Staging and surgical treatment of gastric cancer

Surgery during the COVID-19 pandemic

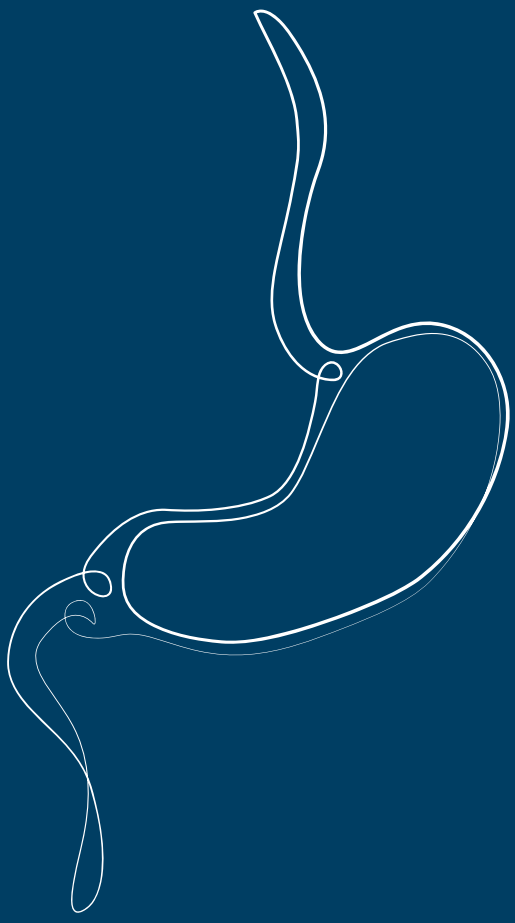
Borgstein, A.B.J.

Publication date
2022

Document Version
Final published version

Staging and Surgical Treatment of Gastric Cancer:

Surgery During The COVID-19 Pandemic



Alexander Berend-Jan Borgstein

Staging and Surgical Treatment of Gastric Cancer:

Surgery During The COVID-19 Pandemic

Alexander Berend-Jan Borgstein

Staging and Surgical Treatment of Gastric Cancer: Surgery During The COVID-19 Pandemic

PhD thesis, University of Amsterdam, The Netherlands

ISBN: 978-94-6423-639-2

Paranymphs: Bastiaan Borgstein & Zachri Ovadja
Cover design and layout: ProefschriftMaken | proefschriftmaken.nl

Financial support for printing of this thesis was kindly provided by: Chipsoft, Nederlandse Vereniging voor Gastro-enterologie, Boudewijn Beerkens & Oya Beerkens-Yavuz, Eveline Jurry & John Fiszbajn, Viatris, Pfizer, Cancer Center Amsterdam, Care 10 and Nordic Pharma B.V.

Staging and Surgical Treatment of Gastric Cancer:

Surgery During The COVID-19 Pandemic

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor

aan de Universiteit van Amsterdam

op gezag van de Rector Magnificus

prof. dr. ir. K.I.J. Maex

ten overstaan van een door het College voor Promoties ingestelde commissie,

in het openbaar te verdedigen in de Agnietenkapel

op 18 maart 2022, te 16:00 uur

door

Alexander Berend-Jan Borgstein

geboren te Leiden

Promotiecommissie

Promotores:	prof. dr. M.I. van Berge Henegouwen	AMC-UvA
	prof. dr. M.G.H. Besselink	AMC-UvA
Copromotores:	dr. S.S. Gisbertz	AMC-UvA
	dr. W.J. Eshuis	AMC-UvA
Overige leden:	prof. dr. O.R.C. Busch	AMC-UvA
	prof. dr. B.P.L. Wijnhoven	Erasmus MC
	prof. dr. O.M. van Delden	AMC-UvA
	prof. dr. D.L. van der Peet	Vrije Universiteit Amsterdam
	prof. dr. F. Roviello	Azienda Ospedaliera Universitaria
	prof. dr. S.E. Geerlings	AMC-UvA

Table of contents

Chapter 1

General introduction and thesis outline

General introduction

Gastric cancer

Gastric cancer is the fifth most occurring malignancy worldwide, with an estimated one million new cases annually[1]. In The Netherlands, around 1200 patients are diagnosed with gastric cancer each year, of which approximately 400 patients undergo potentially curative surgery[2]. Gastric cancer is often diagnosed at an advanced stage, therefore resulting in high mortality rates, making it the third leading cause of cancer-related deaths worldwide[1]. However, there are geographical variations in terms of incidence and mortality of gastric cancer. More than three quarters of all new cases of gastric cancer are diagnosed in Asian countries, such as Japan, China and Korea[1]. The stage of the disease at the time of diagnosis influences the survival rate. In Asian countries, gastric cancer is often diagnosed at an earlier stage because of implemented screening programs[3,4]; as a result, five-year overall survival is around 65-70%[5,6]. In Western countries, gastric cancer is more often diagnosed at an advanced stage, and has a five-year overall survival rate of only around 20%[7].

There are different types of gastric cancer, of which approximately 90% are adenocarcinomas[8]. These tumors can be subdivided into diffuse (undifferentiated) or intestinal (well-differentiated) types of adenocarcinomas, according to the Lauren classification[8]. Diffuse type gastric cancer is associated with worse overall survival compared to intestinal type gastric cancer[9]. Gastric cancer can also be classified according to the WHO[10], the Japanese[11] or the molecular subtype classification[12].

Staging of gastric cancer

Accurate staging of gastric cancer is important to determine the optimal treatment strategy for individual patients. Potentially curative treatment is only possible if metastatic disease is absent and if the tumor is resectable[13]. Metastases and/or a non-resectable primary tumor are present in up to 40% of patients diagnosed with gastric cancer[14,15]. Metastases are most frequently found in the peritoneum[16]. After diagnosis through endoscopy with biopsies, a computed tomography (CT) scan is performed as initial staging procedure. A CT scan however, has limited sensitivity (22-33%) to detect metastases or a non-resectable tumor[17–19]. Therefore, since 2016, the Dutch gastric cancer guideline recommends to perform a staging laparoscopy in all patients with ≥cT3 and/or N+ stage tumor, to exclude occult metastatic and/or non-resectable disease[13,20]. A positron emission tomography (PET)-CT scan does not result in additional detection of metastases or non-resectable disease, as concluded in the recently published Dutch PLASTIC study[21]. Patients with metastases and/or a non-resectable tumor can merely be palliatively treated with i.e. chemotherapy, palliative surgery or radiotherapy.

Multimodal treatment of advanced gastric cancer

Curative treatment for advanced gastric cancer consists of perioperative chemotherapy and a radical resection (a total or subtotal gastrectomy, including lymphadenectomy and omentectomy). The combination of perioperative chemotherapy followed by surgery has

shown to improve overall survival[22–24]. Two large trials, MAGIC[24] and FLOT[23], both have shown that the combination of perioperative chemotherapy followed by surgery improves overall survival with 15 months, compared to patient undergoing only surgery. However, the median age in both trials was 62 years. Therefore, it is unknown whether elderly patients, aged 75 years or older, have a similar survival benefit from the combination of perioperative chemotherapy followed by a gastrectomy, compared to younger patients.

Surgical treatment of advanced gastric cancer

Surgical treatment for advanced gastric cancer includes a total or subtotal gastrectomy. The choice for the type of surgical resection depends on the localization and size of the tumor, and also involves the growth pattern in some guidelines[13,25,26]. The Dutch gastric cancer guideline recommends a tumor-free margin of at least 6 cm, and, if this is not achieved and a more extended resection is possible, a frozen section should be performed[10]. A gastrectomy can be performed open or minimally invasive. In recent years, an increasing percentage of gastrectomies are performed minimally invasive in Western countries. In The Netherlands, the use of minimally invasive gastrectomy has increased from 4% to 53% between 2011 and 2015[27]. Two recent Dutch trials found no difference in hospital stay, oncological efficacy and the rate of postoperative complications between open and minimally invasive gastrectomy[28,29]. In addition, no differences in survival rates were observed. However, several Asian trials described better short-term outcomes, including shorter hospital stay, less blood loss, and fewer wound complications; and comparable long-term outcomes after minimally invasive gastrectomy compared to open gastrectomy[27–29]. In addition to a radical resection, an extended (modified D2) lymphadenectomy and generally a complete removal of the omentum are performed. Several trials have shown a potential long-term survival advantage of the modified D2 (i.e., without splenectomy) lymphadenectomy over the D1 lymphadenectomy[33,34]. An omentectomy is performed to eliminate possible omental metastatic lymph nodes or tumor deposits. However, there is little evidence supporting standard complete omentectomy in the treatment of gastric cancer. Several non-randomized studies found no difference in overall survival between patients undergoing gastrectomy with omentectomy or with omentum preservation[35–39]. A Japanese phase II trial found no difference in short-term postoperative morbidity and shorter operation time in patients undergoing gastrectomy without omentectomy[40]. Therefore, a phase III trial investigating long-term overall survival should be performed and is necessary to investigate the need for routine omentectomy.

Surgery and the COVID-19 pandemic

The COVID-19 pandemic has had an immense impact on the executability of elective surgical care, as medical capacities were reallocated to increase intensive care unit and nursing ward capacities to treat COVID-19 patients. Up to 70% of adult elective surgery and 38% of elective cancer surgery were postponed worldwide during the first twelve weeks of the pandemic[41]. The strategy to postpone elective surgical care was further supported by a large study indicating patients undergoing surgery with a SARS-CoV-2 infection to have increased risk for postoperative pulmonary complications and mortality[42]. However, postponing elective

cancer surgery could lead to tumor progression and subsequent worse survival rates[43]. Patients however feared the possibility of acquiring an in-hospital SARS-CoV-2 infection, which resulted in an increase of pre-hospital delay. This scenario potentially affected the natural course of diseases, not only those of an oncologic nature, but also of appendicitis.

Strategies to continue elective surgical care during the COVID-19 pandemic

Screening strategies, including the use of reverse-transcriptase polymerase chain reaction (RT-PCR) and chest computed tomography (CT), were implemented to detect possible SARS-CoV-2 infections in asymptomatic patients prior to surgery. These screening strategies were implemented to protect patients and healthcare workers from acquiring in-hospital SARS-CoV-2 infection or transmitting the disease to other patients, and by doing so, aimed at preventing adverse outcomes after surgery. These strategies had to be validated before they could be implemented in national and international guidelines.

Safety of performing elective surgical care during the COVID-19 pandemic

With the implementation of preoperative screening guidelines, the safety of continuing or restarting elective surgical care during the COVID-19 pandemic, including gastro-esophageal cancer surgery, had to be established. Pneumonia is the most common postoperative complication in patients undergoing esophageal cancer surgery, occurring in over 20% of patients[44]. Additionally, around 10% of patients require ICU admission after esophagectomy because of postoperative complications[44]. Therefore, preventing a SARS-CoV-2 infection in these patients was especially important, as the rate of pulmonary complications was known to be 50% in patients undergoing surgery with a SARS-CoV-2 infection[42]. In order to prevent additional pressure to the already overloaded ICU's with COVID-19 patients, the safety to continue gastro-esophageal cancer surgery had to be established. This was performed by analyzing a potential increase in the percentage of postoperative pulmonary complications occurring in patients operated during the COVID-19 pandemic.

Thesis outline

This thesis is divided into two parts. **Part I** comprises studies which focus on improving staging and surgical treatment of gastric cancer. In **Part II**, preoperative screening, the safety of performing surgery (including gastro-esophageal cancer surgery) during the COVID-19 pandemic and, specifically, the influence of the pandemic on patients with appendicitis, are assessed.

Part I: Staging and surgical treatment of gastric cancer
Since 2016, the Dutch gastric cancer guideline advises to perform a staging laparoscopy in all patients with a ≥cT3 and/or N+ stage gastric tumor, to detect possible distant metastases. The diagnostic accuracy of staging laparoscopy has mainly been investigated in Asian studies, in which small numbers of patients were included. The avoidable surgery rate, detection rate of metastases and/or loco-regional non-resectability during gastrectomy with curative intent, can be used to measure the value of staging laparoscopy. In **chapter 2** we compared the avoidable surgery rate in gastric cancer patients undergoing gastrectomy, with and without staging laparoscopy, in a population-based cohort study. In **chapter 3** the diagnostic accuracy of staging laparoscopy in patients with advanced gastric cancer was investigated in a single center cohort study.

Curative treatment for gastric cancer consists of perioperative chemotherapy combined with a gastrectomy. However, several trials which showed a survival benefit after the addition of chemotherapy to surgery, included mainly patients aged 70 years or younger. In **chapter 4** we investigated whether elderly patients, aged 75 years or older, have a similar survival benefit from the combination of perioperative chemotherapy and gastrectomy.

A complete omentectomy is part of standard surgical procedure, when performing a radical gastrectomy. In a previous prospective study (OMEGA), the presence of omental metastases was associated with advanced disease and non-curable features. It was questioned whether omentectomy would contribute to a survival benefit in these patients. In **chapter 5** the long-term follow-up results of the OMEGA study are presented. The study protocol for a randomized controlled trial comparing gastrectomy with complete omentectomy or omentum preservation is described in **the appendices**.

Part II: Surgery during the COVID-19 pandemic
Most elective surgical procedures were postponed during the first wave of the COVID-19 pandemic. Different preoperative screening methods were introduced, in order to be able to continue elective surgical care during the remainder of the pandemic. In **chapter 6** the use of preoperative screening with RT-PCR and chest CT in asymptomatic patients is described. Many COVID-19 patients present with gastrointestinal symptoms, besides pulmonary complaints. **Chapter 7** investigates the use of combined chest-abdomen CT to detect COVID-19 in patients presenting with acute gastrointestinal symptoms at the emergency department.

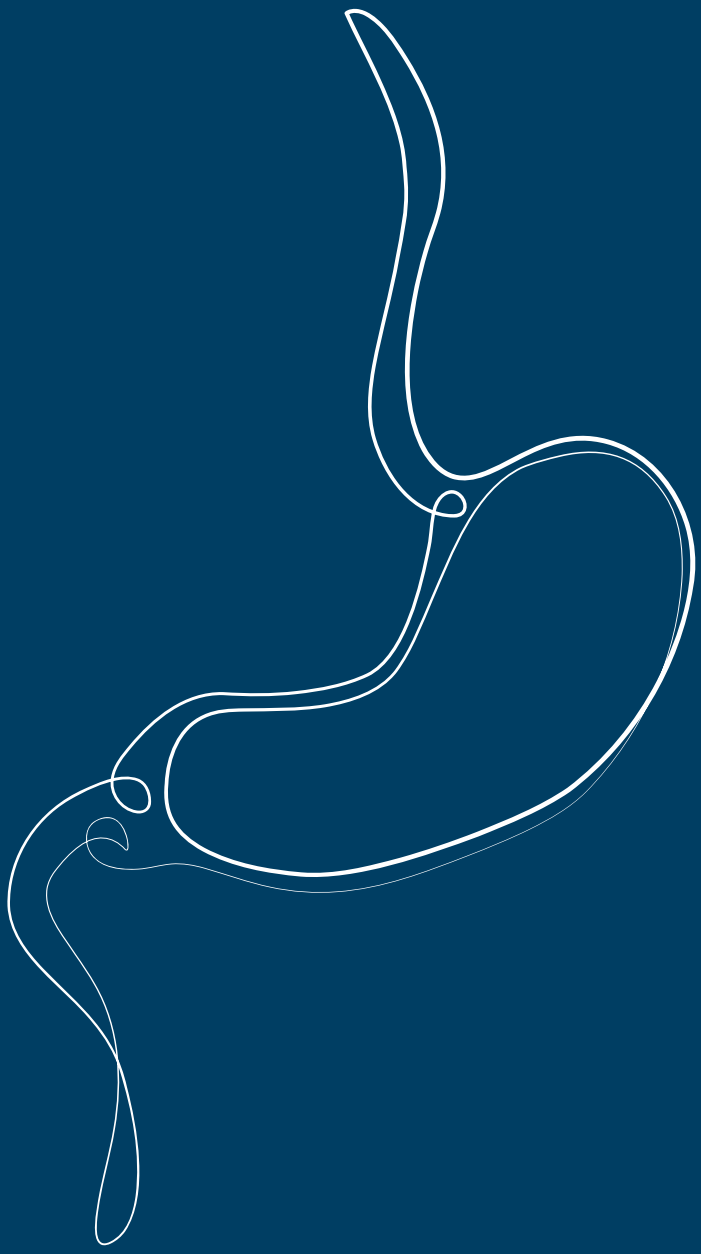
Some centers were able to continue elective surgery, including gastro-esophageal surgery, during the COVID-19 pandemic. In **chapter 8** the safety of performing esophageal cancer surgery during the first wave of the COVID-19 pandemic was investigated in an international multicenter study, in which centers that continued elective esophageal cancer surgery throughout the whole pandemic participated. The safety of reintroducing minimally invasive gastro-esophageal cancer surgery for patients and healthcare workers is evaluated in **chapter 9**. Lastly, prehospital delay may have increased during the first COVID-19, as patients could have been afraid of a possible in-hospital SARS-CoV-2 infection. The influence of COVID-19 on the course of patients with acute appendicitis was investigated in **chapter 10**.

References

1. Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer*. 2019;144(8):1941-1953.
2. Integraal kankercentrum Nederland. Incidentie maagcarcinoom - IKNL. Iknl.Nl. https://iknl.nl/kankersoorten/slokdarm-en-maagkanker/registratie/incidentie. Published 2020.
3. Hamashima C, Kato K, Miyashiro I, et al. Update version of the Japanese guidelines for gastric cancer screening. *Jpn J Clin Oncol*. 2018;48(7):673-683.
4. Jun JK, Choi KS, Lee HY, et al. Effectiveness of the Korean National Cancer Screening Program in Reducing Gastric Cancer Mortality. *Gastroenterology*. 2017;152(6):1319-1328.e7.
5. Oh CM, Won YJ, Jung KW, et al. Cancer statistics in Korea: Incidence, mortality, survival, and prevalence in 2013. *Cancer Res Treat*. 2016;48(2):436-450.
6. Matsuda T, Ajiki W, Marugame T, Ioka A, Tsukuma H, Sobue T. Population-based survival of cancer patients diagnosed between 1993 and 1999 in Japan: A chronological and international comparative study. *Jpn J Clin Oncol*. 2011;41(1):40-51.
7. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA Cancer J Clin*. 2014;64(1):9-29.
8. Smyth EC, Verheij M, Allum W, et al. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2016;27(August):v38-v49.
9. Petrelli F, Berenato R, Turati L, et al. Prognostic value of diffuse versus intestinal histotype in patients with gastric cancer: A systematic review and meta-analysis. *J Gastrointest Oncol*. 2017;8(1):148-163.
10. ID N, RD O, D K, et al. The 2019 WHO classification of tumours of the digestive system. *Histopathology*. 2020;76(2):182-188.
11. Japanese classification of gastric carcinoma: 3rd English edition Japanese Gastric Cancer Association.
12. Chia NY, Tan P. Molecular classification of gastric cancer. *Ann Oncol*. 2016;27(5):763-769.
13. *Evidence Based 2009-05-18 , Verantwoording: Landelijke Werkgroep Gastro-Intestinale Tumoren, Type: Landelijke Richtlijn, Versie: 2.2, Redactionele Aanpassing 2016-07-01 ,.*; 2016. https://www.oncoline.nl/uploaded/docs/Maagcarcinoom/Richtlijn maagcarcinoom.pdf.
14. Hundahl SA. Staging, stage migration, and patterns of spread in gastric cancer. *Semin Radiat Oncol*. 2002;12(2):141-149.
15. Thomassen I, Van Gestel YR, Van Ramshorst B, et al. Peritoneal carcinomatosis of gastric origin: A population-based study on incidence, survival and risk factors. *Int J Cancer*. 2014;134(3):622-628.
16. I T, YR van G, B van R, et al. Peritoneal carcinomatosis of gastric origin: a population-based study on incidence, survival and risk factors. *Int J cancer*. 2014;134(3):622-628.
17. Seevaratnam R, Cardoso R, McGregor C, et al. How useful is preoperative imaging for tumor, node, metastasis (TNM) staging of gastric cancer? A meta-analysis. *Gastric Cancer*. 2012;15
18. Hu Y-F. Staging laparoscopy improves treatment decision-making for advanced gastric cancer. *World J Gastroenterol*. 2016;22(5):1859.
19. Wang Z, Chen JQ. Imaging in assessing hepatic and peritoneal metastases of gastric cancer: A systematic review. *BMC Gastroenterol*. 2011;11.
20. Smyth EC, Verheij M, Allum W, et al. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol*. 2016;27(suppl_5):v38-v49.

21. Gertsen EC, Brenkman HJF, Hillegersberg R van, et al. 18F-Fludeoxyglucose–Positron Emission Tomography/Computed Tomography and Laparoscopy for Staging of Locally Advanced Gastric Cancer: A Multicenter Prospective Dutch Cohort Study (PLASTIC). *JAMA Surg*. October 2021
22. Cats A, Jansen EPM, van Grieken NCT, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. *Lancet Oncol*. 2018;19(5):616-628.
23. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a ra. *Lancet*. 2019;393(10184):1948-1957.
24. Cunningham D, Allum WH, Stenning SP, Weeden S. Perioperative chemotherapy in operable gastric and lower oesophageal cancer: Final results of a randomised, controlled trial (the MAGIC trial, ISRCTN 93793971). *J Clin Oncol*. 2005;23(16_suppl):4001-4001.
25. Smyth EC, Verheij M, Allum W, et al. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2016;27:v38-v49.
26. Japanese gastric cancer treatment guidelines 2018 (5th edition). *Gastric Cancer*. February 2020:1-21
27. Busweiler LAD, Wijnhoven BPL, van Berge Henegouwen MI, et al. Early outcomes from the Dutch Upper Gastrointestinal Cancer Audit. *Br J Surg*. 2016;103(13):1855-1863.
28. van der Veen A, Brenkman HJF, Seesing MFJ, et al. Laparoscopic Versus Open Gastrectomy for Gastric Cancer (LOGICA): A Multicenter Randomized Clinical Trial. *J Clin Oncol*. January 2021:JCO.20.01540.
29. Straatman J, van der Wielen N, Cuesta MA, et al. Surgical techniques, open versus minimally invasive gastrectomy after chemotherapy (STOMACH trial): Study protocol for a randomized controlled trial. *Trials*. 2015;16(1):123.
30. Lee H-J, Hyung WJ, Yang H-K, et al. Short-term Outcomes of a Multicenter Randomized Controlled Trial Comparing Laparoscopic Distal Gastrectomy With D2 Lymphadenectomy to Open Distal Gastrectomy for Locally Advanced Gastric Cancer (KLASS-02-RCT). *Ann Surg*. 2019;270(6).
31. Chen X-Z, Wang S-Y, Wang Y-S, et al. Comparisons of short-term and survival outcomes of laparoscopy-assisted versus open total gastrectomy for gastric cancer patients. *Oncotarget*. 2017;8(32):52366-52380.
32. Kim HH, Han SU, Kim MC, et al. Effect of Laparoscopic Distal Gastrectomy vs Open Distal Gastrectomy on Long-term Survival among Patients with Stage i Gastric Cancer: The KLASS-01 Randomized Clinical Trial. *JAMA Oncol*. 2019;5(4):506-513.
33. Degiuli M, Sasako M, Ponti A, et al. Randomized clinical trial comparing survival after D1 or D2 gastrectomy for gastric cancer on behalf of the Italian Gastric Cancer Study Group.
34. Songun I, Putter H, Kranenbarg EMK, Sasako M, van de Velde CJH. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol*. 2010;11(5):439-449.
35. Hasegawa S, Kunisaki C, Ono H, et al. Omentum-preserving gastrectomy for advanced gastric cancer: A propensity-matched retrospective cohort study. *Gastric Cancer*. 2013;16(3):383-388.
36. Ri M, Nunobe S, Honda M, et al. Gastrectomy with or without omentectomy for cT3-4 gastric cancer: a multicentre cohort study. *Br J Surg*. May 2020.

37. Kim MC, Kim KH, Jung GJ, Rattner DW. Comparative study of complete and partial omentectomy in radical subtotal gastrectomy for early gastric cancer. *Yonsei Med J*. 2011;52(6):961-966.
38. Ha TK, An JY, Youn HG, Noh JH, Sohn TS, Kim S. Omentum-preserving gastrectomy for early gastric cancer. *World J Surg*. 2008;32(8):1703-1708.
39. Sakimura Y, Inaki N, Tsuji T, Kadoya S, Bando H. Long-term outcomes of omentum-preserving versus resecting gastrectomy for locally advanced gastric cancer with propensity score analysis. *Sci Rep*. 2020;10(1):1-9.
40. Murakami H, Yamada T, Taguri M, et al. Short-Term Outcomes from a Randomized Screening Phase II Non-inferiority Trial Comparing Omentectomy and Omentum Preservation for Locally Advanced Gastric Cancer: the TOP-G Trial. *World J Surg 2021 456*. 2021;45(6):1803-1811.
41. Elective surgery cancellations due to the COVID-19 pandemic: global predictive modelling to inform surgical recovery plans. *Br J Surg*. June 2020.
42. Nepogodiev D, Glasbey JC, Li E, et al. Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study. *Lancet*. 2020;0(0).
43. Cai M, Wang G, Wu Y, Wang Z, Wang G, Tao K. Study of the gastrointestinal tumor progression during the COVID-19 epidemic in Wuhan. *Br J Surg*. 2020;107(11):e502-e503.
44. Van Der Werf LR, Busweiler LAD, Van Sandick JW, Van Berge Henegouwen MI, Wijnhoven BPL. Reporting national outcomes after esophagectomy and gastrectomy according to the esophageal complications consensus group (ECCG). *Ann Surg*. 2020;271(6):1095-1101.



PART I

Staging and Treatment of Gastric Cancer

Chapter 2

The role of staging laparoscopy in gastric cancer surgery: a population-based study

Alexander B.J. Borgstein, Mark I. van Berge Henegouwen,
Wytze Lameris, Wietse J. Eshuis and Suzanne S. Gisbertz

European Journal of Surgical Oncology 2020

Abstract

Background

Studies on the value of a staging laparoscopy in detecting metastases in gastric cancer patients show great variation. This study investigates the avoidable surgery rate in patients with and without a staging laparoscopy scheduled for surgery with curative intent.

Methods

This population-based cohort study included all patients with an intentional resection for a potentially curable gastric adenocarcinoma, between 2011 and 2016, registered in the Dutch Upper GI Cancer audit. Patients with and without a staging laparoscopy were compared. The primary outcome was the avoidable surgery rate (detection of metastases and / or locoregional non-resectable tumor during intentional gastrectomy). Secondary outcomes were the negative predictive value, postoperative morbidity and pathology parameters.

Results

2849 patients who underwent an intentional gastrectomy were included. 414 of 2849 (14.5%) patients underwent a staging laparoscopy before initiation of treatment. The avoidable surgery rate was 16.2% in the staging laparoscopy group, compared to 8.5% in the non-staging group ($P < 0.001$), resulting in a negative predictive value of 83.8%. The avoidable surgery rate remained significantly different after correction for possible confounders. The main reason for not executing the gastrectomy was the presence of distant metastasis in both groups. cT and cN stage were significantly higher in patients who underwent a staging laparoscopy.

Conclusions

The staging laparoscopy group had a higher cTN and pTN stage, implicating selection of patients with more advanced disease for a staging laparoscopy. Despite the staging laparoscopy, a higher rate of avoidable surgery was found, suggesting a low sensitivity for detecting metastases or locoregional non-resectability in this patient group.

Introduction

Gastric cancer is the fifth most prevalent type of cancer worldwide and the third most common cause of cancer-related deaths[1]. A gastrectomy, usually combined with perioperative chemotherapy, forms the foundation of curative treatment for gastric cancer. Metastases, mainly peritoneal, are present in up to 40% of newly diagnosed patients with gastric cancer and limit surgical treatment options[2-5].

Computed tomography (CT) scanning of abdomen and thorax is the initial investigation for staging, after gastric cancer has been diagnosed[7]. However, studies have indicated that the sensitivity of CT to detect M1 disease or T4b ranges between 22-33% and 5-69%, respectively[8-11]. Hence, patients with advanced gastric cancer have a high chance of unexpected intraoperative distant metastases or local non-resectability, detected at onset of gastrectomy with curative intent[6].

Current international guidelines advise to perform a staging laparoscopy in ≥ cT3 gastric cancer patients, as studies have shown that a staging laparoscopy before initiation of treatment aids in avoiding an unnecessary laparotomy or laparoscopy for definite surgical treatment[12-14]. Prevention of avoidable surgery ranged between 22-37%, compared to staging with a CT-scan alone[12-14]. However, all studies had a retrospective design, a small sample size and were predominantly performed in Asian countries.

The aim of the current study is to investigate the value of staging laparoscopy by assessing the avoidable surgery rate in gastric cancer patients who underwent surgery with curative intent, with or without staging laparoscopy. Furthermore, this study evaluates factors associated with avoidable surgery.

Materials and Methods

The dataset was obtained from the Dutch Upper Gastrointestinal Cancer Audit (DUCA). This nationwide registry includes all patients in The Netherlands who underwent intentional resection surgery for gastric or esophageal cancer[18]. Patients with non-epithelial tumors or undergoing non-surgical treatment are excluded from the registry. Patients with peritoneal/ liver metastases and / or local non-resectability detected during staging laparoscopy are not included in this registry and could therefore not be included in this study. No ethical approval or informed consent was required for this study, under Dutch law. Because the data in DUCA is anonymous, it is not possible to retrieve missing data from specific hospitals or patients.

Patient Population

All patients with an intentional resection for a potentially curable gastric adenocarcinoma, operated between 2011-2016 and registered in the DUCA were included. Minimal data required for analysis were tumor location, whether or not a staging laparoscopy was

performed and intent of surgery defined at the end of surgical procedure (curative, palliative or no resection). Patients with gastric squamous cell carcinoma or intent of surgery other than curative at the beginning of surgery were excluded. Patients with and without a staging laparoscopy were compared.

Staging and Treatment

Patients are diagnosed with a gastroscopy with biopsies and additional staging is performed by CT scanning of the thorax and abdomen and a PET-CT scan in operable patients with cT3/4 or N+ disease[19]. A staging laparoscopy is recommended in the national guideline in operable patients with cT3/4 gastric cancer before initiation of treatment and if no metastases are detected by imaging[19]. In the first edition of the guideline, it was recommended to consider a staging laparoscopy in cT3/T4 patients with a poorly differentiated tumor. It was stated that laparoscopy is an invasive diagnostic, not suitable for primary staging. The costs and risks were deemed too high for this purpose. The guideline was updated in 2014, and then stated that a staging laparoscopy should be performed in all cT3/4 patients with potentially resectable disease[17-19].

In potentially curable patients with advanced gastric cancer (> cT2N0 or > cT1N1), who are in adequate physical condition, curative therapy consists of perioperative chemotherapy (previously based on the MAGIC scheme[21], nowadays the FLOT scheme[20]), followed by a restaging CT and (sub)total gastrectomy with D2 lymphadenectomy. In selected patients (obstruction or bleeding [tumor characteristics], or unfit patients / comorbidities [patient characteristics]) primary surgery may be performed.

Outcome Measures

The primary outcome was the avoidable surgery rate (detection of peritoneal/liver metastases and / or locoregional non-resectability during intentional gastrectomy). Secondary outcomes were the negative predictive value, postoperative morbidity, cTNM stage, (y)pTNM stage, the R+ resection rate, lymph node yield, the number of metastatic lymph nodes, Lauren classification and tumor regression (pathologically evaluated). In addition, patient and tumor characteristics of patients in the staging laparoscopy group were investigated in a subgroup analysis.

Statistical Analysis

Differences in patient, tumor and treatment characteristics for patients with and without a staging laparoscopy were described using frequency tables. Categorical variables were compared using the $\chi 2$ test. Univariable logistic regression analyses was performed in all patients to identify factors associated with avoidable surgery and to correct for imbalances in baseline characteristics. Variables were added to the multivariable logistic regression model if the variable showed an association with the primary endpoint (*P*-value in univariable analysis ≤ 0.10). The primary outcome was corrected for possible confounders in the multivariable logistic regression analysis. The factors sex, age, body mass index (BMI), American Society of Anesthesiologists (ASA) score, tumor location (antrum was chosen as

reference group, as this tumor location is not associated with increased risk for avoidable surgery and contained the most patients), clinical TN stage, neoadjuvant therapy, urgency of the operation and year of surgery were included in the univariable analysis. The negative predictive value was calculated by dividing the true negatives (staging laparoscopy followed by gastrectomy) by the true negatives + false negatives (staging laparoscopy followed by avoidable surgery).

Additionally, a subgroup analysis including patient and tumor characteristics was performed in the staging laparoscopy group. For all analyses, a 2-sided $P < 0.05$ was considered statistically significant. Statistical analysis was performed in PAWS Statistics version 22 (SPSS, Inc, Chicago, Il, USA).

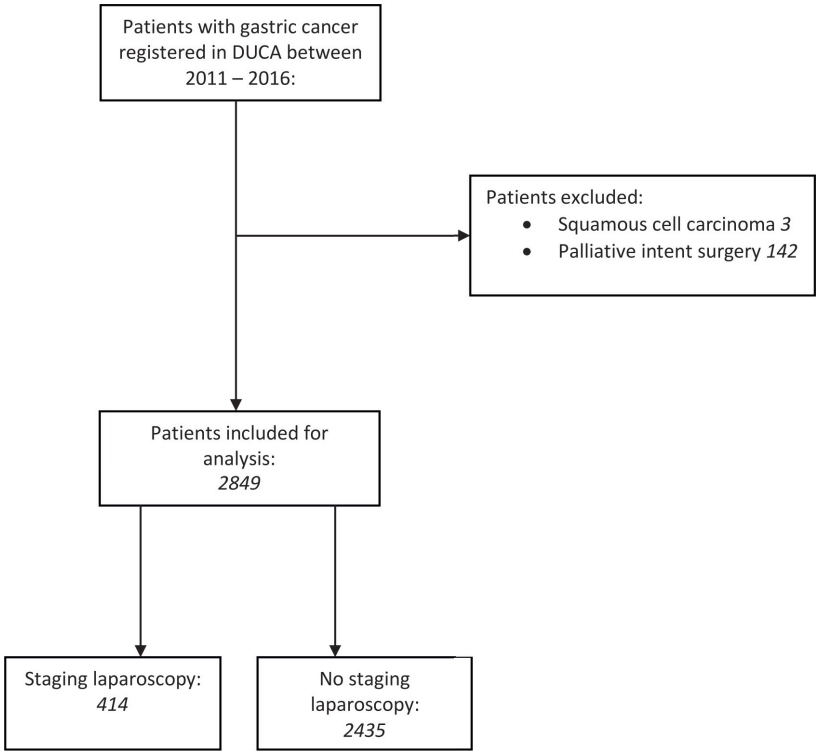


Figure 1. Flowchart of included patients

Results

Patient characteristics

Between January 2011 and December 2016, a total of 2849 patients with a potentially curable gastric adenocarcinoma who underwent surgery with curative intent were registered in the DUCA (figure 1). A staging laparoscopy before initiation of treatment was performed in 414 patients (14.5%). The execution rate of a staging laparoscopy increased from 5.8% in 2011 to 40.1% in 2016. Table 1 summarizes the patient and tumor characteristics of the staging laparoscopy (SL+ group) group and the non-staging laparoscopy (SL- group) group. Patients in the SL- group were older (80.5 vs. 69.7% older than 60 years; $P < 0.001$), more frequently had a BMI >25 (18.6 vs. 13.3%; $P = 0.045$) and an ASA-classification of III or higher (31.6 vs. 23.9%; $P = 0.002$) and a higher rate did not receive neoadjuvant treatment (48.1 vs. 27.3%; $P < 0.001$). Both cT and cN stage were higher in patients who underwent a staging laparoscopy ($P < 0.001$). Patients with a staging laparoscopy had more frequently tumors involving the whole stomach (11.8 vs. 5.4; $P < 0.001$). The number of staging laparoscopies performed increased significantly over the years, from 5.4% (n=24) in 2011 to 40.1% (n=166) in 2016.

Table 2 shows the surgical outcomes. Most operations were elective in both groups (97.6 vs. 95.3%; $P = 0.132$). More patients in the SL+ group underwent a laparoscopic resection (44.0 vs. 33.2; $P <0.001$) and a total gastrectomy (48.8 vs. 35.2%; $P < 0.001$).

Table 1. Baseline patient characteristics

	Total ***n*** **= 2849**	**Staging lap** ***n*** **= 414 (%)**	**Non-staging lap** ***n*** **= 2435 (%)**	***P*-value**
Sex:				0.748
• Male	1775 (62.3)	255 (61.6)	1520 (62.4)	
• Female	1074 (37.7)	159 (38.4)	915 (37.6)	
Age:				< 0.001
• < 60	597 (21.0)	125 (30.3)	472 (19.5)	
• > 60	2242 (78.7)	288 (69.7)	1954 (80.5)	
BMI, kg/m[1]				0.045
• < 20	974 (34.2)	148 (35.7)	826 (33.9)	
• 20 -25	1272 (44.6)	203 (49.0)	1069 (43.9)	
• 25 – 30	423 (14.8)	48 (11.6)	375 (15.5)	
• > 30	82 (2.9)	7 (1.7)	75 (3.1)	
• Unknown	98 (3.5)	8 (1.9)	90 (3.7)	
ASA-classification[2]				0.002
• I	393 (13.8)	72 (17.4)	321 (13.2)	
• II	1578 (55.4)	243 (58.7)	1335 (54.8)	
• ≧ III	851 (29.9)	99 (23.9)	770 (31.6)	
Comorbidity:	2259 (79.3)	314 (75.8)	1945 (79.9)	0.069
• Cardiac	866 (30.4)	87 (21.0)	779 (32.0)	
• Vascular	1133 (39.8)	148 (35.7)	985 (40.5)	
• Diabetes	474 (16.6)	63 (15.2)	411 (16.9)	
• Pulmonary	468 (16.4)	55 (13.3)	413 (17.0)	

	Total *n* = 2849	Staging lap *n* = 414 (%)	Non-staging lap *n* = 2435 (%)	*P*-value
Tumor location:				< 0.001
• Fundus	240 (8.4)	50 (12.1)	190 (7.8)	
• Corpus	851 (29.9)	140 (33.8)	711 (29.2)	
• Antrum	1083 (38.0)	119 (28.7)	964 (39.6)	
• Pylorus	243 (8.5)	34 (8.2)	209 (8.6)	
• Whole stomach	180 (6.4)	49 (11.8)	131 (5.4)	
• Stomach remnant/anastomosis	143 (5.0)	13 (3.1)	130 (5.3)	
• Unknown	109 (3.8)	9 (2.2)	100 (4.1)	
cT-stage:				< 0.001
• T1	181 (6.4)	10 (2.4)	171 (2.9)	
• T2	547 (19.2)	54 (13.0)	493 (20.2)	
• T3	1141 (40.0)	215 (51.9)	926 (38.0)	
• T4	185 (6.5)	69 (16.7)	116 (4.8)	
• Tx	795 (27.9)	66 (15.9)	729 (30.0)	
cN-stage:				< 0.001
• N0	1390 (48.9)	150 (36.2)	1240 (50.9)	
• N1	669 (23.5)	119 (28.7)	550 (22.6)	
• N2	240 (8.4)	64 (15.5)	176 (7.2)	
• N3	39 (1.3)	7 (1.7)	32 (1.3)	
• N+	100 (3.5)	31 (7.5)	69 (2.8)	
• Nx	411 (14.4)	43 (10.4)	368 (15.1)	
Neoadjuvant treatment:				< 0.001
• None	1285 (45.1)	113 (27.3)	1172 (48.1)	
• Chemotherapy	1499 (52.7)	288 (69.6)	1211 (49.8)	
• Chemoradiotherapy	47 (1.6)	13 (3.1)	34 (1.4)	
Year of surgery:				< 0.001
• 2011	336 (11.8)	24 (5.8)	312 (12.8)	
• 2012	403 (14.1)	27 (6.5)	376 (15.4)	
• 2013	543 (19.1)	50 (12.1)	493 (20.2)	
• 2014	572 (20.1)	58 (14.0)	514 (21.1)	
• 2015	476 (16.7)	89 (21.5)	387 (15.9)	
• 2016	519 (18.2)	166 (40.1)	353 (14.5)	

[1]BMI; Body Mass Index. [2]ASA; American Society of Anesthesiology

Table 2. Operative and postoperative results

	Total *n* = 2849	Staging lap *n* = 414 (%)	Non-staging lap *n* = 2435 (%)	*P*-value	Odds ratio (95% CI)
Non-resectable disease:				< 0.001	2.09 (1.55 – 2.81)
• Yes	273 (9.6)	67 (16.2)	206 (8.5)		
• No	2573 (90.3)	346 (83.8)	2227 (91.5)		
Reason non-resectability:				0.321	
• Peritoneal/liver metastases	185 (6.5)	47 (11.4)	138 (5.7)		
• Locoregional non-resectable	131 (4.6)	27 (6.5)	104 (4.3)		
Surgical approach during intentional gastrectomy:				< 0.001	
• Laparoscopy	991 (34.9)	183 (44.0)	808 (33.2)		
• Laparotomy	1852 (65.0)	231 (56.0)	1621 (66.6)		
Operation indication:				0.132	
• Elective	2723 (95.6)	404 (97.6)	2319 (95.3)		
• Urgent	89 (3.1)	9 (2.2)	80 (3.3)		
• Emergency	35 (1.2)	1 (0.2)	34 (1.4)		

	Total *n* = 2849	Staging lap *n* = 414 (%)	Non-staging lap *n* = 2435 (%)	*P*-value	Odds ratio (95% CI)
Surgical resection:				< 0.001	
• Subtotal gastrectomy	1446 (50.8)	127 (30.7)	1319 (54.2)		
• Total gastrectomy	1060 (37.2)	202 (48.8)	858 (35.2)		
Postoperative complications	1064 (37.3)	168 (40.6)	896 (36.8)	0.293	
Intra-abdominal complications:					
• Anastomotic leakage	191 (18.0)	27 (16.1)	164 (18.3)	0.802	
• Bleeding	40 (3.8)	8 (4.8)	32 (3.6)	0.456	
• Chyle leakage	52 (4.9)	11 (6.5)	41 (4.6)	0.228	
Wound complications:					
• Infection/abscess	193 (18.1)	23 (14.0)	170 (19.0)	0.103	
Medical complications:					
• Pulmonary	410 (14.4)	74(44.0)	336 (37.5)	0.112	
• Cardiac	159 (5.6)	24 (14.3)	135 (15.1)	0.790	
• Thromboembolic	38 (1.3)	4 (2.4)	34 (3.8)	0.364	
• Neurologic	116 (4.1)	22 (13.1)	94 (10.5)	0.323	
• Urologic	96 (3.4)	19 (11.3)	77 (8.6)	0.261	
Re-interventions	442 (15.5)	59 (14.3)	383 (15.7)	0.197	
30-day in hospital mortality:					
• Yes	159 (5.6)	22 (5.3)	137 (5.6)	0.671	

Table 3. Histopathological characteristics

	Total *n* = 2576	Staging lap *n* = 347	Non-staging lap *n* = 2229	*P*-value
(y)pT-stage:				< 0.001
• T0	156 (6.1)	19 (5.5)	137 (6.1)	
• T1	380 (14.8)	28 (8.1)	352 (15.8)	
• T2	389 (15.1)	36 (10.3)	353 (15.8)	
• T3	970 (37.7)	132 (38.0)	838 (37.6)	
• T4	565 (22.0)	113(32.6)	452 (20.3)	
• Tx	116 (4.3)	19 (5.5)	97 (4.4)	
(y)pN-stage:				< 0.001
• N0	1112 (43.2)	113 (32.7)	999 (44.8)	
• N1	456 (17.7)	52 (15.0)	404 (18.1)	
• N2	404 (15.7)	67 (19.2)	337 (15.1)	
• N3	470 (18.2)	96 (27.6)	374 (16.8)	
• Nx	132 (5.2)	19 (5.5)	115 (5.2)	
(y)pM-stage:				0.0005
• M0	2228 (86.5)	291 (83.9)	1937 (86.9)	
• M1	151 (5.9)	35 (10.1)	116 (5.2)	
• Unknown	197 (7.6)	21 (6.0)	176 (7.9)	
Radicality of resection:				0.0002
• R0	2197 (85.3)	270 (77.8)	1927 (86.5)	
• R1	260 (10.1)	55 (15.6)	205 (9.3)	
• R2	25 (1.0)	5 (1.4)	20 (0.9)	
• Rx	94 (3.6)	17 (5.2)	77 (3.3)	
Histological type:				< 0.001
• Intestinal type	1002 (38.9)	107 (30.8)	895 (40.2)	
• Diffuse type	749 (29.1)	132 (38.0)	617 (27.7)	
• Mixed type	135 (5.2)	27 (7.8)	108 (4.8)	
• Unknown	690 (26.8)	81 (23.4)	609 (27.3)	

	Total *n* = 2576	Staging lap *n* = 347	Non-staging lap *n* = 2229	*P*-value
Lymph node yield:				< 0.001
• < 15	755 (29.3)	60 (17.3)	695 (31.2)	
• > 15	1794 (69.8)	283 (81.5)	1511 (67.8)	
• Unknown	27 (0.9)	4 (1.2)	23 (1.0)	
Tumor regression after neo-adjuvant therapy:				0.020
• No response	390 (25.2)	79 (26.2)	311 (24.9)	
• Partial response	576 (37.2)	135 (44.9)	441 (35.4)	
• Complete response	146 (9.4)	19 (6.3)	127 (10.2)	
• Unknown	436 (28.2)	68 (22.6)	368 (29.5)	

Table 4. Univariable and multivariable logistic regression model to assess the association of patient, tumour and treatment characteristics with the avoidable surgery rate in the staging laparoscopy group

	Univariable analysis			Multivariable analysis		
	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value
Avoidable surgery				2.31	1.53 – 3.49	< 0.001
Sex:						
• Male	1					
• Female	1.15	0.89 – 1.48	0.289			
Age:						
• < 60	1					
• > 60	0.86	0.64 – 1.15	0.303			
BMI, kg/m^1						
• < 20	1			1		
• 20 -25	0.77	0.59 – 1.02	0.068*	0.77	0.58 – 1.01	0.061
• 25 – 30	0.60	0.39 – 0.91	0.017*	0.62	0.41 – 0.94	0.025*
• > 30	0.73	0.33 – 1.63	0.447	0.78	0.35 – 1.73	0.533
ASA-classification^2						
• I	1					
• II	0.99	0.65 – 1.49	0.949			
• ≧ III	2.20	0.71 – 6.87	0.173			
Tumor location:						
• Antrum	1			1		
• Corpus	1.18	0.85 - 1.64	0.34	1.12	0.81 – 1.57	0.490
• Fundus	1.33	0.82 – 2.16	0.252	1.23	0.75– 2.00	0.414
• Pylorus	1.63	1.04 – 2.57	0.035*	1.60	1.01 – 2.52	0.045*
• Whole stomach	3.24	2.12 – 4.79	0.000*	2.88	1.87– 4.56	< 0.001*
• Stomach remnant/anastomosis	2.15	1.25 – 3.67	0.000*	2.18	1.27 – 3.73	0.005*
cT-stage:						
• T1-T2	1			1		
• T3-T4	7.28	4.10 – 12.92	0.000*	6.68	3.75 – 11.89	< 0.001*
cN-stage:						
• N0	1			1		
• N+	1.99	1.50 – 2.63	0.000*	1.85	1.39 – 2.46	< 0.001*
Neoadjuvant treatment:						
• None	1			1		
• Chemotherapy	0.54	0.42 – 0.70	0.000*	0.48	0.37 – 0.62	< 0.001*
• Chemoradiotherapy/ radiotherapy	0.46	0.14 – 1.48	0.191	0.37	0.11 – 1.21	0.100

	Univariable analysis			Multivariable analysis		
	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value
Operation indication:						
• Elective	1			1		
• Urgent/Emergency	2.80	1.79 – 4.38	0.000*	3.02	1.93 – 4.74	< 0.001*
Year of surgery:						
• 2011	1			1		
• 2012	1.50	0.90 – 2.49	0.117	0.99	0.59 – 1.63	0.962
• 2013	1.59	0.99 – 2.57	0.056*	1.49	0.96 – 2.32	0.076
• 2014	1.22	0.75 – 1.99	0.431	1.54	1.03 – 2.31	0.036*
• 2015	0.92	0.54 – 1.56	0.750	1.17	0.77 – 1.77	0.473
• 2016	1.30	0.79 – 2.13	0.299	0.80	0.51 – 1.27	0.339

Primary and secondary outcomes

A significantly higher rate of avoidable surgery was performed in the staging laparoscopy group: 16.2% (67/414 patients) vs. 8.5% (206/2435 patients; OR 2.09, 95% CI 1.55 – 2.81, *P* < 0.001). The primary outcome remained significantly different after correction for possible confounders (OR 2.31, 95% CI 1.53 – 3.49, *P* < 0.001) (table 4). Main reason for non-resectability in both groups was the presence of distant metastasis. The negative predictive value of staging laparoscopy was 83.8%. There were no significant differences in the rate of postoperative complications between the SL+ and the SL- group (40.6% vs. 36.8%; *P* = 0.293).

The pathological results are shown in table 3. Patients who underwent a staging laparoscopy had a significantly higher (y)pT-stage, (y)pN-stage and (y)pM-stage. Furthermore, a R1 or R2 resection was more frequently observed in the SL+ group (R1 15.6% vs. 9.3%; R2 1.4% vs. 0.9%; *P* = 0.002). In addition, more patients had a diffuse type adenocarcinoma (38.0% vs. 27.7%; *P* < 0.001) and >15 lymph nodes yielded (81.5% vs. 67.8%; *P* < 0.001) in the SL+ group. Finally, complete tumor regression after neoadjuvant therapy was less often observed in the SL+ group (6.3% vs. 10.2%; *P* = 0.020).

Risk factors for avoidable surgery

A tumor location in the whole stomach, pylorus or stomach remnant/anastomosis (versus antrum), a higher cT stage (cT 3-4 versus cT 1-2), a higher cN stage (cN+ versus cN0) and not receiving neoadjuvant therapy (chemotherapy versus no chemotherapy) were associated with detection of peritoneal/liver metastases and/or local non-resectability during intentional gastrectomy (table 4).

Subgroup analysis of the staging laparoscopy group

Subgroup analysis of SL+ patients indicated that non-resectable SL+ patients had a higher rate of ≧cT3 tumors (73.2%), compared to gastrectomy SL+ patients (67.5%; *P* = 0.018). Furthermore, non-resectable SL+ patients received less neoadjuvant therapy: 46.3% vs. 73.3%; *P* <0.001. Finally, a higher rate of urgent operations was performed in non-resectable SL+ patients (7.5% vs. 1.1%, *P* = 0.005).

Discussion

This nation-wide cohort study investigated the value of a staging laparoscopy by evaluating the avoidable surgery rate in patients who underwent surgery with curative intent for gastric cancer. The results show a higher avoidable surgery rate in the staging laparoscopy group compared to the non-staging laparoscopy group (16.2% vs 8.5%; $P < 0.001$), which remained statistically significant after correction for possible confounders. These results suggest a low sensitivity for detecting metastases or locoregional non-resectability by staging laparoscopy in patients scheduled for curative intent gastric cancer surgery.

The avoidable surgery rate of 16.2% after staging laparoscopy that was found in this study is higher than in previous studies. Two single center studies found an avoidable surgery rate of 7.1%[13] and 13.3%[28]. Both studies had small sample sizes, of 98 and 32 patients respectively, compared to this population-based sample of 2849 patients. In addition, in the study by Muntean et al. with the lowest percentage of avoidable surgery (7.1%), 11 out of 45 patients (24.4%) undergoing a staging laparoscopy had a cT2 stage tumor[13], compared to 13.0% in our study group.

A recent meta-analysis found a sensitivity of 85% and a specificity of 100% of staging laparoscopy for detection of peritoneal metastases[14]. As a consequence of the set-up of the national audit (DUCA), where only (intentional) resections are included, sensitivity and specificity could not be calculated in the current study. The negative predictive value of 83.8% was lower than the 92.9% reported by Ramos et al.[14]. However, in terms of inclusion criteria, no distinction was made based on the stage of the gastric tumor in the meta-analysis. Only one study included patients with solitary advanced gastric cancer[21], therefore, our results cannot be compared directly with their findings.

Other studies combined in a meta-analysis[22], found a high specificity, sensitivity and diagnostic accuracy for a staging laparoscopy, however, in these studies staging laparoscopy was compared with other forms of preoperative staging. It is noteworthy that the main objective of our study was not to compare staging laparoscopy to other staging methods.

Tumor location in whole stomach, pylorus or remnant/anastomosis, cT 3-4 stage, cN+ stage and not receiving neoadjuvant therapy were all identified as risk factors for avoidable surgery. These results are in line with those of a previous study reporting on gastric tumor characteristics associated with metastatic disease[23]. The findings of that study indicated that a primary tumor location at the GEJ or whole stomach, poor histologic differentiation, intra-abdominal lymph nodes > 1 cm at CT-scan and cT3/T4 stage gastric tumors were associated with high prevalence of M1 disease[23].

It seems that younger and healthier patients were selected for a staging laparoscopy. Patients in the SL+ group had a lower BMI and ASA score. An explanation could be, that younger and healthier patients are more likely to undergo a staging laparoscopy before being treated

with perioperative chemotherapy, whereas older patients with more comorbidities more often undergo primary surgery, without a staging laparoscopy. Our results substantiate this, as more patients received peri-operative chemotherapy in the SL+ group.

In addition, subgroup analysis of the SL+ group revealed that a higher rate (57.3% vs. 26.7%) of SL+ patients with non-resectable disease did not receive neoadjuvant therapy. Previous studies found a higher curative resection rate and a lower metastatic lymph node rate in gastrectomy patients following neoadjuvant chemotherapy, compared to patients undergoing surgery alone[20,24,25]. However, progression of the disease between the staging laparoscopy and the intentional gastrectomy could also be of influence. Until now, there are no studies that investigated the incidence of interval metastases in advanced gastric cancer. In esophageal cancer, the rate of interval metastases ranges between 8-17%[26-28]. However, most of these studies investigated interval metastases following neoadjuvant chemoradiotherapy, which is usually regarded as a local instead of a systemic therapy. In addition, it is remarkable, that 27% of the patients in the staging laparoscopy group did not receive neoadjuvant chemotherapy, while 98% of these patients were operated electively. Seventy percent of patients in the SL+ group was older than 60 years, 24% had an ASA class 3 or higher and 76% had comorbidities, which explains why perioperative chemotherapy was not deemed indicated. Some centers also perform a staging laparoscopy in patients not scheduled for perioperative chemotherapy, to avoid the chance that the planned surgery cannot be executed due to metastases, since this will dissipate resources.

The results of this study reflect compliance with the Dutch gastric cancer guideline as patients with more advanced disease were selected for a staging laparoscopy[19]. A higher rate of cT3/4 (68.6% vs. 42.8%), cN+ (53.4% vs. 33.9%) and diffuse tumors (38.0% vs. 27.7%) located in the whole stomach (11.8% vs. 5.4%) for which a total gastrectomy (48.8% vs. 35.2%) was performed were found in the SL+ group, which was confirmed by pathology (70.6% vs. 57.9% pT3/4), (61.8% vs. 50.0% pN+) and (10.1% vs. 5.2% pM1). In addition, a higher rate of R+ resections and less regression to neoadjuvant therapy was observed in this group.

The relatively high rate of cT3/4 patients in the SL- group can likely be explained by the recommendation in the 2009 gastric cancer guideline to only consider a staging laparoscopy in patients with cT3/T4 poorly differentiated tumor[17]. The updated version was released in 2014, and since then it is recommended to perform a staging laparoscopy in all cT3/4 gastric cancer patients[19]. During the inclusion period 2011-2016, a gradual increase in the use of a staging laparoscopy was observed from 2011 (5.4%) to 2016 (40.1%). This increase could also be the result of the Dutch centralization for the treatment of gastric cancer in 2013 and the obligatory Dutch Upper GI cancer audit (DUCA), introduced in 2011. A previous study evaluated the implementation of the DUCA and found a trend towards better results for different process and outcome measures in esophageal and gastric cancer treatment[30]. Our findings indicate an increase in the number of hospitals following the Dutch guidelines for gastric cancer, however, an association between year of surgery and avoidable surgery

was not found. Unfortunately, the DUCA does not provide information on hospital level, to guarantee the privacy of participating centers, but is seems that high volume hospitals more often perform staging laparoscopies, as also a higher lymph node yield and more laparoscopic gastrecomies were observed in the SL+ group.

This study has certain limitations. The DUCA database only contains information on patients who were initially planned for a curative gastrectomy. Therefore, this database cannot provide information on patients who were spared avoidable surgery because of a staging laparoscopy. This is the most important limitation of this study and of the DUCA dataset. Other studies have shown that the detection rate of staging laparoscopy for peritoneal metastases ranges between 8 – 44%[8,14]. Even in patients with a low clinical stage (cT1-2 N0), 3,8% of patients were spared surgery[8]. Additionally, 4.6% of patients underwent avoidable surgery because of locoregional non-resectability. In these patients, not only staging laparoscopy but also staging and restaging imaging failed to observe this, and failure cannot only be attributed to the staging laparoscopy.

In addition, the influence of hospital volume on the avoidable surgery rate could not be evaluated, as the DUCA does not provide information that can be traced back to individual hospitals. Another limitation is that the time interval between the staging laparoscopy, neoadjuvant therapy (if applied) and surgery is not registered in the DUCA. The presence of metastases or locoregional non-resectability could also be due to disease progression. Moreover, the baseline characteristics of the SL- and SL+ group show many differences, as has been addressed earlier, which shows selection of certain patients for a staging laparoscopy. Additionally, we have corrected for these imbalances in multivariable analyses. Furthermore, as this is a retrospective study with prospectively collected data, selection bias cannot be ruled out. However, this study is insightful, by showing clearly that there is still a high rate of avoidable surgery after a staging laparoscopy. The current prospective PLASTIC study, that evaluates the impact and cost-effectiveness of PET-CT and staging laparoscopy, may confirm our study results in the near future[6].

In conclusion, a higher rate of avoidable surgery was found in patients who underwent a staging laparoscopy prior to intentional gastrectomy in potentially curable gastric cancer. Future studies should focus on how the diagnostic process of advanced gastric cancer can be improved, in order to prevent avoidable surgery.

References

1. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer. 2019;144(8):1941–53.
2. Shelat VG, Thong JF, Seah M, Lim KH. Role of staging laparoscopy in gastric malignancies - our institutional experience. World J Gastrointest Surg. 2012;4(9):214–9.
3. Bernards N, Creemers GJ, Nieuwenhuijzen GAP, Bosscha K, Pruijt JFM, Lemmens VEPP. No improvement in median survival for patients with metastatic gastric cancer despite increased use of chemotherapy. Ann Oncol. 2013;24(12):3056–60.
4. Thomassen I, Van Gestel YR, Van Ramshorst B, Luyer MD, Bosscha K, Nienhuijs SW, et al. Peritoneal carcinomatosis of gastric origin: A population-based study on incidence, survival and risk factors. Int J Cancer. 2013;134(3):622–8.
5. Hundahl SA. Staging, stage migration, and patterns of spread in gastric cancer. Semin Radiat Oncol. 2002;12(2):141–9.
6. Brenkman HJF, Gertsen EC, Vegt E, van Hillegersberg R, van Berge Henegouwen MI, Gisbertz SS, et al. Evaluation of PET and laparoscopy in STagIng advanced gastric cancer: A multicenter prospective study (PLASTIC-study). BMC Cancer. 2018;18(1).
7. Okines A, Verheij M, Allum W, Cunningham D, Cervantes A. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21(Supplement 5):v50–4.
8. Choi JY oun., Shim KN a., Kim SE u., Jung HK yun., Jung SA e., Yoo K. The clinical value of 18F-fluorodeoxyglucose uptake on positron emission tomography/computed tomography for predicting regional lymph node metastasis and non-curative surgery in primary gastric carcinoma. Korean J Gastroenterol. 2014;64(6):340–7.
9. Seevaratnam R, Cardoso R, McGregor C, Lourenco L, Mahar A, Sutradhar R, et al. How useful is preoperative imaging for tumor, node, metastasis (TNM) staging of gastric cancer? A meta-analysis. Vol. 15, Gastric Cancer. Springer Tokyo; 2012.
10. Wang Z, Chen JQ. Imaging in assessing hepatic and peritoneal metastases of gastric cancer: A systematic review. BMC Gastroenterol. 2011;11.
11. Hu Y-F. Staging laparoscopy improves treatment decision-making for advanced gastric cancer. World J Gastroenterol. 2016;22(5):1859.
12. Nakagawa S, Nashimoto A, Yabusaki H. Role of staging laparoscopy with peritoneal lavage cytology in the treatment of locally advanced gastric cancer. Gastric Cancer. 2007;10:29–34.
13. Muntean V, Mihailov A, Iancu C, Toganel R, Fabian O, Domsa I, et al. Staging laparoscopy in gastric cancer. Accuracy and impact on therapy. J Gastrointest Liver Dis. 2009;18(2):189–95.
14. Ramos RF, Scalon FM, Scalon MM, Dias DI. Staging laparoscopy in gastric cancer to detect peritoneal metastases : A systematic review and meta-analysis. Eur J Surg Oncol. 2016;42(9):1315–21.
15. Guidelines for Diagnostic Laparoscopy - A SAGES Publication. 2010
16. Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D, et al. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol. 2016;27(suppl_5):v38–49.
17. Dutch gastric cancer guidelines. 2009;1–7.

18. Busweiler LAD, Wijnhoven BPL, van Berge Henegouwen MI, Henneman D, van Grieken NCT, Wouters MWJM, et al. Early outcomes from the Dutch Upper Gastrointestinal Cancer Audit. Br J Surg. 2016;103(13):1855–63.
19. Evidence based 2009-05-18 , Dutch gastric cancer guidelines, Version: 2.2. 2016
20. Al-Batran SE, Homann N, Pauligk C, Goetze TO, Meiler J, Kasper S, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4). Lancet. 2019;393(10184):1948–57.
21. Tsuchida K, Yoshikawa T, Tsuburaya A, Cho H, Kobayashi O. Indications for staging laparoscopy in clinical T4M0 gastric cancer. World J Surg. 2011;35(12):2703–9
22. Leake PA, Cardoso R, Seevaratnam R, Lourenco L, Helyer L, Mahar A, et al. A systematic review of the accuracy and indications for diagnostic laparoscopy prior to curative-intent resection of gastric cancer. Vol. 15, Gastric Cancer. Springer Tokyo; 2012.
23 Sarela AI, Lefkowitz R, Brennan MF, Karpeh MS. Selection of patients with gastric adenocarcinoma for laparoscopic staging. Am J Surg. 2006;191(1):134–8.
24. Schuhmacher C, Gretschel S, Lordick F, Reichardt P, Hohenberger W, Eisenberger CF, et al. Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European organisation for research and treatment of cancer randomized trial 40954. J Clin Oncol. 2010;28(35):5210–8.
25. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van De Velde CJH, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11–20.
26. Flamen P. Positron emission tomography for assessment of the response to induction radiochemotherapy in locally advanced oesophageal cancer. Ann Oncol. 2002;13(3):361–8.
27. Weber WA, Ott K, Becker K, Dittler HJ, Helmberger H, Avril NE, et al. Prediction of response to preoperative chemotherapy in adenocarcinomas of the esophagogastric junction by metabolic imaging. J Clin Oncol. 2001;19(12):3058–65.
28. Cerfolio RJ, Bryant AS, Ohja B, Bartolucci AA, Eloubeidi MA. The accuracy of endoscopic ultrasonography with fine-needle aspiration, integrated positron emission tomography with computed tomography, and computed tomography in restaging patients with esophageal cancer after neoadjuvant chemoradiotherapy. J Thorac Cardiovasc Surg. 2005;129(6):1232–41.
29. Yano M, Tsujinaka T, Shiozaki H, Inoue M, Sekimoto M, Doki Y, et al. Appraisal of treatment strategy by staging laparoscopy for locally advanced gastric cancer. World J Surg. 2000;24(9):1130–6.
30. Busweiler LAD, Wijnhoven BPL, van Berge Henegouwen MI, Henneman D, van Grieken NCT, Wouters MWJM, et al. Early outcomes from the Dutch Upper Gastrointestinal Cancer Audit. Br J Surg. 2016;103(13):1855–63.

Chapter 3

Value of staging laparoscopy in patients with advanced gastric cancer: a single center study

Alexander B.J. Borgstein*, Kammy Keywani*, Wietse J. Eshuis, Mark I. van Berge Henegouwen and Suzanne S. Gisbertz

*Shared first authorship

European Journal of Surgical Oncology 2021

Abstract

Background

Most studies exploring the role of staging laparoscopy in gastric cancer are limited by low sample size and are predominantly conducted in Asian countries. This study sets out to determine the value of staging laparoscopy in patients with advanced gastric cancer in a Western population.

Methods

All patients with gastric cancer from a tertiary referral center without definite evidence of non-curable disease after initial staging, and who underwent staging laparoscopy between 2013 and 2020, were identified from a prospectively maintained database. The proportion of patients in whom metastases or locoregional non-resectability was detected during staging laparoscopy was established. Secondary outcomes included the avoidable surgery rate (detection of non-curable disease during gastrectomy with curative intent) and diagnostic accuracy (sensitivity, specificity, accuracy, negative and positive predictive value).

Results

A total of 216 patients were included. Staging laparoscopy revealed metastatic disease in 46 (21.3%) patients and a non-resectable tumor in three (1.4%) patients. During intended gastrectomy, non-curable disease was revealed in 13 (8.6%) patients. Overall sensitivity, specificity and diagnostic accuracy were 76.6%, 100% and 92.6%, respectively. The positive predictive value was 100% and the negative predictive value was 90.3%.

Conclusion

Staging laparoscopy is valuable in the staging process of gastric cancer with a high accuracy in detecting non-curable disease, thereby preventing futile treatment and its associated burden.

Introduction

Gastric cancer remains the fifth most occurring malignancy globally, with an estimated one million new cases annually[1]. The foundation of curative treatment consists of radical gastrectomy, generally in combination with perioperative chemotherapy. Metastases, predominantly peritoneal, are present in up to 40% of newly diagnosed patients with gastric cancer[2,3]. A curative gastrectomy is solely indicated in the absence of metastatic disease, whereas palliative chemotherapy, with or without palliative radiotherapy, is a treatment option for patients with distant metastases or loco-regional non-resectability (T4b stage)[4]. Accurate staging is essential to select the appropriate treatment strategy, and to avoid unnecessary or futile surgery in patients with metastatic disease.

Computed tomography (CT) scanning of the thorax and abdomen is traditionally performed as initial staging modality after the diagnosis of gastric cancer has been established by endoscopy with biopsies. However, studies have shown that CT-scan has limited sensitivity for detecting locally advanced and metastatic disease[5-7]. As a consequence, distant metastases and/or non-resectability are often only revealed at onset of gastrectomy with curative intent. Staging laparoscopy (SL) may prevent gastric cancer patients from undergoing avoidable surgery and futile neoadjuvant therapy. According to current international guidelines, SL should be performed in addition to CT scanning in gastric cancer patients with ≥ cT3 stage tumors[8,9]. The sensitivity of SL to detect distant metastases ranges between 64.3 – 98.9% and avoidable surgery is prevented in 8.5 – 43.8% of all cases[10]. However, most studies investigating the value of staging laparoscopy in gastric cancer are limited by small sample size and included patients with cT1-2 stage tumors. Many studies were conducted in Asian countries, where the prevalence of early-stage gastric cancer is higher compared to the Western world owing to the endemic nature of the disease and the subsequent screening programs.

The aim of this study is to investigate the value of staging laparoscopy in a Western population with advanced gastric cancer without suspicion for metastatic disease or non-resectability after initial staging.

Methods

This single center, cohort study was conducted at the Amsterdam UMC. Consecutive adult patients diagnosed with advanced gastric cancer and who met the inclusion criteria were identified from a prospectively maintained database and included in the study. Ethical approval was waived by the Amsterdam UMC review board because of the retrospective nature of the study.

Study population

Eligible were adult patients with gastric adenocarcinoma (including gastroesophageal junction (GEJ) tumors), clinically staged as cT1-4N0-3M0, without signs of metastatic

disease or a local non-resectable tumor after initial staging, and who underwent a staging laparoscopy between January 1, 2013 and August 30, 2020. Patients who were directly scheduled for gastrectomy, in whom consequently no staging laparoscopy was performed (e.g., in case of obstruction, bleeding tumor, unfitness to receive chemotherapy or endoscopically resectable tumors), patients with gastric cancer recurrence or with other concurrent malignancies were excluded.

Staging and treatment procedures

According to the Dutch gastric cancer guideline, gastric cancer was diagnosed by gastroscopy with biopsies. Staging was performed with CT scanning of thorax and abdomen and additional positron emission tomography-computed tomography (PET-CT) in operable patients with cT3-4 or cN+ stage tumors[9]. A staging laparoscopy was performed in operable patients with ≥cT3 and/or N+ gastric cancer, without signs of metastases or locoregional non-resectability on initial imaging, before perioperative chemotherapy. All patients were naïve for any therapy at the time of staging laparoscopy. Biopsies for histopathological examination were taken from any suspicious lesion detected during staging laparoscopy. When present, ascites was obtained for cytological examination. Standard use of peritoneal lavage cytology is not yet advised in the Dutch guideline because of the lack of high-quality evidence. However, it was performed in this center to detect possible tumor cells in the absence of visible metastases. A positive peritoneal lavage cytology was not considered as metastatic disease, because clinical consequences are not fully understood[11], whereas positive cytology from ascites was considered as metastatic disease and was regarded as an indication for palliative treatment.

If no metastases or locoregional non-resectability was detected during staging laparoscopy, curative treatment generally consisted of perioperative chemotherapy (FLOT scheme[12]), followed by restaging with (PET)-CT and (sub)total gastrectomy with D2 lymphadenectomy. Some patients were directly scheduled for gastrectomy following staging laparoscopy, in case of obstruction, bleeding, unfitness to or wish not to receive chemotherapy. Some patients were treated by neoadjuvant or adjuvant chemoradiotherapy in the setting of a clinical trial[13,14].

Data collection

Clinical and pathologic data of all patients was collected, including age, gender, body-mass index, smoking history, American Society of Anesthesiologists (ASA) classification, comorbidities, diagnostics modalities, tumor location, cTNM classification, Lauren classification, tumor differentiation, Her-2 status, staging laparoscopy outcome and complications, peritoneal lavage cytology outcome, neoadjuvant treatment, surgical approach (laparoscopic/laparotomic), (y)pTNM classification, site of distant metastases and palliative treatment.

Study outcomes

Primary outcome was the proportion of patients in whom metastases or locoregional non-resectability was detected during staging laparoscopy. Secondary outcomes included diagnostic accuracy (sensitivity, specificity, accuracy, negative and positive predictive value), the avoidable surgery rate (detection of metastases or locoregional non-resectability during gastrectomy with curative intent), perioperative and 30-day postoperative outcomes after staging laparoscopy and resection.

Statistical analysis

Baseline characteristics were analyzed using descriptive statistics. Results were presented as mean (SD) for normally distributed variables, median (IQR) for non-normally distributed variables and counts (percentage) for categorical variables. The diagnostic performance (specificity, sensitivity and accuracy) of staging laparoscopy to detect distant metastases was assessed against the restaging findings and final pathological report (pTNM) after gastrectomy. To identify possible risk factors associated with non-curable disease, a multivariable logistic regression was performed. Significant variables (p<0.15) in the univariable analysis were entered into the multivariable analysis. Stepwise backward selection was used to finalize the model (p<0.05 to stay in the model). Missing data was not imputed. Data were analysed using SPSS version 26 (IBM, Armonk, New York, USA).

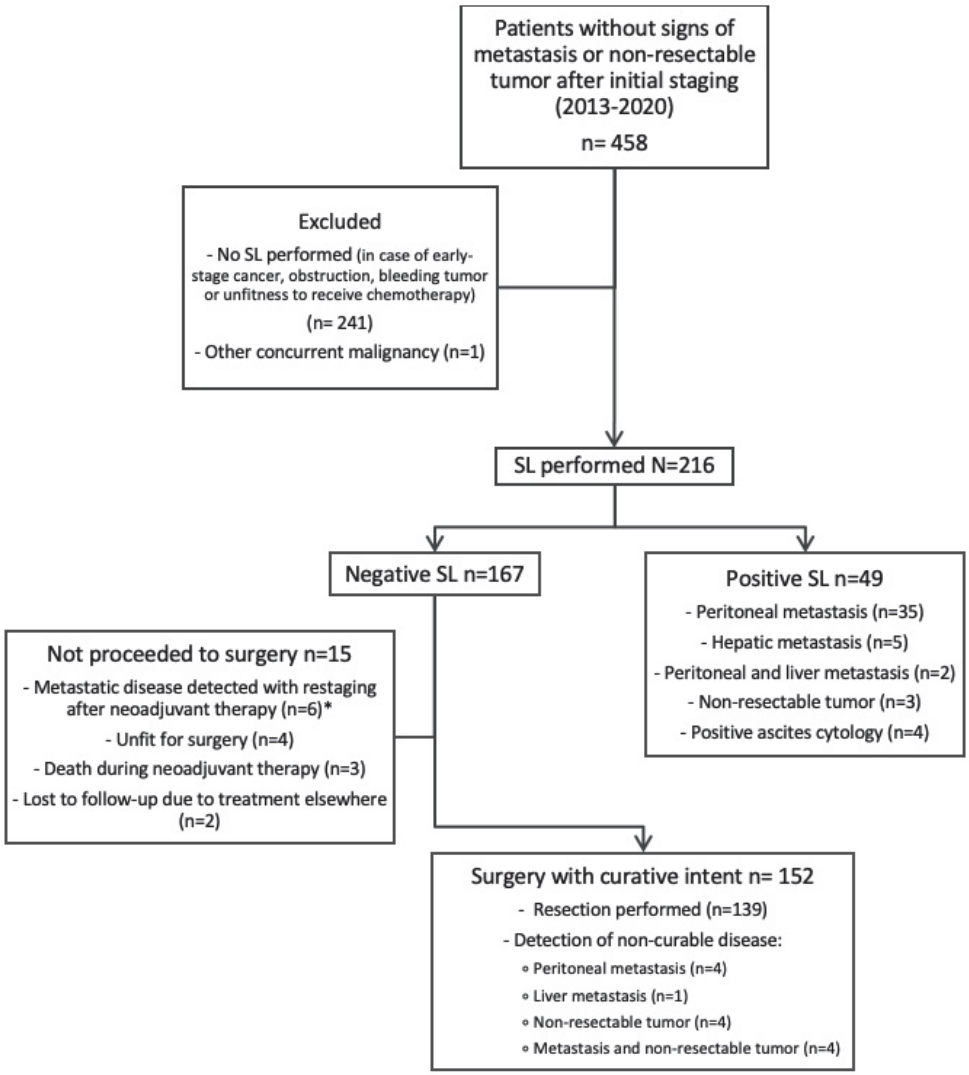


Figure 1. flowchart of included patients

Results

Patient characteristics

216 consecutive patients with a potentially curable gastric adenocarcinoma who underwent a staging laparoscopy were included (figure 1). Table 1 (a,b) summarizes the baseline characteristics of all patients. The mean age was 63 years and 154 out of 216 (71.3%) patients were male. Patients were staged with a CT thorax-abdomen in 30.1% (65 patients) and a PET-CT in 69.9% (151 patients). Fifteen out of 216 (7.0%) patients had a cT1-2 stage gastric tumor and 200 (92.5%) patients had a ≥cT3 stage gastric tumor.

Table 1a. Baseline characteristics of 216 included patients with potentially curable gastric adenocarcinoma who underwent staging laparoscopy

Patients characteristics	N = 216
Age, mean (SD), years	65 (11.5)
Age, range, years	21 – 83
Male sex, no./total no. (%)	154 (71.3)
Body-mass index, median (IQR), kg/m^2	24 (22 – 27)
Body-mass index >30, no./total no. (%)	19 (8.8)
Smoking history, no./total no. (%)	
Never smoked	66 (30.6)
Former smoker	97 (44.9)
Current smoker	50 (23.1)
Unknown	3 (1.5)
ASA classification, no./total no. (%)	
1	24 (11.1)
2	148 (68.5)
3	43 (19.9)
4	1 (0.5)
Comorbidities, no./total no. (%)	
None	139 (64.4)
Cardiac	21 (9.7)
Vascular	10 (4.6)
Diabetes	22 (10.2)
Pulmonary	13 (6.0)
Multiple	11 (5.1)
Charlson Comorbidity Index, no./total no. (%)	
0	25 (11.6)
1	35 (16.2)
2	63 (29.2)
3	50 (23.1)
4+	43 (20.0)

Diagnostics	N = 216
Diagnostics modalities no. (%)	
Gastroscopy	216 (100.0)
EUS	96 (44.4)
CT thorax-abdomen	65 (30.1)
PET-CT thorax-abdomen	151 (69.9)
Tumor characteristics	
Tumor location, no./total no. (%)	
GEJ	51 (23.6)
Cardia	71 (32.9)
Fundus	2 (0.9)
Corpus	33 (15.3)
Antrum	46 (21.3)
Pylorus	5 (2.3)
Diffuse	8 (3.7)
cT-stage, no./total no. (%)	
T1	1 (0.5)
T2	14 (6.5)
T3	171 (79.1)
T4	29 (13.4)
Tx	1 (0.5)
cN-stage, no./total no. (%)	
N0	74 (34.3)
N1	67 (31.0)
N2	41 (19.0)
N3	9 (4.2)
Nx	25 (11.6)
Lauren classification, no./total no. (%)	
Intestinal	101 (46.8)
Diffuse	68 (31.5)
Mixed	7 (3.2)
Unknown	40 (18.5)
Tumor differentiation, no./total no. (%)	
Well	1 (0.5)
Moderate	76 (35.2)
Poorly	88 (40.7)
Undifferentiated	2 (0.9)
Unknown	49 (22.7)
Her-2-Neu status, no./total no. (%)	
Positive	22 (10.2)
Negative	162 (75.0)
Unknown	32 (14.8)

Abbreviations: ASA, American Society of Anesthesiologists; GEJ, Gastroesophageal junction; IQR, interquartile range; SD, standard deviation; CT, computed tomography; PET-CT, positron emission tomography–computed tomography; EUS, Endoscopic ultrasonography;

Table 1b. Diagnostic and tumor characteristics of 216 included patients with potentially curable gastric adenocarcinoma who underwent staging laparoscopy

Staging laparoscopy results

Table 2 provides an overview of the staging laparoscopy results of 216 patients. Staging laparoscopy detected metastases or locoregional non-resectability in 49 (22.7%) patients. Distant metastases were detected in 46 (21.3%) patients. The main location of distant metastases was the peritoneum (76.1%) and four (8.7%) patients had positive ascites. In three (1.4%) patients a non-resectable tumor was detected. Peritoneal lavage cytology was positive in 14 (6.6%) patients, of whom 13 also had metastases detected during SL. The median hospital stay was 0 (0-1) days and no postoperative complications occurred.

Table 2. Staging laparoscopy results of 216 patients with potentially curable gastric adenocarcinoma

	N = 216
Detection of metastasis, no./total no. (%)	46 (21.3)
Location of metastasis, no. (%)	
Peritoneal metastasis	35 (76.1)
Liver metastasis	5 (10.9)
Peritoneal and liver metastasis	2 (4.3)
Ascites	4 (8.7)
Detection of non-resectable tumor, no./total no. (%)	3 (1.4)
Peritoneal lavage cytology, no./total no. (%)	
Positive*	14 (6.5)
Negative	146 (67.6)
Suspect/atypical cells	13 (6.0)
Material insufficient	2 (0.9)
No cytology collected	41 (19.0)
Overall positive SL, no./total no. (%)[#]	49 (22.7)
Intraoperative and 30-day postoperative surgical complications, no./total no. (%)	0 (0.0)
Hospital stay, median (IQR), days	0 (0-1)

Abbreviations: SL, staging laparoscopy; IQR, interquartile range.
[#]Positive SL is defined as positive ascites cytology, positive histology or non-resectable tumor. [*]13 of these 14 patients had metastases detected with SL. One patient with only positive cytology was scored as negative SL and proceeded for treatment with curative intent.

Treatment results

134 (88.2%) patients received neoadjuvant treatment before surgery, which consisted mostly of chemotherapy (82.9%). Fifteen patients out of 167 (9.0%) with a negative staging laparoscopy did not proceed to surgery (figure 1). Four of these patients were unfit for surgery and two were lost to follow-up. In six patients, metastases were detected during restaging after chemotherapy, two with liver metastases and four with para-aortic lymph node metastases and three patients deceased during neoadjuvant therapy, due to complications.

Table 3 shows the surgical outcomes of 152 patients who underwent gastrectomy with curative intent after negative staging laparoscopy. The median time between staging laparoscopy and scheduled gastrectomy was 18 weeks (IQR 15 – 20) in patients treated with neoadjuvant therapy. In patients undergoing upfront surgery, time between staging laparoscopy and scheduled gastrectomy was 5 weeks (IQR 4 – 7).151 (99.3%) patients underwent elective surgery and in 109 (71.7%) patients a minimally invasive procedure was performed. 43 patients (30.9%) underwent a total gastrectomy. In 13 patients (8.6%) non-curable disease was detected during surgery with curative intent. Reasons for non-curable disease were: peritoneal metastases (n=4, 30.8%), liver metastases (n=1, 7.7%), a locally non-resectable tumor (n=4, 30.8%) and a combination of a non-resectable tumor and peritoneal metastases (n=4, 30.8%). Three out of the 13 patients (23.1%) did not receive neoadjuvant chemotherapy, compared to 18 patients (11.8%) in the group who underwent gastrectomy. Of the remaining ten patients, none had disease progression during restaging and the time interval between staging laparoscopy and intended gastrectomy was 16 weeks (compared to 18 weeks in the group of patients who underwent gastrectomy).

The number of patients with postoperative complications was 49 (35.3%) and the mean comprehensive complication index (CCI) was 34. The median length of hospital stay was 8 (7-11) days and the combined in-hospital and 30-day mortality rate was 3.6%.

Table 3. Results of 152 patients who underwent gastrectomy with curative intent after negative staging laparoscopy

	N = 152
Neoadjuvant therapy, no./total no. (%)	
None	18 (11.8)
Chemotherapy	126 (82.9)
Chemoradiotherapy	8 (5.3)
Time between staging laparoscopy and gastrectomy (weeks), median (IQR)	17 (14-20)
Time between staging laparoscopy and gastrectomy without neoadjuvant therapy (weeks), median (IQR)	5 (4-7)
Surgical approach, no./total no. (%)	
Open	38 (25.0)
Minimal invasive	109 (71.7)
Minimal invasive converted to open	5 (3.3)
Operation indication, no./total no. (%)	
Elective	151 (99.3)
Urgent/emergency	1 (0.7)
Detection of non-curable disease during intended gastrectomy no./total no. (%)	13 (8.6)
Nature of non-curable disease, no. (%)	
Peritoneal metastasis	4 (30.8)
Liver metastasis	1 (7.7)
Non-resectable tumor	4 (30.8)
Non-resectable tumor and metastasis	4 (30.8)
Palliative surgical treatment no. (%)	

None	4 (30.8)
Palliative resection	2 (15.4)
Feeding jejunostomy	7 (53.8)
N = 139	
Resection type, no./total no. (%)	
Esophagectomy	29 (20.9)
Total gastrectomy	43 (30.9)
Total gastrectomy + distal esophagectomy	18 (12.9)
Subtotal gastrectomy	49 (35.3)
(y)pT-stage, no./total no. (%)	
T0	18 (12.9)
T1	14 (10.1)
T2	13 (9.4)
T3	60 (43.2)
T4	29 (20.9)
Tx	5 (3.6)
(y)pN-stage, no./total no. (%)	
N0	60 (43.2)
N1	23 (16.5)
N2	31 (22.3)
N3	25 (18.0)
Resection margin, no./total no. (%)	
R0	131 (94.2)
R1	8 (5.8)
Lymph node yield median (IQR)	27 (18-33)
Lymph node yield, no./total no. (%)	
<15	16 (11.5)
>15	123 (88.5)
30-day postoperative complications, no./total no. (%)	49 (35.3)
Maximum Clavien-Dindo, no./total no. (%)	
I	9 (6.5)
II	13 (9.4)
III	15 (10.8)
IV	9 (6.5)
V	3 (2.2)
CCI score, mean (SD)	34 (23.2)
Length of hospital stay (days), median (IQR)	8 (7 – 11)
Readmission within 30-days, no./total no. (%)	17 (12.2)
In hospital and 30-day mortality, no./total no. (%)	5 (3.6)

Abbreviations: CCI, comprehensive complication index; SD, standard deviation; IQR, interquartile range;

Diagnostic accuracy of staging laparoscopy

Table 4 presents the diagnostic accuracy of staging laparoscopy to detect metastatic disease and/or non-resectability in patients with advanced gastric cancer. The overall sensitivity was 76.6% (49/64; 95% CI 64-86%); staging laparoscopy revealed metastatic and/or non-resectability in 49 patients and failed to detect non-curable disease in 15 patients (two cases of liver metastases detected during restaging and 13 non-curable disease detected during surgery). The specificity was 100% (139/139; 95% CI 97-100%); staging laparoscopy correctly predicted curable disease in 139 patients, without any false-positives. The diagnostic accuracy was 92.6% (188/203); Fifteen out of the 216 patients did not proceed to surgery, in thirteen cases this was not related to failure of staging laparoscopy. In the remaining 203 patients, staging laparoscopy correctly discriminated between curable and non-curable disease in 188 cases. The positive predictive value was 100% (49/49) and the negative predictive value was 90.3% (139/154); 154 patients proceeded to surgery, 139 of whom truly had curable disease.

Table 4. Staging laparoscopy diagnostic accuracy in detecting metastatic disease or non-resectability

SL diagnostic accuracy:		**95% CI**
Sensitivity	76.6% (49/64)	64% – 86%
Specificity	100% (139/139)	97% – 100%
Accuracy	92.6% (188/203)	-
PPV	100% (49/49)	91% – 100%
NPV	90.3% (139/154)	84% – 94%

Abbreviations: SL, staging laparoscopy; PPV, positive predictive value; NPV, negative predictive value; CI, confidence interval;

Risk factor associated with non-curable disease

Male sex, tumor located in the cardia, diffuse type and Her-2 positive tumors were associated with non-curable disease in the univariate analyses. No factors were associated with non-curable disease in the multivariable analysis.

Discussion

The present study investigated the value of staging laparoscopy in gastric cancer patients, without signs of metastatic disease or locoregional non-resectable tumor after initial staging. Of the 216 patients who underwent a staging laparoscopy, metastatic disease was detected in 46 (21.3%) and a non-resectable tumor in three (1.4%). Overall, the diagnostic accuracy of staging laparoscopy to detect non-curable disease was high (92.6%).

Our study results show that performing a staging laparoscopy after initial staging prevented 49 (22.7%) patients from undergoing unnecessary neoadjuvant therapy and/or surgery

and the associated burden of these treatments. Peritoneal metastases, which are often not detected with (PET)-CT[15], were predominantly detected by staging laparoscopy. No postoperative complications occurred and the median hospital stay was zero days after staging laparoscopy.

In 28 (16.8%) patients, no gastrectomy was performed after a negative staging laparoscopy. Fifteen of those patients did not proceed to surgery because of various reasons and thirteen patients did not proceed to resection, as non-curable disease was detected during surgery with curative intent. The avoidable surgery rate was 8.6% in the current study.

Our study results are comparable to findings of previous studies, which indicated the yield of staging laparoscopy to detect metastases or a non-resectable tumor to range from 7.8% to 53.4%[16]. The rate of false-negatives of 9.7% appears to be consistent with a review by Fukagawa et al. (2019), which reported a false-negative rate ranging between 0% to 17.2%[17]. It should be noted that in some of the studies included in the review, the aim was to estimate the diagnostic accuracy of staging laparoscopy to detect peritoneal metastases, other clinical findings such as liver metastases or a non-resectable tumor were not incorporated in establishing the false-negatives. Therefore, a lower false-negative rate was seen in some of the included studies.

We found a diagnostic accuracy of 92.6%, sensitivity of 76.6%, and specificity of 100%, which is similar to the results of previous literature. A systematic review by Leake et al. described the sensitivity and specificity of staging laparoscopy to detect metastatic disease to range between 64.3-94.0% and 80.0-100%[18]. Our sensitivity of 76.6% is in the lower range compared to the sensitivity found in the systematic review. However, ten of the 21 articles included in the review described the diagnostic accuracy in patients with early stage gastric cancer (cT1-2 stage). According to the Dutch and international guidelines, staging laparoscopy should be performed in operable patients with ≥cT3 gastric cancer. More than 90% of included patients in the current study had a cT3-4 stage gastric tumor. Previous studies indicated ≥cT3 stage gastric cancer to be related with a higher chance of metastatic disease[19-22].

Recently, another study evaluated the implementation of staging laparoscopy and PET-CT in The Netherlands[23]. The results of this study showed an avoidable surgery rate of 13.7% in 226 patients who underwent staging laparoscopy before surgery. This percentage decreased to 10.4% with the addition of PET-CT before staging laparoscopy. Since 2016, staging laparoscopy and PET-CT are advised by the Dutch gastric cancer guidelines for patients with advanced gastric cancer detected on initial staging[9]. The Dutch PLASTIC trial started in 2017[24], to evaluate the impact and cost-effectiveness of PET-CT and staging laparoscopy in addition to initial staging in patients with advanced gastric cancer in The Netherlands. The study results will be published soon. In the current study, in concordance with our guideline, 70.0% of all included patients underwent both staging laparoscopy and PET-CT before surgery.

The avoidable surgery rate in the current study was lower compared to a previous population-based study[25]. The avoidable surgery rate was 16.2% in 414 patients undergoing gastrectomy with curative intent after staging laparoscopy, which could be explained by the larger proportion of patients with a cT4 tumor (16.7% vs. 13.4%) selected for staging laparoscopy compared to the current study. Serosal invasion (cT4a stage) in gastric tumors is an important factor associated with peritoneal dissemination[26]. Additionally, more patients received neoadjuvant chemotherapy in this study (82.9%) compared to the previous one (69.6%). Previous studies found a higher curative resection rate in patients receiving neoadjuvant chemotherapy before surgery[12,27,28].

A recent population-based study investigated the avoidable surgery rate as part of a composite endpoint *failure to cure* (avoidable surgery, non-radical surgery and 30-day/in-hospital mortality) in gastric cancer patients undergoing surgery between 2011 and 2019 in The Netherlands[29]. The overall avoidable surgery rate was 8.4%, this however, included both patients with and without a staging laparoscopy.

According to the Dutch and European gastric cancer guidelines, staging laparoscopy is recommended in patients with advanced gastric cancer[8,9]. Additionally, current guidelines also recommend neoadjuvant chemotherapy in all operable patients with >T1 N0 stage gastric cancer[8,9]. It can be questioned whether staging laparoscopy should be repeated after neoadjuvant treatment, besides (PET-)CT scanning, in order to evaluate the response to chemotherapy and to exclude occult disease progression. In this study, repeated laparoscopy was not performed. Hence, this question needs to be investigated in future studies, as no other studies have yet investigated this. However, with the increasing use of minimally invasive gastrectomies, occult metastatic or non-resectable disease can also be excluded at the start of the gastrectomy. In this study, 13 (8.6%) patients were non-resectable, of which 11 were detected during a laparoscopic procedure.

Metastases (mainly peritoneal) are present in up to 40% of patients diagnosed with gastric cancer[2,3]. Accurate sub-staging of peritoneal metastases could be used to determine treatment options for gastric cancer patients with peritoneal metastases, as patients with limited peritoneal disease may benefit from HIPEC procedures. This is currently being investigated in several randomized controlled trials[30-32]. It is therefore crucial to systematically perform and describe the staging laparoscopy according to the Peritoneal Cancer Index[33], Gilly Staging[34], P123[35] or the 15th edition of the peritoneal metastasis staging system (P1abc) by the Japanese Classification of Gastric Carcinoma (JCGC)[36]. Recently, a study validated the predictive ability of the P1abc[36] and found that this staging system was superior in predicting overall survival compared to previous staging systems, including JCGC PM staging (P123) and Gilly.

Most studies investigating the value of staging laparoscopy in gastric cancer are limited by small sample size. To our knowledge, this is one of the largest studies in terms of sample size to investigate the value of staging laparoscopy in a Western population.

Moreover, most studies assess the diagnostic performance of staging laparoscopy by the percentage of patients in whom metastatic disease was visually detected and confirmed with histopathological examination[37,38]. However, the value of staging laparoscopy is not assessed against the results of restaging with (PET)-CT or gastrectomy. In our study, diagnostic accuracy was based on the results of staging laparoscopy, restaging with (PET)-CT and surgery with curative intent.

We do acknowledge our study has certain limitations. Non-curable disease detected during restaging after neoadjuvant therapy or at onset of intentional gastrectomy were regarded as failures of staging laparoscopy. However, these false-negatives could be related to disease progression during neoadjuvant therapy. Unfortunately, there are no studies that investigated the incidence of interval metastases in advanced gastric cancer. It is possible, therefore, that the sensitivity of staging laparoscopy is somewhat underestimated in our study. Furthermore, 7.0% of all patients included in this study had cT1-2 stage tumors, in whom staging laparoscopy should not standardly be performed according to the Dutch and international guidelines. Therefore, a certain degree of selection bias cannot be ruled out. Also, this study included 23.6% patients with primary tumors involving the gastroesophageal junction. In clinical practice, the exact origin of GEJ tumors can sometimes be difficult to determine[39]. Thus, the possibility exists that in some of the cases the tumor primarily originated in the distal esophagus instead of the stomach. Lastly, the multivariable logistic regression model to identify possible risk factors associated with non-curable disease could not be performed, as the number of patients was inadequate to create an accurate model.

In conclusion, staging laparoscopy is a safe procedure and has a substantial value in the staging process of gastric cancer with a high diagnostic accuracy. Staging laparoscopy prevented 22.7% of all patients from undergoing unnecessary neoadjuvant chemotherapy and/or surgery and its associated burden and should therefore be a standard clinical staging modality in T3-4 and/or N+ gastric cancer.

References

1. Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer*. 2019;144(8):1941-1953.
2. Hundahl SA. Staging, stage migration, and patterns of spread in gastric cancer. *Semin Radiat Oncol*. 2002;12(2):141-149.
3. Thomassen I, Van Gestel YR, Van Ramshorst B, et al. Peritoneal carcinomatosis of gastric origin: A population-based study on incidence, survival and risk factors. *Int J Cancer*. 2014;134(3):622-628.
4. Bernards N, Creemers GJ, Nieuwenhuijzen GAP, Bosscha K, Pruijt JFM, Lemmens VEPP. No improvement in median survival for patients with metastatic gastric cancer despite increased use of chemotherapy. *Ann Oncol*. 2013;24(12):3056-3060.
5. Seevaratnam R, Cardoso R, McGregor C, et al. How useful is preoperative imaging for tumor, node, metastasis (TNM) staging of gastric cancer? A meta-analysis. *Gastric Cancer*. 2012;15(SUPPL.1).
6. Wang Z, Chen JQ. Imaging in assessing hepatic and peritoneal metastases of gastric cancer: A systematic review. *BMC Gastroenterol*. 2011;11.
7. Hu YF, Deng ZW, Liu H, et al. Staging laparoscopy improves treatment decision-making for advanced gastric cancer. *World J Gastroenterol*. 2016;22(5):1859-1868.
8. Smyth EC, Verheij M, Allum W, et al. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol*. 2016;27(suppl_5):v38-v49.
9. *Evidence Based 2009-05-18 , Verantwoording: Landelijke Werkgroep Gastro-Intestinale Tumoren, Type: Landelijke Richtlijn, Versie: 2.2, Redactionele Aanpassing 2016-07-01 ,.*; 2016. https://www.oncoline.nl/uploaded/docs/Maagcarcinoom/Richtlijn maagcarcinoom.pdf. Accessed December 13, 2018.
10. Leake PA, Cardoso R, Seevaratnam R, et al. A systematic review of the accuracy and indications for diagnostic laparoscopy prior to curative-intent resection of gastric cancer. *Gastric Cancer*. 2012;15(SUPPL.1):38-47.
11. Jamel S, Markar SR, Malietzis G, Acharya A, Athanasiou T, Hanna GB. Prognostic significance of peritoneal lavage cytology in staging gastric cancer: systematic review and meta-analysis. *Gastric Cancer*. 2018;21(1):10-18.
12. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a ra. *Lancet*. 2019;393(10184):1948-1957.
13. Dikken JL, van Sandick JW, Maurits Swellengrebel HA, et al. Neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy for patients with resectable gastric cancer (CRITICS). *BMC Cancer*. 2011;11(1):329.
14. Slagter AE, Jansen EPM, van Laarhoven HWM, et al. CRITICS-II: A multicentre randomised phase II trial of neo-adjuvant chemotherapy followed by surgery versus neo-adjuvant chemotherapy and subsequent chemoradiotherapy followed by surgery versus neo-adjuvant chemoradiotherapy followed by surgery in resectable gastric cancer. *BMC Cancer*. 2018;18(1):1-12.
15. Wang Z, Chen JQ. Imaging in assessing hepatic and peritoneal metastases of gastric cancer: A systematic review. *BMC Gastroenterol*. 2011;11.

16. Parasa S, Desai M, Thoguluva Chandrasekar V, et al. Prevalence of Gastrointestinal Symptoms and Fecal Viral Shedding in Patients With Coronavirus Disease 2019: A Systematic Review and Meta-analysis. *JAMA Netw open*. 2020;3(6):e2011335. doi:10.1001/jamanetworkopen.2020.11335
17. Fukagawa T. Role of staging laparoscopy for gastric cancer patients. *Ann Gastroenterol Surg*. 2019;3(5):496-505.
18. Leake PA, Cardoso R, Seevaratnam R, et al. A systematic review of the accuracy and indications for diagnostic laparoscopy prior to curative-intent resection of gastric cancer. *Gastric Cancer*. 2012;15(SUPPL.1).
19. Grundmann RT, Hölscher AH, Bembenek A, et al. Diagnostik und Therapie des Magenkarzinoms Workflow. *Zentralblatt fur Chir - Zeitschrift fur Allg Visz und Gefasschirurgie*. 2009;134(4):362-374.
20. Fujimura T, Kinami S, Ninomiya I, et al. Diagnostic laparoscopy, serum CA125, and peritoneal metastasis in gastric cancer. *Endoscopy*. 2002;34(7):569-574.
21. de Graaf GW, Ayantunde AA, Parsons SL, Duffy JP, Welch NT. The role of staging laparoscopy in oesophagogastric cancers. *Eur J Surg Oncol*. 2007;33(8):988-992.
22. Sarela AI, Lefkowitz R, Brennan MF, Karpeh MS. Selection of patients with gastric adenocarcinoma for laparoscopic staging. *Am J Surg*. 2006;191(1):134-138.
23. Gertsen EC, Borggreve AS, Brenkman HJF, et al. Evaluation of the Implementation of FDG-PET/CT and Staging Laparoscopy for Gastric Cancer in The Netherlands. *Ann Surg Oncol*. September 2020:1-10.
24. Brenkman HJF, Gertsen EC, Vegt E, et al. Evaluation of PET and laparoscopy in STagIng advanced gastric cancer: A multicenter prospective study (PLASTIC-study). *BMC Cancer*. 2018;18(1):1-7.
25. Borgstein ABJ, van Berge Henegouwen MI, Lameris W, Eshuis WJ, Gisbertz SS. Staging laparoscopy in gastric cancer surgery. A population-based cohort study in patients undergoing gastrectomy with curative intent. *Eur J Surg Oncol*. November 2020.
26. Boku T, Nakane Y, Minoura T, et al. Prognostic significance of serosal invasion and free intraperitoneal cancer cells in gastric cancer. *Br J Surg*. 1990;77(4):436-439.
27. Schuhmacher C, Gretschel S, Lordick F, et al. Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European organisation for research and treatment of cancer randomized trial 40954. *J Clin Oncol*. 2010;28(35):5210-5218.
28. Cunningham D, Allum WH, Stenning SP, Weeden S. Perioperative chemotherapy in operable gastric and lower oesophageal cancer: Final results of a randomised, controlled trial (the MAGIC trial, ISRCTN 93793971). *J Clin Oncol*. 2005;23(16_suppl):4001-4001.
29. Voeten DM, van der Werf LR, Wilschut JA, et al. Failure to Cure in Patients Undergoing Surgery for Gastric Cancer: A Nationwide Cohort Study. *Ann Surg Oncol*. January 2021:1-13.
30. Koemans WJ, Van Der Kaaij RT, Boot H, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy versus palliative systemic chemotherapy in stomach cancer patients with peritoneal dissemination, the study protocol of a multicentre randomised controlled trial (PERISCOPE II). *BMC Cancer*. 2019;19(1):1-8.

31. Glehen O, Passot G, Villeneuve L, et al. GASTRICHIP: D2 resection and hyperthermic intraperitoneal chemotherapy in locally advanced gastric carcinoma: A randomized and multicenter phase III study. *BMC Cancer*. 2014;14(1):1-10. doi:10.1186/1471-2407-14-183 Glehen O, Passot G, Villeneuve L, et al. GASTRICHIP: D2 resection and hyperthermic intraperitoneal chemotherapy in locally advanced gastric carcinoma: A randomized and multicenter phase III study. *BMC Cancer*. 2014;14(1):1-10.
32. Rau B, Loeffler M, Rau H-G, et al. Perioperative chemotherapy and cytoreductive surgery with versus without HIPEC in gastric cancer with limited peritoneal metastases: A randomized phase III study (GASTRIPEC). *J Clin Oncol*. 2015;33(15_suppl):TPS4132-TPS4132.
33. Jacquet P, Sugarbaker PH. Clinical research methodologies in diagnosis and staging of patients with peritoneal carcinomatosis. *Cancer Treat Res*. 1996;82:359-374.
34. Gilly FN, Carry PY, Sayag AC, et al. Regional chemotherapy (with mitomycin C) and intra-operative hyperthermia for digestive cancers with peritoneal carcinomatosis. *Hepatogastroenterology*. 1994;41(2):124-129. https://europepmc.org/article/med/8056398. Accessed June 8, 2021
35. Kajitani T. The general rules for the gastric cancer study in surgery and pathology - Part I. Clinical Classification. *Jpn J Surg*. 1981;11(2):127-139.
36. . Wang J Bin, Liu ZY, Huang XB, et al. Implications for restaging in gastric cancer with peritoneal metastasis based on the 15th Japanese Classification of Gastric Carcinoma: An analysis from a comprehensive center. *Eur J Surg Oncol*. 2020;46(7):1269-1276.
37. Ramos RF, Scalon FM, Scalon MM, Dias DI. Staging laparoscopy in gastric cancer to detect peritoneal metastases: A systematic review and meta-analysis. *Eur J Surg Oncol*. 2016;42(9):1315-1321.
38. Leake PA, Cardoso R, Seevaratnam R, et al. A systematic review of the accuracy and indications for diagnostic laparoscopy prior to curative-intent resection of gastric cancer. *Gastric Cancer*. 2012;15(SUPPL.1).
39. Barbour AP, Rizk NP, Gonen M, et al. Adenocarcinoma of the gastroesophageal junction: Influence of esophageal resection margin and operative approach on outcome. *Ann Surg*. 2007;246(1):1-8.

Chapter 4

Neoadjuvant chemotherapy in elderly patients with gastric cancer undergoing surgery: A population-based cohort study

Alexander B.J. Borgstein*, Kammy Keywani*, Wietse J. Eshuis, Kathelijn S. Versteeg, Sarah Derks, Hanneke W.M. van Laarhoven, Suzanne S. Gisbertz, Rob H.A. Verhoeven and Mark I. van Berge Henegouwen

*Shared first authorship

Submitted for publication

Abstract

Background

Gastric cancer is often diagnosed in elderly patients, with around 60% patients being older than 70 years in 2020. Curative treatment of gastric cancer usually consists of perioperative chemotherapy followed by radical gastrectomy. However, most gastric cancer guidelines are based on trials in which predominantly younger patients were included. It is unknown whether elderly patients have a similar survival benefit from chemotherapy before gastrectomy compared to younger patients.

Methods

This is a population-based cohort study, for which data was obtained from The Netherlands Cancer Registry. Patients with primary resectable gastric adenocarcinoma, with or without neoadjuvant chemotherapy, who were scheduled for a potential curative gastrectomy between 2015 and 2019 were included. The primary outcome is the percentage of elderly patients (age ≥75) who proceeded to surgery after receiving neoadjuvant chemotherapy. Secondary outcomes included overall survival compared between elderly patients with and without neoadjuvant chemotherapy, who underwent a potential curative gastrectomy.

Results

A total of 1995 patients, of whom 746 aged ≥75 years were included in this study. In the group of elderly patients, 275 received neoadjuvant chemotherapy and 471 were directly scheduled for gastrectomy. The percentage of patients not proceeding to surgery after chemotherapy increased with age, to 26% in patients aged >80. Overall survival was comparable between elderly patients with and without neoadjuvant chemotherapy who underwent a potential curative gastrectomy (median 35 vs. 32 months).

Conclusion

Elderly patients treated with neoadjuvant chemotherapy have a similar overall survival compared to elderly patients directly scheduled for gastrectomy. However, the percentage of patients not proceeding to surgery after neoadjuvant chemotherapy increases with older age. Therefore, neoadjuvant chemotherapy should only be given in elderly patients who are fit enough to proceed to surgery afterwards.

Introduction

Gastric cancer is often diagnosed in elderly patients, with around 60% of all patients being over 70 years in 2020[1]. Additionally, more than 30% of patients undergoing potentially curative treatment in The Netherlands were older than 75 years between 2011 and 2019[2]. According to the Dutch and international guidelines, curative treatment with highest chance of cure consists of radical (R0) gastrectomy combined with perioperative chemotherapy[3–5]. These guidelines are based on the outcomes of two large trials, the MAGIC[9] and FLOT[10] studies, which both have shown that perioperative chemotherapy, as part of curative treatment for gastric cancer, improves overall survival with 15 months. In these clinical trials predominantly included younger patients [6–8]. The median age in the MAGIC trial was 62 years (range 23 – 85), with only 20% of all included patients being older than 70 years[9]. In the FLOT trial, the median age was 62 years as well, with 24% of all patient older than 70 years[10]. It is therefore unknown whether elderly patients have a similar survival benefit from perioperative chemotherapy compared to younger patients.

The incidence of comorbidities is higher in elderly patients, 72% of male patients older than 80 years have comorbidities[11]. In a recent study, 33% of patients with potentially curable gastric cancer did not undergo resection between 2015 and 2017[12]. In a multivariable analysis, age >80 years and WHO 3-4 with several comorbidities were associated with not undergoing resection[12]. Additionally, the higher incidence of comorbidities in elderly patients is associated with more adverse events during chemotherapy and surgery[13]. It is questioned whether the same percentage of elderly patients can proceed to surgery after neoadjuvant chemotherapy. Receiving neoadjuvant chemotherapy might deny elderly patients from undergoing a surgical resection because of adverse events and loss of functionality. On the other hand, not receiving neoadjuvant chemotherapy might deny elderly patients from a potential survival benefit. During multidisciplinary meetings, the question often arises whether or not an elderly patient should receive neoadjuvant chemotherapy before surgery.

The primary aim of this study is to investigate the percentage of elderly patients (≥75) who proceeded to surgery after receiving neoadjuvant chemotherapy. The secondary aim is to compare overall survival following neoadjuvant chemotherapy versus surgery alone for elderly patients with primary resectable gastric adenocarcinoma.

Methods

This is a population-based retrospective cohort study, for which data was obtained from The Netherlands Cancer Registry (NCR)[14]. In The Netherlands, the NCR registers all newly diagnosed patients with cancer. New cases are registered via the National Automated Pathology Archive, which sends weekly notifications of all cancers. Additional medical information concerning patient and tumor characteristics, is extracted from medical records by certified data managers of the NCR. Survival status is updated on a yearly basis from the civil registry. At the time of data extraction, survival follow-up had been completed up to 01-

02-2021. Information about progression and recurrences are not recorded as standard by the NCR. This study was approved by the Privacy Review Board of the NCR.

Study population

Eligible were elderly patients (≥ 75 years), with or without neoadjuvant chemotherapy, and younger patients (<75 years) with neoadjuvant chemotherapy, with primary resectable gastric adenocarcinoma, clinical staged as cT1-4A/X, any cN, cM0, who were scheduled for a potential curative gastrectomy between 2015 and 2019. Exclusion criteria were patients aged <75 years without neoadjuvant chemotherapy, treatment with neoadjuvant (chemo) radiotherapy, other concurrent malignancies, or elderly patients without neoadjuvant chemotherapy who did not undergo a resection because of metastases or irresectable tumor detected at onset of gastrectomy, as these patients did not undergo a staging laparoscopy.

Staging and treatment

All patients were staged and treated according to the Dutch gastric cancer guideline[5]. Gastric cancer was diagnosed via gastroscopy with biopsies. Staging was performed with computed tomography (CT) of the thorax and abdomen and an additional positron emission tomography-computer tomography (PET-CT) in operable patients with cT3-4 or cN+ stage tumors. Since 2016, all operable patients with ≥cT3 and/or N+ gastric cancer, without signs of metastases or locoregional non-resectability on initial imaging, undergo a staging laparoscopy before perioperative chemotherapy according to guideline. Curative treatment consists of perioperative chemotherapy (FLOT or MAGIC), followed by restaging with PET-CT and a (sub)total gastrectomy with D2 lymphadenectomy. Patients were directly scheduled for gastrectomy without neoadjuvant therapy in case of obstruction, bleeding, unfitness to or wish not to receive neoadjuvant chemotherapy.

Data selection

The supplied data by NCR included the following variables: age, gender, American Society of Anesthesiologists (ASA) classification, comorbidities, year of diagnosis, tumor location, cTNM classification, tumor differentiation, perioperative treatment (regime and course), pathological response to neoadjuvant treatment, number of patients proceeding to surgery and reasons for not proceeding, resection type, (y)pTNM classification, resection margin, 30-day postoperative complications, length of hospital stay, type of adjuvant treatment and overall survival. Tumor location was categorized as proximal (cardia, fundus and corpus), distal (antrum and pylorus) and whole stomach. The seventh TNM staging edition[15] was used for clinical and pathological TNM staging between 2015-2016, from 2017 onwards the eight edition of the TNM staging[16] was used.

Study outcomes

The primary outcome was the percentage of elderly patients (≥75 years) who proceeded to surgery after neoadjuvant chemotherapy. This outcome measure was also stratified to different age groups. Secondary outcomes included overall survival compared between elderly patients (≥75 years) who received neoadjuvant chemotherapy before potential

gastrectomy, and elderly patients directly scheduled for potential gastrectomy. Overall survival was defined as the time from diagnosis until death from any cause and the analysis included all patients regardless of final treatment (no surgery, curative or palliative resection). Additional secondary outcomes included the percentage of patients who proceeded to surgery after receiving neoadjuvant chemotherapy stratified according to age categories (<70, 70-75, 75-80, 80+), completion of neoadjuvant chemotherapy, R0-resection rate, postoperative complications, hospital stay and 30-day postoperative mortality.

Statistical analysis

Baseline characteristics were analyzed using descriptive statistics. Results were presented as mean (SD) for normally distributed variables, median (range) for non-normally distributed variables and counts (percentage) for categorical variables. Univariate analyses of the two cohorts was compared using independent t-test or Mann-Whitney U test for continuous variables, and χ^2-test or Fisher's exact test for categorial variables, when appropriate. To identify potential factors associated with not proceeding to surgery after neoadjuvant chemotherapy, a multivariable logistic regression analysis was performed. Significant variables in the univariable analysis were entered into the multivariable analysis. Stepwise backward selection was used to finalize the model (p<0.05 to stay in the model). The Kaplan-Meier method was used to estimate overall survival and compared using the log-rank test. Missing data were not imputed. For all analyses, a 2-sided P < 0.05 was considered statistically significant. Data was analysed using SPSS version 26 (IBM, Armonk, New York, USA).

Results

Study populations

A total of 1995 patients, of whom 1249 aged <75 years and 746 aged ≥75 years, were included in this study (figure 1). In the group of elderly patients, 275 received neoadjuvant chemotherapy and 471 patients underwent surgery without neoadjuvant chemotherapy (figure 1). Table 1 summarizes the baseline characteristics of elderly patients, with and without neoadjuvant chemotherapy. Elderly patients directly scheduled for surgery were older (80 vs. 77; p<0.001), with a higher percentage of WHO performance score 2+ (14.4% vs. 4.7%; p<0.001), and with more often cT1-T2 (43.9% vs. 38.2%; p<0.001) and cN0 (70.5% vs. 53.8%; p=0.001) disease. Table S2 describes the baseline characteristics of younger patients with neoadjuvant chemotherapy.

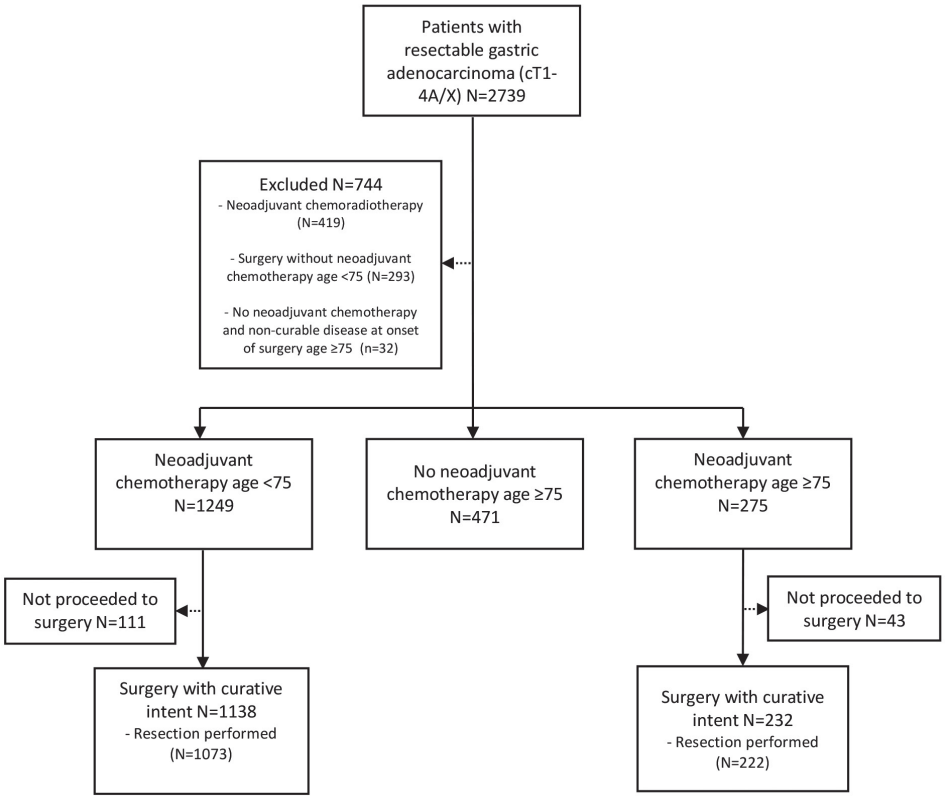


Figure 1. Flowchart of 2739 patients with potentially curable gastric adenocarcinoma

Table 1. Baseline and tumor characteristics of patients age ≥75, with and without neoadjuvant chemotherapy

Patients characteristics	**Neoadjuvant chemotherapy age ≥75 (N=275)**	**No neoadjuvant chemotherapy age ≥75 (N=471)**	***p*-value**
Age, median (IQR), years	77 (76-78)	80 (78-83)	<0.001*
Male sex, no./total no. (%)	172 (62.5)	285 (60.7)	0.622
WHO performance status, no./total no. (%)			<0.001*
0	103 (37.5)	92 (19.5)	
1	96 (34.9)	126 (26.8)	
2+	13 (4.7)	68 (14.4)	
Unknown	63 (22.9)	185 (39.3)	
ASA classification, no./total no. (%)			0.007*
1	7 (2.5)	6 (1.3)	
2	103 (37.5)	195 (41.1)	
3+	78 (28.4)	230 (48.8)	
Unknown	87 (31.6)	40 (8.5)	

Patients characteristics	Neoadjuvant chemotherapy age ≥75 (N=275)	No neoadjuvant chemotherapy age ≥75 (N=471)	*p*-value
Number of comorbidity categories*, no./total no. (%)			0.114
0	112 (40.7)	162 (34.4)	
1	90 (32.7)	159 (33.8)	
2+	55 (20.0)	121 (25.7)	
Unknown	18 (6.5)	29 (6.2)	
Year of diagnosis no./total no. (%)			0.062
2015	52 (18.9)	105 (22.3)	
2016	48 (17.5)	106 (22.5)	
2017	48 (17.5)	92 (19.5)	
2018	70 (25.5)	85 (18.0)	
2019	57 (20.7)	83 (17.6)	
Tumor location, no./total no. (%)			<0.001*
Proximal	126 (45.8)	164 (34.8)	
Distal	99 (36.0)	244 (51.8)	
Whole stomach	39 (14.2)	26 (5.5)	
Unknown	11 (4.0)	37 (7.9)	
cT-stage, no./total no. (%)			<0.001*
T1-T2	105 (38.2)	207 (43.9)	
T3-T4a	132 (48.0)	137 (29.1)	
Tx	38 (13.8)	127 (27.0)	
cN-stage, no./total no. (%)			0.001*
N0	148 (53.8)	332 (70.5)	
N1	80 (29.1)	94 (20.0)	
N2+	39 (14.2)	30 (6.4)	
Nx	8 (2.9)	15 (3.2)	
Tumor differentiation, no./total no. (%)			0.569
Well-moderate	95 (34.5)	174 (36.9)	
Poorly	122 (44.4)	246 (52.2)	
Unknown	58 (21.1)	51 (10.8)	

Patients proceeding to surgery after neoadjuvant chemotherapy

Table 2 describes the neoadjuvant treatment outcomes of all included patients stratified according to age categories. 708 (73.3%) of the patients aged <70 who received neoadjuvant chemotherapy completed all cycles, compared to 148 (62.4%) in patients aged 75-79 and 26 (68.4%) in patients aged >80 (p<0.001). After neoadjuvant chemotherapy, 77 (8.4%) patients aged <70 years, 34 (10.2%) patients aged 70-74 years, 33 (13.9%) patients aged 75-79 years, and 10 (26.3%) patients aged >80 did not proceed to surgery (p<0.001).

Supplement 1 shows the baseline and treatment characteristics of elderly patients who proceeded to surgery and those who did not, after neoadjuvant chemotherapy. Elderly patients who did not proceed to surgery had worse WHO performance status (WHO performance score of ≥2: 11.6% vs. 3.4%; p=0.047). The number of patients who completed

all preoperative chemotherapy cycles was greater in the group who proceeded to surgery (68.5% vs. 34.9%; p<0.001), with more patients receiving docetaxel-based triple regime (34.1% vs. 11.6%; p<0.001).

Table 2. Neoadjuvant treatment and outcomes stratified according to age in the entire cohort

	Young patients (N=1249)		**Elderly patients (N=275)**		
	age <70 (N=916)	**70-74 (N=333)**	**Age 75-79 (N=237)**	**≥80 (N=38)**	***p*-value***
Interval between diagnosis and onset of neoadjuvant therapy (days), median (IQR)	38 (29-50)	40 (31-52)	42 (32-54)	44 (33-55)	<0.001*
Type of neoadjuvant therapy, no./ total no. (%)					0.175
Chemotherapy	899 (98.1)	331 (99.4)	231 (97.5)	37 (97.4)	
Chemo- and targeted therapy	17 (1.9)	2 (0.6)	6 (2.5)	1 (2.6)	
Neoadjuvant chemotherapy regime, no./total no. (%)					<0.001*
ECX/ECC/EOF/EOX	548 (59.8)	178 (53.5)	108 (45.6)	11 (28.9)	
FOLFOX/CAPOX	42 (4.6)	34 (10.2)	45 (19.0)	9 (23.7)	
FLOT/DOC	281 (30.7)	113 (33.9)	72 (30.4)	12 (31.6)	
Other	45 (4.9)	8 (2.4)	12 (5.1)	6 (15.8)	
Course of neoadjuvant regime no./ total no. (%)					<0.001*
Completed all cycles	708 (73.3)	213 (64.0)	148 (62.4)	26 (68.4)	
Reduction in cycles	131 (14.3)	100 (30.0)	71 (30.0)	5 (13.2)	
Unknown	77 (8.4)	20 (6.0)	18 (7.6)	7 (18.4)	
Proceeded to surgery after neoadjuvant therapy no./total no. (%)					<0.001*
No	77 (8.4)	34 (10.2)	33 (13.9)	10 (26.3)	
Reasons for not proceeding to surgery no./total no. (%)					0.004*
Non-curable disease after restaging	48 (62.3)	19 (55.9)	12 (36.4)	1 (10.0)	
Poor functional status	6 (7.8)	2 (5.9)	10 (30.3)	1 (10.0)	
Patient's request	4 (5.2)	2 (5.9)	2 (6.1)	0 (0.0)	
Low tumorload	1 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	
Deceased	2 (2.6)	2 (5.9)	1 (3.0)	0 (0.0)	
Unknown	16 (20.8)	9 (26.5)	8 (24.2)	8 (80.0)	

* p-value is based on analysis of young patients (n=1249 vs. elderly (n=275). Abbreviations: IQR, interquartile range

Table 3 shows the surgical, histopathological, and postoperative outcomes of elderly patients who underwent surgery with curative intent, with and without neoadjuvant therapy. More patients who received neoadjuvant chemotherapy underwent a total gastrectomy, compared to patients with upfront surgery (40.1% vs 26.5%; p=<0.001) and had a (y)pT0 (9.0% vs. 0.0%; p<0.001) stage gastric tumor. Postoperative complication rate (27.9% vs 34.8%; p=0.092), and length of stay (median both groups 8 days; p=0.097) were comparable between groups.

Table 3. Surgical, pathological and adjuvant treatment details and results of patients age ≥75, with and without neoadjuvant chemotherapy

	Neoadjuvant chemotherapy age ≥75 (N=232)	**No neoadjuvant chemotherapy age ≥75 (N=471)**	***p*-value**
Interval between onset of neoadjuvant therapy and surgery (days), median (IQR)	93 (83-105)	-	
Non-curable disease during intended gastrectomy no./total no. (%)	10 (4.3%)	-	
Resection performed	**N=222**	**N=471**	
Resection type, no./total no. (%)			<0.001*
Total gastrectomy	89 (40.1)	125 (26.5)	
Subtotal gastrectomy	117 (52.7)	331 (70.3)	
Esophagectomy	16 (7.2)	15 (3.2)	
Pathological response to neoadjuvant therapy, no./total no. (%)			
Complete	18(8.1)	-	
Subtotal	21 (9.5)	-	
Partial	81 (36.5)	-	
None	60 (27.0)	-	
Unknown	42 (18.9)	-	
(y)pT-stage, no./total no. (%)			<0.001*
T0	20 (9.0)	0 (0.0)	
T1	22 (9.9)	94 (20.0)	
T2	41 (18.5)	56 (11.9)	
T3	91 (41.0)	186 (39.5)	
T4	48 (21.6)	132 (28.0)	
Tx	0 (0.0)	3 (0.6)	
(y)pN-stage, no./total no. (%)			0.062
N0	96 (43.2)	175 (37.2)	
N1	54 (24.3)	92 (19.5)	
N2	34 (15.3)	82 (17.4)	
N3	37 (16.7)	114 (24.2)	
Nx	1 (0.5)	8 (1.7)	
Resection margin, no./total no. (%)			0.059
R0	183 (82.4)	388 (82.4)	
R1	18 (8.1)	52 (11.0)	
R2	0 (0.0)	9 91.9)	

	Neoadjuvant chemotherapy age ≥75 (N=232)	No neoadjuvant chemotherapy age ≥75 (N=471)	*p*-value
Unknown	21 (9.5)	22 (4.7)	
30-day postoperative complications, no./total no. (%)			0.092
Yes	62 (27.9)	164 (34.8)	
Unknown	38 (17.10)	71 (15.1)	
Type of complications, no./total no. (%)			0.091
Pulmonary	17 (27.4)	20 (12.2)	
Cardiac	2 (3.2)	13 (7.9)	
Trombo-embolic	3 (4.8)	4 (2.4)	
Anastomotic leakage	6 (9.7)	15 (9.1)	
Chyle leakage	3 (4.8)	3 (1.8)	
Wound infection	12 (19.4)	30 (18.3)	
Neurological	4 (6.5)	10 (6.1)	
Multiple	17 (27.4)	69 (42.1)	
Length of hospital stay (days), median (IQR)	8 (6-11)	8 (6-14)	0.097
30-day postoperative mortality no. (%)	7 (3.2)	39 (8.3)	0.011
Adjuvant therapy no./total no. (%)			<0.001
Yes	88 (39.6)	5 (1.1)	
Type of adjuvant therapy no./total no. (%)			<0.001
Chemotherapy	84 (95.5)	0 (0.0)	
Chemoradiotherapy	4 (4.5)	5 (100.0)	

Overall survival

Regarding surgical mortality, 30-day postoperative mortality rate was higher in patients directly scheduled for surgery compared to patients treated with neoadjuvant chemotherapy (8.3% vs. 3.2%; p=0.011). The median overall survival time was 35 months (95% CI, 29.2-40.7) for patients preoperatively treated with chemotherapy and 32 months (95% CI, 26.3-38.3) for patients directly scheduled for surgery (p=ns (figure 2 and table 4). The estimated overall survival at 3 and 5 years were 49% and 36% for patients treated with neoadjuvant chemotherapy, compared to 47% and 36% for patients directly scheduled for resection.

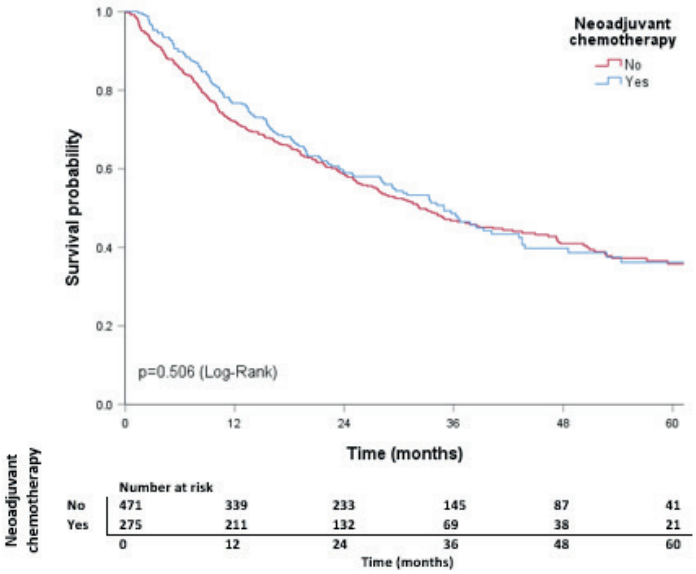


Figure 2. Overall survival in patients age ≥75 treated with and without neoadjuvant chemotherapy

Table 4. Long-term survival of patients age ≥75, with and without neoadjuvant chemotherapy

	Neoadjuvant chemotherapy age ≥75 (N=275)	No neoadjuvant chemotherapy age ≥75 (N=471)	*p*-value
Overall survival (months), median (95% CI)	34.9 (29.2-40.7)	32.3 (26.3-38.3)	0.506
3-year overall survival %	49	47	
5-year overall survival %	36	36	

Discussion

The present study evaluated the percentage of elderly patients, aged 75 years and older, who proceeded to surgery after neoadjuvant chemotherapy in a population-based cohort study. The results show that over 16% did not proceed to surgery after neoadjuvant chemotherapy. Older age and WHO classification of >2 were associated with not proceeding to surgery. Overall survival was similar between elderly patients receiving neoadjuvant chemotherapy followed by gastrectomy, compared to patients directly scheduled for gastrectomy (median 35 vs. 32 months).

The current study results show that age has a significant impact on the possibility to proceed to surgery after neoadjuvant chemotherapy. In the analysis of the whole study population, the percentage of patients not proceeding to surgery after neoadjuvant chemotherapy

increased from 8.4% in patients aged 70 years or younger, to 26.3% in patients aged 80 years or older. Elderly patients who did not proceed to surgery had a worse WHO performance status, completed less cycles of chemotherapy and received FLOT regimen less frequently, compared to elderly patients who did proceed to surgery. FLOT, a docetaxel-based triplet regimen is associated with more treatment-related toxicity in older patients, which could be an explanation for medical oncologists hampering this regimen in elderly patients[17]. To our best knowledge, this is the first study on in which the proportions of elderly patients proceeding to surgery after neoadjuvant chemotherapy were analyzed. Previous studies, in younger patients, show a higher percentage of patients proceeding to surgery after neoadjuvant chemotherapy[10,18,19]. In the FLOT trial, 94.7% and 96.9% of patients proceeded to surgery after either ECF/ECX or FLOT therapy. In the French FNCLCC/FFCD study 96.3% of patients continued to surgery and in the Dutch CRITICS study, in which post-operative chemoradiotherapy was compared with conventional perioperative strategy, 95% and 93% proceeded to surgery. Our study does not answer why less older patients proceeded to surgery. There are various possible reasons, for instance functional decline because of treatment toxicity or progression of disease because of undertreatment. In the randomized FLOT and MAGIC trials, exclusion criteria for patients were renal and liver dysfunction and impaired cardiac function. These conditions are more frequently encountered in the elderly population and therefore it is important to look at outcomes of population-based data.

Elderly patients proceeding to surgery after neoadjuvant chemotherapy have a similar overall survival compared to elderly patients directly scheduled for gastrectomy (35 vs 32 months). Overall survival in elderly patients with neoadjuvant chemotherapy was comparable to previous study results[9,10,18,20], before FLOT was introduced. Median overall survival did not reach the 50 months observed in the FLOT trial. This also seems to apply to the 3-year and 5-year survival rates (ECF/ECX arm: 48% and 36%, FLOT arm: 57% and 45%), which was 49% and 36% in our study. This may be because patients in our cohort were treated with different chemotherapy regimens (MAGIC-scheme: 43.3% and FLOT-scheme: 30.5%), however, this may also be due to undertreatment. Furthermore, perioperative treatment in older or multimorbid patients may have long term side effects impacting long term survival.

One other study evaluated the influence of neoadjuvant (radio-)chemotherapy and surgery on overall survival in elderly patients with gastric and esophageal cancer[21]. The authors concluded that patients should not be excluded from surgical treatment due to age. On the other hand, and in line with our findings, no survival benefit was found in patients aged 70 years or older who received neoadjuvant (radio-)chemotherapy. However, this retrospective, single-center study included a heterogeneous group of patients, including esophageal and gastric cancer patients, with adenocarcinoma and squamous cell carcinoma and patients were treated with neoadjuvant chemotherapy or radiochemotherapy. A previous study found no effect on overall survival in elderly patients (age 70 years or older) with esophageal cancer receiving neoadjuvant radiochemotherapy[22].

In the cohort of elderly patients who received neoadjuvant chemotherapy, 63% of the patients completed all neoadjuvant chemotherapy cycles. This percentage is much lower compared to the results of the MAGIC (90.7%) and FLOT (91%) trials[9,10]. The exact reason for not completing all chemotherapy cycles is unfortunately unknown, as this is not documented by The Netherlands Cancer Registry. Various reasons can be considered, including to toxicity, quality of life and reduced functionality.

In line with previous studies [10,18,20,23,24] although these included predominantly younger patients, no difference was found in postoperative complications and length of stay between elderly patients with and without neoadjuvant chemotherapy. Our results show that elderly patients who are treated preoperatively with chemotherapy are at greater risk for adverse outcomes postoperatively in terms of mortality. Additionally, patients who were treated with neoadjuvant chemotherapy more often had a (y)pT0 gastric tumor. Previous studies found a significant difference in R0 resection between patients preoperatively treated with chemotherapy versus surgery alone as well, the R0 resection rate was similar between both groups in our study[10,25]. This probably partly reflects patients responding to the preoperatively administered chemotherapy.

This study has a number of limitations. It is unknown why the group of elderly patients did not receive chemotherapy and were directly scheduled for a resection. Normally, patients are directly scheduled for a resection in case of obstruction, bleeding, unfitness to or wish not to receive chemotherapy. The Netherlands Cancer Registry does not record why patients are directly scheduled for a resection. In our unmatched analysis, patients directly scheduled for a resection were older and with a higher WHO and ASA classification. Therefore, it seems that less fit patients were directly scheduled for surgery, which could have affected overall survival in the group of elderly patients directly scheduled for surgery. We were not able to correct for these possible confounders as the medical information on which the decision is based to directly schedule a patient for gastrectomy is not documented by the NCR. Secondly, the sample size of the group of patients older than 80 was relatively small. Preferably, we would have performed similar analyses in this group of patients, as the question to whether or not to start with neoadjuvant chemotherapy is especially difficult in these patients. Lastly, in patients aged 80 years and older, more than 25% of patients did not proceed to surgery. It seems that older age, combined with more comorbidities, influences the chance to proceed to surgery after chemotherapy. However, as the exact reasons are not documented, therefore, it is unknown these are the only confounders.

In conclusion, elderly patients treated with neoadjuvant chemotherapy have a similar overall survival compared to elderly patients directly scheduled for gastrectomy. However, the percentage of patients not proceeding to surgery after neoadjuvant chemotherapy increases with older age, which withholds these patients from a curative treatment possibility. Therefore, neoadjuvant chemotherapy should be considered with caution in elderly patients with gastric cancer. More research should be done to optimise treatment strategies and support during treatment for this group of patients.

References

1. Overlevingscijfers van maagkanker. https://www.kanker.nl/kankersoorten/maagkanker/wat-is/overlevingscijfers-maagkanker. Accessed December 17, 2020.
2. Voeten DM, van der Werf LR, Wilschut JA, et al. Failure to Cure in Patients Undergoing Surgery for Gastric Cancer: A Nationwide Cohort Study. *Ann Surg Oncol*. January 2021:1-13. doi:10.1245/s10434-020-09510-6
3. Smyth EC, Verheij M, Allum W, et al. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2016;27(August):v38-v49. doi:10.1093/annonc/mdw350
4. Japanese gastric cancer treatment guidelines 2018 (5th edition). *Gastric Cancer*. February 2020:1-21. doi:10.1007/s10120-020-01042-y
5. *Evidence Based 2009-05-18 , Verantwoording: Landelijke Werkgroep Gastro-Intestinale Tumoren, Type: Landelijke Richtlijn, Versie: 2.2, Redactionele Aanpassing 2016-07-01 ,.*; 2016. https://www.oncoline.nl/uploaded/docs/Maagcarcinoom/Richtlijn maagcarcinoom.pdf. Accessed December 13, 2018.
6. Townsley CA, Selby R, Siu LL. Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. *J Clin Oncol*. 2005;23(13):3112-3124. doi:10.1200/JCO.2005.00.141
7. Aapro MS, Köhne C-H, Cohen HJ, Extermann M. *Never Too Old? Age Should Not Be a Barrier to Enrollment in Cancer Clinical Trials Oncologist ® Geriatric Oncology LEARNING OBJECTIVES*.; 2017. www.TheOncologist.com. Accessed December 17, 2020.
8. Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: A 7-year experience by the US Food and Drug Administration. *J Clin Oncol*. 2004;22(22):4626-4631. doi:10.1200/JCO.2004.02.175
9. Cunningham D, Allum WH, Stenning SP, Weeden S. Perioperative chemotherapy in operable gastric and lower oesophageal cancer: Final results of a randomised, controlled trial (the MAGIC trial, ISRCTN 93793971). *J Clin Oncol*. 2005;23(16_suppl):4001-4001. doi:10.1200/jco.2005.23.16_suppl.4001
10. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a ra. *Lancet*. 2019;393(10184):1948-1957. doi:10.1016/S0140-6736(18)32557-1
11. Van Gestel YRBM, Lemmens VEPP, De Hingh IHJT, et al. Influence of comorbidity and age on 1-, 2-, and 3-month postoperative mortality rates in gastrointestinal cancer patients. *Ann Surg Oncol*. 2013;20(2):371-380. doi:10.1245/s10434-012-2663-1
12. Gertsen EC, Brenkman HJF, Brosens LAA, et al. Refraining from resection in patients with potentially curable gastric carcinoma. *Eur J Surg Oncol*. 2020;(xxxx):1-7. doi:10.1016/j.ejso.2020.10.025
13. Sylvie L, Silvia S, Salah-Eddin AB, et al. Impact of age on the feasibility and efficacy of neoadjuvant chemotherapy in patients with locally advanced oesophagogastric cancer. *Eur J Cancer*. 2015;51(14):1918-1926. doi:10.1016/j.ejca.2015.07.002
14. Cancer Registry. https://iknl.nl/en/ncr. Accessed October 31, 2021.
15. Washington K. 7th Edition of the AJCC Cancer Staging Manual: Stomach. *Ann Surg Oncol 2010 1712*. 2010;17(12):3077-3079. doi:10.1245/S10434-010-1362-Z

16. He X, Wu W, Lin Z, Ding Y, Si J, Sun L. Validation of the American Joint Committee on Cancer (AJCC) 8th edition stage system for gastric cancer patients: a population-based analysis. *Gastric Cancer 2017 213*. 2017;21(3):391-400. doi:10.1007/S10120-017-0770-1
17. Al-Batran SE, Pauligk C, Homann N, et al. The feasibility of triple-drug chemotherapy combination in older adult patients with oesophagogastric cancer: A randomised trial of the Arbeitsgemeinschaft Internistische Onkologie (FLOT65+). *Eur J Cancer*. 2013;49(4):835-842. doi:10.1016/J.EJCA.2012.09.025
18. Ychou M, Boige V, Pignon J-P, et al. Perioperative Chemotherapy Compared With Surgery Alone for Resectable Gastroesophageal Adenocarcinoma: An FNCLCC and FFCD Multicenter Phase III Trial. *J Clin Oncol*. 2011;29:1715-1721. doi:10.1200/JCO.2010.33.0597
19. Cats A, Jansen EPM, van Grieken NCT, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. *Lancet Oncol*. 2018. doi:10.1016/S1470-2045(18)30132-3
20. Cunningham D, Allum WH, Stenning SP, et al. Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer. *http://dx.doi.org/101056/NEJMoa055531*. 2009;355(1):11-20. doi:10.1056/NEJMOA055531
21. Nienhueser H, Kunzmann R, Sisic L, et al. Surgery of gastric cancer and esophageal cancer: Does age matter? *J Surg Oncol*. 2015;112(4):387-395. doi:10.1002/JSO.24004
22. Camerlo A, D'Journo XB, Ouattara M, Trousse D, Doddoli C, Thomas PA. Adenocarcinoma of the esophagus and esophagogastric junction in patients older than 70 years: Results of neoadjuvant radiochemotherapy followed by transthoracic esophagectomy. *J Visc Surg*. 2012;149(3):e203-e210. doi:10.1016/J.JVISCSURG.2012.03.006
23. Ahn HS, Jeong SH, Son YG, et al. Effect of neoadjuvant chemotherapy on postoperative morbidity and mortality in patients with locally advanced gastric cancer. *Br J Surg*. 2014;101(12):1560-1565. doi:10.1002/BJS.9632
24. Li ZY, Shan F, Zhang LH, et al. Complications after radical gastrectomy following FOLFOX7 neoadjuvant chemotherapy for gastric cancer. *World J Surg Oncol*. 2011;9(1):110. doi:10.1186/1477-7819-9-110/TABLES/4
25. Schuhmacher C, Gretschel S, Lordick F, et al. Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European organisation for research and treatment of cancer randomized trial 40954. *J Clin Oncol*. 2010;28(35):5210-5218. doi:10.1200/JCO.2009.26.6114

Supplements

Supplement table 1. Comparison of baseline and neoadjuvant treatment characteristics of elderly patients who did proceed and who did not proceed to surgery after neoadjuvant chemotherapy

Patients characteristics	Not proceeded to surgery age ≥75 (N=43)	Proceeded to surgery age ≥75 (N=232)	*p*-value
Age, median (IQR), years	77 (76-79)	77 (76-78)	0.070
Male sex, no./total no. (%)	31 (72.1)	141 (60.8)	0.159
WHO performance status, no./total no. (%)			0.047*
0	13 (30.2)	90 (38.8)	
1	13 (30.2)	83 (35.8)	
2+	5 (11.6)	8 (3.4)	
Unknown	12 (27.9)	151 (22.0)	
Number of comorbidity categories*, no./total no. (%)			0.782
0	16 (37.2)	96 (41.4)	
1	13 (30.2)	77 (33.2)	
2+	10 (23.3)	45 (19.4)	
Unknown	4 (9.3)	14 (6.0)	
Tumor location, no./total no. (%)			0.130
Proximal	25 (58.1)	101 (43.5)	
Distal	10 (23.3)	89 (38.4)	
Diffuse	7 (16.3)	32 (13.8)	
Unknown	1 (2.3)	10 (4.3)	
cT-stage, no./total no. (%)			0.815
T1-T2	14 (32.6)	91 (39.2)	
T3-T4a	19 (44.2)	113 (48.7)	
Tx	10 (23.3)	28 (12.1)	
cN-stage, no./total no. (%)			0.041*
N0	18 (41.9)	130 (56.0)	
N1	11 (25.6)	69 (29.7)	
N2+	11 (25.6)	28 (12.1)	
Nx	3 (7.0)	5 (2.2)	
Tumor differentiation, no./total no. (%)			0.981
Well-moderate	11 (25.6)	84 (36.2)	
Poorly	14 (32.6)	108 (46.6)	
Undifferentiated	0 (0.0)	0 (0.0)	
Unknown	18 (41.9)	40 (17.2)	
Interval between diagnosis and onset of neoadjuvant therapy (days), median (IQR)	47 (32-57)	42 (31-54)	0.462
Type of neoadjuvant therapy, no./total no. (%)			0.013
Chemotherapy	39 (90.7)	229 (98.7)	
Chemo- and targeted therapy	4 (9.3)	3 (1.3)	
Neoadjuvant chemotherapy regime, no./total no. (%)			<0.001*
ECX/ECC/EOF/EOX	15 (34.9)	104 (44.8)	
FOLFOX/CAPOX	12 (27.9)	42 (18.1)	
FLOT/DOC	5 (11.6)	79 (34.1)	
Other	11 (25.6)	7 (3.0)	

Patients characteristics	Not proceeded to surgery age ≥75 (N=43)	Proceeded to surgery age ≥75 (N=232)	*p*-value
Course of neoadjuvant regime no./total no. (%)			<0.001*
Completed all cycles	15 (34.9)	159 (68.5)	
Reduction in cycles	17 (39.5)	59 (25.4)	
Unknown	11 (25.6)	14 (6.0)	

Abbreviations: IQR, interquartile range

Chapter 5

Role of omentectomy as part of radical surgery for gastric cancer: 5-year follow-up results of a multicenter study

Alexander B.J. Borgstein, Djamila Boerma, Stijn van Esser, Wietse J. Eshuis, Mark I. van Berge Henegouwen, Johanna van Sandick and Suzanne S. Gisbertz

Submitted for publication

Abstract

Background

Curative therapy for gastric cancer usually consists of perioperative chemotherapy combined with a radical (R0) gastrectomy. In addition to a modified D2-lymphadenectony, a complete omentectomy is recommended. However, there is little evidence for a survival benefit of omentectomy. This study presents the follow-up data of the OMEGA-study.

Methods

This multicenter prospective cohort study included 100 consecutive patients with gastric cancer undergoing (sub)total gastrectomy with complete *en bloc* omentectomy and modified D2 lymphadenectomy between March 2012 and April 2014. Primary outcome of the current study was five-year overall survival. Secondary outcomes included median survival, cause of death, and location of metastases. Patients with and without omental metastases were compared. Pathological factors associated with locoregional recurrence and/or metastases were tested with multivariable regression analysis.

Results

Of 100 included patients, five had metastases in the greater omentum. Five-year overall survival was 0.0% in patients with omental metastases and 44.2% in patients without omental metastases (p=0.001). Median overall survival was seven months in patients with omental metastases and 53 months in patients without omental metastases. The main cause of death in both groups was peritoneal metastases. A (y)pT3-4 stage tumor and vasoinvasive growth were associated with locoregional recurrence and/or metastases in patients without omental metastases.

Conclusion

The presence of omental metastases in gastric cancer patients who underwent potentially curative surgery was associated with impaired overall survival. Omentectomy as part of radical gastrectomy for gastric cancer might not contribute to a survival benefit and may therefore be omitted.

Introduction

Gastric cancer is the third most common cause of cancer-related deaths worldwide[1]. Potentially curative therapy usually consists of perioperative chemotherapy combined with a radical (R0) gastrectomy. An adequate resection involves a modified D2 lymphadenectomy and, in addition, a complete omentectomy, to ensure resection of possible omental metastatic lymph nodes and/or tumor deposits[2–6].

The omentum has some important functions within the peritoneal cavity, such as a regional immune response regulator and prevention of small bowel adhesions. High quality evidence indicating a survival benefit after omentectomy is lacking. Several retrospective studies found no difference in long-term outcomes between omentectomy and omentum preservation in gastric cancer[4,7,8]. In a recent multicenter cohort study, the five-year overall survival rate after gastrectomy for advanced gastric cancer was 77.1% in patients with omentectomy versus 79.4% in patients with omentum preservation (not statistically significant)[9]. Currently, a Japanese randomized controlled trial is evaluating 5-year relapse-free survival in patients with and without omentectomy[10].

The OMEGA study (OMEntectomy in radical GAstrectomy for gastric cancer), conducted in The Netherlands, evaluated the incidence of and risk factors for metastases in the greater omentum in patients undergoing radical (sub)total gastrectomy with modified D2 lymphadenectomy for potentially curable gastric cancer[11]. This multicenter prospective cohort study included 100 consecutive patients between March 2012 and April 2014. The primary endpoint was the presence of metastases in the greater omentum.

Only five out of 100 patients (5.0%) had metastases in the greater omentum. The presence of metastases was significantly correlated with a microscopically non-radical resection (R1), tumor expansion in the esophagus or duodenum, linitis plastica, stage III/IV disease and pM1-status. In the current study, we present the long-term overall survival results of the OMEGA-study.

Methods

Study design and participants

The OMEGA study was conducted in one university and three teaching hospitals in The Netherlands between March 20, 2012 and April 17, 2014. The design and short-term study results have been published previously[11]. Patients with a primary gastric adenocarcinoma, stage cT1-4, N0-3 and M0, scheduled to undergo a (sub)total gastrectomy with potentially curative intent were included. Patients younger than 18 years or undergoing palliative surgery were excluded. The study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies[12]. The study was approved by the medical ethics committee and registered with clinicaltrials.gov (NCT02050659).

Procedures

Tumor staging

According to the Dutch gastric cancer guideline[13], patients were clinically staged with an endoscopy with biopsies and a CT scan of the thorax and abdomen. If involvement of the esophagus or another organ was suspected, an endoscopic ultrasonography was performed. Patients with cT3-4 or cN+ stage tumors underwent a staging laparoscopy before the start of neoadjuvant therapy.

Treatment

All patients with a primary gastric adenocarcinoma >cT1N0 received neoadjuvant therapy (three cycles of epirubicin, oxaliplatin, capecitabine), if the patient's condition allowed this. Patients with cT1N0 stage gastric tumor, tumor complications (bleeding/obstruction) or ASA >3 did not receive neoadjuvant therapy and were directly scheduled for a gastrectomy. Patients underwent surgery about 4-6 weeks after completion of the neoadjuvant therapy.

Surgical technique

Patients underwent an open or laparoscopic (sub)total gastrectomy with *en bloc* complete omentectomy and modified D2 lymphadenectomy. In case of a planned subtotal gastrectomy, a tumor-free margin of ≥ 5 cm for intestinal-type adenocarcinoma or ≥ 8 cm for diffuse-type adenocarcinoma was pursued. If this was not possible, frozen section was performed. In case of tumor positive frozen section, a total gastrectomy was performed. A modified D2 lymphadenectomy in total gastrectomy included stations 1-7, 8a, 9 and 11p and in subtotal gastrectomy stations 1, 3, 4sb, 4d, 5-7, 8a and 9. Either a Roux-en-Y or Billroth II was performed to reconstruct gastro-intestinal continuity after resection. The anastomosis was either performed mechanical, semi-mechanical or manual.

The omentum was separated from the specimen distal to the gastroepiploic vessels and just proximal from the level of attachment to the transverse colon after the resection and sent in separately for pathological investigation.

Pathological analysis

A detailed description of the pathological analysis of the omentum has been described in a previous publication[11]. In short, the omentum was divided into three areas (liver, middle and spleen part) according to the anatomical markings provided by the surgeon. The omentum was systematically inspected for lymph nodes and/or tumor deposits with the use of visual inspection, palpation and dissection.

Study outcomes

The primary outcome of the current study was five-year overall survival. Overall survival was defined as the period of time from operation to death from any cause. Patients alive and free of these events were censored at the last follow-up. Secondary endpoints were median overall survival, cause of death, location of metastases, and risk factors associated with locoregional recurrence and/or metastases. Disease-free survival could not be investigated, since all patients with omental metastases had a microscopically non-radical (R1) resection[11], and these patients were formally not disease-free after surgery.

Statistical analysis

Continuous variables were presented as mean with standard deviation and counts with percentages for categorical variables. Multivariable logistic regression analysis was performed in patients without omental metastases to identify risk factors associated with locoregional recurrence and/or metastases. Significant variables in the univariable analysis were entered into the multivariable analysis. Stepwise backward selection was used to finalize the model ($p<0.05$ to stay in the model).

The Kaplan-Meier curves were used to estimate overall survival and compared using the log-rank test. For all analyses, a 2-sided $P < 0.05$ was considered statistically significant. Data were analyzed using SPSS version 26 (IBM, Armonk, New York, USA)

Results

Patients characteristics

A total of 100 consecutive patients who underwent a potentially curative (sub)total gastrectomy for gastric cancer were included. The baseline characteristics have been published before and are summarized in table 1[11].

Table 1. Baseline characteristics of the total study population

Characteristics:	N = 100 (%)
Age, mean (SD), years	64 (15.3)
Sex ratio (M:F)	64:36
Body-mass index, mean (SD), kg/m2	25.5 (4.3)
Smoking status, no./total no.	
Current smoker	18 (18.0)
Quit smoking	35 (35.0)
Alcohol use	
Yes	47 (47.0)
Comorbidities:	
Hypertension	35 (35.0)
Diabetes mellitus	23 (23.0)
Coronary artery disease	
COPD	12 (12.0)
Autoimmune disease	4 (4.0)
Previous abdominal surgery	13 (13.0)
Previous malignancy	9 (9.0)
Renal failure	4 (4.0)
ASA classification, no./total no.	
1	24 (24.0)
2	53 (53.0)
3	23 (23.0)
Clinical T stage, no./total no.	
cT0-2	24 (24.0)
cT3-4	29 (29.0)
cTx	47 (47.0)
Clinical N stage, no./total no.	
cN0	46 (46.0)
cN1-3	36 (36.0)
cNx	18 (18.0)
Perioperative chemotherapy	69 (69.0)

Abbreviations: SD, standard deviation; COPD, chronic obstructive pulmonary disease; ASA, American Society of Anesthesiologists

[a] Three cycles of epirubicin, oxaliplatin, capecitabine.

Surgical and postoperative outcomes

Surgical and postoperative data have been presented before[11]. In short, fifty-two patients (52.0%) underwent a total gastrectomy and in 82 patients (82.0%) a Roux-en-Y reconstruction was performed. Twenty-nine patients (29.0%) underwent a minimally invasive gastrectomy (5 conversions). Postoperative complications occurred in 18 patients (18.0%). Median hospital stay was 10 (8 – 15) days.

Pathological results

In five out of 100 patients (5.0%), metastases were detected in the greater omentum. The presence of metastases in the greater omentum was significantly correlated with a R1 resection margin (p<0.001), tumor involvement of the esophagus or duodenum (p<0.001), location in the proximal third of the stomach or linitis plastica (p=0.002), tumor diameter of ≥ 5 cm, tumor stage III-IV (p=0.010), and (y)pM1-stage (p<0.001).

Five-year follow-up

Table 2 and figure 1 present the five-year follow-up data for patients with and without omental metastases. The five-year overall survival rate was 0.0% (0 out of 5 patients) in patients with omental metastases and 44.2% (42 out of 95 patients) in patients without omental metastases (p=0.001). Median overall survival was seven months (0 – 16.8 months) in patients with omental metastases and 53 months (95% CI 38 – 67 months) in patients without omental metastases.

In patients with omental metastases, the causes of death were the following: two patients died of locoregional recurrence and peritoneal metastases, one patient died of both locoregional recurrence and distant metastases in multiple locations and one patient died of peritoneal metastases. One patient deceased within 30-days postoperatively because of postoperative complications (anastomotic dehiscence of the gastro-enterostomy).

The main causes of death of 53 patients without omental metastases were as follows: 23 patients had distant metastases (43.4%), four patients had locoregional recurrence (7.5%), and nine patients had both locoregional recurrence and distant metastases (17.0%). Metastases were predominantly located in the peritoneum (19 out of 32; 59.3%). In total, 36 out of 95 (37.9%) patients developed recurrence and/or metastases within five years after surgery.

Table 2. 5-year follow-up data of patients with and without metastases in the greater omentum

	Omental metastases (*n*=5)	**No omental metastases (*n*=95)**
Alive, no./total no. (%)		
Yes	0 (0.0)	42 (44.2)
Survival, median (IQR), months	7 (2 – 17)	53 (16 – 60)
Cause of death (%)		
Postoperative complications[#]	1 (20.0)	3 (5.7)
Locoregional recurrence	0 (0.0)	4 (7.5)
Distant metastases	1 (20.0)	23 (43.4)
Locoregional recurrence and distant metastases	3 (60.0)	9 (17.0)
Other cause	0 (0.0)	4 (7.5)
Unknown	0 (0.0)	10 (18.9)
Metastases location, no. (%)	**N = 4**	**N = 32**
Peritoneum	3 (75.0)	19 (59.3)
Lymph nodes	0 (0.0)	3 (9.5)
Liver	0 (0.0)	1 (3.1)
Bone	0 (0.0)	1 (3.1)
Multiple	1 (25.0)	4 (12.5)
Unknown	0 (0.0)	4 (12.5)

Abbreviations: IQR, interquartile rage;
[#] Deceased within 30-days after gastrectomy because of postoperative complications

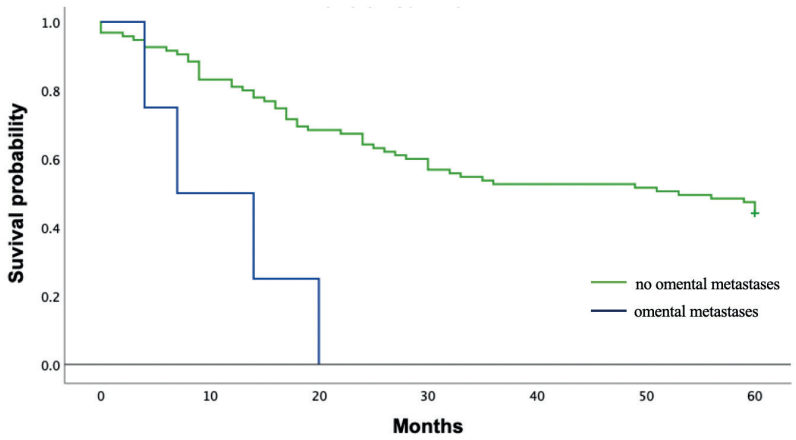


Figure 1. Kaplan-Meier curves for comparison of overall survival between patients with and without metastases in the greater omentum

Risk factors for locoregional recurrence and/or metastases

Multivariable analysis could only be performed in the patients without omental metastases, due to the small sample of patients with omental metastases. Table 3 presents the pathological risk factors associated with locoregional recurrence and/or distant metastases in patients without omental metastases. Both locally advanced (pT3-4) tumor stage (OR 4.21, 95% CI 1.17 – 15.10, *p*=0.027) and the presence of vasoinvasive growth (OR 5.41, 95% CI 1.67 – 17.57, *p*=0.005) were associated with locoregional recurrence and/or metastases.

Table 3. Pathological factors associated with locoregional recurrence and/or metastases in patients without omental metastases, results of uni- and multivariable analyses

	Univariable analysis		Multivariable analysis	
Variables:	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
Central tumor location				
Proximal 1/3	1			
Middle 1/3	0.98 (0.28 – 3.46)	0.975		
Distal 1/3	1.25 (0.44 – 3.55)	0.672		
Complete stomach	2.80 (0.22 – 35.29)	0.426		
Tumor type (Laurén classification)				
Intestinal	1			
Diffuse	1.27 (0.45 – 3.59)	0.649		
Tumor differentiation grade				
Well or moderately	1			
Poorly or undifferentiated	3.11 (1.11 – 8.76)	**0.032***		
Vasoinvasive growth				
No	1		1	
Yes	6.67 (2.17 – 20.48)	**0.001***	5.41 (1.67 – 17.57)	**0.005***
Perineural growth				
No	1			
Yes	4.95 (1.33 – 18.41)	**0.017***		
Pathological tumor category				
(y)pT1-2	1		1	
(y)pT3-4	4.56 (1.64 – 12.68)	**0.004***	4.21 (1.17 – 15.10)	**0.027***
Pathological node category				
(y)pN0	1			
(y)N+	5.12 (1.99 – 13.39)	**0.001***		
Number of lymph nodes resected				
20 – 30	1			
10 – 15	2.20 (0.67 – 7.22)	0.192		
15 – 20	2.00 (0.56 – 7.15)	0.286		
30+	0.94 (0.28 – 3.08)	0.912		

Abbreviations: OR, Odds ration; 95% CI, 95% confidence interval

Discussion

This five-year follow-up study of 100 consecutive gastric cancer patients who underwent a potentially curative gastrectomy with omentectomy showed a significantly impaired overall survival rate in patients with omental metastases compared to those without omental metastases. The five-year overall survival rate was 0.0% in patients with omental metastases, compared to 44.2% in patients without omental metastases (p=0.001).

The previously reported OMEGA study found that the presence of omental metastases was significantly associated with a non-radical resection, tumor expansion in esophagus or duodenum, linitis plastica, stage III/IV disease, and pM1-status[11]. Since the presence of omental metastases was associated with advanced disease, it was suggested that performing an omentectomy might not lead to a survival benefit in these patients. The results of the current study support this suggestion, as the median overall survival was only seven months in patients with omental metastases, compared to 53 months in patients without omental metastases.

The five-year overall survival rate of all patients in this study was 42.0%, which is similar to the average five-year overall survival numbers according to the Dutch Cancer Registry (NKR), which is around 40% for cT2-4a stage gastric tumors in The Netherlands[14]. Additionally, this survival rate was comparable to the overall survival found in previous studies performed in Western countries[15,16]. Long-term overall survival has not yet been investigated separately in gastric cancer patients with omental metastases.

In the group of patients without omental metastases, 36 out of 95 (37.9%) patients developed recurrence or metastases within five years after surgery. Peritoneal metastases was the most common site, which is in line with previous studies indicating peritoneal recurrence to be the main cause of death after gastrectomy for advanced gastric cancer[9,17]. Both a higher tumor stage ((y)pT3-4) and the presence of vasoinvasive growth were associated with locoregional recurrence and/or metastases in patients without omental metastases. These findings are in line with a previous study indicating tumor-related factors to be the strongest predictors of survival among patients with gastric cancer who underwent a potentially curative resection[18].

Performing an omentectomy is a time-consuming and technically demanding procedure in minimally invasive surgery. It is associated with increased risk of intraoperative injury to the colon and mesocolon, early and late postoperative complications. A study by Kim et al., in which 146 patients with advanced gastric cancer were included, the laparoscopic operating time was significantly shorter (25 min) without complete omentectomy, and two omentectomy-related complications were observed (spleen and mesocolon injuries)[19]. Recently, Ri et al. (2020) performed a retrospective cohort study, including 526 patients with cT3-4 gastric cancer who underwent gastrectomy with or without omentectomy[9]. The incidence of postoperative complications (Clavien-Dindo III or higher) was significantly

higher in the group of patients who underwent gastrectomy with omentectomy (17.5% vs. 10.3%). In our study, we could not compare postoperative complications between patients with and without omentectomy, as all patients underwent gastrectomy with omentectomy.

There is no high-quality evidence indicating improved overall survival if gastrectomy is combined with omentectomy. Several studies have made the comparison in a non-randomized fashion. No difference in overall survival or disease-free survival was found between patients with or without omentectomy[8,9,19,20].

Recently, the results of a Japanese phase II trial on omentectomy versus omentum preservation were published[21]. A total of 251 patients undergoing open gastrectomy, without neoadjuvant chemotherapy, were included. Short-term postoperative morbidity was comparable between both cohorts (8.0% vs. 9.0%). The long-term outcomes have to be awaited. A Japanese phase III trial is currently evaluating omentum preserving gastrectomy for patients with resectable gastric cancer in terms of relapse-free survival[10]. In this trial, perioperative chemotherapy and minimally invasive surgery are exclusion criteria. Therefore, the results from this trial are not directly applicable to Western countries, where most patients are treated perioperatively after the results from the MAGIC[22] and FLOT[23] trials. In addition, minimally invasive gastrectomy is frequently performed, even in advanced cases, as oncologic safety was confirmed in both Asian and European trials[24–26].

A randomized controlled trial investigating the influence of omentectomy on survival has not yet been performed in a Western population. Currently, our study group is finalizing the study protocol for a randomized controlled trial, the OMEGA trial (OMEntum preservation versus complete omentectomy in GAstrectomy for gastric cancer). The primary aim of this trial is to investigate whether omentum preservation in gastrectomy for cancer is non-inferior to complete omentectomy in terms of three-year overall survival. The inclusion of patients will start in the second half of the year 2021. Optimally, a prediction model will differentiate patients at high risk for the presence of omental metastases from those with a low risk. Such a model could forecast which patients would benefit from a complete omentectomy. Therefore, the OMEGA trial will stratify patients according to neoadjuvant therapy, type of surgery (total or subtotal gastrectomy) and diffuse or intestinal type gastric tumor.

The current study has certain limitations. The sample size of this study was relatively small and omental metastases were present in just five patients. Therefore, the overall survival analysis was performed with a small number of patients with omental metastases. Secondly, disease-free survival could not be compared between both groups, as all patients with omental metastases underwent a microscopically non-radical (R1) resection. Third, since all patients underwent gastrectomy with omentectomy, the influence of omentum preservation on overall survival could not be investigated. Lastly, previous studies found a significantly higher rate of late intra-abdominal complications in patients who underwent gastrectomy with omentectomy[2]. Information on late postoperative complications was not available for

our cohort. Therefore, the incidence of late intra-abdominal complications could not be investigated in the current study.

Following current national guidelines, adjuvant chemoradiotherapy may be advised in patients who underwent a microscopically non-radical (R1) gastric cancer resection[13,27]. If omentectomy is omitted in the future, it is important to contemplate about the adjuvant treatment strategy in patients in whom a non-radical resection is performed. In the OMEGA study, a non-radical resection was associated with the presence of omental metastases. If the omentum (with potential omental metastases) is still in situ in patients with a microscopically non-radical resection, the discussion of appropriate adjuvant treatment will be a new challenge for the multidisciplinary team.

In conclusion, the presence of omental metastases in gastric cancer patients undergoing potentially curative resection was associated with impaired overall survival. Overall survival rate was 0.0% in patients with omental metastases, compared to 44.2% in patients without omental metastases. Therefore, omentectomy as part of radical gastrectomy for gastric cancer might not contribute to a survival benefit and may be omitted in the future. Our upcoming randomized controlled trial might confirm the non-inferiority of omentum preservation compared to omentectomy in terms of survival.

References

1. Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer*. 2019;144(8):1941-1953.
2. Ha TK, An JY, Youn HG, Noh JH, Sohn TS, Kim S. Omentum-preserving gastrectomy for early gastric cancer. *World J Surg*. 2008;32(8):1703-1708.
3. Lee J, Kim W. Long-term outcomes after laparoscopy-assisted gastrectomy for advanced gastric cancer: Analysis of consecutive 106 experiences. *J Surg Oncol*. 2009;100(8):693-698.
4. Kim MC, Kim KH, Jung GJ, Rattner DW. Comparative study of complete and partial omentectomy in radical subtotal gastrectomy for early gastric cancer. *Yonsei Med J*. 2011;52(6):961-966.
5. Lawrance RJ, Loizidou M, Cooper AJ, Alexander P, Taylor I. Importance of the omentum in the development of intra-abdominal metastases. *Br J Surg*. 1991;78(1):117-119.
6. Hagiwara A, Sawai K, Sakakura C, et al. Complete omentectomy and extensive lymphadenectomy with gastrectomy improves the survival of gastric cancer patients with metastases in the adjacent peritoneum. *Hepatogastroenterology*. 1998;45(23):1922-1929.
7. Hasegawa S, Yamamoto Y, Taguri M, et al. A randomized phase II trial of omentum-preserving gastrectomy for advanced gastric cancer. *Jpn J Clin Oncol*. 2013;43(2):214-216.
8. Hasegawa S, Kunisaki C, Ono H, et al. Omentum-preserving gastrectomy for advanced gastric cancer: A propensity-matched retrospective cohort study. *Gastric Cancer*. 2013;16(3):383-388.
9. Ri M, Nunobe S, Honda M, et al. Gastrectomy with or without omentectomy for cT3-4 gastric cancer: a multicentre cohort study. *Br J Surg*. May 2020.
10. Sato Y, Yamada T, Yoshikawa T, et al. Randomized controlled Phase III trial to evaluate omentum preserving gastrectomy for patients with advanced gastric cancer (JCOG1711, ROAD-GC). *Jpn J Clin Oncol*. 2020;50(11):1321-1324.
11. Jongerius EJ, Boerma D, Seldenrijk KA, et al. Role of omentectomy as part of radical surgery for gastric cancer. *Br J Surg*. 2016;103(11):1497-1503.
12. STROBE Statement: Home. https://www.strobe-statement.org/index.php?id=strobe-home..
13. *Evidence Based 2009-05-18 , Verantwoording: Landelijke Werkgroep Gastro-Intestinale Tumoren, Type: Landelijke Richtlijn, Versie: 2.2, Redactionele Aanpassing 2016-07-01 ,.*; 2016. https://www.oncoline.nl/uploaded/docs/Maagcarcinoom/Richtlijn maagcarcinoom.pdf.
14. Overleving - IKNL. https://iknl.nl/kankersoorten/slokdarm-en-maagkanker/registratie/overleving. Published 2020.
15. Cats A, Jansen EPM, van Grieken NCT, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. *Lancet Oncol*. 2018;19(5):616-628.
16. Shapiro J, van Lanschot JJB, Hulshof MCCM, et al. Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): Long-term results of a randomised controlled trial. *Lancet Oncol*. 2015;16(9):1090-1098.
17. Park DJ, Han SU, Hyung WJ, et al. Long-term outcomes after laparoscopy-assisted gastrectomy for advanced gastric cancer: A large-scale multicenter retrospective study. *Surg Endosc*. 2012;26(6):1548-1553.
18. Posteraro B, Persiani R, Dall'Armi V, et al. Prognostic factors and outcomes in Italian patients undergoing curative gastric cancer surgery. *Eur J Surg Oncol*. 2014;40(3):345-351.

19. Kim DJ, Lee JH, Kim W. A comparison of total versus partial omentectomy for advanced gastric cancer in laparoscopic gastrectomy. *World J Surg Oncol*. 2014;12(1).
20. Sakimura Y, Inaki N, Tsuji T, Kadoya S, Bando H. Long-term outcomes of omentum-preserving versus resecting gastrectomy for locally advanced gastric cancer with propensity score analysis. *Sci Rep*. 2020;10(1):1-9.
21. Murakami H, Yamada T, Taguri M, et al. Short-Term Outcomes from a Randomized Screening Phase II Non-inferiority Trial Comparing Omentectomy and Omentum Preservation for Locally Advanced Gastric Cancer: the TOP-G Trial. *World J Surg*. 2021.
22. Cunningham D, Allum WH, Stenning SP, Weeden S. Perioperative chemotherapy in operable gastric and lower oesophageal cancer: Final results of a randomised, controlled trial (the MAGIC trial, ISRCTN 93793971). *J Clin Oncol*. 2005;23(16_suppl):4001-4001.
23. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a ra. *Lancet*. 2019;393(10184):1948-1957.
24. Kim HH, Han SU, Kim MC, et al. Effect of Laparoscopic Distal Gastrectomy vs Open Distal Gastrectomy on Long-term Survival among Patients with Stage i Gastric Cancer: The KLASS-01 Randomized Clinical Trial. *JAMA Oncol*. 2019;5(4):506-513.
25. Straatman J, van der Wielen N, Cuesta MA, et al. Surgical techniques, open versus minimally invasive gastrectomy after chemotherapy (STOMACH trial): Study protocol for a randomized controlled trial. *Trials*. 2015;16(1):123.
26. van der Veen A, Brenkman HJF, Seesing MFJ, et al. Laparoscopic Versus Open Gastrectomy for Gastric Cancer (LOGICA): A Multicenter Randomized Clinical Trial. *J Clin Oncol*. January 2021:JCO.20.01540.
27. Smyth EC, Verheij M, Allum W, et al. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol*. 2016;27(suppl_5):v38-v49.

PART II

Safety of Performing Surgery During The COVID-19 Pandemic

Chapter 6

Preoperative screening for COVID-19 using chest CT and RT-PCR in asymptomatic patients undergoing elective or emergency surgery

Alexander B.J. Borgstein*, Carl A.J. Puylaert*, Jochem C.G. Scheijmans*, Caroline S. Andeweg, Annemarieke Bartels-Rutten, Geerard L. Beets, Mark I. van Berge Henegouwen, Sicco J. Braak, Roy Couvreur, Freek Daams, Hendrik W. van Es, Lotte C. Franken, Brechtje A. Grotenhuis, Eduard R. Hendriks, Ignace H.J.T. de Hingh, Fieke Hoeijmakers, Joris T. ten Holder, Peter M. Huisman, Geert Kazemier, Floortje van Kesteren, Jurre van Kesteren, Kammy Keywani, Sara Z. Kuiper, Maurits D.J. Lange, Mark E. Lobatto, Arthur W.F. du Mée, Martijn Poeze, Elise M. van Praag, Jorit van Rossen, Hjalmal C. van Santvoort, Wouter J.A. Sedee, Leonard W.F. Seelen, Sarah Sharabiany, Nico L. Sosef, Marian J.R. Quanjel, Jeroen Veltman, Tim Verhagen, Vincent C.J. van de Vlasakker, Pepijn D. Weeder, Jochem R. van Wervan, Nina J. Wesdorp, Susan van Dieren, Alvin X. Han, Colin A. Russell, Menno de Jong, Patrick M.M. Bossuyt, Jet M.E. Quarles van Ufford, Mathis W. Prokop, Suzanne S. Gisbertz, Jan M. Prins, Marc G. Besselink, Marja A. Boermeester, Hester A. Gietema and Jaap Stoker

*Shared first authorship

Annals of Surgery 2020

Abstract

Objective

To determine the yield of preoperative screening for COVID-19 with chest CT and RT-PCR in patients without COVID-19 symptoms.

Summary Background Data

Many centers are currently screening surgical patients for COVID-19 using either chest CT, RT-PCR or both, due to the risk for worsened surgical outcomes and nosocomial spread. The optimal design and yield of such a strategy are currently unknown.

Methods

This multicenter study included consecutive adult patients without COVID-19 symptoms who underwent preoperative screening using chest CT and RT-PCR before elective or emergency surgery under general anaesthesia.

Results

A total of 2093 patients without COVID-19 symptoms were included in 14 participating centers; 1224 were screened by CT and RT-PCR and 869 by chest CT only. The positive yield of screening using a combination of chest CT and RT-PCR was 1.5% (95%CI: 0.8–2.1). Individual yields were 0.7% (95%CI: 0.2–1.1) for chest CT and 1.1% (95%CI: 0.6–1.7) for RT-PCR; the incremental yield of chest CT was 0.4%. In relation to COVID-19 community prevalence, up to ~6% positive RT-PCR was found for a daily hospital admission rate >1.5 per 100,000 inhabitants, and around 1.0% for lower prevalence.

Conclusions

One in every 100 patients without COVID-19 symptoms tested positive for SARS-CoV-2 with RT-PCR; this yield increased in conjunction with community prevalence. The added value of chest CT was limited. Preoperative screening allowed us to take adequate precautions for SARS-CoV-2 positive patients in a surgical population, whereas negative patients needed only routine procedures.

Introduction

After the peak of the COVID-19 outbreak, hospitals around the world are now increasing their elective surgical care.[1,2] The question whether to screen asymptomatic patients prior to surgery for COVID-19 remains unanswered.

Patients infected with SARS-CoV-2 have increased risk of postoperative complications and mortality.[3–5] In addition, surgical patients with undetected COVID-19 could potentially shed SARS-CoV-2, placing hospital workers at risk, particularly during intubation and other aerosolizing procedures.[6–9] Furthermore, if not isolated, patients may infect other hospitalized patients, of whom many are prone to developing severe COVID-19 due to older age and comorbidities.[10,11] In a recent international survey, up to 59% of 264 centers from 37 countries worldwide reported to screen patients scheduled for pancreatic surgery, using chest CT and/or RT-PCR.[12] Given the limited resources, additional costs of screening, the burden of ionizing radiation and the increase of non-COVID surgery there is an urgent need to evaluate the effectiveness of preoperative screening for COVID-19. Secondly, the effectiveness of preoperative screening in relation to changes in COVID-19 community prevalence should be explored. The Infectious Diseases Society of America (IDSA) guideline on COVID-19 diagnosis recently advised preoperative screening using SARS-CoV-2 RT-PCR in all asymptomatic individuals undergoing surgery.[13]

In The Netherlands, the first COVID-19 patient was identified on February 27, 2020, followed by a rapid increase in the number of confirmed patients.[11] In the following weeks, many hospitals started routine preoperative screening in asymptomatic surgical patients as a method to detect asymptomatic COVID-19. Early routine screening was performed with chest computed tomography (CT) only. Facilitated by improved availability of reverse-transcriptase polymerase chain reaction (RT-PCR) in later weeks, a nationwide Dutch guidance protocol was released that advised preoperative screening with chest CT and RT-PCR.

The effectiveness of this preoperative screening protocol in asymptomatic patients is unclear as RT-PCR testing is usually only performed in symptomatic patients. RT-PCR may be prone to sampling error and asymptomatic patients may have lower viral load than symptomatic COVID-19 patients.[14–17] Moreover, chest CT is not recommended for screening in asymptomatic patients[18], although up to 63% of asymptomatic COVID-19 patients are reported to have abnormalities on chest CT.[8,19,20]

The SCOUT study aimed to evaluate the yield of preoperative screening for COVID-19 using chest CT and RT-PCR in adult patients without COVID-19 symptoms, scheduled for elective or emergency surgical or other interventional procedures under general anesthesia.

Methods

Study oversight

The multicenter observational SCOUT study was conducted at three academic and 11 non-academic hospitals in The Netherlands. Because of the observational nature of the study, formal approval was waived by the institutional review board of the Amsterdam UMC, location AMC. This was endorsed by the institutional review board at each participating center. Informed consent was obtained through an opt-out procedure. The study was initiated by the Radiological Society of The Netherlands and the Dutch Surgical Society, in collaboration with the committee which developed the national guidance protocol on preoperative screening for COVID-19, published April 2, 2020.[11]

Study population

Consecutive adult patients (18 years or older) who underwent preoperative screening for COVID-19 were included. Patients were eligible for screening if they were scheduled for any type of surgical or interventional procedure under general anesthesia, both elective or emergency, and if they were asymptomatic. Patients scheduled for elective surgery were contacted by telephone two to three days before surgery and re-checked at admission. Patients undergoing emergency surgery were interviewed at admission. Patients in whom COVID-19 could not be clinically ruled out (i.e. incapacitated emergency patients) were not included.

The study consisted of two cohorts of consecutive asymptomatic patients. The main cohort were patients who underwent combined screening with CT and RT-PCR. The second and preceding cohort were patients who underwent screening with chest CT only. Most participating centers started preoperative screening with chest CT only. A transition to combined screening occurred in most centers after publication of the national guidance protocol on preoperative screening (April 2nd, 2020), advising centers to screen all preoperative patients using this combined approach.[11] Participating centers could include patients both retrospectively and prospectively in each cohort. A standard questionnaire was used for evaluation of symptoms in prospectively included patients (see Supplementary Material for symptom questionnaire). A broad list of symptoms related to COVID-19 were part of the questionnaire. Patients were considered to be asymptomatic if no symptoms suspicious for COVID-19 were present or when symptoms were clearly related to another diagnosis (e.g. in cases of fever or abdominal pain in patients with acute appendicitis). See Supplementary Table S1 on both cohorts' inclusion periods for each participating center.

Data collection

Data were extracted on patient's demographics and clinical characteristics, recent exposure history, screening results for chest CT and RT-PCR and operative management. Abbreviated postal codes were collected to explore regional variations in primary outcome.

Chest CT and RT-PCR: procedure and analysis

According to the guidance protocol, preoperative chest CT was performed using an unenhanced low dose protocol. Chest CT scanning could be combined with a contrast-enhanced abdominal CT, mostly performed in emergency settings. Chest CT was evaluated by the attending radiologist at each local center and reported using a standard reading protocol. In case of abnormal findings, suspicion for COVID-19 was assessed using the CO-RADS classification.[21] This classification encodes the level of suspicion for COVID-19 based on chest CT findings (1, very low suspicion; 2, low suspicion, 3, equivocal, 4, high suspicion, 5, very high suspicion) and has shown excellent performance for diagnosing COVID-19 in symptomatic patients (average area under the receiver operating curve of 0.91 to 0.95).[21]

SARS-CoV-2 RNA detection in nasopharyngeal and/or oropharyngeal swab specimens was performed using RT-PCR assays targeted at the viral envelope, RNA-dependent RNA polymerase and/or nucleocapsid genes according to nationally endorsed and quality-controlled protocols.[22] For positive RT-PCR specimens cycling threshold values were reported.

A positive screening result for detection of COVID-19 was defined as a CO-RADS score 4 or 5 and/or a positive RT-PCR result. According to the national guideline, in these cases surgery was postponed when possible or, in cases of emergency surgery, additional personal protection equipment (PPE) and other precautionary measures were taken to prevent nosocomial spread. In patients who were negative at history taking and preoperative screening, use of standard PPE was considered sufficient. A CO-RADS 3 (equivocal) test result with a negative RT-PCR result was not regarded as a positive screening result. A decision to postpone surgery in these patients was made at the local clinician's discretion after discussion in a multidisciplinary team meeting.[11]

Study outcome and follow-up

The primary study outcome was the yield of detected COVID-19 with chest CT and RT-PCR. Secondary outcomes consisted of the individual yields of chest CT and RT-PCR, the relationship between screening results and differences in community prevalence, and operative management after screening. Two weeks follow-up data were collected for all patients, which consisted of postoperative diagnosis of COVID-19, related complications and intensive care unit admissions.

Relationship to community prevalence

To investigate the relationship between screening results and community prevalence of COVID-19, we stratified patients by their province of residence and screening dates. Publicly available prevalence data were obtained from the Dutch National Institute for Public Health and the Environment.[23] The number of inhabitants per province in 2020 were obtained from the Central Agency of Statistics in The Netherlands.[24] We then separately compared the yield for chest CT and RT-PCR in those provinces among patients to the mean daily COVID-19 admissions per 100,000 inhabitants for the same provinces within a 7-day window around each patient screening (from three days before screening to three days after).

Statistical analysis

Screening results were presented as the number and percentage of patients with a positive screening result, with additional percentages and 95% confidence intervals (CI's). These CI's were calculated using 1000 bootstrapping samples. Anticipating a 2% yield, we calculated that recruiting 1,000 participants would lead to a 95% confidence interval around the estimate that would extend from 1.2% to 3.0%. Analyses were performed with the use of SPSS software, version 26.0.

Results

Patient characteristics

Between March 20, 2020 and April 24, 2020, a total of 2093 asymptomatic patients were included in 14 participating centers: 1224 were screened by a combination of chest CT and RT-PCR and 869 by chest CT only (Figure 1). Demographic and clinical characteristics for patients undergoing combined screening are given in Table 1. There were no significant differences in patient characteristics between the two cohorts (Table 1 and Supplementary Table S2).

Screening results

The results for patients undergoing combined preoperative screening are given in Table 2. Out of 1224 patients, 18 (1.5%) had positive screening results (Table 3, detailed information in Supplementary Table S3), all of which were patients scheduled to undergo either elective (14 patients) or semi-urgent surgery (4 patients), but no emergency surgery. Of these patients, 14 (1.1%) tested positive for SARS-CoV-2 using RT-PCR, while 8 (0.7%) were suspected for COVID-19 based on chest CT results. Therefore, the incremental yield for chest CT was 0.4% (4 patients). Concordant positive results were seen in four patients with both a positive chest CT result and a positive RT-PCR; three of these CT scans were read as CO-RADS 5 (very high suspicion) and one as CO-RADS 4 (high suspicion) (Table 3). When compared against positive RT-PCR results as a reference standard, chest CT had negative findings for 10 of the 14 patients who tested positive for SARS-CoV-2 using RT-PCR (71.4% false negative rate for screening chest CT) (Table 3). Cycling threshold values for positive RT-PCR tests ranged from 20.7 to 37.7, with a median cycling threshold value of 35.0 (IQR 28.3–36.9) (Table S3). In the second cohort of 869 patients with chest CT only, five patients (0.6%; CI 0.1–1.1) had a positive screening result based on chest CT results (all CO-RADS 4). For combined screening, surgery was postponed because of a positive screening result in 17 patients (1.4%). For chest CT only screening, surgery was postponed because of a positive screening result in two patients (0.2%).

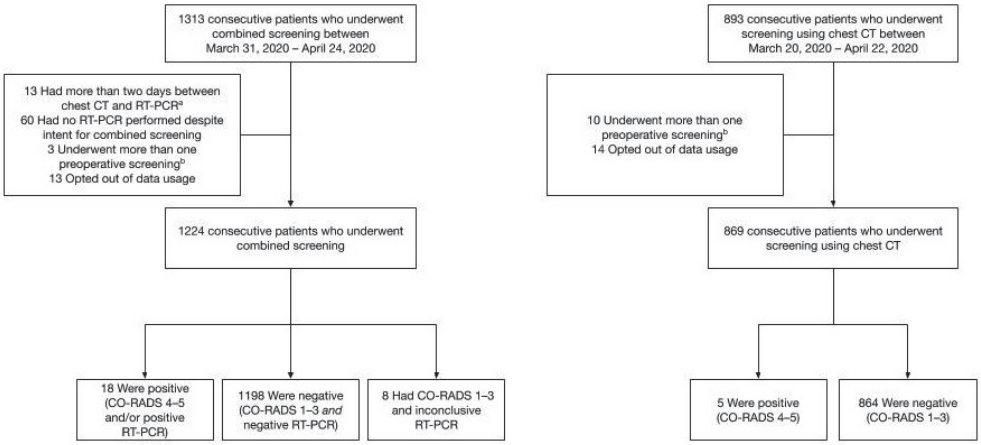


Figure 1. Flow-chart for patients undergoing preoperative screening for both cohorts

CT, computed tomography; RT-PCR, reverse-transcriptase polymerase chain reaction.
[a] These patients all had negative RT-PCR and CO-RADS 1–3.
[b] Some patients underwent multiple screenings during the study period. In case patients were initially screened using chest CT, and followingly using chest CT and RT-PCR, the combined screening was included. For patients with multiple screenings using one strategy, the first screening was included.

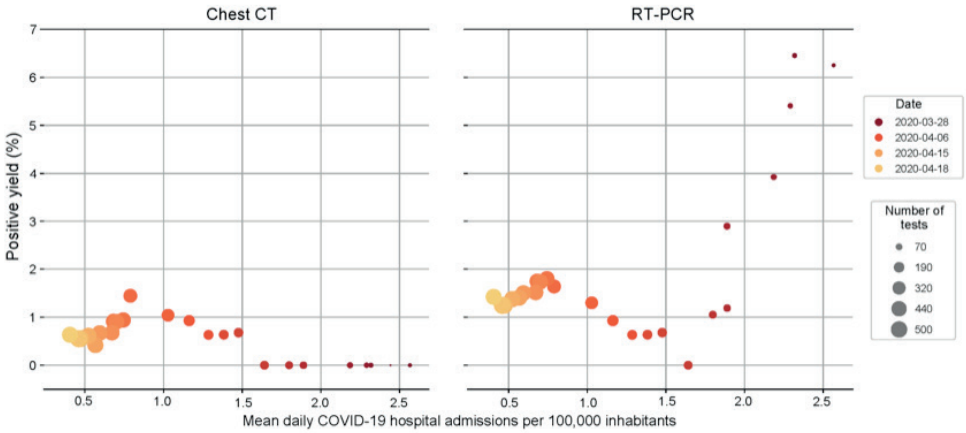


Figure 2. Association of positive yield for chest CT and SARS-CoV-2 RT-PCR of asymptomatic patients with regional and temporal variations in community prevalence, measured by the mean daily COVID-19 related hospital admissions per 100.000 inhabitants.

Left panel: no discernable pattern of association between positive chest CT results and regional and temporal variations of COVID-19 prevalence. **Right panel:** positive yield by RT-PCR markedly increases above mean of 1.5 daily COVID-19 related hospital admissions per 100.000 inhabitants.

Relationship between screening yield and community prevalence

RT-PCR positive yield was related to the COVID-19 community prevalence: relatively high diagnostic yields up to ~6% were observed in specific regions and earlier periods where the mean daily COVID-19 hospital admission rate was above 1.5 per 100,000 inhabitants. The yield remained constant at around ~1% when the hospital admission rate was below 1.5 per 100,000 inhabitants (Figure 2). There was no relationship between the yield from chest CT screening and COVID-19 community prevalence, which was confirmed in both cohorts (Figure 2 and Figure S1).

Follow-up data

Clinical details for the 18 patients with positive results in combined screening are shown in Table S3. Two patients with positive screening RT-PCR developed COVID-19 symptoms within two weeks postoperatively and thus could have been presymptomatic. Two patients with positive screening RT-PCR had been symptomatic within one month before screening, but were asymptomatic for at least 2 days before screening, suggesting possible late-stage COVID-19. The remaining 14 patients did not report any COVID-19 related symptoms before, during or after screening. These included the four patients who had positive chest CT (all CO-RADS 4) with negative RT-PCR results (Supplementary Table 3). Of the five patients who had positive screening results in the chest CT only cohort, three of these five underwent RT-PCR testing with negative results at 1, 1 and 11 days after screening. Two of these patients were tested because of the CO-RADS 4 score at screening, while a third patient was tested because of a newly scheduled surgical procedure. None of the five chest CT positive patients in the chest CT only cohort developed COVID-19 symptoms within two weeks after chest CT screening.

Of 1206 patients who underwent combined screening with negative screening results, 1169 patients underwent surgery, of which none developed symptomatic COVID-19 within two weeks postoperatively. Of 864 patients who underwent screening using chest CT only with negative screening results, 829 patients underwent surgery of which three developed symptomatic COVID-19 postoperatively, diagnosed by positive RT-PCR at one, five and seven days after surgery. None of these three patients were initially screened using RT-PCR. None of them required admission to the intensive care unit postoperatively because of COVID-19.

Table 1. Results of screening with chest CT and SARS-CoV-2 RT-PCR

	Combined screening (n = 1224)		
	Chest CT	**RT-PCR**	**Chest CT and RT-PCR**
Positive screening result, no./total no.[a]	8/1224	14/1224	18/1224
% (95% CI)[b]	0.7 (0.2–1.1)	1.1 (0.6–1.7)	1.5 (0.8–2.2)

CI, confidence interval; CT, computed tomography; RT-PCR, reverse-transcriptase polymerase chain reaction.
[a] positive chest CT result was defined as a CORADS 4-5. A positive result for the combined screening strategy was defined as a CO-RADS 4-5 and/or a positive RT-PCR result.
[b] 95% confidence interval was calculated based on 1000 bootstrap samples

Table 2. Results of screening with chest CT and SARS-CoV-2 RT-PCR

Chest CT[a]		**RT-PCR**		
		Negative/inconclusive[b]	**Positive**	**Total**
Negative	CORADS 1	1090	7	1097
	CORADS 2	75	2	77
	CORADS 3	41	1	42
Positive	CORADS 4	4	1	5
	CORADS 5	0	3	3
Total		1210	14	1224

CT, computed tomography; RT-PCR, reverse-transcriptase polymerase chain reaction.
[a] positive chest CT result was defined as a CORADS 4-5.
[b] of 8 patients the screening RT-PCR was inconclusive. Of these patients 7 had CORADS 1 and one had CORADS 3.

Discussion

This is the first multicenter study to determine the yield of screening for COVID-19 using chest CT and RT-PCR in asymptomatic patients prior to elective or emergency surgery. Combined preoperative screening demonstrated a yield of 1.5%, of which RT-PCR confirmed SARS-CoV-2 infection in 1.1% of patients. Chest CT showed an incremental yield of 0.4%, although these could be false-positive results as none of these patients developed COVID-19 symptoms and no relationship with community prevalence was seen for chest CT results. No postoperative symptomatic COVID-19 infections were seen in patients who had negative RT-PCR screening results. In contrast, three patients who underwent screening using only chest CT with negative results developed postoperative symptomatic COVID-19, suggesting that these infections might have been missed by CT.

Two other studies have investigated the use of RT-PCR as a screening method in asymptomatic patients, but none in patients undergoing surgery or other interventions under general anesthesia.[25,26] Data from both previous studies confirm the association between yield of RT-PCR in asymptomatic patients and number of COVID-19 related hospital admissions. A study from New York City found SARS-CoV-2 infection in 13.7% of 210 asymptomatic women admitted for delivery when the average of daily COVID-19 related hospital admissions was

around 16.0 per 100.000 inhabitants.[25,27] In Iceland, screening of a random population sample using RT-PCR found that 13 of 2283 (0.6%) individuals were positive for SARS-CoV-2. However, six of these 13 individuals reported COVID-19 related symptoms.[26] During this period, the average daily COVID-19 related hospital admissions in Iceland was around 0.78 per 100.000 inhabitants.[28] These data confirm the association between the RT-PCR yield in asymptomatic patients and hospital admissions, as both screening yield and the hospital admission rate were around 20 times higher in New York City as compared to the Iceland population. These, and our findings also suggest that the number of patients with asymptomatic COVID-19 is higher than previously reported.[29,30]

Social distancing measures (limited lock down) were implemented by the Dutch government on March 12, 2020. Peak prevalence for COVID-19 in The Netherlands occurred during the second half of March after which prevalence decreased. While preoperative screening was initiated in several hospitals from March 23 onwards, combined screening with chest CT and RT-PCR was implemented starting on March 31, 2020. As community prevalence decreased in The Netherlands from ~3 to ~1.5 COVID-19 related hospital admissions per 100,000 inhabitants, the RT-PCR yield in our study patients decreased markedly from potentially as high as ~6% to ~1%. The screening yield remained at ~1% as admission rate decreased to ~0.5 per 100,000 inhabitants. The absent relationship between positive chest CT findings and COVID-19 community prevalence further questions the sensitivity of these positive CT findings as related to asymptomatic COVID-19.

Preoperative screening with RT-PCR found infection with SARS-CoV-2 in only 1.1% of patients. Although this yield may seem low, even a small number of undetected cases could have substantial consequences. Data on the impact of COVID-19 on patients undergoing surgery is scarce. Lei et al. (2020) described postoperative outcomes in a group of 34 patients undergoing surgery, all of whom developed symptomatic COVID-19 within 4 days postoperatively and were therefore considered to have been in their incubation period before surgery.[3] Fifteen patients required admission to the intensive care unit (44.1%), while seven patients died (20.5%) postoperatively, both considerably higher than previously reported for hospitalized non-surgical COVID-19 patients. These findings indicate the importance of preoperative screening to prevent adverse postoperative outcomes.

Additionally, asymptomatic patients with SARS-CoV-2 could be shedders of the virus, especially during aerosol generating procedures, thereby placing other patients and hospital workers at risk, especially those performing endotracheal intubation. One study evaluated transmission of SARS-CoV-2 within a skilled nursing facility, by RT-PCR testing on two occasions as part of a facility-wide point-prevalence survey.[27] Forty-eight out of seventy-six (63.0%) residents tested positive for SARS-CoV-2. Of those 48 residents, 27 (56%) were asymptomatic at time of testing. SARS-CoV-2 could rapidly spread through the skilled nursing facility to other residents and staff, probably due to unrecognized asymptomatic and presymptomatic infections. These results indicate symptom-based screening to be insufficient to prevent rapid transmission in skilled nursing facilities. In our study the median

RT-PCR cycle threshold value of the positive PCRs was relatively high, suggesting a low viral load, which may affect the risk for transmission.[31] During aerosol generating procedures such as intubation, however, the risk of transmission is probably increased. [32] By avoiding introduction of COVID-19 positive patients into the hospital, preoperative screening benefits surgical care in preventing nosocomial spread and reducing the use of scarce personal protective equipment.

Our study has some limitations. First, patients undergoing preoperative screening using only chest CT were mostly included retrospectively. Preoperative symptoms were not inquired using a standardized procedure in these patients. Some patients with mild unrecognized complaints could therefore have been unknowingly included. Second, the study was conducted during the quarantine period in The Netherlands, which effectively commenced on March 15th, 2020. Consequently, we experienced a decreasing prevalence during the inclusion period, which may have led to a decreasing yield. This could have affected the accuracy of our positive yield and relationship to community prevalence. Third, a relatively low number of RT-PCR screenings were performed early in the study, when new COVID-19 hospital admissions in The Netherlands were at their highest level.[23] As such, the high positivity rates in the first period could be inflated due to small sample bias. Fourth, no analysis for risk factors could be performed due to the limited number of patients with positive results. Last, we used the daily hospital admission rate as a marker for COVID-19 community prevalence in the population. Although a relationship was found, the exact cut-off value of 1.5 daily admissions per 100,000 inhabitants above which the screening yield increases could vary due to differences between national health care systems, such as the availability of pre-hospital care (e.g. general physicians). Moreover, our study population consisted of surgical patients and thus was not fully representative for the general population.

Preoperative screening with RT-PCR found infection with SARS-CoV-2 in at least 1 in every 100 asymptomatic patients, increasing in conjunction with community prevalence. Given the limited added value, the use of chest CT in preoperative screening is not recommended based on our results. Preoperative screening in asymptomatic COVID-19 patients undergoing surgery should be performed with RT-PCR. The initiation of preoperative screening can be directed by local community prevalence of COVID-19.

References

1. Cobianchi L, Pugliese L, Mis F/, Peloso A, Dal Mas F, Angelos P. To a New Normal: Surgery and COVID-19 during the Transition Phase. Ann Surg. 2020:1.
2. Liang ZC, Chong MSY, Liu GKP, et al. COVID-19 and Elective Surgery. Ann Surg. May 2020:1.
3. Besnier E, Tuech J-J, Schwarz L. We Asked the Experts: Covid-19 Outbreak: Is There Still a Place for Scheduled Surgery? "Reflection from Pathophysiological Data." World J Surg. April 2020:1.
4. Lei S, Jiang F, Su W, et al. Clinical characteristics and outcomes of patients undergoing surgeries during the incubation period of COVID-19 infection. EClinicalMedicine. 2020;0(0).
5. Aminian A, Safari S, Razeghian-Jahromi A, Ghorbani M, Delaney CP. COVID-19 Outbreak and Surgical Practice: Unexpected Fatality in Perioperative Period. Ann Surg. March 2020.
6. Kluytmans-van den Bergh M, Buiting A, Pas S, et al. SARS-CoV-2 infection in 86 healthcare workers in two Dutch hospitals in March 2020. medRxiv. March 2020:2020.03.23.20041913.
7. Chan JFW, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet. 2020;395(10223):514-523.
8. Hu Z, Song C, Xu C, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. Sci China Life Sci. 2020.
9. Hains DS, Schwaderer AL, Carroll AE, et al. Asymptomatic Seroconversion of Immunoglobulins to SARS-CoV-2 in a Pediatric Dialysis Unit. JAMA. May 2020. doi:10.1001/jama.2020.8438
10. Guan W, Ni Z, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020.
11. LEIDRAAD Pre-Operatieve Diagnostische Work Up.
12. A. Oba, T.F. Stoop, M. Lohr et al. Global Survey on Pancreatic Surgery during the COVID-19 Pandemic. Ann Surg. 2020.
13. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Clin Infect Dis. May 2020.
14. Woelfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized cases of coronavirus disease 2019. medRxiv. 2020:2020.03.05.20030502.
15. Ai T, Yang Z, Xia L. Correlation of Chest CT and RT-PCR Testing in Coronavirus Disease. Radiology. 2020;2019:1-8.
16. Fang Y, Zhang H, Xie J, et al. Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR. Radiology. February 2020:200432.
17. Liu R, Han H, Liu F, et al. Positive rate of RT-PCR detection of SARS-CoV-2 infection in 4880 cases from one hospital in Wuhan, China, from Jan to Feb 2020. Clin Chim Acta. 2020;505:172-175.
18. Rubin GD, Haramati LB, Kanne JP, et al. The Role of Chest Imaging in Patient Management during the COVID-19 Pandemic: A Multinational Consensus Statement from the Fleischner Society. Radiology. April 2020:201365.
19. Inui S, Fujikawa A, Jitsu M, et al. Chest CT Findings in Cases from the Cruise Ship "Diamond Princess" with Coronavirus Disease 2019 (COVID-19). Radiol Cardiothorac Imaging. 2020;2(2):e200110.
20. Wang Y, Dong C, Hu Y, et al. Temporal Changes of CT Findings in 90 Patients with COVID-19 Pneumonia: A Longitudinal Study. Radiology. March 2020:200843.

21. Prokop M, van Everdingen W, van Rees Vellinga T, et al. CO-RADS – A categorical CT assessment scheme for patients with suspected COVID-19: definition and evaluation. Radiology. April 2020:201473.
22. Corman VM, Landt O, Kaiser M, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Eurosurveillance. 2020;25(3):2000045.
23. Rijksinstituut voor Volksgezondheid en Milieu | RIVM.
24. CBS StatLine.
25. Sutton D, Fuchs K, D'Alton M, Goffman D. Universal Screening for SARS-CoV-2 in Women Admitted for Delivery. N Engl J Med. April 2020:NEJMc2009316.
26. Gudbjartsson DF, Helgason A, Jonsson H, et al. Spread of SARS-CoV-2 in the Icelandic Population. N Engl J Med. April 2020:NEJMoa2006100.
27. Welcome to NYC.gov | City of New York. Accessed April 29, 2020. https://www1.nyc.gov/
28. COVID-19 in Iceland.
29. Arons MM, Hatfield KM, Reddy SC, et al. Presymptomatic SARS-CoV-2 Infections and Transmission in a Skilled Nursing Facility. N Engl J Med. April 2020:NEJMoa2008457.
30. Mizumoto K, Kagaya K, Zarebski A, Chowell G. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. Eurosurveillance. 2020;25(10):2000180.
31. Chu HY, Englund JA, Starita LM, et al. Early Detection of Covid-19 through a Citywide Pandemic Surveillance Platform. N Engl J Med. May 2020:NEJMc2008646.
32. Weissman DN, de Perio MA, Radonovich LJ. COVID-19 and Risks Posed to Personnel During Endotracheal Intubation. JAMA. April 2020.

Supplement

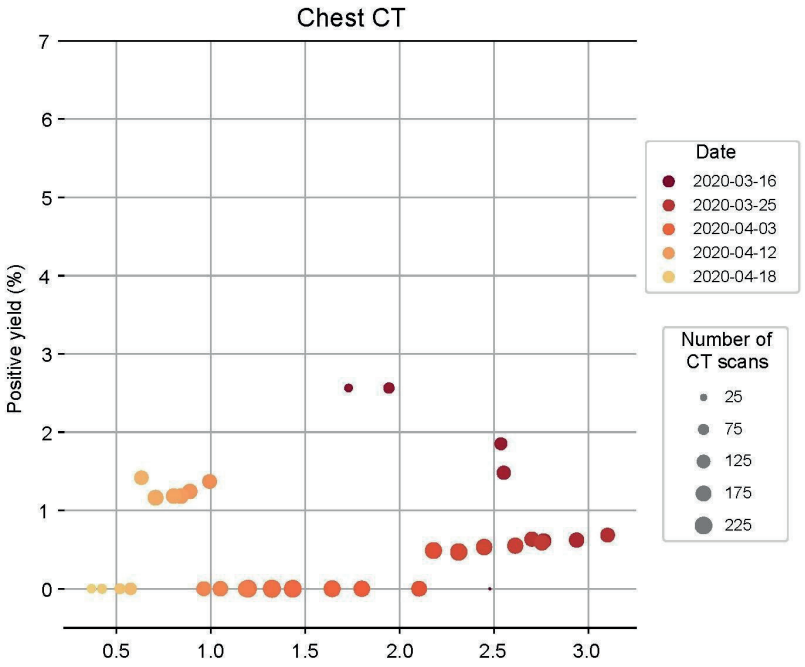


Figure S1. For chest CT only cohort: association of positive yield for chest CT of asymptomatic patients with regional and temporal variations in community prevalence, measured by the mean daily Covid-19 related hospital admissions per 100.000 inhabitants. No discernable pattern of association is seen between positive chest CT results and regional and temporal variations of Covid-19 prevalence

Table S1. Inclusion period and number of included patients per screening strategy and per centre

	Chest CT only screening		**Combined screening using chest CT *and* SARS-CoV-2 RT-PCR**	
Center	**Inclusion period**	**Included**	**Inclusion period**	**Included**
Amsterdam UMC, location AMC, Amsterdam	23/03/2020 - 31/03/2020	55	31/03/2020 - 21/04/2020	154
Amsterdam UMC, location VUmc, Amsterdam	21/03/2020 - 01/04/2020	52	01/04/2020 - 22/04/2020	140
Amphia Hospital, Breda	26/03/2020 - 10/04/2020	36	10/04/2020 - 24/04/2020	52
Antoni van Leeuwenhoek - National Cancer Institute, Amsterdam	27/03/2020 - 12/04/2020	205	12/04/2020 - 23/04/2020	202
Catharina Hospital, Eindhoven			05/04/2020 - 23/04/2020	99
Dijklander Hospital, Hoorn/ Purmerend			08/04/2020 - 21/04/2020	101
Flevo Hospital, Almere			12/04/2020 - 22/04/2020	46

Haaglanden Medical Centre, The Hague	08/04/2020 - 20/04/2020	132		
Maastricht UMC+, Maastricht	20/03/2020 - 18/04/2020	128	18/04/2020 - 23/04/2020	12
Sint Antonius Hospital, Nieuwegein/Utrecht			07/04/2020 - 23/04/2020	166
Sint Jansdal Hospital, Harderwijk/ Lelystad	28/03/2020 - 22/04/2020	91		
Spaarne Gasthuis, Haarlem and Hoofddorp	21/03/2020 - 20/04/2020	129	20/04/2020 - 24/04/2020	24
Tergooi, Hilversum/Blaricum	24/03/2020 - 08/04/2020	35	08/04/2020 - 23/04/2020	71
Ziekenhuisgroep Twente, Hengelo/Almelo	03/04/2020 - 06/04/2020	6	06/04/2020 - 23/04/2020	157
Total		869		1224

Table S2. Demographic and clinical characteristics for patients who underwent screening using chest CT only

	Screening strategy
Characteristic	**Chest CT (N=869)**
Age, median (IQR), years	64 (50–73)
Age, range, years	18–100
Female sex, no./total no. (%)	460/873 (52.9)
Body-mass index, median (IQR), kg/m^2	25.9 (23.5–29.1)
Body-mass index > 30, no./total no. (%)	161/783 (20.6)
Smoking history, no./total no. (%)	
Never smoked	312/716 (43.6)
Former smoker	263/716 (36.7)
Current smoker	141/716 (19.7)
Exposure to source of transmission, no./total no. (%)	
Travel to foreign country within past 14 days	1/365 (0.3)
Contact with COVID-19 positive patient	4/360 (1.1)
Any coexisting condition[a], no./total no. (%)	367/814 (45.1)
Chronic obstructive pulmonary disease	70/860 (8.1)
Diabetes	116/865 (13.4)
Hypertension	295/849 (34.7)
Coronary heart disease	86/847 (10.2)
Heart failure	28/853 (3.3)
Cerebrovascular disease	71/846 (8.4)
ASA classification, no./total no. (%)	
1	173/817 (21.2)
2	421/817 (51.5)
3	213/817 (26.1)
4	10/817 (1.2)
Urgency of surgery, no./total no. (%)	
Elective	574/785 (73.1)
Semi-urgent (< 1 week)	96/785 (12.2)
Emergency (< 24 hours)	114/785 (14.5)

[a] These include the following coexisting conditions: chronic obstructive pulmonary disease, diabetes, hypertension, coronary heart disease, heart failure and cerebrovascular disease.

Table S3. Screening results and follow-up data for asymptomatic patients with positive results in combined screening

Patient	Age/ sex	RT-PCR	CO-RADS	RT-PCR Cycling Threshold	Postponed surgery	COVID-19 symptoms within 14 days after screening	COVID-19 related hospital admission	Follow-up testing	Clinical course
1	24 / M	+	5	22.2	Yes	No	No	Negative RT-PCR at 14 days after screening.	
2	68 / F	+	5	36.7	Yes	No	No	No	Had been admitted one month prior to screening with dyspnea, but with negative RT-PCR. No symptoms at time of screening.
3	55 / F	+	5	37.6	Yes	No	No	No	Passing mild gastrointestinal symptoms two weeks prior to screening.
4	89 / M	+	4	37.2	Yes	No[a]	No[a]	No	
5	70 / M	+	3	31.5	Yes	No	No	No	
6	64 / F	+	2	26.4	Yes	No	No	Negative RT-PCR at 14 days after screening.	
7	75 / M	+	2	37.7	Yes	Yes	No	No	Developed passing fever one day after screening without pulmonary complaints.
8	75 / M	+	1	28.9	No	Yes	Yes	Repeated negative RT-PCR during readmission	Readmitted with non-COVID-19 related pneumonia followed by complete recovery.
9	20 / F	+	1	20.7	Yes	No	No	Negative RT-PCR at 6 and 14 days after screening.	
10	82 / M	+	1	34.9	Yes	No	No	No	
11	81 / F	+	1	36.3	Yes	No	No	Negative RT-PCR at 14 days after screening.	
12	71 / F	+	1	36.8	Yes	No	No	No	
13	55 / M	+	1	32.0	Yes	No	No	No	
14	73 / F	+	1	35.1	Yes	No	No	No	

Patient	Age/ sex	RT-PCR	CO-RADS	RT-PCR Cycling Threshold	Postponed surgery	COVID-19 symptoms within 14 days after screening	COVID-19 related hospital admission	Follow-up testing	Clinical course
15	78 / F	-	4	NA	Yes	No	No	Second negative RT-PCR one day after screening.[b]	
16	84 / F	-	4	NA	Yes	No	No	Second negative RT-PCR one day after screening.[b]	
17	77 / M	-	4	NA	Yes	No	No	No	
18	61 / M	-	4	NA	Yes	No	No	No	

CT, computed tomography; NA, not applicable, RT-PCR, reverse-transcriptase polymerase chain reaction.
[a] This patient did not have symptoms until at least 8 days after screening, but could not be contacted for further follow-up.
[b] These patients received repeat preoperative RT-PCR testing due to the observed CO-RADS 4 score, which was not part of the national guideline.

Standard symptom questionnaire for preoperative COVID-19 screening:
Complaints
Did the patient, in the past 48 hours, have complaints of:
Coughing: yes / no / unknown
Dyspnea: yes / no / unknown
Fever (≥38.0): yes / no / unknown
General malaise: yes / no / unknown
General muscle or joint pain: yes / no / unknown
Headache: yes / no / unknown
Extreme fatigue (new): yes / no / unknown
Sore throat: yes / no / unknown
Common cold: yes / no / unknown
Loss of smell: yes / no / unknown
Loss of taste: yes / no / unknown
Abdominal pain: yes / no / unknown
Diarrhea: yes / no / unknown
Vomiting: yes / no / unknown

Are described complaints suspect for a COVID-19 infection?
yes / no

Has the patient been abroad recently (<2 weeks)?
yes / no / if yes, which country ……

Did the patient have contact with someone with a proven COVID-19 infection?
yes / no / unknown

Chapter 7

Yield of adding chest CT to abdominal CT to detect COVID-19 in patients presenting with acute gastrointestinal symptoms (SCOUT-3): multicenter study

Alexander B.J. Borgstein*, Jochem C.G. Scheijmans*, Carl A.J. Puylaert, Kammy Keywani, Mark E. Lobatto, Ricardo G. Orsini, Tjalco van Rees, Veillinga, Jorit van Rossen, Maeke J. Scheerder, Rogier P. Voermans, Alvin X. Han, Colin A. Russell, Jan M. Prins, Hester A. Gietema, Jaap Stoker, Marja A. Boermeester, Suzanne S. Gisbertz and Marc G. Besselink

*Shared first authorship

Annals of Surgery 2020

Abstract

Objective

To determine the incremental yield of standardized addition of chest CT to abdominal CT to detect COVID-19 in patients presenting with primarily acute gastrointestinal symptoms requiring abdominal imaging.

Summary Background Data

Around 20% of patients with COVID-19 present with gastrointestinal symptoms. COVID-19 might be neglected in these patients, as the focus could be on finding abdominal pathology. During the COVID-19 pandemic several centers have routinely added chest CT to abdominal CT to detect possible COVID-19 in patients presenting with gastrointestinal symptoms. However, the incremental yield of this strategy is unknown.

Methods

This multicenter study in six Dutch centers included consecutive adult patients presenting with acute non-traumatic gastrointestinal symptoms, who underwent standardized combined abdominal and chest CT between March 15, 2020 and April 30, 2020. All CT scans were read for signs of COVID-19 related pulmonary sequelae using the CO-RADS score. The primary outcome was the yield of high COVID-19 suspicion (CO-RADS 4-5) based on chest CT.

Results

A total of 392 patients were included. Radiologic suspicion for COVID-19 (CO-RADS 4-5) was present in 17 (4.3%) patients, eleven of which were diagnosed with COVID-19. Only five patients with CO-RADS 4-5 presented without any respiratory symptoms and were diagnosed with COVID-19. No relation with community prevalence could be detected.

Conclusion

The yield of adding chest CT to abdominal CT to detect COVID-19 in patients presenting with acute gastrointestinal symptoms is extremely low with an additional detection rate of around 1%.

Introduction

Patients with COVID-19 typically present with respiratory symptoms, fever, and/or fatigue [1,2]. However, there is growing evidence that SARS-CoV-2 can affect the small intestine, liver, pancreas and kidneys as well [3]. Hence, patients with COVID-19 may present with gastrointestinal symptoms, including abdominal pain, diarrhea, anorexia or vomiting [2,4–9], with limited respiratory symptoms. One study found that nearly 20% of COVID-19 patients presented with concomitant gastrointestinal symptoms [10], while in another study 16% of COVID-19 patients presented merely with gastrointestinal symptoms [11]. The atypical presentation of this group provides a clinical challenge, as clinicians might focus on finding abdominal pathology. No standardized diagnostic work-up, including the role of routine chest computed tomography (CT), has been described in these patients.

The (pre-COVID-19) Dutch guideline recommends a step-up imaging scheme for patients presenting with acute abdominal pain, starting with ultrasound and followed by abdominal CT if needed [12,13]. During the current COVID-19 pandemic, some centers have implemented standard use of abdominal CT with the standard addition of chest CT in order to detect possible SARS-CoV-2 infections in patients presenting with acute gastrointestinal symptoms, as these symptoms could be related to COVID-19.

However, the yield of combined CT chest-abdomen for detection of COVID-19 in patients with acute gastrointestinal symptoms is unknown. The aim of this study is to evaluate the incremental yield of high COVID-19 suspicion based on standard addition of chest CT to abdominal CT in patients presenting with acute gastrointestnninal symptoms.

Methods

This retrospective, multicenter study was conducted at three academic and three teaching hospitals in The Netherlands. Centers could participate in the study if the combination of chest and abdominal CT was part of the standard diagnostic work-up for patients who presented during the COVID-19 pandemic with acute gastrointestinal symptoms at the emergency department in whom abdominal imaging was required. Ethical approval was waived by the institutional review boards because of the observational nature of the study. Patient data was only used if patients did not opt out for participation for this study.

Study population

Eligible were consecutive adult patients presenting at the emergency department with primarily acute non-traumatic gastrointestinal symptoms, who underwent combined chest-abdominal CT between March 15, 2020 – April 30, 2020. This study period represents the period with the highest COVID-19 prevalence in the Netherland at the start of the pandemic.

Patients were excluded if the primary complaint was other than abdominal (mild respiratory symptoms could be present, but only if interpreted as secondary to the abdominal

complaints), if a chest CT was incomplete (defined as not including the basal lungs up to at least the level of the carina), or if patients were not able to object to participation in the study.

Data collection

Patient demographics, clinical characteristics including emergency department presentation and known risk factors for COVID-19, CT reports and 30-day clinical outcomes were collected from the electronic patient record. For chest CT imaging, the CO-RADS score for suspicion of COVID-19 diagnosis was used (1, very low suspicion; 2, low suspicion, 3, equivocal, 4, high suspicion, 5, very high suspicion) [14]. For abdominal CT, diagnoses causative for the GI-symptoms were collected. Abbreviated postal codes were collected to analyze regional differences in the primary outcome.

Study outcomes

Our primary outcome was the yield of high COVID-19 suspicion based on abdominal CT combined with chest CT (CO-RADS 4-5) in patients presenting with primary acute non-traumatic gastrointestinal symptoms. Patients were diagnosed with COVID-19 if reverse-transcriptase polymerase chain reaction (RT-PCR) results were positive. Alternatively, in patients with CO-RADS 4-5 and negative RT-PCR, the treating physician evaluated the COVID-19 diagnosis based on clinical presentation, CT findings and lab results, as sensitivity of RT-PCR is limited. All RT-PCR's were performed within 24 hours after presentation at the emergency department.

Secondary outcomes were the total number of patients diagnosed with of COVID-19, the yield of COVID-19 suspicion based on chest CT stratified according to the presence of COVID-19 respiratory symptoms and the relationship between COVID-19 community prevalence and positive yield of chest-abdomen CT screening.

Relationship to community prevalence

Patients were stratified by their province of residence and date of presentation at the emergency department to investigate the relationship between the primary outcome and community prevalence of COVID-19. Publicly available prevalence data was obtained from the Dutch National Institute for Public Health and the Environment [15]. The number of inhabitants per province in 2020 were obtained from the Central Agency of Statistics in The Netherlands [16]. The positive yield of COVID-19 diagnoses based on combined chest-abdomen CT and RT-PCR was compared to the mean daily COVID-19 admissions per 100,000 inhabitants within a 7-day window around each patient's presentation at the emergency department.

Statistical analysis

Clinical characteristics were described using frequency tables. Continuous data were presented as mean with standard deviation, unless stated otherwise. Categorical variables were presented as frequencies and percentages. Categorical variables were compared using

the χ^2 test or Fisher's exact test. All P values were based on two-sided tests and $P < 0.05$ was considered statistically significant. Data were analyzed using SPSS version 26 (IBM, Armonk, New York, USA)

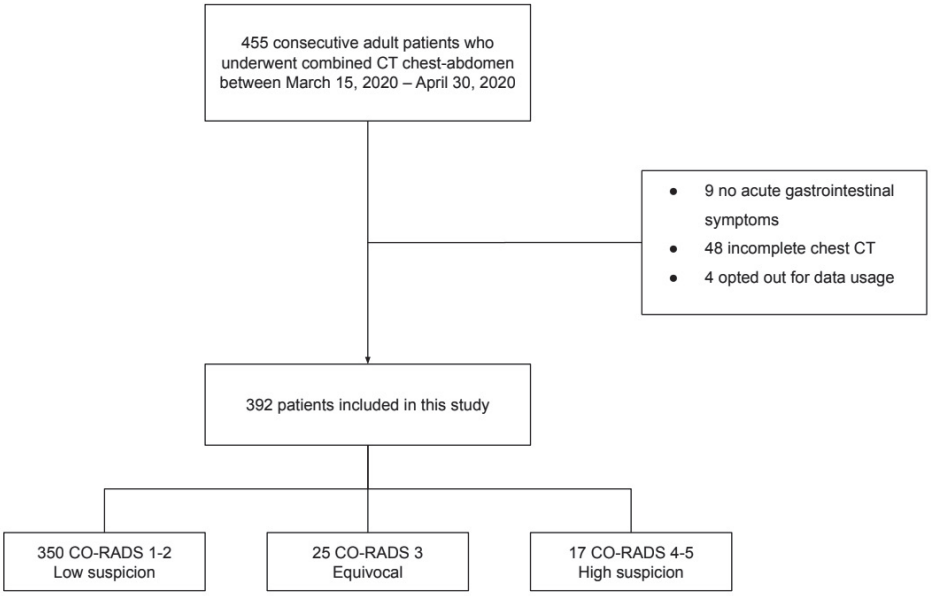


Figure 1. Flowchart of patients undergoing combined CT chest-abdomen for gastrointestinal symptoms

Results

Patient characteristics

Between March 15, 2020 and April 30, 2020, a total of 392 consecutive patients, who presented at the emergency departments of the six participating centers with primary acute non-traumatic gastrointestinal symptoms and underwent combined chest-abdomen CT were included, see figure 1 and Table S1. Table 1 summarizes the characteristics of all patients.

The yield of COVID-19 suspicion

Table 2 describes the yield of COVID-19 suspicion based on combined chest-abdomen CT and primary RT-PCR testing results. In 17 of 392 (4.3%) patients, chest CT was scored as CO-RADS 4 or 5. All of these17 patients underwent RT-PCR testing for SARS-CoV-2; eight tested positive, eight tested negative, and one test was inconclusive. Overall, 11 of 17 patients with CO-RADS 4-5 were diagnosed with COVID-19; three of which were diagnosed with COVID-19 based on CO-RADS 5 and clinical presentation without RT-PCR confirmation.

In 25 (6.4%) patients, chest CT was read as CO-RADS 3. Twenty-two of these 25 patients underwent RT-PCR testing; three patients tested positive, while 19 patients tested negative. In total, four patients with a CO-RADS 3 were diagnosed with COVID-19, one based on clinical presentation and chest CT findings.

Of the 350 patients with a CO-RADS 1-2, 156 had RT-PCR testing. Three patients tested positive, 152 patients tested negative, and one test was inconclusive. Overall, two patients with a CO-RADS 1 (no signs of pulmonary infection) and one patient with a CO-RADS 2 (signs of infection, but judged as not caused by COVID-19) were diagnosed with COVID-19.

Overall, 23 patients with an initial negative RT-PCR received a repeat RT-PCR test within four days after presentation at the emergency department, however, none of these patients tested positive. Therefore, 18 patients (4.6%) were diagnosed with COVID-19: 11 patients with CO-RADS 4-5 and 7 patients with CO-RADS 1-3 plus a positive RT-PCR.

Table S1 describes the yield of COVID-19 suspicion based on combined chest-abdomen CT and RT-PCR results for each of the participating centers. Table S2 summarizes the follow-up information of the 18 proven COVID-19 patients. Eleven patients were admitted to the hospital, no patients were admitted to the intensive care unit and two patients deceased. Of the four COVID-19 patients without RT-PCR confirmation, none received additional RT-PCR testing. One patient was recovering from a previous SARS-CoV-2 infection. One patient was admitted to the hospital for one day and none of these patients were readmitted to the hospital or deceased. Table S3 provides an overview of all definitive diagnoses established within seven days after initial presentation at the emergency department.

CO-RADS stratified for respiratory symptoms

Table 3 summarizes the CO-RADS classification stratified according to the presence of typical COVID-19 respiratory symptoms. According to history taking and physical examination, significantly more patients with a CO-RADS 4-5 were coughing compared to those with CO-RADS 1-2 or CO-RADS 3 (29.4% vs. 9.4% and 12.0%, respectively; *p=0.032)* and/or had fever (70.6% vs. 28.5% and 26.6%, respectively; $p<.001$). In each group (CO-RADS 1-2, 3, or 4-5), one of the patients had been in close contact with a known COVID-19 patient and none of the patients travelled to a foreign country within 14 days before presentation at the emergency department. Overall, five of the eleven patients with CO-RADS 4-5, who were diagnosed with COVID-19, presented without any respiratory symptoms.

Relationship with community prevalence

To assess the relationship between the yield of combined chest-abdomen CT (CO-RADS 4-5) and COVID-19 community prevalence in The Netherlands, the cohort of patients studied was stratified according to their date of diagnosis and province of residence. Aggregating the data in a sliding window of seven days, the combined positive yield was plotted against the mean number of daily COVID-19 admissions per 100,000 inhabitants within the same time period in their respective province (Figure 2 and table S1). There was no discernible

correlation between the yield of high COVID-19 suspicion based on chest-abdomen CT and community prevalence of COVID-19.

Table 1. Baseline characteristics of patients with acute gastrointestinal symptoms who underwent combined CT chest-abdomen

Characteristics	N = 392
Age, median (IQR), years	59 (43 – 73)
Age, range, years	18 – 95
Female sex, no./total no. (%)	214/392 (54.6)
Body-mass index, median (IQR), kg/m^2	21.8 (19.3 – 25.7)
Body-mass index > 30, no./total no. (%)	24/392 (6.1)
Smoking history, no./total no. (%)	
Never smoked	95/392 (24.2)
Former smoker	41/392 (10.5)
Current smoker	61/392 (15.6)
Unknown	195/392 (49.7)
Comorbidities, no./total no. (%)	
Chronic obstructive pulmonary disease	26/392 (6.6)
Diabetes	53/392 (13.5)
Hypertension	118/392 (30.1)
Coronary heart disease	37/392 (9.4)
Heart failure	17/392 (4.3)
Cerebrovascular disease	29/392 (7.4)
ASA classification, no./total no. (%)	
1	40/392 (10.2)
2	46/392 (11.7)
3	44/392 (11.3)
4	6/392 (1.5)
Unknown	256/392 (65.3)

ASA, American Society of Anesthesiologists; CT, computed tomography; IQR, interquartile range.

Table 2. COVID-19 suspicion based on combined chest-abdomen CT findings, with or without RT-PCR confirmation

Chest CT CO-RADS [a] no./total no. (%)		RT-PCR performed [b] no./total no. (%)	Positive no./total no. (%)	Negative no./total no. (%)	Inconclusive no./total no. (%)	COVID-19 diagnosis [c] no./total no. (%)
CO-RADS 1	325/392 (82.9)	136/325 (41.8)	2/136 (1.5)	133/136 (97.8)	1/136 (0.7)	2/325 (0.6)
CO-RADS 2	25/392 (6.4)	20/25 (80.0)	1/20 (5.0)	19/20 (95.0)	0/0 (0.0)	1/25 (4.0)
CO-RADS 3	25/392 (6.4)	22/25 (88.0)	3/25 (13.6)	19/25 (86.4)	0/0 (0.0)	4/25 (16.0)
CO-RADS 4	7/392 (1.6)	7/7 (100.0)	3/7 (42.9)	4/7 (57.1)	0/0 (0.0)	3/7 (42.9)
CO-RADS 5	10/392 (2.6)	10/10 (100.0)	5/10 (50.0)	4/10 (40.0)	1/1 (10.0)	8/10 (80.0)

CT, computed tomography; RT-PCR, reverse-transcriptase polymerase chain reaction;
[a] positive chest CT result was defined as a CO-RADS 4-5
[b] performed at the emergency department or within 24 hours after presentation at the emergency department
[c] definitive COVID-19 diagnosis based on combined CT chest-abdomen, history taking and physical examination; with or without RT-PCR confirmation

Table 3. CO-RADS classification in 392 patients presenting with acute gastrointestinal symptoms, stratified according to the presence of typical COVID-19 respiratory symptoms

Clinical symptoms, no./total no. (%) [a]	Total:	CO-RADS 1-2	CO-RADS 3	CO-RADS 4-5	*P*-value
Cough	38/360 (10.6)	30/318 (9.4)	3/25 (12.0)	5/17 (29.4)	0.032*
Dyspnea	40/352 (11.4)	35/310 (11.3)	3/25 (12.0)	2/17 (11.8)	0.993
Fever (> 38.0)	103/361 (28.5)	85/320 (26.6)	6/24 (25.0)	12/17 (70.6)	< 0.001*
Cold-like symptoms	18/265 (6.8)	13/230 (5.7)	3/20 (15.0)	2/15 (13.3)	0.164
Malaise	99/295 (33.6)	86/260 (33.1)	5/21 (23.8)	8/14 (57.1)	0.110
Exposure to COVID-19, no./total no. (%)					
Travelled to a foreign country within past 14 days	0/204 (0.0)	0/177 (0.0)	0/15 (0.0)	0/12 (0.0)	-
Contact with a known COVID-19 patient	3/207 (1.4)	1/181	1/15 (6.7)	1/11 (9.1)	0.015*

[a] clinical symptom presented if at least 75% of all included patients were questioned for this symptom during emergency presentation

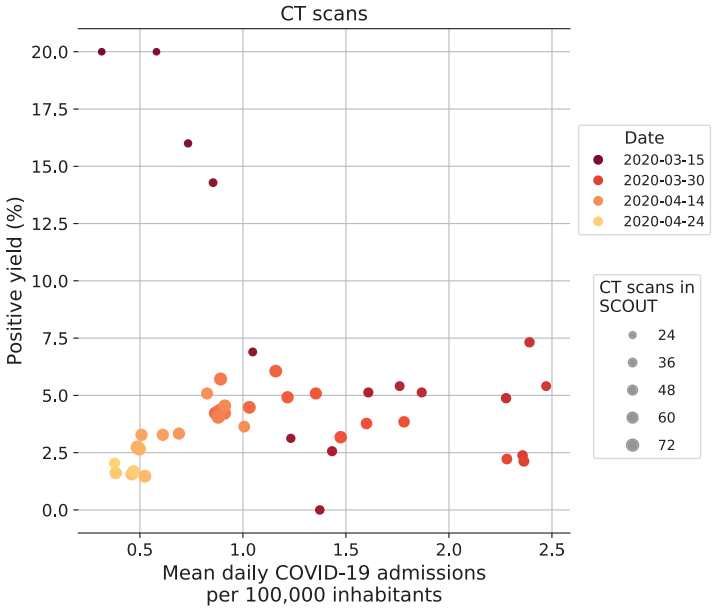


Figure 2. Scatter plot of positive COVID-19 yield based on combined CT chest-abdomen screening (CO-RADS 4-5) against community prevalence, measured by the mean daily COVID-19 related hospital admissions per 100.000 inhabitants. Each dot plots the positive yield of CT chest-abdomen screening within a sliding window of seven days against community prevalence during the same time in the respective province of residence as the patients who were tested. Points are coloured by the date of the 1st day of the seven-day time period and sized by the number of CT screenings performed within each period

Discussion

This study has evaluated the yield of standardized addition of chest CT to abdominal CT for COVID-19 suspicion in patients presenting with primarily acute non-traumatic gastrointestinal symptoms requiring abdominal imaging. The number of chest CT scans suspicious for COVID-19 was 17 (4.3%), of which eleven were diagnosed with COVID-19. Five of the eleven patients with CO-RADS 4-5 and COVID-19 diagnosis presented without any respiratory symptoms.

Hossain et al. investigated the number of COVID-19 diagnoses based on unexpected findings in the included lung zones at CT abdomen/pelvis or cervical spine/neck in patients with non-respiratory symptoms presenting at the emergency department [17]. Out of 2815 included patients, 299 (10.6%) had positive CT lung base/apical findings suggesting COVID-19 pneumonia. All 299 patients underwent RT-PCR testing, of which 44 (14.7%) tested positive for SARS-CoV-2. Siegel et al. reported three patients presenting at the emergency department with abdominal pain, without respiratory symptoms suggesting COVID-19, who underwent abdominal CT and in whom the radiologist was the first to suggest COVID-19 infection because of findings in the lung bases [18]. The authors concluded that COVID-19 may present primarily with abdominal symptoms, and that lung base findings on abdominal CT can provide the first signs of a possible SARS-CoV-2 infection.

One other study investigated the yield of adding routine chest CT to abdominal CT to identify COVID-19 in emergency general surgical admissions [19]. In a research letter, the authors report a total of 212 patients, identifying 12 (5.6%) patients as radiologically suspected for COVID-19, which is in line with our results (4.3%). The reported sensitivity was 60.0%. Overall, the authors concluded that standard inclusion of chest CT, together with abdominal CT, did not contribute to the identification of COVID-19 in emergency general surgical admissions. However, they did not describe the clinical presentation of patients at the emergency department. Therefore, it is unknown how many patients also had pulmonary symptoms, which would initiate diagnostic work-up for COVID-19 independent of the clinical work-up for their abdominal complains. Additionally, the authors did not provide information on RT-PCR results, which are essential to confirm COVID-19 diagnoses.

RT-PCR is the reference standard to establish a SARS-CoV-2 infection [20]. However, although being highly specific, sensitivity is considered to be moderate [21–23]. Therefore, several studies have suggested addition of chest CT to RT-PCR, in patients suspected for COVID-19 to ensure an accurate diagnosis [24,25]. A recent study investigated the added value of chest CT in suspected COVID-19 patients [26]. The primary outcome was the proportion of patients with an initially negative RT-PCR, who had a positive chest CT result (CO-RADS 4-5). In 38 out of 127 (29.9%) patients with a negative or intermediate RT-PCR, chest CT showed a high suspicion for COVID-19. Thirty-one (81.6%) of those patients were diagnosed with COVID-19 after repeated RT-PCR testing or clinical follow-up. In line with these findings, we found a discrepancy between percentage of COVID-19 suspicion based on chest CT (4.3%) and RT-

PCR confirmed SARS-CoV-2 infections (2.0%). However, our patient group was not suspected for COVID-19.

In a previous study we evaluated the yield of preoperative screening for COVID-19 with the use of chest CT and RT-PCR in patients without COVID-19 symptoms. We found that screening with RT-PCR detected SARS-CoV-2 in at least 1 in every 100 asymptomatic patients prior to elective or emergency surgery. The yield increased up to 6% when the daily COVID-19 daily hospital admissions rate exceeded 1.5 per 100,000 inhabitants and was therefore in conjunction with community prevalence of COVID-19. This study was performed during the same period as the current study. Hence, the percentage of COVID-19 patients without respiratory symptoms in the general population was around 6% in our study period. The yield of chest CT in the current study did not increase with community prevalence and did not correlate with the percentage of asymptomatic SARS-CoV-2 positive patients in the general population.

Previous studies found that around 20% of COVID-19 patients present with gastrointestinal symptoms next to respiratory symptoms. Moreover, around 5-16% of patients might present with gastrointestinal symptoms only, without any respiratory complaints (10,11). In our study, significantly more patients with high suspicion of COVID-19 based on chest CT presented with a cough or fever, identified after careful history taking and physical examination. Only five patients with CO-RADS 4-5 and who were diagnose with COVID-19 presented without any respiratory symptoms.

Our study has limitations. First, patients were included retrospectively. The clinical symptoms at presentation were not assessed using a standardized questionnaire. Therefore, some patients with primarily respiratory symptoms or without evident gastrointestinal symptoms might have been unknowingly included. Second, we found that the yield of suspected COVID-19 based on additional CT chest did not correlate with COVID-19 community prevalence. One might have expected that the number of patients with suspected COVID-19 based on chest CT would have increased with higher community prevalence of COVID-19. It is possible that selection bias could have influenced the yield of chest CT. Physicians were more aware for possible SARS-CoV-2 infection as the general COVID-19 knowledge and community prevalence increased in The Netherlands. Therefore, the number of patients who were primarily suspected for COVID-19, with or without respiratory symptoms, during presentation at the emergency department could have been higher in our study period. Hence, yield of the chest CT could have been higher if all patients with solely gastrointestinal symptoms would have been included in this study. Third, 197 (52.5%) patients with CO-RADS 1-3 did not undergo RT-PCR testing. Therefore, it is unknown in how many of these patients without suspicion for COVID-19 based on chest CT findings, acute gastrointestinal symptoms could have been caused by a SARS-CoV-2 infection.

In conclusion, the yield of adding chest CT to abdominal CT to detect COVID-19 in patients presenting with acute gastrointestinal symptoms is extremely low with an additional detection rate of around 1%.

References

1. Velavan TP, Meyer CG. The COVID-19 epidemic. *Trop Med Int Heal*. 2020;25(3):278-280.
2. Guan W, Ni Z, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720.
3. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol*. 2020;92(6):552-555.
4. Sippola S, Grönroos J, Sallinen V, et al. A randomised placebo-controlled double-blind multicentre trial comparing antibiotic therapy with placebo in the treatment of uncomplicated acute appendicitis: APPAC III trial study protocol. *BMJ Open*. 2018;8(11).
5. Chang Z, Mbbs L, Dipspmed M, et al. *COVID-19 and Elective Surgery: 7 Practical Tips for a Safe, Successful and Sustainable Reboot*.
6. Liang ZC, Chong MSY, Liu GKP, et al. COVID-19 and Elective Surgery. *Ann Surg*. May 2020:1.
7. Saeed U, Sellevoll HB, Young VS, Sandbæk G, Glomsaker T, Mala T. Covid-19 may present with acute abdominal pain. *Br J Surg*. 2020;107(7):e186-e187.
8. Han C, Duan C, Zhang S, et al. Digestive Symptoms in COVID-19 Patients With Mild Disease Severity. *Am J Gastroenterol*. 2020;115(6):916-923.
9. Gu J, Han B, Wang J. COVID-19: Gastrointestinal Manifestations and Potential Fecal–Oral Transmission. *Gastroenterology*. 2020;158(6):1518-1519.
10. Pan L, Mu M, Yang P, et al. Clinical Characteristics of COVID-19 Patients With Digestive Symptoms in Hubei, China. *Am J Gastroenterol*. 2020;115:1.
11. Luo S, Zhang X, Xu H. Don't Overlook Digestive Symptoms in Patients With 2019 Novel Coronavirus Disease (COVID-19). *Clin Gastroenterol Hepatol*. 2020;18(7):1636-1637.
12. Gans S, Pols M, Stoker J, Boermeester MA. Richtlijn 'Diagnostiek acute buikpijn bij volwassenen. NTVG. https://www.ntvg.nl/system/files/publications/a7494.pdf. Published 2014.
13. Laméris W, Van Randen A, Wouter Van Es H, et al. Imaging strategies for detection of urgent conditions in patients with acute abdominal pain: Diagnostic accuracy study. *BMJ*. 2009;339(7711):29-33.
14. Prokop M, van Everdingen W, van Rees Vellinga T, et al. CO-RADS – A categorical CT assessment scheme for patients with suspected COVID-19: definition and evaluation. *Radiology*. April 2020:201473.
15. Rijksinstituut voor Volksgezondheid en Milieu | RIVM. https://www.rivm.nl/.
16. StatLine. https://opendata.cbs.nl/#/CBS/nl/.
17. Hossain R, Lazarus MS, Roudenko A, et al. CT Scans Obtained for Nonpulmonary Indications: Associated Respiratory Findings of COVID-19. *Radiology*. May 2020:201743.
18. Siegel A, Chang PJ, Jarou ZJ, et al. Lung Base Findings of Coronavirus Disease (COVID-19) on Abdominal CT in Patients With Predominant Gastrointestinal Symptoms. *Am J Roentgenol*. April 2020:1-3.
19. Brennan C, Morrissey B, Dubois-Marshall S, McAteer D, Qadir A, Ramsay G. COVID-19: No benefit of chest inclusion in acute abdomen CT. *Br J Surg*. August 2020.
20. Cheng MP, Papenburg J, Desjardins M, et al. Diagnostic Testing for Severe Acute Respiratory Syndrome-Related Coronavirus 2: A Narrative Review. *Ann Intern Med*. 2020;172(11):726-734.

21. Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. *JAMA - J Am Med Assoc*. 2020;323(18):1843-1844.
22. Xie X, Zhong Z, Zhao W, Zheng C, Wang F, Liu J. Chest CT for Typical Coronavirus Disease 2019 (COVID-19) Pneumonia: Relationship to Negative RT-PCR Testing. *Radiology*. 2020;296(2):E41-E45.
23. Long C, Xu H, Shen Q, et al. Diagnosis of the Coronavirus disease (COVID-19): rRT-PCR or CT? *Eur J Radiol*. 2020;126.
24. Rubin GD, Ryerson CJ, Haramati LB, et al. The Role of Chest Imaging in Patient Management During the COVID-19 Pandemic: A Multinational Consensus Statement From the Fleischner Society. *Chest*. 2020;158(1):106-116.
25. Ai T, Yang Z, Hou H, et al. Correlation of Chest CT and RT-PCR Testing for Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. *Radiology*. 2020;296(2):E32-E40.
26. Korevaar DA, Kootte RS, Smits LP, et al. Added value of chest CT in suspected COVID-19: an analysis of 239 patients. *Eur Respir J*. July 2020:2001377.

Supplement

Table S1. In- and exclusions, CO-RADS 4-5 and regional COVID-19 community prevalence for each participating center

	Total	Amsterdam UMC, location AMC	Amsterdam UMC, location VUMC	Spaarne Gasthuis	Maastricht UMC+	Haaglanden Medical Center	Hospital Group Twente
Inclusions/exclusions, no./total no. (%)	392 / 61	80 (20.4) / 14 (23.0)	37 (9.4) / 28 (45.9)	112 (28.6) / 11 (18.0)	55 (14.0) / 3 (4.9)	59 (15.1) / 3 (4.9)	49 (12.5) / 2 (3.3)
CO-RADS 4-5, no./total no. (%)[a]	17	6 (35.3)	1 (5.9)	1 (5.9)	6 (35.3)	3 (17.6)	0 (0.0)
Positive RT-PCR[b], no./total no. (%)	14	7 (50.0)	0 (0.0)	1 (7.1)	4 (28.6)	2 (14.3)	0 (0.0)
COVID-19 diagnosis[c]	18	9 (50.0)	0 (0.0)	1 (5.6)	5 (27.7)	3 (16.7)	0 (0.0)
Regional COVID-19 community prevalence[d]	1.23	1.23	1.23	1.23	3.03	1.16	1.10

Abbreviations: RT-PCR, reverse-transcriptase polymerase chain reaction;
[a] positive chest CT result was defined as a CO-RADS 4-5
[b] performed at the emergency department or within 24 hours after presentation at the emergency department
[c] definitive COVID-19 diagnosis based on combined CT chest-abdomen, history taking and physical examination; with or without RT-PCR confirmation
[d] calculated as the average daily COVID-19 hospital admission rate per 100,000 inhabitants, between March 15 and April 30, 2020, for each province of the participating centers (Noord-Holland, Limburg, Zuid-Holland and Overijssel).

Table S2. 30-day follow-up information of 18 COVID-19 patients

Follow-up information:	**N = 18**
Admitted to hospital from emergency department, no./total no. (%)	11/18 (61.1)
ICU admission, no./total no. (%)	0/18 (0.0)
Hospital stay, median (IQR), days	6 (2 – 9)
Mortality, no./total no. (%)	2/18 (11.1)

Table S3. Definitive diagnosis established within seven days after initial presentation in 392 patients presenting with gastro-intestinal symptoms

Diagnosis, no./total no. (%):	**N = 392**
COVID-19	18 (4.6)
Appendicitis	49 (12.5)
Diverticulitis	24 (6.1)
Ileus	33 (8.4)
Inflammatory bowel disease	10 (2.6)
Stomach/intestinal perforation	9 (2.3)
Intestinal ischemia	3 (0.8)
Intestinal herniation	12 (3.1)
Abcess	10 (2.6)
Gastritis	4 (1.0)
Cholecystitis/cholangitis	37 (9.4)
Cholelithiasis	9 (2.3)
Pancreatitis	17 (4.3)
Malignancy	21 (5.4)
Urolithiasis	9 (2.3)
Pyelonefritis	19 (4.8)
Pelvic inflammatory disease	6 (1.5)
Aorta dissection or rupture	5 (1.3)
Other	50 (12.8)
No diagnosis	47 (12.0)

Chapter 8

Safety of performing esophageal cancer surgery during the first wave the COVID-19 pandemic in Europe: a multicenter study

Alexander B.J. Borgstein*, Stefanie Brunner*, Masaru Hayami, Johnny Moons, Hans Fuchs, Wietse J. Eshuis, Suzanne S. Gisbertz, Christiane J. Bruns, Philippe Nafteux, Magnus Nilsson, Wolfgang Schröder, Mark I. van Berge Henegouwen

*Shared first authorship

Annals of Surgical Oncology 2021

Abstract

Background

Many hospitals have postponed elective surgical care during the first wave of the COVID-19 pandemic. Some centers continued elective surgery, including esophageal cancer surgery, with the use of preoperative screening methods. However, there is no evidence supporting the safety of this strategy, as postoperative outcomes after esophageal cancer surgery during the COVID-19 pandemic have not yet been investigated.

Methods

This multicenter study in four European tertiary esophageal cancer referral centers included consecutive adult patients undergoing elective esophageal cancer surgery from a prospectively maintained database in a COVID-19 pandemic cohort (March 1, 2020 – May 31, 2020) and a control cohort (October 1, 2019 – February 29, 2020). The primary outcome was the rate of respiratory failure requiring mechanical ventilation.

Results

The COVID-19 cohort consisted of 139 patients versus 168 patients in the control cohort. There was no difference in the rate of respiratory failure requiring mechanical ventilation (13.7% vs. 8.3%, p=0.127) and number of pulmonary complications (32.4% vs. 29.9%, p=0.646) between the COVID-19 and the control cohort. Overall, postoperative morbidity and the mortality rate were comparable between both cohorts. History taking and RT-PCR were used as preoperative screening methods to detect a possible SARS-CoV-2 infection in all centers. No patients were diagnosed with COVID-19 pre- or postoperatively.

Conclusion

Esophageal cancer surgery during the first wave of the COVID-19 pandemic was not associated with increase of pulmonary complications, as no patients were diagnosed with COVID-19. Esophageal cancer surgery can be performed safely with the use of adequate preoperative SARS-CoV-2 screening methods.

Introduction

Esophageal cancer is the sixth leading cause of cancer-related deaths worldwide [1,2]. Curative treatment for locally advanced esophageal cancer consists of esophagectomy combined with perioperative (radio-)chemotherapy [3,4]. Esophagectomy is a complex surgical procedure and is associated with substantial morbidity, in particular postoperative pneumonia and consecutive respiratory failure [5–8].

Many hospitals have postponed elective surgical care during the first wave of the COVID-19 pandemic. This was necessary as medical resources were shifted to increase intensive care unit capacities, to prevent patients acquiring in-hospital SARS-CoV-2 infections and concerns regarding the safety of healthcare workers and patients [9,10]. This strategy is supported by a recent study demonstrating that patients undergoing surgery with a SARS-CoV-2 infection have increased risk for postoperative pulmonary complications and mortality [11]. Additionally, patients scheduled for esophageal cancer surgery are at high risk for symptomatic COVID-19 because of epidemiologic characteristics of high age, male sex, and high prevalence of obesity, immunosuppression due to neoadjuvant therapy, high prevalence of pre-existing pulmonary comorbidities and transthoracic esophagectomy with single lung ventilation [12–14].

On the other hand, some countries have implemented national guidelines advising the use of preoperative SARS-CoV-2 screening methods to continue elective surgery [15]. Certain international tertiary hospitals, specialized in esophageal cancer, have been able to continue elective cancer surgery with the use of preoperative screening. However, there is no evidence supporting the safety of this strategy, as postoperative outcomes after esophageal cancer surgery during the COVID-19 pandemic have not yet been investigated in detail.

Currently, second COVID-19 waves are occurring around the world. Therefore, it is important to investigate the safety of continuing elective cancer surgery, as postponement substantially increases the number of avoidable cancer deaths demonstrated in a recent national cancer registry analysis [16]. The aim of the current study is to assess the safety of patients undergoing elective esophageal cancer surgery during the COVID-19 pandemic focusing on respiratory failure as the most critical condition of SARS-CoV-2 infection.

Methods

This international, retrospective, multicenter cohort study was conducted at four European tertiary referral hospitals in The Netherlands, Germany, Belgium and Sweden, all specialized in esophageal cancer surgery. All participating centers continued elective esophageal cancer surgery during the first wave of the COVID-19 pandemic. Ethical approval was waived by the Amsterdam UMC review board because of the observational nature of the study. This decision was approved by the institutional review board of each participating center.

Study population

Consecutive adult patients undergoing elective esophageal cancer surgery were included in two cohorts. The first cohort consisted of patients who underwent esophagectomy between October 1, 2019 and February 29, 2020, the control cohort. The second cohort consisted of patients operated between March 1, 2020 and May 31, 2020, the COVID-19 pandemic cohort. This study period reflects the months with the highest COVID-19 prevalence in the participating countries (figure 1).

The following patients were eligible for inclusion: age ≥ 18 years, undergoing either a thoracophrenicolaparotomy, transthoracic, transhiatal esophagectomy, which could be performed open or totally minimally invasive (including hybrid procedure). Pre- and postoperative testing information for SARS-CoV-2 had to be available for patients in the COVID-19 pandemic cohort. Patients undergoing emergency esophagectomy were excluded. Patient data was only used if patients did not opt out for participation in this study.

SARS-CoV-2 testing

Each participating center provided information on the type of pre- and postoperative screening methods used in the COVID-19 cohort. In case of a positive preoperative RT-PCR, surgery would be postponed for two weeks. A repeated RT-PCR test would be performed two days before the new date of surgery, although repeated PCR testing is known to be of limited value, and not advised in all national multidisciplinary guidelines [17]. In the first wave however, knowledge on COVID-19 was limited and repeated RT-PCR testing was performed because of the fear for in-hospital transmission.

Data collection

Patient demographics (age, sex, American Society of Anaesthesiologists score and Charlson Comorbidity Index), tumor and treatment characteristics (histopathological staging, neoadjuvant therapy, type of surgery performed) and postoperative outcomes according to Esophageal Complications Consensus Group (ECCG) definitions [18] were collected from prospectively maintained databases in all centers. Additionally, pre- and postoperative screening results for SARS-CoV-2 infections (for patients in the COVID-19 pandemic group) were collected from the electronic patient record.

Study outcomes

The primary outcome was the rate of respiratory failure requiring mechanical ventilation in both cohorts. Secondary outcomes were overall postoperative morbidity, rate of postoperative pneumonia, number of postoperative SARS-CoV-2 infections, length of stay and hospital readmissions and mortality within 30-days postoperatively. Severity of postoperative complications was graded according to the Clavien-Dindo scale and Comprehensive Complications Index (CCI) [19,20].

Statistical analysis

Univariate analyses of the two cohorts were compared using Mann-Whitney U test for continuous variables, and x^2-test or Fisher's exact test for categorial variables. To identify an association between undergoing esophageal cancer surgery during the COVID-19 pandemic and postoperative respiratory failure requiring mechanical ventilation, a multivariable logistic regression analysis was performed. All *P* values were based on two-sided tests and $P < 0.05$ was considered statistically significant. Data were analysed using SPSS version 26 (IBM, Armonk, New York, USA).

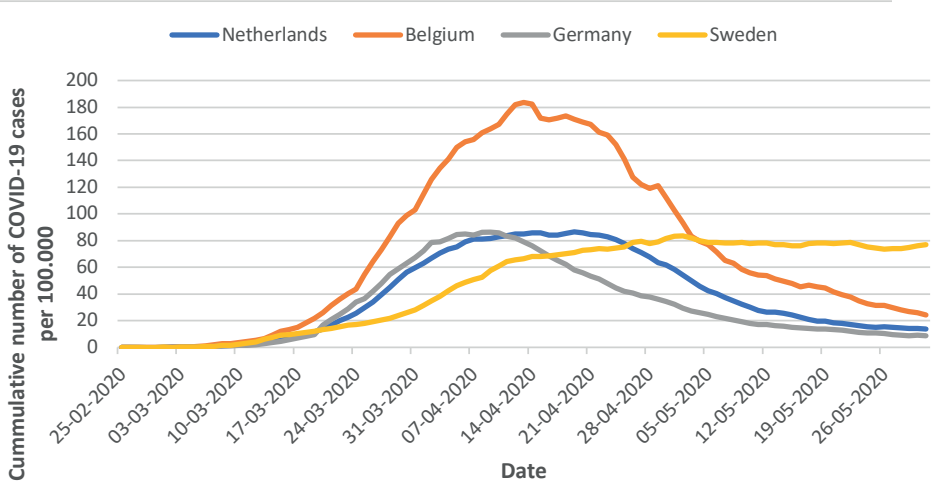


Figure 1. Daily number of new proven COVID-19 cases for the country of each participating center, calculated as the cumulative number for 14-days of COVID-19 cases per 100.000 population [35]

Results

Patient characteristics

Between March 1, 2020 and May 31, 2020, a total of 139 patients underwent esophageal resection for cancer in the COVID-19 pandemic cohort. A total of 168 patients were included in the control cohort between October 1, 2019 and February 29, 2020. Baseline and treatment characteristics of all patients in both cohorts are presented in table 1. Patients operated during the COVID-19 pandemic had a significantly higher ASA score. There were no differences in tumour and treatment characteristics between the patients in both cohorts. Almost 75% of all patients in both cohorts underwent a minimally invasive esophagectomy.

Postoperative outcomes

Table 2 shows the postoperative outcomes of all patients in both cohorts. There was no difference in the total number of postoperative complications (64.0% vs. 63.7%, p=0.951), mean CCI score (44.3 vs. 39.7, p=0.699) and maximum Clavien-Dindo (p=0.317).

The percentage of respiratory failure requiring mechanical ventilation (13.7% vs. 8.3%, p=0.127) and the total number of pulmonary complications were comparable between both cohorts (32.4% vs. 29.9%, p=0.647). The ICU admission rate and length of stay at the ICU were similar in both cohorts. In one center, all patients were admitted to the ICU postoperatively as part of standard care (table S1). There was no difference in the 30-day readmission and mortality rate between the COVID-19 pandemic and control cohort.

Table S1 provides an overview of the postoperative outcomes for each of the participating centers, no statistical differences between centers were observed.

In univariate logistic regression analysis, the odds ratio (OR) for postoperative respiratory failure requiring mechanical ventilation was 1.44 (95% CI 0.80 – 2.58, p=0.222) for patients operated during the COVID-19 pandemic. In a multivariate logistic regression, adjusted for ASA score, surgical approach and surgical procedure, the OR was 1.43 (95% CI 0.76 – 2.70, p=0.272) for patients in the COVID-19 pandemic group.

SARS-CoV-2 testing results

An overview of the screening methods used in each center is provided in table S2. All centers used COVID-19 specific symptoms screening and RT-CPR. However, the date of implementation of the screening methods was different in each hospital.

SARS-CoV-2 testing results of patients in the COVID-19 pandemic cohort are presented in table 3. 134 out of 139 (96.4%) were screened for COVID-19 preoperatively and all were negative. History taking for specific COVID-19 symptoms was performed in most patients (95.0%), followed by white-cell / lymphocyte count (73.4%), RT-PCR (71.9%) and chest CT (11.5%). 36 symptomatic patients (25.9%) received postoperative RT-PCR testing for SARS-

CoV-2, all patients tested negative. Overall, none of the patients were diagnosed with COVID-19, subsequently no surgery was postponed because of screening results.

Table 1. Baseline and treatment characteristics of all patients undergoing esophageal cancer surgery, compared between the COVID-19 pandemic cohort (1 March, 2020 – 31 May, 2020) and the control cohort (1 October, 2020 – 29 February, 2020)

Characteristics	COVID-19 pandemic group (n=139)	Control cohort (n=168)	*P*-value
Age, median (IQR), years	66 (58-71)	67 (60-73)	0.165
Male sex, no./total no. (%)	116 (83.5)	141 (83.9)	0.911
BMI > 25, no./total no. (%)	49.3 (68)	100 (59.5)	0.073
ASA score, no./total no. (%):			0.015
1	14 (10.1)	37 (22.0)	
2	81 (58.3)	90 (53.6)	
3	44 (31.7)	39 (23.2)	
4	0 (0.0)	2 (1.2)	
WHO performance status, no./total no. (%):			0.431
0	75 (54.0)	86 (51.2)	
1	48 (34.5)	62 (36.9)	
2	12 (8.6)	15 (8.9)	
3	2 (1.4)	0 (0.0)	
4	1 (0.7)	0 (0.0)	
Missing	1 (0.7)	5 (3.0)	
Charlson comorbidity index, no./total no. (%)			0.403
0	9 (6.5)	5 (3.0)	
1	24 (17.3)	26 (15.5)	
2	31 (22.3)	49 (29.2)	
3	36 (25.9)	29 (17.3)	
4+	39 (28.0)	59 (35.0)	
Comorbidities, no./total no. (%):			0.254
Myocardial infarction	6 (4.3)	7 (4.2)	
Congestive heart failure	0 (0.0)	0 (00)	
Chronic pulmonary disease	14 (10.1)	14 (8.3)	
Diabetes Mellitus (uncomplicated)	21 (15.1)	16 (9.5)	
Moderate to severe renal disease	0 (0.0)	2 (1.2)	
Multiple	4 (2.9)	12 (7.1)	
Histology, no./total no. (%):			0.672
Adenocarcinoma	108 (77.7)	135 (80.4)	
Squamous Cell Carcinoma	28 (20.1)	30 (17.9)	
Other	3 (2.2)	2 (1.2)	
Clinical T stage, no./total no. (%):			0.416
cT1	7 (5.0)	8 (4.8)	
cT2	13 (9.4)	23 (13.7)	
cT3	106 (76.3)	124 (73.8)	
cT4	3 (2.2)	10 (6.0)	

Characteristics	COVID-19 pandemic group (n=139)	Control cohort (n=168)	*P*-value
cTx	6 (4.3)	10 (6.0)	
Missing	4 (2.9)	0 (0.0)	
Clinical N stage, no./total no. (%):			0.887
cN0	33 (23.7)	44 (26.2)	
cN1	30 (21.6)	33 (19.6)	
cN2	18 (12.9)	27 (16.1)	
cN3	3 (2.3)	4 (2.4)	
cNx	55 (39.6)	60 (35.7)	
Neoadjuvant therapy, no./total no. (%):			0.958
Chemotherapy	36 (25.9)	46 (27.4)	
Chemoradiotherapy	77 (55.4)	91 (54.2)	
Surgical approach, no./total no. (%):			0.280
Open	35 (25.2)	40 (23.8)	
Minimally invasive	104 (74.8)	125 (74.4)	
Minimally invasive converted to open	0 (0.0)	3 (1.8)	
Esophagectomy, no./total no. (%):			0.705
Transhiatal	3 (2.2)	4 (2.4)	
Transthoracic	119 (85.6)	138 (82.1)	
Thoracophrenicolaparotomy	17 (12.2)	26 (15.5)	

Abbreviations: ASA, American Society of Anesthesiologists; IQR, interquartile range; SD, standard deviation

Table 2. Postoperative outcomes of all patients undergoing esophageal cancer surgery, compared between the COVID-19 pandemic cohort and the control cohort

	COVID-19 pandemic group (n=139)	Control cohort (n=168)	*P*-value
Complications, no./total no. (%)			
Yes	89 (64.0)	107 (63.7)	0.951
CCI score, mean (SD)	41.2 (25.5)	39.8 (20.2)	0.699
Maximum Clavien-Dindo, no./total no. (%)			0.317
I	5 (3.6)	8 (4.8)	
II	33 (23.7)	35 (20.8)	
III	25 (18.0)	39 (23.2)	
IV	25 (18.0)	24 (14.3)	
V	5 (3.6)	2 (1.2)	
Pulmonary complications, no./total no. (%):	45 (32.4)	50 (29.9)	0.647
Pneumonia	20 (14.4)	32 (19.0)	0.297
Respiratory failure requiring reintubation	19 (13.7)	14 (8.3)	0.127
ICU admission, no./total no. (%)	69 (49.6)	98 (58.3)	0.128
ICU admission (days), median (IQR)	0 (0-4)	1 (0-3)	0.686
Length of hospital stay (days), median (IQR)	12 (9-16.25)	12.5 (9-17.75)	0.430
Readmission within 30-days, no./total no. (%)			
Yes	16 (11.5)	14 (8.3)	0.184
30-day mortality, no./total no. (%)			
Yes	5 (3.6)	3 (1.8)	0.263

CCI, comprehensive complications index; IQR, interquartile range

Table 3. Pre- and postoperative SARS-CoV-2 testing results of patients in the COVID-19 pandemic cohort (N=139)

Preoperative		**Postoperative**	
COVID-19, no./total no. (%):		COVID-19, no./total no. (%):	
Positive	0 (0.0)	Positive	(0.0)
Negative	134 (96.4)	Negative	36 (25.9)
Not tested	5 (3.6)	Not tested	103 (74.1)
Methods, no./total no. (%)		Methods, no./total no. (%)	
RT-PCR	100 (71.9)	RT-PCR	36 (25.9)
Chest CT	16 (11.5)		
Symptom screening	132 (95.0)		
White-cell / lymphocyte count	102 (73.4)		
Antibody analysis	0 (0.0)		
Surgery postponed, no./total no. (%)			
No	139 (100.0)		

RT-PCR, reverse transcription polymerase chain reaction; CT, computed tomography

Discussion

This study investigated the safety of patients undergoing elective esophageal cancer surgery during the first wave of the COVID-19 pandemic in Europe, comparing that with patients undergoing surgery in a period just before the COVID-19 pandemic. None of the patients in the COVID-19 pandemic cohort were pre- or postoperatively diagnosed with COVID-19. This resulted in a similar rate of patients with respiratory failure requiring mechanical ventilation in both cohorts. Therefore, undergoing esophagectomy during the COVID-19 pandemic was not associated with increased risk of respiratory failure.

The ICU admission rate and length of stay at the ICU were comparable between both cohorts. In one center, all patients went to the ICU postoperatively as part of standard care. None of the participating centers experienced a shortage of ICU beds or delay in ICU readmission because of hospital COVID-19 volume during our inclusion period. The ASA score was higher in the COVID-19 pandemic cohort, with a higher percentage of patients with ASA 2-3. There was no specific reason for this difference.

This is the first study to investigate the short-term postoperative outcomes in patients undergoing elective esophageal cancer surgery during the COVID-19 pandemic.

In the COVID-19 cohort, the percentage of patients with pulmonary complications (32.4%), the rate of respiratory failure requiring mechanical ventilation (13.7%) and the 30-day mortality rate (3.6%) were comparable to the findings of previous studies [7,8,21.]

A recent study by Chenchen et al. investigated the safety of performing cancer surgery during the COVID-19 pandemic [22]. They found that none of the 621 patients tested positive for COVID-19 postoperatively. Shrikhande et al. performed a single center prospective study

examining 494 patients undergoing elective major cancer surgery in India and found that only six patients were diagnosed with COVID-19 postoperatively, none of which required escalating care or intensive care treatment [23]. In line with these findings, no patients were diagnosed with COVID-19 in our cohort, although the COVID-19 community prevalence in Europe was higher in our study period.

Studies performed at the beginning of the COVID-19 pandemic concluded that patients undergoing surgery with a SARS-CoV-2 infection had worse postoperative outcomes, with a high postoperative mortality rate [24]. Increased 30-day mortality was associated with male sex, age >70, ASA score of 3-5, cancer surgery and major surgical procedures. Additionally, oncologic patients undergoing surgery or chemotherapy have increased risk for severe COVID-19 [25]. Based on these findings, international societies advised to postpone elective surgery when possible, including esophageal cancer surgery [13]. A study by the COVIDSurg group has estimated the total number of adult elective operations that were cancelled during the first 12 weeks of the first wave of the COVID-19 pandemic, which was 72.3% [26]. Globally, 37.7% of all cancer operations were cancelled or postponed. The study concluded that if countries would increase their normal surgical capacity by 20% after the COVID-19 pandemic, it would take a median of 45 weeks to clear the accumulation of operations [26]. The question remains whether postponement of cancer surgery leads to progression of the tumor and reduced overall survival. Turaga et al. investigated how long different types of cancer surgery could be safely delayed. The authors concluded that most cancer surgeries can be safely delayed for at least four weeks without having a significant impact on patient survival or cancer progression [27]. However, with a second COVID-19 wave currently developing in Europe, waiting lists will start to increase, which might lead to postponement of elective cancer surgery for more than four weeks.

A Dutch study evaluated the yield of preoperative screening for COVID-19 with chest CT and RT-PCR in asymptomatic patients. RT-PCR detected SARS-CoV-2 in at least 1 in every 100 asymptomatic patients undergoing elective or emergency surgery [28]. This yield increased to 6% when the COVID-19 daily hospital admissions rate exceeded 1.5 per 100,000 inhabitants. The incremental yield of chest CT was only 0.4% and did not contribute to COVID-19 detection. None of the patients who underwent history taking and RT-PCR preoperatively developed symptomatic COVID-19 after surgery [28]. In line with these findings, a recent study by the COVIDSurg group concluded that preoperative RT-PCR testing was beneficial before major surgery and in high SARS-CoV-2 risk areas [29]. Having at least one negative preoperative RT-PCR test was associated with a lower rate of pulmonary complications (OR 0.68, 95 CI 0.68 – 0.98, p=0.040) [29].

In our study, almost all patients in the COVID-19 cohort were screened for COVID-19 specific symptoms preoperatively and 70% underwent RT-PCR testing. RT-PCR testing was used as standard preoperative screening method in all participating centers. However, because of limited testing capacity and differences in implications of national guidelines at the beginning

of the COVID-19 pandemic, not all patients were tested with RT-PCR. Only symptomatic patients underwent RT-PCR testing for COVID-19 postoperatively.

Surgery would have been postponed for two weeks if a patient tested positive for COVID-19 preoperatively, with an additional RT-PCR test two days before the new date of surgery. This strategy would have been applied irrespective of whether a patient received neoadjuvant therapy. A previous study found that the interval between neoadjuvant therapy and esophagectomy could be safely extended to a maximum of ten or more weeks [30].

75% of all patients underwent minimally invasive surgery in both the COVID-19 pandemic cohort and the control cohort. According to the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) and the European Association of Endoscopic Surgery (EAES) guidelines, released during the first wave of the COVID-19 pandemic, minimally invasive surgery was discouraged as these procedures could contaminate surgical staff [31]. Our study did not investigate the rate of SARS-CoV-2 infections among the surgical staff. However, as all patients were screened for COVID-19 preoperatively, the strategy of performing minimally invasive surgery in our cohort was safe.

Our study has some limitations. First, patients were included retrospectively from prospectively maintained databases in all centers. Therefore, the participating centers did not use a similar standardized preoperative COVID-19 screening strategy during the inclusion period. Second, not all patients in the COVID-19 cohort were screened for COVID-19 preoperatively and 75% of patients were not tested postoperatively. Furthermore, only RT-PCR was used postoperatively to diagnose possible COVID-19. RT-PCR is considered the reference standard to establish a SARS-CoV-2 infection, however, sensitivity is considered to be moderate [32]. Hence, asymptomatic COVID-19 patients or patients with a false negative testing results could have been missed. However, clinical follow-up information was obtained for all patients and no patients were suspected for symptomatic COVID-19. Third, surgeons may have selected the healthiest patients to undergo surgery during the peak of the COVID-19 pandemic. Therefore, this patient group might not be representable for the normal population undergoing esophageal cancer surgery. However, no differences were found in baseline characteristics between both cohorts.

Currently, we are facing a second COVID-19 wave in Europe, which is characterized by the appearance of new SARS-CoV-2 variants [32]. Although it is unknown whether these new variants are more infectious, epidemiological data shows that these variants have a higher transmissibility compared to the original variant [32,33]. Hospitals will therefore face a higher number of COVID-19 patients during the upcoming months, which may affect the surgical and ICU capacity. Hence, hospitals that could continue elective cancer surgery during the first COVID-19 wave might have problems continuing cancer care during the second and possibly third wave. Increased lockdown measures and vaccination might prevent such a scenario.

In conclusion, elective esophageal cancer surgery can be performed safely during the COVID-19 pandemic with the use of adequate preoperative SARS-CoV-2 screening methods. With increasing numbers of operations being cancelled or postponed around the world, this study indicates that patients can undergo major cancer surgery during the ongoing COVID-19 pandemic without additional risk for the patient.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*. 2010;127(12):2893-2917.
2. Arnold M, Ferlay J, Van Berge Henegouwen MI, Soerjomataram I. Global burden of oesophageal and gastric cancer by histology and subsite in 2018. *Gut*. 2020;69(9):1564-1571.
3. Lordick F, Mariette C, Haustermans K, Obermannová R, Arnold D, on behalf of the ESMO Guidelines Committee clinicalguidelines@esmo org. Oesophageal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2016;27:v50-v57.
4. Kitagawa Y, Uno T, Oyama T, et al. Esophageal cancer practice guidelines 2017 edited by the Japan esophageal society: part 2. *Esophagus*. 2019;16(1):25-43.
5. Low DE, Kuppusamy MK, Alderson D, et al. Benchmarking Complications Associated with Esophagectomy. *Ann Surg*. 2019;269(2):291-298.
6. Van Der Werf LR, Busweiler LAD, Van Sandick JW, Van Berge Henegouwen MI, Wijnhoven BPL. Reporting national outcomes after esophagectomy and gastrectomy according to the esophageal complications consensus group (ECCG). *Ann Surg*. 2020;271(6):1095-1101.
7. Schröder W, Raptis DA, Schmidt HM, et al. Anastomotic Techniques and Associated Morbidity in Total Minimally Invasive Transthoracic Esophagectomy: Results from the EsoBenchmark Database. *Ann Surg*. 2019;270(5).
8. Kuppusamy MK, Low DE. Evaluation of International Contemporary Operative Outcomes and Management Trends Associated With Esophagectomy. *Ann Surg*. 2020;Publish Ah(Xx):1-11.
9. Besnier E, Tuech JJ, Schwarz L. We Asked the Experts: Covid-19 Outbreak: Is There Still a Place for Scheduled Surgery? "Reflection from Pathophysiological Data." *World J Surg*. 2020;44(6):1695-1698.
10. Aminian A, Safari S, Razeghian-Jahromi A, Ghorbani M, Delaney CP. COVID-19 Outbreak and Surgical Practice: Unexpected Fatality in Perioperative Period. *Ann Surg*. 2020;272(1):e27-e29.
11. Nepogodiev D, Bhangu A, Glasbey JC, et al. Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study. *Lancet*. 2020;396(10243):27-38.
12. McLoughlin JM, Lewis JM, Meredith KL. The impact of age on morbidity and mortality following esophagectomy for esophageal cancer. *Cancer Control*. 2013;20(2):144-150.
13. Barbieri L, Urquijo ET, Parise P, Nilsson M, Reynolds J V., Rosati R. Esophageal oncologic surgery in SARS-CoV-2 (COVID-19) emergency. *Dis Esophagus*. 2020;33(5):1-5.
14. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol*. 2020;21(3):335-337.
15. This D, Sars-cov- IT, Specialists M. Practice guideline Leidraad. 2020:1-11.
16. Bertuzzi AF, Marrari A, Gennaro N, et al. Low Incidence of SARS-CoV-2 in Patients with Solid Tumours on Active Treatment: An Observational Study at a Tertiary Cancer Centre in Lombardy, Italy. *Cancers (Basel)*. 2020;12(9):2352.
17. NVVH. Pre-operatieve diagnostiek naar SARS-CoV-2 infectie bij asymptomatische patiënten ingepland voor chirurgie onder algehele anesthesie. 2020:1-18.

18. Low DE, Alderson D, Cecconello I, et al. International consensus on standardization of data collection for complications associated with esophagectomy: Esophagectomy Complications Consensus Group (ECCG). *Ann Surg*. 2015;262(2):286-294.
19. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240(2):205-213.
20. Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien PA. The comprehensive complication index: A novel continuous scale to measure surgical morbidity. *Ann Surg*. 2013;258(1):1-7.
21. Merkow RP, Bilimoria KY, McCarter MD, et al. Short-term outcomes after esophagectomy at 164 American College of Surgeons National Surgical Quality Improvement Program Hospitals: Effect of operative approach and hospital-level variation. *Arch Surg*. 2012;147(11):1009-1016.
22. Ji C, Singh K, Luther AZ, Agrawal A. Is Elective Cancer Surgery Safe During the COVID-19 Pandemic? *World J Surg*. 2020;44(10):3207-3211.
23. Shrikhande S V., Pai PS, Bhandare MS, et al. Outcomes of Elective Major Cancer Surgery During COVID 19 at Tata Memorial Centre. *Ann Surg*. 2020;272(3):e249-e252.
24. Nepogodiev D, Glasbey JC, Li E, et al. Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study. *Lancet*. 2020;0(0).
25. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol*. 2020;21(3):335-337.
26. Elective surgery cancellations due to the COVID-19 pandemic: global predictive modelling to inform surgical recovery plans. *Br J Surg*. June 2020.
27. Turaga KK, Girotra S. Are we harming cancer patients by delaying their cancer surgery during the COVID-19 pandemic? 2020.
28. Puylaert CAJ, Scheijmans JCG, Borgstein ABJ, et al. Yield of Screening for COVID-19 in Asymptomatic Patients Prior to Elective or Emergency Surgery Using Chest CT and RT-PCR (SCOUT). *Ann Surg*. 2020;Publish Ah.
29. Collaborative C. Preoperative nasopharyngeal swab testing and postoperative pulmonary complications in patients undergoing elective surgery during the SARS-CoV-2 pandemic. *Br J Surg*.
30. van der Werf LR, Dikken JL, van der Willik EM, et al. Time interval between neoadjuvant chemoradiotherapy and surgery for oesophageal or junctional cancer: A nationwide study. *Eur J Cancer*. 2018;91:76-85.
31. SAGES and EAES Recommendations Regarding Surgical Response to COVID-19 Crisis - SAGES. https://www.sages.org/recommendations-surgical-response-covid-19/.
32. Fang Y, Zhang H, Xie J, et al. Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR. *Radiology*. February 2020:200432.
33. WHO | SARS-CoV-2 Variant – United Kingdom of Great Britain and Northern Ireland. https://www.who.int/csr/don/21-december-2020-sars-cov2-variant-united-kingdom/en/.
34. Volz, E., Mishra, S., Chand, M., Barrett, J. C., Johnson, R., Geidelberg, L., Ferguson NM. Transmission of SARS-CoV-2 lineage B.1.1.7. in England: Insights from linking epidemiological and genetic data. *medRxiv*. 2021.
35. Download the daily number of new reported cases of COVID-19 by country worldwide. https://www.ecdc.europa.eu/en/publications-data/download-todays-data-geographic-distribution-covid-19-cases-worldwide.

Supplement

Table S1. Number of esophagectomies, surgical approach and postoperative outcomes in each of the participating centers

	Total (N=307)	Amsterdam UMC	University Hospital Cologne	UZ Leuven	Karolinska University Hospital
Inclusions, no./total no. (%)	307	58 (18.9)	112 (36.5)	107 (34.9)	30 (9.8)
Surgical procedure, no./total no. (%)					
Open	75 (24.4)	5 (8.6)	16 (14.3)	53 (49.5)	1 (3.3)
Minimally invasive	229 (74.6)	53 (91.4)	96 (85.7)	53 (49.5)	27 (90.0)
MI converted to open	3 (1.0)	0 (0.0)	0 (0.0)	1 (0.9)	2 (6.7)
Type of resection, no./total no. (%)					
Transthoracic	257 (83.7)	56 (96.6)	111 (99.1)	65 (60.7)	25 (83.3)
Transhiatal	7 (2.3)	1 (1.7)	1 (0.9)	0 (0.0)	5 (16.7)
Thoracophrenicolaparotomy	43 (14.0)	1 (1.7)	0 (0.0)	42 (39.3)	0 (0.0)
Postoperative complications, no./total no. (%)					
Yes	196 (63.8)	37 (63.8)	63 (56.3)	76 (71.0)	20 (66.7)
Respiratory failure requiring mechanical ventilation	33 (10.8)	3 (5.3)	11 (9.8)	16 (15.0)	3 (10.0)
Pneumonia	52 (16.9)	13 (22.4)	12 (10.7)	22 (20.6)	5 (16.7)
ICU admissions	167 (54.4)	24 (41.4)	111 (99.1)	27 (25.2)	5 (16.7)
30-day mortality	8 (2.6)	1 (1.7)	4 (3.6)	3 (2.8)	0 (0.0)

Table S2. Preoperative SARS-CoV-2 screening methods used between 1 March, 2020 and 31 May, 2020 for patients undergoing esophageal cancer surgery in each of the participating centers

Centers:	Screening methods:	Duration:
Amsterdam UMC	1. Chest CT 2. Symptoms screening 3. RT-PCR	1. 15 March – 23 April 2. 30 March – 31 May 3. 16 April – 31 May
Univeristy Hospital Cologne	1. Symptoms screening 2. RT-PCR 3. White-cell / lymphocyte count	1. 1 March – 31 May 2. 1 March – 31 May 3. 1 March – 31 May
UZ Leuven	1. Symptoms screening 2. RT-PCR 3. White-cell / lymphocyte count	1. 18 March – 31 May 2. 18 March – 31 May 3. 18 March – 31 May
Karolinska University Hospital	1. Chest CT 2. Symptoms screening 3. RT-PCR	1. 2 April – 31 May 2. 2 April – 31 May 3. 2 April – 31 May

Chapter 9

Is re-introducing major open and minimally invasive surgery during COVID-19 safe for patients and healthcare workers? An international, multicentre cohort study in the field of esophago-gastric surgery

Mohamed Alasmar, Afsana Kausar, Alexander B.J. Borgstein, Johnny Moons, Sophie Doran, Stefano de Pascale, Rafael Restrepo, Apollonia Verrengia, Mariella Alloggio, Ana Moro Delgado, Sacheen Kumar, Ismael Díez del Val, Simone Giocapuzzi, Gian Luca Baiocchi, Marta de Vega Irañeta, Gabriel Salcedo, Peter Vorwald, Uberto F. Romario, Philippe Nafteux, Suzanne S. Gisbertz, Asif Chaudry, Bilal Alkhaffaf

Annals of Surgical Oncology 2021

Abstract

Background

The COVID-19 pandemic has resulted in unparalleled changes to patient care including the suspension of cancer surgery. Concerns regarding COVID-related risks to patients and healthcare workers with the reintroduction of major complex minimally invasive and open surgery have been raised. This study examines the COVID-19 related risks to patients and healthcare workers following the re-introduction of major esophago-gastric (EG) surgery.

Methods

This was an international, multi-center, observational study of consecutive patients treated by open and minimally invasive esophagectomy and gastrectomy for malignant or benign disease. Patients were recruited from nine European centers serving regions with a high population incidence of COVID-19 between 1st May and 1st of July 2020. The primary endpoint was 30-day COVID-19 related mortality. All staff involved in the operative care of patients were invited to complete a health-related survey to assess the incidence of COVID-19 in this group.

Results

158 patients were included in the study (71 esophagectomy, 82 gastrectomy). 87 patients (57%) underwent MIS (59 esophagectomy, 28 gastrectomy). A total of 403 staff were eligible for inclusion of which 313 (78%) completed the health survey. Approaches to mitigate against the risks of COVID-19 for patients and staff varied amongst centers. No patients developed COVID-19 in the post-operative period. 2 healthcare workers developed self-limiting COVID-19.

Conclusion

Precautions to minimise the risk of COVID-19 infection have enabled the safe reintroduction of minimally invasive and open EG surgery for both patients and staff. Further studies are necessary to determine the minimum requirements for mitigations against COVID-19.

Background

The global COVID-19 pandemic has seen unprecedented changes to the provision of healthcare so that services can focus their efforts on managing the crisis. Due to significant concerns pertaining to the safety of surgery and the associated increased morbidity and mortality, many elective operative programmes were suspended[1]. Following the first 'peak' of the pandemic, many regions began the re-introduction of elective surgery on a priority-basis. Cancer surgery was high on this priority list.

Despite significant improvements in approaches to peri-operative care over the last decade, surgery for esophago-gastric (EG) cancer is still associated with significant morbidity[2–4]. Whilst wide-ranging mitigations for COVID-19 have become commonplace, the re-introduction of EG surgery has rightly highlighted concerns. Despite their need for life-saving treatments, patients remain fearful about their risk of acquiring COVID-19 in hospital[5,6]. In addition to the increased risk posed to patients, there may also be an unquantified risk to medical staff involved in operative cases where the abdominal and thoracic cavities are exposed for long periods[7,8]. As a result, some centers have been reluctant to re-start minimally invasive surgery (MIS) programmes because of the perceived risks of the escape of aerosolised COVID-19 viral particles from the abdominal and thoracic cavities under high pressure.

Proponents of MIS argue that these risks are not evidence-based and can be easily mitigated with the use of adequate personal protective equipment (PPE). Whilst healthcare services have been keen to ensure that adequate PPE is available for staff, it is not known what the minimum necessary requirements for PPE are in the context of COVID-19. Furthermore, in centers where the provision of MIS was commonplace, suspending these approaches may be exposing patients to wound and respiratory complications which would result in longer lengths of stay in hospital. This would be particularly disadvantageous at a time where the risk of contracting COVID-19 in hospital may be significant[9].

This study aimed to assess, in the context of significant regional levels of COVID-19, the safety of reintroducing MIS and open surgery for EG disease, both from the perspective of the patient and healthcare workers. The objectives included:

- To determine current practice with respect to mitigations aimed at reducing the risks of COVID-19 amongst patients undergoing EG surgery and healthcare workers involved in their care.

- In the context of these mitigations, to determine the incidence of COVID-19 and non-COVID-19 morbidity and mortality in both MIS and open surgery for EG cancer surgery.

- In the context of these mitigations, to determine the risk of 'patient-to-staff' transmission of COVID-19 amongst healthcare workers involved in the operative care of EG surgical patients.

Methods

Study design
This was an international, multi-center, observational study of patients who were scheduled for elective minimally invasive or open esophagectomy or gastrectomy. To assess the potential risk to healthcare workers of undertaking these procedures, all staff members who were present in theater at the time of surgery were asked to complete an anonymous COVID-related health questionnaire.

Setting
Participant data was collected from nine specialist European centers for EG surgery. Each center served patients from populations which had been particularly affected by the COVID-19 pandemic from the perspective of infections and deaths (UK, Italy, Spain, Belgium and The Netherlands).

Participants
Consecutive patients who had undergone EG surgery between the 1st of May 2020 and the 1st of July 2020 at each center were included. Patients were followed up for a minimum of 30-days. The following eligibility criteria for patients was applied:

- Aged 18 and over
- Procedure: esophagectomy or gastrectomy (partial or total)
- Pathology: malignant and benign disease
- Operative approach: totally minimally invasive, hybrid minimally invasive or totally open surgery

All healthcare workers involved in the care of the patient within the operating theater were invited to complete an anonymous health survey (supplementary appendix 1). This group was the focus of our survey as they were deemed at particular risk from potential 'patient-to-staff transmission' due to their involvement in aerosol generating procedures (intubation, extubation, minimally invasive surgery surgery and thoracic surgery). Local collaborators completed a register of eligible staff members during each case to ensure all eligible healthcare workers could be contacted to complete the survey. This non-validated questionnaire was developed by the study team with the objective of identifying the incidence of COVID-19 in medical staff involved in the care of included patients. Surveys were sent out after the 15th of July (14 days after the final included patient underwent surgery) to accommodate for a COVID incubation period of up to 2 weeks[10]. Regular weekly reminders were sent out for a period of four weeks to ensure a survey response rate of at least 70% was achieved.

Procedures

Laboratory testing for COVID-19 was based on viral RNA detection by quantitative reverse transcription polymerase chain reaction (RT-PCR). Sampling, including nasopharyngeal swabs and bronchoalveolar lavage, and analyses were undertaken according to local hospital protocols. RT-PCR testing was available in all participating centers. Esophagectomy included both two-stage (intra-thoracic anastomosis) and three stage (cervical anastomosis) approaches. Totally minimally invasive esophagectomy (tMIE) was defined as surgery using laparoscopic and thoracoscopic techniques, with hybrid minimally invasive esophagectomy (hMIE) defined as surgery using a laparoscopic approach with open thoracotomy. Both total and partial gastrectomy requiring alimentary reconstruction were included, however, wedge excision of gastric lesions were excluded from the analysis.

Variables

Data was collected prospectively by each local collaborating team using a standardised Microsoft Excel spreadsheet. Patient demographics (age, sex, performance status, ASA grade, charlson co-morbidity index), disease data (histology, disease stage, neo-adjuvant therapy), COVID-19-related variables (previous RT-PCR testing and results), and operative approach were collected for each case.

Participating centers were also asked to describe local precautions employed to reduce the risk of COVID-19 to both patients and staff (e.g. patient and staff screening or testing, patient flow in hospital, and intra-operative mitigations). In addition, data from the European Center for Disease Prevention and Control (https://www.ecdc.europa.eu/) was collected to describe COVID-19 related hospital and intensive care unit occupancy, and death before and during the study period[11]. This was the preferred method of contextualising our findings due to the significant limitations associated with testing in the first wave of the pandemic.

Outcomes

The primary patient outcome was 30-day COVID-related mortality (confirmed by RT-PCR test) with the day of surgery defined as day 0. Secondary outcomes were COVID-19 infection (confirmed by RT-PCR test), non-COVID related respiratory complications and other complications as defined by established international guidelines (www.esodata.org and www.gastrodata.org) in the field of EG surgery[12,13]. Severity of outcomes was graded according to the Clavien-Dindo (CD) scale and Comprehensive Complications Index (CCI)[14,15]. The primary outcome from the healthcare worker survey was the incidence of COVID-19 infection.

Study Size

A sample size was not applicable to this study. Whilst recruiting centers were defined as 'high-volume' in comparison with others across Europe (at least 50-100 major EG cases per annum), it was necessary to balance this against the likely lower operative volumes as a result of the pandemic. Our aim was to produce relevant and externally valid evidence

within a relatively short period of time and so a pragmatic target of at least 100 eligible cases was set by the study management team.

Data Sources
Only routine, anonymized patient data was collected with no change to clinical pathways.

Data analysis
Descriptive statistics were used to report participant characteristics and outcomes in this study including mean, standard deviation and 95% confidence intervals where appropriate. Patients outcomes were grouped according to surgery type (esophagectomy or gastrectomy) and operative approach (open or minimally invasive surgery). Hybrid minimally invasive esophagectomy (e.g. laparoscopic abdomen and open thoracotomy) was included in the minimally invasive group. Statistical analyses of the present study were performed using the R statistical package (R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/).

Results

Overview
A total of 158 patients and 403 healthcare workers were eligible for inclusion into the study. Figure 1 illustrates the weekly incidence of COVID-19 related impacts in the regional populations served by participating centers since the start of the pandemic. Table 1 describes the precautions taken by centers to reduce the COVID-related health risk amongst patients and healthcare workers. No center mirrored another with respect to mitigations across all domains (hospital precautions, patient screening, staff screening and protection, and intra-operative precautions).

Patient outcomes
A summary of the 158 eligible patient characteristics is presented in table 1. A total of 71 esophagectomies and 82 gastrectomies were completed. Three cases (1.9%) were abandoned and two (1.3%) gastrectomy were converted to a palliative bypass due to metastatic disease. A total of 67 (42.4%) open procedures, 88 (55.7%) minimally invasive (71 totally minimally invasive, 16 laparoscopy and open thoracotomy and 1 laparotomy with thoracoscopy), and 3 (1.9%) minimally invasive converted to open procedures were undertaken. Data completeness with at least 30-day follow up was achieved in all cases. Primary and secondary outcomes for each operative approach of the 153 completed cases are summarized in table 3. Supplementary appendix 1 provides a comprehensive anonymized report of all patient outcomes by center as defined by established international guidelines in the field of EG surgery[12,13].

Pre-operative COVID testing was undertaken in 149 patients (94%), with one center not adopting a routine pre-operative testing policy at the time of the study. Two of the 149 tested (1.3%) were found to be positive for COVID resulting in the postponement of their

surgery. One patient tested negative two weeks later whilst the other required multiple tests over the course of 6 weeks before a negative COVID-19 test was achieved. Both proceeded with surgery with curative intent as planned.

With respect to the primary outcome, thirty-nine (24.7%) patients underwent post-operative RT-PCR testing for suspected COVID infections of which none were positive. One death was reported (0.6%) which was ascribed to respiratory failure following an open total gastrectomy in whom post-operative RT-PCR testing for COVID was negative. Median length of stay in hospital was 10 days (esophagectomy 12 days, gastrectomy 8 days), with 153 (97.5%) being discharged home and the remaining 4 (2.5%) to an intermediate care facility.

Healthcare survey outcomes

Of the 403 healthcare workers eligible for inclusion into this study, 313 (77.7%) completed the COVID-related health survey (characteristics and outcomes summarized in table 4). All centers had access to RT-PCR testing for staff members suspected of COVID. With respect to the primary outcome, two (0.6% of total responses) healthcare workers (1 surgeon, 1 scrub nurse) from the same hospital tested positive for COVID during the study period. Both had participated in fewer than 5 gastrectomies, no esophagectomies and no minimally invasive surgery. Both participants reported that household members had shown symptoms of COVID and/or tested positive.

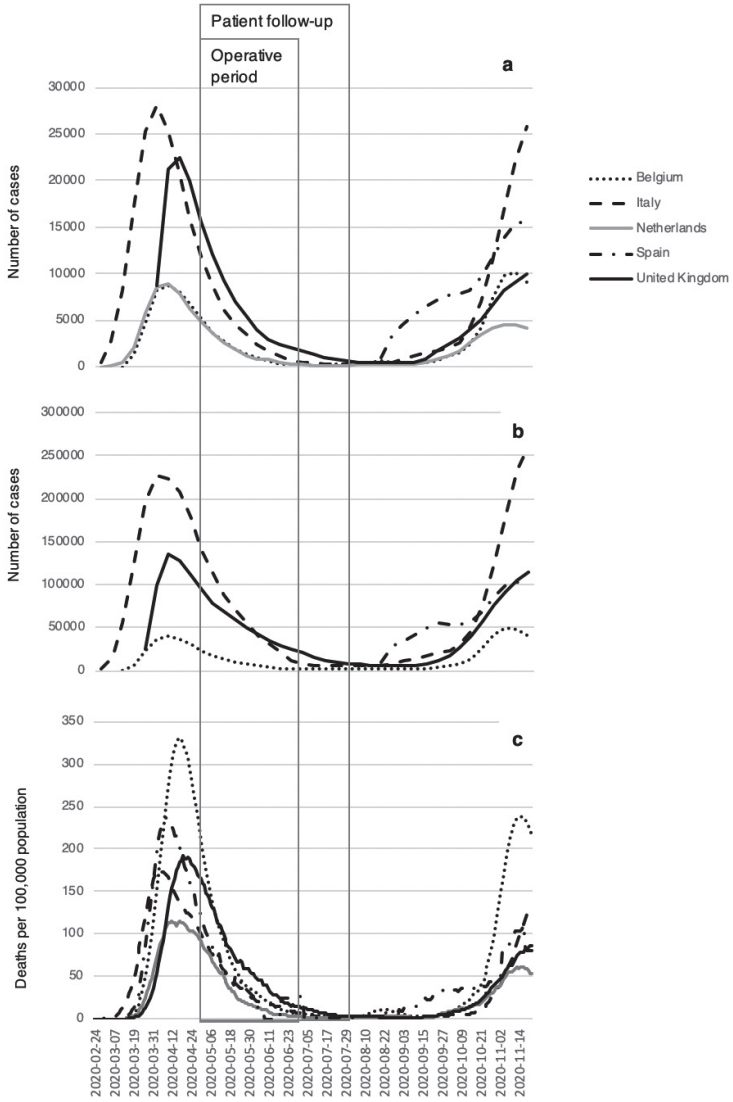


Figure 1. Population impacts of COVID-19 during our study period a) intensive care occupancy b) hospital occupancy and c) deaths

Table 1. Precautions taken to minimize the risk of COVID-19 infections amongst patients and medical staff

Precaution		Amsterdam	Bilbao	Brescia	Leuven	London	Madrid	Manchester	Milan	Verona
Hospital	COVID-free hospital	No	No	No	No	No	No	No	Yes	No
	COVID-free area within hospital managing COVID patients	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes
	Admission to COVID-free ITU/HDU	Yes	Yes	No	Yes	No	No	No	Yes	Yes
	Admission to COVID-free area within ITU/HDU managing COVID patients	Yes		Yes		Yes	Yes	Yes		Yes
	Discharge from ITU to dedicated COVID-free ward	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes
Patient screening	Pre-op isolation	No	No	No	No	14 days Patient and family	No	14 days Patient and family	No	No
	Pre-op PCR-antigen testing	48 hours pre-operatively	Yes	Yes	24 hours pre-operatively	72 hours pre-operatively	27-96 hours pre-operatively	72 hours pre-operatively	24 to 48 hours pre-operatively	No
	Pre-op CT chest to rule out occult COVID infection	Until 15th of May	No	Yes	No	Yes	No	No	No	Yes
	Post-op isolation	No	No	No	No	None	No	14 days patient and family.	Not routinely	No
Staff screening and protection	Staff testing	Only if complaints	No	Yes	No	Yes (if symptomatic)	Yes	No	Yes but late	Yes
	Staff screening	No	Intermittently	No	No	No	Yes	No	Yes but late	Yes

Precaution		Amsterdam	Bilbao	Brescia	Leuven	London	Madrid	Manchester	Milan	Verona
	Theatre staff personal protective equipment	Surgical mask, eye protection, gloves, gown, hair net	FFP2/FFP3 mask, surgical mask, single gown, single glove.	FFP3 mask, visor, single gown, double glove, overshoes, headset	FFP3 mask, Visor, single gown, double glove, apron. Respirator Hoods.	FFP3 mask, Visor, single gown	FFP2 and double mask, Waterproof long-sleeved gown . Closed safety glasses. Exclusive footwear without perforations	FFP3 mask, Visor, single gown, double glove, apron. Respirator Hoods.	FFP3 for anaesthetists, FFP2 for surgeons.	FFP3 mask, Visor, single gown, double glove, apron. Respirator Hoods
Intra-operative precautions	Balloon ports	No	Sometimes	Yes	Yes	Yes	No	Yes	no	Yes
	Dedicated CO2 management system.	Yes	Initially	Yes	Yes	Yes	Yes	Initially	Yes	Yes

Table 2. Characteristics of patient participants

Demographics:	**n=158 (%)**
Age	64.5 (mean) (SD 10.80)
Sex:	
Male	108 (68.35%)
Female	50 (31.65%)
Charlson Co-morbidity Index	4 (mean) (SD 2.12)
WHO Performance status:	
0	84 (53.16%)
1	57 (36.08%)
2	12 (7.59%)
3	2 (1.27%)
Unknown	3 (1.27%)
ASA:	
1	10 (6.33%)
2	92 (58.23%)
3	52 (32.91%)
4	4 (2.53%)
Disease	
Benign	13 (8.23%)
Malignant	145 (91.77%)
Malignant Subtype:	145
Adenocarcinoma	112 (77.2%)
Squamous Cell Carcinoma	16 (11%)
GIST	9 (6.2%)
Others	7 (4.8%)
Unknown	1 (0.7%)
Cancer Stage:	128
1	15 (11.72%)
2	45 (38.28%)
3	51 (39.84%)
4	9 (7.03%)
Unknown	8 (6.25%)
Neoadjuvant Therapy:	
Chemotherapy	64 (40.51%)
Chemoradiotherapy	39 (24.68%)
Surgery alone	55 (34.81%)

SD = standard deviation

Table 3. Outcomes of patients undergoing esophago-gastric resectional surgery between 1st May and 31st of June 2020

	All cases	Oesophagectomy			Gastrectomy		
	n=158	All n=71	Open n=12	Minimally Invasive n=59	All n=82	Open n=54	Minimally Invasive n=28
Complications (any grade) (%)	94 (59.49%)	49 (69.01%)	9 (75.00%)	40 (67.80%)	45 (54.88%)	37 (68.52%)	8 (28.57%)
Worst Clavien-Dindo grade:							
1 (%)	21 (13.29%)	4 (5.63%)	2 (16.67%)	2 (3.39%)	17 (20.73%)	14 (25.93%)	3 (10.71%)
2 (%)	44 (27.85%)	24 (33.80%)	5 (41.67%)	19 (32.20%)	20 (24.39%)	17 (31.48%)	3 (10.71%)
3 (%)	16 (10.13%)	10 (14.08%)	1 (8.33%)	9 (15.25%)	6 (7.32%)	4 (7.41%)	2 (7.14%)
4 (%)	12 (7.59%)	11 (15.49%)	1 (8.33%)	10 (16.95%)	1 (1.22%)	1 (1.85%)	0
5 (%)	1 (0.63%)	0	0	0	1 (1.22%)	1 (1.85%)	0
Mean CCI	15.6	23.0	23.8	22.9	9.3	11.5	5.0
Standard deviation	*19.3*	*20.5*	*20.8*	*20.4*	*16.4*	*17.9*	*12.2*
95% Confidence interval	*12.52 – 18.59*	*13.14 – 32.89*	*6.24 – 43.10*	*7.71 – 38.01*	*5.30 – 13.30*	*-3.76 – 26.79*	*-1.81 – 11.88*
COVID-19 Infection:							
Not tested (%)	116 (73.42%)	56 (78.87%)	11 (91.67%)	45 (76.27%)	60(73.17%)	38 (70.37%)	22 (78.57%)
Tested negative (%)	37 (23.41%)	13 (18.31%)	1 (8.33%)	14 (23.73%)	22 (26.83%)	16 (29.63%)	6 (21.43%)
Tested positive (%)	0	0	0	0	0	0	0
Respiratory Complications:	55 (34.81%)	37 (52.11%)	5 (41.67%)	32 (54.24%)	18 (21.95%)	13 (24.07%)	5 (17.86%)
Pneumonia (%)	24 (15.19%)	12 (16.90%)	2 (16.67%)	10 (16.95%)	12 (14.63%)	7 (12.96%)	5(17.86%)
Pneumothorax (%)	5 (3.16%)	4(5.63%)	0	4(6.78%)	1 (1.22%)	1 (1.85%)	0
Pleural effusion requiring additional drainage procedure (%)	15 (9.49%)	13 (18.31%)	3 (25.00%)	10 (16.95%)	2 (2.44%)	2 (3.70%)	0
Acute aspiration (%)	2 (1.27%)*	2 (2.82%)	0	2 (3.39%)	0	0	0
Chest tube drainage for >10 days post-op (%)	1 (0.63%)	1 (1.41%)	0	1 (1.69%)	0	0	0
Respiratory failure requiring reintubation (%)	8 (5.06%)	5 (7.04%)	0	5 (8.47%)	3 (3.66%)	3 (5.56%)	0

*1 patient who had their procedure abandoned suffered this complication. CCI = Comprehensive Complication Index.

Table 4. Characteristics of healthcare workers who completed COVID-related health survey

	N= 313
Job title	
Anaesthetic support staff	23 (7.4%)
Anaesthetists	68 (21.7%)
Surgeon	96 (30.7%)
Scrub nurse	97 (31.0%)
Other theatre team	17 (5.4%)
Other	12 (3.3%)
Days worked in theatre	
<10	26 (8.3%)
10-20	54 (17.3%)
21-30	55 (17.6%)
31-40	53 (16.9%)
>40	125 (39.9%)
Number of EG surgeries participated in	
<5	181 (57.8%)
5-10	76 (24.3%)
11-15	25 (8.0%)
16-20	15 (4.8%)
>20	16 (5.1%)
Number of non-EG surgeries participated in	
0	9 (2.9%)
<5	42 (13.4%)
5-10	37 (11.8%)
11-15	33 (10.5%)
16-20	42 (13.4%)
>20	150 (47.9%)
COVID-related information	
Required to isolate prior to study	50 (16.0%)
Tested for COVID prior to study:	124 (39.6%)
Negative	106 (33.9%)
Positive	18 (5.75%)
Required to isolate or be tested during study:	40 (12.78%)
Negative	38 (12.1%)
Positive	2 (0.6%)
Suspected or confirmed positive members of household	19 (6.0%)

Discussion

This study investigated the re-introduction of open and minimally invasive gastrectomy and esophagectomy during the first wave of the COVID-19 pandemic. Our results suggest that, despite significant levels of COVID-19 in local populations, mitigations against the risk of COVID-19 infection were sufficient to safely reintroduce major EG surgery across Europe. Furthermore, concerns surrounding the use of MIS have not been substantiated in our multi-center cohort, suggesting that laparoscopic and thoracoscopic surgery can continue without risk to patients or healthcare workers in the operating theater. Patients were generally older, suffered from co-morbidities and would potentially be exposed to devastating consequences had they contracted COVID-19[1]. Furthermore, the centers included in this study served populations particularly affected by COVID-19. Hence, whilst our case-study focused on patients undergoing major EG surgery, the results are likely applicable to many patient groups, and provide data that can be used to reassure both patients and healthcare workers.

Approaches to minimise the risk of developing COVID-19 in both patients and staff undoubtedly contributed to our findings. However, these approaches were not uniform or standardised and reflects a lack of evidence-base, and differing local, national and international responses from governments and professional societies. Understanding what constitutes 'minimum required precautions' is a topic which requires further exploration. As a minimum, all patients in our study were managed in COVID-19 'free' areas within hospitals and most were tested pre-operatively without needing pre- or post-operative isolation. The greatest levels of variation seemed to relate to the level of PPE worn by staff in theater. Whilst necessary, precautions must be carefully balanced against unintended consequences such as the devastating impact on surgical waiting lists which may now take years to rectify[16,17]. For example, policies that require both patients and their households to self-isolate before major elective surgery are simply impractical for most, potentially psychologically harmful, and may in fact hinder the efficient utilisation of scarce operating theater capacity. In our study, most centers did not require patients to isolate pre-operatively. Whilst it is possible that a proportion of patients may have initiated a form of isolation or 'social-distancing', our data suggests that this does not need to be prescriptive. Furthermore, others have suggested that the use of some PPE may be associated with significant challenges during intra-operative communication between staff members[18]. As local, regional and national PPE recommendations evolve, careful evaluation will be required to ensure that patients and staff remain safe. Whilst it should be recognised that the local population incidence of COVID-19 will play a factor, we recommend that further evidence-based guidance from national and international professional societies be developed so that guidance can be updated.

In the current climate, minimizing the direct risks of COVID-19 to patients undergoing major complex surgery is paramount. However, as EG surgery is associated with significant risk of complications, a 'safe' surgical pathway for this patient group must also ensure that

appropriate resources are available to manage morbidity in the post-operative period. Our study suggests that collaborators were able to deliver safe care to patients and achieve low levels of morbidity and mortality. However, many healthcare services have 'redeployed' vitally important members of surgical, anaesthetic and nursing teams, and diverted intensive care resources to help manage the pandemic. This leaves elective surgical services vulnerable and has led to large numbers of elective cancellations[17]. Many of the centers included in our study had suspended their surgical programmes during the initial peak incidence of the pandemic for this reason. Some collaborators adopted different approaches and rationalized regional services so that high risk surgery was undertaken on 'cold operative sites' where patients with COVID-19 where not admitted. The lead collaborating center in our study aimed to limit hospital occupancy to around 60 per cent during the first wave, so that resources could be appropriately shared between COVID-19, emergency and cancer surgery patients. Such figures are not necessarily applicable to other centers, which must take into account the number of complex/major surgical services within the hospital, the local population levels of COVID-19 and available resources.

One of the unintended consequences of the pandemic has been the devastating impact on patients with disease unrelated to COVID-19. Several guidelines which detail how surgical care should be prioritized during this time have been developed for clinical practice[19,20]. Whilst delaying cancer surgery would understandably risk the repercussions of disease progression, many other patients with conditions that impact severely on quality of life have also been affected. Most collaborating centers only undertook cancer surgery when elective programmes first recommenced. However, as confidence grew that patients could be treated safely, a small number of surgical cases for benign disease were successfully undertaken. The argument for undertaking (complex) benign elective cases during the pandemic is one which should be considered alongside local resource availability and therefore broad recommendations cannot be made. Whilst it is understandable that this subset of patients will be prioritized differently to cancer cases, the results of delays in this cohort should not be ignored.

The background incidence of COVID-19 in the local population is a key consideration when reflecting on this study's findings. We opted to describe the impact of COVID-19 in terms of hospitalizations, intensive care unit bed occupancy and deaths, as testing capabilities were significantly limited during the first wave of the pandemic. This enables more reliable comparisons between the first pandemic wave to be made with subsequent waves, allowing healthcare professionals and managers to use previous experience, aid decision-making and service organization. Collaboration was purposefully sought from centers serving populations significantly impacted by the pandemic. Healthcare services, medical staff and patients can therefore be reassured that our findings are likely to be widely applicable. Furthermore, whilst we included patients from regions which had seemingly past their 'peak' incidence, the COVID-19 prevalence remained significant during our operative period. Nonetheless, all the regions included in this study have since been through additional surges of COVID-19 cases, and it is unquestionable that at the time of writing, we are in a second, and in some

cases third, wave of the pandemic. It is possible that as some regions surpass the regional COVID-19 prevalence which occurred during our study, and despite robust mitigations, COVID-19 infections may begin to appear in patients undergoing major complex surgery with devastating impacts. Recent estimates from the World Health Organization suggest that populations will remain at risk for at least the next two years[21]. It is therefore essential to establish robust systems which will provide the safe treatment of complex life-shortening or life-changing disease for the foreseeable future and ensure that outcomes continue to be monitored and transparently reported.

It has been suggested that MIS may expose medical staff to increased risk of contracting COVID-19 infection due to the possibility of virus aerosolization in surgical smoke[7,8]. In addition, it is generally accepted that operative times are longer for MIS compared to open surgery, particularly in the field of EG disease, potentially extending the viral exposure. Initially, these concerns resulted in guidance based on low-level evidence advising healthcare services to avoid MIS where possible[22]. Many groups have now updated their recommendations with less cautionary language. Nonetheless, the initial guidance meant that some patients could not be offered surgical approaches which, particularly in the case of EG surgery, can lead to fewer complications and a shorter length in hospital stay[23–25]. Two healthcare workers developed self-limiting COVID-19 infections during the study period. Both had participated in fewer than five open gastrectomy surgeries with no involvement in either MIS or esophagectomy. Both reported that household members had exhibited symptoms and/or tested positive for COVID suggesting that their cases were not nosocomial. Our findings therefore support the continued use of MIS on the proviso that risk-reducing precautions are maintained. Again, what these precautions should entail is a matter which requires further study. For example, whilst recruiting centers did not uniformly use balloon ports to reduce the risk of smoke escape, all used some form of dedicated smoke evacuation filter.

The strengths of this study include its prospective, multi-center design. We considered the safety not only of patients but also of medical staff of whom 77% completed their health survey. To our knowledge, this is the first study in this field examining the reintroduction of major complex EG surgery across several centers during the COVID-19 pandemic. Furthermore, our study considered the background incidence of COVID in the local populations of each participating center and its relation to the first pandemic ‘peak’.

There are some limitations which require further discussion. We adopted a pragmatic approach to measuring the incidence of COVID-19 amongst healthcare workers. We opted to invite those who were involved in the operative care of patients to complete the survey. This was because the study aimed partly to provide data about the safety of minimally invasive surgery to staff. It could be argued that other healthcare workers such as nurses may similarly be at increased risk from patient to staff transmission. The anonymous nature of our health survey aimed to encourage all types of medical staff, some of whom had never previously participated in research, to engage in an open and transparent manner.

However, such an approach relies purely on self-reporting which is associated with inherent limitations. For example, the survey would not establish a reliable understanding of how many healthcare workers had contracted COVID and remained asymptomatic, as not all the recruiting centers adopted regular testing for their employees. The rate of asymptomatic COVID-positive healthcare workers will vary from location to location, and is also likely to change as the pandemic progresses[26]. And whilst the risk of nosocomial infection between healthcare workers is likely to be low[27], there remains a possibility of in-hospital transmission which mandates the continued need for PPE. Furthermore, medical staff involved in the peri-operative care of patients often worked across numerous specialties. Had the COVID-19 infection rates amongst staff been significant, it would have been difficult to discern whether this was due to a particular type of surgery or indeed whether the infection was acquired outside of the hospital environment. However, given the extremely low incidence of COVID amongst staff, we do not believe that this influenced the findings of our study. Finally, it is accepted that establishing accurate population incidence of COVID is difficult [25]. Moreover, the accuracy of laboratory testing used to ascertain whether patients contracted COVID is associated with its own challenges[28]. As such, we acknowledge that these factors may have impacted on the findings presented in this study.

Conclusions

Major minimally invasive and open EG surgery has been safely reintroduced in centers serving populations significantly affected by COVID-19. Differing approaches to mitigations against COVID-19 resulted in no infections amongst patients. Only two healthcare workers tested positive for (self-limiting) COVID during the study period. Further study is urgently needed to understand the minimum precautionary measures required to ensure patients and staff remain safe.

References

1. Nepogodiev D, Bhangu A, Glasbey JC, et al. Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study. *Lancet*. 2020;396(10243):27-38. doi:10.1016/S0140-6736(20)31182-X
2. Michalowski J, Salvador A, Napper R. *Commissioned by Healthcare Quality Improvement Partnership National Oesophago-Gastric Cancer Audit 2018 An Audit of the Care Received by People with Oesophago-Gastric Cancer in England and Wales 2018 Annual Report*.; 2018.
3. Low DE, Kuppusamy MK, Alderson D, et al. Benchmarking Complications Associated with Esophagectomy. *Ann Surg*. 2019;269(2):291-298. doi:10.1097/SLA.0000000000002611
4. Messager M, De Steur WO, Van Sandick JW, et al. Variations among 5 European countries for curative treatment of resectable oesophageal and gastric cancer: A survey from the EURECCA Upper GI Group (EUropean REgistration of Cancer CAre). *Eur J Surg Oncol*. 2016;42(1):116-122. doi:10.1016/j.ejso.2015.09.017
5. Fear of Covid-19 Leads Other Patients to Decline Critical Treatment - The New York Times. https://www.nytimes.com/2020/05/25/health/coronavirus-cancer-heart-treatment.html. Accessed December 5, 2020.
6. Where Are All the Patients? Addressing Covid-19 Fear to Encourage Sick Patients to Seek Emergency Care | Catalyst non-issue content. https://catalyst.nejm.org/doi/full/10.1056/CAT.20.0193. Accessed December 5, 2020.
7. Pavan N, Crestani A, Abrate A, et al. Risk of Virus Contamination Through Surgical Smoke During Minimally Invasive Surgery: A Systematic Review of the Literature on a Neglected Issue Revived in the COVID-19 Pandemic Era. *Eur Urol Focus*. 2020;6(5):1058-1069. doi:10.1016/j.euf.2020.05.021
8. Mowbray NG, Ansell J, Horwood J, et al. Safe management of surgical smoke in the age of COVID-19. *Br J Surg*. May 2020. doi:10.1002/bjs.11679
9. Carter B, Collins JT, Barlow-Pay F, et al. Nosocomial COVID-19 infection: examining the risk of mortality. The COPE-Nosocomial study (COVID in Older PEople). *J Hosp Infect*. 2020;0(0). doi:10.1016/j.jhin.2020.07.013
10. Lauer SA, Grantz KH, Bi Q, et al. The incubation period of coronavirus disease 2019 (CoVID-19) from publicly reported confirmed cases: Estimation and application. *Ann Intern Med*. 2020;172(9):577-582. doi:10.7326/M20-0504
11. Download data on the weekly subnational 14-day notification rate of new COVID-19 cases. https://www.ecdc.europa.eu/en/publications-data/weekly-subnational-14-day-notification-rate-covid-19. Accessed September 13, 2020.
12. Baiocchi GL, Giacopuzzi S, Marrelli D, et al. International consensus on a complications list after gastrectomy for cancer. *Gastric Cancer*. 2019;22(1):172-189. doi:10.1007/s10120-018-0839-5
13. Low DE, Alderson D, Cecconello I, et al. International consensus on standardization of data collection for complications associated with esophagectomy: Esophagectomy Complications Consensus Group (ECCG). *Ann Surg*. 2015;262(2):286-294. doi:10.1097/SLA.0000000000001098
14. Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien PA. The comprehensive complication index: A novel continuous scale to measure surgical morbidity. *Ann Surg*. 2013;258(1):1-7. doi:10.1097/SLA.0b013e318296c732

15. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240(2):205-213. doi:10.1097/01.sla.0000133083.54934.ae
16. Covid 'wrecking ball' through NHS waiting times — Royal College of Surgeons. https://www.rcseng.ac.uk/news-and-events/media-centre/press-releases/covid-wrecking-ball-through-nhs-waiting-times/. Accessed August 22, 2020.
17. Collaborative Covids. Elective surgery cancellations due to the COVID-19 pandemic: global predictive modelling to inform surgical recovery plans. *Br J Surg*. 2020. doi:10.1002/bjs.11746
18. Mathews JA, Blencowe NS, Adcock S, et al. 'Theatre Comm' - optimising communication in surgical theatres during COVID-19. *Br J Surg*. July 2020. doi:10.1002/bjs.11834
19. Surgeons AC of. COVID-19 Guidelines for Triage of Thoracic Patients. https://www.facs.org/covid-19/clinical-guidance/elective-case/thoracic-cancer. Accessed January 16, 2021.
20. Federation of Surgical Speciality Associations. COVID-19 documents - FSSA. https://fssa.org.uk/covid-19_documents.aspx. Accessed January 16, 2021.
21. Coronavirus pandemic could be over within two years - WHO head - BBC News. https://www.bbc.co.uk/news/world-53870798. Accessed August 22, 2020.
22. Hajibandeh S, Hajibandeh S, Maw A. Recommendations on key practical measures in laparoscopic surgery during the COVID-19 pandemic. *Br J Surg*. 2020;107(9):e316-e317. doi:10.1002/bjs.11772
23. Mariette C, Markar SR, Dabakuyo-Yonli TS, et al. Hybrid Minimally Invasive Esophagectomy for Esophageal Cancer. *N Engl J Med*. 2019;380(2):152-162. doi:10.1056/NEJMoa1805101
24. Feike Kingma B, de Maat MFG, van der Horst S, van der Sluis PC, Ruurda JP, van Hillegersberg R. Robot-assisted minimally invasive esophagectomy (RAMIE) improves perioperative outcomes: A review. *J Thorac Dis*. 2019;11(Suppl 5):S735-S742. doi:10.21037/jtd.2018.11.104
25. Lee HJ, Hyung WJ, Yang HK, et al. Short-term outcomes of a multicenter randomized controlled trial comparing laparoscopic distal gastrectomy with D2 lymphadenectomy to open distal gastrectomy for locally advanced gastric cancer (KLASS-02-RCT). *Ann Surg*. 2019;270(6):983-991. doi:10.1097/SLA.0000000000003217
26. Treibel TA, Manisty C, Burton M, et al. COVID-19: PCR screening of asymptomatic health-care workers at London hospital. *Lancet*. 2020;395(10237):1608-1610. doi:10.1016/S0140-6736(20)31100-4
27. Sikkema RS, Pas SD, Nieuwenhuijse DF, et al. COVID-19 in health-care workers in three hospitals in the south of The Netherlands: a cross-sectional study. *Lancet Infect Dis*. 2020;0(0). doi:10.1016/S1473-3099(20)30527-2
28. Watson J. Interpreting a covid-19 test result. doi:10.1136/bmj.m1808

Chapter 10

Patients with acute appendicitis during the COVID-19 pandemic (SCOUT-4): a multicenter, retrospective study

Alexander B.J. Borgstein*, Jochem C.G. Scheijmans*, Carl A.J. Puylaert, Wouter J. Bom, Said Bachiri, Eduard A. van Bodegraven, Amarins T.A. Brandsma, Floor M. ter Brugge, Steve M.M. de Castro, Roy Couvreur, Lotte C. Franken, Marcia P. Gaspersz, Michelle R. de Graaff, Hannah Groenen, Suzanne C. Kleipool, Toon J.L. Kuypers, Milou H. Martens, David M. Mens, Ricardo G. Orsini, Nando J.M.M. Reneerkens, Thomas Schok, Wouter J.A. Sedee, Shahzad Tavakoli Rad, José H. Volders, Pepijn D. Weeder, Jan M. Prins, Hester A. Gietema, Jaap Stoker, Suzanne S. Gisbertz, Marc G.H. Besselink, Marja A. Boermeester, the SCOUT Collaboarative Study group

*Shared first authorship

BMC Emergency Medicine 2021

Abstract

Background

During the COVID-19 pandemic, a decrease in the number of patients presenting with acute appendicitis was observed. It is unclear whether this caused a shift towards more complicated cases of acute appendicitis. We compared a cohort of patients diagnosed with acute appendicitis during the 2020 COVID-19 pandemic with a 2019 control cohort.

Methods

We retrospectively included consecutive adult patients in 21 hospitals presenting with acute appendicitis in a COVID-19 pandemic cohort (March 15 – April 30, 2020) and a control cohort (March 15 – April 30, 2019). Primary outcome was the proportion of complicated appendicitis. Secondary outcomes included prehospital delay, appendicitis severity, and postoperative complication rates.

Results

The COVID-19 pandemic cohort comprised 607 patients vs. 642 patients in the control cohort. During the COVID-19 pandemic, a higher proportion of complicated appendicitis was seen (46.9% vs. 38.5%; p=0.003). More patients had symptoms exceeding 24 hours (61.1% vs. 56.2%, respectively, p=0.048). After correction for prehospital delay, presentation during the first wave of the COVID-19 pandemic was still associated with a higher rate of complicated appendicitis. Patients presenting >24 hours after onset of symptoms during the COVID-19 pandemic were older (median 45 vs. 37 years; p=0.001) and had more postoperative complications (15.3% vs. 6.7%; p=0.002).

Conclusion

Although the incidence of acute appendicitis was slightly lower during the first wave of the 2020 COVID-19 pandemic, more patients presented with a delay and with complicated appendicitis than in a corresponding period in 2019. Spontaneous resolution of mild appendicitis may have contributed to the increased proportion of patients with complicated appendicitis. Late presenting patients were older and experienced more postoperative complications compared to the control cohort.

Background

The first wave of the 2020 COVID-19 pandemic resulted in a reduction of acute care surgeries[1]. Lockdown measures, patients' fear of contracting COVID-19 during hospital visits, and reluctance to burden the overloaded healthcare system by requesting care for non-COVID complaints, may have led to a higher threshold for seeking medical care.

For appendicitis, an increased prehospital delay during the pandemic has been reported[2,3]. Also, a shift towards a higher proportion of complicated appendicitis cases has been described, both in adults and children[2-6], as well as a decrease in the total number of patients compared to the weeks prior to COVID[7,8]. Although all previous studies show the same shift towards relatively more complicated appendicitis patients, the cohorts were small and control groups were insufficient. Patients with uncomplicated appendicitis may have stayed at home and recovered spontaneously[7,8], which would support the theory that uncomplicated and complicated appendicitis are different diseases and not simply different grades of severity[9-11].

A recent meta-analysis in the pre-COVID era showed that delayed appendectomy up to 24 hours in patients with presumed uncomplicated appendicitis does not increase the risk for developing complicated appendicitis[12]. Moreover, conservative treatment with antibiotics has been proven to be as safe and effective as surgical treatment in patients with uncomplicated appendicitis[13,14]. Some uncomplicated appendicitis may indeed resolve spontaneously[9,10,15,16].

The present study aims to compare the proportions of uncomplicated and complicated appendicitis in adult patients presenting during the first wave of the COVID-19 pandemic with a control cohort from the corresponding time period in 2019.

Methods

This retrospective multicenter study was conducted at two academic and nineteen non-academic hospitals in The Netherlands. Ethical approval was waived by a central institutional review board because of the observational nature of the study. This decision was endorsed by the institutional review board of each participating center. Permission of patient participation was obtained through an opt-out procedure, as was customary for COVID-19 related observational research.

Study population

Consecutive adult patients (≥ 18 years) presenting with a diagnosis of acute appendicitis were included in two cohorts. The pandemic cohort included patients presenting between March 15 and April 30, 2020, immediately after the start of the COVID-preventing semi-lockdown measures in The Netherlands. The pre-pandemic control cohort included patients presenting in the corresponding period in 2019, between March 15 and April 30.

Patients were identified by searching the electronic patient file databases via ICD-10 codes (appendicitis, acute abdominal pain, peritonitis or intra-abdominal abscesses) and searching emergency department (ED) patient lists and surgery lists from that period. Patients were included if the final diagnosis was acute appendicitis. No formal sample size calculation was performed, but a fixed inclusion period was set. Post hoc power analysis was executed based on the proportion of patients with complicated appendicitis.

Data collection

Patient demographics, comorbidities, clinical and imaging data from the ED, information about treatment modality, operation notes, pathology results, and 30-day clinical follow-up were collected from electronic patient records. Times of arrival at the ED and start of treatment were also retrieved, as well as imaging diagnosis. If patients were operated within 30 days after initially being treated conservatively with antibiotics, 30-day postoperative follow-up was collected. Participants were pseudonymized to ensure patient's privacy.

Definitions

Appendicitis severity was determined according to the operation notes and pathology reports, or imaging reports in cases of conservative treatment. In those cases where more than one imaging modality was used, reports of the imaging modality that confirmed the diagnosis of appendicitis were used.

Uncomplicated appendicitis was defined as an inflamed appendix or periappendicitis without signs of necrosis or perforation as described by surgeon and pathologist. Complicated appendicitis was defined as inflammation of the appendix with presence of gangrene, evident necrosis or perforation, as described by the pathologist, and/or presence of perforation or abscess formation, as described by the surgeon. Conservatively treated patients with a periappendicular abscess or widespread infiltration on imaging, were also scored as complicated. If the pathologist found a normal appendix, the latter overruled the diagnosis of the surgeon. In the few cases where no histological analysis was performed, e.g. because of full necrosis of the appendix, the diagnosis as established during surgery was used.

Conservative treatment was defined as initial treatment with antibiotics and/or percutaneous drainage of a periappendicular abscess. In operated patients, the in-hospital delay or time to surgery was defined as the time between presentation at the ED and the start of the operation. Postoperative complications were scored according to the Clavien-Dindo scale[17]. Complications scored as III or higher were defined as severe complications.

Study outcomes

The primary outcome of this study was the difference in appendicitis severity distribution (i.e., the proportion of patients presenting with complicated appendicitis) between the COVID-19 pandemic cohort (2020) and the control cohort (2019). Secondary outcomes were the differences in baseline characteristics, pre- and in-hospital delay, number of perforated

appendicitis, type of treatment, postoperative complications, complications in general, and the daily rate of patients presenting with acute appendicitis between both cohorts.

Statistical analysis

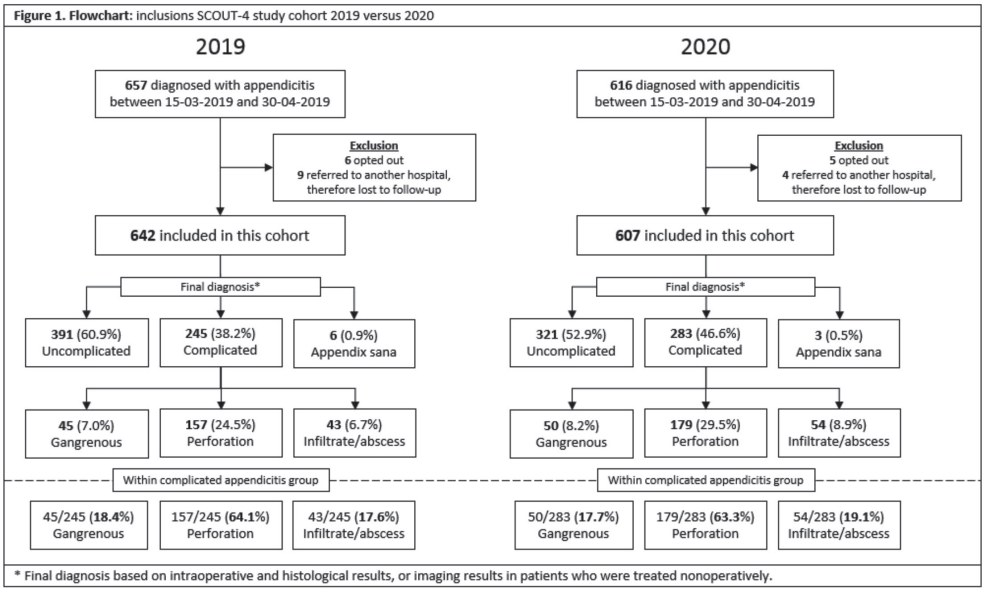
The cohorts were compared and stratified for appendicitis severity and duration of symptoms. This duration was dichotomized by visual analysis of a chart of the duration of symptoms at presentation, see supplements. Confidence intervals for proportions were calculated by the Wilson score method without continuity correction. Univariate analyses were performed using the Chi-squared or Fisher's exact test for categorical variables, and the Mann-Whitney U test for continuous variables. To quantify the possible association between presentation during the COVID-19 pandemic and having complicated appendicitis, a multivariable logistic regression analysis was performed, adjusted for duration of symptoms longer than 24 hours. A post hoc power analysis was conducted. All P values were based on two-sided tests and $P < 0.05$ was considered statistically significant. Missing data were not imputed, but described as missing. Data were analyzed using SPSS for Windows version 26 (IBM, Armonk, New York, USA).

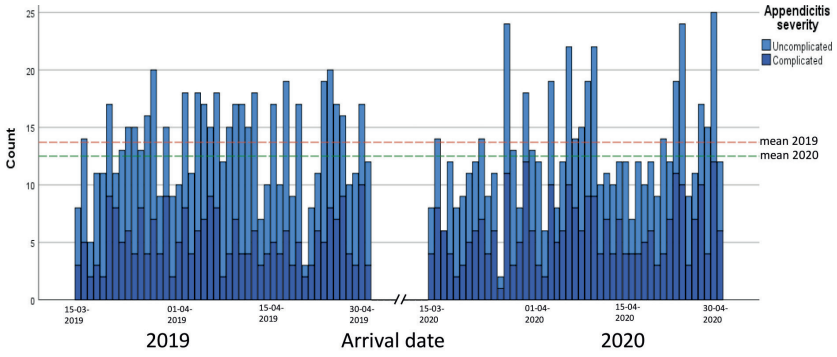
Results

Between March 15 and April 30, 607 out of 616 eligible patients with acute appendicitis were included in the pandemic cohort (2020) and 642 of 657 eligible patients in the control cohort (2019), see Figure 1. Only 1.5% and 2.3% of eligible patients were excluded from the pandemic and control cohort, respectively. During the COVID-19 pandemic, an absolute decrease of 5.5% (95% C.I. 4.0-7.5%) in the numbers of patients diagnosed with appendicitis was seen as compared to 2019; this was a 6.2% (95% C.I. 4.6-8.3%) decrease in all eligible patients (Figure 1). The mean daily presentation rate was constant over time in both cohorts (Figure 2). Demographic and clinical characteristics of patients in both cohorts are presented in Table 1. Comorbidities such as diabetes and coronary artery disease were somewhat more common in the pandemic cohort. However, no significant differences in comorbidities among cohorts were seen. All patients underwent diagnostic imaging before treatment. In 2020, more patients were diagnosed by CT (and not ultrasound (US)) compared to 2019 (51.9% vs. 34.9%, p<0.001) because of COVID-related restricted use of US.

Appendicitis severity

As shown in Table 1 and Figure 3, in the 2020 pandemic cohort a higher proportion of patients presented with complicated appendicitis compared to the 2019 control cohort (46.6% vs. 38.2%, respectively, p=0.008). The perforation rate in the 2020 cohort was 29.5% versus 24.5% in the control cohort (p=0.045). Focusing only on complicated appendicitis patients, no differences in perforation rate (63.3% vs. 64.1%, p=0.84) or rate of periappendiculair infiltrate/abscess formation (19.1% vs. 17.6%, p=0.65) were found between the 2020 and 2019 cohorts (Table 2).





Figrure 2. Daily presentations of patients with acute appendicitis

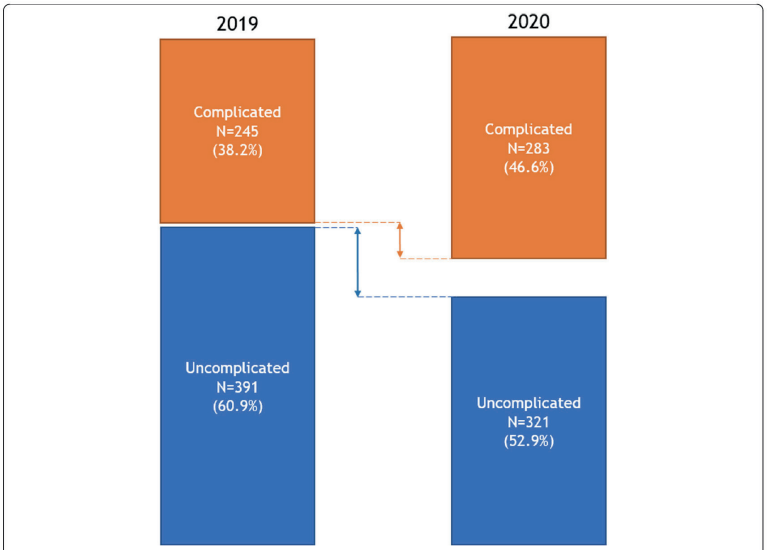


Fig. 3 Total number of patients, stratified by type of acute appendicitis: 2019 control cohort vs. 2020 COVID cohort

Duration of symptoms

In the 2020 pandemic cohort, relatively more patients presented at the hospital with symptoms present for >24 hours compared to the control cohort (61.1% vs. 56.2%, p=0.048; Table 1). In the group of patients with complicated appendicitis, more late presentations were seen in the pandemic group than in the 2019 control group (76.2% vs. 68.0%, p=0.039; Table 2). This difference was not seen in patients with uncomplicated appendicitis (51.5% vs. 51.4%, p=0.98; Table S1).

Table 1. Baseline: Clinical characteristics of all patients, 2019 pre-COVID cohort compared to 2020 COVID cohort

Characteristic	2019 control cohort (n=642)	2020 COVID-19 cohort (n=607)	*P* value
Age, median (IQR), years	40 (28-57)	42 (29-58)	0.183
Female sex, no./total no. (%)	322/642 (50.2)	318/607 (52.4)	0.430
ASA >1, no./total no. (%)	263/595 (44.2)	254/524 (48.5)	0.153
COPD, no./total no. (%)	13/630 (2.1)	11/599 (1.8)	0.774
Diabetes Mellitus, no./total no. (%)	24/631 (3.8)	34/596 (5.7)	0.117
Heart failure, no./total no. (%)	11/631 (1.7)	11/597 (1.8)	0.896
Coronary artery disease, no./total no. (%)	17/631 (2.7)	28/598 (4.7)	0.064
Active smoker, no./total no. (%)	61/293 (20.8)	63/275 (22.9)	0.547
Duration of symptoms >24 hours , no./total no. (%)	358/637 (56.2)	371/601 (61.1)	0.048
Severity of appendicitis, no./total no. (%)			0.008
Uncomplicated	391/642 (60.9)	321/607 (52.9)	

Characteristic	2019 control cohort (n=642)	2020 COVID-19 cohort (n=607)	*P* value
Gangrenous	45/642 (7.0)	50/607 (8.2)	
Perforation	157/642 (24.5)	179/607 (29.5)	
Infiltrate/Abscess	43/642 (6.7)	54/607 (8.9)	
Normal (sana)	6/642 (0.9)	3/607 (0.5)	
Conservative treatment, no./total no. (%)	41/642 (6.4)	63/607 (10.4)	0.011
Complication within 30 days, no./total no. (%)	72/642 (11.5)	76/607 (12.5)	0.475

Abbreviations: ASA, American Society of Anesthesiologists; COPD, Chronic Obstructive Pulmonary Disease; IQR, interquartile range.

Table 2. Comparison of patients with complicated appendicitis for 2019 pre-COVID cohort vs. 2020 COVID cohort

Characteristic	2019 control cohort (n=245)	2020 COVID-19 cohort (n=283)	*P* value
Age, median (IQR), years	49 (33-65)	50 (32-64)	0.946
ASA >1, no./total no. (%)	126/225 (56.0)	131/239 (54.8)	0.797
Duration of symptoms >24 hours, no./total no. (%)	164/241 (68.0)	214/281 (76.2)	**0.039**
Types of complicated appendicitis, no./total no. (%)			
Gangrenous	45/245 (18.4)	50/283 (17.7)	0.835
Perforation	157/245 (64.1)	179/283 (63.3)	0.843
Abscess or infiltrate	43/245 (17.6)	54/283 (19.1)	0.651
Conservative treatment, no./total no. (%)	31/245 (12.7)	41/283 (14.5)	0.540
In-hospital delay in operated patients, median (IQR), hours	7.8 (5.0-13.3)	6.7 (4.6-12.1)	0.152
Postoperative complication*, no./total no. (%)	40/214 (18.7)	45/242 (18.6)	0.979
Severe postoperative complication*°, no./total no. (%)	11/245 (5.1)	13/281 (5.4)	0.904

Abbreviations: ASA, American Society of Anesthesiologists; IQR, interquartile range.
* Patients for whom surgery was the initial treatment.
○ Severe complications are defined as Clavien-Dindo IIIa or higher.

In Table 3, patients are stratified according to duration of symptoms at presentation; ≤24 hours or >24 hours. During the COVID-19 pandemic, patients presenting after >24 hours were older than patients presenting within 24 hours after onset of symptoms (median 45 years (31-60) vs. 37 years (28-52); p=0.001). In the control group, no age difference was seen in time of presentation. Additionally, a larger proportion of patients with an increased risk for a more severe course of COVID-19 (age ≥ 60 years) presented after >24 hours during the COVID-19 pandemic compared to the control 2019 cohort (72.2% vs 60.3%, p=0.039; table S3). Patients with complicated appendicitis and symptoms for >24 hours had a comparable perforation rate in both cohorts (64.0% vs. 66.5%, p=0.62; see supplementary Table S2).

In a univariate logistic regression analysis, the odds ratios (ORs) for complicated appendicitis were 1.41 (95% CI: 1.12-1.76) for patients presenting during the COVID-19 pandemic and 2.79 (95% CI: 2.12-3.55) for patients with symptoms for more than 24 hours. In multivariate logistic regression including both variables, these associations persisted, with ORs of 1.38 (95% CI: 1.10-1.75) for presentation during the COVID-19 pandemic and 2.75 (95% CI: 2.16-3.51) for duration of symptoms >24 hours, respectively.

Table 3. Characteristics and outcomes of patients with appendicitis, stratified for duration of symptoms, ≤24 hours vs. >24 hours, in 2019 pre-COVID cohort and 2020 COVID cohort

Characteristic	2019 control cohort (n=637)□		*P* value	2020 COVID-19 cohort (n=601)□		P value
	≤ 24 hours (n=279)	> 24 hours (n=358)		≤ 24 hours (n=230)	> 24 hours (n=371)	
Age, median (IQR), years	40 (28-55)	41 (27-58)	0.707	37 (28-52)	45 (31-60)	0.001
Age ≥ 60 years, no./total no. (%)	54/279 (19.4)	82/358 (22.9)	0.278	37/230 (16.1)	96/371 (25.9)	0.005
Female sex, no./total no. (%)	151/279 (54.1)	169/358 (47.2)	0.083	124/230 (53.9)	189/371 (50.9)	0.479
ASA >1, no./total no. (%)	115/263 (43.7)	145/327 (44.3)	0.881	106/211 (50.2)	145/309 (46.9)	0.458
Comorbidity, no./total no. (%)	22/273 (8.1)	24/348 (6.9)	0.583	20/223 (9.0)	44/363 (12.1)	0.235
Severity of appendicitis, no./total no. (%)			<0.001¥			<0.001¥
Uncomplicated	201/279 (72.0)	189/358 (52.8)		163/230 (70.9)	154/371 (41.5)	
Gangrenous	26/279 (9.3)	19/358 (5.3)		17/230 (7.4)	32/371 (8.6)	
Perforation	44/279 (15.8)	109/358 (30.4)		41/230 (17.8)	137/371 (36.9)	
Infiltration/abscess	7/279 (2.5)	36/358 (10.1)		9/230 (3.9)	45/371 (12.1)	
Normal (sana)	1/279 (0.4)	5/358 (1.4)		0/230 (0)	3/371 (0.8)	
Conservative treatment, no./total no. (%)	8/279 (2.9)	33/358 (9.2)	0.001	5/230 (2.2)	57/371 (15.4)	<0.001¥
In-hospital delay in operated patients, median (IQR), hours	7.6 (5.0-14.7)	7.0 (4.8-11.8)	0.076	7.2 (4.4-13.2)	6.2 (4.3-10.0)	0.057
Complication within 30 days, no./total no. (%)	28/279 (10.0)	42/358 (11.7)	0.292	16/230 (7.0)	60/371 (16.2)	0.001
Postoperative complication*, no./total no. (%)	26/271 (9.6)	41/325 (12.6)	0.245	15/225 (6.7)	48/313 (15.3)	0.002
Severe postoperative complication*°, no./total no. (%)	4/271 (1.5)	10/325 (3.1)	0.279¥	5/225 (2.2)	15/313 (4.8)	0.165¥

Abbreviations: ASA, American Society of Anesthesiologists; IQR, interquartile range.
¥ Fischer exact test was performed
□ In 2019 5 patients and in 2020 6 patients missed data about the duration of symptoms.
* Patients for whom surgery was the initial treatment.
○ Severe complications are defined as Clavien-Dindo IIIa or higher.

Initial treatment

During the COVID-19 pandemic, 544 (89.6%) patients underwent surgery compared to 601 (93.6%) patients in the 2019 control cohort (p=0.011). Of these patients, 532 (97.8%) and 587 (97.7%) were operated laparoscopically. In respectively five (0.9%) and ten (1.7%) cases, the procedure was converted to open appendectomy. The median in-hospital time to surgery during the COVID-19 pandemic was 6.5 (4.3-11.8) hours, which was shorter than the 7.4 (4.9-13.6) hours in the 2019 control cohort (p=0.004). In the 2020 cohort, 63 (10.4%) patients were initially treated conservatively versus 41 (6.4%) in the 2019 control cohort (p=0.011), see Tables 1 and Table S4. The majority of these patients were diagnosed with complicated appendicitis (65.1% in 2020 and 75.6% in 2019). Within the 2020 pandemic cohort, a higher proportion of conservatively treated patients were diagnosed with complicated appendicitis by use of initial CT compared to the 2019 control cohort, see Table S5.

Complications

No differences were found in number of postoperative complications between the COVID-19 cohort and the 2019 control cohort. However, in patients presenting during the COVID-19 pandemic, more complications were seen in patients presenting with symptoms for more than 24 hours compared to patients who present earlier (16.2% vs. 7.0%; p=0.001). This difference was not found within the 2019 control cohort (Table 3). Within the 2020 cohort, 12 patients tested positive for COVID-19. Eleven were confirmed by RT-PCR and one was diagnosed based on chest CT (Table S6).

Power analysis

Post hoc power analysis was performed. The cohort sizes of 642 and 607 patients, proportions of patients with complicated appendicitis of 46.6% and 38.2% and an α of 0.05 resulted in a power of 85.2%, which was considered as being sufficient.

Discussions

This large multicenter study compared adult patients presenting with acute appendicitis during the COVID-19 pandemic with patients presenting in the corresponding period of the pre-COVID year 2019. Although only a slight decrease of patients presenting with acute appendicitis was observed during the first COVID-19 wave compared to 2019, a higher proportion presented with complicated appendicitis. The perforation rate among patients with complicated appendicitis, however, was unaffected. During the COVID-19 pandemic, more patients presented with a prehospital delay of more than 24 hours. These patients were older and endured more postoperative complications compared to patients presenting with symptoms for less than 24 hours. This association was not found in the 2019 control cohort.

Present data suggest an association between prehospital delay and complicated appendicitis. This is in line with previous, small studies describing higher proportions of complicated appendicitis during the COVID-19 pandemic. Dreifuss et al found complicated appendicitis in

seven (46.7%) out of 15 adult Argentinian patients with acute appendicitis during April 2020 compared to 11 (16.9%) out of 65 patients during April 2018 and 2019[3]. Patients in the 2020 cohort show a longer delay in presentation than the control group (58.4 vs. 32.8 hours)[3]. These differences are confirmed by Gao et al, who analyzed a Chinese cohort of 163 patients who presented with appendicitis between June 2019 and April 2020[2]. They find complicated appendicitis in 51.7% of patients and a mean prehospital delay of 65.0 hours in the epidemic cohort (presentation after January 1st), compared to 12.4% complicated appendicitis and a mean delay of 17.3 hours in the pre-epidemic cohort (both $p<0.001$)[2]. Gao et al show a significant increase in requests for conservative treatment during the COVID-19 outbreak[2]. Both increased prehospital delay and reduced willingness to be operated may be explained by fear of contracting SARS-CoV-2 in hospitals[2]. Our data showed a longer prehospital delay during the pandemic and a significant higher age in patients who presented more than 24 hours after onset of symptoms. Fear of a SARS-CoV-2 infection could have caused this delay particularly in older patients, as those patients have an intrinsic higher risk for a more severe course of COVID-19[18]. This may have resulted in some form of inclusion bias, because mild cases may have resolved spontaneously by refraining from consultation with a doctor.

Multivariable regression analysis showed an association between complicated appendicitis and presentation during the first wave of the COVID-19 pandemic, independent of late presentation. This implies that another factor could have influenced the appendicitis severity during the pandemic. An Israeli study showed a significant decrease in patients admitted with uncomplicated appendicitis during the first weeks since the onset of COVID-19, compared to an antecedent period; 204 uncomplicated appendicitis cases pre-pandemic to 111 during the pandemic. The number of complicated cases and the prehospital delay in both cohorts were comparable[7]. Neufeld et al also describe a significant decrease of the number of presented uncomplicated appendicitis cases during the COVID-19 pandemic compared to the two years before[8]. The number of complicated cases in their multicenter cohort, consisting of 956 adult acute appendicitis patients, remained stable[8]. The authors of both studies hypothesized that the successful resolution of mild appendicitis at home could explain the decrease in total number of patients[7,8]. In our 2020 COVID-19 cohort, a similar absolute decrease of the total number of uncomplicated appendicitis cases was found. Since the decrease of uncomplicated cases was greater than the increase of complicated cases, part of the patients with mild, uncomplicated appendicitis may have resolved spontaneously at home. This would be in line with epidemiological and clinical studies underlining two different entities of appendicitis[9-11] and the conclusion of Tankel and Neufeld et al[7,8]. However, the absolute decrease found in our study was relatively small compared to other studies such that 'normal' annual variability of acute appendicitis as a cause for the decrease cannot be ruled out. The difference between present study and the Israelian study could be explained by the lower mean age in the latter study (43 vs 23 years) [7]. Moreover, it may be concluded that the COVID-19 pandemic and the semi-lockdown measures in The Netherlands discouraged patients to visit an emergency department to a lesser extent than it did the Israelian patients during complete lockdown.

Significantly more patients were treated conservatively during the COVID-19 pandemic compared to the 2019 control cohort. However, the increase from 6.4% to 10.4% was much lower than the increase reported by the HAREM study group: adult patients presenting with acute appendicitis during the COVID-19 lock-down in the UK showed a more radical shift with 271 of 500 (54%) patients treated conservatively[19]. In this first report of the HAREM cohort no differentiation between uncomplicated and complicated appendicitis is provided and definitive conclusions have to wait until the final results become available[19]. Within our cohorts, most conservatively managed patients were cases of complicated appendicitis, receiving antibiotics with or without percutaneous drainage for a periappendiceal abscess, which is common practice[20]. More patients underwent initial CT during the pandemic, which may have resulted in better diagnosis of complicated cases and thereby more conservative treatment. In addition, we observed a limited increase of conservative treatment in uncomplicated cases (2.6% to 6.9%), which could also have been the result of the renewed Dutch national guideline (July 2019), stating that conservative treatment could be considered for uncomplicated appendicitis[21]. In The Netherlands, the national guideline was not changed to discourage the surgical treatment of acute appendicitis during the COVID-19 pandemic, which was done in some other countries, e.g. the UK. Therefore, the effect of the COVID-19 pandemic on the management of acute appendicitis in The Netherlands was minimal. Furthermore, the effect was predominantly explained by the shift towards more cases of complicated appendicitis.

Compared to previous large observational audits of acute appendicitis patients[22-24], a higher proportion of patients with complicated appendicitis was seen in both our pandemic and control cohorts. This difference may be caused by the definition we used for complicated appendicitis, which was based on the combined surgical and histological diagnoses, instead of only the surgical[22] or histological[23] diagnosis. Moreover, a low rate of normal appendices and the inclusion of conservatively treated patients, who were mostly diagnosed with complicated appendicitis in our cohorts, may have contributed to the discrepancy.

We found a significantly shorter in-hospital delay within the pandemic group. The median in-hospital time to surgery during the COVID-19 pandemic was 6.5 (4.3-11.8) hours, which was significantly shorter than the 7.4 (4.9-13.6) hours in the 2019 control cohort (p=0.004). One could argue that the reason for this shorter in-hospital delay is due to the fact that patients had a more severe disease presentation as more patients in the pandemic cohort had complicated appendicitis and surgeons were therefore keener to operate quickly. However, we think that this difference was mainly influenced by logistic reasons. During the first wave of the COVID-19 pandemic, most of elective surgery was cancelled, resulting in more opportunities for immediate operations such as emergency appendectomies. Furthermore, it is unlikely that this shorter in-hospital delay compared to controls affected the number of complicated appendicitis cases. Complicated and uncomplicated appendicitis are most likely two different disease entities and, as illustrated by a recent meta-analysis of van Dijk et al., in-hospital delay up to 24 hours does not lead to a higher rate of complicated appendicitis.[12]

The findings of this study should be interpreted in light of some limitations. First, data were collected retrospectively and data were only available for patients who actually presented at the hospital. Therefore, the proportion of patients with complicated appendicitis within the total number of patients with acute appendicitis is most likely biased by the number of patients with a mild appendicitis not presenting in a hospital and who experienced spontaneous resolution of symptoms at home. Second, the semi-lockdown in The Netherlands was less strict compared to measures taken by other countries. This may have resulted in less impact of the COVID-19 pandemic on the presentation of patients with acute appendicitis compared to other countries such as Israel or Spain.

Strengths of this study are the large number of included patients and the multicenter cohort design. A control cohort from the corresponding time period in 2019 was included and no missing data were reported for primary outcomes. Another strength of this study is that a high proportion of patients in this cohort was treated surgically, resulting in confirmed diagnoses based on combined surgical and histological reports in the vast majority of patients. Finally, the inclusion period started at the moment of the national semi-lockdown in The Netherlands instead of starting after the first COVID-19 patient was diagnosed, resulting in the largest expected effect of the COVID-19 pandemic on disease outcomes. The first wave of COID-19 provided a unique circumstance for research. Further research during other COVID-19 waves and in other health care settings is encouraged.

Conclusion

A slight decrease of patients presenting with acute appendicitis was found during the first wave of COVID-19 compared to a corresponding period in 2019. A decrease of uncomplicated cases was observed, while the proportion of complicated cases increased. This increase cannot only be explained by the increased prehospital delay during the COVID-19 pandemic, nor can it merely be explained by progression of uncomplicated to complicated appendicitis over time. More likely, part of the patients with mild, uncomplicated appendicitis may have resolved spontaneously at home, which is in line with the theory that uncomplicated and complicated appendicitis are different diseases and not simply different grades of severity.

References

1. Cano-Valderrama O, Morales X, Ferrigni CJ, et al. Acute Care Surgery during the COVID-19 pandemic in Spain: Changes in volume, causes and complications. A multicentre retrospective cohort study. *Int J Surg.* 2020;80:157-161.
2. Gao Z, Li M, Zhou H, et al. Complicated appendicitis are common during the epidemic period of 2019 novel coronavirus (2019-nCoV). *Asian J Surg.* 2020.
3. Dreifuss NH, Schlottmann F, Sadava EE, Rotholtz NA. Acute appendicitis does not quarantine: surgical outcomes of laparoscopic appendectomy in COVID-19 times. *The British journal of surgery.* 2020.
4. Velayos M, Munoz-Serrano AJ, Estefania-Fernandez K, et al. Influence of the coronavirus 2 (SARS-Cov-2) pandemic on acute appendicitis. *An Pediatr (Engl Ed).* 2020;93(2):118-122.
5. Lee-Archer P, Blackall S, Campbell H, Boyd D, Patel B, McBride C. Increased incidence of complicated appendicitis during the COVID-19 pandemic. *J Paediatr Child Health.* 2020;56(8):1313-1314.
6. Raffaele A, Cervone A, Ruffoli M, et al. Critical factors conditioning the management of appendicitis in children during COVID-19 Pandemic: experience from the outbreak area of Lombardy, Italy. *The British journal of surgery.* 2020.
7. Tankel J, Keinan A, Blich O, et al. The Decreasing Incidence of Acute Appendicitis During COVID-19: A Retrospective Multi-centre Study. *World journal of surgery.* 2020;44(8):2458-2463.
8. Neufeld MY, Bauerle W, Eriksson E, et al. Where did the patients go? Changes in acute appendicitis presentation and severity of illness during the coronavirus disease 2019 pandemic: A retrospective cohort study. *Surgery.* 2020.
9. Cobben LP, de Van Otterloo AM, Puylaert JB. Spontaneously resolving appendicitis: frequency and natural history in 60 patients. *Radiology.* 2000;215(2):349-352.
10. Andersson RE. The natural history and traditional management of appendicitis revisited: spontaneous resolution and predominance of prehospital perforations imply that a correct diagnosis is more important than an early diagnosis. *World journal of surgery.* 2007;31.
11. Livingston EH, Fomby TB, Woodward WA, Haley RW. Epidemiological similarities between appendicitis and diverticulitis suggesting a common underlying pathogenesis. *Archives of surgery (Chicago, Ill : 1960).* 2011;146(3):308-314.
12. van Dijk ST, van Dijk AH, Dijkgraaf MG, Boermeester MA. Meta-analysis of in-hospital delay before surgery as a risk factor for complications in patients with acute appendicitis. *The British journal of surgery.* 2018;105(8):933-945.
13. Sallinen V, Akl EA, You JJ, et al. Meta-analysis of antibiotics versus appendicectomy for non-perforated acute appendicitis. *The British journal of surgery.* 2016;103(6):656-667.
14. Rollins KE, Varadhan KK, Neal KR, Lobo DN. Antibiotics Versus Appendicectomy for the Treatment of Uncomplicated Acute Appendicitis: An Updated Meta-Analysis of Randomised Controlled Trials. *World journal of surgery.* 2016;40(10):2305-2318.
15. Park HC, Kim MJ, Lee BH. Randomized clinical trial of antibiotic therapy for uncomplicated appendicitis. *The British journal of surgery.* 2017;104(13):1785-1790.
16. Sippola S, Gronroos J, Sallinen V, et al. A randomised placebo-controlled double-blind multicentre trial comparing antibiotic therapy with placebo in the treatment of uncomplicated acute appendicitis: APPAC III trial study protocol. *BMJ Open.* 2018;8(11):e023623.

17. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Annals of surgery.* 2004;240(2):205-213.
18. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature.* 2020;584(7821):430-436.
19. Javanmard-Emamghissi H, Boyd-Carson H, Hollyman M, et al. The management of adult appendicitis during the COVID-19 pandemic: an interim analysis of a UK cohort study. *Tech Coloproctol.* 2020.
20. Di Saverio S, Podda M, De Simone B, et al. Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines. *World journal of emergency surgery : WJES.* 2020;15(1):27.
21. Dutch Society for Surgery NvvH. Richtlijn Acute Appendicitis (Dutch Guideline Acute Appendicitis). https://richtlijnendatabase.nl/richtlijn/acute_appendicitis/startpagina_-_acute_appendicitis.html. Published 2019. Accessed 08-02-2021.
22. van Rossem CC, Bolmers MD, Schreinemacher MH, van Geloven AA, Bemelman WA, Snapshot Appendicitis Collaborative Study G. Prospective nationwide outcome audit of surgery for suspected acute appendicitis. *The British journal of surgery.* 2016;103(1):144-151.
23. Collaborative: NSR, Bhangu A, Richardson C, et al. Multicentre observational study of performance variation in provision and outcome of emergency appendicectomy. *The British journal of surgery.* 2013;100(9):1240-1252.
24. Yeh DD, Eid AI, Young KA, et al. Multicenter Study of the Treatment of Appendicitis in America: Acute, Perforated, and Gangrenous (MUSTANG), an EAST Multicenter Study. *Annals of surgery.* 2019.

Supplement

Figure S1. Duration of symptoms at presentation, cohort 2019 versus 2020

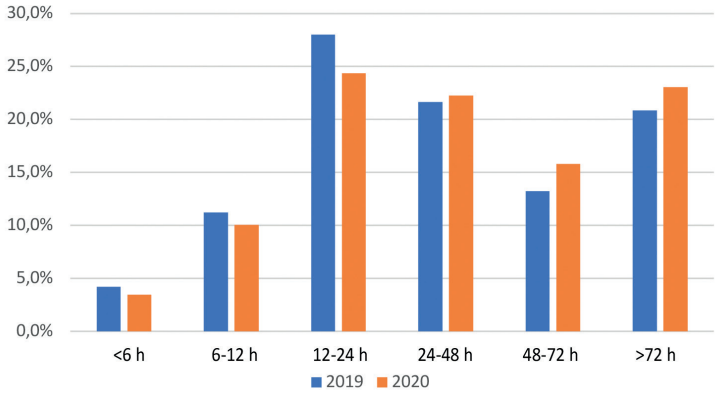


Figure S1. Duration of symptoms at presentation, cohort 2019 versus 2020

Table S1. Comparison of patients with uncomplicated appendicitis for 2019 pre-COVID cohort vs. 2020 COVID cohort

Characteristic	2019 control cohort (n=391)	2020 COVID-19 cohort (n=321)	*P* value
Age, median (IQR), years	36 (26-52)	37 (28-51)	0.227
ASA >1, no./total no. (%)	136/364 (37.4)	121/282 (42.9)	0.153
Duration of symptoms >24 hours, no./total no. (%)	201/390 (51.5)	163/317 (51.4)	0.975
Conservative treatment, no./total no. (%)	10/391 (2.6)	22/321 (6.9)	**0.006**
In-hospital delay in operated patients, median (IQR), hours	7.0 (4.8-14.1)	6.3 (4.1-10.7)	**0.003**
Postoperative complication*, no./total no. (%)	28/381 (7.3)	18/298 (6.0)	0.501
Severe postoperative complication*°, no./total no. (%)	4/381 (1.0)	7/298 (2.3)	0.227¥

Abbreviations: ASA, American Society of Anesthesiologists; IQR, interquartile range.
¥ Fischer exact test was performed
* Patients for whom surgery was the initial treatment.
○ Severe complications are defined as Clavien-Dindo IIIa or higher.

Table S2. Comparison of patients with complicated appendicitis and with symptoms for more than 24 hours, 2019 pre-COVID cohort versus 2020 COVID cohort

Characteristics	Cohort 2019 (n=164)	Cohort 2020 (n=214)	*P* value
Age, median (IQR), years	49 (32-65)	52 (33-65)	0.689
Female sex, no./total no. (%)	64/164 (39.0)	101/214 (47.2)	0.112
ASA >1, no./total no. (%)	81/147 (55.1)	91/177 (51.4)	0.508
Severity of appendicitis, no./total no. (%)			
Gangrenous	19/164 (11.6)	32/214 (15.0)	0.342
Perforation	109/164 (66.5)	137/214 (64.0)	0.621
Abscess or infiltrate	36/164 (22.0)	45/214 (21.0)	0.828
Complications within 30 days, no./total no. (%)	25/164 (15.2)	46/214 (21.5)	0.123

Abbreviations: ASA, American Society of Anesthesiologists; IQR, interquartile range

Table S3. Comparison of patients with an age of 60 years or higher of the 2019 pre-COVID cohort and 2020 COVID cohort

Characteristics	Cohort 2019 (n=138)	Cohort 2020 (n=136)	*P* value
Female sex, no./total no. (%)	64/138 (46.4)	72/136 (52.9)	0.277
ASA >1, no./total no. (%)	111/130 (85.4)	95/105 (90.5)	0.238
Duration of symptoms >24 hours, no./total no. (%)	82/136 (60.3)	96/133 (72.2)	0.039
Severity of appendicitis, no./total no. (%)			0.132¥
Uncomplicated	57/138 (41.3)	42/136 (31.6)	
Gangrenous	11/138 (8.0)	5/136 (3.7)	
Perforation	56/138 (40.6)	68/136 (50.0)	
Abscess or infiltrate	13/138 (9.4)	19/136 (14.0)	
Complications within 30 days, no./total no. (%)	27/138 (19.6)	26/136 (191.1)	0.925
Patients older than 60 years, presented with durations of symptoms >24 hours			
	N=82	N=96	
Complications within 30 days, no./total no. (%)	18/82 (22.0)	20/96 (20.8)	0.856

Abbreviation: ASA, American Society of Anesthesiologists
¥ Fischer exact test was performed

Table S4. Comparison of conservatively treated patients with appendicitis, 2019 pre-COVID cohort versus 2020 COVID cohort

Characteristic	Cohort 2019 (n=41)	Cohort 2020 (n=63)	*P* value
Severity of appendicitis based on imaging, no./total no. (%)			0.339¥
Uncomplicated	10/41 (24.4)	22/63 (34.9)	
Gangrenous	0/41 (0)	0/63 (0)	
Perforation	2/41 (4.9)	6/63 (9.5)	
Abscess or infiltrate	29/41 (70.7)	35/63 (55.6)	
Radiological drainage (initial treatment), no./total no. (%)	6/41 (14.6)	11/63 (17.5)	0.873¥
Complication during the first 30 days, no./total no. (%)	3/41 (7.3)	11/62 (17.7)	0.154¥
Appendectomy within 30 days, no./total no. (%)	4/41 (9.8)	11/63 (17.5)	0.394¥
Severity of appendicitis based on appendectomy within 30 days, no./total no. (%)			0.506¥
Uncomplicated	3/4 (75)	3/11 (27.3)	
Gangrenous	0/4 (0)	1/11 (9.1)	
Perforation	0/4 (0)	4/11 (36.4)	
Abscess or infiltrate	1/4 (25)	2/11 (18.2)	
Postoperative complication*, no./total no. (%)	0/4 (0)	3/10 (30.0)	0.505¥
Severe postoperative complication*°, no./total no. (%)	0/4 (0)	1/10 (10.0)	1.000¥

¥ Fischer exact test was performed
* Patients for whom surgery was the initial treatment.
○ Severe complications are defined as Clavien-Dindo IIIa or higher.

Table S5. Comparison of conservatively treated patients by final (imaging) diagnosis and imaging modality, 2019 pre-COVID cohort versus 2020 COVID cohort

Characteristic	2019 control cohort			2020 COVID-19 cohort		
	Uncomplicated appendicitis	Complicated appendicitis		Uncomplicated appendicitis	Complicated appendicitis	
		Perforated	Infiltrate/ abscess		Perforated	Infiltrate/ abscess
US only	4	1	11	6	0	4
CT only	4	1	4	9	5	19
US + CT/MRI*	2	0	14	7	0	11*
	10	31 (76%)		22	39 (64%)	
Total	41			61		

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging; US, ultrasound.
* Only one patient was diagnosed by MRI after US.

Table S6. COVID-19 positive appendicitis patients

COVID-19 positive	**Cohort 2020 (n=12)**
Severity of appendicitis based on imaging, no./total no. (%)	
Uncomplicated	3/12 (25)
Gangrenous	0/12 (0)
Perforation	8/12 (66.7)
Abscess or infiltrate	1/12 (8.3)
Conservative treatment, no./total no. (%)	3/12 (25)
COVID-19 diagnosis based on	
RT-PCR	11/12 (91.7)
CT	1/12 (8.3)

Chapter 11

Summary

Part I: Staging and surgical treatment of gastric cancer

According to the international gastric cancer guidelines, a staging laparoscopy should be performed in all operable patients with ≥cT3 and/or N+ gastric cancer, without signs of non-curable disease on initial imaging. However, the exact value of staging laparoscopy in gastric cancer is unknown, as most previous studies were performed in Asian countries with small sample sizes (less than 100 patients).

In **chapter 2**, the value of staging laparoscopy in gastric cancer staging was investigated by evaluating the avoidable surgery rate during intentional gastrectomy in a population-based cohort study. The avoidable surgery rate was higher in patients who underwent a staging laparoscopy before gastrectomy compared to patients without a staging laparoscopy. This could be due to the selection of patients with more advanced disease for staging laparoscopy. Additionally, the results suggest a low sensitivity to detect metastases or locoregional non-resectability. To analyze the detection rate and diagnostic accuracy of staging laparoscopy for non-curable disease we performed a single center cohort study in **chapter 3**. Staging laparoscopy was shown to be valuable in the staging process of gastric cancer, with a high accuracy in detecting non-curable disease, thereby preventing futile treatment.

Curative treatment of gastric cancer consists of perioperative chemotherapy and gastrectomy. The addition of perioperative chemotherapy has been shown to increase overall survival in several randomized trials. However, most patients included in these studies were younger than 75 years old. It was unknown whether elderly patients (aged above 75), or patients with comorbidities have a similar survival benefit of perioperative chemotherapy combined with gastrectomy. In **chapter 4**, the rate of elderly patients proceeding to surgery following neoadjuvant chemotherapy (as part of perioperative chemotherapy) was compared to younger patients. Additionally, overall survival was compared between elderly patients with and without perioperative chemotherapy. A similar overall survival rate was found in elderly patients treated with neoadjuvant chemotherapy, compared to elderly patients directly undergoing gastrectomy. However, the rate of elderly patients who did not proceed to surgery after chemotherapy increased with older age (up to 25% in patients aged over 80 years old).

In addition to a gastrectomy, a modified D2 lymphadenectomy and a complete omentectomy are performed as standard part of a radical gastrectomy in curative treatment of gastric cancer, although there is little evidence to support a survival benefit of performing an omentectomy. In the Dutch multicenter OMEGA study, the incidence of omental metastases was only five percent out of a total of 100 patients1. Additionally, the presence of omental metastases was associated with non-curable disease at different sites. It was concluded that omentectomy might not have contributed to a survival benefit in these patients. In **chapter 5** the long-term overall survival results of the OMEGA study were investigated. It was found that the presence of omental metastases was associated with impaired overall survival.

Performing an omentectomy did not seem to contribute to a survival benefit in patients with omental metastases.

Part II: Surgery during the COVID-19 pandemic

The COVID-19 pandemic hugely affected the possibility to perform elective surgical care, as patients who underwent surgery with a SARS-CoV-2 infection had an increased risk for postoperative complications and mortality, and because medical resources were shifted to treat COVID-19 patients. Preoperative screening strategies, including chest CT and RT-PCR, were introduced in order to continue elective surgical care safely. **Chapter 6** evaluated the yield of preoperative screening for COVID-19 using chest CT and RT-PCR in asymptomatic patients scheduled for elective or emergency surgery. Around 1% of all asymptomatic patients tested positive for COVID-19 with the use of RT-PCR and were not operated. This yield increased to around 6% in conjunction with community prevalence of COVID-19. No patients developed symptomatic COVID-19 postoperatively. The added value of chest CT was limited and is therefore not recommended.

Around 20% of patients with a SARS-CoV-2 infection present with gastrointestinal symptoms, besides pulmonary complaints. During the beginning of the COVID-19 pandemic, possible COVID-19 diagnoses may have been neglected in these patients as physicians focused on finding abdominal pathology. Many centers implemented the standard use of combined chest and abdominal CT to detect possible COVID-19 in patients presenting with gastrointestinal symptoms. In **chapter 7** the yield of high COVID-19 suspicion based on chest CT findings was investigated. The yield of adding chest CT to abdominal CT to detect COVID-19 in patients presenting with acute gastrointestinal symptoms was extremely low, with an additional detection rate of around 1%.

Elective cancer surgery, including esophageal cancer surgery, could be continued in most European countries during the first wave of the COVID-19 pandemic with the implementation of preoperative screening strategies with RT-PCR. However, the safety of this strategy had to be established. **Chapter 8** describes a multicenter study with four European tertiary oesophageal cancer referral centers, that continued elective esophageal cancer surgery during the first COVID-19 wave. This study concluded that esophageal cancer surgery could be performed safely with the use of adequate preoperative SARS-CoV-2 screening methods. The percentage of postoperative pulmonary complications was similar in the COVID-19 cohort compared to the pre-COVID-19 cohort. In **chapter 9** the safety of re-introducing esophago-gastric surgery for patients and healthcare workers during the COVID-19 pandemic was investigated in an international, multicenter study. The use of adequate precautions made it possible to safely reintroduce minimally invasive and open esophago-gastric surgery after the first COVID-19 wave.

During the first wave of the COVID-19 pandemic, patients feared the possibility of acquiring an in-hospital SARS-CoV-2 infection, which resulted in pre-hospital delay. The course of

many diseases, including acute appendicitis, may have been affected by this scenario. In **chapter 10** two cohorts of patients diagnosed with acute appendicitis were compared in a multicenter cohort study. The proportion of complicated appendicitis was compared between patients diagnosed with appendicitis during the COVID-19 pandemic and a cohort diagnosed with appendicitis in the same time period a year before. The incidence of acute appendicitis was slightly lower during the first wave of the 2020 COVID-19 pandemic compared to the corresponding period in 2019, as more patients presented with a delay and with complicated appendicitis. Late presenting patients were older and experienced more postoperative complications compared to the control cohort**.**

Chapter 12

Discussion and future perspective

Discussion and future perspectives

This thesis includes a variety of studies addressing staging, perioperative treatment, and surgical treatment of gastric cancer. Additionally, this thesis includes several studies investigating the influence of the COVID-19 pandemic on surgical care, especially esophagogastric cancer surgery and surgery for acute appendicitis. This chapter discusses the main findings of this thesis, along with the future perspectives of gastric cancer treatment, and of surgery during the COVID-19 pandemic.

Part I: Staging and surgical treatment of gastric cancer

Staging laparoscopy has been recommended by the Dutch gastric cancer guidelines in all operable patients with potentially resectable cT3-4 gastric cancer before initiation of treatment since 2014[2]. However, in the first edition of the gastric cancer guideline released in 2009, it was recommended to perform a staging laparoscopy only in cT3-4 patients with a poorly differentiated tumor[3], as the costs and risks of staging laparoscopy were deemed too high to be used as a standard primary staging tool.

As the exact value of staging laparoscopy remained unclear, this was investigated in **chapters 2 and 3**[4–6]. Since 2011, the number of performed staging laparoscopies has increased. However, in our study, the percentage of avoidable surgery remained high between 2011 and 2016, compared to previous studies[7,8]. One possible explanation could be the relatively higher percentage of cT3-4 stage tumors included in our study, compared to the previous studies. Additionally, more than 50% of the patients who underwent a staging laparoscopy, and in whom non-curable disease was detected during intended gastrectomy, did not receive neoadjuvant chemotherapy. Previous studies found a higher percentage of patients undergoing a curative resection following neoadjuvant chemotherapy[9,10].

In a single center study (**chapter 3**), staging laparoscopy was shown to be of additional value in the staging process of gastric cancer, with a high accuracy for detecting non-curable disease. The diagnostic accuracy, specificity, and sensitivity were comparable to the results of a systematic review[11]. Furthermore, the avoidable surgery rate after staging laparoscopy was lower compared to our population-based study. This could be related to a lower percentage of patients with a cT4 tumor and more patients receiving neoadjuvant chemotherapy. cT4 gastric tumors have serosal invasions, which is a known factor to be associated with peritoneal dissemination[12]. Recently, the results of the Dutch prospective PLASTIC study confirmed our findings. This study concluded, in line with our results, that staging laparoscopy should be recommended by the gastric cancer guidelines for patients with cT3 or higher and/or N+ disease, as it adds value in the process of staging by detecting peritoneal metastases[13].

According to the Dutch and international gastric cancer guidelines, curative treatment of gastric cancer consists of perioperative chemotherapy followed by a gastrectomy[2,14]. Overall survival has increased in recent years with the addition of perioperative chemotherapy[9,10].

In elderly patients (>75 years old) the combination of chemotherapy with gastrectomy results in a similar overall survival compared to elderly patients directly scheduled for a gastrectomy. However, we found that the percentage of patients not proceeding to surgery after chemotherapy increases with age up to 15% for patients over 75 years and 25% in patients aged 80 years and older (**chapter 4**). The previous MAGIC[9] and FLOT[10] trials both included predominantly younger patients, with a median age of 62 in both trials. Elderly patients have more comorbidities, which is associated with more adverse events during perioperative chemotherapy and gastrectomy[15,16]. The percentage of patients not proceeding to surgery was associated with an older age and a higher WHO performance. Additionally, the percentage of elderly patients who had a reduction in the number of chemotherapy cycles was higher compared to the findings of both the MAGIC and FLOT trials. Receiving neoadjuvant chemotherapy might deny elderly patients from undergoing a potential curative resection, especially in patients aged 80 years and older. One other study has evaluated overall survival in elderly patients undergoing (radio-) chemotherapy and surgery for gastric and esophageal cancer. This study found no survival benefit in patients aged 70 years or older who receive neoadjuvant therapy, compared to only receiving surgery. However, this was a retrospective, single center study in which a heterogeneous group of patients with esophageal and gastric cancer, with both adenocarcinoma and squamous cell carcinoma, was included. Therefore, patients with older age and comorbidities should undergo neoadjuvant treatment with caution.

Omentectomy might be omitted as part of radical gastrectomy in the future (**chapter 5**). The presence of omental metastases is associated with non-curable disease and performing an omentectomy does not seem to improve overall survival in these patients. Several non-randomized studies have resulted in similar findings[18–21]. Currently, a Japanese phase III trial is investigating omentum preservation versus omentectomy for patients with resectable gastric cancer in terms of relapse-free survival[22]. However, perioperative chemotherapy and minimally invasive gastrectomy are exclusion criteria in this trial. In the Western world, most patients are treated with perioperative chemotherapy since the MAGIC[9] and FLOT[10] trials. Additionally, gastrectomy is often performed minimally invasive, even in advanced cases, as oncological safety has been confirmed in both Asian and Western trials[23–25]. Therefore, the results of the Japanese trial are not directly applicable to Western countries. Our study group is currently finalizing the preparation for a randomized controlled study, the OMEGA trial, (**OME**ntum preservation versus complete omentectomy in **GA**strectomy for gastric cancer). This trial will evaluate whether omentum preservation is non-inferior in terms of three-year overall survival compared to a complete omentectomy.

Future perspectives

Staging laparoscopy adds value in the process of gastric cancer staging, by detecting peritoneal metastases[13] (**chapter 3**). However, the percentage of avoidable surgery (detection of metastases and/or irresectable tumor during gastrectomy) remains around 8-10% even in those patients who underwent staging laparoscopy[7]. The addition of indocyanine green fluorescence (ICG), or another photosensitizer, during staging laparoscopy might improve

the detection of occult metastases and thereby prevent patients from undergoing futile treatment and delayed introduction of systemic treatment (or e.g. HIPEC). Two pilot studies investigated the diagnostic value of 5-Aminolevulinic acid (5-ALA) during staging laparoscopy for advanced gastric cancer[26,27]. 5-ALA is a photosensitizer that can be used for fluorescence. Both studies found an improved detection rate of peritoneal metastases with 5-ALA fluorescence, compared to the detection with white light. A future randomized controlled trial is needed to investigate the use of fluorescence during staging laparoscopy in a larger number of patients.

Laparoscopic gastrectomy has been widely accepted in the field of gastric cancer surgery. Several Asian randomized controlled trials have found lower rates of postoperative complications and similar long-term postoperative outcomes, compared to open gastrectomy[28–32]. Two Dutch trials found comparable short- and long-term outcomes between laparoscopic and open gastrectomy[24,25]. Laparoscopic gastrectomy still has certain shortcomings, including limited movements, 2D vision, and amplification of hand tremors[33–35]. In recent years the practice of robotic surgery has increased in the field of upper gastrointestinal surgery. Robotic surgery has certain advantages compared to laparoscopic surgery, including 3D vision, easier instrument movements, and filtration of potential tremors[36–39]. Recently, a Japanese randomized controlled trial compared short-term surgical outcomes between laparoscopic and robotic gastrectomy[40]. Overall, the incidence of postoperative complications was lower in the group of patients who underwent a robotic gastrectomy. A future randomized controlled trial performed with a Western patient population is needed to confirm these findings.

Finally, surgery forms the cornerstone of curative treatment for locally advanced gastric cancer. However, the value of a surgical resection in metastatic disease is still unknown. Growing evidence shows a potential role of gastrectomy combined with a resection of metastases, especially in the case of liver involvement[41]. Liver metastases are present in up to 40% of patients with advanced gastric cancer, of which 70% is only metastasized to the liver and not to other organs[42]. A recent study found an improved overall survival in carefully selected patients with advanced gastric cancer, who underwent gastrectomy and resection of the hepatic metastases[41]. Currently, a phase III trial is investigating the role of metastatic resection, besides gastrectomy, in patients with limited metastatic disease[43].

During the last decade, research has been performed on the role of cytoreductive surgery (CRS) followed by hypertermic intraperitoneal chemotherapy (HIPEC) in patients with peritoneal metastases. In a recent meta-analysis, overall survival improved with the combination of CRS follow by HIPEC, however, this benefit was associated with increased risk of postoperative complications[44]. Recently, a new minimally invasive procedure using pressurized intraperitoneal aerosol chemotherapy (PIPAC) has been introduced as a treatment for patients with peritoneal metastases. This new procedure is thought to achieve deeper peritoneal penetration because of the gaseous state of the chemotherapy compared to liquid chemotherapy in HIPEC[45]. The results of a prospective study have to be waited for[46].

Part II: Surgery during the COVID-19 pandemic

The COVID-19 pandemic has had a major effect on routine hospital services, including the possibility to perform elective surgical care, as a result of the reallocation of medical resources to (i) treat COVID-19 patients, and (ii) secure patient safety. The reduction of elective surgical care was necessary to protect patients from potential in-hospital acquired COVID-19 or undergoing surgery with a SARS-CoV-2 infection and its associated pulmonary complications and mortality[47]. The COVIDSurg group has performed multiple studies during the COVID-19 pandemic. One study estimated that globally 72.3% of all adult elective operations and 37.7% of all cancer operations were cancelled or postponed during the first 12 weeks of the first wave of the COVID-19 pandemic[48]. Most types of cancer surgery can be safely delayed for four weeks without having a significant impact on tumor progression or survival[49]. However, with increasing numbers of COVID-19 cases around the world and the fear for the development of multiple COVID-19 waves, preoperative screening strategies had to be developed to be able to continue elective surgical care safely.

Around 30% of COVID-19 patients are asymptomatic[50]. Identifying these patients is a challenge, as most patients are unaware that they are infected, unless tested. Moreover, at least 50% of newly diagnosed cases of COVID-19 originate from exposure to asymptomatic COVID-19 patients[51]. Therefore, screening strategies had to be implemented to detect especially asymptomatic patients. In The Netherlands, a national guideline was established on how to screen patients for COVID-19 preoperatively[52]. This guideline advised to take a questionnaire in all patients to detect COVID-19 related symptoms. In asymptomatic patients, a chest CT and RT-PCR were additionally used to detect a possible SARS-CoV-2 infection. RT-PCR testing was valuable in detecting asymptomatic COVID-19 (**chapter 6**). The combination of RT-PCR and chest CT detected SARS-CoV-2 in 1.5% of asymptomatic patients. However, the yield of RT-PCR increased to 6% in relation with community COVID-19 prevalence. The yield of chest CT was 0.4% and the yield showed no relationship with community prevalence. Two other studies confirmed the association between yield of RT-PCR in asymptomatic patients and the number of COVID-19 related hospital admissions[53,54]. Another study also concluded that preoperative screening with RT-PCR was beneficial before major surgery[55]. With the use of preoperative screening, elective esophageal and gastric cancer surgery could be performed safely during the COVID-19 pandemic (**chapter 8 and 9**). The percentage of pulmonary complications requiring mechanical ventilation were comparable to pre COVID-19 studies[56].

Around 20% of patients with COVID-19 present with gastrointestinal symptoms only, which include nausea, vomiting, loss of appetite, and diarrhea[57–59]. During the beginning of the COVID-19 pandemic, COVID-19 infections in patients presenting merely with gastrointestinal symptoms could be easily have been missed, as physicians were focused on detecting COVID-19 especially in patients presenting with respiratory symptoms. With the standard addition of chest CT to abdominal CT it was thought that a potential SARS-CoV-2 infection could be detected in patients presenting with gastrointestinal symptoms. However, the yield of adding chest CT to abdominal CT to detect COVID-19 in patients presenting with

acute gastrointestinal symptoms was low (**chapter 7**). These findings were supported by a study concluding that the standard addition of chest CT, together with abdominal CT, did not contribute to the identification of COVID-19 in emergency general surgical admissions[60]. However, this study did not describe the clinical presentation at the emergency department. Therefore, it is unknown how many patients did have pulmonary complaints besides gastro-intestinal symptoms. In our study, patients with pulmonary symptoms were excluded. Lastly, patients with low suspicion for COVID-19 based on chest CT (CO-RADS 1-3), did not undergo a routine RT-PCR testing. Hence, the percentage of COVID-19 in patients presenting with merely gastro-intestinal symptoms could have been higher.

The COVID-19 pandemic has provided a special circumstance in which the theory that uncomplicated and complicated appendicitis are actually two different diseases could be investigated. Different studies have provided evidence for the theory that uncomplicated and complicated appendicitis are different disease entities, and not different grades of severity of the same disease[61–63]. During the COVID-19 pandemic, multiple studies reported a pre-hospital delay for patients presenting with acute appendicitis[64,65]. Moreover, a higher proportion of complicated appendicitis was described in different studies[63–68]. In line with these findings, we found a higher proportion of patients presenting with complicated appendicitis during the COVID-19 pandemic compared to a control cohort (**chapter 10**). In a multivariable analysis, the association between complicated appendicitis and presentation during the COVID-19 pandemic remained after correction for pre-hospital delay. Therefore, it is likely that another factor may have influenced the higher proportion of complicated appendicitis during the pandemic. It was suggested that a part of the patients with mild, uncomplicated appendicitis, may have resolved spontaneously at home, supporting the theory of different disease entities.

Future perspectives

The COVID-19 pandemic will continue to impact the ability of hospitals to perform elective surgical care during the ongoing pandemic. The number of COVID-19 infections has reduced with the introduction of vaccines against the SARS-CoV-2 virus[69]. However, the need for COVID-19 patients to be admitted to the hospital will remain with the emergence of new variants of the virus, unvaccinated people and less efficacy of the vaccines over time[70]. Additionally, vaccinated people can still contract COVID-19, and new virus variants could evolve with increased transmissibility[71]. New waves of COVID-19 are expected to emerge on a yearly basis during the upcoming years. A recent study found that COVID-19 is usually milder in vaccinated individuals, however, mortality remains high among hospitalized patients[72,73]. Therefore, preoperative screening with RT-PCR will still be needed in the near future, however, the approach will be different. According to the Dutch general surgical guidelines, RT-PCR testing should only be used in unvaccinated patients aged 65 and older[74].

Elective surgical care, including cancer surgery, can safely be continued during potential new COVID-19 waves with adequate preoperative screening strategies for unvaccinated patients (**chapter 8 and 9**). This also includes minimally invasive surgery[75]. However, constantly

evaluating the safety of performing elective surgery care will remain necessary during the pandemic. New waves of COVID-19 and potential new variants of the virus might jeopardize the safety of patients undergoing surgery. Therefore, additional research could be needed to ensure the safety of patients undergoing surgical care during the COVID-19 pandemic.

References

1. Jongerius EJ, Boerma D, Seldenrijk KA, et al. Role of omentectomy as part of radical surgery for gastric cancer. *Br J Surg*. 2016;103(11):1497-1503.
2. *Evidence Based 2009-05-18 , Verantwoording: Landelijke Werkgroep Gastro-Intestinale Tumoren, Type: Landelijke Richtlijn, Versie: 2.2, Redactionele Aanpassing 2016-07-01 ,*.; 2016. https://www.oncoline.nl/uploaded/docs/Maagcarcinoom/Richtlijn maagcarcinoom.pdf.
3. Tumoren G. Maagcarcinoom Inhoudsopgave. 2009:1-7.
4. Leake PA, Cardoso R, Seevaratnam R, et al. A systematic review of the accuracy and indications for diagnostic laparoscopy prior to curative-intent resection of gastric cancer. *Gastric Cancer*. 2012;15(SUPPL.1).
5. Fukagawa T. Role of staging laparoscopy for gastric cancer patients. *Ann Gastroenterol Surg*. 2019;3(5):496-505.
6. Gertsen EC, Borggreve AS, Brenkman HJF, et al. Evaluation of the Implementation of FDG-PET/CT and Staging Laparoscopy for Gastric Cancer in The Netherlands. *Ann Surg Oncol 2020 284*. 2020;28(4):2384-2393.
7. Voeten DM, van der Werf LR, Wilschut JA, et al. Failure to Cure in Patients Undergoing Surgery for Gastric Cancer: A Nationwide Cohort Study. *Ann Surg Oncol*. January 2021:1-13.
8. Muntean V, Mihailov A, Iancu C, et al. Staging laparoscopy in gastric cancer. Accuracy and impact on therapy. *J Gastrointest Liver Dis*. 2009;18(2):189-195.
9. Cunningham D, Allum WH, Stenning SP, Weeden S. Perioperative chemotherapy in operable gastric and lower oesophageal cancer: Final results of a randomised, controlled trial (the MAGIC trial, ISRCTN 93793971). *J Clin Oncol*. 2005;23(16_suppl):4001-4001.
10. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a ra. *Lancet*. 2019;393(10184):1948-1957.
11. Leake PA, Cardoso R, Seevaratnam R, et al. A systematic review of the accuracy and indications for diagnostic laparoscopy prior to curative-intent resection of gastric cancer. *Gastric Cancer*. 2012;15(SUPPL.1):38-47.
12. Boku T, Nakane Y, Minoura T, et al. Prognostic significance of serosal invasion and free intraperitoneal cancer cells in gastric cancer. *Br J Surg*. 1990;77(4):436-439.
13. Gertsen EC, Brenkman HJF, Hillegersberg R van, et al. 18F-Fludeoxyglucose–Positron Emission Tomography/Computed Tomography and Laparoscopy for Staging of Locally Advanced Gastric Cancer: A Multicenter Prospective Dutch Cohort Study (PLASTIC). *JAMA Surg*. October 2021:e215340-e215340.
14. Smyth EC, Verheij M, Allum W, et al. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2016;27(August):v38-v49.
15. Van Gestel YRBM, Lemmens VEPP, De Hingh IHJT, et al. Influence of comorbidity and age on 1-, 2-, and 3-month postoperative mortality rates in gastrointestinal cancer patients. *Ann Surg Oncol*. 2013;20(2):371-380.

16. Sylvie L, Silvia S, Salah-Eddin AB, et al. Impact of age on the feasibility and efficacy of neoadjuvant chemotherapy in patients with locally advanced oesophagogastric cancer. *Eur J Cancer*. 2015;51(14):1918-1926.
17. Nienhueser H, Kunzmann R, Sisic L, et al. Surgery of gastric cancer and esophageal cancer: Does age matter? *J Surg Oncol*. 2015;112(4):387-395.
18. Hasegawa S, Kunisaki C, Ono H, et al. Omentum-preserving gastrectomy for advanced gastric cancer: A propensity-matched retrospective cohort study. *Gastric Cancer*. 2013;16(3):383-388.
19. Ri M, Nunobe S, Honda M, et al. Gastrectomy with or without omentectomy for cT3-4 gastric cancer: a multicentre cohort study. *Br J Surg*. May 2020.
20. Kim DJ, Lee JH, Kim W. A comparison of total versus partial omentectomy for advanced gastric cancer in laparoscopic gastrectomy. *World J Surg Oncol*. 2014;12(1).
21. Sakimura Y, Inaki N, Tsuji T, Kadoya S, Bando H. Long-term outcomes of omentum-preserving versus resecting gastrectomy for locally advanced gastric cancer with propensity score analysis. *Sci Rep*. 2020;10(1):1-9.
22. Sato Y, Yamada T, Yoshikawa T, et al. Randomized controlled Phase III trial to evaluate omentum preserving gastrectomy for patients with advanced gastric cancer (JCOG1711, ROAD-GC). *Jpn J Clin Oncol*. 2020;50(11):1321-1324.
23. Kim HH, Han SU, Kim MC, et al. Effect of Laparoscopic Distal Gastrectomy vs Open Distal Gastrectomy on Long-term Survival among Patients with Stage i Gastric Cancer: The KLASS-01 Randomized Clinical Trial. *JAMA Oncol*. 2019;5(4):506-513.
24. van der Wielen N, Straatman J, Daams F, et al. Open versus minimally invasive total gastrectomy after neoadjuvant chemotherapy: results of a European randomized trial. *Gastric Cancer 2020 241*. 2020;24(1):258-271.
25. van der Veen A, Brenkman HJF, Seesing MFJ, et al. Laparoscopic Versus Open Gastrectomy for Gastric Cancer (LOGICA): A Multicenter Randomized Clinical Trial. *J Clin Oncol*. January 2021:JCO.20.01540.
26. Kishi K, Fujiwara Y, Yano M, et al. Staging laparoscopy using ALA-mediated photodynamic diagnosis improves the detection of peritoneal metastases in advanced gastric cancer. *J Surg Oncol*. 2012;106(3):294-298.
27. Murayama Y, Ichikawa D, Koizumi N, et al. Staging fluorescence laparoscopy for gastric cancer by using 5-aminolevulinic acid. *Anticancer Res*. 2012;32(12):5421-5428.
28. Katai H, Mizusawa J, Katayama H, et al. Survival outcomes after laparoscopy-assisted distal gastrectomy versus open distal gastrectomy with nodal dissection for clinical stage IA or IB gastric cancer (JCOG0912): a multicentre, non-inferiority, phase 3 randomised controlled trial. *lancet Gastroenterol Hepatol*. 2020;5(2):142-151.
29. Kim W, Kim HH, Han SU, et al. Decreased Morbidity of Laparoscopic Distal Gastrectomy Compared With Open Distal Gastrectomy for Stage I Gastric Cancer: Short-term Outcomes From a Multicenter Randomized Controlled Trial (KLASS-01). *Ann Surg*. 2016;263(1):28-35.
30. Kim HH, Han SU, Kim MC, et al. Effect of Laparoscopic Distal Gastrectomy vs Open Distal Gastrectomy on Long-term Survival Among Patients With Stage I Gastric Cancer: The KLASS-01 Randomized Clinical Trial. *JAMA Oncol*. 2019;5(4):506-513.

31. Hu Y, Huang C, Sun Y, et al. Morbidity and Mortality of Laparoscopic Versus Open D2 Distal Gastrectomy for Advanced Gastric Cancer: A Randomized Controlled Trial. *J Clin Oncol*. 2016;34(12):1350-1357.
32. Yu J, Huang C, Sun Y, et al. Effect of Laparoscopic vs Open Distal Gastrectomy on 3-Year Disease-Free Survival in Patients With Locally Advanced Gastric Cancer: The CLASS-01 Randomized Clinical Trial. *JAMA*. 2019;321(20):1983-1992.
33. Park JM, Jin SH, Lee SR, et al. Complications with laparoscopically assisted gastrectomy: multivariate analysis of 300 consecutive cases. *Surg Endosc*. 2008;22(10):2133-2139.
34. Jiang X, Hiki N, Nunobe S, et al. Postoperative pancreatic fistula and the risk factors of laparoscopy-assisted distal gastrectomy for early gastric cancer. *Ann Surg Oncol*. 2012;19(1):115-121.
35. Ojima T, Nakamura M, Nakamori M, et al. Robotic radical lymphadenectomy without touching the pancreas during gastrectomy for gastric cancer. *Medicine (Baltimore)*. 2019;98(13):e15091.
36. Lu J, Zheng CH, Xu B Bin, et al. Assessment of Robotic Versus Laparoscopic Distal Gastrectomy for Gastric Cancer: A Randomized Controlled Trial. *Ann Surg*. 2021;273(5):858-867.
37. Ojima T, Hayata K, Yamaue H. Robotic complete lymphadenectomy at the splenic hilum during total gastrectomy for advanced gastric cancer (with video). *J Visc Surg*. 2019;156(2):173-174.
38. Kim YM, Son T, Kim H Il, Noh SH, Hyung WJ. Robotic D2 Lymph Node Dissection During Distal Subtotal Gastrectomy for Gastric Cancer: Toward Procedural Standardization. *Ann Surg Oncol*. 2016;23(8):2409-2410.
39. Lee S, Kim JK, Kim YN, et al. Safety and feasibility of reduced-port robotic distal gastrectomy for gastric cancer: a phase I/II clinical trial. *Surg Endosc*. 2017;31(10):4002-4009.
40. Ojima T, Nakamura M, Hayata K, et al. Short-term Outcomes of Robotic Gastrectomy vs Laparoscopic Gastrectomy for Patients With Gastric Cancer: A Randomized Clinical Trial. *JAMA Surg*. 2021;156(10):954-963.
41. Markar SR, Mikhail S, Malietzis G, et al. Influence of surgical resection of hepatic metastases from gastric adenocarcinoma on long-term survival: Systematic review and pooled analysis. *Ann Surg*. 2016;263(6):1092-1101.
42. Qiu MZ, Shi SM, Chen ZH, et al. Frequency and clinicopathological features of metastasis to liver, lung, bone, and brain from gastric cancer: A SEER-based study. *Cancer Med*. 2018;7(8):3662-3672.
43. Al-Batran SE, Goetze TO, Mueller DW, et al. The RENAISSANCE (AIO-FLOT5) trial: effect of chemotherapy alone vs. chemotherapy followed by surgical resection on survival and quality of life in patients with limited-metastatic adenocarcinoma of the stomach or esophagogastric junction - a phase III trial of the German AIO/CAO-V/CAOGI. *BMC Cancer*. 2017;17(1).
44. Desiderio J, Chao J, Melstrom L, et al. The 30-year experience—A meta-analysis of randomised and high-quality non-randomised studies of hyperthermic intraperitoneal chemotherapy in the treatment of gastric cancer. *Eur J Cancer*. 2017;79:1-14.
45. Alyami M, Hübner M, Grass F, et al. Pressurised intraperitoneal aerosol chemotherapy: rationale, evidence, and potential indications. *Lancet Oncol*. 2019;20(7):e368-e377.
46. International Registry of Patients Treated With Pressurized IntraPeritoneal Aerosol Chemotherapy (PIPAC) - Full Text View - ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03210298.
47. Nepogodiev D, Glasbey JC, Li E, et al. Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study. *Lancet*. 2020;0(0).

48. Elective surgery cancellations due to the COVID-19 pandemic: global predictive modelling to inform surgical recovery plans. *Br J Surg*. June 2020.
49. Turaga KK, Girotra S. Are we harming cancer patients by delaying their cancer surgery during the COVID-19 pandemic? 2020.
50. Nishiura H, Kobayashi T, Miyama T, et al. Estimation of the asymptomatic ratio of novel coronavirus infections (COVID-19). *Int J Infect Dis*. 2020;94:154.
51. Johansson MA, Quandelacy TM, Kada S, et al. SARS-CoV-2 Transmission From People Without COVID-19 Symptoms. *JAMA Netw Open*. 2021;4(1):e2035057-e2035057.
52. *LEIDRAAD Pre-Operatieve Diagnostische Work Up*.
53. Sutton D, Fuchs K, D'Alton M, Goffman D. Universal Screening for SARS-CoV-2 in Women Admitted for Delivery. *N Engl J Med*. 2020;382(22):2163-2164.
54. Gudbjartsson DF, Helgason A, Jonsson H, et al. Spread of SARS-CoV-2 in the Icelandic Population. *N Engl J Med*. April 2020:NEJMoa2006100.
55. Collaborative C. Preoperative nasopharyngeal swab testing and postoperative pulmonary complications in patients undergoing elective surgery during the SARS-CoV-2 pandemic. *Br J Surg*.
56. Kuppusamy MK, Low DE. Evaluation of International Contemporary Operative Outcomes and Management Trends Associated With Esophagectomy. *Ann Surg*. 2020;Publish Ah(Xx):1-11.
57. Pan L, Mu M, Yang P, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: A descriptive, cross-sectional, multicenter study. *Am J Gastroenterol*. 2020;115(5):766-773.
58. Luo S, Zhang X, Xu H. Don't Overlook Digestive Symptoms in Patients With 2019 Novel Coronavirus Disease (COVID-19). *Clin Gastroenterol Hepatol*. 2020;18(7):1636.
59. Yang L, Tu L. Implications of gastrointestinal manifestations of COVID-19. *Lancet Gastroenterol Hepatol*. 2020;5(7):629-630.
60. Brennan C, Morrissey B, Dubois-Marshall S, McAteer D, Qadir A, Ramsay G. COVID-19: No benefit of chest inclusion in acute abdomen CT. *Br J Surg*. 2020;107(11):e474-e475.
61. EH L, TB F, WA W, RW H. Epidemiological similarities between appendicitis and diverticulitis suggesting a common underlying pathogenesis. *Arch Surg*. 2011;146(3):308-314.
62. RE A. The natural history and traditional management of appendicitis revisited: spontaneous resolution and predominance of prehospital perforations imply that a correct diagnosis is more important than an early diagnosis. *World J Surg*. 2007;31(1):86-92.
63. Cobben LPJ, Otterloo AM de van, Puylaert JBCM. Spontaneously Resolving Appendicitis: Frequency and Natural History in 60 Patients1.
64. Gao Z, Li M, Zhou H, et al. Complicated appendicitis are common during the epidemic period of 2019 novel coronavirus (2019-nCoV). *Asian J Surg*. 2020;43(10):1002.
65. Dreifuss NH, Schlottmann F, Sadava EE, Rotholtz NA. Acute appendicitis does not quarantine: surgical outcomes of laparoscopic appendectomy in COVID-19 times. *Br J Surg*. 2020;107(10):e368-e369.
66. M V, AJ M-S, K E-F, et al. Influence of the coronavirus 2 (SARS-Cov-2) pandemic on acute appendicitis. *An Pediatr*. 2020;93(2):118-122.
67. P L-A, S B, H C, D B, B P, C M. Increased incidence of complicated appendicitis during the COVID-19 pandemic. *J Paediatr Child Health*. 2020;56(8):1313-1314.

68. Raffaele A, Cervone A, Ruffoli M, et al. Critical factors conditioning the management of appendicitis in children during COVID-19 Pandemic: experience from the outbreak area of Lombardy, Italy. *Br J Surg*. 2020;107(11):e529-e530.
69. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med*. 2020;383(27):2603-2615.
70. Thomas SJ, Moreira ED, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months. *N Engl J Med*. 2021;385(19):1761-1773.
71. Graham MS, Sudre CH, May A, et al. Changes in symptomatology, reinfection, and transmissibility associated with the SARS-CoV-2 variant B.1.1.7: an ecological study. *Lancet Public Heal*. 2021;6(5):e335-e345.
72. Egan C, Knight S, Baillie K, Harrison E, Docherty A, Semple C. Hospitalised vaccinated patients during the second wave, update April '21.
73. Docherty A, Mulholland R, … NL-TLR, 2021 undefined. Changes in in-hospital mortality in the first wave of COVID-19: a multicentre prospective observational cohort study using the WHO Clinical Characterisation. *Elsevier*.
74. Richtlijnmodule Preoperatieve screening naar SARS-CoV-2 infectie bij asymptomatische patiënten ingepland voor chirurgie onder algehele anesthesie.
75. Chadi SA, Guidolin K, Caycedo-Marulanda A, et al. Current Evidence for Minimally Invasive Surgery During the COVID-19 Pandemic and Risk Mitigation Strategies: A Narrative Review. *Ann Surg*. 2020;272(2):e118-e124.

Appendices

OMEGA study protocol

ASO Author reflection

Summary in Dutch

List of publications

List of contributing authors

PhD portfolio

Acknowledgements

Curriculum Vitae

Omentum preservation versus complete omentectomy in gastrectomy for gastric cancer (OMEGA): study protocol for a randomized controlled trial

Alexander B.J. Borgstein, Kammy Keywani, Marc J. van Det, Peter van Duivendijk, Boudewijn van Etten, Erwin van der Harst, Joost Heisterkamp, Sjoerd M. Lagarde, Misha D.P. Luyer, Sheraz R. Markar, Sybren L. Meijer, Jean P. Pierie, Franco Roviello, Jelle P. Ruurda, Johanna W. van Sandick, Meindert Sosef, Ernst-Jan Spillenaar Bilgen, Wobbe O. de Steur, Wietse J. Eshuis, Mark I. van Berge Henegouwen and Suzanne S. Gisbertz

Submitted for publication

Abstract

Background
Curative therapy for gastric cancer usually consists of perioperative chemotherapy and a radical (R0) gastrectomy. An adequate resection includes a modified D2 lymphadenectomy, and, in addition, a complete removal of the greater omentum, to ensure the removal of possible microscopic disease. The omentum functions as regulator of regional immune responses to prevent infections and, prevents adhesions which could lead to bowel obstructions. There is little evidence regarding survival benefit of routine complete omentectomy during gastrectomy. The OMEGA trial investigates if omentum preservation during gastrectomy for cancer is non-inferior to the general current practice of complete omentectomy.

Methods
OMEGA is a randomized controlled, open, parallel, non-inferiority, multicenter trial. Eligible patients are operable (ASA <4) and have resectable (≦cT4aN3bM0) gastric cancer. Patients will be randomized in a 1:1 ratio between (sub)total gastrectomy with omentum preservation or complete omentectomy. In total, 654 patients will be randomized. The primary objective is to investigate whether omentum preservation in gastrectomy for cancer is non-inferior to complete omentectomy in terms of three-year overall survival. Secondary outcomes include surgical outcomes, early and late postoperative outcomes, hospital and intensive care unit stay, readmission rate, quality of life, disease-free survival and cost-effectiveness.

Discussion
The OMEGA trial investigates if omentum preservation during gastrectomy for gastric cancer is non-inferior to complete omentectomy in terms of three-year overall survival. The OMEGA trial will provide insights whether complete omentectomy could be omitted, thereby potentially reducing overtreatment.

Background

Gastric cancer is the fifth most prevalent type of cancer worldwide and the third most common cause of cancer-related deaths[1]. Overall, survival has improved in recent decades with the introduction of (neo)adjuvant therapies; however, a radical (R0) gastrectomy remains the foundation of curative treatment. An adequate resection involves a modified D2 lymphadenectomy, and, in addition, a complete removal of the greater omentum, an omentectomy, to ensure the removal of possible micrometastatic disease.

The omentum has several functions in the peritoneal cavity. It contributes to the defense against infections, by functioning as regulator of regional immune responses[2–5]. Furthermore, the omentum prevents the occurrence of adhesions, which can lead to small bowel obstruction[6,7]. In gastric cancer surgery, omentectomy is a time-consuming procedure, especially in laparoscopic surgery. It is laparoscopically technically demanding and has been shown to increase the risk of intraoperative injuries to the colon and mesocolon[8]. Additionally, omentectomy leads to an increased risk of early postoperative complications, such as abdominal abscess, ileus, and wound infections in various types of surgery[9–14]. Also, late abdominal complications, such as ileus and mechanical small bowel obstruction, occur more often after complete omentectomy[10].

There is little evidence supporting routine complete omentectomy in gastrectomy for cancer. No randomized controlled trials comparing complete omentectomy with omentum preservation in gastrectomy for cancer have been published yet, although, recently, the study protocol of a phase III trial that will be conducted in Japan has been released, following the results of the phase II study by the same group[15,16]. Several studies have made the comparison in a non-randomized fashion[17–21]. Most of these studies were carried out in Asian countries, where gastric cancer is much more prevalent, more patients are identified by screening programs and are diagnosed with early gastric cancer accordingly. These patients are rarely treated with perioperative chemotherapy. Hence, comparison of Asian and Western studies on gastric cancer should be made with caution. Theoretically, the bursa omentalis should be resected together with the omentum to prevent potential peritoneal metastases. However, a large trial and recent meta-analysis concluded that gastrectomy with bursectomy is not superior in terms of overall survival compared to gastrectomy without bursectomy, therefore, bursectomy is not recommended to perform as standard for cT3-4 gastric cancer[22,23].

To our knowledge, the influence of omentectomy on survival has not yet been investigated in a Western gastric cancer population. Therefore, the necessity of complete omentectomy in gastrectomy for cancer is unclear for Western practice. Hence, this randomized controlled trial is being performed to assess whether omentum preservation during gastrectomy for gastric cancer is non-inferior to complete omentectomy in terms of overall survival.

Methods

Objective
Primary objective: to compare preservation of the omentum distal to the gastroepiploic vessels with complete omentectomy in gastrectomy for cancer in terms of three-year overall survival

Study design and setting
OMEGA is a randomized controlled, open, parallel, non-inferiority, multicenter trial. Eligible patients have to be operable (ASA <4) with resectable (≦cT4aN3bM0) gastric cancer. Patients will be randomized in a 1:1 ratio between radical (sub)total gastrectomy with omentum preservation or complete omentectomy. Patients will be stratified according to center, neoadjuvant therapy and type of surgery (total or subtotal gastrectomy). In total, 654 patients will be randomized. The study will be conducted in six Dutch university hospitals, twelve Dutch teaching hospital and two international university hospital (Siena and Oxford), all performing more than 20 gastrectomies annually. The Data and Safety Monitoring Board monitors patient safety.

Inclusion criteria
In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- primary resectable gastric adenocarcinoma, clinical stage T2-4a N0-3 M0 or cT1N+
- ASA 1-3 (able to undergo surgery)

Scheduled for open or minimally invasive (sub)total gastrectomy with modified D2-lymphadenectomy, with or without perioperative chemotherapy

- Age above 18
- Able to complete questionnaires in Dutch, English or Italian and to come to outpatient clinic visits
- Written informed consent
- Esophageal invasion < 2 cm

Exclusion criteria
A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Locally advanced gastric cancer requiring multi-visceral excision

- Indication for HIPEC (e.g. in PERISCOPE trial[24])
- Pregnancy
- Previous malignancy (excluding non-melanoma skin cancer, pancreatic neuroendocrine tumor (pNET) <2cm, and gastrointestinal stromal tumor (GIST) <2cm), unless no evidence of disease and diagnosed more than three years before diagnosis of gastric cancer, or with a life expectancy of more than five years from date of inclusion)
- Serious concomitant systemic disorders that would compromise the safety of the patient or his/her ability to complete the study, at the discretion of the investigator
- Previous gastric or omental surgery
- Indication for thoracotomy/thoracoscopy

Recruitment and participants

Eligible patients will be approached for entry into the trial at the first outpatient visit at the surgery department after the diagnosis of gastric cancer. The rationale for the study is explained to the patient. A written patient information sheet is provided and patients will be given the opportunity to ask questions. After a sufficient reflection period, the willing patients are asked to sign the informed consent before any study intervention. Written informed consent is obtained by surgeons, surgical registrars or trained research nurses. When consent has been obtained, the original form is kept in the study file and a copy is given to the patient. Baseline data as well as baseline quality of life questionnaires are collected.

Sample size

The primary endpoint is three-year overall survival. According to survival numbers from the Dutch Cancer Registry (NKR), three-year overall survival after gastrectomy is approximately 50% in The Netherlands. A non-inferiority margin of 5% for three-year overall survival probability is used and under the alternative it is assumed that the experimental group has an enhanced outcome of 5% because of improved early and late morbidity. Under the common assumption of exponential survival times, the hazard ratio under the null hypothesis of non-inferiority is 1.15 and the hazard ratio under the alternative hypothesis equals 0.862. At the minimum follow-up of three years at least 50% and 45% are expected to have an event (i.e. death) in the control arm and experimental arm, respectively. Assuming one-sided testing at a significance level of 5%, 311 patients are needed in each study arm to achieve 80% power (PASS 15 Power Analysis and Sample Size Software (2017). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass). Dropouts will be rare, with proportion dropping out expected to be at most 5%. After correction for drop-out we plan to include 327 patients in each of the

two arms (654 in total), requiring an accrual rate of 27 patients per month with an accrual period of two years. All patients will be followed-up until three years after randomization.

Randomization and blinding
Patients will be randomized in a 1:1 ratio between gastrectomy with complete omentectomy or omentum preservation. Randomization will be performed preoperatively, the day before or on the day of the operation. Randomization will be done with the use of an online computer program and stratified by participating center, neoadjuvant therapy, Lauren classification, type of operation (subtotal or total gastrectomy). Blinding for the type of investigational treatment will not be performed. Patients will be excluded in case metastases and/or non-resectability are detected at the beginning of gastrectomy with curative intent.

Standard treatment
Patients will be staged according to the international gastric cancer guidelines[25,26]. Patients will be diagnosed by upper GI endoscopy with biopsies, and staged with (PET-) CT scan and diagnostic laparoscopy with or without peritoneal lavage for cytological examination (if perioperative chemotherapy is planned). Endoscopic ultrasound will be performed on indication. Patients will be treated with perioperative chemotherapy according to the FLOT scheme[27] or any other scheme, unless contraindicated because of patient factors (age, comorbidities) or tumor factors (bleeding or obstruction).

In patients scheduled for perioperative chemotherapy, the gastrectomy will be performed approximately 4 – 6 weeks after completion of the neoadjuvant phase. Those not treated with chemotherapy will be directly scheduled for surgery. Surgery will be performed according to treatment allocation: omentum preservation or complete omentectomy. Surgical quality assurance will be applied to all participating centers before patients can be included in the trial. Monitoring of surgical quality will also be performed during the trial.

Gastrectomy with omentectomy
The operation will start with the establishment of resectable disease. Optionally, the abdominal cavity will be washed with 1000 mL saline 0,9% at body temperature. After two minutes the saline will be collected and sent in for pathological examination. In case of established resectable disease, a laparoscopic or open (sub)total gastrectomy will be performed. A subtotal gastrectomy will be performed if a tumor-free distance of at least 6 cm to the proximal resection margin can be obtained. If this is cannot be achieved, a frozen section should be performed to ensure a negative proximal margin. If a distal resection margin of less than 6 cm is obtained and a more extended resection is possible, a frozen section is advised according to the international guidelines[25,26]. In all other cases, a total gastrectomy is indicated.

The hepatogastric ligament is opened close to the liver. A D2 lymphadenectomy (according to the Japanese gastric cancer guideline) is performed (Stations 1, 3-8a, 9, 11p and 12a in subtotal gastrectomy and stations 1-7, 8a, 9, 11p, 11d and 12a in total gastrectomy. The

right & left gastric a/v are ligated at the base (including lymphadenectomy station five). A complete omentectomy is performed en bloc or separately (by discretion of the surgeon). The right & left gastroepiploic a/v are ligated (including lymphadenectomy at station six) and the short gastric vessels in case of a total gastrectomy. The duodenum and esophagus or proximal stomach are divided and the specimen is removed. A Roux-Y entero-enterostomy is created with a biliary limb of approximately 20 cm and an alimentary limb of approximately 50 cm. A Roux-en-Y esophagojejunostomy or gastrojejunostomy is performed. Lymph node stations are sent in separately to the pathology department except for those in close proximity to the primary tumor, these are marked with sutures or beads. In case of a complete omentectomy the omentum is ex-vivo (or in-vivo) dissected of the specimen and after marking sent in separately for pathological examination.

Gastrectomy with omentum preservation

The same procedures are performed regarding gastrectomy and lymphadenectomy. However, the gastrocolic ligament is divided distal from the gastroepiploic arcade and proximal from the transverse colon and the distal part (on the transverse colon side) is not resected. In case of omentum preservation, if available, indocyanine green (ICG) 0,1 mg/kg will be administered intravenously and time to fluorescence will be recorded as well as whether areas of the omentum remain non-fluorescent, which will be registered as number of cm^2.

Postoperative management

Patients in both study groups will receive similar standard post-operative treatment. In all centers an ERAS protocol has been implemented[28]. The gastric tube is removed at the end of the operation.

Primary endpoint

The primary endpoint is overall survival at three-years after the operation, defined as the period of time between operation and death from any cause. Patients alive at last follow-up are censored.

Secondary endpoints

Secondary outcomes are operating time, intraoperative blood loss, intraoperative complications, postoperative complications, defined according to the Clavien-Dindo classification[29] and comprehensive complication index (CCI)[30], late intra-abdominal complications, defined as complications related to the initial operation, occurring between >30 days and five years after surgery, distribution of lymph node metastases, R0 resection rate, defined as the percentage of patients that underwent a microscopically complete (R0) resection, rate of malignant cells in cytology, serum CRP levels at postoperative days 2, 3, and 5, molecular sub classification of gastric cancer (in centers that have molecular sub classification available), ICG fluorescent enhancement of omentum in omentum preservation group (in centers that have ICG fluorescence available), compliance to allocated treatment, escalation of care, hospital stay, defined as time interval between date of surgery and date

of hospital discharge, intensive care length of stay, readmission rate within 30-days after surgery, reintervention rate within 30-days after surgery, reoperation rate within three years after surgery, cost effectiveness, quality of life at baseline, 3, 6, 9, 12 and 24 months (the following questionnaires will be used: EQ-5D-5L, QLQ-C30, QLQ-OG25, CIPN, Happiness, HADS and work productivity)[31], 3- & 5-year disease-free survival, defined as the period of time from operation to locoregional recurrence, distant metastases, recurrent gastric cancer or death from any cause. Patients alive and free of all these events will be censored at the last follow-up, 5-year overall survival, defined as the period of time from operation to death from any cause. Patients alive and free of all these events will be censored at the last follow-up.

Baseline values

Baseline characteristics are age, sex, medical history, previous surgery, length and weight, weight loss, American Society of Anaesthesiologists class (ASA), WHO performance status, Charlson Comorbidity Index, tumor location, differentiation, Lauren classification and schedule and completion of perioperative therapy.

Follow-up

Follow-up visits will be scheduled 2 weeks after surgery, followed by every three months for the first year, every six months the second to fourth year and once yearly until the fifth postoperative year. Patients will be followed-up with additional diagnostics (CT thorax/abdomen, endoscopy, EUS) on indication only, according to the international gastric cancer guideline[25,26].

Statistical analysis

Descriptive statistics will be calculated to summarize patients' groups included in each of trial arms. Mean and standard deviation will be presented for normally distributed continuous variables. Median plus interquartile-range (IQR) will be presented continuous variables that are skewed and for ordinal variables. Dichotomous and nominal data will be summarized by means of frequencies and percentages.

Non-inferiority of the experimental treatment in terms of overall survival will be tested using Cox-regression. Non-inferiority will be concluded if the upper limit of the 90% confidence interval falls below the non-inferiority hazard ratio of 1.15, corresponding to a one-sided non-inferiority test at significance level of 5%. Survival will be presented graphically using Kaplan-Meier curves. All analyses will be according to the intention to treat principle. A per protocol analysis will also be performed. The experimental treatment will be declared non-inferior if non-inferiority is shown in both the intention to treat and the per protocol analysis.

Secondary outcomes will be compared between groups using appropriate statistical methods, such as independent samples t-test for normally-distributed continuous outcomes, Mann-Whitney tests for continuous outcomes that are not normally distributed

or ordinal outcomes. Categorical outcomes will be compared using chi-square test or Fisher's exact test in case of low (expected) cell counts. Repeatedly measured outcomes will be compared between arms using linear mixed models. Secondary time-to-event outcomes will be compared the using log-rank test. Secondary endpoints will be tested at a two-sided significance level of 5%. Effect sizes suitable for the type of outcome measure will be provided (mean differences, ratio of geometric means, relative risks, hazard ratios) together with their 95% confidence interval.

Subgroup analysis for the effect of experimental treatment on overall survival will be performed for the following subgroups: patient characteristics (age, male/female), diffuse/intestinal type gastric tumor, subtotal/total gastrectomy, and minimally invasive/open gastrectomy. Effect modification will use Cox regression with the subgroup variable, the arm and their two-way interaction. Additionally, stratified analyses will be performed where HR is calculated separately in each of the subgroups.

Quality of life data will be graphically represented across all time points and analyzed according to the manuals and will presented as domain and summarized scores. Questionnaire outcome comparisons will be analyzed using linear mixed models.

Safety

A single formal interim analysis will take place after 145 deaths (approximately 50% of the total number expected during the trial period) have been observed. At this interim analysis, the trial will be stopped for futility if the hazard ratio exceeds the non-inferiority hazard ratio of 1.15[26]. The trial will be stopped for superiority if the p-value for testing HR=1 versus HR<1 is below 0.001 (Peto approach). Stopping and declaring the experimental treatment non-inferior will not be considered as this is generally not recommended.

Discussion

The OMEGA trial is an international randomized controlled trial, with European renowned gastric cancer centers, that will investigate whether omentum preservation during gastrectomy for cancer is non-inferior to the current practice of complete omentectomy in terms of overall survival. Several non-randomized studies found no difference in overall survival between gastrectomy with or without omentectomy. However, most of these studies were carried out in Asian countries. Hence, the necessity of complete omentectomy in gastrectomy for cancer is still unclear.

Omentectomy was often performed together with a bursectomy to prevent potential peritoneal metastases. However, a previous trial concluded that bursectomy did not provide a survival benefit over gastrectomy without bursectomy[23]. Therefore, guidelines advise to perform a gastrectomy with D2 lymphadenectomy and omentectomy, without bursectomy, for cT3-4 gastric cancer. Recently, the results from a Japanese phase II trial which investigated short term outcomes in patients undergoing gastrectomy with and without omentectomy

for gastric cancer were published[32]. No difference was found in postoperative morbidity between both groups. Currently, a phase III trial is conducted in Japan[15]. The aim of this trial is to confirm the non-inferiority of omentum preservation compared with omentectomy in patients with cT3 or cT4a gastric cancer in terms of relapse-free survival. However, in both Japanese trials, patients receiving neoadjuvant therapy and patients undergoing minimally invasive gastrectomy are excluded. Therefore, the results from these studies cannot directly be applied to the Western world. The OMEGA trial will be the first Western prospective study that will determine if gastrectomy with complete omentectomy can be omitted in the future.

Trial status

Patient recruitment will start from October 2021 onwards and is scheduled to finish two years later.

References

1. Ferlay J, Colombet M, Soerjomataram I, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int J Cancer*. 2019;144(8):1941-1953. doi:10.1002/ijc.31937
2. Agca B, Paksoy M, Polat E, et al. Influence of omentectomy on peritoneal defense mechanisms in an experimental model of intra-abdominal infection. *Eur Surg Res*. 2003;35(1):35-40. doi:10.1159/000067033
3. Wang AW, Prieto JM, Cauvi DM, Bickler SW, De Maio A. The Greater Omentum—A Vibrant and Enigmatic Immunologic Organ Involved in Injury and Infection Resolution. *SHOCK*. 2020;53(4):384-390. doi:10.1097/SHK.0000000000001428
4. Buscher K, Wang H, Zhang X, et al. Protection from septic peritonitis by rapid neutrophil recruitment through omental high endothelial venules. *Nat Commun*. 2016;7(1):1-7. doi:10.1038/ncomms10828
5. Meza-Perez S, Randall TD. Immunological Functions of the Omentum. *Trends Immunol*. 2017;38(7):526-536. doi:10.1016/j.it.2017.03.002
6. Platell C, Cooper D, Papadimitriou JM, Hall JC. The omentum. *http://www.wjgnet.com/*. 2000;6(2):169-176. doi:10.3748/WJG.V6.I2.169
7. Ariake K, Yokoyama S, Doi T, Takemura S, Kajiwara T, Kuroda F. Effect of omentum removal on the risk for postoperative adhesive small bowel obstruction recurrence: A case-control study. *Int J Surg*. 2015;13:27-32. doi:10.1016/j.ijsu.2014.11.031
8. Kim DJ, Lee JH, Kim W. A comparison of total versus partial omentectomy for advanced gastric cancer in laparoscopic gastrectomy. *World J Surg Oncol 2014 121*. 2014;12(1):1-6. doi:10.1186/1477-7819-12-64
9. McGillicuddy EA, Schuster KM, Davis KA, Longo WE. Factors predicting morbidity and mortality in emergency colorectal procedures in elderly patients. *Arch Surg*. 2009;144(12):1157-1162. doi:10.1001/archsurg.2009.203
10. Ha TK, An JY, Youn HG, Noh JH, Sohn TS, Kim S. Omentum-preserving gastrectomy for early gastric cancer. *World J Surg*. 2008;32(8):1703-1708. doi:10.1007/s00268-008-9598-5
11. Yokoyama Y, Hirakawa H, Wang H, Mizunuma H. Is omentectomy mandatory in the operation for ovarian cancer? Preliminary results in a rat study. *Eur J Obstet Gynecol Reprod Biol*. 2012;164(1):89-92. doi:10.1016/j.ejogrb.2012.05.020
12. Cerci C, Eroglu E, Sutcu R, Celikbas B, Kilbas A. Effects of omentectomy on the peritoneal fibrinolytic system. *Surg Today*. 2008;38(8):711-715. doi:10.1007/s00595-007-3705-3
13. Bass AJ, Thorsson V, Shmulevich I, et al. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature*. 2014;513(7517):202-209. doi:10.1038/nature13480
14. Kim MC, Kim KH, Jung GJ, Rattner DW. Comparative study of complete and partial omentectomy in radical subtotal gastrectomy for early gastric cancer. *Yonsei Med J*. 2011;52(6):961-966. doi:10.3349/ymj.2011.52.6.961
15. Sato Y, Yamada T, Yoshikawa T, et al. Randomized controlled Phase III trial to evaluate omentum preserving gastrectomy for patients with advanced gastric cancer (JCOG1711, ROAD-GC). *Jpn J Clin Oncol*. 2020;50(11):1321-1324. doi:10.1093/jjco/hyaa113

16. Murakami H, Yamada T, Taguri M, et al. Short-Term Outcomes from a Randomized Screening Phase II Non-inferiority Trial Comparing Omentectomy and Omentum Preservation for Locally Advanced Gastric Cancer: the TOP-G Trial. *World J Surg*. 2021. doi:10.1007/s00268-021-05988-7
17. Sakimura Y, Inaki N, Tsuji T, Kadoya S, Bando H. Long-term outcomes of omentum-preserving versus resecting gastrectomy for locally advanced gastric cancer with propensity score analysis. *Sci Rep*. 2020;10(1):1-9. doi:10.1038/s41598-020-73367-8
18. Haverkamp L, Brenkman HJF, Ruurda JP, ten Kate FJW, van Hillegersberg R. The Oncological Value of Omentectomy in Gastrectomy for Cancer. *J Gastrointest Surg*. 2016;20(5):885-890. doi:10.1007/s11605-016-3092-4
19. Hasegawa S, Kunisaki C, Ono H, et al. Omentum-preserving gastrectomy for advanced gastric cancer: A propensity-matched retrospective cohort study. *Gastric Cancer*. 2013;16(3):383-388. doi:10.1007/s10120-012-0198-6
20. Kim DJ, Lee JH, Kim W. A comparison of total versus partial omentectomy for advanced gastric cancer in laparoscopic gastrectomy. *World J Surg Oncol*. 2014;12(1):64. doi:10.1186/1477-7819-12-64
21. Ri M, Nunobe S, Honda M, et al. Gastrectomy with or without omentectomy for cT3-4 gastric cancer: a multicentre cohort study. *Br J Surg*. May 2020. doi:10.1002/bjs.11702
22. Xiong B, Ma L, Huang W, Cheng Y, Luo H, Wang K. Efficiency of bursectomy in patients with resectable gastric cancer: An updated meta-analysis. *Eur J Surg Oncol*. 2019;45(8):1483-1492. doi:10.1016/J.EJSO.2019.01.020
23. Kurokawa Y, Doki Y, Mizusawa J, et al. Bursectomy versus omentectomy alone for resectable gastric cancer (JCOG1001): a phase 3, open-label, randomised controlled trial. *Lancet Gastroenterol Hepatol*. 2018;3(7):460-468. doi:10.1016/S2468-1253(18)30090-6
24. Koemans WJ, Van Der Kaaij RT, Boot H, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy versus palliative systemic chemotherapy in stomach cancer patients with peritoneal dissemination, the study protocol of a multicentre randomised controlled trial (PERISCOPE II). *BMC Cancer*. 2019;19(1):420. doi:10.1186/s12885-019-5640-2
25. Smyth EC, Verheij M, Allum W, et al. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol*. 2016;27(suppl_5):v38-v49. doi:10.1093/annonc/mdw350
26. Japanese gastric cancer treatment guidelines 2018 (5th edition). *Gastric Cancer*. February 2020:1-21. doi:10.1007/s10120-020-01042-y
27. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a ra. *Lancet*. 2019;393(10184):1948-1957. doi:10.1016/S0140-6736(18)32557-1
28. Mortensen K, Nilsson M, Slim K, et al. Consensus guidelines for enhanced recovery after gastrectomy Enhanced Recovery After Surgery (ERAS ®) Society recommendations on behalf of the Enhanced Recovery After Surgery (ERAS ®) Group. 2014. doi:10.1002/bjs.9582
29. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240(2):205-213. doi:10.1097/01.sla.0000133083.54934.ae

30. Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien PA. The comprehensive complication index: A novel continuous scale to measure surgical morbidity. *Ann Surg*. 2013;258(1):1-7. doi:10.1097/SLA.0b013e318296c732
31. Prospective observational cohort study of oesophagogastric cancer patients (POCOP): A Dutch nationwide cohort — Amsterdam UMC - Vrije Universiteit Amsterdam. https://research.vumc.nl/en/publications/prospective-observational-cohort-study-of-oesophagogastric-cancer. Accessed July 28, 2020.
32. Murakami H, Yamada T, Taguri M, et al. Short-Term Outcomes from a Randomized Screening Phase II Non-inferiority Trial Comparing Omentectomy and Omentum Preservation for Locally Advanced Gastric Cancer: the TOP-G Trial. *World J Surg 2021 456*. 2021;45(6):1803-1811. doi:10.1007/S00268-021-05988-7

ASO Author reflection: Safety of performing esophageal cancer during the first wave of the COVID-19 pandemic in Europe

Alexander B.J. Borgstein and Mark I. van Berge Henegouwen

Annals of Surgical Oncology 2021

Past

Many centers in the world postponed elective surgical care during the first wave of the COVID-19 pandemic, due to a number of factors. Firstly, hospitals had to shift medical resources to increase intensive care unit (ICU) capacities and other wards to treat increasing numbers of COVID-19 patients. Secondly, to prevent patients and healthcare workers from potentially acquiring in-hospital SARS-CoV-2 infections. This strategy to postpone elective surgery was supported by a large study indicating patients undergoing surgery with a SARS-CoV-2 infection to have increased risk for postoperative pulmonary complications and mortality[1]. Many centers were forced to postpone treatment for esophageal cancer patients for a long period of time. Moreover, some centers switched to alternative treatment measures, including definite chemoradiotherapy.

On the other hand, some centers were able to continue elective cancer surgery, including esophageal cancer surgery, with the use of effective preoperative screening methods[2]. However, there was no evidence supporting the safety of continuing elective esophageal cancer surgery during the first wave of the COVID-19 pandemic. Additionally, several societies released guidelines in which the use of minimally invasive surgery was discouraged, as these procedures could potentially contaminate surgical staff with SARS-CoV-2.

Present

The current international, multicenter cohort study assessed the safety of continuing esophageal cancer surgery, by comparing the rate of respiratory failure requiring mechanical ventilation between a COVID-19 cohort and a control cohort of patients undergoing elective esophageal cancer surgery[3]. The rate of respiratory failure requiring mechanical ventilation was comparable between both cohorts (13.7% in the COVID-19 cohort vs. 8.3% in the control cohort), as was the number of pulmonary complications (32.4% vs. 29.9%). Additionally, there was no difference in the overall 30-day mortality rate between both cohorts. Preoperative history taking and RT-PCR testing were used in all participating centers as screening methods and no patients tested positive for COVID-19 pre- or postoperatively. 75% of all esophagectomies was performed minimally invasive. Our study did not assess the COVID-19 presence among the surgical staff. However, as no patients were diagnosed with COVID-19 pre- or postoperatively, minimally invasive surgery could be used safely.

The results of the current study provide evidence for the safety of continuing elective esophageal cancer surgery, and potentially all other major cancer surgery, during the ongoing COVID-19 pandemic under the condition that a secure screening protocol is in place for patients undergoing esophageal cancer surgery.

Future

A study concluded that up to 72% of all adult elective surgery was cancelled globally during the first twelve weeks of the COVID-19 pandemic[4]. Additionally, almost 38% of all cancer surgery has been postponed. There are no studies yet indicating tumor progression or worse overall survival because of postponement of cancer surgery. However, one might expect this relationship to be present. Recently, a study analyzed the progression of gastrointestinal tumors in patients presenting during the COVID-19 pandemic. Patients with gastric cancer underwent less surgery and were diagnosed with more lymph node (pN+) and distant metastases (cM1)[5]. This study indicates the importance of continuing cancer surgery and our study provides the evidence that it can be performed safely with adequate preoperative screening methods.

Currently most countries worldwide are going through a second COVID-19 wave and some are even facing a potential third one. These new waves are characterized by the introduction of new SARS-CoV-2 variants, which have an even higher transmissibility. Therefore, hospitals may face increased numbers of COVID-19 patients in the coming months, which will affect surgical and ICU capacities. However, with use patient selection and adequate preoperative screening methods, elective cancer surgery can be continued. Tumor progression because of postponement of surgical care or the use of less effective alternative treatment options could be prevented.

References

1. Nepogodiev D, Glasbey JC, Li E, et al. Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study. *Lancet*. 2020;0(0). doi:10.1016/S0140-6736(20)31182-X
2. Puylaert CAJ, Scheijmans JCG, Borgstein ABJ, et al. Yield of Screening for COVID-19 in Asymptomatic Patients Prior to Elective or Emergency Surgery Using Chest CT and RT-PCR (SCOUT). *Ann Surg*. 2020;Publish Ah. doi:10.1097/sla.0000000000004218
3. Borgstein ABJ, Brunner S, Hayami M, et al. Safety of Esophageal Cancer Surgery During the First Wave of the COVID-19 Pandemic in Europe: a Multicenter Study. *Ann Surg Oncol.* 2021. In Press.
4. Elective surgery cancellations due to the COVID-19 pandemic: global predictive modelling to inform surgical recovery plans. *Br J Surg*. June 2020. doi:10.1002/bjs.11746
5. Cai M, Wang G, Wu Y, Wang Z, Wang G, Tao K. Study of the gastrointestinal tumor progression during the COVID-19 epidemic in Wuhan. *Br J Surg*. 2020;107(11):e502-e503. doi:10.1002/bjs.11965

Summary in Dutch

Dit proefschrift getiteld 'stadiëring en chirurgische behandeling van het maagcarcinoom; chirurgie tijdens de COVID-19 pandemie' bestaat uit twee delen.

Deel I: stadiëring en chirurgische behandeling van het maagcarcinoom

In **hoofdstuk 2** is de waarde van de diagnostische laparoscopie bij de stadiëring van het maagcarcinoom onderzocht. Hierbij is gekeken naar het percentage onnodige chirurgie (open-dicht) in twee cohorten. Patiënten met en zonder een diagnostische laparoscopie werden vergeleken in een populatie-gebaseerde cohortstudie. Het percentage onnodige chirurgie was hoger in de groep met patiënten die een diagnostische laparoscopie had ondergaan voordat zij een potentiële gastrectomie ondergingen. Deze resultaten geven aan dat vooral patiënten met een hoger tumor stadium een diagnostische laparoscopie ondergaan. Daarnaast suggereren de uitkomsten beperkte sensitiviteit van de diagnostische laparoscopie om peritoneale metastases vast te stellen. In **hoofdstuk 3** is de diagnostische nauwkeurigheid van de diagnostische laparoscopie onderzocht. Diagnostische laparoscopie is belangrijk bij de stadiering van het maagcarcinoom, mede door een hoge nauwkeurigheid voor het vaststellen van een niet curatief maagcarcinoom. Hierdoor kan voorkomen worden dat patiënten een onnodige behandeling ondergaan.

De curatieve behandeling van een maagcarcinoom bestaat uit perioperatieve chemotherapie gevolgd door een gastrectomie. De toevoeging van chemotherapie zorgt voor een betere overlevingskans. Echter, in de studies die deze betere overlevingskans laten zien, zijn vooral jongere patiënten (<70 jaar oud) geïncludeerd. In **hoofdstuk 4** is de waarde van neoadjuvante chemotherapie bij oudere patiënten (>75 jaar oud) met een maagcarcinoom onderzocht. De lange termijn overleving was gelijk voor patiënten met en zonder chemotherapie die een gastrectomie hadden ondergaan. Hoe ouder de patiënt, hoe kleiner het percentage dat aan chirurgie toekomt na chemotherapie. Meer dan 25% van patiënten ouder dan 80 jaar kreeg na de chemotherapie geen operatie.

Naast een gastrectomie wordt er een D2 lymfadenectomie en omentectomie uitgevoerd bij de curatieve chirurgische behandeling van het maagcarcinoom. Er is echter weinig bewijs voor een betere overleving na het routinematig uitvoeren van de omentectomie. In de OMEGA-studie is onderzocht hoe vaak omentale metastasen voorkwamen bij patiënten met een maagcarcinoom. 5 uit 100 patiënten hadden omentale metastases, en allen hadden een tumor in een ver gevorderd stadium. In **hoofdstuk 5** zijn de lange termijn uitkomsten van de OMEGA-studie onderzocht. De gemiddelde overleving was significant slechter voor patiënten met omentale metastasen, ondanks het uitvoeren de omentectomie. Deze resultaten laten zien dat het standaard uitvoeren van een omentectomie tijdens gastrectomie mogelijk niet bijdraagt aan een betere overlevingskans.

Deel II: chirurgie tijdens de COVID-19 pandemie

De COVID-19 pandemie heeft een grote invloed gehad op de mogelijkheid om electieve chirurgie te kunnen uitvoeren, mede door de onzekerheid omtrent de veiligheid van patiënten en omdat medische middelen werden ingezet om COVID-19 patiënten te behandelen. Preoperatieve screening strategieën middels RT-PCR werden geïntroduceerd om chirurgische zorg veilig te kunnen continueren tijdens de pandemie. In **hoofdstuk 6** is de opbrengst van het standaard screenen met RT-PCR voor COVID-19 in asymptomatische patiënten voor electieve en spoedoperaties onderzocht. Ongeveer 1% van alle asymptomatische patiënten testten preoperatief positief voor COVID-19. Dit percentage steeg tot ongeveer 6% in samenhang met stijgende prevalentie van COVID-19 in Nederland.

Ongeveer 20% van alle COVID-19 patiënten presenteert zich met gastro-intestinale klachten, naast pulmonale symptomen. Gedurende het begin van de COVID-19 pandemie hebben verschillende centra standaard de combinatie CT-thorax-abdomen ingezet om mogelijke COVID-19 infecties te detecteren bij patiënten die zich presenteerde met acute buikklachten op de spoedeisende hulp. In **hoofdstuk 7** is de opbrengst van COVID-19 detectie middels CT-thorax-abdomen bij patiënten met acute buikklachten op de spoedeisende hulp onderzocht. De opbrengst was zeer laag, met een extra detectie van COVID-19 in 1% van de geïncludeerde patiënten.

Met behulp van preoperatieve screening methodes kon electieve chirurgie gecontinueerd worden tijdens de COVID-19 pandemie. De veiligheid van deze strategie moest echter wel onderzocht worden. In **hoofdstuk 8 en 9** is de veiligheid van het uitvoeren van electieve gastro-oesofageale kanker chirurgie tijdens de COVID-19 pandemie onderzocht. Hieruit bleek dat de operaties veilig konden worden uitgevoerd, en het percentage postoperatieve complicaties en mortaliteit waren vergelijkbaar met uitkomsten van voor de COVID-19 pandemie.

De COVID-19 pandemie heeft ervoor gezocht dat patiënten minder snel naar het ziekenhuis kwamen, waardoor het zogeheten *pre-hospital delay* toenam. Hierdoor werd het natuurlijke beloop van verschillende ziekten beïnvloedt. In **hoofdstuk 10** is het natuurlijke beloop van appendicitis acuta onderzocht. Twee cohorten werden met elkaar vergeleken, een COVID-19 en een pre-COVID-19 cohort. Het percentage acute appendicitis was lager in de COVID-19 cohort, maar het percentage patiënten dat zich in een later stadium presenteerde en een gecompliceerde appendicitis acuta had was hoger in deze cohort. Patiënten die zich in een later stadium presenteerden waren ouder en hadden meer postoperatieve complicaties.

List of publications

Alexander B.J. Borgstein, Mark I. van Berge Henegouwen, Wytze Lameris, Wietse J. Eshuis, Suzanne S. Gisbertz. Staging laparoscopy in gastric cancer surgery. A population-based cohort study in patients undergoing gastrectomy with curative intent. European Journal of Surgical Oncology. 2021; *47*(6), 1441-1448.

Alexander B.J. Borgstein*, Kammy Keywani*, Wetse J. Eshuis, Mark I. van Berge Henegouwen, Suzanne S. Gisbertz. Staging laparoscopy in patients with advanced gastric cancer: A single center cohort study. European Journal of Surgical Oncology. 2021; in press. First published online 8 aug 2021. (*shared authorship)

Alexander B.J. Borgstein*, Carl A.J. Puylaert*, Jochem C.G. Scheijmans*, Carline S. Andeweg, Annemarieke Bartels-Rutten, Geerard L. Beets, Mark I. van Berge Henegouwen, Sicco J. Braak, Roy Couvreur, Freek Daams, Hendrik W. van Es., Lotte C. Franken, Brechtje A. Grotenhuis, Eduard R. Hendriks, Ignace H.J.T. de Hingh, Fieke Hoeijmakers, Joris T. ten Holder, Peter M. Huisman, Geert Kazemier, Floortje van Kesteren, Kammy Keywani, Sara Z. Kuiper, Maurits D.J. Lange, Mark E. Lobatto, Arthur W. F. du Mée, Martijn Poeze, Elise M. van Praag, Jorit van Rossen, Hjalmar C. van Santvoort, Wouter J.A. Sedee, Leonard W.F. Seelen, Sarah Sharabiany, Nico L. Sosef, Marian J.R. Quanjel, Jeroen Veltman, Tim Verhagen, Vincent C.J. de Vlasakker, Pepijn D. Weeder, Jochem R. van Werven, Nina J. Wesdorp, Susan van Dieren, Alvind X. Han, Colin A. Russell, Menno D. de Jong, Patrick M. M. Bossuyt, Jet M.E. Quarles van Ufford, Mathias W. Prokop, Suzanne S. Gisbertz, Jan M. Prins, Marc G. Besselink, Marja A. Boermeester, Hester A. Gietema, Jaap Stoker. Yield of screening for COVID-19 in asymptomatic patients before elective or emergency surgery using chest CT and RT-PCR (SCOUT). Annals of Surgery. 2020. *272*(6), 919. (*shared authorship).

Alexander B.J. Borgstein*, Jochem C.G. Scheijmans*, Carl A.J. Puylaert, K. Keywani, Mark E. Lobatto, Ricardo G. Orsini, Tjalco van Rees Veillinga, Jorit van Rossen, Maeke J. Scheerder, Rogier P. Voermans, Alvin X. Han, Colin A. Russell, Jan M. Prins, Hester A. Gietema, Jaap Stoker, Marja A. Boermeester, Suzanne S. Gisbertz, Marc G. Besseling. Yield of adding chest CT to abdominal CT to detect COVID-19 in patients presenting with acute gastrointestinal symptoms (SCOUT-3). Annals of Surgery. 2020. Published online. (*shared authorship).

Alexander B.J. Borgstein*, Jochem C.G. Scheijmans*, Carl A.J. Puylaert, Wouter J. Bom, Said Bachiri, Eduard A. van Bodegraven, Amarins T.A. Brandsma, Floor M. ter Brugge, Steve M.M. de Castro, Roy Couvreur, Lotte C. Franken, Marcia P. Gaspersz, Michelle R. de Graaff, Hannah Groenen, Suzanne C. Kleipool, Toon J.L. Kuypers, Milou H. Martens, David M. Mens, Ricardo G. Orsini, Nando J.M.M. Reneerkens, Thomas Schok, Wouter J.A. Sedee, Shahzad Tavakoli Rad, José H. Volders, Pepijn D. Weeder, Jan M. Prins, Hester A. Gietema, Jaap Stoker, Suzanne S. Gisbertz, Marc G. Besselink, Marja A. Boermeester. Impact of the COVID-19 pandemic on

incidence and severity of acute appendicitis: a comparison between 2019 and 2020. BMC Emergence Medicine. 2021. 21.1: 1-10. (*shared authorship).

Alexander B.J. Borgstein*, Stefanie Brunner*, Masaru Hayami, Johnny Moons, Hans Fuchs, Wietse J. Eshuis, Suzanne S. Gisbertz, Christiane J. Bruns, Philippe Nafteux, Magnus Nilsson, Wolfgang Schröder, Mark I. van Berge Henegouwen. Safety of esophageal cancer surgery during the first wave of the COVID-19 pandemic in Europe: a multicenter study. Annals of Surgical Oncology. 2021. 28; 4805-4813. (*shared authorship)

Alexander B.J. Borgstein, Djamila Boerma, Stijn van Esser, Wietse J. Eshuis, Mark I. van Berge Hengouwen, Johanna W. van Sandick, Suzanne S. Gisbertz. Omentectomy as part of radical surgery for gastric cancer: 5-year follow-up results of a multicenter prospective cohort study. Submitted for publication.

Alexander B.J. Borgstein*, Kammy Keywani*, Wietse J. Eshuis, Kathelijn S. Versteeg, Sarah Derks, Hanneke W.M. van Laarhoven, Suzanne S. Gisbertz, Rob H.A. Verhoeven, Mark I. van Berge Henegouwen. Neoadjuvant chemotherapy in elderly patients with gastric cancer undergoing surgery: a population-based cohort study. Submitted for publication. (*shared authorship).

Mohammed Alasmar, Afsana Kausar, **Alexander B.J. Borgstein**, Johnny Moons, Sophie Doran, Stefano de Pascale, Rafael Restrepo, Appollonia Verrengia, Mariella Alloggio, Ana Moro Delgado, Sacheen Kumar, Ismael Díez del Val, Simone Giocapuzzi, Gian Luca Baiocchi, Marta de Vega Irañeta, Gabriel Salcedo, Peter Vorwald, Uberto Fumagalli Romario, Philippe Nafteux, Suzanne S. Gisbertz. Mohammed Asif Chaudry, Bilal Alkhaffaf. Is re-inotroducing major open and minimally invasive surgery during COVID-19 safe for patients and healthcare workers? An international multicenter cohort study in the field of oesophago-gastric surgery. Annals of Surgical Oncology. 2021. 29; 4816-4826.

Alexander B.J. Borgstein, Mark I. van Berge Henegouwen. ASO author reflections: safery of perfoming esophageal cancer surgery during the first wave of the COVID-19 pandemic in Europe: a multicenter study. Annals of Surgical Oncology. 2021. 28; 4814-4815.

Alexander B.J. Borgstein, Wietse J. Eshuis, Suzanne S. Gisbertz, Mark I. van Berge Henegouwen. Robotic sentinel lymph node procedure after endoscopic submucosal dissection of high risk early gastric cancer: a case report. International journal of cancer science & therapy. 2020.

COVIDSurg Collaborative, **Alexander B.J. Borgstein**, Mortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study. The Lancet. 2020. 396 (10243). 27-38.

List of contributing authors

C.S. Andeweg, MD, PhD
Department of Surgery
St Jansdal Hospital, Harderwijk, The Netherlands

S. Bachiri, MD
Department of Surgery
Noordwest Hospital Group, Alkmaar, The Netherlands

A. Bartels-Rutten, MD, PhD
Department of Radiology
Netherlands Cancer Institute, Amsterdam, The Netherlands

G.L. Beets, MD, PhD
Department of Surgical Oncology
Netherlands Cancer Institute, Amsterdam, The Netherlands

Prof. M.I. van Berge Henegouwen, MD, PHD
Department of Surgery
Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

Prof. M.G. Besselink, MD, PhD
Department of Surgery
Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

E.A. van Bodegraven, MD
Department of Surgery
Albert Schweitzer Hospital, Dordrecht, The Netherlands

D. Boerma, MD, PhD
Department of Surgery
St. Antonius Hospital, Nieuwegein, The Netherlands

Prof. M.A. Boermeester, MD, PhD
Department of Surgery
Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

W.J. Bom, MD
Department of Surgery
Amsterdam UMC, Amsterdam Gastroenterology Endocrinology Metabolism, University of Amsterdam, Amsterdam, The Netherlands

Prof. P.M.M. Bossuyt, PhD
Department of Clinical Epidemiology, Biostatistics and Bioinformatics
Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

S.J. Braak, MD, PhD
Department of Radiology
Hospital Group Twente, Almelo, The Netherlands

A.T.A. Brandsma, MD
Department of Surgery
Isala Hospital, Zwolle, The Netherlands

F.M. ter Brugge, MD
Department of Surgery
Hospital Group Twente, Almelo, The Netherlands

S. Brunner, MD
Department of General, Visceral, Cancer and Transplantation Surgery
University Hospital of Cologne, Cologne, Germany

Prof. C.J. Bruns, MD, PhD
Department of General, Visceral, Cancer and Transplantation Surgery
University Hospital of Cologne, Cologne, Germany

S.M.M. de Castro, MD, PhD
Department of Surgery
OLVG, Amsterdam, The Netherlands

R. Couvreur, MD
Department of Surgery
Haaglanden Medical Center, Den Haag, The Netherlands

F. Daams, MD, PhD
Department of Surgery
Cancer Center Amsterdam UMC, VU University Amsterdam, The Netherlands

S. Derks, MD, PhD,
Department of Medical Oncology
Cancer Center Amsterdam, Amsterdam UMC, VU University Medical Center, Amsterdam, The Netherlands

S. van Dieren, PhD
Department of Surgery
Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

H.W. van Es, MD, PhD
Department of Radiology
Sint Antonius Hospital, Nieuwegein, The Netherlands

W.J. Eshuis, MD, PhD
Department of Surgery
Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

S. van Esser, MD, PhD
Department of Surgery
Reinier de Graaf Gasthuis, Delft, The Netherlands

L.C. Franken, MD, PhD
Department of Surgery
Flevo Hospital, Almere, The Netherlands

Prof. H. Fuchs, MD, PhD
Department of General, Visceral, Cancer and Transplantation Surgery
University Hospital of Cologne, Cologne, Germany

M.P. Gaspersz, MD, PhD
Department of Surgery
Maasstad Hospital, Rotterdam, The Netherlands

H.A. Gietema, MD, PhD
Department of Radiology
Maastricht UMC+, Maastricht, The Netherlands

S.S. Gisbertz, MH, PHD
Department of Surgery
Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

M.R. de Graaff, MD
Department of Surgery
Gelre Hospitals, Apeldoorn, The Netherlands

B.A. Grotenhuis, MD, PhD
Department of Surgical Oncology
Netherlands Cancer Institute, Amsterdam, The Netherlands

H. Groenen, MD
Department of Surgery
Tergooi Hospitals, Hilversum, The Netherlands

A.X Han, PhD
Laboratory of Applied Evolutionary Biology Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

M. Hayami, MD, Phd
Division of Surgery, Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinskja Institutet and Department of Upper Abdominal Diseases Karolinska University Hospital, Stockholm, Sweden

E.R. Hendriks, MD
Department of Surgery Tergooi Hospitals, Hilversum, The Netherlands

I.H.J.T. de Hingh, MD, PhD
Department of Surgery Catharina Hospital, Eindhoven, The Netherlands

F. Hoeijmakers, MD
Department of Surgery Dijklander Hospital, Hoorn, The Netherlands

J.T. ten Holder, MD
Department of Pulmonary Medicine Haaglanden Medical Center, Den Haag, The Netherlands

P.M. Huisman, MD
Department of Radiology Tergooi Hospitals, Hilversum, The Netherlands

Prof. G. Kazemier, MD, PhD
Department of Surgery Cancer Center Amsterdam UMC, VU University Amsterdam, Amsterdam, The Netherlands

F. van Kesteren, MD, PhD
Department of Radiology Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

J. van Kesteren, MD
Department of Surgery Dijklander Hospital, Hoorn, The Netherlands

K. Keywani, MD
Department of Surgery Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

S.C. Kleipool, MD
Department of Surgery OLVG, Amsterdam, The Netherlands

S.Z. Kuiper, MD
Department of Surgery Maastricht UMC+, Maastricht, The Netherlands

T.J.L. Kuypers, MD
Department of Surgery Elisabeth - Tweesteden Hospital, Tilburg, The Netherlands

Prof. H.W.M. van Laarhoven, MD, PhD
Department of Medical Oncology Cancer Center Amsterdam, Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, The Netherlands

W. Lameris, MD, PhD
Department of Surgery Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

M.D.J. Lange, MD
Department of Surgical Oncology Netherlands Cancer Institute, Amsterdam, The Netherlands

M.E. Lobatto, MD, PhD
Department of Radiology
Spaarne Gasthuis, Haarlem and Hoofddorp, The Netherlands

M.H. Martens, MD, PhD
Department of Surgery
Zuyderland Medical Center, Sittard-Geleen/ Heerlen, The Netherlands

A. du Mée, MD
Department of Radiology
Amphia Hospital, Breda, The Netherlands

D.M. Mens, BSc
Department of Surgery
Amphia Hospital, Breda, The Netherlands

J. Moons, MSc
Department of Surgery
Universitair Ziekenhuis Leuven, Leuven, Belgium

Prof. P. Nafteux, MD, PhD
Department of Surgery
Universitair Ziekenhuis Leuven, Leuven, Belgium

Prof. M. Nilsson, MD, PhD
Division of Surgery, Department of Clinical Science, Intervention and Technology (CLINTEC), Karolinskja Institutet and Department of Upper Abdominal Diseases Karolinska University Hospital, Stockholm, Sweden

R.G. Orsini, MD, PhD
Department of Surgery
Maastricht UMC+, Maastricht, The Netherlands

Prof. M. Poeze, MD, PhD
Department of Surgery
Maastricht UMC+, Maastricht, The Netherlands

E.M. van Praag, BSc
Department of Surgery
Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

Prof. J.M. Prins, MD, PhD
Department of Internal Medicine, Division of Infectious Diseases
Amsterdam Institute for Infection and Immunity (AI&II), Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

W.M. Prokop, MD, PhD
Department of Radiology
RadboudUMC, Nijmegen, The Netherlands

C.A.J. Puylaert, MD, PhD
Department of Radiology and Nuclear Medicine, Amsterdam Gastroenterology Endocrinology Metabolism
Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

T. van Rees Veillinga, MD
Department of Radiology
Haaglanden Medical Center, Den Haag, The Netherlands

N.J.M.M. Reneerkens, MD
Department of Surgery
Dijklander Hospital, Hoorn, The Netherlands

J. van Rossen, MD
Department of Radiology
Hospital Group Twente, Almelo, The Netherlands

J.W. van Sandick, MD, PhD
Department of Surgical Oncology
Netherland Cancer Institute- Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands

Prof. H.C. van Santvoort, MD, PhD
Department of Surgery
UMC Utrecht Cancer Center, UMC Utrecht, The Netherlands

J.C.G. Scheijmans, MD
Department of Surgery, Amsterdam Gastroenterology Endocrinology Metabolism
Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

M.J. Scheerder, MD
Department of Radiology and Nuclear Medicine. Amsterdam Gastroenterology Endocrinology Metabolism
Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

Prof. W. Schröder, MD, PhD
Department of General, Visceral, Cancer and Transplantation Surgery
University Hospital of Cologne, Cologne, Germany

T. Schok, MD
Department of Surgery
VieCuri Medisch Centrum for Noord-Limburg, Venlo, The Netherlands

W.J.A. Sedee, MD
Department of Emergency Medicine
St Jansdal Hospital, Harderwijk, The Netherlands

L.W.F. Seelen, MD
Department of Surgery
Sint Antonius Hospital, Nieuwegein, The Netherlands

S. Sharabiany, MD
Department of Surgery
Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

N.L. Sosef, MD
Department of Surgery
Spaarne Gasthuis, Haarlem and Hoofddorp, The Netherlands

Prof. J. Stoker, MD, PhD
Department of Radiology and Nuclear Medicine
Amsterdam Gastroenterology Endocrinology Metabolism, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

S. Tavakoli Rad, MD
Department of Surgery
Sint Antonius Hospital, Nieuwegein, The Netherlands

M.J.R. Quanjel, MD, PhD
Department of Pulmonary Medicine
Sint Antonius Hospital, Nieuwegein, The Netherlands

J. Veltman, MD, PhD
Department of Radiology
Hospital Group Twente, Almelo, The Netherlands

T. Verhagen, MD
Department of Surgery
Hospital Group Twente, Almelo, The Netherlands

R.H.A. Verhoeven, PhD
Department of Research and Development, Netherlands Comprehensive Cancer Organization (INKL) Utrecht, The Netherlands
Department of Medical Oncology, Amsterdam UMC, University of Amsterdam, Cancer Centre Amsterdam, Amsterdam, The Netherlands

K.S. Versteeg, MD
Department of Medical Oncology
Amsterdam UMC, Cancer Center Amsterdam, Amsterdam, The Netherlands

V.C.J. van de Vlasakker, MD
Department of Surgery
Catharina Hospital, Eindhoven, The Netherlands

R.P Voermans, MD, PhD
Department of Gastroenterology & Hepatology
Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

J.H. Volders, MH, PhD
Department of Surgery
Rijnstate Hospital, Arnhem, The Netherlands

P.D. Weeder, MD
Department of Surgery
Spaarne Gasthuis, Haarlem and Hoofddorp, The Netherlands

J.R. van Werven, MD, PhD
Department of Radiology
Amphia Hospital, Breda, The Netherlands

N.J. Wesdorp, MD
Department of Surgery
Cancer Center Amsterdam UMC, VU University Amsterdam, Amsterdam, The Netherlands

H.M.E. Querles van Ufford, MD, PhD
Department of Radiology
Haaglanden Medical Center, Den Haag, The Netherlands

PhD portfolio

Name PhD student:	A.B.J. Borgstein
PhD period:	November 2019 – November 2021
Names of PhD supervisors:	Prof. dr. M.I. van Berge Henegouwen, Prof. dr. M.G. Besselink
Names of co-supervisor(s):	dr. S.S. Gisbertz, dr. W.J. Eshuis

1. PhD training

	Year	ECTS
General courses		
• Practical Biostatistics	2020	1.4
Seminars, workshops and master classes		
• Annual retreat, Cancer Centre Amsterdam	2020	0.5
• Weekly Upper GI research meeting, Amsterdam UMC	2019-2021	1.0
Presentations		
• Staging laparoscopy in gastric cancer surgery. A population-based cohort study in patients undergoing gastrectomy with curative intent, *Wetenschapsdag Chirurgie, Amsterdam, 2020*	2020	0.5
• Staging laparoscopy in gastric cancer surgery. A population-based cohort study in patients undergoing gastrectomy with curative intent, *Digestive Disease Days, Veldhoven, 2020*	2020	0.5
• Staging laparoscopy in gastric cancer surgery. A population-based cohort study in patients undergoing gastrectomy with curative intent, *CCA, Noordwijkerhout, 2020*	2020	0.5
• Staging laparoscopy in gastric cancer surgery. A population-based cohort study in patients undergoing gastrectomy with curative intent, *Wetenschapsdag Chirurgie, Amsterdam, 2020*	2020	0.5
• Staging laparoscopy in gastric cancer surgery. A population-based cohort study in patients undergoing gastrectomy with curative intent, *The European Association of Endoscopic Surgery, Krakow, 2020*	2020	0.5
• Safety of esophageal cancer surgery during the first wave of the COVID-19 pandemic in Europe: a multicenter study, *The Royal Australasian College of Surgeons Annual Scientific Congress , virtual congress, 2021*	2021	0.5
• Safety of esophageal cancer surgery during the first wave of the COVID-19 pandemic in Europe: a multicenter study, *The European Society for Diseases of the Esophagus, Milan, 2022*	2022	0.5
(Inter)national conferences		
• Wetenschapsdag Chirurgie, Amsterdam	2019	0.5
• Cancer Center Amsterdam Retreat, Noordwijkerhout	2020	0.5

2. Teaching

	Year	ECTS
Lecturing		
• Weekly Upper GI research meeting, Amsterdam UMC	2020-2021	2.0
Tutoring, Mentoring		
• MD student Kammy Keywani	2020-2022	2.0

Acknowledgements

Met veel plezier heb ik de afgelopen jaren aan dit proefschrift gewerkt. Ik wil graag iedereen bedanken die een bijdrage heeft geleverd aan dit proefschrift en zonder wie dit proefschrift niet tot stand was gekomen. Ik wil een aantal mensen daarnaast in het bijzonder bedanken.

Mijn promotor **Prof. dr. van Berge Henegouwen, beste Mark,** jij hebt mij de kans gegeven om al tijdens mijn coschappen te starten met onderzoek binnen de UpperGI groep. Wat begon als een wetenschappelijke stage ging over in een mooi promotietraject. Vanaf het eerste moment voelde ik mij thuis in de onderzoeksgroep, mede door jouw benaderbare en vriendelijke rol als promotor. Dankzij jouw kritische blik op mijn stukken en jouw drive voor het opstarten van nieuwe projecten heb ik mijn proefschrift in een relatief korte periode met succes kunnen afronden. Daarnaast heb ik genoten van de borrels die jij samen met Suzanne hebt georganiseerd.

Mijn promotor **Prof. dr. Besselink, beste Marc**, jij bent betrokken geraakt bij mijn promotietraject toen wij allebei onderdeel uitmaakten van de SCOUT-studiegroep. Mede dankzij jouw inzet, scherpe blik en nieuwe onderzoeksideeën hebben wij als groep in een korte termijn verschillende COVID-19 gerelateerde studies kunnen opzetten en uitvoeren.

Mijn copromotor **dr. Gisbertz, beste Suzanne,** samen met Mark heb jij mij vanaf het begin begeleidt. Mede door jouw enthousiasme en constante drive heb jij mij weten te inspireren. Met jouw oog voor detail heb jij al mijn stukken verbeterd. Ik heb veel geleerd in de periode waarin wij samen onderdeel uitmaakten van de SCOUT-studie groep en waarin wij intens samenwerkten.

Mijn copromotor **dr. Eshuis, beste Wietse**, dank voor jouw begeleiding tijdens mijn promotietraject. Jouw kritische blik heeft veel van mijn studies naar een hoger niveau gebracht.

Leden van mijn promotiecommissie, **Prof. dr. Busch, Prof. dr. Wijnhoven, Prof. dr. van der Peet, Prof. dr. van Delden, Prof. dr. Geerlings,** hartelijk dank dat u mijn proefschrift heeft willen lezen en beoordelen. A special thank you also to **Prof. dr. Roviello** for taking part in my doctorate committee.

Daarnaast alle coauteurs die hebben bijgedragen aan dit proefschrift, dank voor jullie input en nieuwe inzichten.

Alle overige leden van de SCOUT-studie groep, **Prof. dr. Boermeester, Prof. dr. Stoker, Prof. dr. Prins, dr. Gietema,** ik heb met veel plezier met jullie samengewerkt gedurende de eerste maanden van de COVID-19 pandemie. Door het samenbrengen van verschillende specialismen en het werken in hoog tempo aan verschillende studies heb ik veel kunnen

leren. In het bijzonder ook dank aan **Jochem Scheijmans** en **Carl Puylaert** voor de fijne samenwerking en voor onze eindeloze Teams sessies.

Alle collega's van de UppgerGI onderzoeksgroep. **Annelijn,** dank voor de begeleiding tijdens het begin van mijn promotietraject. **Eliza, Minke, Daan, Marianne, Sofie, Nannet, Egle en Maxime,** dank voor de fijne samenwerking en gezelligheid. **Kammy,** ik heb jou eerst als student mogen begeleiden. Jij bent betrokken geweest bij alle SCOUT-studies en wij hebben daarnaast nog enkele studies samen uitgevoerd. Inmiddels heb jij mijn onderzoeksplek overgenomen en ga jij verder met de OMEGA-studie. Dank voor de fijne samenwerking en jouw inzet.

Alle chirurgen en assistenten in het Onze Lieve Vrouwe Gasthuis Oost, bedankt voor de fijne werkomgeving waarin ik mijn eerste klinische ervaring heb kunnen opdoen.

Mijn paranimf en grote broer **Bastiaan,** ik vind het een hele eer en bijzonder dat jij op 18 maart naast mij staat als paranimf. In een grote familie met alleen maar artsen heb jij ervoor gekozen om rechten te studeren en bouw jij aan een succesvolle carrière in Kopenhagen. Dit is iets wat ik bewonder en waar ik veel respect voor heb. Als paranimf hoop ik jou ook een kijkje te hebben gegeven in het werk waar ik de afgelopen jaren mee bezig ben geweest. Ik kijk uit naar mijn volgende reisjes naar Kopenhagen en naar het nieuwe hoofdstuk in jouw leven dat aankomende juni samen met Rikke begint. **Rikke**, jij bent al lang in onze familie en je bent een geweldige schoonzus.

Mijn tweede paranimf **Zachri,** een van mijn beste vrienden sinds de middelbare school. Ik ben ook paranimf geweest tijdens jouw promotie en vindt het fantastisch dat jij nu naast mij staat als mijn paranimf. Wij kunnen samen uren kletsen over de medische wereld en ons onderzoek. Dit is iets waar ik heel erg van kan genieten. Jij hebt dit jaar een volgende stap gezet in jouw carrière met een opleidingsplek bij de plastische chirurgie, wat zeer verdiend is. In navolging van jou hoop ik ook binnenkort in opleiding te komen.

Mijn zusje **Isabelle,** ook jij hebt gekozen voor de geneeskunde en werkt inmiddels alweer een jaar als assistent chirurgie in het Antoni van Leeuwenhoek ziekenhuis. Wij zijn beide geïnteresseerd in de snijdende specialismen en jij hoopt aankomend jaar in opleiding tot KNO-arts te komen. Ik weet zeker dat het je gaat lukken en ik hoop dat wij nog vele jaren samen kunnen werken in de medische wereld.

Mijn (grote) schoonfamilie, **Eveline en John**, jullie hebben altijd veel interesse getoond in mijn werk en zijn nauw betrokken geweest gedurende mijn gehele promotietraject. Jullie hebben altijd goede adviezen en Fré en ik zijn altijd welkom bij jullie, iets waar ik heel dankbaar voor ben. Ik wens jullie veel succes met jullie nieuwe project in Italië. **Boudewijn en Oya,** jullie hebben mijn promotietraject met veel aandacht gevolgd en waren altijd benieuwd naar de nieuwste ontwikkelingen. Ik geniet van onze etentjes waarin ik elke keer een korte samenvatting gaf van de huidige gang van zaken. Dank voor jullie adviezen en betrokkenheid.

Boudy, Janneke, Char en Lucas & Tal, Maarten, Gi, Ly en Dita voor het luisteren naar mijn verhalen over mijn onderzoek en de gezelligheid tijdens etentjes en feestjes.

Al mijn goede vrienden, waaronder **FJ, Oliver, Daan, Jan, Florian, Wessel,** dank voor de gezelligheid en jullie interesse in mijn onderzoek.

Lieve **Mam** en **Pap**, zonder jullie was dit allemaal niet mogelijk geweest. Jullie hebben mij van jongs af aan met de medische wereld in aanraking laten komen en door jullie inspirerende verhalen heb ik ook gekozen voor een leven als arts. Ik kan altijd bij jullie terecht voor adviezen en jullie steunen mij in al mijn keuzes. Jullie hebben mij de mogelijkheid gegeven om verschillende studies te doen wat mij uiteindelijk tot hier heeft gebracht. Ik ben jullie heel erg dankbaar en hoop dat we dit succes op 18 maart groots kunnen vieren.

Mijn lieve **Fréderique**, jij bent zeer betrokken geweest bij mijn promotietraject. Veel van mijn artikelen heb jij doorgelezen en al mijn presentaties heb ik met jou doorgenomen. Jij staat altijd klaar om mijn verhalen aan te horen en weet altijd het juiste tegen mij te zeggen. Door corona hebben wij veel samen thuisgewerkt. De drive en precisie die jij hebt in jouw werk hebben mij geïnspireerd en ik heb daar veel van kunnen leren. Ik ben ontzettend trots op jou en hou van je. Ik kijk uit naar onze toekomst samen.

Curriculum Vitae

Alexander Berend-Jan Borgstein was born on the 16th of June 1992 in Leiden, The Netherlands. He graduated from secondary school at the Kennemer Lyceum in Overveen in 2010. After secondary school he started studying at University College Utrecht, an honours college, where he studied pre-med as part of a bachelor of science. During his bachelor degree, he spent six months at the University of Connecticut in the United States, as part of an exchange program. In 2014, he graduated cum laude from University College Utrecht.

After obtaining his bachelors degree, Alexander started medical school via the "zij-instroom" trajectory at the University of Amsterdam. During his studies, he developed a special interest in surgery. Prior to starting his rotations, he spent three months in Malawi to work at the pediatric surgery department. During his clinical rotations, Alexander began doing research in the field of upper gastrointestinal surgery under the supervision of Prof. dr. van Berge Henegouwen and dr. Gisbertz. After obtaining his medical degree in 2019, he started as a PhD-student under supervision of Prof. dr. van Berge Henegouwen en Prof. dr. Besselink at the University of Amsterdam/Amsterdam Universitair Medisch Centrum. His research focused on staging and surgical treatment of gastric cancer. He was also part of the SCOUT-study group, which investigated the safety of performing surgery during the COVID-19 pandemic.

Alexander is currently working as a surgical resident not in training at the Onze Lieve Vrouwe Gasthuis under supervision of dr. Gerhards.