncol*, *27*(11), 4079-4081. https://doi.org/10.1245/s10434-020-08690-5

Di Leo, A., Pedrazzani, C., Bencivenga, M., Coniglio, A., Rosa, F., Morgani, P., Marrelli, D., Marchet, A., Cozzaglio, L., Giacopuzzi, S., Tiberio, G. A., Doglietto, G. B., Vittimberga, G., Roviello, F., & Ricci, F. (2014). Gastric stump cancer after distal gastrectomy for benign disease: clinicopathological features and surgical outcomes. *Annals of Surgical Oncology*, *21*(8), 2594-2600. https://doi.org/10.1245/s10434-014-3633-6

Galata, C., Ronellenfitsch, U., Weiß, C., Blank, S., Reißfelder, C., & Hardt, J. (2020). Surgery for Gastric Remnant Cancer Results in Similar Overall Survival Rates Compared with Primary Gastric Cancer: A Propensity Score-Matched Analysis. *Ann Surg Oncol*, *27*(11), 4196-4203. https://doi.org/10.1245/s10434-020-08669-2

Helsedirektoratet. (2021). *Nasjonalt handlingsprogram for kreft i magesekken* https://www.helsedirektoratet.no/retningslinjer/kreft-i-magesekken-handlingsprogram/oppfolging-og-kontroll-etter-avsluttet-kurativ-behandling

Kondo, K. (2002). Duodenogastric reflux and gastric stump carcinoma. *Gastric Cancer*, *5*(1), 16-22. https://doi.org/10.1007/s101200200002

Lagergren, J., Lindam, A., & Mason, R. M. (2012). Gastric stump cancer after distal gastrectomy for benign gastric ulcer in a population-based study. *Int J Cancer*, *131*(6), E1048-1052. https://doi.org/10.1002/ijc.27614

Mak, T. K., Guan, B., Peng, J., Chong, T. H., Wang, C., Huang, S., & Yang, J. (2021). Prevalence and characteristics of gastric remnant cancer: A systematic review and meta-analysis. *Asian J Surg*, *44*(1), 11-17. https://doi.org/10.1016/j.asjsur.2020.03.012

Mezhir, J. J., Gonen, M., Ammori, J. B., Strong, V. E., Brennan, M. F., & Coit, D. G. (2011). Treatment and outcome of patients with gastric remnant cancer after resection for peptic ulcer disease. *Ann Surg Oncol*, *18*(3), 670-676. https://doi.org/10.1245/s10434-010-1425-1

Murphy, G., Pfeiffer, R., Camargo, M. C., & Rabkin, C. S. (2009). Meta-analysis shows that prevalence of Epstein-Barr virus-positive gastric cancer differs based on sex and anatomic location. *Gastroenterology*, *137*(3), 824-833. https://doi.org/10.1053/j.gastro.2009.05.001

Nishikawa, J., Yanai, H., Hirano, A., Okamoto, T., Nakamura, H., Matsusaki, K., Kawano, T., Miura, O., & Okita, K. (2002). High prevalence of Epstein-Barr virus in gastric remnant carcinoma after Billroth-II reconstruction. *Scand J Gastroenterol*, *37*(7), 825-829.

Ohashi, M., Katai, H., Fukagawa, T., Gotoda, T., Sano, T., & Sasako, M. (2007). Cancer of the gastric stump following distal gastrectomy for cancer. *Br J Surg*, *94*(1), 92-95. https://doi.org/10.1002/bjs.5538

Ohira, M., Toyokawa, T., Sakurai, K., Kubo, N., Tanaka, H., Muguruma, K., Yashiro, M., Onoda, N., & Hirakawa, K. (2016). Current status in remnant gastric cancer after distal gastrectomy. *World J Gastroenterol*, *22*(8), 2424-2433. https://doi.org/10.3748/wjg.v22.i8.2424

Ojima, T., Iwahashi, M., Nakamori, M., Nakamura, M., Naka, T., Katsuda, M., Iida, T., Tsuji, T., Hayata, K., Takifuji, K., & Yamaue, H. (2010). Clinicopathological characteristics of remnant gastric cancer after a distal gastrectomy. *J Gastrointest Surg*, *14*(2), 277-281. https://doi.org/10.1007/s11605-009-1090-5

Sagatun, L., Jianu, C. S., Fossmark, R., Mårvik, R., Nordrum, I. S., & Waldum, H. L. (2014). The gastric mucosa 25 years after proximal gastric vagotomy. *Scand J Gastroenterol*, *49*(10), 1173-1180. https://doi.org/10.3109/00365521.2014.950979

Schaefer, N., Sinning, C., Standop, J., Overhaus, M., Hirner, A., & Wolff, M. (2007). Treatment and prognosis of gastric stump carcinoma in comparison with primary proximal gastric cancer. *Am J Surg*, *194*(1), 63-67. https://doi.org/10.1016/j.amjsurg.2006.12.037

Sharma, B. K., Walt, R. P., Pounder, R. E., Gomes, M. D., Wood, E. C., & Logan, L. H. (1984). Optimal dose of oral omeprazole for maximal 24 hour decrease of intragastric acidity. *Gut*, *25*(9), 957-964. https://doi.org/10.1136/gut.25.9.957

Shimada, H., Fukagawa, T., Haga, Y., & Oba, K. (2016). Does remnant gastric cancer really differ from primary gastric cancer? A systematic review of the literature by the Task Force of Japanese Gastric Cancer Association. *Gastric Cancer*, *19*(2), 339-349. https://doi.org/10.1007/s10120-015-0582-0

Sinning, C., Schaefer, N., Standop, J., Hirner, A., & Wolff, M. (2007). Gastric stump carcinoma - epidemiology and current concepts in pathogenesis and treatment. *Eur J Surg Oncol*, *33*(2), 133-139. https://doi.org/10.1016/j.ejso.2006.09.006

Stalsberg, H., & Taksdal, S. (1971). Stomach cancer following gastric surgery for benign conditions. *Lancet*, *2*(7735), 1175-1177. https://doi.org/10.1016/s0140-6736(71)90489-2

Takeno, S., Hashimoto, T., Maki, K., Shibata, R., Shiwaku, H., Yamana, I., Yamashita, R., & Yamashita, Y. (2014). Gastric cancer arising from the remnant stomach after distal gastrectomy: a review. *World J Gastroenterol*, *20*(38), 13734-13740. https://doi.org/10.3748/wjg.v20.i38.13734

Tatsugami, M., Ito, M., Tanaka, S., Yoshihara, M., Matsui, H., Haruma, K., & Chayama, K. (2012). Bile acid promotes intestinal metaplasia and gastric carcinogenesis. *Cancer Epidemiol Biomarkers Prev*, *21*(11), 2101-2107. https://doi.org/10.1158/1055-9965.Epi-12-0730

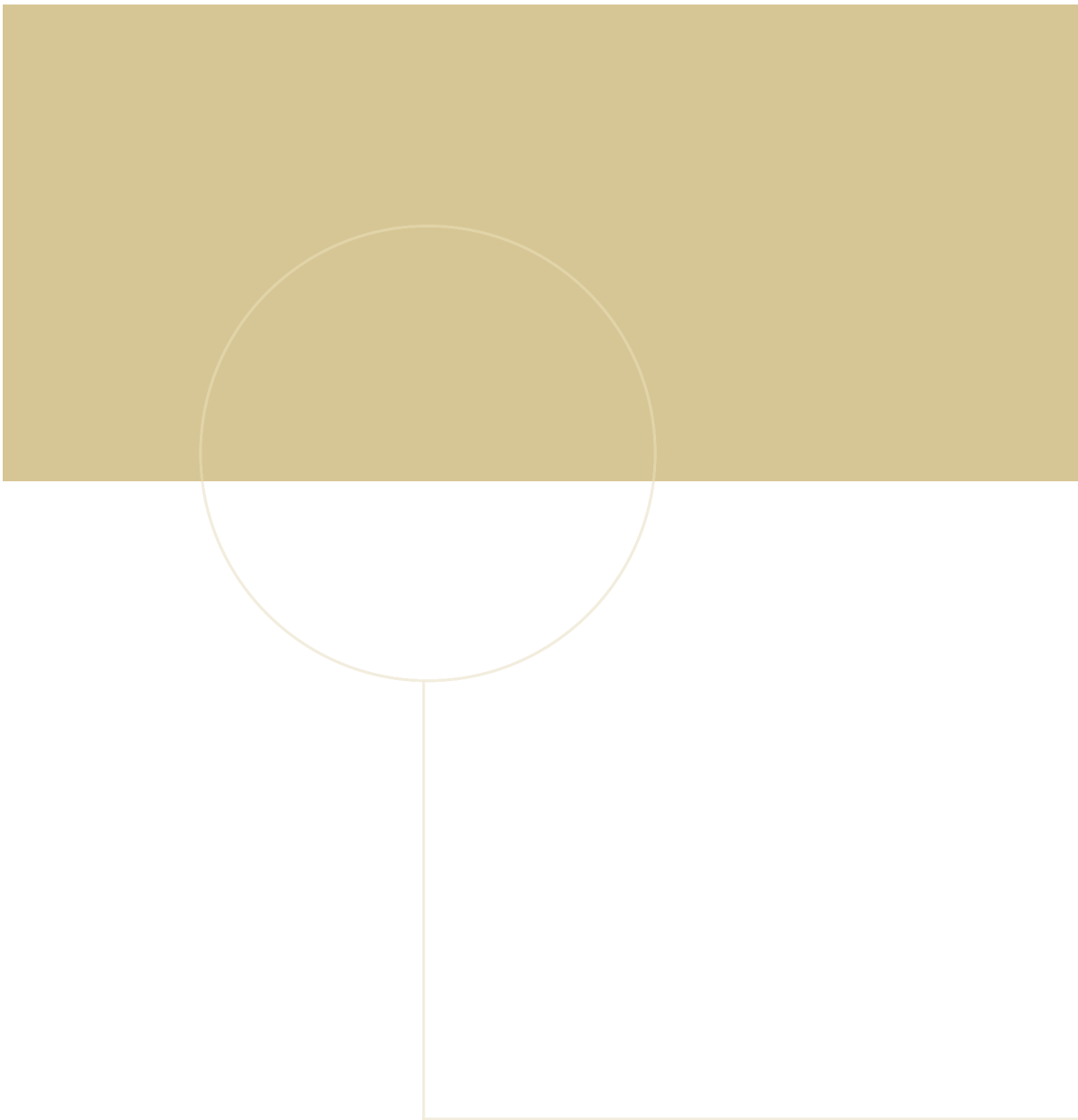
Tersmette, A. C., Offerhaus, G. J., Tersmette, K. W., Giardiello, F. M., Moore, G. W., Tytgat, G. N., & Vandenbroucke, J. P. (1990). Meta-analysis of the risk of gastric stump cancer: detection of high risk patient subsets for stomach cancer after remote partial gastrectomy for benign conditions. *Cancer Research*, *50*(20), 6486-6489.

Viste, A., Bjørnestad, E., Opheim, P., Skarstein, A., Thunold, J., Hartveit, F., Eide, G. E., Eide, T. J., & Søreide, O. (1986). Risk of carcinoma following gastric operations for

benign disease. A historical cohort study of 3470 patients. *Lancet*, *2*(8505), 502-505. https://doi.org/10.1016/s0140-6736(86)90368-5

Viste, A., Øvrebø, K., Maartmann-Moe, H., & Waldum, H. (2004). Lanzoprazole promotes gastric carcinogenesis in rats with duodenogastric reflux. *Gastric Cancer*, *7*(1), 31-35. https://doi.org/10.1007/s10120-003-0264-1

https://www.wcrf.org/cancer-trends/stomach-cancer-statistics/



NTNU

Norwegian University of
Science and Technology