VEDLEGG TIL BRUKERTUVALGSSAK 45-2020 NOMOGRAM

Protocol: Using Norwegian and US Rectal Cancer Quality of Care Registry Data for Personalized Precision Cancer Care. Development of Nomogram Decision Aids to Optimize Rectal Cancer Treatment

Version: 13th of October 2019

Knut Magne Augestad, MD, PhD
Consultant GI Surgeon
Department of Surgery
Sandnessjøen Regional Hospital
Researcher
Department of Quality and Research
University Hospital North Norway
Tromsø, Norway
knut.magne.augestad@unn.no

Deborah S Keller MS MD FACS, FASCRS
Assistant Professor of Surgery, Division of Colorectal Surgery
New York Presbyterian Hospital-Columbia University Medical Center
New York, USA
dsk2101@cumc.columbia.edu

Arne Engebreth Færden
Associate Professor and Consultant Surgeon
Department of Gastrointestinal Surgery
Akershus University Hospital
Oslo, Norway
Arne.Engebreth.Faerden@ahus.no

Marianne Grønlie Guren MD, PhD
Senior Consultant Oncology
Oslo University Hospital
Oslo, Norway
Member, Norwegian Gastrointestinal Cancer Group (NGICG), Colorectal
Oslo, Norway
UXARUR@ous-hf.no

Samantha Nemeth PhD
Statistician
Population Sciences Group, Herbert Irving Comprehensive Cancer Center
New York Presbyterian Hospital-Columbia University Medical Center
New York, NY 10032
skn2115@cumc.columbia.edu

Inger Kristin Larsen MSc, PhD
Epidemiologist
Department of Registration
The Cancer Registry of Norway
Oslo, Norway
Inger.Kristin.Larsen@kreftregisteret.no

Ravi Kiran, MD, FACS, FASCRS
Kenneth A. Forde Professor of Surgery (in Epidemiology)
Columbia University Medical Center and Mailman School of Public Health
Director, Center for Innovation and Outcomes Research
Chief and Program Director, Division of Colorectal Surgery
New York Presbyterian Hospital-Columbia University Medical Center
New York
rpk2118@cumc.columbia.edu

Attachments to the protocol:

1. The Norwegian Data inspectorate: "Vurdering av personvernkonsekvenser for forskningsprosjekt UNN (DPIA) May 2019".
2. Approval from the Norwegian Data inspectorate May 2019.

Declarations

The authors have no relevant conflicts of interest. The authors have received no external funding sources to support this protocol.

Abstract

Rectal cancer is a complex disease involving treatment options in terms of neoadjuvant, surgery, and adjuvant therapy. The current standards for staging do not consider prognostic factors, which could influence the tumor's response, oncologic outcomes, and the associated best treatment. With the viable treatment options, there is an increased need to personalize the management decisions and tailor treatment to the individual patient's risk profile. During recent years, nomograms have gained increased popularity as important decision aids for cancer patients and clinicians. No work to date has evaluated their impact in rectal cancer decision making across international data. In the proposed project, we plan to use data from two databases (The Norwegian Colorectal Cancer Registry and Division of Colorectal Surgery at Columbia University Medical Center) to develop nomograms for three distinct outcome states: a complete response after neoadjuvant radiochemotherapy (RCT), metastatic disease to the liver, and metastatic disease to the lungs. We envision that these nomograms may be used as essential decision aids to guide precision treatment for rectal cancer. This multi-part proposal is a collaborative project between the Norwegian Colorectal Cancer Registry, University Hospital of North Norway, Norway and Division of Colorectal Surgery, Department of Surgery, New York Presbyterian-Columbia University Medical Center, and could be the gateway to several valuable future works.

Background

Standardization of surgical technique, imparting training, and then evaluating outcomes are the cornerstones of quality improvement in surgery. The Norwegian model sets the standard of care in rectal cancer, with national training programs for TME, population-based registries, and assessment of patient outcomes for continuous quality improvement. [1] Over time, continuous quality improvement has taken place to refine the processes and further improve outcomes for rectal cancer patients. [2,3] One crucial variable introduced amidst these processes is the use of laparoscopic surgery. Other variables, such as improved staging by magnetic resonance imaging (MRI), the advent of multidisciplinary tumor boards to guide management decisions, mandatory standardization of surgical techniques, such as total mesorectal excision (TME), preoperative chemoradiotherapy, and reporting protocols, may also have a significant impact. These consensus-based endpoints have been defined. [2] However, their influence is yet to be fully assessed in a robust dataset with long-term outcomes. As the rest of the world develops processes to assess outcomes with rectal cancer, the Norwegian registry has detailed, mature data allowing an evidence-based analysis of the impact of quality improvement across multiple dimensions in rectal cancer management. From the Norwegian registry data, there is the possibility of addressing outstanding issues, developing future standards for precision cancer care, and making valuable contributions to the existing body of literature. The further specific benefit could be applied to rectal cancer management.

Norway may be a worldwide example of best practices and quality outcomes in rectal cancer surgery. The gold standard for curative resection in rectal cancer is the TME. [4] In

1993, Norway launched a national rectal cancer initiative and implemented the TME as the preferred technique for rectal resections. This conceptual framework became the Norwegian Rectal Cancer Project, and an international example for quality improvement in rectal cancer surgery. [5-7] The TME has resulted in reproducible significant reductions in local recurrence rate and improved disease free and overall survival. [8-11]The performance of a proper TME remains the main prognostic factor for disease recurrence. [12,13] As TME quality of care and the technical aspects of the operative procedure are optimized, other factors that affect the patient outcomes are recognized. Preoperatively, neoadjuvant chemoradiotherapy (nCRT) can have a significant impact on the tumor, and overall outcomes in terms of reduced local recurrence rates. nCRT can downstage 50-60% of tumors, with approximately 10-30% of patients demonstrating a pathologic complete response (pCR). [8,11]The pCR patients have also been shown to have better postoperative outcomes. There is a need to identify the locally advanced cancer patients who will have a complete response to nCRT, as there is the potential to avoid over-treatment and unnecessary surgery. Postoperatively, we know that numerous clinicopathological and treatment variables are strong predictors of recurrent disease, including rectal cancer tumor height, TNM stage, nodal involvement, venous invasion, and circumferential resection margin (CRM). [14-16] The present challenge is to tailor the treatment and identify patients that have the most substantial benefit of a certain treatment choice. The current standards for staging, the American Joint Committee on Cancer (AJCC) TNM staging manual, does not incorporate many critical patient and tumor specific prognostic factors, such as sex, age, tumor size, primary site, pre-treatment carcinoembryonic antigen (CEA), tumor deposits, circumferential resection margin (CRM), primary tumor grade, primary T

category, and primary N category, and tumor regression after neoadjuvant therapy. By using a model that takes into account the above-mentioned factors along with TNM stage, clinicians may have the ability to accurately predict the tumor response to treatment, metastasis, and survival outcomes.

A nomogram is a simple graphical representation of complex mathematical formulas that use disease characteristics to determine an individualized prognosis. Nomograms serve as decision aids that may be used in a personalized medicine model to predict future events. [17] In surgery, nomograms have been described that combine several independent factors to build a statistical model for estimating prognosis in multiple malignancies, including colorectal cancer, and for patient counseling of prognosis. Recent relevant publications have described developing nomograms to predict the recurrence of colon cancer, the incidence of metachronous postoperative colorectal lesions, 1- and 3-year overall survival and cancer-specific survival in patients with colorectal cancer liver metastases (CRLM), and survival in in locally recurrent colon cancer and curatively resected colorectal cancer. [18-22]

As nomograms can account for common clinicopathologic factors and expanded tumor and patient heterogeneity, they may provide a more individualized outcome prediction and prognostication than current staging system. [17] With the rich, personalized data able to be incorporated into the modeling, nomograms can provide a more individualized outcome prediction and could aid clinicians and patients in the treatment decision-making process. We believe that the data aggregated in the Norwegian Colorectal Cancer Registry

represents an excellent source for the development of nomogram and decision aids for rectal cancer treatment.

Objectives

Our objective is to develop decision aids (nomograms) that can be used to personalize rectal cancer treatment. Our hypothesis is that accurate nomogram can be created for these risk factors. These nomograms may be used as e-health decision aids in the multidisciplinary treatment of rectal cancer and provide a more individualized outcome prognostication than that afforded by the current staging system and clinicopathologic factors considered. It may also become an excellent supportive tool in the shared decision-making setting. This means that the specific objectives for this study are:

1) To determine potentiating factors for a) complete response (pCR) after neoadjuvant chemoradiotherapy.

2) To determine the risk factors for metastatic recurrence (local recurrence and distant metastases) of rectal cancer.

3) To apply the identified risk factors to develop three separate nomograms: the probability of pCR (preoperatively), the probability of recurrence (local and distant metastases), the probability of lung metastases (postoperatively) and the probability of liver metastases (postoperatively) in rectal cancer.

4) To design the nomogram, using the significant risk factors from the multivariate analyses.

5) To validate the NCR nomogram with a) a split dataset from NCR and b) a US institutional database (New York Presbyterian-Columbia University Medical Center).
6) Compare risk factors from the NCR nomogram with matched data fields from New York Presbyterian-Columbia University Medical Center

Specific Endpoints

Specific endpoints, towards nomogram development, will be:

- To perform a comparative analysis of outcomes with matching fields from an international rectal cancer registry with an institutional quality and outcomes database.
- To identify patient, tumor, clinical, and surgical factors that may predict a pathologic complete response (pCR) in rectal cancer.
- To determine if there are patient, tumor, clinical and surgical factors that predict metastases in the liver and lungs
- To use identified high risk factors to develop three nomograms: probability of complete response, probability of recurrent cancer disease and probability of local recurrence.
- To implement an easily accessible e-health tool for shared decision-making and a multidisciplinary team decision-aid.

We anticipate multiple additional projects will be developed from the collaborative work above, including identifying differences in practice patterns, recurrence patterns, and management in 2 separate countries, describing the predictability of a nomogram,

specifically for the preoperative pCR state- a unique application, and further application of the nomograms developed in prospective trials. The investigators plan to apply for funding to support the future works upon the success of the current proposal.

Study Design

This multipart proposal is based on a retrospective review of a prospectively maintained database, i.e. the Cancer Registry of Norway that will use data abstracted from the registry. All eligible rectal cancer patients will be included, and the basis for the population sample. All data collection is routinely available institutional data that describes the demographics, staging, perioperative, and postoperative outcomes of the patients.

The outcome variables will be compared to a prospective institutional registry in the Division of Colorectal Surgery at Columbia University Medical Center. The HIPAA compliant and IRB-approved database has matching fields from 2013 onward, which can be used for comparative analysis.

After the comparative analysis, registries will be reviewed to identify patients who underwent resection for rectal cancer with curative intent after completing neoadjuvant chemo radiation and had a pathologic complete tumor response (ypT0N0) in the surgical histopathology. In eligible patients, the patient and tumor demographics, and perioperative clinical variables will be assessed. Multivariate regression models will be created to determine the relationship between the patient, tumor, and imaging variables and a pCR.

Study Population

We aim to perform a retrospective longitudinal analysis of data extracted from the Norwegian Colorectal Cancer Registry (NCCR), a disease specific registry within the Cancer Registry of Norway (CRN). In Norway, the CRN is a compulsory database that records all cases of solid malignant tumors. Data from NCCR are linked with data from the Norwegian Death Registry, using the unique personal identification number. A similar system of compulsory reporting of deaths to the Statistics of Norway (Folkehelseregisteret) ensures an accurate death date, including all cancer related deaths. This reporting system ensures that all new cancers are recorded. Patients with locally advanced who underwent curative resection (i.e. T1-4, M0, R0 resection) for rectal cancer through an abdominal approach, from 1st of January 1, 1996 until December 31, 2018, with a follow-up interval of at least one year will be included in analyses.

The New York Presbyterian-Columbia University Medical Center database is a prospectively maintained IRB-approved divisional quality and outcomes database, with detailed patient demographic, intraoperative, and postoperative outcome variables for all patients having abdominal surgery from January 1, 2013 to the present. Columbia University Medical Center is a world leading academic medical center serving a large local, regional and international catchment area of public and private patients in all medical and surgical disciplines. The division of Colorectal Surgery at Columbia University Medical Center is comprised of 7 board certified colorectal surgeons that perform approximately 600 abdominal resections and 1200 anorectal procedures for benign and malignant colorectal disease annually. The institutional database provides over 300 variables that describe the patient, preoperative risk status, diagnosis, procedure, and outcome metrics

after surgery, in a data capture more detailed than available from any population or administrative databases. The database is maintained in real-time by the research team at the Division of Colorectal Surgery at Columbia University Medical Center and Center for Innovations and Outcomes Research center on a Columbia University Medical Center server, with all associated security measures.

Detailed Subject Eligibility

Inclusion criteria:

1. Subjects with stages I-III rectal cancer adenocarcinoma with a colorectal resection and have records in the Cancer Registry of Norway or in the Department of Colorectal Surgery at New York Presbyterian-Columbia University Medical Center
2. Subjects who are 18 years of age and older
3. The colorectal resection was performed via an abdominal approach.
4. Subjects of either gender
5. For the pCR component:
    a. Clinically staged locally advanced disease that is selected to receive long course neoadjuvant chemo-radiotherapy with a subsequent restaging with pelvic MRI and curative resection through an abdominal approach.
6. For the metastatic component
    a. Curatively resected (i.e. T1-4, R0, M0) rectal cancer patients enrolled in a follow-up program.

Exclusion criteria:

1. Patients under 18 years of age
2. Patients with incomplete medical records for the outcomes of interest, including tumor pathology, histology, and survival outcomes
3. Patients that underwent a procedure through an endoscopic or transanal approach only.
4. Non-operative treatment

Data Collection

A special advisor at the Cancer Registry of Norway (Kristin Oterholt Knudsen), is in charge of the data collection. The surgical information below will be collected as part of this study. The variables are however not limited to this, and we aim to include any variable information pertaining to the nomogram validity, i.e.

- Year of diagnosis
- Number of rectal cancer cases performed for curative intent
- Patient Demographics (age, gender, hospital of surgery)
- Date of primary surgery
- Preoperative staging information, including the initial MRI staging and results (anal verge distance to tumor, anal verge group, tumor location, fixed tumor)
- Use of neoadjuvant chemoradiotherapy and adjuvant chemotherapy radiotherapy (radiotherapy dose)
- Diagnosis and clinical TNM staging
- Name of procedure
- Operative details (Surgical method; Conversion; Perforation during surgery, Diverting stoma; TME)

- Postoperative details (Anastomosis leakage; Complication, Reoperation, and Mortality rates within 30 days; Adjuvant radiochemotherapy)
- Oncologic details (TME grade, Histology/ Differentiation, Staging; (ypTNM); Distal margin, Lymph node statuses; Residual tumor, recurrence site, DFS, OS, Salvage surgery, Other treatment of metastasis (radiochemotherapy), Local Recurrence, Date of local recurrence, Date of observed metastases, Localization of metastasis, Date of death, Time from surgery to death, Time from surgery to local recurrence, Time from surgery to observed metastasis.
- Molecular prognostic factors: Microsatellite instability (i.e. repetitive sequences mutation sequences of DNA), KRAS mutations, BRAF proto-oncogene.

Statistical Analysis

The Principal Investigators (Augestad/Keller), will together with statistician Samantha Nemeth at New York Presbyterian Hospital-Columbia University Medical Center, perform statistical analyses and management. Demographic data will be analyzed using students t-test, Chi square or Fishers exact test as appropriate. Normally distributed data will be presented as means +/-SD of the mean, non-normally distributed data will be presented as medians +/- quartiles and categorical data will be presented as raw data and frequencies. Recurrence and survival data will be evaluated using Kaplan-Meier curves. The concordance index (C-index), which can estimate the predicting ability between observed and predicted outcome, will be used to evaluate the discrimination of the nomograms. [19,23] Recurrence and survival data will be evaluated using Kaplan-Meier curves and cox regression. In regression analysis the dependent variables will include the short-term

outcomes, pathological review and long-term outcomes (local pelvic recurrence, metastases in the liver and lungs). The independent variables will include the pre-operative and intra-operative data. A P-value less than 0.05 will be considered statistically significant. We will adhere to the framework for building nomograms as proposed by Iasonos et al (Figure 1). [24]

1. Description of the patient population

The primary patient population will be patients with curatively resected rectal cancers and a record in NCR (see inclusion and exclusion criteria).

2. Define the outcome

Outcomes will be a) Complete response after neoadjuvant radiochemotherapy b) Time to local and distant metastases c) Pelvic local recurrence d) Liver metastases e) Lung metastases (all outcomes are described in detail above).

3. Identify potential covariates

As the intended use of the nomogram is for patient decision support, it is essential that we include variables that are available at predefined time points in the rectal cancer pathway (i.e. preoperative data: will be used to design the nomogram for complete response; preoperative and postoperative data including radio-chemotherapy and surgical management: will be used to construct the nomogram for time to local and distant metastases).

4. Construct the nomogram – statistical package

We will mainly follow the guidelines for using R to construct a nomogram, provided by Zhang et al. [25] The data will be analyzed utilizing SPSS and R, and will be developed based on independent risk factors and using the rms package in R The disease-free survival (i.e.

time to overall recurrence, time to local recurrence, time to distant metastases) will be analyzed using the rcorrp.cens (Hmisc) package in R. The scores of each predictive variable will be calculated using the nomogramEx package in R. (version 3.5.0, R Project for Statistical Computing, Vienna, Austria).

5. Validate the model

a) Internal validation. Initially, we will validate the model on Norwegian data e.i. split the data in two/thirds and build the model on one part of the data and validate the model on the remaining one/third of the data.

b) External validation: It might be challenging to develop a model that works well on both Norwegian and Columbian data. In this situation, we will build the model on data from both Norway and Columbia and split the data into training data and test data. We do however think this part of the project is important, to increase the generalizability. For nomogram validation purposes, approximately 1000 patients with rectal cancer will be included from the Columbia database.

Limitations

As there is no race effect included in the model, and the model will be based on a 90% white Norwegian population, it is not clear that outcomes for a more diverse population with certain comorbidities and risk factors will be accurately predicted from this specific nomogram. If the nomogram was built on patients who underwent surgery and had large tumor lesions, it will not perform as well on patients with small lesions, because they were underrepresented or absent in the original data. A probability will still be estimated by the nomogram, but this estimate may not be relevant. One must be cautious about extrapolating

from regression models built on different populations. Thus, we will initially perform an internal validation of the nomogram, using a split dataset from NCR. Secondly, to increase the generalizability, we will perform an external validation of the nomogram. Towards this, we might experience that the model is not so useful for the setting in Columbia, but still useful for Norwegian patients.

Dissemination plan

Given the timely subject manner, novelty, and potential impact on patient care, widespread dissemination of the results is planned in the surgical and oncologic communities. Submission of abstracts to international, national, and regional conferences with publication of peer-reviewed manuscripts based on above distinct aims. Depending on the strength of the results, higher impact factor journals, are targeted.

Manuscripts

This process involves submitting articles in peer-reviewed journals in order to communicate the research. The first article will identify essential predictors of complete pathological response and develop a nomogram for complete response. The second article will investigate predictors of distant metastases, including location and stage of rectal tumours, and the development of a nomogram for to estimate the probability of metastatic recurrence. The third article will investigate the predictors of local recurrence, and a nomogram to predict local pelvic recurrence.

Workshop

A data session with national and international partners will be arranged to discuss and strengthen the empirical analysis, national, and international collaborative network. The dissemination through the arranged workshop will be done at an early stage in the project in order to discuss the findings in the preliminary phase. This will also establish collaboration partners for further discussions of findings and results.

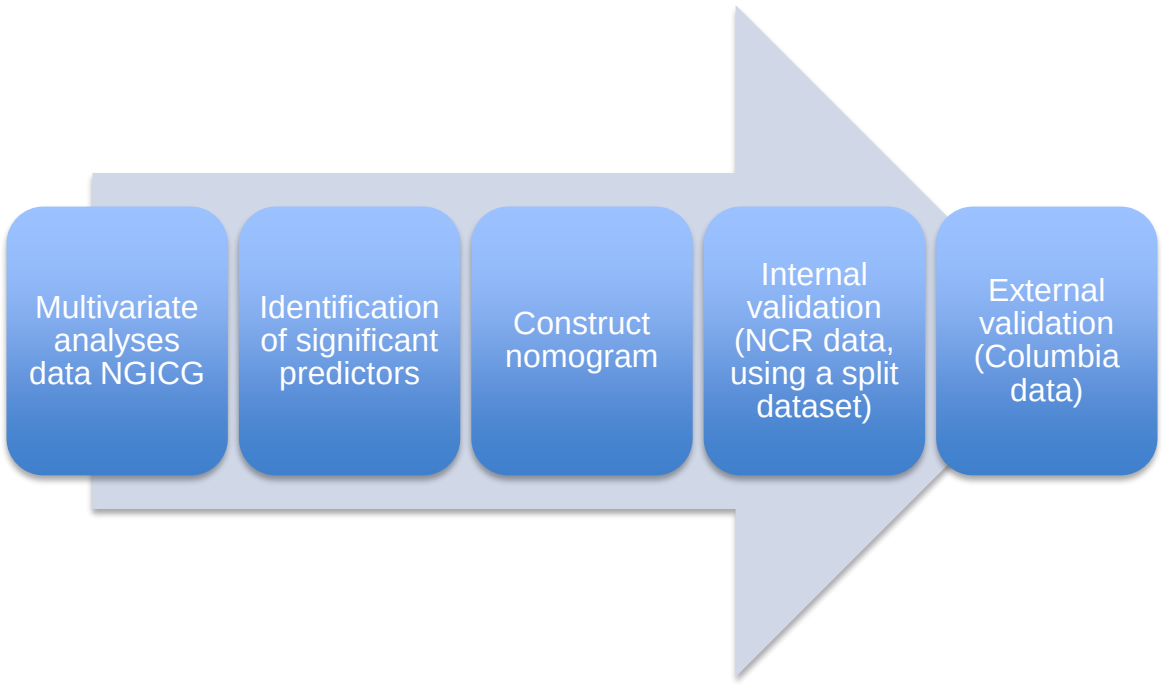

Figure 1. Nomogram development for complete response and distant metastases. The steps suggested by Jasonos et al will be followed. [24] After significant covariates are identified, we will perform an internal validation with a split dataset from NCR. To increase the generalizability, we will then perform an external validation in the New York Presbyterian-Columbia University Medical Center quality registry. Finally we will build a model using both Norweigan and Columbian data.

Waiver of Informed Consent

A waiver of informed consent is not being sought as there is no direct interaction with patients, the research meets no more than minimal risk, the welfare of the participants will not be adversely affected; and the research could not be conducted without the waiver. This is in accordance with the regulations from the Norwegian Data Inspectorate.

Confidentiality – Use of REDCap

Data will be recorded contemporaneously on a dedicated, secure server running the Research Electronic Data Capture (REDCap) web application. [26] REDCap allows collaborators to enter and store data in a secure system. No patient identifiable data (name, date of birth, address, etc) will be recorded on REDCap. Registered local investigators will have individual password-protected access to their unit's data entered on to REDCap. In order to facilitate entry of outcome data, investigators will need a way to link REDCap records to patient records. This will be achieved by keeping a password protected spreadsheet containing a look-up table. This should cross-reference the automatically generated REDCap ID number for each patient, against their local identifier number.

The University Hospital of North Norway will provide administrative support for the project and the REDCap system and will host the system (see the protocol attachment). Many hospitals already use these data collection tools to measure clinical practice and drive improvements in healthcare in multiple disease settings.

The project will adhere to the European Union (GDPR, General Data Protection Regulations), The Cancer Registry of Norway and New York Presbyterian-Columbia

University Medical Center data confidentiality regulations. Data confidentiality will be protected as access to the data output will be restricted and protected. The data will be stored at a secure server (including REDCap) organized by University Hospital of North Norway. The database will be de-identified of private health information. Paper forms will not be used. Only members of the research team will have access to the data. Identifiable information will not be reused or disclosed to any person outside the study, except as identified in an approved protocol or as required by law for authorized oversight of this research study or as specifically approved for use in another study by a review board. The responsibility for data and safety monitoring will be shared by the PI and study team members.

Study Completion

There is no active protocol involving patients for this study. Completion of participation in the study is not applicable. All analysis for study endpoints will be performed from retrospective review of the prospectively maintained registry.

Risks/discomforts

There is no active protocol involving patients for this study. Risks/ discomforts are not applicable.

Data Safety Monitoring Plan/ Adverse Events

There are no therapeutics, devices, or active protocols for this study, thus no adverse events are expected and a safety evaluation plan is not applicable. This study will be monitored to ensure the identification, documentation and analysis of all data, compliance with the protocol, and compliance with the terms of the participating Institutional Review Board (IRB) or Joint Research Office (JRO) to protect the safety and rights of all patients, their personal medical information, and federal and local regulations. Any unforeseen adverse events will be reported to the IRB/ JRO.

International and national partners

The research will be performed in close collaboration with the Cancer Registry of Norway, The Norwegian Colorectal Cancer Registry, and the Division of Colorectal Surgery, Department of Surgery, New York Presbyterian-Columbia University Medical Center. The research group will rely on the research environment and statistical expertise facilitated by the Department of Surgery, New York Presbyterian-Columbia University Medical Center.

Research Group and roles

Principal investigator (PI): *Knut Magne Augestad*, MD, PhD, GI Surgeon and researcher. Visiting Professor of Research, Division of Colorectal Surgery, Department of Surgery, New York Presbyterian-Columbia University Medical Center. Dr. Augestad is a specialist in gastrointestinal and general surgery, and an active researcher with a PhD degree. He has

participated on more than 80 scientific articles (colorectal surgery, surgical education, surgical technology) and has written 6 book chapters.

Co investigator/PI: *Deborah S Keller* MS MD, Assistant Professor of Surgery, Division of Colorectal Surgery, Department of Surgery, New York Presbyterian-Columbia University Medical Center, New York. Dr. Keller is an Assistant Professor in the division of Colon and Rectal Surgery and member of the Cancer Population Sciences Group in the Herbert Irving Comprehensive Cancer Center at Columbia University Medical Center in New York, NY. Dr. Keller is a surgical scientist, with dedicated research interests in enhanced recovery, applying technology to improve surgical quality, socioeconomic issues in colorectal cancer care, and developing standards for rectal cancer management.

Statistician: *Samantha Nemeth*, MPH, Department of Surgery, New York Presbyterian-Columbia University Medical Center, New York. Ms. Nemeth is a graduate of Columbia University's school of Public Health and earned her Masters in Statistics. With a background in health care management and biostatistics, she currently serves the Division of Colorectal Surgery by providing hospital and physician-level analytic reports concerning their CCSOD and administrative and population data sources, including NSQIP and the National Cancer Data Base.

Co-investigator: *Inger Kristin Larsen,* Researcher and lead epidemiologist at the Norwegian Cancer Registry. She has extensive expertise in data handling, data quality and has participated in several major longitudinal studies using data from the Norwegian Cancer Registry.

Co-investigator: *Arne Engebreth Færden,* Consultant and Associate Professor at Akershus University Hospital. Dr Færden has a long reputation as a surgeon and researcher

within the field of colorectal cancer. He is a member of the Norwegian Gastrointestinal Cancer Group - Colorectal (NGICG-CR). In this project he will serve as a liaison between the Principal Investigator and NGICG.

Liaison to the Norwegian Colorectal Cancer Registry - and mentor: *Marianne Grønlie Guren* MD, PhD, Senior Consultant, Department of Oncology, Oslo University Hospital and member of Norwegian Gastrointestinal Cancer Group, Colorectal, Oslo Norway. As a member of the research group in NGICG-CR, she will serve as a liaison between NGICG-CR and the Columbia University Medical Center Research Group.

Main mentor: *Ravi Kiran* MD, FACS, Kenneth A. Forde Professor of Surgery (in Epidemiology), Columbia University Medical Center and Mailman School of Public Health Director, Center for Innovation and Outcomes Research Chief and Program Director, Division of Colorectal Surgery, New York Presbyterian-Columbia. Dr. Ravi P. Kiran is the chief and program director of the Division of Colorectal Surgery at New York-Presbyterian/Columbia University Medical Center. He is also the Director of the Center for Innovation and Outcomes Research in the Department of Surgery, and a Professor in the Mailman School of Public Health at Columbia University.

Main Mentor: Bjørn Møller, Head, Department of Registration, The Cancer Registry of Norway. Dr Bjørn Møller will serve as main mentor and liaison to the Norwegian Cancer Registry.

Acknowledgements

The project will be performed in memory of Dr. Jan Norum MD, PhD, Former Professor of Oncology, UiT – The Arctic University of Norway, Tromsø, Norway.

References

1 Wibe A, Eriksen MT. Total mesorectal excision for rectal cancer – what can be achieved by a national audit? *Colorect Dis*. 2003 Aug 13; **5**: 471–477.

2 Manwaring ML, Ko C, Fleshman JW Jr., Beck DE, Schoetz DJ Jr., Senagore AJ, *et al.* Identification of Consensus-Based Quality End Points for Colorectal Surgery. *Dis Colon Rectum*. 2012 Mar; **55**: 294–301.

3 Wilson M, Collyar D, Chingos T, Oza A. Review of outcomes and endpoints in cancer trials: bridging the divide. *Lancet Oncology*. 2014 Dec 18; **16**: e43–e52.

4 Heald RJ, Husband EM, Ryall RDH. The mesorectum in rectal cancer surgery—the clue to pelvic recurrence? *Br J Surg*. 1982 Oct; **69**: 613–616.

5 Wibe A, Møller B, Søreide O. A National Strategic Change in Treatment Policy for Rectal Cancer— Implementation of Total Mesorectal Excision as Routine Treatment in Norway. A National Audit. *Dis Colon Rectum*. 2002 Oct 23;: 1–10.

6 Wibe A, Carlsen E, Dahl O, Tveit KM, Weedon-Fekjær H, Hestvik UE, *et al.* Nationwide quality assurance of rectal cancer treatment. *Colorectal Dis*. 2006 Mar; **8**: 224–229.

7 Wibe A, Syse A, Andersen E, Tretli S, Myrvold HE, Søreide O, *et al.* Oncological outcomes after total mesorectal excision for cure for cancer of the lower rectum: anterior vs. abdominoperineal resection. *Dis Colon Rectum*. 2004 Jan; **47**: 48–58.

8 Wasmuth H, Rekstad LC, Tranø G. The outcome and the frequency of pathological

complete response after neoadjuvant radiotherapy in curative resections for advanced rectal cancer: a population-based study. *Colorectal Dis*. 2016 Jan; **18**: 67–72.

9 Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, *et al.* Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *Journal of Clinical Oncology*. 2012 Jun 1; **30**: 1926–1933.

10 Glimelius B, Myklebust TÅ, Lundqvist K, Wibe A, Guren MG. Two countries - Two treatment strategies for rectal cancer. *Radiother Oncol*. 2016 Dec; **121**: 357–363.

11 Guren MG, Körner H, Pfeffer F, Myklebust TÅ, Eriksen MT, Edna T-H, *et al.* Nationwide improvement of rectal cancer treatment outcomes in Norway, 1993-2010. *Acta Oncol*. 2015 Nov; **54**: 1714–1722.

12 Heald RJ. Rectal Cancer. The Basingstoke Experience of Total Mesorectal Excision 1978-1997. *Archives of Surgery*. 1998 Oct 17; **133**: 894–899.

13 Martling A, Cedermark B, Johansson H, Rutqvist LE, Holm T. The surgeon as a prognostic factor after the introduction of total mesorectal excision in the treatment of rectal cancer. *Br J Surg*. 2002 Aug; **89**: 1008–1013.

14 Augestad KM, Bakaki PM, Rose J, Crawshaw BP, Lindsetmo RO, Dørum LM, *et al.* Metastatic spread pattern after curative colorectal cancer surgery. A retrospective, longitudinal analysis. *Cancer Epidemiol*. 2015 Oct; **39**: 734–744.

15 Augestad KM, ROolv-Ole L, Stulberg J, Reynolds H, Senagore A, Champagne B, *et*

al. International preoperative rectal cancer management: staging, neoadjuvant treatment, and impact of multidisciplinary teams. *World J Surg*. 2010 Aug 12; **34**: 2689–2700.

16 Augestad KM, ROolv-Ole L, Reynolds H, Stulberg J, Senagore A, Champagne B, *et al.* International trends in surgical treatment of rectal cancer. *The American Journal of Surgery*. 2011 Mar; **201**: 353–358.

17 Kattan MW. Nomograms Are Difficult to Beat. *European Urology*. 2008 Apr; **53**: 671–672.

18 Weiser MR, Landmann RG, Kattan MW, Gonen M, Shia J, Chou J, *et al.* Individualized Prediction of Colon Cancer Recurrence Using a Nomogram. *Journal of Clinical Oncology*. 2008 Jan 20; **26**: 380–385.

19 Kawai K, Ishihara S, Yamaguchi H, Sunami E, Kitayama J, Miyata H, *et al.* Nomogram Prediction of Metachronous Colorectal Neoplasms in Patients With Colorectal Cancer. *Annals of Surgery*. 2015 May; **261**: 926–932.

20 Kanemitsu Y, Shida D, Tsukamoto S, Ueno H, Ishiguro M, Ishihara S, *et al.* Nomograms predicting survival and recurrence in colonic cancer in the era of complete mesocolic excision. *BJS Open*. 2019 Apr 26; **375**: 1030.

21 Valentini V, van Stiphout RGPM, Lammering G, Gambacorta MA, Barba MC, Bebenek M, *et al.* Nomograms for Predicting Local Recurrence, Distant Metastases, and Overall Survival for Patients With Locally Advanced Rectal Cancer on the Basis of European Randomized Clinical Trials. *Journal of Clinical Oncology*. 2011 Aug 8;

29: 3163–3172.

22 Verver D, van Klaveren D, Franke V, van Akkooi ACJ, Rutkowski P, Keilholz U, *et al.* Development and validation of a nomogram to predict recurrence and melanoma-specific mortality in patients with negative sentinel lymph nodes. *Br J Surg*. 2019 Feb 6; **106**: 217–225.

23 Iasonos A, Schrag D, Raj GV, Panageas KS. How To Build and Interpret a Nomogram for Cancer Prognosis. *Journal of Clinical Oncology*. 2008 Mar 10; **26**: 1364–1370.

24 Iasonos A, Schrag D, Raj GV, Panageas KS. How To Build and Interpret a Nomogram for Cancer Prognosis. *Journal of Clinical Oncology*. 2008 Mar 10; **26**: 1364–1370.

25 Zhang Z, Kattan MW. Drawing Nomograms with R: applications to categorical outcome and survival data. *Ann Transl Med*. 2017 May; **5**: 211–211.

26 Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomedical Informatics* 2009 Apr; **42**: 377–381.