

Age-Related Risk of Caecum Cancer After an Episode of Appendicitis (AA-CC). A Nationwide Analyses

Summary: Acute appendicitis is a common surgical disease. There are in Norway performed 6000 appendectomies annually. However, several controversies exist related to appendicitis treatment, the association between acute appendicitis and caecum cancer (AA-CC) being one of these controversies. Some studies show that the rate of AA-CC increases more than ten times after the age of 40, and in Norway, we refer many patients >40 years old to a colonoscopy. However, many surgeons dispute this age limit, and considerable variation exists between hospitals. At the same time, there is a considerable epidemiological shift, where colon cancer among the young (early-onset colon-rectal cancer, EOCRC) is on the rise. Towards this, considerable uncertainty exists about when patients surgically treated for appendicitis should perform a colonoscopy. This project aims to analyze the age-related association between acute appendicitis and caecum cancer and to develop Norwegian guidelines for a potential AA-CC.

1. Introduction

1.1. The rise of colorectal cancer among the young

Colon cancer is the third largest cancer type and the incidence is growing, especially among the younger patients. The incidence of colorectal cancer in younger adults are rising alarmingly, and the underlying reason for this phenomenon is not known. Genetic predisposition may play a role, never the less few of these cases are found within hereditary cancer syndromes. Thus, other causes must be sought, and environmental causes have been predicted as a casual factor for the observed incidence rise. This is however disputed, as environmental factors should lead to a general increase in colorectal cancer, across all ages. Similarly, the molecular phenotype of the early onset colorectal cancer (EOCRC) has considerable heterogeneity, and up to date, no obvious cancer molecular subtype has been identified. Similarly, there are no internationally accepted definition of EOCRC, and different cut of ages has been used. This hampers the interpretation of epidemiological studies. Of importance, is the rising incidence of EOCRC. It is estimated that within 10 years, 1 in 10 colon cancers and 1 in 4 rectal cancers will be diagnosed in adults younger than 50 years. Towards this, younger patients tend to present with a more advanced disease. (1) With this in mind, this project aims to explore the association between appendicitis and caecum cancers. With the increasing incidence of EOCRC, the proposed project will foster new and important knowledge related EOCRC, which is important for surgeons, health care workers and decision makers.

1.2. Emergency surgery

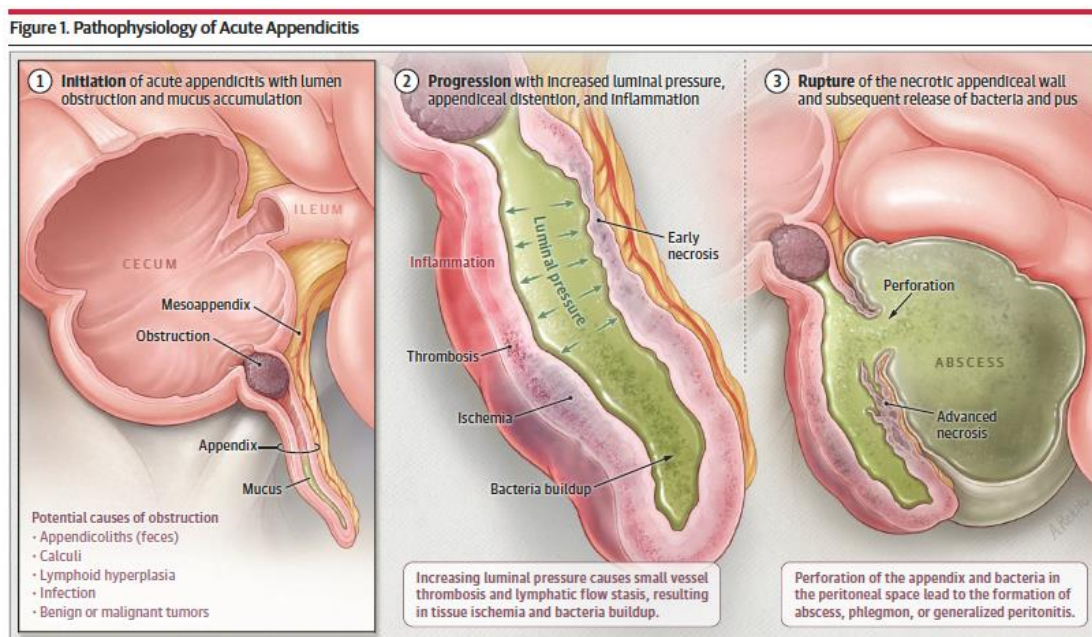
In 2004 the global volume of surgery was estimated at 234 million operations yearly. Of these, approximately 49 million are defined as general surgical emergencies (1). At a national basis, the Norwegian HARM study showed that 55,2% of all gastrointestinal surgical procedures in Norway were emergent and represents a significant work burden for the surgical society (2).

In high-income countries, it is estimated that approximately 10-11% of all surgical interventions each year are emergency procedures (1, 4). In contrast to elective surgery, there is limited room to optimize the physical and mental state of patients before emergency interventions. Therefore, well-defined and evidence-based treatment algorithms are especially needed for emergency surgery. However, there are few treatment algorithms with academic consensus for surgical emergencies. On the contrary, it is easier to find algorithms

for elective cancer surgery than to find the same for emergency procedures. One of the main reasons is that emergency patients are particularly difficult to include in clinical trials. The complexity of the acutely ill surgical patient may explain why emergency general surgery accounts for 47% of mortalities and 28% of complications in surgery (4).

This research project aims to explore the linkage between a common cause for acute surgery, i.e., acute appendicitis and the association with colon cancers (AA-CC). A secondary objective is to reduce overdiagnosis and overtreatment in the diagnosis of colon cancer after AA, by reducing unnecessary colonoscopies.

Figure 1. The pathophysiology of acute appendicitis. Malignant tumours might cause lumen obstruction and subsequent appendicitis. In Moris D, Paulson EK, Pappas TN. Diagnosis and Management of Acute Appendicitis in Adults: A Review. JAMA 2021; 326(22): 2299-311.



1.3. Appendicitis globally and nationally

Appendicitis is one of the most common reasons for emergency abdominal surgery worldwide (3). We diagnose over 6000 Norwegians (3, 4) with the condition every year. Each year, between 600 and 700 patients are admitted to Akershus University Hospital (Ahus) with appendicitis. These patients represent a significant work burden, thus systematic and evidence-based guidelines are needed. Thus, colonoscopy referrals need to be evidence based. Lack of systemized and evidence-based guidelines corresponds well with findings internationally in several studies (4).

2. Needs description

We expect the benefits of this study to be large. The objective of this trial is to assess the age-related risk increase for colon cancer after an episode of appendicitis, an area of great uncertainty. A secondary objective is to develop Norwegian guidelines for colonoscopy referral after an episode of acute appendicitis

2.1. Knowledge gaps

Although appendicitis is a common disease, the knowledge gaps within the field are broad, and briefly described in the sections below:

2.1.1. Controversies Related to Appendicitis Scoring Systems:

Unnecessary radiological examinations expose the patient to an increased risk of malignancy. The newly updated Jerusalem guidelines from the World Society of Emergency Surgery (WSES) recommend using appendicitis scoring systems (AAS/AIR score) to assess the risk of appendicitis in patients before deciding to do radiological examinations. (5-11).

2.1.2. Excess use of radiology services:

Even though the Jerusalem guidelines recommendation to restrict the use of CT scans in appendicitis patients was controversial, the consensus still was clear. However, a large South Korean study confirmed in 2020 that unnecessary radiological examinations, i.e. CT scans, expose the patient to an increased risk of malignancy. This study supports the restrict guidelines from WSES. (3, 5, 12)

2.1.3. Antibiotics as the primary treatment of appendicitis:

Antibiotic resistance is one of the biggest threats to global health, food security and development today, according to WHO. Simultaneously, half of the world's population does not have access to surgical expertise when in need of emergency surgery (2). This dilemma calls for critical assessment for when to use antibiotics for surgical conditions and how to develop internationally recognized surgical guidelines leading to optimized resource utilization (3)(13, 14)(15)(16)(17).

2.1.4. Appendicitis among the pregnant:

The clinical evaluation of a pregnant patient with right lower quadrant pain (RLQ pain) is challenging. The sensitivity of ultrasound in pregnant women after the first trimester is disputed (18, 19). CT scans during pregnancy are not recommended, due to suspected risks for both mother and foetus (20). MRI has quickly becoming the examination method of choice (21), but only a few Norwegian hospitals offers emergency MRI (22-24).

2.1.5. Appendicitis in children:

Appendicitis is the far most common surgical emergency in children (25)(26). At the same time, the most available radiological modality, CT, is not recommended in children. On top of this, the clinical symptoms are vaguer and the rate of complications higher in children than in adult patients with appendicitis (26)(27) (28) (26).

Focus area for this research protocol:

2.1.6. Acute appendicitis associated colon cancer (AA-CC):

Appendicitis in the elderly, especially when diagnosed at >40 years old are associated with underlying colon cancer disease. The physiological mechanism leading to this phenomenon is unknown, but it is hypothesising that a colon tumour may obstruct the appendix lumen. An area of significant knowledge gap is at what age a colonoscopy is recommended after a surgical treatment of appendicitis (6, 29, 30).

The risk of acute appendicitis that is secondary to caecum cancers increases with age, there is no consensus on what age colonoscopy should be performed to detect a potential cancer. Colonoscopy is a resource consuming examination, and differences in the inflection age for colonoscopy, may have significant cost implications. Ahus has implemented colonoscopy after appendicitis in patients > 40 years old, as one of few hospitals in Norway. All though colonoscopy could uncover underlying malignancy (31), colonoscopy also has its side effects

with a perforation rate of 0.016-0.8% in diagnostic procedures. Iatrogenic colonic perforations have a mortality as high as 5-25% (32).

In a recent meta-analysis, 8 studies including >4000 patients were included. They found that the risk of colon cancer in patients aged 40 and higher and appendicitis, is 10 times higher than the general population. The study group suggest routine use of colonoscopy among patient that is 40 years and older, that is surgically or medically (i.e., with antibiotics) treated (33).

3. Hypotheses, aims and objectives

Our objective is to, in a large national data sample, define the age-related risk of caecum cancer after an episode of acute appendicitis, and to identify at which age a colonoscopy (after an episode of appendicitis) should be recommended. This project will provide valuable insight to the incidence and natural history of caecum cancer, diagnosed after an episode of acute appendicitis.

Our research hypotheses are

1. It exists an inflection point with significant age-related increase in the AA-CC risk
2. The mean age of the AA-CC group has decreased during the last 10 years
3. The incidence of metastatic disease in the AA-CC group has increased
4. The number of colonoscopies after AA has increased.

4. Project methodology

The Norwegian quality registries provides a unique opportunity to explore the linkage between appendicitis and caecum cancer. In this project, we will combine two national registries, i.e. The Norwegian Patient Registry and The Norwegian Colorectal Cancer Registry.

Study population: All patients operated of for appendicitis (NCSP code JAH00, JAH01) diagnosed with caecum cancer (C18.0, C18.1, C182 and C183) within 90 days.

The Norwegian Patient Registry (NPR): The Norwegian Government administers NPR. Data from the NPR is developed in order to help improve our knowledge of health services, treatment and medical conditions, which in turn will help improve the health service and health policy. The primary goal for NPR is to contribute to medical and health research, including research which can give knowledge concerning health services, treatment effects, diagnoses and the disease's causes, distribution and development and preventive measures. There are 565 different NCSP and NCMP (Nomesco Classification of Surgical/Medical Procedures) codes in NPR. We will extract relevant NCSP and NCMP codes from NPR. Similarly, complications identified and extracted from NPR are shown in appendix 2, and are in accordance with requirements from the Agency for Health Service and Quality. Elective surgical patients aged 18 years or over were identified through the source of admission code, procedure code and procedure date for an operation. Patients who had a principal procedure within two days of admission were included in the study. We excluded those who were 90 years or older, those who were transferred to an acute hospital, and those with missing data in discharge status, gender, age, year, or principal diagnosis. The selected data from NPR were linked to the Norwegian Registry of Births, Deaths and Marriages data, which includes all death records, in order to identify those patients who died after discharge but within 30 days of admission

The Norwegian Colorectal Cancer Registry: We aim to perform a retrospective longitudinal analysis of data extracted from the Norwegian Colorectal Cancer Registry (NCCR) and combine two datasets, i.e., NCCR and NPR. NCCR is 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 tumours. 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 colon cancer who underwent curative resection (i.e., T1-4, M0, R0 resection) through an open abdominal or laparoscopic approach with a follow-up interval of at least one year will be included in analyses.

Inclusion and exclusion criteria:

Patients > 18 years old undergoing appendectomy in Norway will be included, whereas patients more than 99 years old will be excluded. Period of interest to be decided.

Variables at interest

Extracted from NPR

Demographics:

- Sex
- Age
- Occupation
- BMI
- Charlson comorbidity index

Temporal data (date to date):

- Time from admittance to surgery
- Length of stay
- Time to any readmission

Nomesco Classification of Surgical Procedures (NCSP):

- Appendectomy JEA00
- Appendectomy with drainage JEA10
- Laparoscopic appendectomy JEA01
- Any second surgeries within 30 days postoperative.

Complications or second surgeries (reoperation):

- See appendix 1 for definition of postoperative complications.
- Second surgeries, i.e., all reoperations after the initial appendectomy, see appendix 1.

Extracted from NCCR

- Demographics
- Location of the tumour
 - Caecum, colon ascendens, transversum, descendens, sigmoid or rectum
- Tumor staging, TNM (tumor, lymph node, metastases)
- Disseminated cancer disease, i.e., metastatic disease to the liver, lungs or localized
- Histopathology of primary tumor, i.e., number of lymph nodes, perineural growth, venous growth, differentiation, adenocarcinoma, mucin, other.
- Type of colon cancer surgery, right sided hemicolectomy, open or laparoscopic.
- Immune profile: microsatellite stable, KRAS, BRAF
- Temporal data (for Kaplan Meyer calculations). Date of primary cancer surgery, date of cancer recurrence, date of death.

Definition of an appendicitis associated colon cancer (AA-CC)

AA-CC is defined as any colon cancer diagnosed within 90 days after an episode of appendicitis, which is either surgically or medically treated.

Aspects related to the data extraction from NPR and NCCR

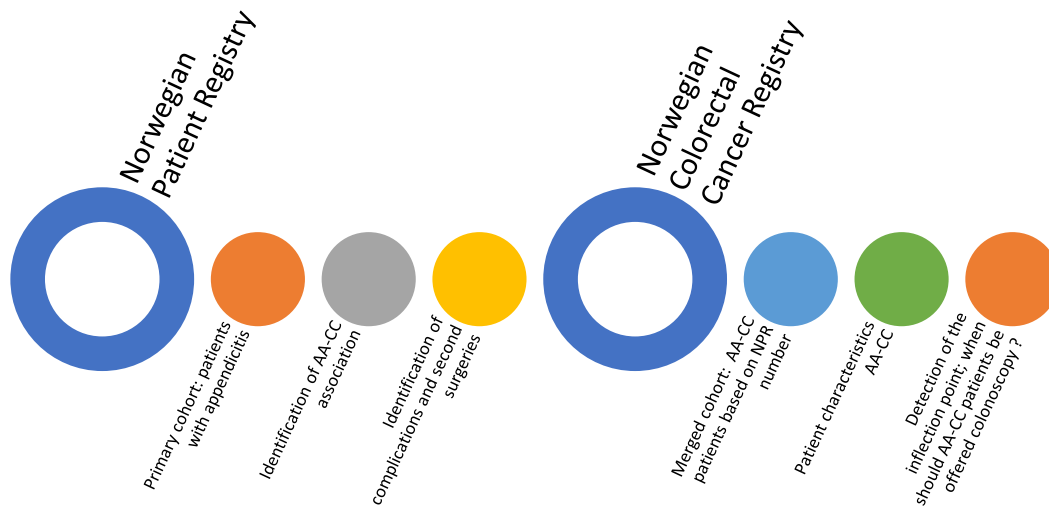


Figure 1. Flow of the analyses with merging of two quality registries. AA-CC: acute appendicitis associated colon cancer.

Endpoints

Primary endpoint:

Age related inflection point of AA-CC (estimated with NPR data)

Secondary endpoints:

Reoperations and postoperative complications (estimated with NPR data)

Identification of risk factors associated with AA-CC (multivariate analyses, with NPR and NCCR data).

Description of AA-CC tumour characteristics (from NCCR data)

Characteristics of increased time to caecum cancer diagnosis.

Statistical analyses:

We present results as means and standard deviations (SDs) or frequencies and percentages, as appropriate. Groups will be compared by using χ^2 - or Fisher's exact test for categorical variables, and Student's t-test or a suitable non-parametric alternative for continuous variables. We will categorize the patients in different groups according to their age and risk of AA-CC. Adjusted hazard ratio (AHR) for overall risk of complications will be estimated using multiple Cox proportional hazards model, and adjusted for a priori determined known prognostic variables (risk factors) for a high complication rate. Multiple logistic regression model will be estimated to assess patient characteristics associated with high vs. low adult appendicitis score.

Project arrangements, method selection and analyses

Necessary equipment, infrastructure and access to resources

The Department of Gastrointestinal Surgery at Ahus is the largest surgical department in Norway, and the access to resources and infrastructure is broad. Necessary offices and research infrastructure (access to software, statistical support) is also provided by the *University of Oslo (UiO)*. UiO is fully integrated in the department and numerous of research projects at the department are merged with the UiO infrastructure. Statistical support and other logistic resources will be provided by the Norwegian Cancer Society.

5. Participants, organization and collaborations

Project participants and their roles, organization and positioning in the research group:

Professor (Associate) Knut Magne Augestad will be the principal investigator. Augestad has done extensive research in the field of gastrointestinal surgery. He is an associate professor at UiO and a senior consultant at Ahus' surgical department.

Ingeborg Steinholt, MD, is a resident in general and gastrointestinal surgery. She is currently employed as a clinical fellow in surgery at the University of Oslo and is accepted at the PhD program at UiO.

Collaborators from NGICG:

Professor Arne Wibe: Director of the Norwegian Gastrointestinal Cancer Group Colorectal (NGICG-CR) and Professor of Surgery at St. Olav University Hospital, Trondheim Norway.

Professor Hartwig Kørner. Former Director NGICG-CR. Professor of Surgery at University of Bergen

Liv Marit Dørum, NCCR: is the head of the Norwegian Colorectal Cancer Registry and will assist in trial logistics and provide advise related to the NCCR data

International collaborators

Ann Arbor, Michigan, USA: Professor Samantha Hendren

Aarhus University Hospital: Professor Peter Christensen

Columbia University, New York: Professor Ravi Kiran

Budget

We ask for funding of a PhD candidate 50% over 6 years. Out of pocket expenses (data extraction, handling, analyses, travel, PC equipment) will be funded by either the Division of Surgery at Helgelandssykehuset or external funding. Knut Magne Augestad is funded by the University of Oslo. The Norwegian Colorectal Cancer Registry will contribute with statistical expertise, with a statistician in part time position.

6. Plan for activities, visibility and dissemination

The project begun with application work in the fall of 2021. We have drafted a work package plan starting in the winter/spring of 2022.

Work package 1 (WP 1): Establishment of the research environment. Establish safe data handling routines, ethical application and data extraction in collaboration with the Norwegian Institute of Public health and Norwegian Colorectal Cancer Registry

Work package 2 (WP 2): Data analyses

Work package 3 (WP 3): Publication of at least two journal articles

	2022				2023			
WP 1								
Literature review								
Data extraction								
WP 2								
Analysing data of the inflection point AA-CC								
WP 3								
Conference poster								
Two journal articles AA-CC								
Summarizing workshop								

7. Plan for implementation

The usefulness of this research is broad and possible to implement in actual-world practice within a short time frame. Our main objective is to identify the age-related inflection point of AA-CC. This may provide a national guidance of when patients with acute appendicitis should be offered colonoscopy. If the study confirms our research hypotheses, the path to real-world implementation is short (estimated 1-2 years). Reduction of over diagnostics is a prioritized political goal and thus, national policymakers may use our results to reduce colonoscopies at a national level. Secondly, we envision that our research may be the gateway to several other valuable projects. Of particular interest is to develop other innovative projects where data from NPR, NCCR and other valuable registries are merged.

8. Plan for dissemination

Articles, conference abstracts and posters: Given the timely subject matter, novelty, and potential impact on patient care, widespread dissemination of the results is planned in the surgical communities, as well as 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. This process involves submitting articles in peer-reviewed journals in order to communicate the research. The first article (*target journal British Journal of Surgery*) will identify patient related with AA-CC. The second article (*target journal Colorectal Disease*) will present the cancer characteristics of AA-CC and their potential of metastatic disease. We aim to publish our results in mainstream media channels (Dagens Medisin, Dagbladet) and publish popular science press releases. Finally, we aim to publish our results at international and national conferences, of special interest is the annual European Society of Coloproctology (ESCP) and the Norwegian Surgical Association Annual Conference.

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

9. User involvement

The "Brukerutvalg" (BU) at Helgelandssykehuset will be informed about the trial. We aim to involve end users as advisors during the actual research and during workshops. We aim to establish a reference group of experienced end users, whom we can consult continuously during the actual research process. In this project, "users" are defined as patients, preferably patients operated for colon cancer. We aim to have regular meetings with a representative for the BU, at least one annual meeting. BU will also be invited to assist the team during the research.

10. Ethical considerations

We have applied for exemption from patient consent to extract data retrospectively. This is due to the large number of patients covered by the studies and because the data extract goes back many years. It is never desirable to extract data without patient consent, but we consider the alternative impossible in these studies. We also believe the benefit for society will outweigh the potential disadvantages for the individual patient. Several measures will be taken in collaboration with the local data protection office to ensure minimal privacy risk for the patients included in the studies.

This study is not considered to have any negative benefits for the included patients. Nor do we consider them to be at any enhanced risk due to this study. On the other hand, for society, evidence that can defend decreased use of colonoscopies in a large patient group can give extended benefits, both for individual patients in the future, but also for health economics and socioeconomic sustainability in the health sector.

11. References

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