Doctoral theses at NTNU, 2023:255

Øystein Høydahl

Older patients with colorectal cancer at Levanger Hospital 1980-2016

Doctoral thesis

NTNU
Norwegian University of Science and Technology
Thesis for the Degree of
Philosophiae Doctor
Faculty of Medicine and Health Sciences
Department of Clinical and Molecular Medicine

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Norwegian University of
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Trondheim, September 2023

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Sammendrag

Kreft i tykk- og endetarm har blitt den vanligste kreftsykdommen i Norge med unntak av brystkreft for kvinner og prostatakreft for menn. Sykdommen rammer i hovedsak eldre mennesker og har en insidens-topp rundt 70 års alder. Andelen eldre har økt i Norge de siste tiårene og vil fortsette å øke i årene som kommer. Moderne medisinsk behandling bidrar til at vi lever lenger, forventet levealder stiger, og de eldste aldersgruppene utgjøres av en stadig større andel av befolkningen. I takt med denne utviklingen forventer vi et økende press på helsetjenestene.

Riktig behandling av pasienter med kreft i tykk- og endetarm er viktig for å tilby best mulig behandling på individ-nivå, og for optimal utnyttelse av helseressursene. Retningslinjer for utredning og behandling følger av Helsedirektoratets handlingsprogram og er bortsett fra enkelte unntak like på tvers av aldersgruppene. Dette til tross for at evidensen i stor grad er basert på kunnskaper om yngre pasienter. Eldre pasienter utelates ofte fra kliniske studier på tross av at det er viktige forskjeller mellom aldersgruppene. Kunnskaper om yngre pasienter ikke alltid er direkte overførbare til de eldre. Yngre pasienter utgjør generelt sett en mer homogen gruppe, mens det hos eldre pasienter er store individuelle forskjeller hva angår aldersassosierte faktorer som må hensyntas ved behandling av kreft.

Å tilby en best mulig, individ-tilpasset behandling er en av de største utfordringene ved behandling av eldre pasienter med kreftsykdom. Dagens standard har rom for forbedring. Seleksjonen til de ulike behandlingsformene baseres på kunnskaper om pasienten og pasientens sykdom. Den multimodale evalueringen av pasienter må favne bredere slik at våre beslutninger baseres på et større grunnlag. Prehabilitering før behandlingsstart og intensivert tverrfaglig oppfølging gjennom behandlingsforløpet kan bidra til at flere klarer å gjennomgå tiltenkt behandling, forebygge behandlingsassosierte komplikasjoner, og forbedre overlevelse.

I Studie 1 undersøkte vi trender i insidens og presentasjon av kreft i tykk- og endetarm ved Sykehuset Levanger for perioden 1980 til 2016. Basert på våre observasjoner beregnet vi den videre insidensutviklingen frem mot 2040. Våre funn viste at insidensen av kreft i tykk- og endetarm nært fordoblet seg gjennom observasjonsperioden, hovedsakelig grunnet primært preventive (livsstilsrelaterte) årsaker. Analysene våre indikerte at påvirkningen fra primært preventive årsaker har nådd et toppunkt. Sammenlignet med insidensnivået i siste del av studien forventer vi en økning på 70% frem mot 2040. Økningen vil hovedsakelig skyldes at befolkningen blir eldre, og være spesielt merkbar i aldersgruppen 80 år.

I Studie 2 undersøkte vi diagnostikk og behandling av pasientene med tykktarmskreft ved Sykehuset Levanger i perioden 1980 til 2016, med et spesielt søkelys på åttiåringene. Studien viste at insidensen av kreft i tykktarm hos åttiåringene mer enn fordoblet seg gjennom studieperioden. Åttiåringene som

gjennomgikk kirurgisk behandling med kurativt siktemål, hadde lavere korttidsoverlevelse enn de yngre pasientene. Åttiåringene som overlevde de første nitti dagene etter kirurgi, hadde like god relativ langtidsoverlevelse som de yngre pasientene. Den relative andelen av åttiåringer som ble behandlet med kirurgi økte gjennom observasjonstiden. Tiltak som forbedrer korttidsoverlevelsen, vil være nøkkelen til å forbedre langtidsoverlevelsen hos åttiåringer som blir operert med kurativt siktemål i fremtiden.

I Studie 3 undersøkte vi behandling av pasientene med endetarmskreft ved Sykehuset Levanger i perioden 1980 til 2016, med et spesielt søkelys på pasientene ≥80 år. Våre resultater viste at pasientene ≥80 år hadde mindre sjanse for å bli behandlet med kurativt siktemål sammenlignet med de yngre pasientene, på tross av like sykdomsstadier ved diagnosetidspunktet. Det var generelt en høy komplikasjonsrate ved stor kirurgi for endetarmskreft, og pasientene ≥80 år hadde mer alvorlige komplikasjoner enn de yngre pasientene. Pasientene ≥80 år som gjennomgikk kirurgisk behandling med kurativt siktemål hadde lik relativ langtidsoverlevelse som de yngre pasientene.

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CONTENT

1. Acknowledgements 7
2. List of papers 9
3. Abbreviations 10
4. Definitions 11
5. Summary 19
6. Introduction to the study 21
6.1. Epidemiology 21
6.2. Older patients in Norway 23
6.3. Anatomy 24
6.4. Biology 26
6.5. Prevention of CRC 27
6.5.1. Primary prevention and modifiable risk factors 27
6.5.2. Secondary prevention and non-modifiable risk factors 28
6.5.3. Tertiary prevention 29
6.6. Clinical presentation, diagnostic work-up and staging 29
6.7. Surgical treatment of CRC 30
6.7.1. Polypectomy 30
6.7.2. Major resections for colon cancer 31
6.7.3. Major resections for rectal cancer 32
6.7.4. Minimally invasive surgery 34
6.7.5. Surgery for colorectal metastases 35
6.7.6. Palliative surgery 35
6.7.7. Emergency surgery 35
6.8. Complications related to surgical treatment of CRC 36
6.8.1. Acute surgical complications 36
6.8.2. Infectious complications 37
6.8.3. Stoma-related complications 37
6.8.4. Low anterior resection syndrome 37
6.9. Oncological treatment of CRC 38
6.9.1. Adjuvant and neoadjuvant treatment 38
6.9.2. Palliative treatment 38
6.10. Survival 39
6.11. Special considerations in older patients with CRC 40
6.11.1. Frailty 40
6.11.2. Comprehensive geriatric assessment 41

6.11.3. Geriatric syndromes 41
6.11.4. Prehabilitation 42
6.11.5. Patient preference 43
7. Aims of the study 44
8. Material and methods 45
8.1. Description of the cohort 45
8.2. Study design 45
8.3. Clinical follow-up 45
8.4. Statistical analyses 46
8.5. Ethical approval 48
9. Summary of results 49
9.1. Paper I 49
9.2. Paper II 49
9.3. Paper III 49
10. Discussion 51
10.1. Discussion of main findings 51
10.2. Study design 59
10.3. Limitations 59
11. Conclusions 60
11.1. Paper I 60
11.2. Paper II 60
11.3. Paper III 60
12. Final reflections and future perspectives 61
13. References 62
14. Errata 80
15. Papers I-III 81

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Levanger, April 2023

Øystein Høydahl

2. List of papers

Paper I) Høydahl, Ø., Edna, TH., Xanthoulis, A., Lydersen S., Endreseth B.

Long-term trends in colorectal cancer: incidence, localization, and presentation.

BMC Cancer. 2020 Nov; 20, 1077.
https://doi.org/10.1186/s12885-020-07582-x

Paper II) Høydahl, Ø., Edna, TH., Xanthoulis, A., Lydersen S., Endreseth B.

Octogenarian patients with colon cancer – postoperative morbidity and mortality are the major challenges.

BMC Cancer. 2022 Mar; 22, 302.

https://doi.org/10.1186/s12885-022-09384-9

Paper III) Høydahl, Ø., Edna, TH., Xanthoulis, A., Lydersen S., Endreseth B.

The impact of age on rectal cancer treatment, complications and survival.

BMC Cancer. 2022 Sep; 22, 975.

https://doi.org/10.1186/s12885-022-10058-9

These papers will be referred to by their Roman numerals.

3. Abbreviations

ADL	Activities of Daily Living
ASA	The American Society of Anesthesetiologists
BMI	Body Mass Index
CCI	Charlson Comorbidity Index
CD	Clavien-Dindo
CEA	Carcinoembryonic Antigen
CGA	Comprehensive Geriatric Assessment
CI	Confidence Interval
CME	Complete Mesocolic Excision
CRC	Colorectal Cancer
CRM	Circumferential Resection Margin
HAI	Healthcare-associated Infections
HDI	Human Development Index
HP	Hartmann's Procedure
IR	Incidence Rate
IRR	Incidence Rate Ratio
MDT	Multidisiplinary Team
OR	Odds Ratio
PME	Partial Mesorectal Excision
QoL	Quality of Life
SD	Standard Deviation
SSI	Surgical Site Infection
TME	Total Mesorectal Excision

4. Definitions

Octogenarian patient:

A patient whose age is in the eighties.

Colon cancer:

We defined colon cancer as adenocarcinomas located above 15 cm from the anal verge.

- We defined right-sided colon tumours as tumours localized in the caecum, ascending colon, hepatic flexure, or transverse colon.
- We defined left-sided colon tumours as tumours localized in the splenic flexure, descending colon, or sigmoid colon.

Rectal cancer:

We defined rectal cancer as adenocarcinomas located within 15 cm of the anal verge, measured with a rigid proctoscope.

- The proximal rectum was defined at 12-15 cm.
- The middle rectum was defined at 6-11 cm.
- The distal rectum was defined at 0-5 cm.

TNM classification:

The TNM classification of malignant tumours, 6th edition, was used to assign cancer stages [1].

T categories – primary tumour

Tx: Primary tumour cannot be assessed

T0: No evidence of primary tumour

Tis: Carcinoma in situ; intraepithelial or invasion of lamina propria

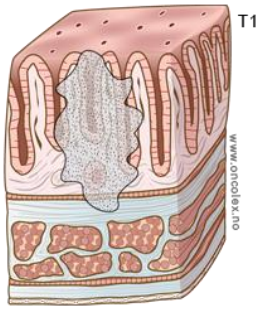
T1: Tumour invades submucosa

T2: Tumour invades muscularis propria

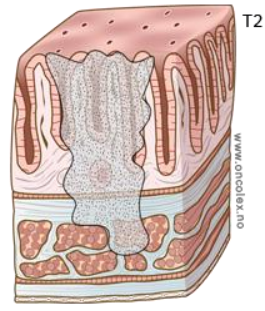
T3: Tumour invades through the muscularis propria into pericolorectal tissues

T4a: Tumour penetrates to the surface of the visceral peritoneum

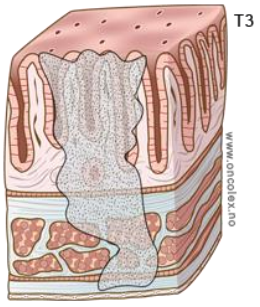
T4b: Tumour directly invades or is adherent to other organs or structures



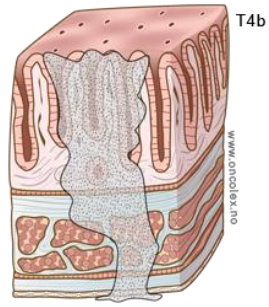
T1: Tumour invades submucosa



T2: Tumour invades muscularis propria



T3: Tumour invades through the muscularis propria into pericolorectal tissues



T4: Tumour penetrates to the surface of the visceral peritoneum, or directly invades or is adherent to other organs or structures

Figure 1. T categories in colorectal cancer.

Source: https://kreftlex.no/Tykk-og-endetarmskreft/BAKGRUNN/Stadier

N categories – regional lymph node metastasis

Nx: Regional lymph nodes cannot be assessed

N0: No regional lymph node metastasis

N1: Metastasis in 1-3 regional lymph nodes

N1a: Metastasis in one regional lymph node

N1b: Metastasis in 2-3 regional lymph nodes

N1c: Tumour deposit(s) in the subserosa, mesentery, or non-peritonealized pericolic or perirectal tissues without regional nodal metastasis

N2: Metastasis in four or more regional lymph nodes

N2a: Metastasis in 4-6 regional lymph nodes

N2b: Metastasis in seven or more regional lymph nodes

M categories – distant metastasis

M0: No distant metastasis

M1: Distant metastasis

M1a: Metastasis confined to one organ or site

M1b: Metastasis in more than one organ/site or the peritoneum

The additional description with a prefix defines the TNM-stage with respect to time frame of treatment.

cTNM:	Clinical classification	Designated before treatment
ycTNM:	Clinical evaluation	Designated after neo-adjuvant chemoradiotherapy for rectal cancer
pTNM:	Pathological classification	Designated after surgery
ypTNM:	Pathological evaluation	Designated after surgery in patients with neo-adjuvant chemoradiotherapy for rectal cancer

Stage of disease for CRC as proposed by the American Joint Committee on Cancer (AJCC) [2]:

AJCC stage	Tumour	Node	Metastasis
Stage 0	Tis	N0	M0
Stage I	T1, T2	N0	M0
Stage II	T3, T4	N0	M0
Stage III	Any T	N1, N2	M0
Stage IV	Any T	Any N	M1

Extent of disease:

The annual report *«Cancer in Norway»* by the Cancer Registry of Norway classifies stages as follows [3]:

Localised stage: All cases where the tumour is confined to the primary organ

Regional stage: All cases where the tumour has invaded neighbouring tissue outside of the primary organ or metastasised to regional lymph nodes

Distant stage: All cases where the tumour has metastasised to other organs or distant lymph nodes

Unknown: All cases where the primary origin of the tumour is not known and cases with insufficient information to set stage

The term *locally advanced colorectal cancer* is commonly used, although a standardized definition is lacking. Locally advanced colorectal cancer may be defined as a primary cancer with invasion to adjacent structures or extensive regional lymph node involvement.

America Society of Anesthesiologists (ASA) score [4]:

The ASA Physical Status Classification System is a system to assess pre-anaesthesia medical co-morbidities.

ASA I: A normal healthy patient

ASA II: A patient with mild systemic disease

ASA III: A patient with severe systemic disease

ASA IV: A patient with severe systemic disease that is a constant threat to life

ASA V: A moribund patient who is not expected to survive without the operation

ASA VI: A declared brain-dead patient whose organs are being removed for donor purposes

Charlson Comorbidity Index [5]:

The Charlson Comorbidity Index is a weighted index to predict the risk of death within one year of hospitalization for patients with specific comorbid conditions.

Residual tumour classification:

The residual tumour classification denotes presence or absence of a residual tumour after treatment [6]. It is implemented in the 8th edition of the TNM classification and yields essential information regarding tumour status after treatment, further therapy, and prognosis [7].

The R classification categories are defined as:

RX: The presence of residual tumour cannot be assessed

R0: No residual tumour

R1: Microscopic residual tumour

R2: Macroscopic residual tumour

In Paper II and Paper III, we further classified R0 resections into two groups:

i: R0 resection without tumour perforation

ii: R0 resection with tumour perforation

The Clavien-Dindo classification of surgical complications [8]:

Grade I:	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, or radiological interventions Acceptable therapeutic regimens are: Drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II:	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included
Grade III:	Requiring surgical, endoscopic, or radiological intervention
Grade III-a:	Intervention not under general anaesthesia
Grade III-b:	Intervention under general anaesthesia
Grade IV:	Life-threatening complication (including CNS complications) requiring IC/ICU-management
Grade IV-a:	Single organ dysfunction (including dialysis)
Grade IV-b:	Multi organ dysfunction
Grade V:	Death of a patient
Suffix `d:	If the patient suffers from a complication at the time of discharge (see examples in Appendix B, http://Links.Lww-.com/SLA/A3), the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication

Surgical procedures:

- Right hemicolectomy – a resection of the terminal ileum, caecum, ascending colon, hepatic flexure and proximal third of the transverse colon, and construction of an anastomosis
- Transverse resection – a segmental resection of the transverse colon and construction of an anastomosis
- Left hemicolectomy – a resection of the distal third of the transverse colon, splenic flexure, descending colon, and sigmoid colon, and construction of an anastomosis
- Sigmoid resection and high anterior resection – a resection of the sigmoid colon or the rectosigmoid junction with an anastomosis above the peritoneal reflection
- Hartmann's procedure – a resection of the sigmoid colon or sigmoid colon and rectum (proctosigmoidectomy) with the construction of a terminal stoma
- Low anterior resection – a resection of the rectum with an anastomosis below the peritoneal reflection
- Abdominoperineal resection – a resection of the sigmoid colon, the rectum, and the anus, and construction of a terminal stoma
- Proctocolectomy – a total colectomy with resection of the rectum and anus, and construction of a terminal stoma

Elective surgery:

Surgical procedures that were scheduled in advance.

Emergency surgery:

Acute surgical procedures due to the evidence of bowel obstruction or perforation.

Local recurrence:

Colon cancer: Recurrent perianastomotic, paracolic, or peritoneal disease after a primary radical resection, with or without metastases.

Rectal cancer: Recurrent pelvic disease after a primary radical resection, with or without metastases.

Metastases:

Synchronous: Occurrence of a metastatic tumour within six months after detection of the primary tumour.

Metachronous: Occurrence of a metastatic tumour more than six months after detection of the primary tumour.

5. Summary

Background: In Norway, CRC is the second most common cancer for both sexes combined. The incidence has increased during the last decades due to changes in the population and an increasing exposure to lifestyle-associated risk factors. In the years to come, the healthcare system will care for an increasing number of older patients, and further knowledge concerning this group is mandatory to offer an optimal care of treatment.

Aims: The purpose of the first study was to assess trends in incidence and presentation of CRC in a stable population in Mid-Norway during a period of 37 years. Secondarily, we wanted to predict the future burden of CRC in the same catchment area. The purpose of the second study was to evaluate the relative survival in octogenarian patients with colon cancer after a major resection with curative intent. The purpose of the third study was to evaluate treatment, complications, and survival in patients aged ≥80 years treated for rectal cancer.

Methods: Paper I-III were single centre, retrospective cohort studies. All studies included a cohort of patients diagnosed with CRC at Levanger Hospital during 1980 to 2016.

In Paper I, all 2268 patients diagnosed with CRC between 1980 and 2016 were included. Poisson regression was used to calculate changes in incidence rate ratio and to predict future changes in CRC incidence. We adjusted for changes in the population in terms of age and sex distribution to assess associations between changes in incidence and the relation to primary preventable factors.

In Paper II, all 1530 patients diagnosed with colon cancer at Levanger Hospital between 1980 and 2016 were included. We performed logistic regression to test for associations between 90-day mortality and explanatory factors. We performed relative survival analyses to identify factors associated with short- and long-term survival.

In Paper III, all 666 patients treated for rectal cancer at Levanger Hospital between 1980 and 2016 were included. We performed logistic regression to test for associations between complications, 90-day mortality, and explanatory factors. We performed relative survival analyses to identify factors associated with short- and long-term survival.

Results: In Paper I, we observed an incidence increase in CRC of 94.5% between 1980 and 2016. Changes in the population with respect to sex and age contributed to 28% of the observed increase, whereas 72% was attributed to lifestyle associated factors. Based on estimated demographic changes we predicted a further incidence increase of 70% by 2040, primarily due to a further ageing of the population.

In Paper II, the incidence of colon cancer more than doubled among octogenarian patients during the 37-year observation period. Over time, the rate of octogenarian patients selected for a major resection with curative intent increased and surpassed the observed increase in incidence. Hence, an increasing rate of octogenarian patients was considered eligible for surgery. After a major resection with curative intent, octogenarians had a significantly adverse 90-day mortality rate of 9.3%, compared to 0.4% in patients <65 years. In octogenarian patients who survived the first 90 days, the long-term relative survival rate was 99.7%, and comparable to that of younger patients.

In Paper III, we observed a lower rate of major resections with curative intent in patients ≥80 years with rectal cancer, despite comparable disease stages across age-groups. After a major resection with curative intent, patients ≥80 years had a non-significantly adverse 90-day mortality rate of 5.9%, compared to 0.8% in patients <65 years. In patients ≥80 years who survived the first 90 days, the estimated rates of long-term relative survival, local recurrences, and metastases, were comparable to the rates of younger patients. Postoperative complications were observed in 47.6% of patients undergoing major resections with curative intent. The severity of complications increased with age, ASA score and blood loss. The rate of reoperations increased over time.

Conclusions: The incidence of CRC increased from 1980 to 2016 primarily due to an increasing exposure to lifestyle-associated risk factors. The incidence will continue to increase in the years to come mainly due to a further ageing of the population. In patients ≥80 years treated for CRC with a major resection with curative intent, the short-term mortality was adverse compared to younger patients. In patients ≥80 years who survived the first 90 days postoperative, the rates of long-term relative survival, local recurrences, and metastases, were comparable to that of younger patients. Major resections for rectal cancer were associated with a high rate of complications. Complication rates did not differ across age-groups, but patients ≥80 years had more severe complications.

6. Introduction to the study

6.1. Epidemiology

The global burden of CRC is high, with 1,931,590 new cases in 2020, accounting for 10% of all new cancer cases worldwide [9,10]. It is the second most common cancer in women and the third most common cancer in men. Globally, the distribution varies between nations, and the incidence is approximately 4-6 times higher in high/very high HDI countries [11,12].

Norwegian incidence rates are among the highest in the world [11]. In 2021, 3204 new cases of colon cancer and 1346 new cases of rectal cancer were reported. For both sexes combined, CRC is the second most common cancer. The incidence of CRC has doubled since the 1970s [3].

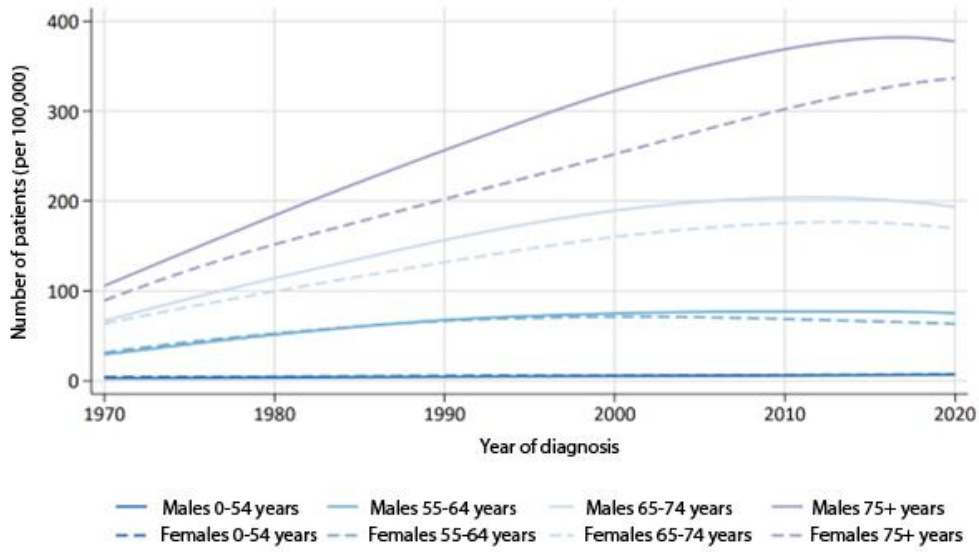


Figure 2. Incidence rates of colon cancer during 1970-2020 in Norway [13].

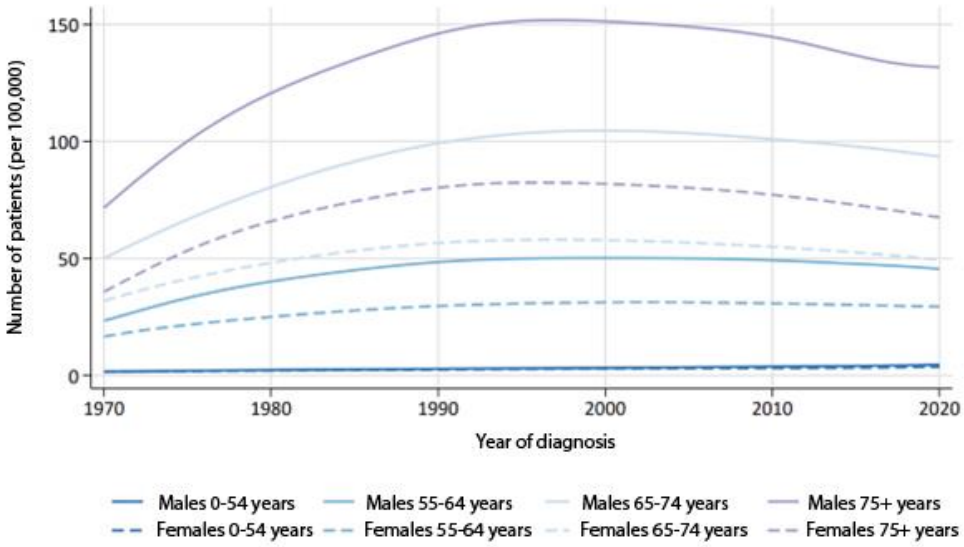


Figure 3. Incidence rates of rectal cancer during 1970-2020 in Norway [13].

The Norwegian population has increased from 3,866,468 persons in 1970, to 5,488,984 persons in 2023 [14]. The Norwegian society has undergone a rapid socioeconomic development during this period. Exposure to lifestyle-associated risk factors have increased paralleling the increasing wealth. The development in Norway coincides with several other countries where increasing incidence rates of CRC paralleling increasing HDI have been observed [12].

During 2017-2021 the age-standardised incidence rates per 100,000 person-years (Norwegian standard) for colon and rectal/rectosigmoid cancer with respect to stage were [3]:

		Colon cancer		Rectal/rectosigmoid cancer	
		Male	Female	Male	Female
	Total	56.6	52.5	30.1	18.3
Localized	T1-T3, N0, M0	10.1	9.3	7.3	4.7
Regional	T1-T4, N+, M0	29.6	27.5	13.9	8.3
Distant	T1-T4, N0-N2, M+	12.9	11.9	5.9	3.5
Unknown		3.9	3.9	2.9	1.8

6.2. Older patients in Norway

Older patients is a somewhat arbitrary defined term and used interchangeably with terms such as *aged individuals* or *seniors*. In most developed countries the chronological age of 65 years, at which one can receive pension benefits, is accepted as the definition of *old* [15]. It may be further categorized into *young old* (65-74), *old old* (75-84) and *oldest old* (≥85) [16,17].

Life-expectancy in Norway has increased from 75.7 years in 1980 to 83.2 years in 2020, currently 81.2 years for males and 84.7 for females. The gap between the sexes has narrowed as life-expectancy has increased more in males [18,14].

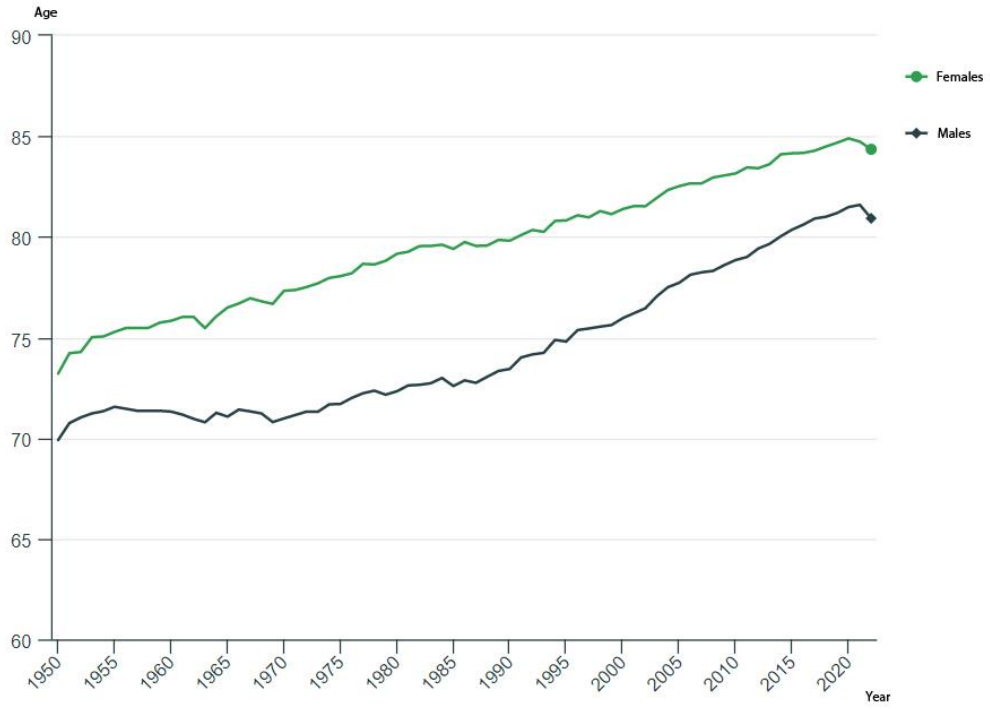


Figure 4. Life-expectancy in Norway.

Source: Statistics Norway, 2022, https://www.ssb.no/befolkning/fodte-og-dode/statistikk/dode/artikler/forventa-levealder-falt-i-2022

6.3. Anatomy

The colon starts where the terminal ileum enters the large bowel through the ileocaecal valve and ends with the sigmoid colon. Clinically, the sacral promontory indicates the recto-sigmoidal junction, which is then followed by the rectum, starting 15 cm orally to the anal verge (the junction between the anal and perianal skin).

The right colon is a retroperitoneal structure covered by the posterior peritoneum on its lateral and ventral surface. The transverse colon is the most mobile part of the colon and considered completely intraperitoneal as it is wrapped by peritoneum. The descending colon is covered by peritoneum on the anterior, lateral, and medial border, whereas the posterior surface is adherent to the posterior abdominal wall. The colon is approximately 150 cm long.

Embryologically, the right colon originates from the midgut, whereas the left colon and rectum originates from the hindgut. The superior mesenteric artery supplies the right colon, whereas the inferior mesenteric artery supplies the left colon. The superior rectal artery, a branch of the inferior mesenteric artery, supplies the proximal rectum, whereas the rectal arteries emerging from the internal iliac arteries supply the middle and distal rectum.

The venous drainage of the right and left colon runs through the superior and inferior mesenteric vein, respectively. These veins drain further into the portal system, which is of clinical relevance, as liver metastases is the most common metastasis pattern for colon cancer [19]. The venous drainage of the rectum is more complex, as the proximal rectum drains into the portal route, whereas the middle and distal rectum drain into the middle and inferior rectal veins, further into the external iliac veins and the inferior vena cava. Pulmonary metastases are more common for lower rectal cancers [20].

The structure of the bowel wall has four functional layers: mucosa, submucosa, muscularis propria and serosa/adventitia.

- The *mucosal* layer consists of the epithelium, a supporting layer of lamina propria and a thin muscle layer of muscularis mucosae.
- The *submucosal* layer supports the mucosa. It contains larger blood vessels, lymphatics, and nerves.
- The *muscularis propria* consists of smooth muscle and is the basis of the peristaltic contraction.
- The *serosa* is the outermost layer of the bowel wall wherever the bowel is lined by the visceral peritoneum. It contains mesothelial layers that secrete serous fluid. The *adventitia* is the outermost layer wherever the bowel is not lined by visceral peritoneum. It is made up of loose connective tissue that fixates the bowel.

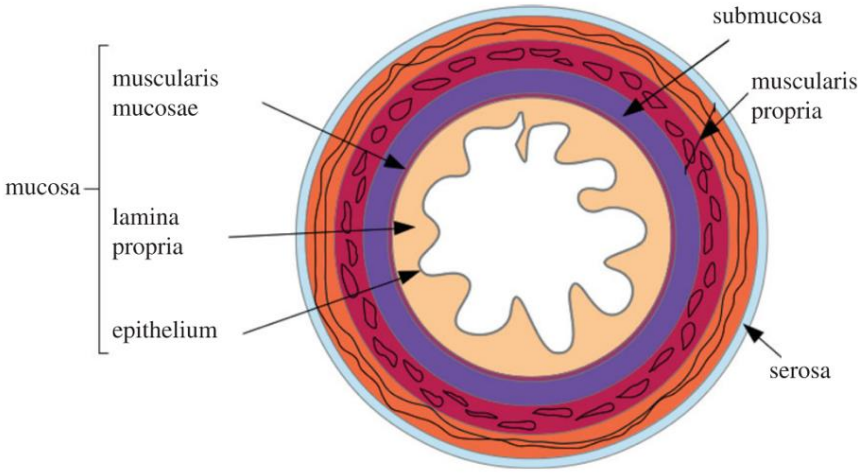


Figure 5. Schematic view of the four functional layers of the bowel wall [21].

6.4. Biology

CRC develops through a stepwise molecular and genetic alteration of normal colonic or rectal epithelial cells, caused by microenvironmental impact [22]. Accumulation of mutations inactivate tumour-suppressor genes and activate oncogenes. The following loss of genomic stability promotes growth of malignant cells through clonal expansion. Cancer develops as these cells penetrate deeper into the bowel wall. Stem cells or stem cell-like cells are assumed to be origin cells for the majority of CRC [23]. Organ-specific multipotent adult stem cells can be found in several tissue types of the body and may turn into any cell type in the tissue they are located [24]. As they possess the longevity to accumulate mutations and the ability to self-renew, they are highly suspected as initiator cells of cancer development [25].

Approximately 70% of CRC cases occur in a sporadic fashion, whereas 25% of the patients have a family disposition for CRC, and 5% of the cases occur as hereditary syndromes due to highly penetrating germlines [26]. Hereditary syndromes may be further categorized into those associated with polyposis, i.e., familial adenomatous polyposis (FAP), and hamartomatous polyposis syndrome; and those not associated with polyposis, hereditary non-polyposis syndrome (HNPCC), known as Lynch syndrome [27].

There are two major precursor lesions behind most cases of CRC [28]. The first one is considered the classic CRC formation, frequently called the *adenoma-carcinoma pathway*. Cancers develop from an aberrant crypt to an adenomatous polyp, which in turns evolves to CRC. The process takes an

estimated 10-15 years, and accounts for 70-90% of CRC. Adenomatous polyps exhibit a heterogenous molecular biology, which may explain why only 10% progress to CRC, with different patterns regarding tumour progression, metastases, and relapse [29,30].

The second major group of precursor lesions are the serrated polyps. They undergo the so-called *serrated neoplasia pathway*, accounting for 10-20% of CRC [31]. Neoplastic serrated lesions are histologically characterized by a saw-toothed appearance of epithelial glandular crypts. Serrated lesions possess distinct macroscopic characteristics that makes them more difficult to detect by endoscopy compared to conventional adenomas [27].

Cancer in the colon and rectum has to a large extent been considered the same entity with structural and functional similarities, anatomically starting from the ileocaecal valve, and ending at the dentate line. Recent reports have challenged this view and demonstrated that factors impact differently on disease development between the colon and the rectum [32,33].

Proximal colon cancers are predominantly exophytic tumours, distal colon cancers predominantly endophytic ring-shaped, whereas rectal cancers may have various appearances [32]. Rectal cancers have higher rates of local recurrences and lung metastases compared to colon cancers [19]. Peritoneal dissemination is more common in right-sided colon cancer, whereas left-sided colon cancer affects lungs and liver more often, and more frequently cause bowel obstruction [34]. Right-sided colon cancers are more frequent in women and associated with a more aggressive course of disease [35].

6.5. Prevention of CRC

As CRC is one of the most common cancers at a global level, it is also one of the most preventable cancers [36]. Preventive measures may be categorized as *primary preventive* addressing *modifiable factors*, and *secondary preventive* addressing *non-modifiable factors.* Additionally, *tertiary preventive measures* aim to reduce the impact and increase survival of established disease.

6.5.1. Primary prevention and modifiable risk factors

There is compelling evidence that CRC is closely related to lifestyles, as incidence rates have increased rapidly in countries adopting western living habits [37,38]. Cigarette smoking, obesity, high alcohol consumption, diabetes mellitus, and high consumption of red and processed meat, are established *modifiable risk factors*, whereas physical activity, intake of fish, fruits and vegetables, hormone replacement therapy and NSAIDs, may protect against disease development. High intake of milk and whole grains may reduce the risk for CRC [36,39].

Due to the massive incidence increase during the last decades one may question the sustainability of current preventive strategies. Present recommendations advocate a normal body weight and a healthy lifestyle with physical activity and a reasonable diet [40]. Shared benefits of such recommendations regarding other diseases multiply the potential health gain and is of particular relevance for future generations as they have the biggest potential to reduce the burden of CRC.

6.5.2. Secondary prevention and non-modifiable risk factors

Sex, age, ethnicity, family history and genetic predispositions are *non-modifiable risk factors* for CRC development [39]. Due to the slow transformation from normal epithelium to cancer, there is a wide time-window to detect and treat adenomas, as well as detection of earlier stages of CRC. Hence, it is a disease suitable for screening programs [41].

Population-based, organised screening programs are implemented in several European countries, Australia, and Canada, whereas opportunistic screening is implemented in the US and some European countries [42,43]. Screening may involve *stool tests*; immunochemical faecal occult blood test (iFOBT)/faecal immunological testing (FIT), and *endoscopic examinations*; sigmoidoscopy or colonoscopy.

A 2016 evidence report from the Knowledge Centre at the Norwegian Institute of Public Health found that a screening program with sigmoidoscopy lowers CRC incidence and mortality, whereas a screening program with faecal samples lowers mortality but is unlikely to reduce incidence. The report could not draw conclusions regarding the effects of screening colonoscopy due to lacking research evidence, nor could it demonstrate any of the screening methods to reduce the total number of deaths [44]. A recent paper by Bretthauer et. al. evaluated the effect of colonoscopy screening among 84,585 participants in Poland, Norway, and Sweden, and reported a 0.28% risk of death from CRC in the invited group, compared to 0.31% in the usual care group [45].

A pilot study enrolling more than 140,000 Norwegian citizens, conducted to examine the feasibility of a Norwegian screening program, has been running since 2012. It demonstrated superior results for repeated FIT testing compared to sigmoidoscopy with regards to participation rate and detection rate of CRC and large adenomas [46]. The Norwegian CRC screening program started to enrol patients in 2022 and aims to recruit patients aged 55-65 years of age, with repeated FIT testing as the primary screening method.

A parallel study to compare the effects of primary colonoscopy will be conducted, and the intention is to offer colonoscopy as the primary investigation as capacity increases [47]. Colonoscopy capacity is limited in Norway for the time being. A FIT screening program will require 20,000 colonoscopies

annually whereas a colonoscopy-based screening program will require 50,000 colonoscopies annually [48].

Challenges regarding CRC screening have been debated in previous reports [49-51]. A beneficial screening program relies on a high participation rate. The Norwegian 2012 pilot study demonstrated a 52% participation rate for sigmoidoscopy and a 68% participation rate for three cumulative FIT tests [46]. This compares to participation rates reported in other countries [52,53].

6.5.3. Tertiary prevention

Some of the modifiable risk factors associated with the development of CRC have also been demonstrated to affect survival in diagnosed individuals. Tertiary preventive measures aim to reduce the impact of disease in patients with an established diagnose. Smoking and alcohol consumption have been associated with adverse survival rates in diagnosed patients, whereas physical activity may relieve symptoms such as fatigue, and have a favourable impact on QoL and survival [36]. Obese patients may have similar survival to normal-weight patients; hence weight reduction is not recommended as a tertiary preventive measure [54]. Dietary adjustments have not consistently shown to enhance survival but may have a positive effect on the general health. Ongoing studies explore the potential benefits of aspirin in tertiary prevention. Vitamin D supplementation may improve survival in patients with disseminated disease [36].

6.6. Clinical presentation, diagnostic work-up and staging

The clinical manifestations of CRC vary depending on tumour localization and characteristics. Occult bleeding and anaemia occur more frequently in right-sided colon cancer [55]. Change of bowel habits, abdominal pain, and symptoms due to obstruction, are more common in left-sided colon cancer [56]. Macroscopic bleeding is more common in sigmoid colon and rectal tumours. Weight loss and asthenia may be symptoms of disseminated disease.

The systematic examination of a patient to determine the extent of the disease is defined as staging and is essential to offer patients an individually adjusted care. The diagnostic approach adheres to Norwegian national guidelines, and consists of a clinical examination, a colonoscopy with biopsy, a CT scan of the thorax, abdomen and pelvis, an MRI scan of the pelvis whenever rectal cancer is suspected, and a serum carcinoembryonic antigen measurement [57]. A digital rectal examination may reveal distal or middle rectal tumours. A proctoscopy should be performed to measure the distance from the anal verge to the distal limit of rectal tumours.

The fundamental finding for a CRC diagnosis is a histopathological verification of an adenocarcinoma by examining the endoscopic biopsy specimen. CT examinations yield information regarding the local extent of the disease and distant metastases. MRIs yield additional information regarding the local extent of rectal tumours. Endorectal ultrasound may aid in the differentiation of early-stage rectal cancers [58]. CEA measurement may have limited diagnostic value as about one third of patients have normal levels, but grossly elevated levels may indicate metastatic disease or recurrent disease in patients with normalized levels after treatment [59,60].

The diagnostic work-up of CRC at Levanger Hospital has been conducted in concordance with guidelines since 1980, implemented by dr. Tormod Bjerkeset. These guidelines later became the basis for the Norwegian national guidelines, implemented in 1993. Traditionally, the Dukes' classification system has been used for CRC staging [61]. The latest Norwegian national guidelines advocate use of the TNM classification, 8th edition [62]. This classification system is more detailed and gives more comprehensive information with respect to disease stage.

Once the diagnostic work-up is completed there is a summary meeting of the multidisciplinary team where the diagnostic findings are presented, the clinical stage of disease is defined, and treatment planning is undertaken.

6.7. Surgical treatment of CRC

The cornerstone of curative CRC treatment is surgical removal of the tumour. In selected patients, endoscopic resections or local excisions may be adequate. However, a resection of the tumour-bearing bowel segment with sufficient proximal and distal margins, en bloc with the regional lymphovascular tissue, is the therapeutic strategy of choice in most cases. For both colon and rectal cancer, sharp dissection within the mesofascial interface along the embryological planes is the applicable technique. This is reflected by the abbreviations CME (complete mesocolic excision) for colon cancer treatment, and TME (total mesorectal excision) for rectal cancer treatment. The overall treatment objective is to achieve an optimal oncological resection while preserving functionality.

6.7.1. Polypectomy

Malignant polyps with adenocarcinomas that have not extended beyond the submucosa may be eligible for endoscopic resections. Pedunculated polyps (polyps with stalks) are classified according to the Haggitt's classification [63]. Haggitt level 1 and 2 polyps may be radically removed by endoscopic

resections when there is no proof of endovascular invasion, endolymphatic invasion, or a low grade of differentiation. A formal resection should be applied in cases of uncertain R status.

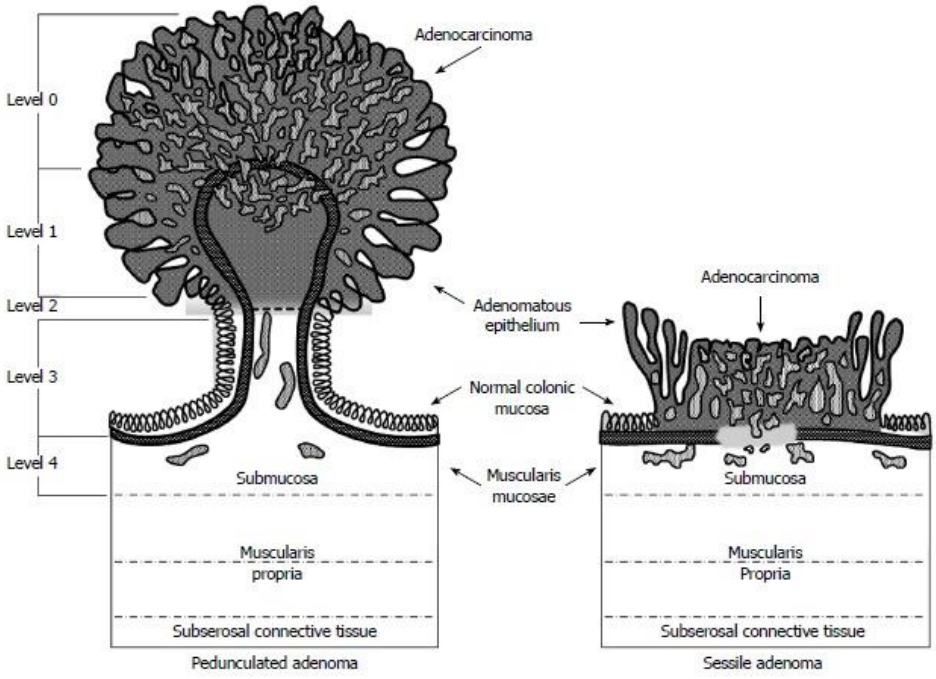


Figure 6. Anatomic landmarks of pedunculated and sessile polyps [64].

Sessile polyps and pedunculated polyps of Haggitt level 4 should be evaluated with respect to the invasion of the submucosa (Sm classification) [65]. Rectal polyps of class Sm1 and pedunculated polyps with uncertain R status may be removed by a full wall excision (TEM or TAMIS). A formal resection is advocated for colon polyps, although there is supporting evidence of favourable outcomes after endoscopic submucosal dissection (ESD) [66].

6.7.2. Major resections for colon cancer

The applicable treatment for colon cancer with the intention to cure is a resection of the tumour-bearing segment and the lymphovascular tissue. Resection margins of 10 cm are recommended by the

Norwegian national guidelines, except in the rectosigmoid junction, where 5 cm is considered adequate [57]. Dissection within the mesofascial interface while preserving the colon and mesocolon in an intact envelope, as described by Hohenberger et. al., is the mainstay surgical principle [67]. The principles of the no-touch technique and en bloc resection are still valid technical aspects to prevent perioperative tumour cell dissemination [68]. Locally advanced T4 tumours with invasion in adjacent structures should be resected en bloc to obtain R0 resections.

Lymph nodes in the lymphovascular tissue are divided into three regions:

- N1 – pericolic lymph nodes
- N2 – intermediate lymph nodes
- N3 – central lymph nodes

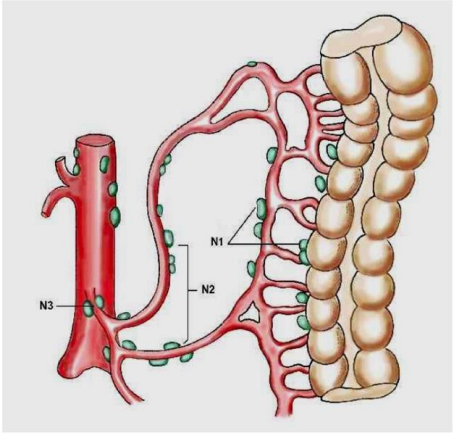


Figure 7. Schematic figure of lymph node stations in the left colon [57].

The extent of the lymphovascular resection is a topic of ongoing debate. A D2 resection (involving the N2 lymph nodes) is advocated as a minimum by the Norwegian national guidelines [57]. The benefits of a central ligation ("high tie») and a D3 resection in terms of good oncological outcomes, a higher number of harvested lymph nodes, and the potential of curative resections in patients with central lymph node metastases, should be acknowledged, but reports have demonstrated that vascular injuries may be more frequent [69,70]. Conflicting evidence exists regarding the benefits of a D3 resection with respect to long-term survival [71-73]. It will hopefully be clarified by ongoing randomised trials [74,70].

6.7.3. Major resections for rectal cancer

Dr. Tormod Bjerkeset was a pioneer within the field of surgery in Norway during the late 1970s. He started his career at the Department of Surgery, Haukeland University Hospital in Bergen, Norway, and was appointed chief of the Department of Surgery at Innherred Hospital (later Levanger Hospital)

from 1980. New techniques evolved in this era as rectal cancer surgery was associated with unacceptably high rates of local recurrence [75]. Dr. Bjerkeset advocated the use of surgical dissection outside the mesorectal fascia under visual control. This technique was applied to all patients at the hospital and adheres to the principles of total mesorectal excision (TME).

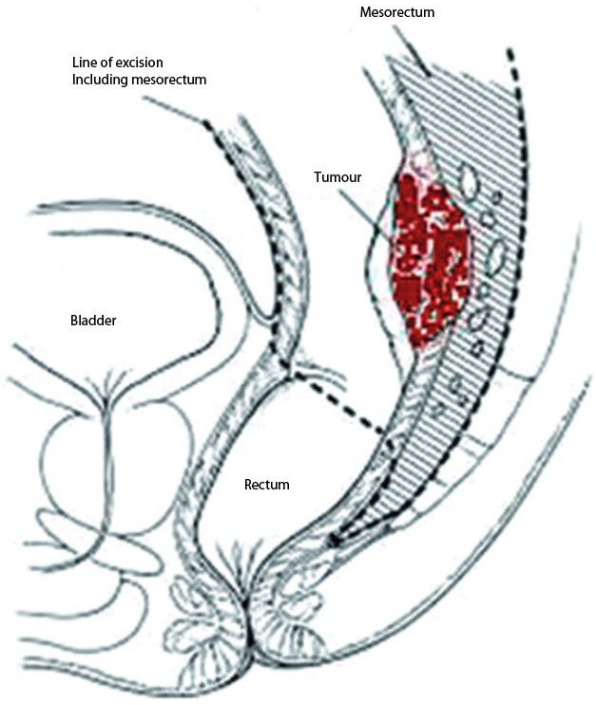


Figure 8. Principles and extent of Total Mesorectal Excision (TME) [76].

Bill Heald is recognized as the father of the TME technique. This technique was presented in 1982 and would be the most important hallmark of rectal cancer surgery in the years to come, resulting in lower rates of local recurrence and improved survival [77]. A TME is defined by a complete removal of the rectum and the lymphovascular tissue in the mesorectum. By sharp dissection along the mesofascial interface, termed «the holy plane» by Heald, an optimal oncological resection is achieved whereas preservation of nearby anatomical structures is possible [78]. Dissection in the holy plane allows for adequate circumferential resection margins. A partial mesorectal excision (PME) with a 5 cm distal margin is applicable for proximal rectal tumours [79].

Considerations with respect to the extent of the resection depend on tumour localization and various tumour characteristics. Generally, a low anterior resection, with or without a diverting stoma, applies for tumours in the proximal and middle rectum. A Hartmann's procedure may be a feasible solution in

selected patients due to the avoidance of an anastomosis and the potentially hazardous effects of an anastomotic leak. An abdominoperineal resection applies for tumours in the distal rectum.

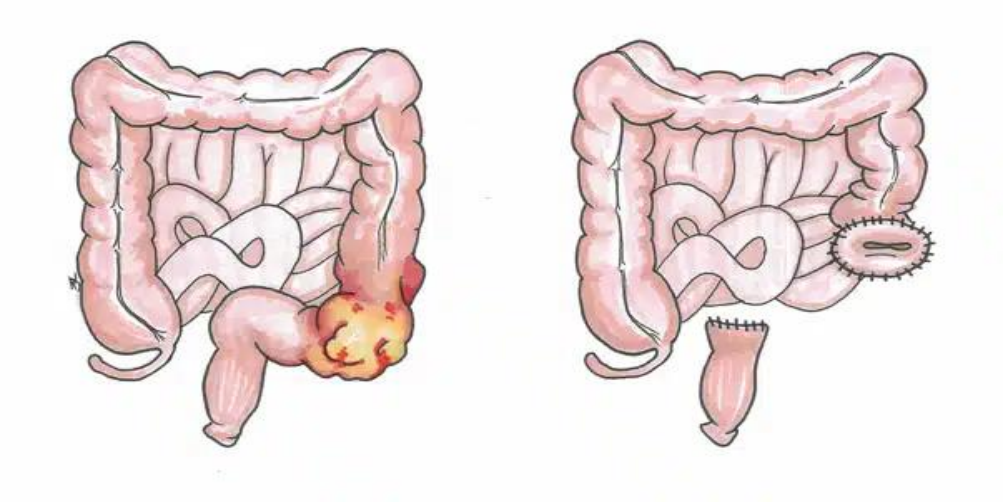


Figure 9. Hartmann's procedure.

Source: https://teachmesurgery.com/consent/emergency-general/consent-hartmanns-procedure/

6.7.4. Minimally invasive surgery

The first laparoscopic colon resection was reported in 1991 and started an era where laparoscopic surgery for CRC would be increasingly dominating [80]. Minimally invasive surgery has now become the preferred approach when treating CRC. In 2021, 75.6% of Norwegian patients with colon cancer and 84.2% of patients with rectal cancer underwent laparoscopic surgery [81].

Previous papers comparing open and laparoscopic surgery in patients with colon cancer have demonstrated equal outcomes with respect to oncological outcomes and complication rates [82]. Laparoscopic surgery may be superior regarding incisional hernias and adhesional intestinal obstruction [83].

Comparison of open and laparoscopic surgery for rectal cancer has demonstrated equal outcomes with respect to short- and long-term survival [84]. Shorter length of stay and lower complication rates have favoured laparoscopic surgery. However, recent reports have demonstrated inferior oncological quality of the histological specimen in patients treated with a laparoscopic approach, although the impact on long-term survival remains uncertain [85].

Reports comparing outcomes between older and younger patients after minimally invasive surgery for CRC have demonstrated equal outcomes across age-groups, hence minimally invasive surgery is a feasible approach in older patients with CRC [86-88].

Robotic surgery has become increasingly popular and more available in recent years. It is especially beneficial when performing rectal resections due to the tight anatomical space in the pelvis [89]. Transanal microinvasive procedures may be a feasible treatment in selected patients with early-stage rectal cancer [90].

6.7.5. Surgery for colorectal metastases

Surgery for CRC metastases has become frequently more common during the last decades. Roughly 20% of the patients have synchronous liver metastases at the time of diagnosis, 25-40% of the patients develop liver metastases during their later course of disease [91], and 5-10% develop lung metastases [92,93]. Treatment options for CRC have increased in number and quality, resulting in a higher proportion of patients found eligible for metastases surgery. In selected patients, treatment with curative intention may be attainable even in the setting of disseminated disease [94]. Cytoreductive surgery and hyperthermic intraoperative chemotherapy (HIPEC) may be considered in cases of isolated peritoneal dissemination [95].

6.7.6. Palliative surgery

A palliative resection, diverting stoma or by-pass, may be the only feasible treatment in cases with symptoms due to obstruction or severe anaemia. Previous reports have documented a declining rate of palliative procedures over the last decades [96,97]. Improvements in oncological and palliative care may partly explain this trend. Patients considered for palliative surgery are more often older with co-morbid conditions [98,99]. Surgical intervention in this group of patients is associated with high perioperative morbidity and mortality, with a reported median survival of 1-6.5 months [100,101]. The role of primary tumour resections in Stage 4 disease should be addressed in future studies as current evidence have demonstrated inconsistent results with respect to survival [102].

6.7.7. Emergency surgery

Roughly 10-30% of patients with CRC present with emergency symptoms necessitating acute care [103,104]. Most patients have colon cancer, and the most common symptoms include obstruction,

perforation, and bleeding. Emergency surgical treatment of CRC is associated with high morbidity and mortality [105,106]. Older patients are more likely to present with emergency symptoms and more frequently have physiological derangements, malnutrition, dehydration and associated co-morbid conditions. Moreover, they have higher rates of advanced cancers with lymphovascular invasion and synchronous lever metastases [107].

6.8. Complications related to surgical treatment of CRC

The rates of complications related to CRC surgery depend on factors such as tumour localisation, stage of disease, surgical procedure, patient selection, level of institution, and rate of emergency surgery [108]. The various kinds of surgical procedures may result in different alterations and reconstructions of the GI tract, and complications may range from acute infectious complications to permanent physical derangements [109]. Complications may be particularly devastating in older patients with limited capacity to withstand the associated physiological stress, hence an important determinant when choosing upon the individual treatment strategy.

Surgical complications may be classified according to various classification systems [110,111]. One of the most common classification systems was proposed by Clavien and Dindo and classifies complications according to the therapy necessary to treat them [8].

6.8.1. Acute surgical complications

Anastomotic leaks are one of the most feared complications related to CRC surgery with reported rates of 2-20% [112-114]. They are associated with higher recurrence rates and increased morbidity and mortality [115]. Rectal resections have higher leak rates compared to colon resections, with the level of the anastomosis being the most important predictive factor [116-118].

Postoperative paralytic ileus is a common complication after CRC surgery, and is affected by factors such as anaesthesia, inflammation, and surgical trauma. Enhanced recovery after surgery (ERAS) protocols and laparoscopic surgery have been demonstrated to lower rates of postoperative ileus [119].

Postoperative bleedings associated with CRC surgery are reported in 1-14% of all cases and depend on tumour-related characteristics, patient co-morbidities, the use of anticoagulants/antiplatelet drugs, and the performed surgical procedure [120].

6.8.2. Infectious complications

The term *surgical site infection* (SSI) denotes infections in the incision or the deep tissues at the operation site occurring within 30 days after surgery. SSIs are reported in 3-45% of cases of open CRC surgery, and increase the risk of postoperative mortality, length of ICU stay, length of stay, and re-admission rates [121,122]. A recent systematic review identified male gender, obesity, diabetes mellitus, ASA score, cigarette smoking, tumour location and albumin level as patient-related risk factors for SSIs but did not demonstrate an association with age. Treatment-related risk factors encompassed laparoscopic surgery, operation time, blood loss, blood transfusion and abdominal surgical history [123].

Infections acquired in hospital or health care institutions such as pneumonia or urinary tract infections, appearing 48 hours or more after hospital admission or within 30 days after receiving health care, are defined as *healthcare associated infections* (HAIs), previously termed *nosocomial infections* [124]. A 2018 prospective report, evaluating 448 Chinese patients treated for CRC, demonstrated a HAI rate of almost 9% and on average a 6-day prolonged LOS [125].

6.8.3. Stoma-related complications

The construction of a diverting or terminal stoma may be a temporary or permanent measure in CRC treatment. Stoma-related complications are frequent with reported rates of 10-70%. They are commonly classified as early and late, ranging from skin irritation, high-output stomas, and necrosis, to parastomal hernia, prolapse, and stenosis. Distressing complications such as odour, leakage, and soiling occur frequently with negative impact on QoL [126,127].

6.8.4. Low anterior resection syndrome

Low anterior resection syndrome (LARS) is a constellation of symptoms following rectal resections [128]. Symptoms occur due to impaired anorectal function and encompasses symptoms such as diarrhoea, urgency, incomplete emptying, and incontinence. A Swedish series examining 481 patients undergoing a curative resection for rectal cancer reported a LARS prevalence rate of 77.4%, with 53.1% of the patients experiencing major LARS [129].

6.9. Oncological treatment of CRC

6.9.1. Adjuvant and neoadjuvant treatment

Adjuvant chemotherapy is given with the intention to eradicate micro-metastases and improve long-term survival in Stage III and selected patients with Stage II colon cancer. It is recommended to start within 6 weeks after surgery and is commonly given as 3- or 6-months regimens. Norwegian guidelines for CRC treatment advocate adjuvant treatment for patients >75 years only in selected cases [57]. Trials have investigated the role of neoadjuvant chemotherapy in T3-T4 colon cancer and demonstrated improved surgical outcomes, whereas benefits with respect to long-term survival are unclear [130,131]. Although advocated by some authorities abroad, adjuvant chemotherapy is not part of standard care of treatment for rectal cancer in Norway as current evidence to support this is insufficient [132].

Preoperative neoadjuvant radiotherapy with concomitant chemotherapy is given in selected cases of rectal cancer. The introduction of neoadjuvant radiotherapy in addition to the TME technique, was a major hallmark of rectal cancer treatment during the 1980s, resulting in considerable improvement concerning local recurrence rates and long-term survival [133].

Postoperative adjuvant radiotherapy with concomitant chemotherapy is shown to reduce the rate of local recurrences and improve survival for rectal cancer in cases with R1- and R2-resections, tumour perforations or bowel perforations in proximity to the primary tumour [134].

Chemotherapy may be applicable as both neoadjuvant and adjuvant treatment in selected cases of CRC with liver metastases. Approximately 20-30% of these patients may be selected for operative treatment [91]. In a neoadjuvant setting the use of chemotherapy may convert borderline resectable tumours into resectable tumours. The benefits of adjuvant chemotherapy after hepatic resections are not settled, although previous reports have demonstrated increased survival [135,136].

6.9.2. Palliative treatment

Roughly 25% of patients with CRC are not eligible for curative treatment due to disseminated disease at the time of diagnosis, and approximately 50% of patients will develop metastases in the later course of disease [137]. Treatment of this patient group focuses on improved QoL, reduced symptom load, and prolonged survival.

Palliative radiotherapy may yield local control and relieve symptoms in patients with non-resectable rectal cancer or local recurrences [138]. These patients may have considerable complaints and morbidity due to tumour invasion, such as pain, hydronephrosis, diarrhoea, and rectal bleeding.

Palliative radiotherapy may be a feasible treatment in older, co-morbid patients with resectable tumours, where a radical resection is not considered an option due to the physiological impact associated with surgery, or in patients with short life expectancy [138].

Chemotherapy should be considered as palliative treatment in patients with disseminated disease. It may alleviate symptoms, reduce tumour associated complications, and prolong survival [139]. A 2012 report by Glimelius et. al. reported increased median survival from 6 months 24 months in metastatic CRC since the 1980s due to improvements in chemotherapy [140].

6.10. Survival

Next to lung cancer, CRC is the second leading cause of cancer deaths both worldwide and at a national level [10]. In Norway, the long-term relative survival in patients with colon cancer has increased from 48.6% during 1981-1985 to 69.7% during 2017-2021. The long-term relative survival for rectal/rectosigmoid cancer has increased from 43.8% to 71.9% in the respective periods.

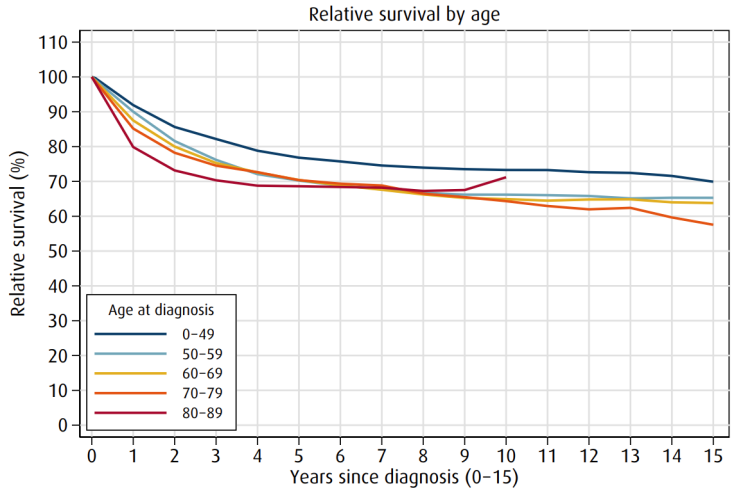


Figure 10. Relative survival up to 15 years after diagnosis of colon cancer in Norway [3].

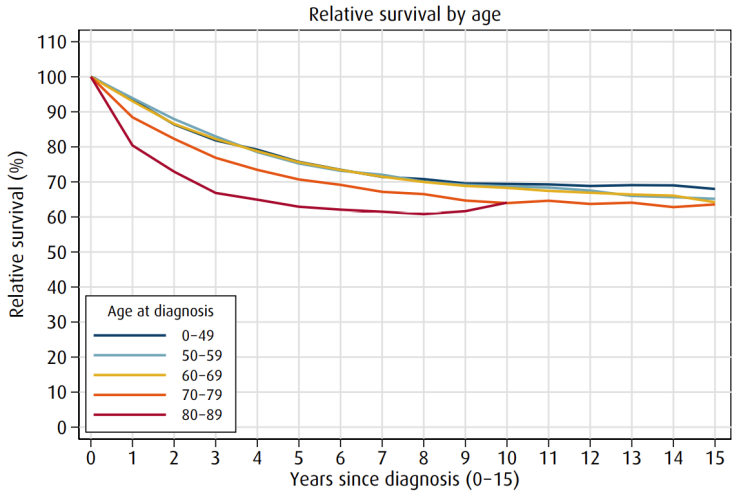


Figure 11. Relative survival up to 15 years after diagnosis of rectosigmoid or rectal cancer in Norway [3].

During 2017-2021 the five-year relative survival rates for localised, regional, and distant colon cancer were 97.1%, 85.3% and 16%, respectively. The five-year relative survival rates for localised, regional, and distant rectal/rectosigmoid cancers were 97.5%, 81.2% and 25%, respectively [3].

6.11. Special considerations in older patients with CRC

Approximately 60% of patients treated for CRC are >70 years of age and 40% are >75 years of age at diagnosis [141]. These rates are expected to increase in the coming years. Balancing between adverse survival rates associated with undertreatment and increased morbidity and mortality associated with overtreatment is one of the main challenges when treating older patients with CRC.

6.11.1. Frailty

Although there is no internationally recognised standard definition, frailty may be defined as a distinctive, age-associated health state due to a deterioration in multiple body systems, resulting in a physiological decline in the capability to withstand stress [142]. Frailty differs from ageing, disability, and co-morbidity, yet it is closely related to these factors [143]. In Norwegian language *vulnerability* is commonly used, or synonyms such as *weakness*, *incapacity*, or *fragility*. Socioeconomic factors, psychological factors, nutritional state, polypharmacy, physical activity, and co-morbid conditions are linked with frailty development [143].

Frailty has been demonstrated to occur in roughly half of patients >65 years undergoing surgery for CRC and 6-86% of older patients with cancer [144]. It is associated with higher risk of complications, readmissions, increased LOS and decreased long-term survival [145].

The exact pathophysiological aetiology behind frailty is not known, but a cumulative age-associated cellular damage and an inability to maintain system homeostasis is anticipated [146]. Pre-frailty or latent frailty is recognised as a precursor to frailty and may manifest as frailty in the presence of acute stressors, such as acute illness or injuries.

6.11.2. Comprehensive geriatric assessment

A comprehensive geriatric assessment (CGA) is a thorough interdisciplinary evaluation of a patient's global health, functional status and reserve capabilities, and the benchmark test to detect frailty. It is both a diagnostic tool and a treatment process, aiming to maximize the overall health in aged patients. A CGA may yield important prognostic information that may impact on treatment strategies, predict changes in QoL, reveal unknown geriatric conditions, and allow targeted interventions in older patients [147].

Despite evidence favouring the use of CGA, there is an underutilization of this tool in the diagnostic and perioperative work-up of patients with CRC [148]. A standard method for the measurement of frailty is desirable, as it would allow for a consistent recognition of frailty. CGAs may be time consuming and necessitate the involvement of multiple specialists. However, simplified and less time-consuming assessment tools have been proposed. They may be feasible in everyday practice and as effective as CGAs [142].

6.11.3. Geriatric syndromes

Geriatric syndromes refer to health conditions common in older patients which may have multifactorial causes and are not necessarily associated with distinct organ-related pathology. They may have major impact on QoL and are associated with morbidity and poor outcomes [149]. The list includes several conditions, such as incontinence, malnutrition, pressure ulcers, falls, gait disorders, fatigue, dizziness, delirium, and cognitive impairment. In a review of patients admitted to vascular and urology units, these conditions were present in nearly one third of the patients >65 years old [150].

The most common understanding of the association between frailty and geriatric syndromes defines frailty as a geriatric syndrome [151]. However, there is some inconformity in the literature [152].

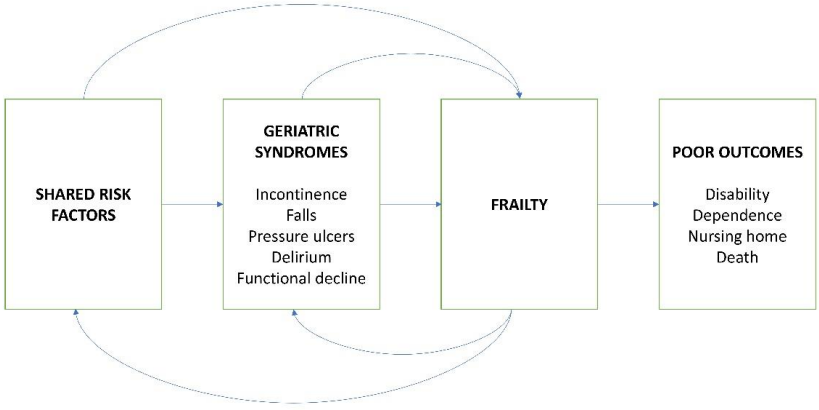


Figure 12. Association between frailty and geriatric syndromes.

Geriatric syndromes are important to detect, as multi-faceted interventions can be initiated to prevent further functional impairment. They should gain special attention in both the preoperative work-up and the post-operative course of CRC treatment, as interventional measures may improve postoperative outcomes [150].

6.11.4. Prehabilitation

The traditional approach to treating patients with major surgery has been to perform the surgical procedure and then focus on postoperative care, with the goal of restoring the patient's baseline levels of physiological capacity, cognition, ADL, and QoL. Efforts have been made to enhance the postoperative convalescence, such as implementation of ERAS protocols [153]. A 2004 paper evaluating patients ≥60 years undergoing major abdominal surgery, reported a 20-40% loss in physiological and functional capacity postoperatively. Additionally, 10-50% had prolonged disability and did not recover to the preoperative level after 6 months [154].

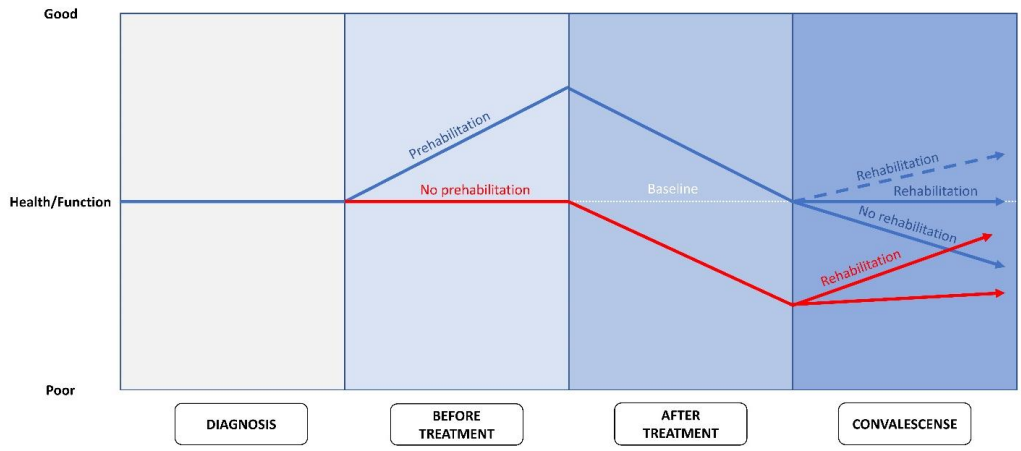


Figure 13. Principles of prehabilitation.

Efforts to improve the capacity to withstand stress in advance of surgery is termed prehabilitation and may consist of multimodal interventions such as nutritional optimalisation, physical exercise, anxiety reduction, optimalisation of co-morbid conditions, and smoking/alcohol cessation [155]. The preoperative phase may be a better period to enhance factors that contribute to a quick recovery, as the patient may be more motivated and can take active part in the preparations. It may increase patient autonomy and lessen the psychological and physiological trauma. The components and the duration of prehabilitation must be designated according to the surgical procedure and in concordance with results from a CGA.

6.11.5. Patient preference

A dilemma when treating older patients with CRC is that the effects of treatment may impact severely on QoL. Potential beneficial and adverse effects of treatment must be thoroughly assessed. It is of relevance to define the prioritized treatment aims in partnership with the patient. Treatment aims in older patients may deviate from those in younger patients, as they are more likely to choose functional status over survival [156]. A 2022 systematic review, evaluating patient preference for treatment outcomes in oncology, found QoL to be most important for older patients next to survival [157]. Well-informed patients are more satisfied and less likely to regret treatment decisions [158,159]. A 2014 systematic review concluded that the most consistent determinant affecting older patients' cancer treatment decisions were the physicians' recommendations [160].

7. Aims of the study

The incidence of CRC has increased over the last decades and is expected to increase in the years to come. We wanted to evaluate how the incidence of CRC has changed and predict future changes in our hospital's catchment area. Paralleling the increasing incidence, older patients will constitute a successively greater share of the population with CRC. We wanted to evaluate short- and long-term survival in octogenarian patients undergoing a major resection with curative intent for colon cancer, and evaluate treatment, postoperative complications, and survival in patients ≥80 years treated for rectal cancer.

In more detail, the aims of the three studies were to:

Paper I:

Assess trends in incidence and presentation of CRC during 1980 to 2016 in a stable population in Mid-Norway and predict the future burden of CRC in the same catchment area.

Paper II:

Evaluate the long-term relative survival of octogenarian patients with colon cancer after a major resection with curative intent.

Paper III:

Evaluate treatment, postoperative complications, and survival in patients ≥80 years treated for rectal cancer.

8. Material and methods

8.1. Description of the cohort

All patients diagnosed with CRC at Levanger Hospital during the 37-year period between January 1980 and December 2016 were included. Patients were identified through the discharge diagnosis in the patient administrative system, using ICD-8 diagnosis codes 153.01 to 154.19, ICD-9 codes 153.0 to 154.1, and the ICD-10 codes C18.0 to C20. To ensure a complete cohort, all data were crosschecked and confirmed with data in the Norwegian Cancer Registry. The Norwegian Cancer Registry registers all new cases of cancer in Norway. The cohort represents an unselected population.

Levanger Hospital is the primary hospital for 10 municipalities in North-Trøndelag County, located in Mid-Norway. The hospital's catchment area has remained unchanged throughout the observation period. The population rose by 19% from 83,890 in 1980 to 99,566 in 2016. North-Trøndelag County consists of a long coastline, large farmlands, and forests. Mean income and education level are slightly less than the national average. Agriculture is the most important industry.

Patients with malignancies other than adenocarcinoma (pseudomyxoma peritonei, neuroendocrine tumours, sarcomas, GISTs and lymphomas) were excluded from the cohort.

8.2. Study design

Paper I is a single centre retrospective cohort study. All 2268 patients diagnosed with CRC at Levanger Hospital during 1980 to 2016 were included.

Paper II is a single centre retrospective cohort study. All 1530 patients diagnosed with colon cancer at Levanger Hospital during 1980 to 2016 were included.

Paper III is a single centre retrospective cohort study. All 666 patients treated for rectal cancer at Levanger Hospital during 1980 to 2016 were included.

8.3. Clinical follow-up

Clinical follow-ups were conducted according to local guidelines from 1980 to 1992. Starting in 1993, follow-ups were conducted according to similar national guidelines [57]. Follow-ups lasted for 5 years but were extended in selected cases. Follow-up time was calculated as the patient-years at risk, starting from the date of admission. The end of follow-up was December 31st, 2018.

8.4. Statistical analyses

Analyses were performed with STATA 16 (StataCorp. College Station, TX: StataCorp LLC), IBM SPSS Statistics 25 (IBM Corp. Armonk, NY: IBM Corp), and StatXact 9 (Cytel. Waltham, MA).

The Cochran-Armitage exact trend test was used to test for trends in proportions; for example, the proportion of Hartmann's procedures performed per decennium, or the proportions of elective surgeries vs. emergency surgeries in different age groups.

The Joncheere-Terpstra test was used to test for trends between an ordinal independent variable and an ordinal dependent variable; for example, trends in age-groups across time-periods, or trends in blood loss volumes across time-periods.

The Kaplan-Meier method is a statistical method used to analyse time to event data, commonly used in survival analyses. Kaplan-Meier analyses were performed to estimate 5-year rates of local recurrences and metastases.

The Exact Unconditional z-pooled test was used to compare binomial proportions; for example, the percentage of reoperations, relative to the percentage of emergency or elective primary operations.

Logistic regression analysis

Logistic regression analysis is used to study the association between a categorical dependent variable and one or more independent variables. In most settings, the dependent variable is dichotomous, and the appropriate version is *binary logistic regression*, usually for short denoted *logistic regression*. This was used to study associations between 90-days mortality and different explanatory variables.

O*rdinal logistic regression* is used when the dependent variable has three or more ordinal outcomes; for example, tumour stage by time-period, or ASA score in different age-groups.

Multinomial logistic regression is used when the dependent variable has three or more multinomial (unordered) outcomes; for example, type of treatment in different age-groups, or localization of tumour in different time-periods.

Relative survival analysis

Relative survival analysis was used in Paper II and Paper III. Relative survival may be defined as the ratio of the proportion of observed survivors in a cohort of individuals with a specific disease, compared to the proportion of expected survivors in the general population, over a certain time period.

In our studies, the observed survival in the group with cancer was divided by the expected survival of a comparable group in the general Norwegian population, matched with respect to age, sex, and calendar year of investigation. The Norwegian population survival probabilities were downloaded from the Human Mortality Database, for every year from 1980, calculated for groups and stratified by sex and age [161].

The relative survival analyses were estimated with the Ederer II method and analysed with STATA 16 (StataCorp. College Station, TX: StataCorp LLC). The Ederer II method is one of the most common methods to calculate relative survival. Matched individuals are considered to be at risk until the corresponding patient is censored or dies.

Multivariable analyses

Multivariable analysis is used to determine the relative contributions of different causes to a single outcome. Multivariable analyses were performed with a full likelihood approach.

Incidence rate, incidence rate ratio, Poisson regression

The overall incidence of CRC was defined as the number of new cases in the defined population within one year. The incidence rate was defined as the incidence divided by the total person-time at risk during the same year. Incidence rate ratio was defined as the ratio between two incidence rates. Effects of calendar year and age on the number of patients presenting with CRC was calculated with Poisson regression and illustrated with fractional polynomials (Paper I).

Survival and mortality

Overall survival:

The proportion of patients still alive for a defined time period after they were diagnosed with a disease.

Relative survival:

The ratio of patients who survived after they were diagnosed with a disease, compared to survival of the general population from which they arise, matched for sex, age and time period.

Short-term mortality:

Mortality within 90 days after surgery.

Long-term relative survival:

Long-term relative survival in patients who survived the first 90 days after surgery.

8.5. Ethical approval

The Regional Committee for Medical and Health Research Ethics (REC) granted permission for the study (Reference: 2016/2172/REK Midt). The project was performed in accordance with the Declaration of Helsinki. Written informed consent was waived due to the retrospective observational nature of the study. All treatment was given according to local guidelines from 1980 to 1992, and according to similar, national guidelines from 1993 to 2016.

9. Summary of results

9.1. Paper I

In the first paper, we included all 2268 patients diagnosed with CRC at Levanger Hospital from 1980 to 2016. We used Poisson regression to calculate the incidence rate ratio (IRR) and analysed factors associated with changes in incidence.

The incidence of CRC in the catchment area of Levanger Hospital increased from 43/100,000 person-years during 1980 to 1984, to 84/100,000 person-years during 2012 to 2016. The annual unadjusted IRR increased by 1.8%, corresponding to an overall incidence increase by 94.5%. Lifestyle-associated factors could be attributed to 72% of this increase, whereas changes in the population regarding sex and age could be attributed to 28%. Our predictions estimate a 40% incidence increase by 2030 and a 70% incidence increase by 2040, compared to the incidence rate in the last five-year period (2012-2016). Over time, we observed a higher rate of earlier cancer stages.

9.2. Paper II

In the second paper, we evaluated survival in octogenarian patients treated for colon cancer with a major resection with curative intent. All 1530 patients treated for colon cancer at Levanger Hospital from 1980 to 2016 were included. We examined short- and long-term survival and analysed explanatory variables, with a special focus on octogenarian patients.

The short-term mortality rate after a major resection with curative intent was 9.3% in octogenarian patients, and significantly higher than in younger patients. In octogenarians surviving the first 90 days after surgery, the long-term relative survival was 98.7% and comparable to the long-term relative survival rates of younger patients. The incidence of colon cancer in octogenarian patients more than doubled when comparing the first time-period (1980 to 1989) to the last (2010 to 2016). An increasing proportion of octogenarian patients were selected for surgery. Age, ASA score, and emergency surgery were associated with adverse short-term survival, whereas a CCI, ASA score, TNM stage, residual tumour, and emergency surgery, were associated with adverse long-term survival.

9.3. Paper III

In the third paper, we evaluated treatment, complications, and survival in patients ≥80 years treated for rectal cancer. All 666 patients treated for rectal cancer at Levanger Hospital from 1980 to 2016 were

included. We examined short- and long-term survival and analysed explanatory variables, with a special focus on patients ≥80 years.

Patients ≥80 years were less likely to undergo radical treatment for rectal cancer, despite comparable cancer stages across age-groups. The rate of postoperative complications was 47.6%. The severity of complications was associated with age, ASA score and >400 ml perioperative blood loss. Patients ≥80 years undergoing a major resection with curative intent, had a non-significant adverse short-term mortality of 5.9% compared to younger patients. In patients ≥80 years surviving the first 90 days after surgery, the long-term relative survival was comparable to that of younger patients.

10. Discussion

10.1. Discussion of main findings

Substantial changes regarding incidence, diagnostics, treatments, and outcomes of CRC have taken place since the 1980s and to current date. Changes in living habits, exposure to risk factors, increased life expectancies, and altered age compositions of the population, have resulted in increasing incidence rates of CRC. Precise diagnostic tools have become readily available and led to a higher number of patients undergoing a diagnostic work-up for suspected CRC. Multidisciplinary teams have established a new benchmark for the evaluation of the diagnostic work-up and treatment decision making. Evolvements in the fields of surgery and oncology have multiplied treatment options, improved quality, and increased survival rates.

Older patients constitute more than half of the patients with CRC. This proportion will increase in the years to come. Older patients differ markedly from younger patients due to great individual differences regarding co-morbid conditions, polypharmacy, physiological and cognitive impairments, frailty, social networking, and functional dependency [162,163]. The proportion of patients undergoing curative treatment for CRC decreases with age [164]. Those selected for curative treatment have adverse rates of morbidity and mortality compared to younger patients, which demonstrates the challenge regarding treatment selection [165,166].

The present work emphasizes the importance of keeping these rates at a minimum level. Older patients with increased co-morbidity and high ASA scores are especially prone to undergo adverse events such as emergency surgery, perioperative blood loss, and postoperative complications. Future improvements in the quality of CRC treatment in older patients rely on measures aiming to lower rates of morbidity and short-term mortality. This is the key to further improve long-term survival in this patient-group.

Staging

Modern CRC treatment is based on an adequate diagnostic work-up and exact staging of the disease. Disease stage is the most important prognostic factor [167]. Previous reports have demonstrated age-specific, gender-specific, and geographical differences with respect to CRC staging [168,169]. Gabriel. et. al. demonstrated more advanced disease in African Americans and Hispanics <50 years of age [170], whereas White et. al. found higher rates of Stage I disease at diagnosis among males [169]. A 2019 population-based study reported known stage in 88.9% of Norwegian patients with CRC, compared to 83.2% in English patients and 94.3% in Swedish patients. Patients with unknown stage were less likely to undergo resectional surgery and had survival rates comparable to patients with advanced

stages [171]. In our cohort, we observed a declining rate of unknown disease stage throughout the study period. It was initially higher among older patients, but in the last observation period no patients ≥80 years had unknown stage. This may indicate a liberal and age-independent approach to the diagnostic work-up of suspected CRC. The Norwegian health care system is fully funded by the government, which may have contributed to this observation, as every citizen has free access to state-of-the-art medical services.

Throughout the observation period we observed a trend towards earlier disease stages at diagnosis. This could be due to the increased availability of diagnostic tools and lowered threshold for diagnostic work-up but could also imply a higher awareness of disease among physicians and patients. Diverging time trends have been observed in previous papers [172-174]. We observed no significant differences in stage distribution across age-groups, indicating the relevance of factors other than age on the impact of disease stage at diagnosis. Observations of earlier stages in older patients and increased rates of advanced disease in younger individuals have been demonstrated in previous reports. This may imply a more aggressive tumour biology and a more severe impact of lifestyle-associated factors in younger patients [174,175,170]. In our cohort, right-sided colon cancer occurred more frequently in older individuals which coheres with previous observations [176-178]. Previous papers have demonstrated adverse outcomes for right-sided colon cancer [179-181].

Treatment decision making

Treatment discrepancies across age-groups despite comparable disease stages have been reported by other authors [165,166]. These observations may seem reasonable, as the prevalence of co-morbid conditions and age-related impairments that may contradict treatment are higher in the aged population [162]. The 2018 EURECCA report evaluated treatment and survival in octogenarian patients with colon cancer in several European countries and demonstrated substantial variation in treatment despite similar national treatment guidelines [182]. Treatment decision making in older patients may be liable to subjective judgements or institutional culture. The inclination to undertreat older patients is apparent.

One of the most essential considerations during treatment decision making is to evaluate the individual patient´s prerequisites to undergo the intended treatment weighed against potential risks. Patient-related factors are generally approached based on the interpretation of the examining physician and previous medical records. ASA score is one of the most common risk scores in everyday clinical practice [183]. In our cohort, it was the only objective criterion used in preoperative risk stratification and consistently associated with postoperative complications and increased short-term mortality. The subjective nature of clinical evaluations and interpretations, coupled with a limited number of patient-related factors, limits the usefulness of this tool for treatment decision making in older patients[184]. In our cohort, CCI was retrospectively analysed and found to be associated with adverse postoperative

outcomes. A previous report has shown that CCI may be a useful predictor of treatment outcomes in older patients with CRC[185].

A higher proportion of older patients are considered eligible for treatment nowadays compared to the 1980s [186]. Substantial progress has been made regarding treatment of medical conditions, and advances in surgical, anaesthetic, and intensive care techniques have improved perioperative morbidity and mortality. A Dutch 2012 report conducted to assess the impact of comorbidity on postoperative outcomes after CRC surgery, concluded that comorbidity was an independent risk factor for adverse outcomes irrespective of comorbidity measure, but had limited value in risk stratification [187]. Due to the complexity of older patients, assessments that delve beyond a numerical or categorical registration of their co-morbid conditions are necessary to assist in treatment selection. Implementation of relevant objective assessments should gain priority to surmount current standards.

Surgery

In our cohort of patients with colon cancer, patients aged ≥80 years were more likely to undergo emergency surgery, associated with increased morbidity and mortality. A Norwegian 2021 report demonstrated increased rates of emergency surgery with age, advanced disease, and comorbidity [107]. Patients in the emergency setting may suffer from uncorrected medical conditions, ongoing therapy with unfavourable medications, physiological derangements, and immunosuppression. This may increase complication rates and rule out definitive surgery [188,189]. In our cohort of patients with colon cancer, anaemia was associated with postoperative complications. Anaemia has previously been associated with adverse postoperative outcomes, although it was unclear if it was an independent risk factor, or a marker of underlying disease [190]. Tumour dissemination and a more aggressive tumour biology may contribute to the adverse long-term survival [191].

In previous literature, the association between emergency surgery and adverse postoperative outcomes are consistent, whereas the association with age is diverging [104,192]. Rates may vary between countries, selection of patients, and by the definition of emergency surgery [107]. The observed rates in our study coincide with previous reports [193]. In a 2016 paper by Renzi et. al., 16-22% of patients with emergency CRC had three or more consultations where they presented relevant symptoms during the year before diagnosis [194]. A high awareness of disease among caretakers and primary physicians are especially relevant in this patient-group.

The impact of age on elective surgery is especially prominent regarding rectal cancer treatment [195]. The most common procedure of choice, a low anterior resection, is an extensive surgical procedure and involves the construction of an anastomosis. The fear of anastomotic leaks, associated with increased morbidity and mortality, may be decisive in cases with poor performance status and severe

co-morbid conditions. The rate of anastomotic leaks is higher for rectal resections compared to colon resections, and the impact on functional and oncological outcome is more severe [196].

Older patients are more likely to undergo non-restorative procedures or local excisions [195,197] . We observed an increasing proportion of patients undergoing a HP for rectal cancer. This has also been observed by other authors [198]. The HP rate increased five-fold during the study period and could partly be explained by the increasing rate of older patients with higher ASA scores. Nevertheless, the increase in the HP rate superseded the increase in rate of older patients; hence additional explanatory factors must have contributed to this observation.

The most apparent advantage of a HP is the avoidance of an anastomosis. In our cohort, the increasing rate of this procedure could reflect an attempt to counterbalance the risk of severe complications. Objective criteria should lay the grounds for the selection of surgical strategies, as both HPs and low anterior resections are encumbered with high rates of morbidity due to stoma-related complications and low anterior resection syndrome, respectively. A 2012 Cochrane review found no differences in quality of life among stoma and non-stoma patients treated for rectal cancer [199]. Verweij et. al. reported comparable outcomes in older and younger patients with respect to limitations and psychosocial impact, although the need for help with ostomy care was higher among older patients [200].

Adaption of treatment strategies in older individuals is necessary to offer an optimal individually adjusted care. Older patients are likely to prioritise QoL above survival [156]. Physicians may be forced to balance treatment aims in between an ideal oncological result and an acceptable functional result. Physical limitations may be decisive for the choice of surgical strategy and may justify a less aggressive treatment approach.

Complications

Major resections for CRC surgery are associated with high rates of morbidity and mortality, with reported rates of 30-40% and 6-8%, respectively [201-204]. In our cohort of rectal cancer patients, the severity of postoperative complications increased with age and the rate of reoperations increased over time. A parallel increase in ASA scores might reflect higher rates of frail patients. The increased accessibility to precise diagnostic tools may have led forward to a more aggressive surgical approach regarding complications. Over time, more surgeons were involved in rectal cancer treatment, which may have contributed to a less cohesive strategy. In our cohort, perioperative blood loss was associated with postoperative complications for patients undergoing both colon- and rectal-cancer surgery. This emphasizes the importance of meticulous surgical technique and optimization of the surgical team when treating older patients.

The individually adjusted treatment planning in older patients must contemplate the impact of potential surgical complications. The tolerance to withstand surgery-associated physiological trauma and the ability to adapt to anatomical alterations of the gastrointestinal tract, may vary considerably. Consequently, older patients´ ability to cope with potential complications must constitute a more decisive factor in the treatment decision, compared to younger patients. Additionally, postoperative complications in older patients may impact on a multitude of levels, such as prolonging LOS, increasing morbidity and mortality, and causing a substantial social and emotional burden on both the patient and the patient's family [205].

The most critical period for patients undergoing major surgery for CRC is the initial postoperative phase. In our cohort, short-term mortality increased with age in patients undergoing major resections with curative intent. This observation coheres with previous reports. Heriot et. al. demonstrated increasing age to be associated with higher short-term mortality, when evaluating 8,077 patients undergoing resectional surgery for CRC [206]. In a cohort of 19,080 patients treated for CRC, Marusch et al. demonstrated higher rates of general postoperative complications (e.g., pneumonia, cardiovascular complications) in older patients, whereas no differences were observed regarding procedure-specific complications [207]. These observations uncover a window of opportunities to improve current standards and highlight the need for more aggressive prophylactic measures and increased focus on medical surveillance during the initial postoperative period.

A cooperative care with geriatricians has shown to improve postoperative outcomes in orthopaedic patients [208]. We believe the potential of such an implementation in the field of colorectal surgery may benefit older patients with CRC and should be further investigated. Previous reports have demonstrated higher mortality rates for older patients within the first year after curative CRC surgery [209-212]. This may imply that short-term mortality of typically 90 days may underestimate the impact of surgery and reflect the need for a reinforced and multimodal postoperative care, extending beyond the initial postoperative period.

Oncological treatment

Discrepancies across age-groups concerning oncological treatment of CRC are well documented. A 2019 report demonstrated inferior rates of adjuvant chemotherapy for Stage III colon cancer and neoadjuvant radiotherapy for Stage II and Stage III rectal cancer, after adjusting for comorbidity, tumour characteristics, curative resections, and socioeconomic factors [213]. Yet, current evidence may suggest comparable benefits in older age-groups compared to younger patients [214]. The Norwegian guidelines for CRC treatment advise on individual selection of patients aged ≥75 years of age, depending on level of function and co-morbid conditions [57].

Exclusion of older patients from clinical trials is a concern due to the scarce knowledge regarding efficacy, tolerance, and treatment outcomes in older individuals [215,216]. Due to the great heterogeneity of this patient group concerning functional dependency, physiologic capability and co-morbidity, age alone should not preclude these patients from oncological treatment. Fear of more frequent and more toxic effects of radio- and chemotherapy is the major concern for withdrawing treatment in older patients. Current evidence is conflicting and cannot settle the role of oncological treatment but may indicate that careful selection and individually adjusted treatment doses may be beneficial in selected cases [217]. Future trials that include older patients are necessary to address this question and clarify the role of oncological treatment in older patients.

Comprehensive geriatric assessment

In our cohort, older patients who survived the impact of major surgery and the first 90 days postoperative, had long-term relative survival comparable to younger patients. This coheres with previous literature [218,219]. We observed a decreasing short-term mortality rate throughout the study period, which could rely on several factors. There has been substantial progress in the treatment of medical conditions, and improvements in the perioperative care. The development of guidelines for enhanced recovery after surgery have accelerated the postoperative convalescence and improved short-term mortality rates [153]. Despite improvements in short-term mortality, the early postoperative phase is still the obstacle for older patients with CRC, and the key to improve long-term survival.

The delicate matter when treating older patients with CRC is the challenging task of selecting the correct patients for the appropriate treatment. Treatment decision making is in general a cooperative task between multiple specialists of the MDT, based on objective diagnostic findings. In older individuals there may be cases of doubt, in which final treatment decisions may be undertaken in an outpatient setting with the physician, the patient and the patient's family. The physicians' advice weighs heavily in such consultations and may bias treatment decisions [160]. Hence, a key question is: to what extent are our risk stratifications and treatment recommendations based on objective, valid criteria?

A thorough comprehension of the impact of surgery in older patients is a difficult skill to master and may be judged differently from one physician to another. Information regarding activities of daily living, social frailty, and cognitive impairments may be emphasised to various extent. Preclusion of older patients from surgery based on chronological age is advised against. The International Society of Geriatric Oncology recommends a comprehensive evaluation in patients >65 years undergoing surgical treatment for CRC [141]. CGAs may identify vulnerabilities that can be addressed to enhance postoperative outcomes, such as malnutrition and fatigue, and may aid in the prediction of treatment outcomes [220-222]. Despite supporting evidence, it seems difficult to implement such evaluations as

standard care of treatment. They may be time-consuming, there may be limited economical resources or limited access to relevant specialists [223].

A CGA is the benchmark of frailty assessments and involves physical, functional, social and environmental assessments, psychological evaluations, medication reviews, and clinical follow-ups [224]. Frailty screening tools for surgeons in the ambulatory setting exist and have shown to be as effective as a CGA in predicting postoperative outcomes [142]. A feasible solution may be a simplified frailty screening of older patients as a standard care of treatment, and further referral to geriatricians whenever frailty is detected.

Prehabilitation

Prehabilitation has gained increasing interest in the surgical milieu in recent years and is based on the idea that the impact of the surgical hit will bring the patient's physiological status back to baseline, rather than below. The 2022 guidelines from the American Society of Colon and Rectal Surgeons recommends a preoperative, multimodal optimalization in frail older adults undergoing surgery [142]. A 2022 Cochrane review by Molenaar et. al. concluded that prehabilitation may result in improved functional capacity, lower complication rates and less emergency department visits postoperatively. The certainty of evidence ranged from moderate to very low [225]. Other reports have shown no effect of prehabilitation, and due to the heterogeneity of prehabilitation programs it has not been possible to draw firm conclusions [155,226]. Improvements in ASA scores by prehabilitation could potentially lower the risk for postoperative complications and improve short-term mortality. The role of prehabilitation and its optimal content should be further explored and will hopefully be clarified through future studies [227].

Incidence trends

The Norwegian society has benefitted from remarkable economic growth during the last decades thanks to governmental income from the petroleum industry. The country has undergone an urbanisation leading forward to diminished differences among citizens in the cities and the countryside. The exposure to known CRC risk factors are most likely equally prevalent across the nation.

Throughout this period, the human development index (HDI) has increased. The HDI parameter is a composite measure for assessing a nation's long-term progress in life expectancy, educational level, and per capita income. For years, Norway has figured on the top of this list, along with the other Scandinavian countries, western European countries, the United States, and Australia [228]. HDI is an important measure in the context of CRC, as a common trait of high HDI nations is CRC incidence and mortality rates among the highest in the world [229,230].

A 2017 report assessing global patterns of CRC, found stabilising or declining CRC rates in high HDI countries, but rapidly increasing CRC rates in low- and mid-income countries, adopting western lifestyle factors [12]. Coherent with the above-mentioned report, we observed a CRC incidence increase of 94.5% in our cohort. The incidence increased less prominently from around year 2000. We did a statistical estimation of the aetiological factors and found that 28% of the incidence increase was related to changes in the population (age and sex), whereas 72% was related to lifestyle-associated factors. Previous papers have also attributed a substantial proportion of CRC cases to lifestyle-associated factors [231,232]. Based on our predictions, we expect a further incidence increase of 70% by 2040. The future incidence increase will primarily be due to a further aging of the population and will be especially evident among octogenarians.

Extensive research has been conducted to understand the pathophysiology behind, map aetiological factors associated with, and develop preventive strategies against CRC. Our observations indicate that the impact of lifestyle-associated factors may have reached a steady-state situation. Failures of current primary preventive strategies should be acknowledged, given that primary prevention has the biggest potential for incidence reduction.

10.2. Study design

10.3. Limitations

Paper I-III were all retrospective cohort studies implying certain weaknesses. The quality of the database was dependent on the quality of the individual patient records. The quality of the patient records has improved throughout the study period, and an unknown number of complications may have gone unnoticed especially during the earlier years of the study. Hence, the numbers of complications must be considered minimum numbers. Additionally, the quality of the database made it impossible to do a consistent recording of complications according to current standards, i.e., HAIs and SSIs.

There is a possibility for selection bias, as we could have missed old, frail patients, that were not admitted for treatment. However, we do believe this accounts for a small number of patients as the access to the Norwegian healthcare system is cost-free for all citizens. Unrecorded confounders may have affected decisions regarding patient selection and treatment. Due to the observational nature of the studies, we could only investigate associations but not causality.

A strength of the local database was the possibility to register numerous patient related parameters that are not offered by national registries. The database was quality checked by the same individual, assuring a consistent registration of parameters for the entire cohort.

In Paper III, 51 patients underwent treatment for rectal cancer in other institutions. The inclusion of these patients in the cohort of rectal cancer patients could have altered some of the results.

The future prediction of cancer incidence depends on several uncertain factors, hence, must be interpreted with caution.

11. Conclusions

11.1. Paper I

- The overall incidence rate of CRC increased by 94.5% from 1980 to 2016, of which 72% may be attributed to lifestyle-associated factors.
- The impact of lifestyle-associated factors seemed to have reached a maximum, steady-state level around year 2000-2010.
- We expect a further incidence increase in the years to come, estimated to a 70% increase by 2040. It will be especially prominent among octogenarians.

11.2. Paper II

- We observed a major progress in CRC staging from 1980 to 2016 towards an age-independent approach. Stage of disease was equally distributed across age-groups.
- The rate of patients selected for major resections with curative intent decreased with age, whereas the proportion of octogenarians found eligible for surgery increased throughout the study period.
- The short-term mortality after a major resection with curative intent increased significantly with age, whereas the long-term relative survival in octogenarian patients who survived the first 90 days was comparable to that of younger patients.

11.3. Paper III

- The rate of patients selected for major resections with curative intent decreased with age despite comparable disease stages across age-groups. Age was associated with a non-curative treatment approach.
- Major resections with curative intent were associated with a high rate of complications. The severity of complications increased with age.
- The rate of patients that underwent HPs increased with age, and the rate of HPs increased throughout the study period.
- The short-term mortality after a major resection with curative intent increased non-significantly with age. It decreased throughout the study period. The long-term relative survival in patients ≥80 years who survived the first 90 days was comparable to that of younger patients.

12. Final reflections and future perspectives

From the physicians´ perspective in the everyday clinical work, we have a clear impression that older patients constitute an increasingly larger proportion of patients treated for CRC. Patients in their eighties are more often the rule rather than the exception. We often debate whether our patients are suited to undergo the intended treatment. Although we skilfully try to master this selection, and have our patients' best interest at heart, we must question whether our discussions are based on *the knowledge* that in fact points us in direction of the right decisions.

The current work confirms the development towards increasingly older patients and demonstrates that it will continue in the years to come. As the incidence of CRC has increased, it seems that the impact of lifestyle-associated risk factors has reached a maximum level. As CRC to a considerable extent is a preventable disease, and recent reports have observed increasing CRC rates among younger individuals, this calls for a review of current preventive strategies [233]. We must strive to reverse this trend and aim for decreasing CRC incidence rates for future generations.

One of the main challenges regarding future CRC treatment, is to accommodate the increasingly larger proportion of older patients. To surpass current treatment standards, we must acknowledge these patients as a separate entity of cancer patients and assure that treatment standards embrace the specific traits and needs of this group. Morbidity and mortality associated with CRC treatment may be severe, and hospital expenses due to complications after CRC surgery are substantial [234]. Improvements in the quality of our work will be reflected in terms of lower rates of morbidity and mortality, and a more cost-effective healthcare service [235].

In the present work, long-term survival converged across age-groups among patients undergoing major resections with curative intent, whereas short-term mortality was adversely associated with age. To improve short-term survival, we believe the following should gain future attention:

- The potential of prehabilitation should be further investigated as improvements in the patient´s overall health may reduce the risk of postoperative complications and mortality.
- In older patients with CRC, a cooperative work with geriatricians should be undertaken as an obligatory part throughout the treatment course.
- Optimisation of the surgical team is imperative to ensure high quality surgical procedures.
- Meticulous postoperative care, extending beyond the initial postoperative phase, must be undertaken at a multimodal level for early detection and optimal treatment of both procedure specific and general medical complications.

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14. Errata

Paper I:

- In *Table 1*, Stage should be followed by "(TNM)".
- In the section *Methods*, last paragraph, and in *Table 1* the correct age groups are <65, 65-74, 75-79, 80-84 and ≥85.
- In the section *Strengths and weaknesses* the correct year for the implementation of guidelines at a national level is 1993.

Paper II:

- In *Table 4*, the correct ASA score group is 4-5.
- In *Table 6*, the P value of <0.001 is missing in the age group ≥90 years, unadjusted odds ratio.
- In *Table 7*, the correct ASA score group is 4-5.
- In the section *Long-term relative survival, local recurrence, and metastasis after a major resection with curative intent*, third paragraph, first sentence, the correct sentence is: "Factors associated with long-term relative survival are presented in Table 7."

Paper III:

- In *Abstract*, section *Results*, last sentence, the correct sentence is: "Among patients that survived the first 90 days, the long-term relative survival rates…"
- In the section *Results*, page 5, second paragraph, the correct sentence is: "The 90-day morality, overall survival, and long-term relative survival rates…"
- In the section *Results - Patients with stages I-III disease treated with a major resection with curative intent*, second paragraph, the correct sentence is: "The proportion of patients with CCI scores ≥2 increased over time."
- In the section *Results - Short- and long-term survival among patients that underwent a major resection with curative intent*, first sentence, the correct sentence is: "The 90-day mortality, overall survival, and long-term relative survival rates in patients…"
- In *Table 5*, the correct ASA score group is 4-5.

15. Papers I-III

PAPER I

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RESEARCH ARTICLE Open Access

Long-term trends in colorectal cancer: incidence, localization, and presentation

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Abstract

Background: The purpose of this study was to assess trends in incidence and presentation of colorectal cancer (CRC) over a period of 37 years in a stable population in Mid-Norway. Secondarily, we wanted to predict the future burden of CRC in the same catchment area.

Methods: All 2268 patients diagnosed with CRC at Levanger Hospital between 1980 and 2016 were included in this study. We used Poisson regression to calculate the incidence rate ratio (IRR) and analyse factors associated with incidence.

Results: The incidence of CRC increased from 43/100,000 person-years during 1980–1984 to 84/100,000 person-years during 2012–2016. Unadjusted IRR increased by 1.8% per year, corresponding to an overall increase in incidence of 94.5%. Changes in population (ageing and sex distribution) contributed to 28% of this increase, whereas 72% must be attributed to primary preventable factors associated with lifestyle. Compared with the last observational period, we predict a further 40% increase by 2030, and a 70% increase by 2040. Acute colorectal obstruction was associated with tumours in the left flexure and descending colon. Spontaneous colorectal perforation was associated with tumours in the descending colon, caecum, and sigmoid colon. The incidence of obstruction remained stable, while the incidence of perforation decreased throughout the observational period. The proportion of earlier stages at diagnosis increased significantly in recent decades.

Conclusion: CRC incidence increased substantially from 1980 to 2016, mainly due to primary preventable factors. The incidence will continue to increase during the next two decades, mainly due to further ageing of the population.

Keywords: Colorectal cancer, Incidence, Presentation, Trends, Epidemiology

Background

Colorectal cancer (CRC) is the fourth most common cancer and the second most common cause of cancer death globally [1]. In 2018 the age-standardized (world) incidence for CRC was 19.7/100,000, higher in males than in females (23.6/100,000 vs. 16.3/100,000) [2]. The distribution of CRC burden varies widely, with increasing incidence in countries where the human development index (HDI) is high [3]. Among the Nordic countries, Denmark and Norway have the highest incidence. In Norway the age-standardized (world) incidence of CRC in 2012–16 was 44.9/100,000 in males and 37.4/100,000 in females. The estimated annual increases during the last 10 years were 0.5% among males and 1.1% in females [4]. The incidence of CRC is expected to increase by 33% in 2024–2028, caused mainly by an ageing population [5].

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In Western countries CRC is primarily a disease of the elderly, with a peak incidence at around 70 years of age. The aetiology is multifactorial, and most patients are affected in a sporadic manner. Approximately three-quarters have a negative family history [6]. It is well documented that primary preventable causes such as unfavourable diet, obesity, alcohol, smoking, and low physical activity increase the risk of CRC [7].

Based on a continuous exposure to these risk factors, and an expected ageing of the population [8], the number of patients with CRC will grow in the coming years. Knowledge of trends in incidence and clinical characteristics of CRC patients is imperative to tailor diagnostic work-up and treatment, as well as in development of a strategy to meet future changes in the patient population. As the burden on the health care system continues to rise, it will be important to focus on quality and optimal utilization of resources through adequate organization of the services, standardized care pathways, and individualised treatment.

The focus on primary prevention of CRC will continue, but further achievements in reducing CRC incidence are uncertain and will possibly affect future generations. Secondary prevention by screening programs has been proven to reduce the incidence of CRC among attendees in the long run [9]. In Norway, national screening for CRC will be implemented for patients in their mid-fifties in the coming years. Although important, these preventive measures will not have a significant impact on CRC incidence among the rapidly increasing elderly part of the Norwegian population.

This study was designed to analyse epidemiologic trends in patients diagnosed with CRC for nearly four decades, with respect to incidence, presentation of disease, and stage. Secondarily we wanted to use this knowledge to estimate the future burden of CRC.

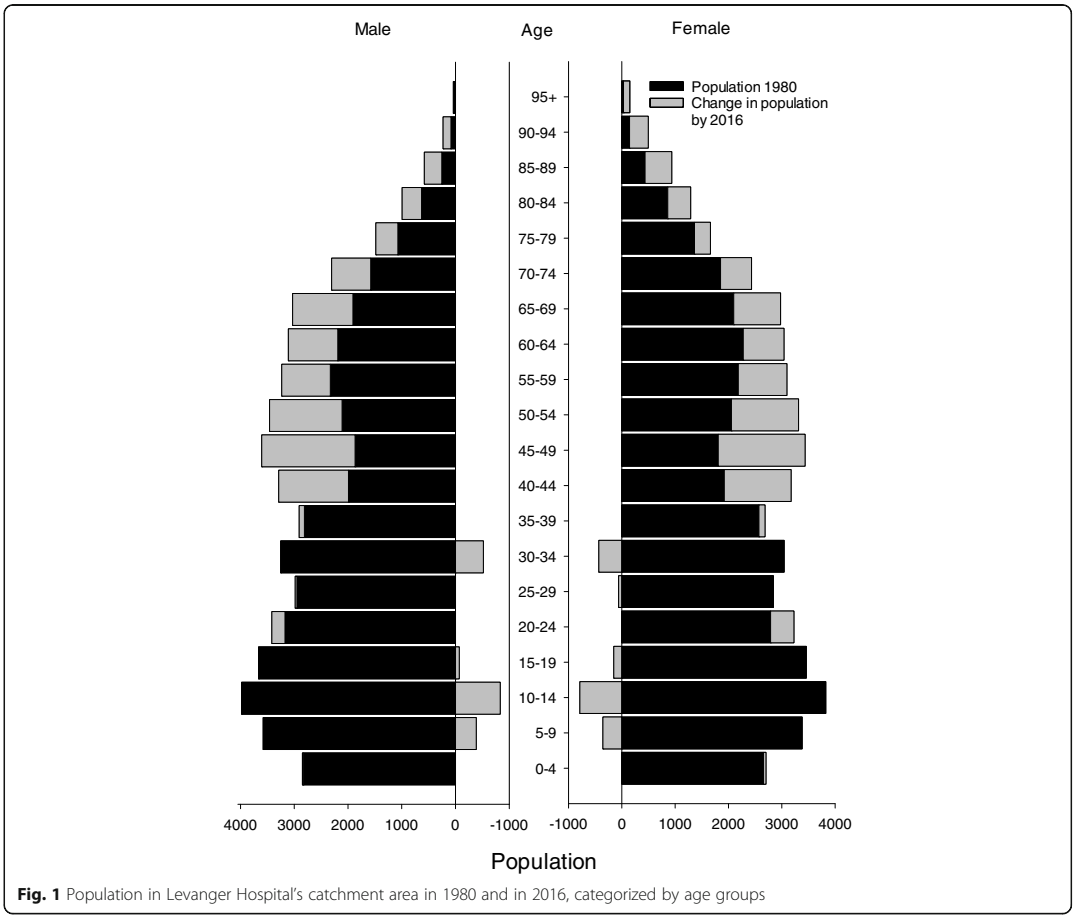

Fig. 1 Population in Levanger Hospital's catchment area in 1980 and in 2016, categorized by age groups

Methods

All patients with CRC admitted to Levanger Hospital during the 37-year period between January 1980 and December 2016 were included in this study. Levanger Hospital serves as the primary hospital for 10 municipalities in North-Trøndelag County, located in Mid-Norway. The county consists of a long coastline as well as large farmlands and forests. The population lives in small towns, villages, or in rural areas. Agriculture is the most important industry. Mean income and education level are slightly less than the national average. The population rose from 83,890 in 1980 to 99,566 in 2016 (a 19% increase). Figure 1 displays changes in the distribution of age in our catchment area and compares 1980 with 2016. Figure 2 displays the population in 2018 and the estimated population in 2040 [8]. The catchment area remained unchanged throughout the observation period. The patients represented an unselected population.

The patients were identified through the discharge diagnoses in the patient administrative system of the hospital, using ICD-8 diagnosis codes 153.01 to 154.19, ICD-9 codes 153.0 to 154.1, and the ICD-10 codes C18.0 to C20. Patients with cancer of the appendix (C18.1) were excluded. Data were retrieved from the health records of all patients. We registered demographic variables, date of admission, presentation (bowel obstruction or spontaneous perforation), localization of the tumour, and stage according to the *TNM classification of malignant tumours*, 6th edition [10]. The database was confirmed by comparing data from the Norwegian Cancer Registry 1980–2016.

Patients with malignancies other than adenocarcinomas (pseudomyxoma peritonei, neuroendocrine tumours, sarcomas [GIST], and lymphomas) were excluded, leaving 2268 patients with CRC in the final cohort. A histological diagnosis of adenocarcinoma was

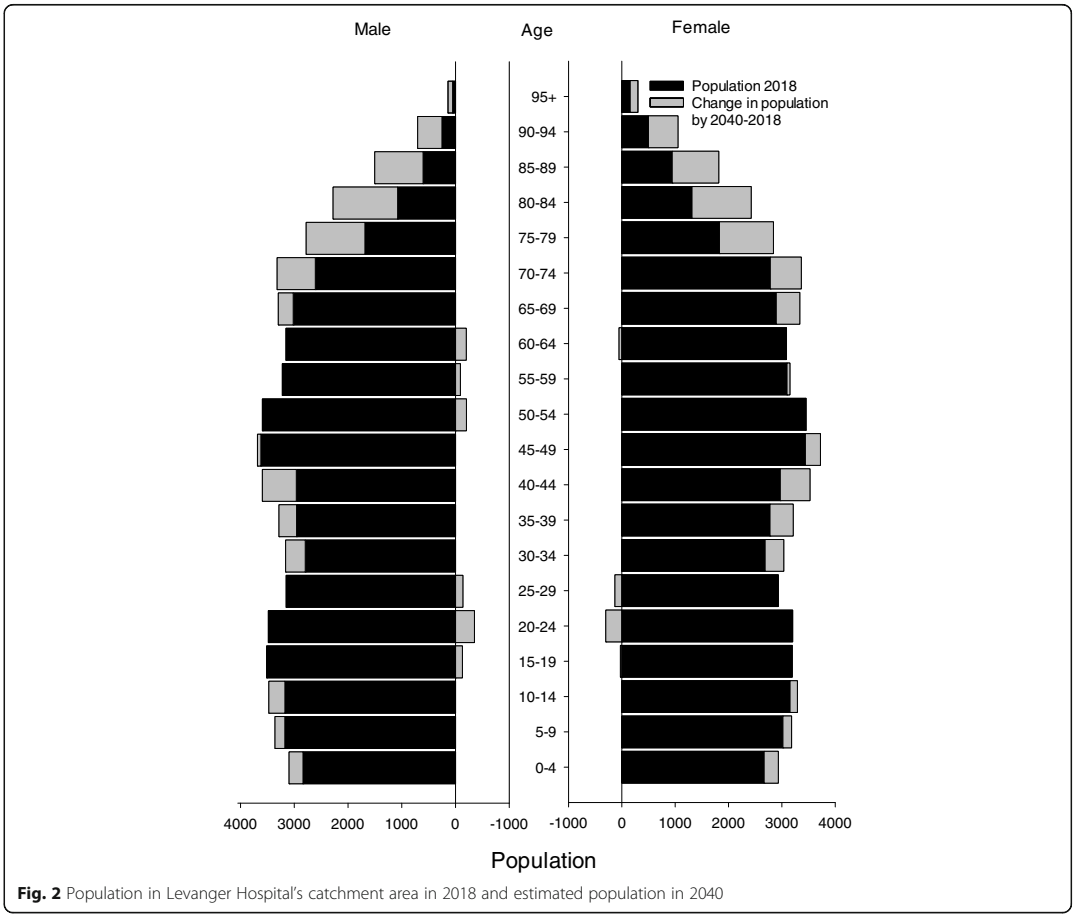

Fig. 2 Population in Levanger Hospital's catchment area in 2018 and estimated population in 2040

available in 2159 patients (95.2%). In the remaining 109 patients (4.8%) the diagnosis was made without a biopsy and based upon a combination of CT-findings, CEA level, colon X-ray, clinical findings, and medical history. These were older, frail patients not fit for surgery or oncological treatment.

Colonic cancer located from the caecum to the transverse colon was defined as right sided. Cancer located from the left flexure to the sigmoid colon was defined as left-sided colon cancer [11]. Rectal cancer was defined as cancer located within 15 cm of the anal verge, with upper, middle, and lower rectum distanced 12–15 cm, 6–11 cm, and 0–5 cm from the anal verge, respectively.

We categorized patients into five age groups: < 65 years, 65–74 years, 75–79 years, 80–84 years, and > 85 years. Trends in calendar years were analysed using five-year periods.

Statistical analysis

The Cochran-Armitage test was used to test for trends in proportions. Logistic regression analysis was used to test for association between intestinal obstruction and perforation at admission as dependent variables and different explanatory variables. Ordinal logistic regression was used to test associations in doubly ordered r x c tables, as in stage by decades. Multinomial logistic regression analysis was used in singly ordered r x c tables, as in the localization of the tumour depending on decade.

The overall incidence of CRC was defined as the number of new cases of CRC in the defined population within 1 year. The incidence rate (IR) was defined as the incidence divided by the total person-time at risk during the same year. The incidence rate ratio (IRR) was defined as the ratio between two incidence rates. The incidence of cancer was analysed using Poisson regression with CRC as the dependent variable and sex, age in five-year intervals (20–24, 25–29, up to 90–94, 95–99), and calendar year from 1980 to 2016 as covariates. Nonlinear relationships were explored by using fractional polynomials [12].

Where relevant, we also adjusted the regression analyses for age, sex, year of diagnosis, and T-stage, which were a priori regarded as plausible confounders.

Age and sex distributions for the 10 municipalities around Levanger Hospital for every year from 1980 to 2016, and information on the expected numbers of males and females by 2030 and 2040, were obtained from Statistics Norway [8].

Two-sided *P*-values < 0.05 were considered significant. Means were reported with the range (minimum to maximum) and standard deviation (SD) where relevant. Ninety-five percent confidence intervals (CI) were reported where relevant. Analyses were carried out in Stata 15, IBM SPSS Statistics 25, and StatXact 9.

Results

Study population

The characteristics of the 2268 patients diagnosed with CRC between 1980 and 2016 are presented in Table 1. There were 1194 (53%) males and 1074 females. Two-thirds ($n = 1551$, 68%) of cases were colon cancers. The mean age in colon cancer patients was 72.2 (32.9–96.1, SD 11.1) years in males and 73.1 (20.3–99.6, SD 11.5) years in females. Corresponding numbers for rectal cancer patients were 70.9 (21.6–94.3, SD 10.7) and 70.4 (35.2–97.1, SD 12.0) years, respectively. The mean annual number of new CRC patients from 1980 to 1986 was 38 patients per year compared with 83 patients per year for 2007 to 2016. The group of patients above 85 years increased, representing 6% in the first period and 13% in the last period. We observed non-significant variations in tumour localization throughout the observation period. Figure 3 displays the distribution of patients according to sex and age throughout the study period.

Incidence

The overall unadjusted incidence rate during the 37 years was 66.1/100,000 person-years, 63.1/100,000 person-years in females, and 69.3/100,000 person-years in males. During the first 5 years the overall incidence rate was 43/100,000 person-years, compared with 85/100,000 person-years during the last 5 years.

The incidence rate for CRC increased with every calendar year and with increasing age. The incidence rate increased by 1.2926% for each calendar year when *age and sex* were adjusted for. This corresponded to an increase in 60.8% (1.012926^{37}) throughout the entire observation period. When adjusted for *age only*, the increase in incidence rate was 1.2953% per year. Hence, a negligible proportion (0.0027, 1.2953% minus 1.2926%) of the increased incidence rate was attributed to sex. When *neither age nor sex* were adjusted for, the increase in incidence rate was 1.808% for each calendar year, corresponding a total increase of 94.1% (1.01808^{37}). The increase in incidence rate attributed to the ageing of the population and sex distribution was 0.512% (1.808% minus 1.2926%), equivalent to a 28% relative increase (0.512/1.808 = 28%). Factors *other than* sex *and ageing of the population* were the main reasons for the incidence increase, and 72% of the observed increase must be attributed to them.

Table 2 shows the IRRs of CRC as a function of age and calendar year, for males and females separately. There was a significant increase in incidence rate for both sexes with calendar year and age, apart from left-sided colonic cancer for women and rectal cancer for men.

Figure 4a shows the absolute number of patients distributed by 5-year age-groups and sex. Figure 4b shows the same patients compared with the number of persons

Table 1 Characteristics of CRC for each calendar period of admission

Year	1980–1986	1987–1996	1997–2006	2007–2016	Total	*P* value
Patients						0.53 [a]
Male	136 (51)	270 (54)	341 (51)	447 (54)	1.194	
Female	133 (49)	234 (46)	322 (49)	385 (46)	1.074	
Age						0.004 [b]
< 65	75 (28)	130 (26)	189 (29)	183 (22)	577	
65–75	83 (31)	179 (36)	173 (26)	272 (33)	707	
75–80	50 (19)	76 (15)	122 (18)	142 (17)	390	
80–85	46 (17)	75 (15)	109 (16)	128 (15)	358	
> 85	15 (6)	44 (9)	70 (11)	107 (13)	236	
Localization						0.29 [c]
Right colon	99 (37)	177 (35)	252 (38)	327 (39)	855	
Left colon	78 (29)	168 (33)	211 (32)	239 (29)	696	
Rectum	92 (34)	159 (32)	200 (30)	266 (32)	717	
Acute presentation						
Colorectal obstruction	23 (8.6)	57 (11.3)	63 (9.5)	88 (10.6)	231	0.69 [a]
Perforation	18 (6.7)	17 (3.4)	20 (3.0)	13 (1.6)	68	< 0.001 [a]
Stage						
I	34 (13)	53 (11)	92 (14)	173 (21)	353	< 0.001 [d]
II	81 (30)	163 (32)	243 (37)	309 (37)	798	
III	70 (26)	119 (24)	133 (20)	174 (21)	495	
IV	65 (24)	128 (25)	155 (23)	174 (21)	524	
Unknown	19 (7)	41 (8)	40 (6)	2 (0.2)	103	

Values in parenthesis are percentages of column total
[a] Cochran-Armitage exact trend test
[b] Ordinal logistic regression with calendar period as covariate
[c] Multinomial logistic regression with calendar period as covariate
[d] Ordinal logistic regression with calendar period as covariate, for known stages

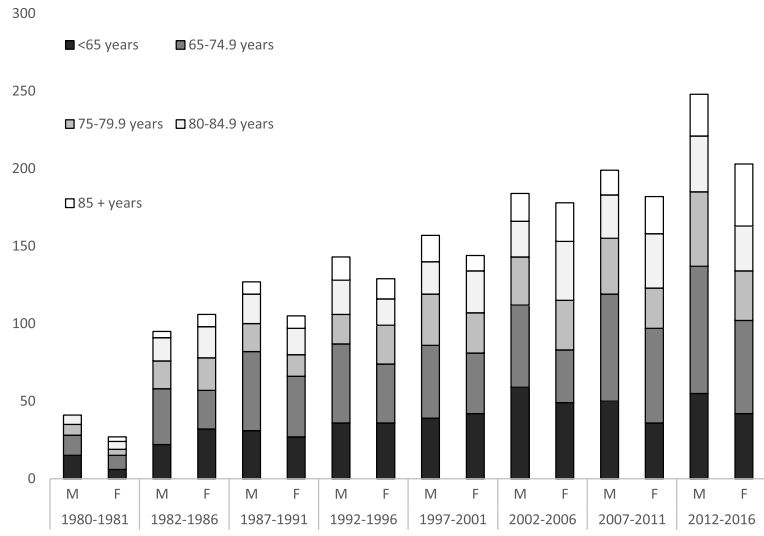

Fig. 3 Number of new cases per 5-year period for both sexes and age groups. *The two columns to the very left represent a 2-year period*

Table 2 Factors associated with CRC. Adjusted IRRs from Poisson regression. Calendar year and age as covariates

	Male		Female	
	IRR (CI)	*P* value	IRR (CI)	*P* value
Total colorectal cancer $n = 2173$ [a]				
Calendar year	1.0133 (1.0078–1.0189)	< 0.001	1.0127 (1.0068–1.0186)	< 0.001
Age (per 5 years)	1.0807 (1.0764–1.0850)	< 0.001	1.0691 (1.0650–1.0732)	< 0.001
Right sided colonic cancer $n = 841$				
Calendar year	1.0208 (1.0111–1.0306)	< 0.001	1.0148 (1.0059–1.0238)	0.001
Age (per 5 years)	1.0887 (1.0811–1.0964)	< 0.001	1.0798 (1.0730–1.0866)	< 0.001
Left sided colonic cancer $n = 686$				
Calendar year	1.0155 (1.0055–1.0256)	0.002	1.0093 (0.9990–1.0197)	0.077
Age (per 5 years)	1.0797 (1.0721–1.0872)	< 0.001	1.0627 (1.0557–1.0697)	< 0.001
Rectal cancer $n = 646$				
Calendar year	1.0042 (0.9950–1.0136)	0.37	1.0130 (1.0013–1.0249)	0.030
Age (per 5 years)	1.0743 (1.0674–1.0813)	< 0.001	1.0607 (1.0528–1.06856)	< 0.001

[a] Ninety-five patients admitted to Levanger Hospital from the area of Namsos Hospital, mostly because of centralization of rectal cancer during the later years, have been excluded from these incidence analyses. They were not included because that area was not an original part of the primary population area of Levanger Hospital

of the same sex and age in this area of Trøndelag. The figure shows that CRC was becoming more frequent as age increased.

Figure 5 shows the results of possibly nonlinear effects of age and calendar year for CRC, using fractional polynomials. The lower figures in Fig. 5 show a straight line as a function of age, for both males and females. This confirms that the assumption of a linear effect of age on the logarithm of incidence is a good approximation to reality in our data. In other words, the risk of colorectal cancer increases by a factor of approximately 1.081 per 5 years for males and 1.069 per 5 years for females (Table 2) throughout the lifetimes we have in our study. Regarding the effect of calendar year, the upper two figures indicate a nonlinear effect of calendar year: the increase in incidence was largest in the first years from

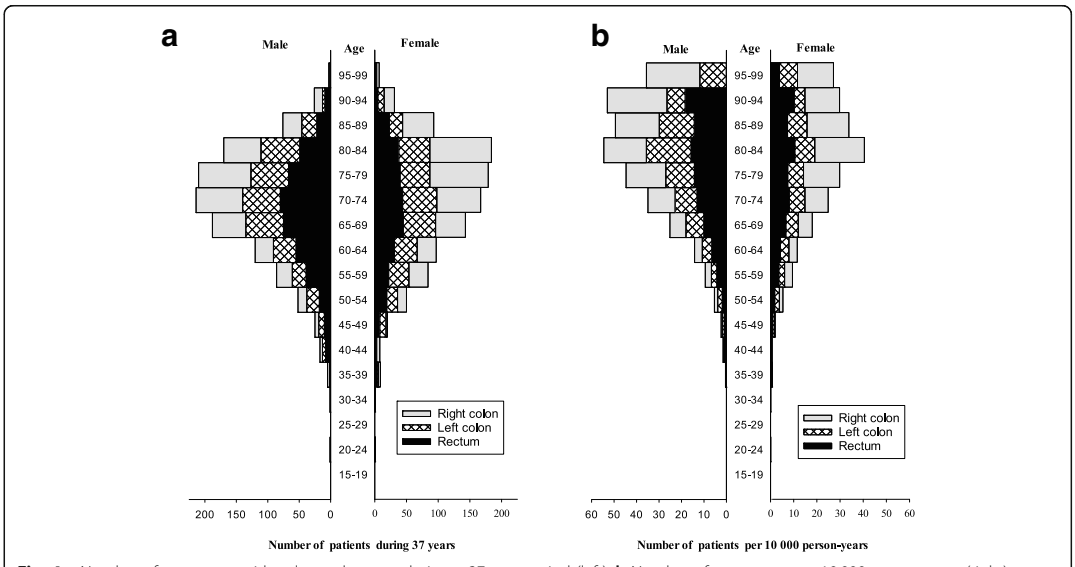

Fig. 4 **a** Number of new cases with colorectal cancer during a 37-year period (left). **b** Number of new cases per 10,000 person-years (right)

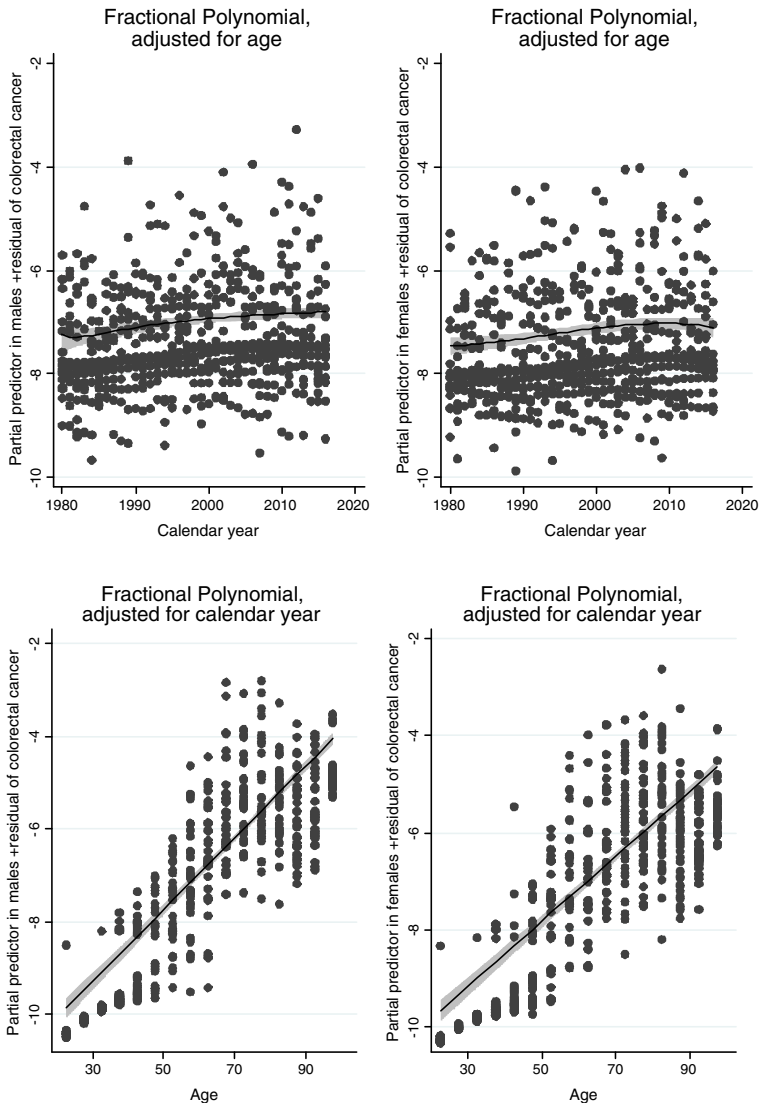

Fig. 5 Effects of calendar year and age on the number of patients presenting with colorectal cancer. Effects of calendar year and age on the number of patients presenting with colorectal cancer in a Poisson regression with fractional polynomials (confidence intervals are shaded grey, logarithmic scale on the y-axis, *males in the figures to the left*). The increase for each calendar year diminished in the later years. The effect of age was linear in both males and females

1980, and seems to have flattened out between 2000 and 2010. From around 2000 there was less of an increase or no increase in age-adjusted incidence.

Predicting the future burden of colorectal cancer

The results of the Poisson analysis with fractional polynomials showed that the calendar-year effect seemed to flatten out around 2000 to 2010. The predicted numbers of CRC cases in future years are based on the mean incidence rates for the latest 10 years of the study period (2007–2016) for each 5-year age group, separately for males and females. A Poisson model was used to predict the number of cases occurring by 2030 and by 2040; see the results in Fig. 6. In the year 2030, the model

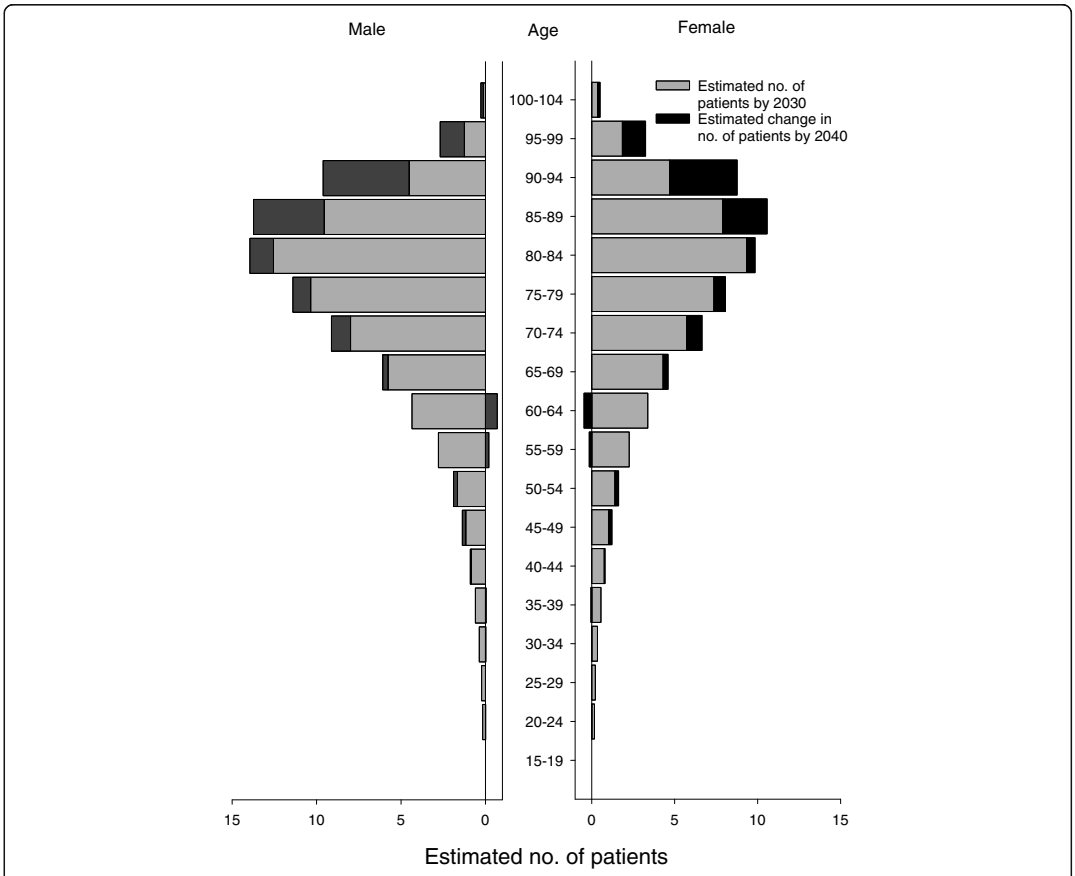

Fig. 6 Estimated numbers of new cases with CRC by 2030 and 2040

estimates a total of 116 (50% prediction interval: 109–124) new CRC patients in our catchment area, including 65 males and 52 females. Corresponding numbers for the year 2040 are 79 males and 62 females, totalling 141 patients (50% prediction interval: 133–150).

Stage

Stage for each time period is shown in Table 1. The proportion of earlier stages increased significantly in recent decades. There were substantially fewer patients with unknown stage. Table 3 shows stage as a dependent variable with regard to sex, age, decade, and localization of the obstructing tumour. The results of multivariable analyses showed that older age, diagnosis in recent years, and distal location were associated with earlier stages.

Colorectal obstruction and perforation

Acute colorectal obstruction was the presenting symptom in 231 of 2268 patients (10.2%). Table 4 shows presentation with acute colorectal obstruction with regard to sex, age, calendar year, and localization of the obstructing tumour. Multivariable analysis showed that acute colorectal obstruction was associated most commonly with tumours in the left flexure and the descending and sigmoid colon. It was significantly less frequent with rectal tumours. There were no associations between colorectal obstruction and sex or age.

Spontaneous colorectal perforation occurred in 68 of 2268 patients (3.0%). Table 5 shows spontaneous colorectal perforation with regard to sex, age, calendar year, and localization of the obstructing tumour. Perforation was associated with tumours in the descending colon (5.4%), caecum (4.9%), and sigmoid colon (4.8%). Perforation became significantly less frequent as time passed,

Table 3 Stage at presentation. Ordinal logistic regression with known stage at presentation as the dependent variable.[a]

	Unadjusted odds ratio	*P* value	Adjusted odds ratio	*P* value
Female sex	1.03 (0.89–1.20)	0.69	0.99 (0.84–1.15)	0.85
Age	0.994 (0.987–1.001)	0.080	0.99 (0.986–0.999)	0.046
Year of diagnosis	0.981 (0.974–0.989)	< 0.001	0.98 (0.974–0.989)	< 0.001
Location				
Right colon	1		1	
Left colon	0.86 (0.72–1.03)	0.11	0.83 (0.69–1.004)	0.055
Rectum	0.64 (0.53–0.77)	0.004	0.62 (0.51–0.75)	< 0.001

[a] Sex, age, year of diagnosis, and location of the primary tumour as covariates. Unadjusted, and adjusted for age, sex, and year

and was not associated with sex or increasing age. In the last period perforation occurred in 1.6% of the patients.

Discussion

Incidence

This observational survey was completed to assess epidemiological and clinical trends in CRC over a 37-year period, and to estimate future changes in the patient population. The overall incidence rate of CRC increased by 90% during the study period. Of this observed increase, 28% was attributed to changes in the population (age and sex), whereas 72% was related to other factors. According to our estimates, the number of new CRC patients, particularly octogenarians, will continue to rise in the coming years. We shall expect a 40% increase in 2030 and a 70% increase in 2040, compared with mean incidence rates the past 10 years.

The local incidence rate in our catchment area was somewhat below the national level in 1980–1984, but increased to the national level during the last 5 year period of the study [13]. Our county, as well as other rural areas of Norway, has undergone some urbanisation throughout this period. Differences in lifestyle among Norwegian citizens living in the cities and in the countryside are diminishing, and the population is to an increasing extent exposed to the same risk factors. Global patterns show a marked increase in the incidence of CRC in countries adopting modern Western living habits [3]. Norway has enjoyed rapid social and economic development since the 1970s, in great extent due to the oil industry. There has been an increase in the rates of

Table 4 Colorectal obstruction. Logistic regression with colorectal obstruction at presentation as the dependent variable[a]

	Colorectal obstructions (%)	Unadjusted odds ratio	*P* value	Adjusted odds ratio	*P* value
Female sex	121/1074 (11.3)	1.25 (0.95–1.64)	0.11	1.18 (0.88–1.59)	0.28
Age		1.011 (0.999–1.024)	0.08	1.01 (0.996–1.023)	0.18
Year of diagnosis		1.004 (0.991–1.017)	0.57	1.02 (1.001–1.031)	0.037
T-Stage			< 0.001		< 0.001
1–2	3/418 (0.7)	1		1	
3	134/1202 (11.1)	17.4 (5.50–55)	< 0.001	15.6 ((4.90–49)	< 0.001
4	71/437 (16.2)	26.8 (8.4–86)	< 0.001	29.7 (9.16–96)	< 0.001
Unknown	11/89 (12.4)	19.5 (5.3–72)	< 0.001	20.3 (5.40–76)	< 0.001
Location			< 0.001		< 0.001
Caecum	31/288 (10.8)	7.80 (2.35–26)	0.001	6.40 (1.90–22)	0.003
Ascending colon	26/310 (8.4)	5.92 (1.77–20)	0.004	4.98 (1.47–16.9)	0.010
Right flexure	8/99 (8.1)	5.69 (1.47–22)	0.012	4.64 (1.19–18.1)	0.027
Transverse colon	22/158 (13.9)	10.5 (3.07–36)	< 0.001	9.39 (2.72–32)	< 0.001
Left flexure	21/62 (33.9)	33.1 (9.44–116)	< 0.001	27.5 (7.61–99)	< 0.001
Descending colon	19/93 (20.4)	16.6 (4.77–58)	< 0.001	18.7 (5.24–66)	< 0.001
Sigmoid	83/541 (15.3)	11.7 (3.66–38)	< 0.001	11.8 (3.63–38)	< 0.001
Proximal rectum	11/220 (5.0)	3.40 (0.94–12.4)	0.063	2.72 (0.70–10.5)	0.15
Middle rectum	7/300 (2.3)	1.55 (0.40–6.05)	0.53	1.69 (0.43–6.70)	0.45
Distal rectum	3/197 (1.5)	1		1	

[a] Sex, age, year of diagnosis, and location of the primary tumour as covariates. Unadjusted, and adjusted for age, sex, year of diagnosis, and T-stage

Table 5 Spontaneous colorectal perforation. Logistic regression with spontaneous colorectal perforation at presentation as dependent variable[a]

	Perforations (%)	Unadjusted odds ratio	*P* value	Adjusted odds ratio	*P* value
Female sex	30/1074 (2.8)	0.87 (0.54–1.42)	0.59	0.81 (0.48–1.35)	0.42
Age		0.99 (0.97–1.005)	0.13	0.98 (0.96–1.01)	0.14
Year of diagnosis		0.96 (0.93–0.98)	< 0.001	0.97 (0.94–0.99)	0.009
T-Stage			< 0.001		< 0.001
1–2	1/418 (0.2)	1		1	
3	27/1202 (2.2)	9.58 (1.30–71)	0.027	8.57 (1.16–64)	0.036
4	38/437 (8.7)	39.7 (5.43–291)	< 0.001	36.7 (4.97–272)	< 0.001
Unknown	0/89 (0)	0	0.997	0	0.997
Location					
Caecum	14/288 (4.9)	10.0 (1.31–77)	0.027	9.25 (1.18–73)	0.034
Ascending colon	5/310 (1.6)	3.12 (0.37–28)	0.03	3.59 (0.41–31)	0.25
Right flexure	3/99 (3.0)	6.13 (0.63–60)	0.12	5.17 (0.52–52)	0.16
Transverse colon	2/158 (1.3)	2.51 (0.23–28)	0.45	2.38 (0.21–27)	0.49
Left flexure	2/62 (3.2)	6.53 (0.58–73)	0.13	5,60 (0.49–64)	0.17
Descending colon	5/93 (5.4)	11.14 (1.28–97)	0.029	13,7 (1.54–123)	0.019
Sigmoid	26/541 (4.8)	9.90 (1.33–73)	0.025	11.9 (1.57–90)	0.017
Proximal rectum	5/220 (2.3)	4.56 (0.53–39)	0.14	5.40 (0.61–48)	0.13
Middle rectum	5/300 (1.7)	3.32 (0.39–29)	0.28	2.68 (0.29–25)	0.38
Distal rectum	1/197 (0.5)	1		1	

[a] Sex, age, year of diagnosis, and location of the primary tumour as covariates. Unadjusted, and adjusted for age, sex, year of diagnosis, and T-stage. Distal rectal cancer was used as the reference location

obesity and diabetes in our county [14, 15], as well as in the rest of the country. Only 30% of the Norwegian population fulfil the recommended level of daily physical activity. On the other hand, there has been a decrease in daily smokers, from 36% in 1980 to 12% in 2018 [8].

Other reports have findings comparable to ours, attributing a large proportion of the increase in CRC incidence to preventable risk factors [16]. In the United Kingdom, one-third of all cancers are attributed to smoking, and one third to diet, nutrition, and physical activity [17]. Despite public initiatives to reduce the exposure to known risk factors – for example, advice regarding physical activity, smoking and diet – incidence levels have increased. From the present report, it seems that the effect of preventable risk factors on the incidence of CRC reached a peak around 2000–2010, with a more stable incidence in later years. Whether this is an effect of increased knowledge of risk factors and consequent behavioural changes in the population or indicates a maximum steady-state level of exposure to these risk factors in the population is disputable.

CRC is a disease with a multifactorial genesis primarily affecting the population in a sporadic manner, with a peak incidence in persons older than 70 years of age. The proportion of elderly patients has increased throughout our observation period, and this trend will continue in the future. Especially noticeable is the increasing number of patients above 85 years of age. According to the Norwegian national guidelines on CRC, a 33% increase in incidence is expected by 2024–2028, mainly due to ageing of the population [5]. Our predictions coincide with the numbers presented in those guidelines.

Among the OECD countries, Norway is fourth in life expectancy. Other countries at the top of this list are also high HDI countries with high incidences of CRC (e.g., Switzerland, Japan, Australia, and Sweden) [18]. Norwegian life expectancy has increased by 7.5 years since the 1980s, and we found that 28% of the increased incidence in CRC could be attributed to increased age.

The Norwegian health care system is fully funded by the government. Hence, every Norwegian citizen has access to state-of-the-art medical services, and can seek medical help at any time, regardless of income. Colonoscopy and CT are nowadays, in contrast with the 1980s, considered low-threshold examinations. General practitioners can refer patients for these examinations within 9 calendar days (fast-track examination), if cancer is suspected. This may contribute to the high incidence levels, earlier stages detected, and decrease in the number of perforations at presentation observed in Norway recently.

Decreasing incidences of CRC are observed in countries with established screening programs [19, 20]. A national Norwegian screening program is currently being planned, enrolling patients at the age of 55 years. An increase in incidence rates must be expected before the incidence rates decline. Implementation of this screening program will not affect incidence among patients aged above 55 years at the time of implementation. During the first years after the Second World War, Norway experienced all-time-high birth rates. As life expectancy continues to increase in Norway, these large cohorts of elderly citizens not undergoing screening will result in an increased number of elderly CRC patients. In combination, these two factors will contribute to a peak in CRC incidence in the coming years. In a longer timeframe, however, we might observe falling incidence rates as the result of screening. Declining birth rates in Norway may augment this change in an even longer perspective.

Stage

In this study there was a trend towards earlier stages at diagnosis in recent decades. This might reflect more awareness of the disease among both patients and primary care physicians, better access to colonoscopy, and a more widespread use of CT with improved quality. These findings are contrary to other studies, which have reported unchanged or increasing rates of advanced stages with time [21–23]. Screening-detected cancer patients present with earlier stages of disease compared with non-screening-detected patients [24–28]. The patients in this study were all diagnosed before the introduction of systematic screening for CRC, indicating that the shift towards earlier stages at presentation will continue in the future. Distal localizations had earlier stages compared with proximal tumours, in accord with previous reports [29, 30].

Colorectal obstruction and perforation

Previous reports found emergency presentation of colorectal cancer in 9–32% of the patients, primarily due to colorectal obstruction and bowel perforation [31–37]. The incidence of complete obstruction has been reported as 8.3 to 22.9%, and the perforation rates from 2.3 to 3.6% [31, 34, 36–42]. We found comparable rates, of 10.5 and 3.1% of the patients, respectively. Neither colorectal obstruction nor spontaneous perforation was associated with age in the present study, contrary to findings in previous reports [42]. Primary tumour localization to the left flexure had the highest rate of obstruction, at 34%. Two other studies found that almost half of the tumours with this localization resulted in obstruction [42, 43]. The rate of spontaneous perforation diminished significantly during the study period. This might be due to a more effective health care system with shorter waiting times prior to surgery in patients presenting with obstructive symptoms or stenotic tumours at the time of colonoscopy.

Strengths and weaknesses

This study included a complete cohort of patients diagnosed with CRC over 37 years at a single institution serving a catchment area that remained unchanged throughout the study period. All patients with suspected CRC in our region were referred to our hospital for diagnostic work-up. Data were accessible at an individual level, and completed with data from the Norwegian Cancer Registry. Preoperative examinations, treatment and follow-up followed local guidelines (standardized policies) throughout the period, and similar guidelines were implemented at a national level in 2009. As all patients were included, we avoided selection bias. The population in our county is a stable population, suitable for epidemiologic studies [44]. The study reflects the epidemiology of elective as well as emergency admission of patients with colorectal cancer on a population basis.

The retrospective design implies certain weaknesses. The quality of the database was dependent on the quality of the individual records of the patients. By combining the data from the Norwegian cancer registry with our own database, we believe that the data used to calculate incidences were nearly complete. We may have missed some old, frail patients with symptoms of CRC who were treated at home or in nursing homes, without further investigation. The incidence in very old persons might thus be higher than reported.

Predictions of future cancer incidence depend upon a number of uncertain factors, and numbers must be interpreted with caution [45]. The numbers of CRC cases predicted to occur by 2030 and by 2040 in the present study assumed the same age- and gender-specific incidence rates as the means of the rates that were observed during 2007–2016.

Future perspectives

The most striking results of predicting future CRC cases occurring by 2030 and by 2040 were the continuous increase in CRC cases in our catchment area and the high numbers of octogenarians, the latter reflecting the impact of increased life expectancy in Norway in the coming years. Awareness of risk factors and systematic screening may reduce the incidence rates. Measures to also reduce the risk of CRC in the elderly non-screened parts of the population should be considered.

In the coming years, the Norwegian health care system must prepare for an increasing number of patients diagnosed with CRC. A large proportion of these patients will be 80–90 years of age. The planned national

screening program will not have an impact on CRC incidence among inhabitants aged above 55 years. In the screened part of the population, an initial increase in incidence and a shift towards earlier stages of CRC at presentation should be expected. In the long run, both screening and changes in the population may result in a decline in CRC incidence. Knowledge of these changes in patient volume and characteristics is imperative in order to establish a rational and effective organization of health services to accommodate these patients.

The current study demonstrates that a substantial number of cancer cases can be attributed to preventable causes. Increased knowledge concerning these causes is imperative to complete the puzzle regarding risk factors and disease development. The adverse development regarding obesity and lifestyle-related diseases accentuates the reality that current primary preventive strategies lack effectivity. Given the fact that more than two-thirds of CRC cases might be preventable, a key question is whether changes in these factors can be expected, and what impact this might have on disease development.

Conclusion

The CRC incidence rate increased by 90% from 1980 to 2016, mainly due to preventable factors. The incidence will continue to increase during the next two decades, primarily because of further ageing of the population. Continuous focus on preventive strategies, as well as awareness of changes in patient characteristics and volume are imperative to ensure adequate capacity, high quality and efficient patient care in the future.

Abbreviations

CI: Confidence interval; CRC: Colorectal cancer; HDI: Human development index; IR: Incidence rate; IRR: Incidence rate ratio; SD: Standard deviation

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We declare no conflicts of interest in connection with the current study.

Authors' contributions

ØH: Made substantial contributions to the design of the work, interpretation of the data, and drafting and revising the manuscript. THE: Made substantial contributions to the design of the work, the analysis and interpretation of the data, and drafting and revising the manuscript. AX: Made substantial contributions to the design of the work, and revising the manuscript. SL: Made substantial contributions to the design of the work, analysis and interpretation of the data, and revising the manuscript. BHE: Made substantial contributions to the design of the work, the analysis and interpretation of the data, and drafting and revising the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The dataset used for this study is located on a secure server in the Hospital's data system. Requests regarding the dataset can be addressed to Øystein Høydahl. The database was confirmed by comparing data from the Norwegian Cancer Registry 1980–2016. Data obtained from the Norwegian Cancer Registry is available by application to the registry.

Ethics approval and consent to participate

The Regional Committee for Medical and Health Research Ethics (REC) gave permission for the study (2016/2172/REK midt).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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PAPER II

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RESEARCH Open Access

Octogenarian patients with colon cancer – postoperative morbidity and mortality are the major challenges

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Abstract

Background: Few studies have addressed colon cancer surgery outcomes in an unselected cohort of octogenarian patients. The present study aimed to evaluate the relative survival of octogenarian patients after a major resection of colon cancer with a curative intent.

Methods: All patients diagnosed with colon cancer at Levanger Hospital between 1980 and 2016 were included. We performed logistic regression to test for associations between 90-day mortality and explanatory variables. We performed a relative survival analysis to identify factors associated with short- and long-term survival.

Results: Among 237 octogenarian patients treated with major resections with curative intent, the 90-day mortality was 9.3%. Among 215 patients that survived the first 90 days, the 5 year relative survival rate was 98.7%. The 90-day mortality of octogenarian patients was significantly higher than that of younger patients, but the long-term survival converged with that of younger patients. Among octogenarian patients, the incidence of colon cancer more than doubled during our 37-year observation period. The relative increase in patients undergoing surgery exceeded the increase in incidence; hence, more patients were selected for surgery over time. A high 90-day mortality was associated with older age, a high American Society of Anaesthesiologists (ASA) score, and emergency surgery. Moreover, worse long-term survival was associated with a high Charlson Comorbidity Index, a high ASA score, a worse TNM stage, emergency surgery and residual tumours. Both the 90-day and long-term survival rates improved over time.

Conclusion: Among octogenarian patients with colon cancer that underwent major resections with curative intent, the 90-day mortality was high, but after surviving 90 days, the relative long-term survival rate was comparable to that of younger patients. Further improvements in survival will primarily require measures to reduce the 90-day mortality risk.

Keywords: Colon cancer, Octogenarians, Treatment, Survival, Epidemiology

Background

Colon cancer mainly occurs among older individuals. In Nordic countries, increases have been observed in the population, life expectancy, and incidence of colon cancer over the last few decades. These trends are likely to continue; thus, the number of older patients with colon cancer will continue to increase [1, 2], and a significant

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proportion of these patients will be octogenarians (i.e., aged 80–89 years) [3, 4].

In Norway, a standardized evidence-based approach to assessing and treating colon cancer has been established at a national level [5]. The final treatment strategy for an individual patient should be based on an accurate staging of the disease and on patient-related factors. The national guidelines recommend that multidisciplinary teams undertake treatment decision-making. Guidelines related to adjuvant chemotherapy administration and follow-up times are recommended according to the patient's chronological age.

In the literature, the group of older patients with colon cancer is a vaguely defined term. The definition of 'older age' ranges from ≥ 65 to > 80 years [6–8]. The mainstay of treatment for colon cancer is radical surgery, and this is combined with chemotherapy in selected subgroups of patients. Previous reports have noted that both radical surgery and chemotherapy are increasingly underused with increasing patient age [7, 9]. Despite some variation, several studies have also reported that postoperative morbidity and mortality increased with increasing age [10, 11]. Although it is well known that, overall, long-term survival decreases with increasing age, estimates of long-term disease-free and relative survival rates have varied for older patients treated for colon cancer.

The present study aimed to evaluate the trends, treatments, and outcomes observed over a period of nearly four decades in patients diagnosed with colon cancer. In particular, we investigated octogenarian patients. Over time, this heterogeneous group of patients has become larger. Therefore, it is of paramount importance to raise our awareness of patient-related factors and their impact on cancer treatment outcomes in older patients. Based on this knowledge, we can establish evidence-based, individualized treatment strategies.

Methods

This study included 1530 consecutive patients admitted with colon cancer at Levanger Hospital during 1980–2016. Levanger Hospital is the primary hospital of 10 municipalities in Norway, and the catchment area remained unchanged throughout the study period. The population increased by 18%, from 83,890 inhabitants in 1980, to 99,566 inhabitants in 2016. During this period, the average age of the population also increased. In particular, the number of octogenarian inhabitants increased by 73%, from 2184 individuals in 1980, to 3800 individuals in 2016 [4].

Through the hospital administrative system, we accessed the health records for all patients that were discharged with diagnosis codes of the International Classification of Diseases, 8th revision (ICD-8) from 153.1 to 153.9, with ICD-9 codes from 153.0 to 153.9, and with ICD-10 codes from C18.0 to C19. Data on all patients were recorded, crosschecked, and confirmed with data from the Norwegian Cancer Registry, during 1980–2016. From the hospital database, we retrieved data on demographic and logistic variables, comorbidities, treatment, tumour characteristics (including histopathology), complications after treatment, and short- and long-term outcome measures.

We defined colon cancer as any tumour located above 15 cm from the anal verge. Right colon tumours were defined as tumours localized in the caecum, ascending colon, hepatic flexure, or transverse colon. Left colon tumours were defined as tumours localized in the splenic flexure, descending colon, or sigmoid colon. Tumours located within 15 cm from the anal verge were defined as rectal cancer, and we excluded these and cancers localized in the appendix.

We characterized patient comorbidity with the American Society of Anaesthesiology (ASA) score and the Charlson Comorbidity Index (CCI) [12, 13]. We defined anaemia at admission, as advocated by the World Health Organization, as blood haemoglobin levels below 13 g/dL in males and below 12 g/dL in females [14]. We also defined "moderate to severe" anaemia as haemoglobin levels below 11 g/dL in males and 10 g/dL in females. Surgical complications were defined according to the Clavien-Dindo classification of surgical complications, grades I-V [15]. Surgical complications were recorded as in-hospital complications from the day of admission to the day of discharge.

Disease stages were based on the TNM classification, sixth edition [16]. An R0 resection was defined as no detectable residual tumour postoperatively; an R1 resection was defined as a microscopic residual tumour detected in a postoperative histological examination; and an R2 resection was defined as a macroscopic residual tumour detected after surgical treatment [17]. An R0 resection was further classified into two groups: an R0 without tumour perforation and an R0 with tumour perforation. Tumour perforations included both spontaneous (12) and iatrogenic perforations (9).

Patients were categorized into five groups, according to treatment intent: (*i*) a major resection with curative intent (R0 and R1), (*ii*) a polypectomy, (*iii*) a major resection with non-curative intent, (*iv*) a bypass/stoma, and (*v*) best supportive care.

Emergency surgery was defined as surgery due to evidence of a large bowel obstruction or large bowel perforation. The laparoscopic colon resection technique was gradually introduced during the last part of the study period. A total of 49 patients underwent laparoscopic

surgery. In ten of these patients, the procedure was converted to open surgery.

Staging varied throughout the observation period. Staging was based on complete clinical and histopathological examinations of the resected specimen in 84.9% (1299/1530) of patients; a clinical examination and histopathological examination of a tumour biopsy in 7.8% (120/1530) of patients; a pathological evaluation during an autopsy in 1.4% (21/1530) of patients, and clinical evaluations alone in 5.9% (90/1530) of patients.

Since 1993, the Norwegian national guidelines for treatment of colon cancer advocated that all patients aged 75 years or under with Stage III disease should be evaluated for adjuvant chemotherapy. Later, this recommendation was applied to selected patients with Stage II disease [5].

Follow-ups were initially conducted according to local guidelines. Starting in 1993, they were based on very similar, national guidelines [5]. The follow-up time was calculated as the patient-years at risk, starting from the date of admission. The study endpoints were: local recurrence, metastasis, or death, regardless of cause. The mean follow-up time was 6.05 years (standard deviation [SD] = 6.89, range: 0–38.7 years). The end of follow-up was December 31st, 2018.

Statistical analyses

The Exact Unconditional z-pooled test was used to compare binomial proportions; for example, the percentage of reoperations, relative to the percentage of emergency or elective primary operations. The Cochran Armitage exact trend test was used to test for trends in proportions; for example, the proportions of elective surgeries vs. emergency surgeries in different age groups. The Joncheere-Terpstra test was used to test for the distribution of age, as a dependent variable, across 10-year age groups, as the independent variable. The 5 year rates of local recurrence and metastases were estimated with the Kaplan–Meier method.

Logistic regression analyses were performed to assess associations between the 90-day mortality, as the dependent variable, and different explanatory variables. Ordinal logistic regressions were performed to analyse the associations in doubly-ordered r × c tables; for example, the ASA score stratified by age group. The resulting odds ratios (ORs) represent a common OR estimate for any 2 × 2 table that would occur, if the r × c table was collapsed to a 2 × 2 table, based on any cut-off threshold, along the columns and rows. Multinomial logistic regression analyses were performed in singly ordered r × c tables; for example, the type of treatment, stratified by age groups.

Relative survival analysis

Relative survival was defined as a measure of mortality compared to the general population. The observed survival in the group with cancer was divided by the expected survival of a comparable group in the general Norwegian population, matched by age, sex, and the calendar year of investigation. Relative survival was estimated with the Ederer II method and analysed with STATA 16 [18]. Multivariable analyses were performed with a full likelihood approach. Norwegian population survival probabilities were downloaded from the Human Mortality Database, for every year from 1980, calculated for groups stratified by sex and age [19].

Two-sided p-values < 0.05 were considered significant. Means are reported with the range (minimum to maximum) and SD, where relevant. Ninety-five percent confidence intervals (95% CI) are reported, when relevant. Analyses were carried out in Stata 16, IBM SPSS Statistics 25, and StatXact 9.

Results

Study population

Table 1 presents the characteristics of all 1530 patients admitted with colon cancer between 1980 and 2016. There were 750 males (49%) and 780 females, with mean ages of 72.3 (range: 32.9–96.1, SD: 11.1) years and 73.2 (range: 20.3–99.6, SD: 11.6) years, respectively. The mean age of the population increased from 71.5 years, in 1980–1989, to 74.5 years, in 2010–2016 ($p = 0.001$). The mean number of patients admitted per year increased by 109%, from 27.4 patients/y in 1980–1989 to 57.4 patients/y in 2010–2016. The number of octogenarian patients increased by 131%, from 6.7 to 15.5 patients admitted per year, respectively.

The mean CCI, the mean ASA score, and the proportion of patients with right-sided colon cancer increased with increasing age. We observed no differences in stages among the age groups. Over time, the percentage of patients diagnosed with stage I or II disease increased from 41%, in 1980–1989, to 58% in 2010–2016 ($p < 0.001$). The number of patients with an unknown stage declined over time and was zero in the last time period (2010–2016).

Overall, 89% (1359/1530) of all patients diagnosed with colon cancer underwent a surgical treatment, including a major resection, a polypectomy, or a palliative procedure. The rate of surgeries decreased as patient age increased. During the study period, the percentage of octogenarian patients that underwent a major resection with curative intent increased over time. It was 54% (36/67), in the first time-period (1980–1989), and 61% (66/108), in the last time-period (2010–2016).

Table 1 Characteristics of all patients admitted with colon cancer during the 1980–2016 study period

Characteristic	Total, $n=1530$	Age group (years)						*P* value
		<65, $n=353$	65–74, $n=451$	75–79, $n=281$	80–84, $n=269$	85–89, $n=124$	≥90, $n=52$	
Sex								0.031[a]
Females	780 (51)	181 (23)	210 (27)	139 (18)	148 (19)	70 (9)	32 (4)	
Males	750 (49)	172 (23)	241 (32)	142 (19)	121 (16)	54 (7)	20 (3)	
Calendar year								< 0.001[b]
1980–1989	274 (18)	70 (26)	89 (33)	45 (16)	49 (18)	18 (7)	3 (1)	
1990–1999	367 (24)	85 (23)	115 (31)	73 (20)	56 (15)	29 (8)	9 (3)	
2000–2009	487 (32)	129 (27)	121 (25)	85 (18)	100 (21)	33 (7)	19 (4)	
2010–2016	402 (26)	69 (17)	126 (31)	78 (19)	65 (16)	44 (11)	21 (5)	
Charlson Comorbidity Index								< 0.001[b]
0	1076 (70)	300 (85)	321 (71)	187 (66)	165 (61)	75 (61)	28 (54)	
1–2	358 (23)	51 (14)	100 (22)	72 (26)	81 (30)	39 (32)	15 (29)	
> 2	96 (6)	2 (1)	30 (7)	22 (8)	23 (9)	10 (8)	9 (17)	
ASA score								< 0.001[b]
1–2	832 (54)	282 (80)	284 (63)	134 (48)	94 (35)	28 (23)	10 (19)	
3	598 (39)	66 (19)	147 (33)	131 (47)	150 (56)	76 (61)	28 (54)	
4–5	100 (7	5 (1)	20 (4)	16 (6)	25 (9)	20 (16)	14 (27)	
Localization								< 0.001[a]
Right colon	845 (55)	166 (47)	232 (51)	174 (62)	158 (59)	79 (64)	36 (69)	
Left colon	685 (45)	187 (53)	219 (49)	107 (38)	111 (41)	45 (36)	16 (31)	
Stage (TNM)								0.14[d]
I	189 (12)	42 (12)	61 (14)	34 (12)	34 (13)	15 (12)	3 (6)	
II	582 (38)	127 (36)	160 (36)	117 (42)	101 (38)	47 (38)	30 (58)	
III	331 (22)	78 (22)	120 (27)	62 (22)	54 (20)	12 (11)	5 (10)	
IV	377 (25)	102 (29)	102 (23)	60 (21)	66 (25)	35 (27)	12 (23)	
Unknown	51 (3)	4 (1)	8 (2)	8 (3)	14 (5)	15 (12)	2 (4)	
Treatment intent categories								< 0.001[c]
Curative intent								
Major resection[f]	1034 (68)	239 (68)	328 (73)	204 (73)	172 (64)	67 (54)	24 (46)	
Polypectomy	38 (3)	10 (3)	11 (2)	11 (4)	6 (2)	0	0	
Non-curative intent								
Major resection	220 (19)	62 (18)	64 (14)	39 (14)	38 (14)	14 (11)	3 (6)	
Bypass/stoma	67 (4)	17 (5)	17 (4)	6 (2)	14 (5)	11 (9)	2 (4)	
Best supportive care	171 (11)	25 (7)	31 (7)	21 (8)	39 (15)	32 (26)	23 (44)	
Surgery								0.005[b]
Elective surgery[e]	1081 (82)	263 (83)	339 (83)	217 (88)	176 (79)	72 (78)	14 (48)	
Emergency surgery	240 (18)	55 (17)	70 (17)	32 (12)	48 (21)	20 (22)	15 (52)	

Values are the number of patients (%), unless otherwise indicated. [a]Cochran-Armitage exact trend test; [b]Ordinal logistic regression with age group as covariate; [c]Multinomial logistic regression with age group as covariate

[d] Ordinal logistic regression with age group as covariate, for known stages; [e]Including polypectomy; [f]Including *R0* resection, *R0* resection with perforation and *R1* resection

The rate of emergency surgery remained stable over time. However, emergency surgery was required more frequently as patient age increased. The rates were 16% (157/976) among patients younger than 80 years and 22% (68/316) among octogenarian patients. The mean hospital stay after a major resection with curative intent decreased from 17.0 days (range: 2–67, SD: 11.7) during 1980–1989 to 9.7 days (range: 4–47, SD: 6.3) during 2010–2016.

Mortality within 90 days for all patients

Overall, the 90-day mortality rate after admission was 13.5% (206/1530). The mortality rate increased successively as patient age increased. Mortality rates were 6.5% in patients < 65 years, 22.4% in octogenarian patients, and 44.2% in patients above 90 years ($p < 0.001$). During 1980–1989, 21.2% (58/274) of all admitted patients died within 90 days. In comparison, during 2010–2016, only 10.9% (44/402) of patients died. Table 2 presents the prognostic factors we identified that were associated with mortality within 90 days after admission. The odds of death increased with increasing patient age.

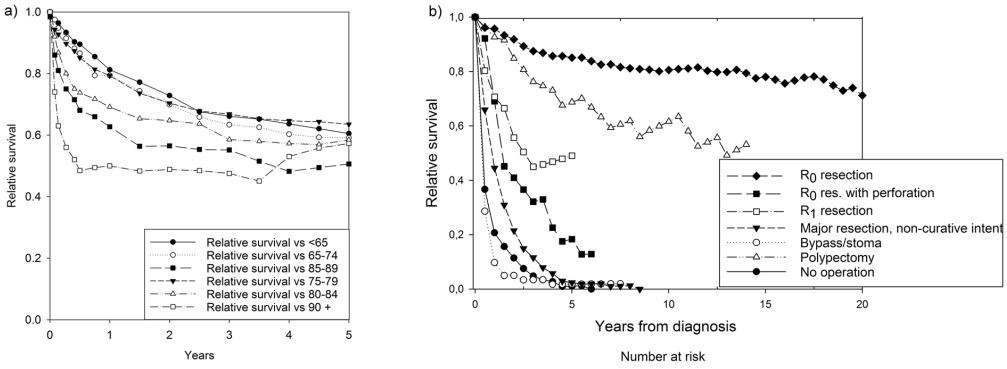
Long-term relative survival rates for all patients

Overall, the 5 year relative survival rate for all patients was 58.5% (95% CI: 55.2 to 61.6). Figure 1a presents the 5 year relative survival rates, stratified by age groups. Patients aged 75–79 years had the highest 5 year relative survival rate, at 63.1% (95% CI: 55.2 to 70.6), compared to 55.4% (95% CI: 47.4 to 63.5) in octogenarian patients. Figure 1b presents the relative survival rates stratified by treatment intent categories. The 5 year relative survival rate for the R0 resection group was 85.1% (95% CI: 81.2 to 88.7), compared to 49.1% (95% CI: 22.1 to 75.6) for the R1 resection group, and 18.3% (95% CI: 4.6 to 41.2) for the R0 resection with perforation group.

Table 2 Factors associated with 90-day mortality for all patients admitted with colon cancer in 1980–2016; $n = 1530$

Factors	Unadjusted odds ratio (95% CI)	*P* value	Adjusted odds ratio (95% CI)	*P* value
Age (years)				
< 65	1 (reference)		1 (reference)	
65—74	1.44 (0.84 to 2.44)	0.18	1.41 (0.74 to 2.69)	0.30
75 – 79	1.78 (1.01 to 3.13)	0.045	1.92 (0.95 to 3.88)	0.070
80—84	3.69 (2.20 to 6.18)	< 0.001	2.64 (1.35 to 6.16)	0.005
85 – 89	5.20 (2.91 to 9.30)	< 0.001	2.42 (1.11 to 5.29)	0.027
≥ 90	11.38 (5.70 to 22.72)	< 0.001	5.85 (2.30 to 14.87)	< 0.001
Calendar year	0.97 (0.96 to 0.98)	< 0.001	0.94 (0.92 to 0.96)	< 0.001
Female sex	0.76 (0.57 to 1.03)	0.072	0.76 (0.52 to 1.13)	0.18
CCI	1.65 (1.39 to 1.95)	< 0.001	1.39 (1.10 to 1.77)	0.006
ASA score				
1–2	1 (reference)		1 (reference)	
3	2.82 (1.98 to 4.05)	< 0.001	1.92 (1.21 to 3.06)	0.006
4–5	21.59 (13.26 to 35.14)	< 0.001	6.94 (3.69 to 13.05)	< 0.001
Anaemia[a]	1.44 (1.06 to 1.96)	0.019	1.19 (0.78 to 1.83)	0.42
Emergency surgery	3.12 (2.23 to 4.35)	< 0.001	4.90 (2.99 to 8.05)	< 0.001
Localization (left vs. right)	0.87 (0.64 to 1.17)	0.35	0.78 (0.52 to 1.18)	0.24
TNM-stage				
I	1 (reference)		1 (reference)	
II	2.72 (1.06 to 6.99)	0.038	1.60 (0.54 to 4.74)	0.39
III	1.17 (0.63 to 4.89)	0.29	1.30 (0.40 to 4.23)	0.67
IV	17.61 (7.06 to 43.92)	< 0.001	5.29 (1.57 to 17.80)	0.007
Unknown	32.71 (11.51 to 92.99)	< 0.001	1.78 (0.46 to 6.86)	0.40
Treatment intent categories				
Curative intent				
Major resection	1 (reference)		1 (reference)	
Polypectomy	0.59 (0.08 to 4.43)	0.59	1.59 (0.18 to 13.92)	0.68
Non-curative intent				
Major resection	5.03 (3.20 to 7.91)	< 0.001	1.28 (0.55 to 9.98)	0.56
Bypass/stoma	28.80 (16.22 to 50.83)	< 0.001	10.23 (4.03 to 26.00)	< 0.001
Best supportive care	19.78 (12.95 to 30.21)	< 0.001	9.56 (4.21 to 21.71)	< 0.001

Results are from a logistic regression analysis, with death within 90 days as dependent variable; unadjusted: analysis performed with one covariate at a time; adjusted: analysis performed with all listed covariates included simultaneously. *CCI* Charlson Comorbidity Index, classified in three levels: 0, 1 and 2 +; [a]Anaemia was defined as < 13 g/dL in males and < 12 g/dL in women (based on WHO recommendations)



Patients at risk

Age						
<65	353	314	269	233	217	202
65-74	451	386	324	280	246	210
75-79	281	233	192	198	149	130
80-84	269	190	155	138	111	92
85-89	124	79	57	48	34	27
90 +	52	22	17	13	9	8

Number at risk

R0 resection	995	838	634	474	345	250	180	127	83
R0 res. with perf.	21	8	3	2	2	2			
R1 resection	18	9	6	6	4	1			
Major resection, non-curative intent	220	44	5	1					
Bypass/stoma	67	3	1	1					
Polyppectomy	38	30	19	10	9	6	5	1	1
No surgery	171	16	1						

Fig. 1 Survival of patients with colon cancer during 1980–2016. **a** 5-year relative survival for all patients in each age group; table columns represent the number of patients at risk at surgery (time = 0) and every 1 year thereafter. **b** Long term relative survival for all patients, classified by treatment intent; table columns represent the number of patients at risk at surgery (time = 0) and every 2.5 years thereafter

Among patients < 65 years, the 2 year relative survival rates were: 32.6% (95% CI: 21.3 to 44.4) after a major resection with non-curative intent, 0% after a bypass/stoma, and 12.2% (95% CI: 0.3 to 28.1) after the best supportive care. The corresponding rates in octogenarian patients were: 18.8% (95% CI: 8.8 to 32.3) after a major resection with non-curative intent, 0% after a bypass/stoma, and 18.1% (95% CI: 9.3 to 29.8) after the best supportive care.

After excluding patients that died within the first 90 days, the overall 5 year relative survival rate was 67.2% (95% CI: 63.7 to 70.6). Patients aged < 65 years had the lowest 5 year relative survival rate, at 64.4% (95% CI: 58.7 to 69.6), compared to 71.0% (95% CI: 61.3 to 80.6) in octogenarian patients. Table 3 presents the prognostic factors we identified that were associated with long-term relative survival, among patients that survived 90 days after admission.

Patients with stage I-III disease that underwent a major resection with curative intent

Table 4 presents the characteristics of all 1021 patients with colon cancer, stages I-III, that were treated with a major resection with curative intent (R0 and R1). Of these patients, 487 (48%) were males and 534 were females, with mean ages of 71.7 (range: 32.9–91.2, SD: 10.6) and 72.8 (range: 20.3–99.6, SD: 11.1) years, respectively. The mean number of patients per calendar year increased from 17.5 patients/y in 1980–1989 to 38.7 patients/y in 2010–2016. The mean number of octogenarian patients per year increased from 3.6 to 9.3 patients, respectively. A laparotomy was performed in 974 (95.4%) patients compared to a laparoscopic procedure in 47 (4.6%) patients. Ten of the laparoscopic procedures were converted to open surgery.

Postoperative complications and 90-day mortality after a major resection with curative intent

In 9.6% of cases, the Clavien-Dindo score was 3 or more. Anastomotic leakage was diagnosed in 2.5% (26/1021), and wound dehiscence in 1.7% (17/1021) of patients. A reoperation was required after 12.1% (17/141) of emergency resections, compared to 5.6% (49/880) of elective resections ($p = 0.004$). Table 5 presents the risk factors we identified that were associated with postoperative complications.

Among patients with colon cancer stages I-III, mortality within 90 days after admission was 4.4% (45/1021). The 90-day mortality rates increased successively with increasing age. The rates were 0.4% among patients aged < 65 years, 9.3% in octogenarian patients, and 34.8% in patients above 90 years old ($p < 0.001$). Table 6 presents the factors we identified that were associated with death within 90 days.

Table 3 Factors associated with long-term relative survival in 1324 patients that survived 90 days after admission

Factors	Unadjusted hazard ratio (95% CI)	*P* value	Adjusted hazard ratio (95% CI)	*P* value
Age (years)				
< 65	1 (reference)		1 (reference)	
65—74	1.05 (0.81 to 1.36)	0.69	1.22 (0.94 to 1.61)	0.12
75—79	0.93 (0.67 to 1.29)	0.66	1.16 (0.83 to 1.62)	0.37
80 – 84	1.02 (0.71 to 1.46)	0.91	0.92 (0.64 to1.33)	0.65
85 – 89	1.36 (0.83 to 2.25)	0.23	0.86 (0.52 to 1.42)	0.56
≥ 90	1.26 (0.44 to 3.60)	0.67	1.17 (0.56 to 2.47)	0.68
Female sex	1.14 (0.92 to 1.41)	0.23	1.28 (1.04 to 1.58)	0.021
Calendar year				
1980–1989	1 (reference)		1 (reference)	
1990–1999	0.95 (0.70 to 1.29)	0.74	0.68 (0.50 to 0.93)	0.016
2000–2009	0.69 (0.51 to 0.93)	0.016	0.55 (0.40 to 0.74)	< 0.001
2010–2016	0.58 (0.42 to 0.82)	0.002	0.43 (0.31 to 0.61)	< 0.001
CCI	1.36 (1.20 to 1.55)	< 0.001	1.24 (1.07 to 1.43)	0.004
ASA score				
1–2	1 (reference)		1 (reference)	
3	1.32 (1.06 to 1.65)	0.013	1.27 (0.98 to 1.64)	0.066
4–5	4.65 (3.07 to 7.04)	< 0.001	1.95 (1.23 to 3.12)	0.005
Emergency surgery	2.09 (1.62 to 2.68)	< 0.001	1.42 (1.09 to 1.86)	0.010
TNM-stage				
I	1 (reference)		1 (reference)	
II	1.75 (0.66 to 4.65)	0.26	1.36 (0.69 to 2.68)	0.37
III	6.61 (2.61 to 16.74)	< 0.001	4.71 (2.47 to 8.99)	< 0.001
IV	44.81 (17.96 to 111)	< 0.001	3.39 (1.68 to 6.85)	0.001
Unknown	24.29 (8.67 to 68.05)	< 0.001	1.48 (0.65 to 3.34)	0.35
Treatment intent categories				
Curative intent				
Major resection	1 (reference)		1 (reference)	
Polypectomy	1.62 (0.71 to 3.74)	0.25	3.82 (1.54 to 9.48)	0.004
Non-curative intent				
Major resection	16.13 (12.51 to 20.80)	< 0.001	9.50 (5.94 to 15.18)	< 0.001
Bypass/stoma	25.50 (16.59 to 39.20)	< 0.001	19.38 (10.82 to 34.69)	< 0.001
Best supportive care	21.22 (15.74 to 28.61)	< 0.001	22.24 (12.26 to 37.28)	< 0.001

Results are from a multivariable analysis; unadjusted: performed with one covariate at a time; adjusted: performed with all listed covariates included simultaneously.
CCI Charlson Comorbidity Index, classified as 0, 1, or 2 +

Long-term relative survival, local recurrence, and metastasis after a major resection with curative intent

Overall, the 5 year relative survival rate was 83.2% (95% CI: 79.4. to 86.8) for all patients with stages I-III disease that underwent major resections with a curative intent. Relative survival rates after a major resection with curative intent in patients who survived 90 days are presented in Fig. 2. Patients aged 65–74 years had the lowest 5 year relative survival rate: 79.0% (95% CI: 72.9 to 84.4), compared to 88.4% (95% CI: 77.0 to 99.1) in octogenarian patients.

When we excluded patients that died within the first 90 days, the overall 5 year relative survival rate was 87.5% (95% CI: 83.6 to 91.1). In this group, patients aged 65–74 years had the lowest 5 year relative survival rate: 81.2% (95% CI: 75.1 to 86.6), compared to 98.7% (95% CI: 86.5 to 110.0) in octogenarian patients.

Factors associated with relative long-term survival are presented in Table 7. Long-term relative survival rates did not differ significantly between the different age groups. A similar multivariable analysis performed in a selected group of patients with stage III colon cancer

Table 4 Characteristics of patients with colon cancer stages I-III that underwent major resections with curative intent

Characteristic	Total, $n=1021$	Age group (years)						*P* value
		<65, $n=233$	65–74, $n=327$	75–79, $n=201$	80–84, $n=171$	85–89, $n=66$	≥90, $n=23$	
Sex								0.043[a]
Females	534 (52)	121 (52)	156 (48)	105 (52)	99 (58)	38 (58)	15 (65)	
Males	487 (48)	112 (48)	171 (52)	96 (48)	72 (42)	28 (42)	8 (35)	
Calendar year								0.011[b]
1980–1989	175 (17)	50 (29)	61 (35)	28 (16)	27 (15)	9 (5)	0 (0)	
1990–1999	241 (24)	55 (23)	79 (33)	49 (20)	35 (15)	16 (7)	7 (3)	
2000–2009	334 (33)	82 (25)	92 (28)	64 (19)	67 (20)	18 (5)	11 (3)	
2010–2016	271 (27)	46 (17)	95 (35)	60 (22)	42 (16)	23 (9)	5 (2)	
ASA score								<0.001[b]
1–2	591 (58)	190 (82)	215 (66)	94 (47)	69 (40)	19 (29)	4 (17)	
3	395 (39)	41 (18)	101 (31)	101 (50)	93 (54)	44 (67)	15 (65)	
4	35 (3)	2 (1)	11 (3)	6 (3)	9 (5)	3 (5)	4 (17)	
Localization								<0.001[a]
Right colon	573 (56)	103 (44)	179 (55)	130 (65)	105 (61)	43 (65)	13 (57)	
Left colon	448 (44)	130 (56)	148 (45)	71 (35)	66 (39)	23 (35)	10 (43)	
Stage (TNM)								0.050[b]
I	154 (15)	33 (14)	54 (17)	25 (12)	27 (16)	12 (18)	3 (13)	
II	548 (54)	125 (54)	157 (48)	116 (58)	91 (53)	43 (65)	16 (70)	
III	319 (31)	75 (32)	116 (35)	60 (30)	53 (31)	11 (17)	4 (17)	
R-status								0.44[c]
R0—resection	983 (96.3)	223 (96)	317 (97)	196 (98)	160 (94)	64 (97)	23 (100)	
R0—resection with perforation	20 (2)	7 (3)	5 (2)	3 (2)	4 (2)	1 (2)	0 (0)	
R1—resection	18 (2)	2 (1)	4 (1)	2 (1)	7 (4)	1 (2)	0 (0)	
Type of resection								0.003[c]
Right hemicolectomy	504 (49)	87 (37)	156 (48)	113 (56)	99 (58)	37 (56)	12 (52)	
Transverse resection	24 (2)	5 (2)	9 (3)	4 (2)	2 (1)	4 (6)	0 (0)	
Left hemicolectomy	131 (13)	39 (17)	44 (14)	27 (13)	12 (7)	4 (6)	5 (22)	
Sigmoid and high anterior resections	267 (26)	75 (32)	89 (27)	41 (20)	43 (25)	16 (24)	3 (13)	
Hartmann's operation	35 (3)	10 (4)	12 (4)	5 (2)	3 (2)	3 (4)	3 (13)	
Subtotal resection	55 (5)	15 (6)	17 (5)	10 (5)	11 (6)	2 (3)	0 (0)	
Other resections	5 (1)	2 (1)	0 (0)	1 (1)	1 (1)	1 (2)	0 (0)	
Emergency surgery								0.13[a]
Yes	141 (14)	30 (13)	47 (14)	20 (10)	27 (16)	7 (11)	10 (43)	
No	880 (86)	203 (87)	280 (86)	181 (90)	144 (84)	59 (89)	13 (57)	

Values are the number of patients (%), unless otherwise indicated. [a]Cochran-Armitage exact trend test; [b]Ordinal logistic regression with age group as covariate; [c]Nominal logistic regression with age group as covariate

revealed that patients with left-sided colon cancer had better survival than those with right-sided colon cancer (OR = 0.55, 95% CI: 0.33 to 0.91; $p=0.02$). This effect was not found in separate analyses of patients with stage I or stage II colon cancer.

Local recurrence was diagnosed in 4.4% (43/973) of patients. The overall estimated 5 year local recurrence rate was 4.5% (95% CI: 3.7 to 5.3). The estimated 5 year local recurrence rates after an R0 resection, an R1 resection, or a resection with tumour perforation were 4.3% (95% CI: 3.6 to 5.0), 43.2% (95% CI: 10.2 to 76.2), and 57.5% (95% CI: 19.1 to 95.9), respectively. The estimated 5 year local recurrence rates were not affected by age.

Metastatic disease was diagnosed in 20% (195/973) of patients. The overall estimated 5 year metastasis rate was 22.5% (95% CI: 19.5 to 25.5). The estimated 5 year local metastasis rates after an R0 resection, an R1 resection, or a resection with tumour perforation were 21.2% (95% CI: 18.2 to 24.2), 45.5% (95% CI: 17.9 to 73.1),

Table 5 Factors associated with postoperative complications[a] after major resections with curative intent (R0 and R1); $n = 1021$[b]

Factors	Unadjusted odds ratio (95% CI)	*P* value	Adjusted odds ratio (95% CI)	*P* value
Age (years)				
< 65	1 (reference)		1 (reference)	
65—74	1.51 (1.08 to 2.11)	0.016	1.35 (0.94 to 1.96)	0.11
75 – 79	2.13 (1.47 to 3.08)	< 0.001	1.51 (0.99 to 2.28)	0.053
80—84	2.83 (1.93 to 4.17)	< 0.001	1.96 (1.27 to 3.03)	0.002
85 – 89	2.96 (1.73 to 5.03)	< 0.001	2.14 (1.18 to 3.87)	0.013
≥ 90	7.60 (3.11 to 18.58)	< 0.001	5.36 (2.11 to 13.61)	< 0.001
Female sex	0.99 (0.78 to 1.25)	0.95	1.15 (0.89 to 1.49)	0.28
Calendar year				
1980–1989	1 (reference)		1 (reference)	
1990–1999	0.46 (0.32 to 0.67)	< 0.001	0.44 (0.30 to 0.66)	< 0.001
2000–2009	0.43 (0.30 to 0.60)	< 0.001	0.50 (0.33 to 0.94)	0.001
2010–2016	0.47 (0.33 to 0.68)	< 0.001	0.61 (0.40 to 0.94)	0.025
ASA score				
1–2	1 (reference)		1 (reference)	
3	2.00 (1.56 to 2.56)	< 0.001	1.43 (1.08 to 1.90)	0.013
4–5	19.07 (9.56 to 38.05)	< 0.001	10.86 (5.19 to 22.73)	< 0.001
Emergency surgery	2.51 (1.75 to 3.60)	0.001	2.30 (1.57 to 3.39)	< 0.001
Anaemia (g/dL haemoglobin)				
Female ≥ 12.0, Male ≥ 13.0	1 (reference)		1 (reference)	
Female 10–11.9, Male 11–12.9	1.97 (1.47 to 2.64)	< 0.001	2.26 (1.64 to 3.11)	< 0.001
Female < 10, Male < 11	4.76 (3.53 to 6.43)	< 0.001	5.61 (4.01 to 7.84)	< 0.001
Surgery duration (minutes)				
< 90	1 (reference)		1 (reference)	
90–179	1.01 (0.73 to 1.38)	0.96	0.96 (0.67 to 1.39)	0.84
≥ 180	2.24 (1.48 to 3.38)	0.001	1.52 (0.89 to 2.58)	0.13
Blood loss (mL)				
0–200	1 (reference)		1 (reference)	
201–400	1.21 (0.88 to 1.65)	0.24	1.48 (1.04 to 3.11)	0.029
401–800	1.67 (1.20 to 2.32)	0.002	2.16 (1.45 to 3.21)	< 0.001
> 800	3.69 (2.41 to 5.65)	< 0.001	4.13 (2.44 to 7.01)	< 0.001

[a] Complications were classified according to Clavien-Dindo grades; [b]Patients included those with stages I-III colon cancer during 1980–2016

and 70.4% (95% CI: 47.2 to 93.6), respectively. The estimated 5 year metastasis rates were not affected by age.

Chemotherapy

Starting in 1993, adjuvant chemotherapy was given to 53% (72/137) of patients under 75 years of age that underwent a major resection with curative intent for stage III disease. Among these patients, 28% (16/58) received adjuvant chemotherapy in 1993–2004, and 71% (56/79) received adjuvant chemotherapy in 2005–2016. Among patients aged 75–84 years, a selected group of 13% (11/85) received adjuvant chemotherapy. Among patients treated with a major resection with curative intent for stage II disease, 7% (15/214) received adjuvant chemotherapy.

Among patients that underwent palliative surgery or best supportive care, 34.5% (158/458) received palliative chemotherapy. This rate remained stable throughout the study period. The percentage of patients given palliative chemotherapy decreased as age increased. Palliative chemotherapy was given to 76% (79/104) of patients < 65 years, compared to 2.7% (4/148) of octogenarian patients.

Discussion

In this series, the rate of patients selected for surgical treatment decreased as patient age increased. Nevertheless, postoperative morbidity and 90-day mortality rates increased as patient age increased. During the study period, the percentage of octogenarian patients that

Table 6 Factors associated with 90-day mortality after major resections with curative intent (R0 or R1); $n = 1021$[a]

Factor	Dead within 90 days (%)	Unadjusted odds ratio (95% CI)	*P* value	Adjusted odds ratio (95% CI)	*P* value
Age (years)					
< 65	1/233 (0.4)	┐			
65 – 74	8/327 (2.4)	├ 1 (reference)		1 (reference)	
75 – 79	6/201 (3.0)	┘			
80 – 84	13/171 (7.6)	4.09 (1.91 to 8.77)	< 0.001	3.90 (1.60 to 9.52)	0.003
85 – 89	9/66 (13.6)	7.85 (3.29 to 18.73)	< 0.001	10.72 (3.74 to 30.71)	< 0.001
≥ 90	8/23 (34.8)	26.52 (9.77 to 72.01)		19.76 (5.53 to 70.5)	< 0.001
Female sex		0.54 (0.29 to 0.9976)	0.049	0.51 (0.24 to 1.08)	0.077
Calendar year					
1980-1989	12/175 (6.8)	1 (reference)		1 (reference)	
1990-1999	12/241 (5.0)	0.71 (0.31 to 1.62)	0.42	0.49 (0.17 to 1.38)	0.18
2000-2009	10/334 (3.0)	0.42 (0.18 to 0.99)	0.048	0.29 (0.09 to 0.84)	0.022
2010-2016	11/271 (4.1)	0.57 (0.25 to 1.33	0.20	0.45 (0.17 to 1.20)	0.11
ASA score				3.77 (2.12 to 6.69)	< 0.001
1–2	10/591 (1.7%)	1 (reference)		1 (reference)	
3	20/395 (5.1%)	3.10 (1.43 to 6.69)	0.004	1.51 (0.63 to 3.59)	0.35
4	15/35 (42.9%)	43.58 (17.44 to 108)	< 0.001	12.60 (4.26 to 37.25)	< 0.001
Emergency surgery		10.24 (5.50 to 19.09)	< 0.001	6.80 (3.24 to 14.28)	< 0.001

[a] Patients included those with stages I-III colon cancer during 1980–2016; results are from a logistic regression analysis, with death as the dependent variable; unadjusted: performed with one covariate at a time; adjusted: performed with all listed covariates included simultaneously

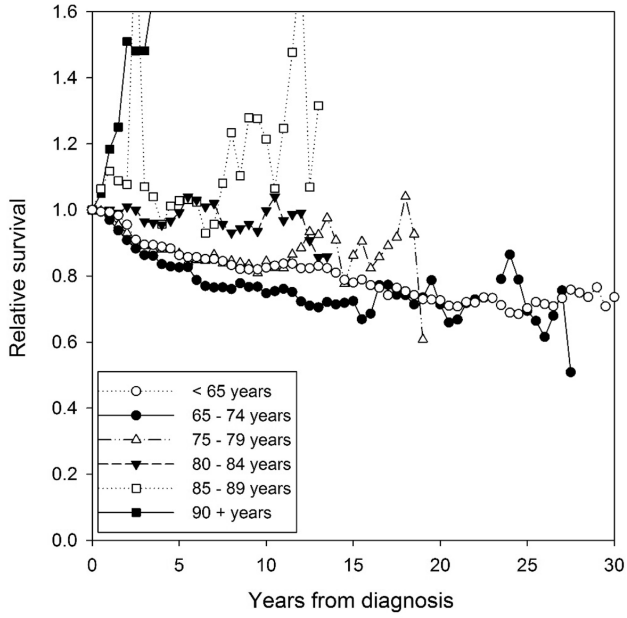
underwent a major resection with curative intent increased, and the 90-day mortality was reduced. However, among patients that survived the first 90 days, long-term relative survival was independent of age.

All patients

Previous studies have pointed out age-related disparities in multimodal cancer treatments [9, 20]. In patients with colon cancer, individual treatment plans are based on accurate disease staging. In the first period (1980–1989) of the present study, we observed a transient trend towards a higher proportion of older patients with unknown disease stages. During the study period, we found significant progress in staging availability and precision, and focus was placed on the importance of preoperative staging, irrespective of patient age. Nevertheless, the proportion of patients with unknown stages among octogenarian patients in this series was low, compared to the proportions based on national data from several European countries [21]. Moreover, the disease stages at admission were equally distributed across the age groups, and the proportion of patients that presented with stage IV disease (25%) was comparable to proportions reported previously [22, 23].

Surgery is the cornerstone of colon cancer treatment. The primary objective of surgery is either radical resection or endoscopic resection, for early-stage tumours. Palliative surgery may be indicated as part of a multimodal treatment in patients with advanced disease or in cases with obstruction. Overall, the percentage of patients that underwent surgical treatments in this series was 89%. This percentage decreased as age increased. Surgery was performed in 93% of patients younger than 80 years and 82% of octogenarian patients. These findings were comparable to national data from European countries, where surgical treatment rates ranged between 59 and 79% among patients 80 years and older [21]. Variations in the overall rates of patients that undergo surgical treatment for colon cancer among different series are likely to depend on demographic, socioeconomic, and clinically related factors. The availability of healthcare services in our catchment area was high, and the threshold for referring patients to the hospital, irrespective of age, was low. However, because comorbidity increased with age, the rate of patients considered unsuitable for surgical treatment was relatively high among older patients.

The overall rate of patients that underwent emergency surgery in this series was 16%, and the rate increased with increasing age. Previous studies have shown significant variability (8–34%) in the rates of emergency surgery; these differences might be due to differences in the definition of emergency surgery and the selection of patient cohorts [24–26]. The rate of emergency surgery



Number at risk

< 65 years	227	202	179	153	133	119	98	71	51	42	32	23	5
65 - 74 years	311	259	197	146	109	73	52	34	22	14	8	3	1
75 - 79 years	193	154	111	74	49	33	17	9	2	1			
80 - 84 years	151	123	82	50	28	12	4	2					
85 - 89 years	56	43	22	9	4	1	1						
90 years +	16	13	6	2									

Fig. 2 Relative survival after colon cancer resection with curative intent in patients that survived 90 days. Relative survival is stratified by age group. Table columns represent the number of patients at risk at surgery (time = 0) and every 2.5 years thereafter

in this series was lower than the 25% reported previously, in a comparable population-based study from Sweden [27]. We observed that the rate of emergency surgery declined throughout the 37 years of the study. This finding might be related to a continuous increase in the availability of health care services, including the implementation of fast-track examinations, when alarm symptoms indicated colorectal cancer, and a higher societal awareness of this disease.

In parallel with the increases in population aging and the number of older patients admitted to hospital with colon cancer, the rate of octogenarian patients that underwent surgery increased. Hence, the proportion of octogenarian patients considered eligible for surgery has increased. A comparison of general health between the current and previous generations is difficult to assess objectively, and we lack evidence that older people in the current generation are healthier than those in previous generations [28, 29]. However, comorbid disease treatments and perioperative care have improved during the last few decades, and these advances have lowered the threshold for surgery [30–32].

The literature has shown variability in the rates of short-term mortality among patients with colon cancer. Clearly, differences in patient populations and differences in patient selection procedures for different treatment options, primarily surgical treatments, have major impacts on the outcome. In the present study, the overall 90-day mortality was 13.5%, and it increased, with increasing age, to 22.4% among octogenarian patients. These rates were comparable to rates reported in other unselected population-based series [26, 33]. We found that comorbidity, advanced TNM-stages, and emergency surgery had profound negative effects on the

Table 7 Factors associated with relative long-term relative survival, among patients that survived 90 days; $n = 976$[a]

Factor	Unadjusted hazard ratio (95% CI)	*P* value	Adjusted hazard ratio (95% CI)	*P* value
Age (years)				
< 65	1 (reference)		1 (reference)	
65—79	1.30 (0.84 to 2.03)	0.24	1.0005 (0.62 to 1.60)	0.998
≥ 80	0.58 (0.19 to 1.71)	0.32	0.73 (0.36 to 1.47)	0.38
Female sex	1.52 (0.98 to 2.36)	0.061	1.56 (1.03 to 2.36)	0.035
Calendar year				
1980–1989	1 (reference)		1 (reference)	
1990–1999	0.80 (0.47 to 1.35)	0.40	0.74 (0.44 to 1.24)	0.25
2000–2009	0.48 (0.28 to 0.85)	0.011	0.54 (0.31 to 0.93)	0.027
2010–2016	0.36 (0.18 to 0.70)	0.003	0.46 (0.25 to 0.85)	0.013
CCI	1.39 (1.14 to 1.68)	0.001	1.39 (1.12 to 1.73)	0.003
ASA score				
1–2	1 (reference)		1 (reference)	
3	1.85 (1.23 to 2.81)	0.003	1.64 (1.03 to 2.60)	0.036
4	5.45 (2.45 to 12.12)	< 0.001	4.79 (2.09 to 10.97)	< 0.001
Emergency surgery	3.07 (1.99 to 4.73)	< 0.001	2.13 (1.35 to 3.35)	0.001
Left vs. right colon	0.94 (0.62 to 1.43)	0.77	0.75 (0.49 to 1.14)	0.18
TNM-stage				
I	1 (reference)		1 (reference)	
II	3.92 (0.49 to 31.57)	0.20	1.98 (0.55 to 7.12)	0.30
III	16.81 (2.16 to 131)	0.007	8.17 (2.36 to 28.3)	0.001
R-status				
R0—resection	1 (reference)		1 (reference)	
R0—resection with perforation	9.78 (5.42 to 17.66)	< 0.001	4.81 (2.47 to 9.35)	< 0.001
R1—resection	3.54 (1.24 to 10.14)	0.018	3.25 (1.20 to 8.84)	0.021

[a] Patients included those with stages I-III colon cancer during 1980–2016, treated with a major resection with curative intent (R0 and R1). Results are from a multivariable analysis; unadjusted: performed with one covariate at a time; adjusted: performed with all listed covariates included simultaneously. *CCI* Charlson Comorbidity Index, classified as 0, 1, 2, or 3 +

90-day mortality. These associations were consistent with those demonstrated in previous reports [34, 35]. We noted a 48% reduction in the overall 90-day mortality rate, between the first and last decades of the observational period. The basis for this improvement was multifactorial, but it was driven by the general, continuous progress in medical treatments during the study period. Although we observed a significant increase in short-term mortality with increasing age, the long-term relative survival rates of young and old patient groups converged over time, and after 5 years, survival was independent of age. The 5 year relative survival among all patients was 58.5%, comparable to rates reported in previous studies on unselected series of patients with colon cancer [36].

Patients with stages I-III disease that underwent a major resection with curative intent

Among patients with stages I-III disease at diagnosis, 92.6% (1021/1102) were treated with a major resection with curative intent, comparable to the proportions reported previously in studies on colon cancer [37]. Although the rate was lower among octogenarian patients (90.1%, 237/263), it was similar to the overall rate, which indicated that the approach to surgical treatment remained consistent, irrespective of age. During the first part of this study, the selection of patients for a major resection with curative intent was performed by a traditional interdisciplinary team, which included the surgeon and the anaesthesiologist. This selection was primarily based on a clinical evaluation combined with the ASA-score. Later, the focus changed, and treatment decisions were increasingly performed by multidisciplinary teams, which also included oncologists, radiologists, and pathologists [5].

The overall rate of postoperative morbidity, defined as a Clavien-Dindo score of 3 or more, was 9.6%, and the overall 90-day mortality was 4.4%. We observed a significant reduction in both postoperative morbidity and mortality during the study, and as in other series, we

confirmed that high ASA scores and the need for emergency surgery had negative impacts on both endpoints. Moreover, high peri-operative blood loss increased the postoperative morbidity, which highlighted the importance of the surgical technique [38]. Finally, preoperative anaemia was significantly associated with an increased risk of postoperative complications. In a previous meta-analysis by Fowler et al., preoperative anaemia was also associated with a poor postoperative outcome [39]. Accordingly, methods for detecting and treating preoperative anaemia would be beneficial.

The major challenge in treating colon cancer, which was noted in this series and confirmed by others, is the significant increase in postoperative morbidity and mortality with increasing age, even after a thorough patient selection process. In this series, octogenarian patients selected to undergo major curative surgery had a significantly increased risk of postoperative morbidity and mortality compared to younger patients. The mortality rate was 0.4% among patients aged < 65 years, and it increased by 25-fold, to 10.1%, in octogenarian patients.

Nevertheless, the 5 year relative survival rate in this series was equivalent across age groups, consistent with findings in previous series [36, 40–42]. Among patients that survived 90 days after surgery, long-term survival was most significantly negatively impacted by the TNM stage, the R-status, and the presence of a tumour perforation [36, 40–42]. As observed previously [36, 40–42], the negative effect of emergency surgery persisted past the postoperative period. This finding highlighted the need to enhance the focus and follow-up for this group of patients.

As the population ages, octogenarian patients will become the most common group with colon cancer. Consequently, measures are needed to reduce the excess rates of postoperative morbidity and mortality among older patients. Increasing the focus on the process of selecting patients to different levels of treatment will be highly important, both for the individual patient and for the healthcare system. It is essential to perform geriatric assessments systematically in the preoperative work-up [43–45], pay attention to the concept of prehabilitation [46], and increase focus on patient preferences [47]. Recent reports have demonstrated the value of a geriatric assessment in summarizing the patient's degree of frailty and predicting postoperative morbidity and mortality for older patients with colon cancer [48]. The Society for Geriatric Oncology has recommended these assessments for all patients with cancer that are over 70 years of age [49]. In a systematic review, more than half of older patients with cancer were considered to be in a pre-frailty or frailty condition [50], and both these conditions were associated with adverse postoperative outcomes.

Most efforts to reduce postoperative morbidity and mortality rates have focused on the peri-operative and immediate postoperative statuses. Thus, the concept of prehabilitation prior to surgery has not gained sufficient attention. As part of this concept, the geriatric assessment evaluates several individual modifiable factors relevant to status optimization prior to surgery [51]. Moreover, a multidisciplinary team approach was shown to improve the postoperative outcome in frail patients [52]. Currently, an ongoing prospective multicentre study is examining multimodal prehabilitation for patients with colorectal cancer. Hopefully, those results will provide valuable information regarding the role of prehabilitation in the future management of older patients with cancer [46].

Numerous factors contribute to heterogeneity in the group of older patients with cancer. It is important to consider that personal patient preferences regarding treatment decisions might vary substantially among older patients. In the late stages of life, some needs, like preserving the remaining quality of life, may outweigh the need for radical treatment [47, 53]. It has been shown that the physician's recommendation was the most decisive factor in influencing the patient's decision [54]. That finding emphasized the importance of a thorough, and preferably evidence-based, foundation for the physician's advice.

Strengths and weaknesses

The main strength of this study was the transparent presentation of a consecutive, population-based cohort of patients with colon cancer that were treated in accordance with current evidence-based guidelines over a period of 37 years. Our institution was the primary hospital for a stable population throughout this extensive observational period, and thus, the cohort was suitable for evaluating trends over time. We believe that octogenarian patients with colon cancer will emerge as an important entity; thus, the results from this series provide important contributions to the current state of the field.

The main limitation of the study was its retrospective design. Due to its observational nature, we could not investigate causality. Moreover, the results may not be applicable to the older population, in general. Frail and unfit patients might not have been referred to our hospital, due to their clinical status. Finally, unknown or unrecorded confounders might have affected decisions regarding patient selection and treatment.

Conclusion

This study showed that octogenarian patients treated for colon cancer had adverse 90-day mortality rates, but among those that survived 90 days postoperatively, the long-term survival rate was equivalent to that of younger patients. The increasing fraction of older patients in years to come will become a major challenge in treating colon cancer. In addressing that challenge, early disease detection, followed by prehabilitation, a multidisciplinary approach with a geriatric assessment, and a meticulous post-operative follow up will be essential factors for improving treatment results and surmounting current standards.

Abbreviations

ASA: American Society of Anaesthesiology; CCI: Charlson Comorbidity Index; CI: Confidence interval; SD: Standard deviation.

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Authors' contributions

ØH: Made substantial contributions to the design of the work, the interpretation of data, and drafting and revising the manuscript. THE: Made substantial contributions to the design of the work, the analysis and interpretation of data, and drafting and revising the manuscript. AX: Made substantial contributions to the design of the work and revising the manuscript. SL: Made substantial contributions to the design of the work, the analysis and interpretation of data, and revising the manuscript. BHE: Made substantial contributions to the design of the work, the analysis and interpretation of data, and drafting and revising the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The dataset used for this study is located on a secure server in the Levanger Hospital data system. The database was confirmed by comparing data with corresponding data in the Norwegian Cancer Registry 1980–2016 (https://www.kreftregisteret.no). The data are not publicly available as their containing information could compromise the privacy of research participants.

Declarations

Ethics approval and consent to participate

The project was performed in accordance with the Declaration of Helsinki. The Regional Committee for Medical and Health Research Ethics (REC) in Norway approved the study (2016/2172/REK midt). Written informed consent was waived due to the retrospective observational nature of the study. All treatment was given according to local guidelines from 1980–1992, and according to similar, national guidelines from 1993–2016.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Publisher's Note

PAPER III

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The impact of age on rectal cancer treatment, complications and survival

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Abstract

Background The number of older patients with rectal cancer is increasing. Treatment outcome discrepancies persist, despite similar treatment guidelines. To offer the oldest patients optimal individually adjusted care, further knowledge is needed regarding treatment strategy and outcome. The present study aimed to evaluate treatment, postoperative complications, and survival in older patients treated for rectal cancer.

Methods This retrospective study included all 666 patients (*n*=255 females, *n*=411 males) treated for rectal cancer at Levanger Hospital during 1980-2016 (*n*=193 <65 years, *n*=329 65-79 years, *n*=144 ≥80 years). We performed logistic regression to analyse associations between complications, 90-day mortality, and explanatory variables. We performed a relative survival analysis to identify factors associated with short- and long-term survival.

Results Despite a similar distribution of cancer stages across age-groups, patients aged ≥80 years were treated with a non-curative approach more frequently than younger age groups. Among patients aged ≥80 years, 42% underwent a non-curative treatment approach, compared to 25% of patients aged <65 years, and 25% of patients aged 65-79 years. The 90-day mortality was 15.3% among patients aged ≥80 years, compared to 5.7% among patients aged <65 years, and 9.4% among patients aged 65-79 years.

Among 431 (65%) patients treated with a major resection with curative intent, the 90-day mortality was 5.9% among patients aged ≥80 years (*n*=68), compared to 0.8% among patients aged <65 years (*n*=126), and 3.8% among patients aged 65-79 years (*n*=237). The rate of postoperative complications was 47.6%. Pneumonia was the only complication that occurred more frequently in the older patient group. The severity of complications increased with three factors: age, American Society of Anaesthesiologists score, and >400 ml perioperative blood loss. Among patients that survived the first 90 days, the relative long-term survival rates, five-year local recurrence rates, and metastases rates were independent of age.

Conclusion Patients aged ≥80 years were less likely to undergo a major resection with curative intent and experienced more severe complications after surgery than patients aged <80 years. When patients aged ≥80 years were treated with a major resection with curative intent, the long-term survival rate was comparable to that of younger patients.

Keywords Rectal cancer, Elderly, Treatment, Survival, Epidemiology

Introduction

The incidence of rectal cancer in Norway is among the highest in the world [1]. Moreover, the aging of the population has led to a high number of older patients. Questions remain to be resolved regarding rectal cancer

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treatment in this heterogeneous group of patients to offer optimal individualized care.

Treatments for rectal cancer have evolved over the last four decades. Diagnostic tools have become more available. The diagnostic work-up is performed according to standardized protocols that apply across age-groups [2]. The implementation of total mesorectal excision (TME) and the addition of preoperative radiotherapy for locally advanced tumours have improved survival [3, 4]. Minimally invasive surgery has reduced surgical trauma, and protocols to enhance recovery after surgery have become a standard part of treatment [5, 6]. The modern principles in rectal cancer treatments, including TME and preoperative radiotherapy, have been applied to all patients treated at Levanger Hospital since 1980. A prospective protocol for the operative strategy, radiotherapy, and surveillance was established, and excellent results were reported after the first ten years [7].

The fundamental treatment for rectal cancer includes a resection of the tumour-bearing segment of the rectum. This procedure is associated with substantial postoperative morbidity [8]. Complications may be fatal, particularly in aged, vulnerable patients with low capacity to withstand physiological stress. This risk has had a heavy impact on the choice of treatment for aged patients, and thus, it may adversely affect both functional results and survival. The number of older patients with rectal cancer is expected to increase in the years to come [9]; thus, deeper knowledge is needed to pursue individually optimized care.

The present study aimed to evaluate treatment, complications, and survival in patients with rectal cancer during 1980-2016, with a special focus on the older patients.

Methods

This study included all patients treated for rectal cancer at Levanger Hospital during 1980-2016. Levanger Hospital was the primary hospital of 10 municipalities in Norway, and the catchment area remained unchanged throughout the study period. The population increased by 18%, from 83,890 inhabitants in 1980, to 99,566 inhabitants in 2016.

We identified patients through the hospital administrative system and reviewed health records for all patients discharged with diagnosis codes for rectal cancer, based on the International Classification of Diseases, 8th revision (ICD-8) codes 154, ICD-9 codes 154, and ICD-10 codes C20. To ensure a complete cohort, the retrieved data were crosschecked and confirmed with data recorded in the Norwegian Cancer Registry during 1980-2016. We retrieved data on demographic variables, comorbidities, treatment, tumour characteristics, histopathology, postoperative complications, and short- and long-term survival.

During the study period, 51 patients in our catchment area were referred for treatment to other hospitals; 33 patients were referred to the nearest university hospital for preoperative radiotherapy and underwent surgery there; and 18 patients chose to receive treatment in another hospital. These patients were not included in our cohort. The characteristics of these patients are presented Table 9 in Appendix. This study included a total of 666 patients treated for rectal cancer.

Rectal cancer was defined as a tumour located within 15 cm of the anal verge, measured with a rigid proctoscope. The rectal sections were defined according to the distance above the anal verge: the proximal rectum was at 12-15 cm; the middle rectum was at 6-11 cm; and the distal rectum was at 0-5 cm.

Disease stages were classified according to the TNM classification, sixth edition [10]. Signs of residual tumour after surgery were classified as R0 - no microscopic residual tumour; R1 - microscopically involved resection margin; and R2 - macroscopic residual tumour. A major resection with curative intent was defined as a resection of the tumour-bearing segment of the rectum, including R1-resections and tumour perforations, with no radiological or preoperative signs of metastases. Major resections were performed according to TME principles [3, 11]. In four patients, the resections were performed laparoscopically, all in the last part of the study period (2010-2016). A histopathological verification of cancer was missing in 20 of 666 patients (3%); however, the rectal cancer diagnosis was evident from other examinations. Among these 20 patients, 7 underwent non-resection procedures, and 13 underwent best supportive care, without resection.

Preoperative radiotherapy was recommended for patients with fixed, locally advanced tumours, according to national guidelines established in 1993 [12]. During 1980-1999, referrals for radiotherapy were based on proctoscopy and digital examinations. In 2000, magnetic resonance imaging of the rectum became available at our hospital, and it was used as the decisive diagnostic modality for evaluating tumour resectability. All patients selected for radiotherapy were referred to the nearest university hospital. The majority of patients received 2 Gy $\times$25, but in selected cases, patients received 5 Gy $\times$5.

For this study, patients were categorized into groups according to treatment intent. The curative intent group included patients with (*i*) a major resection (R0 and R1) or (*ii*) a polypectomy. The non-curative intent group included patients with (*iii*) a major resection, (*iv*) a bypass/stoma, or (*v*) best supportive care.

Comorbid conditions were classified according to the American Society of Anaesthesiology (ASA) score and

the Charlson Comorbidity Index (CCI) [13, 14]. Emergency surgery was defined as a surgery due to evidence of large bowel obstruction or large bowel perforation.

Postoperative complications included any deviation from the normal postoperative course during the same hospital admission, and were noted in the patient records. The severity of postoperative complications was graded according to the Clavien-Dindo (CD) classification of surgical complications [15].

Clinical follow-up was initially conducted according to local guidelines. Starting in 1993, follow-ups were conducted according to similar national guidelines [2]. Normal follow-ups lasted for 5 years, but they were extended in selected cases. The follow-up period for this study ended on December 31st, 2018. The mean follow-up time was 6.12 years (range: 0.02 – 34.04, SD: 5.78).

Survival time calculations started from the date of admission and ended at the last known date that the patient was alive or the date of death. Patients that were alive December 31st, 2018, were counted as censored cases. The mean follow-up time with regard to survival was 6.89 years (range: 0.01 - 37.88, SD: 7.49).

Statistical analysis

The Cochran Armitage exact trend test was performed to test for trends in proportions; for example, the proportion of Hartmann's procedures (HPs) performed per decennium.

The Joncheere-Terpstra test was performed to test for the distribution of blood loss volumes (dependent variable) across decennium periods (independent variables). Kaplan-Meier analyses were performed to estimate the 5-year rates of local recurrences and metastases.

Logistic regression analysis was performed to test for associations between the 90-day mortality (dependent variable) and different explanatory variables. Ordinal logistic regression was performed to test for associations in doubly ordered r × c contingency tables; for example, the ASA scores in different age groups. The resulting odds ratio (OR) was a common OR estimate for any 2 × 2 contingency table that would occur, if the r ×c table were collapsed to a 2 × 2 table, based on any cut-off threshold, along the columns and rows. Multinomial logistic regression analysis was performed in singly ordered r x c contingency tables; for example, the type of treatment in different age groups.

Relative survival analysis

Relative survival is a measure of mortality compared to the general population. The observed survival in the group with cancer was divided by the expected survival of a comparable group in the general Norwegian population, matched with respect to age, sex, and the calendar year of investigation. Relative survival was estimated with the Ederer II method and analysed with STATA 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC) [16]. Multivariable analyses were performed with a full likelihood approach. We retrieved data on Norwegian population survival probabilities for every year, starting from 1980, calculated for groups divided by sex and age, from the Human Mortality Database [17].

Two-sided *P*-values <0.05 were considered significant. Means are reported with the range (minimum to maximum) and standard deviation (SD), where relevant. Ninety-five percent confidence intervals (CIs) are reported, where relevant. Analyses were performed with STATA 16 (StataCorp. College Station, TX: StataCorp LLC), IBM SPSS Statistics 25 (IBM Corp. Armonk, NY: IBM Corp), and StatXact 9 (Cytel. Waltham, MA).

Results

All patients

The characteristics of all 666 patients treated for rectal cancer in 1980-2016 are presented in Table 1. Patients were predominantly male (61.7%), and the mean age was 70.6 years (range: 35.2-97.2, SD: 11.1). Among males, the mean age was 70.3 years (range: 40.7-94.3, SD: 10.3), and among females, the mean age was 71.0 years (range: 35.2-97.1, SD: 12.2). The mean age increased insignificantly from 69.9 years in 1980-1989 to 71.2 years in 2010-2016. The mean number of patients diagnosed with rectal cancer increased from 12.8 patients/year in 1980-1989 to 25.3 patients/year in 2010-2016. We also observed an insignificant increase over time in the proportion of patients aged ≥80 years.

The CCI and ASA score increased with increasing age. Distal tumours were more prevalent in the oldest age group. The rate of patients with stages I and II tumours increased throughout the study period, but the rate of patients with unknown stages declined; only one patient had an unknown stage in the last time period (2010-2016). Overall, 17% of patients aged ≥80 years had an unknown tumour stage. This rate declined from 41.7% in 1990-1999 to 0% in 2010-2016. The distribution of tumour stages did not differ between age groups.

The overall rate of patients treated with a major resection with curative intent was 65%, and this rate remained consistent throughout the study period. The rate varied across age-groups; it was 65% among patients under 65 years old, 72% among patients 65-79 years old, and 47% among patients ≥80 years old. The distribution of treatment intent categories differed across age groups. The

Table 1 Characteristics of 666 patients admitted to the hospital with rectal cancer during 1980-2016

Characteristic	Total, n (%)	<65 years old, n (%)	65-79 years old, n (%)	80+ years old, n (%)	*p*
Sex					0.16 [a]
Female	255 (38)	73 (38)	115 (35)	67 (47)	
Male	411 (62)	120 (62)	214 (65)	77 (53)	
Calendar-year (row %)					0.23[b]
1980-1989	128 (19)	37 (19) (29)	71 (22) (56)	20 (14) (16)	
1990-1999	178 (27)	51 (26) (29)	91 (28) (51)	36 (25) (20)	
2000-2009	183(27)	54 (28) (30)	86 (26) (47)	43 (30) (24)	
2010-2016	177 (27)	51 (26) (29)	81 (25) (46)	45 (31) (25)	
Charlson Comorbidity Index					
0	497 (75)	162 (84)	253 (77)	82 (57)	<0.001[b]
1	70 (11)	18 (9)	38 (11)	14 (10)	
2 +	99 (15)	13 (7)	38 (11)	48 (33)	
ASA score					<0.001[b]
1-2	402 (60)	160 (83)	204 (62)	38 (26)	
3	235 (35)	30 (16)	115 (35)	90 (63)	
4-5	29 (4)	3 (2)	10 (3)	16 (11)	
Localization (distance proximal to the anal verge)					0.006 [b]
Proximal (12-15 cm)	210 (32)	71 (37)	102 (31)	37 (26)	
Middle (6-11 cm)	280 (42)	81 (42)	140 (42)	59 (41)	
Distal (0-5 cm)	176 (26)	41 (21)	87 (27)	48 (33)	
Stage (TNM)					0.89[c]
I	150 (23)	49 (25)	73 (22)	28 (19)	
II	195 (29)	51 (26)	110 (33)	34 (24)	
III	153 (23)	43 (22)	77 (23)	33 (23)	
IV	124 (19)	42 (22)	58 (18)	24 (17)	
Unknown	44 (7)	8 (4)	11 (3)	25 (17)	
Treatment intent categories					<0.001[d]
Curative intent					
Major resection	433 (65)	127 (66)	238 (72)	68 (47)	
Polypectomy	41 (6)	18 (9)	8 (2)	15 (10)	
Non-curative intent					
Major resection	58 (9)	24 (12)	27 (8)	7 (5)	
Bypass/Stoma	47 (7)	9 (5)	22 (7)	16 (11)	
Best supportive care [f]	87 (13)	15 (8)	34 (10)	38 (26)	
Surgery					0.68[a]
Elective surgery [g]	551 (95)	169 (95)	280 (95)	102 (96)	
Emergency surgery	28 (5)	9 (5)	15 (5)	4 (4)	

[a] Cochran-Armitage exact trend test

[b] Ordinal logistic regression with the age group as a covariate

[c] Ordinal logistic regression with the age group as a covariate, for known stages

[d] Multinomial logistic regression with the age group as a covariate

[e] Palliative surgery (stoma, by-pass, palliative resection)

[f] Including palliative radiochemotherapy in 3 cases

[g] Including polypectomy

proportion of patients that underwent best supportive care was higher among patients ≥80 years old.

Among patients treated with a non-curative intent, 27.1% (52/192) received chemotherapy. Chemotherapy was performed in 54.2% (26/48) of patients <65 years old, 30.1% (25/83) of patients 65-79 years old, and 1.6% (1/61) of patients ≥80 years old. In examining different time periods, we found that chemotherapy was performed in

36.1% (13/36) of patients during 1980-1989, 13.8% (8/58) during 1990-1999, 34% (17/50) during 2000-2009, and 29.2% (14/48) during 2010-2016.

Radiotherapy was administered to 33% (63/192) of the patients in the non-curative treatment intent group. Among these, 13 patients underwent radiotherapy as a part of a curative treatment plan, and 50 patients underwent palliative radiotherapy. Among the patients treated with palliative radiotherapy, 29 had metastases at diagnosis.

The 90-day mortality, overall survival, and relative long-term survival rates for all patients are presented in Table 2. The 90-day mortality after admission was 9.6%, and it increased significantly with age. In addition, the five-year overall and relative survival rates in patients that survived the first 90 days decreased with age. Prognostic factors associated with 90-day mortality are presented in Table 3. Age was not a significant factor, but the calendar year of treatment, a high ASA score, and the treatment intent category were significant independent variables. The five-year relative survival rates among all patients were 62.6% (95% CI: 51.2 to 73.1) during 1980-1989, 48.9% (95% CI: 40.1 to 57.6) during 1990-1999, 61.4% (95% CI: 52.3 to 69.9) during

Table 2 Analysis of 90-day mortality, five-year overall survival, and five-year relative survival, according to age group

Age group	Patients	Death within 90 days	Patients that survived 90 days (602 patients)	
Years	N	N/total, (%)	Overall survival	Relative survival
		p=0.004 [a]	% (95% CI) p<0.001 [b]	% (95% CI) p<0.001 [c]
<65	193	11 / 193 (5.7)	69.9 (63.1 to 76.7)	72.9 (65.3 to 79.3)
65 - 79	329	31 / 329 (9.4)	56.0 (50.2 to 61.8)	66.9 (59.9 to 73.5)
80 +	144	22 / 144 (15.3)	25.6 (17.6 to 33.6)	48.3 (34.2 to 63.6)
Total	666	64 / 666 (9.6)	54.0(49.8 to 58.2)	66.3 (61.2 to 71.1)

[a] Cochran Armitage exact trend test

[b] Log Rank test

[c] Log likelihood

Table 3 Logistic regression results identified factors associated with death within 90 days for all patients diagnosed with rectal cancer in 1980-2016

Factor	Death within 90 days, N/total	Unadjusted odds ratio (95% CI)	*p* value	Adjusted odds ratio (95% CI)	*p* value
Age (years)					
<65	11/193 (7%)	1 (reference)		1 (reference)	
65 - 79	32/329 (9.7%)	1.78 (0.88 to 3.62)	0.11	1.31 (0.58 to 2.97)	0.51
80+	22/144 (15.3%)	2.98 (1.40 to 6.37)	0.005	1.12 (0.43 to 2.91)	0.82
Calendar year		0.96 (0.94 to 0.99)	0.003	0.94 (0.91 to 0.97)	<0.001
ASA score					<0.001
1-2	23/402 (5.7%)	1 (reference)		1 (reference)	
3	28/235 (11.9%)	2.23 (1.25 to 3.97)	0.006	1.64 (0.81 to 3.29)	0.17
4-5	14/29 (48.3%)	15.38 (6.63 to 35.67)	<0.001	4.18 (1.40 to 12.50)	0.01
Emergency surgery	4/27 (14.8%)	1.68 (0.56 to 5.01)	0.36	1.04 (0.27 to 4.05)	0.95
Treatment intent categories					
Curative intent					
Major resection	14/433 (3.2%)	1 (reference)		1 (reference)	
Polypectomy	0/41	1		1	
Non-curative intent					
Major resection	5/58 (8.6%)	2.82 (0.98 to 8.15)	0.055	2.16 (0.73 to 6.4)	0.16
Bypass, stoma	14/47 (29.8%)	12.70 (5.59 to 28.86)	<0.001	11.11 (4.46 to 27.66)	<0.001
Best supportive care	32/87 (36.8%)	17.41 (8.75 to 34.65)	<0.001	15.99 (7.21 to 35.44	<0.001

Logistic regression was performed with death within 90 days as the dependent variable. Unadjusted was performed with one covariate at a time; adjusted was performed with all the listed covariates simultaneously

2000-2009, and 67.6% (95% CI: 58.1 to 76.3) during 2010-2016.

Patients with stages I-III disease treated with a major resection with curative intent

The characteristics of 431 (64.7%) patients with rectal cancer stages I-III that were treated with a major resection with curative intent (R0 and R1) are presented in Table 4. These patients were predominantly males (63.1%). The mean age remained stable during the study period; the mean ages were 69.1 (range: 40.7-91.8, SD: 9.7) years in males and 69.8 (range: 37.4-91.6, SD: 11.5) years in females. The mean annual number of patients that underwent a major resection with curative intent doubled over time, from 8.2 patients/year in 1980-1989 to 16.3 patients/year in 2010-2016. Tumour stages, tumour localizations, and the use of radiotherapy were equally distributed across the age groups. CCI and ASA scores increased with age. Older patients less often underwent an anterior resection or an abdominoperineal resection, and more often underwent an HP, compared to younger patients. The rate of HPs decreased from 3.7% (3/82) during 1980-1989 to 2.6% (3/116) during 1990-1999; thereafter, the rate increased to 14.3% (17/119) during 2000-2009 and to 22.8% (26/114) during 2010-2016 ($p<0.001$).

The proportion of patients with CCI scores ≥2 increased steadily over time. The proportions were 7.3% (6/82) in 1980-1989, 12.1% (14/116) in 1990-1999, 7.6% (9/119) in 2000-2009, and 14.9% (17/114) in 2010-2016. The proportion of patients with ASA scores >2 also increased throughout the observational period. The proportions were 19.5% (16/82) in 1980-1989, 36.2% (42/116) in 1990-1999, 28.6% (34/119) in 2000-2009, and 42.1% (48/114) in 2010-2016 ($p=0.008$).

Preoperative radiotherapy was administered to 7.3% (6/82) of patients during 1980-1989, 0.9% (1/116) of patients during 1990-1999, 26.1% (31/119) of patients during 2000-2009, and 29.8% (34/114) of patients during 2010-2016 ($p<0.001$).

Postoperative complications

Major complications (CD ≥3) occurred in 13.5% (58/431) of all patients; they occurred in 10.3% (13/126) of patients aged ≤65 years, 14.4% (34/236) of patients aged 65-79 years, and 15.9% (11/69) of patients aged ≥80 years ($p=0.24$). The proportion of patients with major complications increased from 11.0% (9/82) during 1980-1989, to 13.8% (16/116) during 1990-1999, then decreased to 10.9% (13/119) during 2000-2009, and then increased to 21.1% (24/114) during 2010-2016 ($p=0.035$). An anastomotic leak was diagnosed in 4.9% (21/431) of patients, and wound dehiscence was diagnosed in 1.9% (8/431) of patients.

Infective complications occurred in 35.7% (154/431) of patients that underwent a major resection with a curative intent. The most common infective complications were urinary tract infections (18.6%, $n=80/431$), wound infections (10.7%, $n=46/431$), intra-abdominal abscesses (5.6%, $n=24/431$), and pneumonia (3.5%, $n=15/431$). Pneumonia was the only complication that occurred significantly more frequently in the oldest group (≥80 years: 8.8%, $n=6/68$) compared to younger patients (<80 years: 2.5%, $n=9/363$; $p=0.015$).

Blood loss declined in each decade; the mean blood loss volumes were 1388 ml (range: 300-9000, SD: 1182) during 1980-1989, 1216 ml (range 200-10000, SD: 1234) during 1990-1999, 732 ml (range: 50-3300, SD: 647) during 2000-2009, and 427 ml (range 0-2500, SD: 328) during 2010-2016 ($p<0.001$). Blood transfusions were administered to 87.8% (72/82) of patients in 1980-1989, compared to 26.3% (30/114) of patients in 2010-2016.

A reoperation (CD ≥3b) was required in 11.4% (49/431) of all patients that underwent a major resection. The frequency of reoperations increased during the last part of the study period; it was 7.3% (6/82) during 1980-1989, 9.5% (11/116) during 1990-1999, and 9.2% (11/119) during 2000-2009, but increased to 18.4% (21/114) during 2010-2016 ($p=0.037$). Reoperations were performed in 8.8% (6/68) of patients aged ≥80 years and in 11.9% (43/363) of patients aged <80 years ($p=0.60$).

Ordinal multivariable logistic regression analyses of risk factors associated with the CD severity of postoperative complications are presented in Table 5. Independent risk factors were: increasing age, increasing ASA scores, and perioperative blood loss >400 ml.

Short- and long-term survival among patients that underwent a major resection with curative intent

The 90-day mortality, overall survival, and relative long-term survival rates in patients with rectal cancer stage I-III that underwent a major resection with curative intent are presented in Table 6. The 90-day mortality rate after admission was 3.2%.

The five-year overall survival rates decreased significantly with age. The 10-year, 20-year, and 30-year estimated survival rates were 51.6% (95% CI: 46.4 to 56.8), 27.4% (95% CI: 21.8 to 33.0), and 7.9% (95% CI: 2.9 to 12.9), respectively. The mean survival time was 13.2 years (95% CI: 12.0 to 14.4).

The five-year relative survival rates decreased insignificantly with age in this patient group (Table 6). The 10-year, 20-year, and 30-year relative survival rates were 79.6% (95% CI: 71.5 to 87.3), 82.6% (95% CI: 66.6

Table 4 Characteristics of 431 patients with stages I-III rectal cancer that underwent a major resection with curative intent in 1980-2016, grouped according to age

Characteristic	Total n (%)	Age <65 years, n (%)	Age 65-79 years, n (%)	Age 80+ years, n (%)	*P*-value
Proportion of total	431/666 (65)	126/193 (65)	237/328 (72)	68/144 (47%)	
Sex					0.29 [a]
Females	159 (37)	46 (37)	81 (34)	32 (47)	
Males	272 (63)	80 (63)	156 (65)	36 (53)	
Calendar-year (row %)					0.50 [b]
1980-1989	82 (19)	23 (28)	49 (60)	10 (12)	
1990-1999	116 (27)	31 (27)	71 (62)	14 (12)	
2000-2009	119 (28)	38 (32)	60 (50)	21 (18)	
2010-2016	114 (26)	34 (30)	57 (50)	23 (20)	
Charlson Comorbidity Index					0.001 [b]
0	350 (81)	114 (90)	187 (79)	49 (72)	
1	35 (8)	7 (6)	22 (9)	6 (9)	
2 +	46 (11)	5 (4)	28 (12)	13 (19)	
ASA score					<0.001 [b]
1-2	291 (68)	108 (86)	157 (66)	26 (38)	
3	138 (32)	18 (14)	78 (33)	42 (62)	
4-5	2 (0.5)	0	2 (1)	0	
Localization in rectum					0.25 [b]
Proximal	153 (36)	51 (40)	79 (33)	23 (34)	
Middle	178 (41)	50 (40)	99 (42)	29 (43)	
Distal	100 (23)	25 (20)	59 (25)	16 (24)	
Stage (TNM)					0.16 [b]
I	119 (28)	38 (30)	66 (28)	15 (22)	
II	173 (40)	49 (39)	99 (42)	25 (37)	
III	139 (32)	39 (31)	72 (30)	28 (41)	
Radiochemotherapy					0.12 [c]
No	345 (80)	96 (76)	190 (80)	59 (87)	
Preoperatively	71 (16)	23 (18)	39 (16)	9 (13)	
Postoperatively	14 (3)	7 (6)	7 (3)	0	
Both pre- and postoperatively	1 (0.2)	0	1 (0.4)	0	
Treatment					<0.001 [c]
AR	276 (64)	89 (71)	155 (65)	32 (47)	
APR	104 (24)	30 (24)	62 (26)	12 (18)	
Hartmann's procedure	48 (11)	7 (6)	18 (8)	23 (34)	
Proctocolectomy	3 (1)	0	2 (1)	1 (1)	
Surgery					0.33 [a]
Elective surgery	421 (98)	125 (99)	230 (97)	66 (97)	
Emergency surgery	10 (2)	1 (1)	7 (3)	2 (3)	
R stage					0.42 [b]
R0	405 (94)	121 (96)	222 (94)	62 (91)	
R0 with perforation	14 (3)	3 (2)	7 (3)	4 (6)	
R1	12 (3)	2 (2)	8 (2)	2 (3)	

AR anterior resection, *APR* abdominoperineal resection

[a] Cochran-Armitage exact trend test

[b] Ordinal logistic regression with age group as a covariate

[c] Multinomial logistic regression with age group as a covariate

Table 5 Factors associated with postoperative complications, based on Clavien-Dindo scores, in 431 patients treated for Stages I-III rectal cancer with a major resection with curative intent (R0 and R1)

Factor	Unadjusted odds ratio (95% CI)	*p* value	Adjusted odds ratio (95% CI)	*p* value
Age (years)				
<65	1 (reference)		1 (reference)	
65 - 79	2.07 (1.36 to 3.14)	0.001	1.91 (1.22 to 2.99)	0.005
80 +	2.22 (1.26 to 3.90)	0.005	2.20 (1.15 to 4.22)	0.017
Female sex	0.83 (0.57 to 1.19)	0.31	0.96 (0.65 to 1.41)	0.82
Calendar-year				
1980-1989	1 (reference)		1 (reference)	
1990-1999	0.46 (0.27 to 0.79)	0.004	0.49 (0.28 to 0.87)	0.014
2000-2009	0.34 (0.20 to 0.58)	<0.001	0.56 (0.30 to 1.02)	0.059
2010-2016	0.44 (0.26 to 0.75)	0.003	1.12 (0.56 to 2.25)	0.75
Preoperative radiochemotherapy	1.11 (0.68 to 1.80)	0.68	0.98 (0.56 to 1.71)	0.93
ASA score				
1–2	1 (reference)		1 (reference)	
3	1.80 (1.23 to 2.65)	0.003	1.74 (1.14 to 2.68)	0.011
4	20.99 (1.05 to 421)	0.047	11.04 (0.70 to 173)	0.087
Treatment				
AR	1 (reference)		1 (reference)	
APR	2.05 (1.33 to 3.14)	0.001	1.25 (0.77 to 2.00)	0.37
Hartmann's procedure	1.52 (0.86 to 2.66)	0.15	1.11 (0.55 to 1.71)	0.76
Emergency surgery	1.16 (0.39 to 3.47)	0.79	0.44 (0.13 to 1.56)	0.21
Surgery (duration in min)				
<90	1 (reference)		1 (reference)	
90-179	2.15 (0.98 to 6.47)	0.55	1.50 (0.53 to 4.20)	0.44
180 +	6.76 (2.58 to 17.7)	<0.001	2.41 (0.78 to 7.46)	0.13
Blood loss (ml)				
0-200	1 (reference)		1 (reference)	
201-400	0.94 (0.39 to 2.26)	0.90	1.04 (0.41 to 2.65)	0.93
401-800	2.73 (1.20 to 6.22)	0.017	2.59 (1.03 to 6.53)	0.043
>800	5.60 (2.47 to 12.69)	<0.001	5.37 (2.01 to 14.33)	0.001

Ordinal multivariable logistic regression analysis was performed with the Clavien-Dindo score as the dependent variable. Unadjusted: performed with one covariate at a time; adjusted: performed with all the listed covariates simultaneously

Table 6 Rates of 90-day mortality, five-year overall survival, and five-year relative survival, according to age [*]

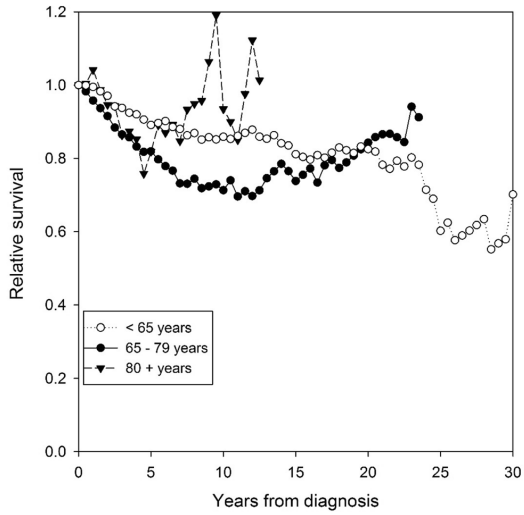
Age group	Patients	Death within 90 days	Patients that survived 90 days (417 patients)	
Years	N	N/total (%)	Overall survival	Relative survival
		p=0.061 [a]	% (95% CI) p<0.001 [b]	% (95% CI) p=0.12 [c]
<65	126	1 / 126 (0.8)	86.8 (80.6 to 93.0)	90.5 (82.8 to 95.6)
65-79	237	9 / 237 (3.8)	67.9 (61.7 to 74.0)	81.4 (75.6 to 88.2)
80+	68	4 / 68 (5.9)	40.8 (28.5 to 52.7)	74.2 (51.9 to 95.9)
Total	431	14 / 431 (3.2)	69.4 (64.7 to 73.6)	84.2 (78.5 to 89.3)

[a] Cochran Armitage exact trend test

[b] Log Rank test

[c] Log likelihood

[*] This analysis included patients with rectal cancer stages I-III that underwent a major resection with curative intent



Number at risk

< 65 years	125	121	98	80	68	64	50	42	33	24	15	7	4
65 - 79 years	228	153	206	117	79	52	41	25	17	10	6	5	1
80 years +	64	51	30	15	10	5	2						

Fig. 1 Relative survival after resection with curative intent among patients that survived 90 days (*N*=417) in different age groups. Each column represents 2.5 years.

to 99.4), and 73.1% (95% CI: 35.9 to 128), respectively. Relative survival rates in patients that survived 90 days after a major resection with curative intent varied with the age-group (Figure 1). The five-year relative survival rates in patients that survived the first 90 days also varied over time; they were 89.4% (95% CI: 74.8 to 100) during 1980-1989, 72.0% (95% CI: 60.3 to 82.2) during 1990-1999, 87.1% (95% CI: 76.1 to 95.7) during 2000-2009, and 90.4% (95% CI: 78.9 to 99.0) during 2010-2016.

The five-year relative survival rates depended on the type of resection. At five years after R0 resections, R0 resections with a tumour perforation, or R1 resections, survival rates were 86.4% (95% CI: 80.5 to 91.5), 57.1% (95% CI: 22.2 to 88.3), and 34.8% (95% CI: 8.3 to 66.5), respectively.

Multivariable analyses identified several factors associated with 90-day mortality (Table 7). Mortality increased with increasing age and ASA scores, and decreased over time (i.e., calendar year).

Prognostic factors associated with long-term relative survival are presented in Table 8. Age was not significantly associated with relative survival. However, CCIs $\geq$3, increasing ASA scores, emergency surgeries, and stage III disease were significantly inversely associated with long-term survival.

Table 7 Factors associated with death within 90 days, in 431 patients treated for rectal cancer stages I-III with a major resection with curative intent (R0 or R1 resection) in 1980-2016

Factor	Unadjusted odds ratio (95% CI)	*p* value	Adjusted odds ratio (95% CI)	*p* value
Age (years)	1.08 (1.02 to 1.16)	0.011	1.08 (1.004 to 1.16)	0.036
Calendar year	0.94 (0.89 to 0.99)	0.023	0.92 (0.87 to 0.98)	0.006
ASA score [a]	3.43 (1.24 to 9.48)	0.018	3.33 (1.08 to 10.31)	0.037

Multivariable logistic regression analysis was performed with death as the dependent variable. Unadjusted: performed with one covariate at a time; adjusted: performed with all the listed covariates simultaneously

[a] ASA scores were compared between the following groups: 1-2, 3, 4-5

Table 8 Factors associated with long-term relative survival in 417 patients treated for rectal cancer stages I-III with a major resection and curative intent (R0 and R1) that survived 90 days postoperatively *(270 died during the observation period)*

Factor	Unadjusted hazard ratio (95% CI)	*p* value	Adjusted hazard ratio (95% CI)	*p* value
Age (years)				
<65	1 (reference)		1 (reference)	
65 - 79	2.25 (0.95 to 5.32)	0.065	1.82 (0.71 to 4.67)	0.22
80 +	2.92 (0.86 to 9.77)	0.081	1.58 (0.42 to 5.93)	0.50
Female sex	1.24 (0.60 to 2.56)	0.57	1.17 (0.60 to 2.29)	0.65
Calendar year				
1980-1989	1 (reference)		1 (reference)	
1990-1999	1.63 (0.60 to 4.43)	0.34	0.95 (0.35 to 2.60)	0.92
2000-2009	1.01 (0.36 to 2.87)	0.98	0.74 (0.27 to 2.05)	0.57
2010-2016	0.52 (0.13 to 2.13)	0.36	0.42 (0.13 to 1.34)	0.14
Charlson Index				
0	1 (reference)		1 (reference)	
1	2.97 (1.14 to 7.74)	0.026	2.06 (0.83 to 5.12)	0.12
2	4.09 (1.71 to 9.78)	0.002	1.78 (0.66 to 4.82)	0.26
3 +	6.08 (1.91 to 19.31)	0.002	4.90 (1.47 to 16.30)	0.010
ASA score				
1-2	1 (reference)		1 (reference)	
3-4	3.43 (1.70 to 6.91)	0.001	2.37 (1.11 to 5.05)	0.026
Emergency surgery	7.19 (2.63 to 19.64)	<0.001	4.88 (1.23 to 19.41)	0.025
TNM-stage				
I-II	1 (reference)		1 (reference)	
III	3.72 (1.67 to 8.29)	0.001	2.70 (1.32 to 5.52)	0.007
Type of resection				
R_0 - resection	1 (reference)		1 (reference)	
R_0 - resection with perforation	2.92 (0.78 to 10.94)	0.11	1.20 (0.23 to 6.21)	0.83
R_1 - resection	5.98 (2.26 to 15.84)	<0.001	2.03 (0.65 to 6.37)	0.23

Unadjusted: performed with one covariate at a time; adjusted: performed with all the listed covariates simultaneously

Local recurrence and metastasis among patients that underwent a major resection with curative intent

Local recurrence was diagnosed in 7% (29/417) of patients with rectal cancer stage I-III that underwent a major resection with curative intent. The overall estimated five-year local recurrence rate was 7.3% (95% CI: 4.5 to 10.1). The estimated five-year local recurrence rates after an R0 resection, an R0 resection with tumour perforation, and an R1 resection were 4.9% (95% CI: 2.5 to 7.3), 29.7% (95% CI: 0.1 to 59.3), and 78.8% (95% CI: 52.4 to 100), respectively. The five-year local recurrence rates varied by the decade of treatment; they were 4.4% (95% CI: 0 to 9.4) during 1980-1989, 18.5% (95% CI:10.3 to 26.7) during 1990-1999, 2.1% (95% CI: 0 to 5.1) during 2000-2009, and 5.9% (95% CI: 0.7 to 11.1) during 2010-2016 (p<0.001). The estimated five-year local recurrence rates were not affected by age.

Metachronous metastases were diagnosed in 21.8% (91/417) of patients. The overall estimated five-year metastasis rate was 22.6% (95% CI: 18.2 to 27.0). The estimated five-year metastasis rates after an R0 resection, an R0 resection with tumour perforation, and an R1 resection were 19.5% (95% CI: 15.1 to 23.9), 58.3% (95% CI: 29.7 to 86.9), and 86.4% (95% CI: 61.6 to 100), respectively. The estimated five-year metastasis rates did not vary significantly by the treatment decade or patient age.

Discussion

The present study showed that the TNM stage at presentation was equally distributed across age groups. The overall rate of patients treated with a major resection with curative intent was 65%, but the rate varied across age groups: it was 47% among patients aged ≥80 years. One or more postoperative complications occurred in 47.6% of patients. The rates of postoperative complications were independent of age, except for pneumonia, which was more common in patients aged ≥80 years.

The severity of postoperative complications, based on the CD score, increased with patient age, ASA score, and perioperative blood loss. The 90-day mortality rate was 3.2%, and the rate increased with age: it was 5.9% among patients aged ≥80 years. In patients that survived the first 90 days, the rates of five-year relative survival, local recurrences, and metastases were independent of age.

All patients

The incidence of rectal cancer has increased since the 1980s, at both the global and national levels. The main reasons for this increase are an increasing human development index [18], an aging population [19], and an age-independent approach to the diagnostic work-up of suspected cancer. We observed a successive increase in the rectal cancer incidence during the study period and a trend towards an increase in the rate of patients aged ≥80 years. Despite scarce evidence and a demand for knowledge, older patients are frequently excluded from clinical trials [20]. The present study included an unselected consecutive series of all patients treated for rectal cancer at a local hospital during nearly four decades, with a focus on patients aged ≥80 years.

It has been well documented that inequities concerning rectal cancer treatment occur across age groups [21]. The optimal treatment for an individual patient is based on a complete staging of the disease. In the present series, the rate of patients with an unknown stage declined over time, and it was low compared to other series [22]. Tumour stages were evenly distributed across age groups, consistent with previous reports [23]. Although the disease stage is typically the defining determinant in treating younger patients, factors associated with increasing age highly influence treatment options in older patients [24].

In Norway, a standardized diagnostic work-up applies to all patients with rectal cancer [2]. It culminates in a summary meeting of a multidisciplinary team (MDT), where treatment options are considered in detail, based on diagnostic findings and the defined stage of disease. A thorough, objective evaluation of the patient's functional and physiological status and the patient's personal preferences regarding treatment are not emphasized in routine care; however, adding these features to routine care would constitute a major improvement in guidance for making decisions for these patients [25].

A non-curative treatment approach was applied to 28.7% of the patients in this study, consistent with previously reported 25-30% rates for incurable disease at diagnosis [1]. Despite a similar stage distribution between age groups at diagnosis, the rate of patients that underwent a non-curative treatment increased with age. Among patients aged ≥80 years, 42% underwent non-curative treatments. Only 17% of the older patients had verified stage IV disease at diagnosis, but 25% underwent non-curative treatment with an unknown stage of disease or a potentially resectable disease. Limitations regarding treatment in older patients are related to the coinciding peak incidences of co-morbid diseases, cognitive impairments, and physical impairments [26]. In the present study, objective measures of co-morbidity, ASA, and CCI scores increased significantly with age.

Palliative resection procedures were more common in younger age groups; the older patients more frequently underwent best supportive care. The overall rate of chemotherapy was 27.1%, and it declined substantially with patient age. Individualized treatment regimens may be well tolerated in older patients with good performance status, hence chronological age should not preclude these patients from chemotherapy [27, 28].

The overall rate of procedures with curative intent was 71.3%. The rate of major resections was 65.1% and the rate of polypectomies was 6.2%. These rates were comparable to the major resection rates of 59.9-70.8% reported recently in an evaluation of Scandinavian and English patients with rectal cancer during 2010-2012 [22]. The present study found a resection rate of 66.3% in our Norwegian population. Resection rates decline consistently with increasing age, and they have varied substantially between countries, despite comparable treatment guidelines. In the present study, 47.2% of patients aged ≥80 years underwent a major resection with curative intent. In comparison, Swedish patients aged >75 years had resection rates of 61.9%, and English patients aged >75 years had resection rates of 45.7%.

The overall 90-day mortality rate was 9.6%. It increased with age, but decreased significantly throughout the study period. Among patients that survived the first 90 days in this series, the five-year relative survival rate was 66.3%. The rate decreased from 72.9% in patients aged <65 years to 48.3% in patients aged ≥80 years. The overall five-year relative survival rates for Norwegian patients with rectal cancer have increased successively over the years, from 43.8% during 1980-1984 to 72.4% during 2016-2020 [1, 29]. Comparable rates during 2012-2016 have been reported in the other Nordic countries and the Netherlands [30, 31].

Selecting the appropriate individualized treatment for rectal cancer is a major challenge in efforts to reduce morbidity and increase survival. The adverse effects of over-treatment may cause unnecessary harm, but under-treatment may reduce survival. Older patients with reduced physiological reserves are particularly prone to the adverse effects of cancer treatment,

regardless of whether the approach is curative. This dilemma is reflected by differences in treatment rates, and it underlines the need for additional improvements in the treatment selection process for this group of patients.

Patients with stages I-III disease treated with a major resection with curative intent

Overall, an anterior resection was the most common procedure, with a rate of 64%. Patients aged ≥80 years had lower anterior resection rates (47%) and were more frequently treated with an HP (34%). This observation was consistent with previous findings [32, 33]. The main advantage of a HP is that it avoids an anastomosis, which eliminates the potentially fatal effects of an anastomotic leak. Among older patients with reduced tolerability for surgical complications, the HP stands out as a safe choice. In this series, only three patients underwent surgery with a laparoscopic approach. Minimally invasive surgery should be considered for older patients as previous studies have demonstrated comparable postoperative outcomes as in younger patients [34].

A Swedish study that examined the postoperative outcome of an HP for rectal cancer found an overall HP rate identical to that found in the present study (11%). They reported that the HP was performed predominantly in older patients (mean age 79 years) with increased comorbidities, elevated ASA scores, and a poor WHO performance status [35]. In fragile patients, HP has the benefits of a shorter operative time, less bleeding, and a lower rate of serious complications, compared to other treatments. However, we lack evidence that clearly favours either the anterior resection or the HP [36]. A substantial number of patients that undergo anterior resections experience low anterior resection syndrome (LARS) [37]. However, the adverse effects of an end-colostomy due to a HP are well-documented [38].

Throughout the study period, in older individuals, the procedure of choice was increasingly an HP. The frequency of HPs increased from 3.7%, in the first observation period, to 22.8% in the last observation period. The increasing use of an HP over time was also observed previously by other authors [39, 40]. The increasing proportion of older patients with comorbidities over time in our cohort might partly explain this observation. However, because the HP rate increased faster than the increasing proportion of older patients over time, our findings also indicated that there was a general trend towards an increased use of HP.

Following rectal cancer surgery, older patients are encumbered with considerable morbidity, ranging from acute infectious complications to permanent functional derangements [41]. Nevertheless, a limited number of studies have addressed complications in this group of patients [42]. Complication rates depend on patient selection for the study, the rate of emergency surgery, the stage of disease, and the level of the institution. The rate of complications in the present study was considerable (47.6%). Although high, this rate was comparable to rates found in previous studies (21-61%) [32, 43]. Rates of major complications (CD ≥3) and anastomotic leaks were also comparable to those found in previous studies [42]. Complication rates did not differ significantly between patients under and over age 80 years, except for pneumonia, which was more common in older patients. Measures to prevent pneumonia in patients that require surgery have been shown to be effective [44], and should be considered routine care in older patients that undergo rectal cancer surgery. The elevated rate of severe complications that we observed in older patients highlighted their reduced capacity to withstand adverse postoperative events.

The rate of reoperations increased significantly during the study period, from 7.3% during 1980-1989 to 18.4% during 2010-2016. In comparison, a 2011 report of nearly 250,000 English patients observed a reoperation rate of 7.4% [45]. The increasing number of older patients with high ASA categories in recent years might have contributed to this observation. The increasing use of HP was likely an attempt to counterbalance the risk of severe complications that might require reoperations. The number of surgeons that performed rectal cancer surgeries increased throughout the study period; this factor may have adversely impacted the rate of postoperative morbidity, due to the complexity of these procedures. Rectal cancer surgery should be applied by highly experienced teams and in concordance with the latest knowledge. Previous studies that evaluated associations between complication rates and treatment volumes have shown conflicting results [46, 47].

The 90-day mortality in patients aged ≥80 years that underwent a major resection with curative intent was 5.9%, compared to an overall 90-day mortality of 3.2%. These rates were low, compared to rates reported previously [48, 49]. These relatively low rates could indicate that the selection of individuals fit for surgery was appropriate in this series. The five-year relative survival rate for all patients that underwent a major resection with curative intent was 84.2%. In comparison, the Norwegian national relative five-year survival rates for localized, regional, and metastasized rectal cancer during 2016-2020 were 98.2%, 81.5%, and 22.4%, respectively [1]. In contrast, the relative survival for patients that underwent surgery for stages I-III disease was 88.5% during

2016-2020 [50]. Previous reports that compared relative survival across age groups of patients treated with curative intent have shown acceptable long-term survival rates among older patients [32, 51–53]. Therefore, resection surgery should not be withheld based on chronological age.

In the present study, the overall five-year local recurrence rate was 7.3%. During the 1990s, treatment guideline violations, reflected by a low (0.9%) rate of preoperative radiotherapy, resulted in a high local recurrence rate (18.5%) and an adverse relative survival rate (72.0%) for that period [4]. During the two later time-periods, local recurrence rates declined in parallel with an increase in relative survival, as the rate of preoperative radiotherapy increased [54]. The increasing use of radiotherapy observed in the present study was also observed at a national level [55]. The estimated five-year metastasis rate after an R0 resection was 19.5%. This rate was comparable to the national rates (20.2-22.1%) during 2006-2020, for patients that underwent resections for stages I-III disease [50].

Strengths and weaknesses

The main strength of the present study was the inclusion of a large number of consecutive patients treated for rectal cancer at a local hospital, in accordance with evidence-based guidelines. Another strength was the long-term observation period of 37 years. Our institution was the primary hospital for a stable population throughout the observational period, and the population was suitable for evaluating trends over time [56]. Complications for each patient were retrieved from hospital records. Norwegian referral policies are practically age-independent; hence, we believe only a small number of patients was not included in the scope of the current report.

The main limitation of the study was its retrospective design. Unknown or unrecorded confounders might have affected decisions regarding patient selection and treatment. An unknown number of complications may have gone unnoticed, and thus, were not included in the hospital records, especially during the earlier years of the study period. Consequently, the numbers of complications presented in this report must be viewed as minimums. A number of patients (n=51) in our catchment area underwent treatment at other institutions and were excluded from this study. In the excluded group, the 90-day mortality and the five-year relative survival rate among those that survived the first 90 days were nearly identical to those observed in the cohort included in this study. However, the addition of these 51 patients to our study cohort might have altered some of the results.

Future perspectives

The number of older patients with rectal cancer is predicted to escalate in the years to come. This escalation will increase the burden on healthcare systems, at both the national and global levels. Improvements in selecting and treating older patients with rectal cancer might enhance results and optimize the utilization of healthcare resources.

Prehabilitation is gaining interest in the surgical milieu and aims to enhance the individual patient's starting point prior to surgery. Currently, studies have been investigating the potential of prehabilitation in patients with rectal cancer, and the results may impact the future treatment of older patients [57, 58].

Studies on the effect of age on morbidity have produced conflicting results [59, 60]. Our observation that more severe complications occurred with increasing age may partly be explained by a higher proportion of frail patients in the oldest age groups compared to younger age groups. Frailty may be present in the absence of comorbid conditions, and it could be a factor in 25-46% of patients over 65 years old that undergo surgery for colorectal cancer [61]. The impact of frailty in patients undergoing surgery for colorectal cancer has been investigated, and it should be emphasized in future clinical practice [62, 63]. Due to the increasing proportion of older patients with rectal cancer, we believe that a comprehensive geriatric assessment should be included as part of the routine work-up.

Physicians may be forced to reconsider treatment aims in older patients, because this group of patients is likely to choose functional status above survival [64]. This choice interferes with one of the most fundamental principles in treating patients with cancer. Moreover, as patients approach the end of life, their personal preferences regarding medical treatment might be more decisive than ever before.

Conclusion

This study showed that patients aged ≥80 years were less likely to undergo a major resection with curative intent compared to younger patients, despite comparable disease stages. The rate of complications following rectal cancer surgery was high across all ages, but the severity of complications increased with age. Patients aged ≥80 years that underwent a major resection with curative intent had long-term survival rates comparable to their younger counterparts. The future care of older patients with rectal cancer demands highly specialized teams that can focus on the distinctive demands in this specific group of patients.

Appendix

Table 9.

Table 9 Characteristics of 51 patients diagnosed with rectal cancer during 1980-2016 that were referred to other hospitals for treatment

Characteristic	Total	1980-1989	1990-1999	2000-2009	2010-2016
Age group, years					
<65	25 (49)	0 (0)	0 (0)	10 (59)	15 (47)
65-80	22 (43)	0 (0)	1 (50)	6 (35)	15 (47)
80+	4 (8)	0 (0)	1 (50)	1 (6)	2 (6)
Charlson Comorbidity Index					
0	40 (78)	0 (0)	2 (100)	15 (88)	23 (72)
1	5 (10)	0 (0)	0 (0)	0 (0)	5 (16)
2+	6 (12)	0 (0)	0 (0)	2 (12)	4 (13)
ASA score					
1-2	40 (78)	0 (0)	0 (0)	13 (76)	27 (84)
3	9 (18)	0 (0)	1 (50)	4 (24)	4 (13)
4-5	2 (4)	0 (0)	1 (50)	0 (0)	1 (3)
Localization (Distance from anal verge)					
Proximal (12-15 cm)	10 (20)	0 (0)	0 (0)	3 (18)	7 (22)
Middle (6-11 cm)	20 (39)	0 (0)	2 (100)	9 (53)	9 (28)
Distal (0-5 cm)	21 (41)	0 (0)	0 (0)	5 (29)	16 (50)
Stage (TNM)					
I	13 (25)	0 (0)	0 (0)	5 (29)	8 (25)
II	16 (31)	0 (0)	0 (0)	6 (35)	10 (31)
III	7 (14)	0 (0)	0 (0)	2 (12)	5 (16)
IV	13 (25)	0 (0)	0 (0)	4 (23)	9 (28)
Unknown	2 (4)	0 (0)	2 (100)	0 (0)	0 (0)
Treatment intent categories					
Curative intent					
Major resection	33	0 (0)	0 (0)	10 (63)	23 (78)
Polypectomy	4	0 (0)	2 (100)	2 (13)	0 (0)
Non-curative intent					
Major resection	8	0 (0)	0 (0)	2 (13)	6 (20)
Bypass/Stoma	1	0 (0)	0 (0)	0 (0)	1 (3)
Best supportive care	2	0 (0)	0 (0)	2 (13)	0 (0)

Four patients (7.8%) died within 100 days. For the remaining patients, the 5-year relative survival was 67.1% (95% CI: 49.5-81.2)

Abbreviations

APR	Abdominoperineal resection
ASA	American Society of Anaesthesiology
CCI	Charlson Comorbidity Index
CD	Clavien-Dindo
CI	Confidence interval
HP	Hartmann's procedure
LARS	Low anterior resection syndrome
MDT	Multidisciplinary team
OR	Odds ratio
SD	Standard deviation
TME	Total mesorectal excision

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Authors' contributions
ØH: Made substantial contributions to the design of the work, the acquisition and interpretation of data, and drafting and revising the manuscript. THE: Made substantial contributions to the design of the work, the acquisition, analysis and interpretation of data, and drafting and revising the manuscript. AX: Made substantial contributions to the design of the work, acquisition of data, and revising the manuscript. SL: Made substantial contributions to the design of the work, supervision of the analysis and interpretation of data, and revising the manuscript. BHE: Made substantial contributions to the design of the work, the interpretation of data, and major contributions drafting and revising the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The dataset used for this study is located on a secure server in the Levanger Hospital data system. The dataset was confirmed by comparing data with corresponding data in the Norwegian Cancer Registry 1980-2016 (https://www.kreftregisteret.no). The dataset generated and analysed during the current study are not publicly available as their containing information could compromise the privacy of research participants, but are available from the corresponding author on a reasonable request.

Declarations

Ethics approval and consent to participate
The project was performed in accordance with the Declaration of Helsinki. The Regional Committee for Medical and Health Research Ethics (REC) in Norway approved the study (2016/2172/REK midt). Written informed consent was waived due to the retrospective observational nature of the study. All treatment was given according to local guidelines from 1980-1992, and according to similar, national guidelines from 1993-2016.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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