Colorectal Cancer in Norway

National Treatment Guidelines and Outcomes

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Scientific environment

This thesis is the result of work performed in conjunction with the Norwegian Colorectal Cancer Group, a subgroup of the Norwegian Gastro-Intestinal Cancer Group. I worked at the Department of Gastrointestinal Surgery at Stavanger University Hospital both as a Senior Consultant Surgeon and as head of the department. I have been a member of the Surgical Research Group of Stavanger University Hospital and have been affiliated with the Institute of Surgical Sciences at the University of Bergen during the period in which I performed my thesis work.

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Abbreviations

AJCC	American Joint Committee on Cancer
APR	Abdominoperineal resection
CC	Colon cancer
CI	Confidence interval
CIN	Chromosomal instability
CRM	Circumferential resection margin
CRN	Cancer Registry of Norway
CRT	Chemoradiotherapy
CT	Computer tomography
CRC	Colorectal cancer
CEA	Carcinoembryonic antigen
LN	Lymph nodes
LR	Local recurrence
MDT	Multidisciplinary team
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
NCCR	Norwegian Colorectal Cancer Registry
PET	Positron emission tomography
R0	No residual disease

R1	Microscopic residual disease
R2	Macroscopic residual disease
TNM	Tumour-node-metastasis
TME	Total mesorectal excision
UICC	Union for International Cancer Control

Contents

1. Summary

1.1 Background

Since the early 1990s, there has been increased attention on the management of patients with rectal cancer, both in Norway and in many other countries. The Norwegian Rectal Cancer Registry, which was established in 1994, provides feedback regarding patient outcomes to all hospitals involved in rectal cancer surgery. A new operative technique, total mesorectal excision or TME, was introduced at the same time, and pre-operative radiotherapy was introduced as part of the primary treatment. Eventually, several low-volume hospitals discontinued surgery for rectal cancer.

With regard to colon cancer, adjuvant chemotherapy for patients with lymph node metastases was introduced in 1997. No other systematic changes in colon cancer treatment took place until 2007, when a national Colon Cancer Registry was established. The Norwegian Colorectal Cancer Registry was established by combining these two registries.

1.2 Purpose of the study

We wished to investigate the consequences of implementing national guidelines with a strong focus on rectal cancer as compared to colon cancer during the time period of 1994 to 2003. In particular, we aimed to compare short- and long-term survival at the national level. In addition, we wanted to investigate lymph node harvest in colon cancer patients in Norway, as this has been suggested to be a quality indicator in colon cancer surgery.

1.3 Materials and methods

Data were provided by the Cancer Registry of Norway and by the Norwegian Rectal Cancer Registry for Paper I and Paper II. For Paper III, the new Colorectal Cancer

Registry, which was established in 2007, provided the data. Using these data in combination with mortality data from Statistics Norway, we compared relative survival for colon and rectal cancer in different time periods and excess mortality in colon and rectal cancer at various time intervals during the five-year period after treatment. For Paper III, we identified colon cancer patients who were curatively resected in 2007 and 2008. We studied variables that might be indicative of poor (i.e. <9) lymph node harvest and identified patients with lymph node positive disease.

1.4 Results

We found no difference in survival between colon and rectal cancer in the time period 1994–1996. However, rectal cancer showed significantly better survival than colon cancer in 2001–2003. Most patient groups showed increased survival between the 1994-1996 timeperiod to the 2001-2003 timeperiod; the exception was colon cancer patients >75 years of age with lymph node metastasis. Rectal cancer patients had lower short-term mortality than colon cancer patients. By about four years after primary surgery, rectal cancer patients had a higher mortality than colon cancer patients.

We found the following factors to be associated with poor lymph node harvest, which has been proposed as an indicator of poor-quality treatment: being elderly, being male, having sigmoid cancer and the presence of a short distal margin. However, none of these factors was significant when it came to identifying patients with positive lymph nodes.

1.5 Conclusion

After the introduction of national treatment guidelines, the survival of rectal cancer patients surpassed the survival of colon cancer patients. Short-term mortality was lower in rectal cancer patients, and 5-year survival was higher than for colon cancer. There is a need for an increased focus on colon cancer patients, and in particular on patients > 75 years of age with lymph node positive disease.

2. List of publications

I B. S. Nedrebø K. Søreide M. T. Eriksen L. M. Dørum, J. T. Kvaløy, J. A. Søreide and H. Kørner. Survival effect of implementing national treatment strategies for curatively resected colonic and rectal cancer.
British Journal of Surgery 2011;98: 716-723

II B. S. Nedrebø K. Søreide M. T. Eriksen, J. T. Kvaløy, J. A. Søreide and H. Kørner. Excess mortality after curative surgery for colorectal cancer changes over time and differs for patients with colon versus rectal cancer.
Acta Oncologica, 2012 Oct 29. (Epub ahead of print)

III B. S. Nedrebø K. Søreide M. T. Eriksen A Nesbakken, J. A. Søreide and H. Kørner. Assessment of risk factors associated with poor lymph node harvest after colon cancer surgery in a national cohort.

Colorectal Disease, in press.

3. Introduction

3.1 History

Cancer has been observed in dinosaur samples from 200 million years ago and seems to be inherently associated with life.[1] Osteosarcoma and metastatic disease has been found in mummified bodies from the Middle East and South America. The first recorded dissections of humans took place about 500 BC, and Hippocrates (460–377 BC) was the first to recognise cancer as a distinctive disease with both local and distant consequences[1]. Hippocrates was also one of the first proctology surgeons, and his written work, "On haemorrhoids," describes how to cut, excise and cauterize the haemorrhoids[2]. However, Hippocrates advised against surgical treatment of cancer, an attitude that remained predominant in medicine for about 2000 years[2].

Rectal cancer was first described in the 14th century by John of Arderne. The following are excerpts from his writing.

"A bubo is a tumour developing within the anus in the rectum – with great hardness, but little aching. This I say, before it ulcerates, is nothing else than a hidden cancer, that may not in the beginning of it be known by the sight of the eye."

"But after passage of time it ulcerates and wastes all of the circumference of it so that it may never be cured with man´cure."

"The patient cannot keep himself from going to the privy because of the aching and sharp pain… hard faeces are passed and sometimes it cannot get out because of the stricture."[2]

Surgery for colorectal cancer was reported in a few cases in the 18th century, replacing medical treatment that mainly comprised enema, venae section, laxatives and ointments during the 19th century. Alexis Littré (Paris, France) was probably the first to suggest the use of a stoma for anus atresia in 1710 by creating a sigmoideostomy. The first stoma for a patient with rectal cancer was described in

1776 by the French surgeon Pillore[2]. At that time, surgery was seen as the last resort i.e. for use when all conservative treatments, including large doses of mercury, had failed. Pillore created a caecostomy that had a favourable immediate postoperative course, but the patient died from peritonitis on the 18th postoperative day. Autopsy showed that there was nothing wrong with the stoma, but 1 kg of mercury had lodged in a narrowing of the small intestine and had eroded the small intestine.[2]

The first successful surgical resection of rectal cancer treatment, which was a transanal excision, was performed in 1826 by Lisfranc (Paris, France)[1]. The patient recovered fully with no relapse. Another 8 patients subsequently underwent the same operation, 6 of whom survived. This operation was performed for tumours below the level of the peritoneal reflection by pulling down the rectum with the tumour and amputating the distal rectum. According to Nettler, this was in fact an anal excision without any curative potential, and most patients died within two years.[1]

During the second half of the 19th century, the basis of modern medicine was laid. This paradigm shift included a better understanding of pathology, pathophysiology and hygiene. The introduction of general anaesthesia enabled surgeons to develop more complex surgical procedures, thus setting the stage for modern surgical oncology. Increasing numbers of surgeons continued to carry out perineal excisions. Theodor Billroth is said to have excised the rectum more than 40 times before 1872.

The course for colon cancer took a different path than that of rectal cancer, with the creation of an anastomosis being the most important challenge. The first successful resection with a primary anastomosis for large bowel cancer seems to have been performed by Reybard in 1833. The patient died one year later due to recurrence. The operation was criticized, and for a long time palliative defunctioning by colostomy was the suggested treatment of choice. As late as 1880, only 10 resections had been reported in the literature, 7 of which were failures. Later, resection and double barrel stoma was introduced, followed by internal anastomosis.[3]

Modern treatment of rectal cancer had its start in 1906, when Miles performed a combined abdomino-perineal operation for rectal cancer. One stage of the operation

was performed via the abdomen with the creation of an end-colostomy, and the other via the perineum. Removal of regional lymph nodes was an important part of the procedure that helped reduce local recurrence rates. Miles' major contribution was to identify the lymphatic spread of cancer cells upwards, downwards and laterally. He therefore assumed that removal of the following was essential for the cure of rectal cancer: the entire rectum, including the anal canal, sphincters, levator ani muscles, ischiorectal fat, most of the sigmoid colon and mesocolon along with the central lymph nodes of the superior haemorrhoidal and inferior mesenteric vessel.[3] Even so, until 1920 there were still studies published about the natural history of untreated colorectal cancer. These reports showed a mean time to death of 24 months, with some patients surviving more than 10 years[3].

During the last century, there has been tremendous progress in terms of the development and improvement of surgical techniques, anaesthetic techniques, antibiotics, stoma care and surgical approach. In 1967, Turnbull proposed a no-touch technique that would avoid blood-borne metastases for colon cancer [4]. The circular stapler for low rectal anastomosis was introduced in 1970. During the 1960s, the first effective chemotherapeutic agents were introduced, including fluorouracil (5-FU), which has remained an important part of colorectal cancer treatment for 40 years.

During the 1980s, cure of colon and rectal cancer that was limited to a localised disease was considered feasible by surgical resection. However, the prognosis of patients with rectal cancer was dramatically inferior compared to patients with colon cancer due to local recurrences in more than 30% of the patients [5, 6]. In 1983, the British surgeon Bill Heald reported a large patient series with a very low local recurrence rate of 4%[7]. He showed that a refined surgical technique that took into account the correct surgical planes was essential for achieving local tumour control as a prerequisite for cure. This technique, termed "total mesorectal excision" or TME, includes complete removal of the fatty tissue behind the rectal tube, its associated lymph nodes and the satellite tumours within its enveloping fascia, which is the mesorectal fascia.[8] While TME was met with initial scepticism, the concept of TME has been adopted by the surgical community and was considered the standard surgical

technique for rectal cancer during the 1990s[9]. Currently, TME is performed not only in open surgery but also via laparoscopy[10] and using robot-assisted techniques[11].

For colon cancer, there were basically no major changes in surgical techniques during this time (1980-2000). The only major treatment change was the introduction of adjuvant chemotherapy for lymph node positive disease. A more detailed description of the evolution of treatment guidelines during the last 20 years is given in Chapter 9, "The Evolution of Norwegian Treatment Guidelines."

3.2 Epidemiology

From a global perspective, there were an estimated 12.7 million cancer cases and 7.6 million cancer deaths worldwide in 2008[12]. In the industrialised world, breast cancer in women and lung cancer in men are the most common causes of death from cancer, followed closely by colorectal cancer for both sexes. In Norway, around 3500 new cases were diagnosed in 2007. While colorectal cancer is ranked second to prostate cancer for men and breast cancer for women, it represents the most common cancer that affects both sexes.[13] Approximately 5% of all men and 4% of all women in Norway will be diagnosed with colorectal cancer before age 75.[14]

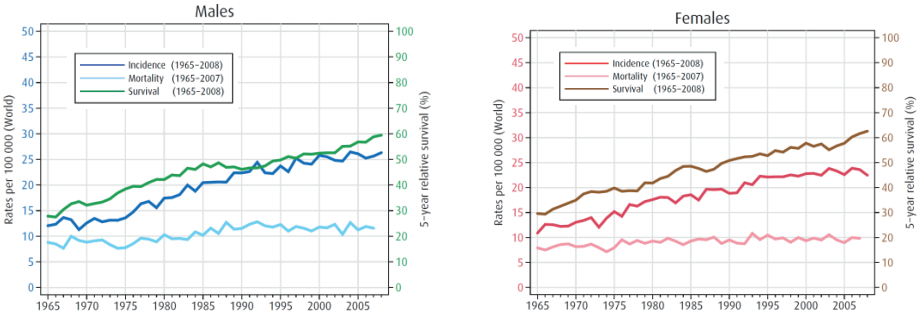
3.2.1 Geographical distribution

The distribution of colorectal cancer shows great geographical variations. The highest incidence is in Europe and North America[15], and Norway is one of the Western countries with the highest incidence[16]. In contrast, incidence rates are considerably lower in Africa, Asia and South America[17]. However, incidence rates are increasing even in these countries, possibly as the result of changing lifestyles that have become more westernized. There is less variation in terms of incidence within countries compared to variations between countries, although some studies have shown higher incidence in subpopulations of patients with low income and low educational levels[18].

3.2.2 Incidence according to age and sex

While the incidence of colon cancer is evenly distributed in both sexes, there are considerable differences in distribution according to sex for rectal cancer. For unknown reasons, rectal cancer occurs about 50% more often in men than in women. With median ages of 75 years for colon cancer and 72 years for rectal cancer, in Norway colorectal cancer is mostly a disease that affects elderly patients. The incidence increases with increasing age. Patients under 40 years of age are uncommon, with this age group accounting for approximately 2–4% of patients with colorectal cancer.

a) Colon Cancer **b) Rectal Cancer**



c) Colon Cancer **d) Rectal Cancer**

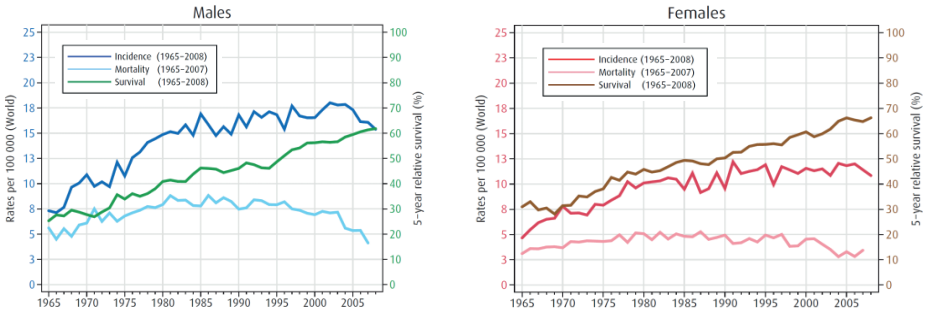
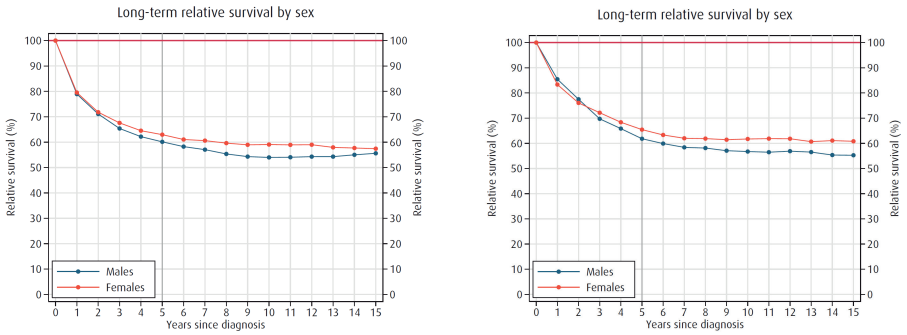


Figure 1. Trends in age- and sex-adjusted incidence rates. Five-year relative survival and mortality rates for a) colon cancer and b) rectal cancer. Relative survival up to 15 years after diagnosis for c) colon cancer and d) rectal cancer in men and women.

Source: Cancer in Norway 2008

a) Colon Cancer **b) Rectal Cancer**



c) Colon Cancer **d) Rectal Cancer**

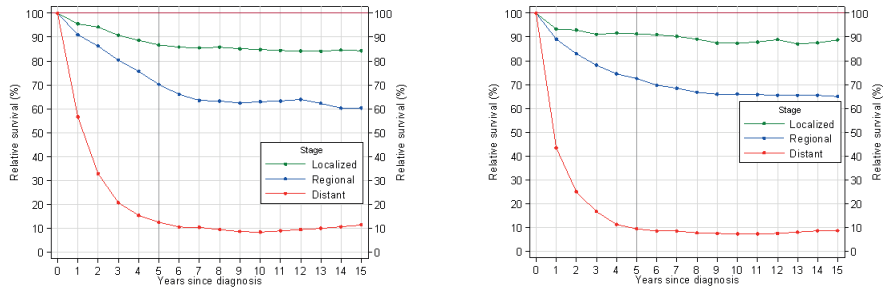


Figure 2. Relative survival according to sex for a) colon cancer and b) rectal cancer and according to stage for c) colon cancer and d) rectal cancer.

Source: Cancer in Norway 2008

3.2.3 Anatomical distribution of colon and rectal cancer

The colon and rectum are located in the abdominal cavity (Figure 3), starting in the right lower quadrant with the caecum and its accompanying appendix vermiformis

where the small bowel enters the large bowel at the valvula Bauhini. The colon then continues upward into the ascending colon before it turns via the right flexure to the transverse colon. This part of the colon, and continuing until the last third of the transverse colon, receives its blood supply from the superior mesenteric artery and is usually defined as the “right colon”. The remaining part of the colon consists of the left flexure and extends downward into the descending colon before it reaches the sigmoid colon. This part, usually termed the “left colon,” is supplied with blood by the inferior mesenteric artery. The promontory usually indicates the recto-sigmoidal junction, and the rectum is usually defined as the section that is 15 cm from the anal verge. The major blood supply of the rectum is the superior rectal artery, a branch of the inferior mesenteric artery, along with the often-inconsistent middle rectal artery that emerges from the internal iliac artery and collateral vessels from the inferior rectal artery.

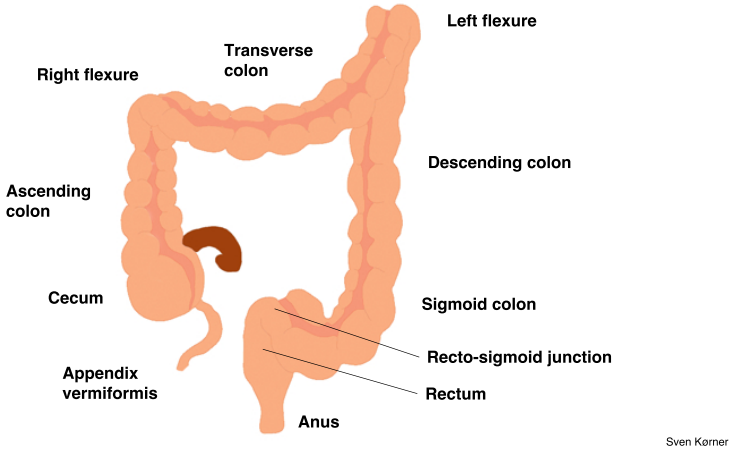


Figure. 3: Gross anatomy of the colon.

Approximately one-third of all colorectal cancer patients have rectal cancer, while two-thirds have colon cancer. With regard to colon cancer, 50% of the tumours are localized in the sigmoid colon, 25% in the right colon and 25% in the remaining parts of the large bowel i.e. the right flexure, transverse colon, left flexure or descending

colon. However, recently a trend of increased incidence of right-sided tumours has been shown that is particularly evident in the oldest patients.[19] With regard to rectal cancer, there is an even distribution of tumours located in the upper, middle and lower third of the rectum.

3.3 Etiology

Although there are defined genetic syndromes associated with colorectal cancer, environmental factors undoubtedly also play a major role. Specifically, immigrants moving from an area of low incidence to an area of high incidence are at greater risk of developing the disease. This has been shown for Japanese moving to Hawaii and California, for Puerto Ricans moving to the USA, and for European-born Jews who moved to Israel who were compared to Africa-born Jews.[3]

A number of dietary factors are proposed to be important in the development of colorectal cancer, including a lack of dietary fibre, a diet high in animal fat and low vegetable intake[20]. Excessive alcohol consumption, low potassium intake, low selenium intake, too much fluoride and/or low folate have also been suggested as contributing factors, but the evidence is not clear[20].

Long-standing inflammation, as in ulcerative colitis, is a well established risk factor for colorectal cancer[21], as are genetic predisposition[22] and smoking[23].

3.4 Genetic factors

The cause of colorectal cancer can be genetic or the consequence of long-standing inflammatory or sporadic. Approximately 75% of adenocarcinomas occur sporadically, and 25% of the patients are thought to develop colorectal cancer secondary to familial syndromes[22]. However, only 5% of cases can be identified as

the result of a defined genetic condition. The best-known syndrome is hereditary non-polyposis colon cancer or HNPCC, which involves a defect in one of the mismatch repair genes (MMR). Other genetic syndromes include familial adenomatous polyposis syndrome (FAP), in which there is a mutation in the tumour suppressor gene APC (adenomatous polyposis coli), Peutz-Jeghers syndrome and juvenile polyposis syndrome[22].

Traditionally, the dominant theory of colorectal cancer development has been the adenoma-carcinoma sequence, which posits that carcinomas of the colon evolve from pre-existing, pre-malignant lesions, such as adenomas[24]. However, only a few adenomas transform into cancer[24]. On the other hand, malignant tumours of the colorectum derived from flat or depressed *de novo* lesions of the mucosa are described in up to 30% of cases without preceding polypous lesions[25]

There are two histological types of polyps, adenoma polyps and hyperplastic polyps. Hyperplastic polyps are probably not associated with an increased risk of cancer. The transformation of polyps from adenoma to carcinoma involves several genetic alterations:

a. Chromosomal instability

b. Epigenetic changes

c. Microsatellite instability

Chromosomal instability represents changes at the chromosomal level, with alterations in the number of chromosomes or parts of the chromosomes in all somatic cells. Mutation of the APC gene is one cause of this type of alteration[22, 26].

Epigenetic changes involve changes in DNA methylation that do not alter the genome but which do alter the expression of certain genes and which can turn off gene expression.

Microsatellites are repetitive sequences of DNA. The length of these microsatellites varies greatly from person to person, but each person has microsatellite sequences of

a set length. These repeated sequences are common and normal. If the DNA repair genes are defective (e.g. mismatch repair genes), these sequences are more prone to have changes that result in alterations in genes and thus in altered protein expression.

Clinically, microsatellite instability can be detected in 15–20% of sporadic colorectal cancers. These cancers are associated with particular clinical and morphological findings;[27-30] specifically, they are more often found in the right colon and are often larger tumours that show low differentiation and that have a low incidence of metastases. Chromosomal instability is found in 80–85% of patients with colon cancer, and are more often in the left side of the colon and show a higher frequency of metastatic spread.

4. Clinical presentation and diagnosis

Early stage colorectal cancer is asymptomatic. Clinical symptoms are scarce and develop slowly over time. There are, however, a few symptoms or signs that most often lead to diagnostic evaluation. These include lower gastrointestinal bleeding or occult bleeding with resultant microcytic/iron deficiency anaemia, changes in bowel habits and abdominal pain.[31] Colorectal cancer can also progress and present as large bowel obstruction or even as perforation, either at the site of the tumour or proximally, usually in the caecum due to ischemia of the bowel wall as the result of dilatation of the proximal colon and increased tension in the bowel wall. Up to 20–25% of colon cancer cases present as emergencies; in contrast, only a small number of rectal cancer cases present as emergencies[32, 33].

Locally advanced tumours may present with other symptoms, such as with pneumaturia if a colovesical fistula is present, with hydronephrosis if the growth obstructs the ureter or with other symptoms, depending on the tumour location.

4.1 Diagnosis

There are several aspects of the colorectal cancer patient evaluation. First, a diagnosis must be established; second, the extent of the disease must be established; and third, the patient's fitness for treatment must be determined.

The diagnosis is usually made in the elective setting via endoscopy, i.e. colonoscopy and/or proctoscopy. The barium enema technique used in the past has been mostly abandoned, and virtual colonoscopy, or CT colonography, is currently considered just as good as colonoscopy for detecting cancers[34]. Several studies have shown a detection rate of >95% for polyps ≥10 mm and close to 100% sensitivity for cancer[35]; thus, this modality has gained popularity in recent years. However, colonoscopy is still the gold standard, as it is known to have high sensitivity and specificity. The effectiveness and sensitivity depend, however, on the skill and experience of the endoscopist, both in terms of reaching the caecum and detecting the relevant

pathology[36]. For rectal cancer, in addition to colonoscopy, clinical examination (digital palpation and rigid proctoscopy) is of the greatest importance for correctly interpreting modern imaging results. This is the key for describing the clinical appearance of the tumour, such as the correct distance from the anal verge and upper level of the pelvic floor to the inferior border of the tumour, and for noting signs of tethering or infiltration into neighbouring structures. Correct interpretation of imaging results is critical for making the best treatment decisions regarding choice of surgical procedures or use of neoadjuvant preoperative treatment.

4.2 Preoperative workup

For assessing the distant spread of colorectal cancer, traditional imaging consisted of plain ultrasound of the liver and a chest x-ray examination. However, CT scan of the chest has a higher sensitivity (75–87%)[36] and is usually the method of choice nowadays. For the liver, both contrast-enhanced CT examination and contrast-enhanced ultrasound have higher sensitivity and specificity and are the preferred methods[36]. Accordingly, it is currently recommended in many countries that CT scan of the abdomen and chest should be performed as part of the routine work-up, with supplementation of other examinations if relevant, such as MRI of the liver, contrast-enhanced ultrasound of the liver, gynaecological examination, cystoscopy or other urologic examinations (cystography, urography). PET (positron emission tomography) combined with CT is a new modality that focuses on metastatic lesions that are hard to detect by imaging, but PET has not yet become a routine part of the preoperative workup[37].

At present, serum-carcinoembryonic antigen measurement (CEA) is the only biochemical tumour marker that is used widely for colorectal cancer. Although, CEA is limited as a diagnostic aid as about one-third of patients have normal levels, its role in follow-up is better defined[27,38]. However, highly elevated preoperative CEA levels indicate disseminated disease.

Preoperative workup for rectal cancer

For rectal cancer, there is convincing evidence that some tumours should be treated with preoperative radiochemotherapy when the local tumour staging indicates locally advanced disease. In contrast, preoperative neoadjuvant treatment is virtually never indicated in colon cancer for localised tumours without metastases. The decision to give preoperative radiochemotherapy for rectal cancer is based on a MRI scan or/and endorectal ultrasound. Both modalities have advantages and disadvantages in terms of overstaging and understaging errors for T- and N-status.

MRI is usually the method of choice for staging, and T3 and T4 staging by MRI is correct in approximately 85% of tumours[39, 40]. Even more importantly, MRI can predict involvement of the circumferential resection margin by the tumour with a sensitivity of 94% and a specificity of 85%[41]. The MERCURY trial showed that MRI could predict the circumferential resection margin within 0.5 mm of the margin found by histopathology examination[42]. Nodal staging is less accurate, with 85% of predicted lymph nodes on MRI confirmed by histopathological examination; in addition, a negative MRI cannot predict negative nodes.[40]

Endorectal ultrasound (ERUS)

One study showed that ERUS is accurate for early stages of tumours (i.e., intramucosal neoplasia, T1 and T2), with a sensitivity of 94% and a specificity of 86%; however, its accuracy is lower in more advanced cancers[43]. There are still limitations regarding N-stage, and the mesorectum and peritoneum cannot be visualised. This is a serious limitation in terms of predicting involvement of the circumferential resection margin. Thus, the role of ERUS in more advanced tumours is limited compared to MRI[40].

In 1990, randomised trials compared preoperative radiotherapy with postoperative therapy and also compared preoperative therapy of different doses to surgery alone, along with the addition of chemotherapy[44]. Preoperative radiotherapy showed lower local recurrence rates, but there was no effect on survival compared to postoperative

radiotherapy[45]. It was also demonstrated that postoperative radiotherapy had greater toxicity and was associated with lower compliance[46].

Two important randomized studies compared preoperative radiotherapy with surgery alone.[47, 48]. Both studies found that preoperative radiotherapy reduced the risk of local recurrence by approximately 50%. The Swedish trial, but not the Dutch TME trial, showed an influence on survival. The Swedish trial was performed before TME surgery was established. Results from these trials resulted in guidelines in Sweden and the Netherlands that are more liberal in terms of the use of preoperative radiotherapy compared to Norway—in Norway, preoperative radiochemotherapy is restricted by criteria indicating circumferential resection margin (CRM) involvement. This is based partly on one of the studies from the Norwegian Rectal Cancer Registry showing that a predicted CRM of ≤3 mm is a risk factor for local failure[49].

Accordingly, the Norwegian guidelines as of 2010 state that patients with T4 tumours or with tumours that have a predicted CRM of ≤3 mm from either the tumour or a malignant deposit, i.e. a lymph node or satellite tumour, should be offered preoperative radiochemotherapy. Further, if a non-radiated tumour turns out to have involved CRM, postoperative radiochemotherapy is recommended.

4.3 Fitness for treatment

Treatment of colorectal cancer is associated with an overall morbidity of 15–20%[50] and a perioperative mortality of 3–5% [51]. Due to the characteristics of the disease, half of the patients are elderly and have increased comorbidities; thus, assessment of fitness for treatment is particularly important to achieve the best possible treatment outcome[52, 53]. While curing the cancer is the major treatment goal for the majority of patients, elderly and frail patients may be better served by an approach tailored to their physical and mental condition in terms of developing an individual treatment goal. It has been shown that even octo- and nonagenarians tolerate surgery for colorectal cancer quite well provided that risk factors are identified and primary

surgery is optimised to minimize complications[54]. This involves a general medical examination with a special focus on respiratory and cardiovascular status. In particular, the following may need attention or treatment in order to minimize perioperative risk factors: poor nutritional status, poorly controlled diabetes mellitus, frailty, jaundice, previous surgery, previous pulmonary embolus or deep vein thrombosis, dementia, reduced kidney function and other conditions. Anaemia may need to be treated. Finally, the function of the sphincter apparatus needs to be assessed to make an informed decision of whether to use a stoma.

5. Staging

Staging, i.e. systematic examination of the patient to determine the extent of the malignant disease, is very important for determining the patient's prognosis. Staging is even more important for making the best treatment decisions for the individual patient. The first classification system that had clinical importance was proposed by Dukes in 1930. This system was based on the pathologist's detailed description of the removed specimen with regard to tumour invasion into or beyond the bowel wall and assessment of whether regional lymph nodes were affected by metastatic tumour cells[55]:

Stage A: *Growth of the primary tumour limited to the wall of the rectum or colon, without extension into the perirectal or pericolic tissue*

Stage B: *The growth of the primary tumour extends through the bowel wall into the perirectal or pericolic tissue*

Stage C: *Any level of growth of the primary tumour combined with the presence of metastases to the regional lymph nodes are involved with the tumour*

Stage D: *Presence of disseminated disease regardless of any level of tumour growth or lymph node metastases*

The clinical importance of Dukes' classification system stems from its foundation on lymph node status, which has strong prognostic power; in fact, the presence of lymph node metastases is currently considered the single most important factor for predicting treatment outcomes and is the main criterion for determining the use of adjuvant chemotherapy.

In the years that followed, it became clear that additional factors influenced prognosis and that there was need for a more detailed classification system, and the "tumour-node-metastasis" or TNM staging system was introduced in 1978. The latest (AJCC 7th edition) version of the TNM staging system is shown below.

5.1 T categories for colorectal cancer[56]

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

5.2 N categories for colorectal cancer[56]

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 nonperitonealized periocolic or perirectal tissues without regional nodal metastasis

N2: Metastasis in 4 or more regional lymph nodes

N2a: Metastasis in 4–6 regional lymph nodes

N2b: Metastasis in 7 or more regional lymph nodes

5.3 M categories for colorectal cancer[56]

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 Cancer Registry of Norway, established in 1951, has traditionally used the terms "localised" or "regional" in its main database to indicate lymph node metastases.[57] However, the Norwegian Rectal Cancer Registry, and (after 2007) the Norwegian Colorectal Cancer Registry, uses the TNM classification system. For this reason, the two first papers in this thesis, which are based in part on data from the main database of the CRN, were limited in terms of being able to distinguish more than only between lymph node positive and lymph node negative disease. The TNM classification (AJCC 6th edition) was used in paper III.

6. Treatment of colorectal cancer

6.1 Treatment options

The principles of surgery for colorectal cancer are the same as for open or laparoscopic surgery, but the surgery can be performed with either curative or palliative intention. For the universal goal of curative resection, it is important to remove the tumour with a sufficient margin proximal or distal to the tumour and to ensure sufficient removal of the mesocolon or mesorectum with its vascular pedicle and its accompanying lymph nodes. For palliative procedures, the clinician must make the best choices according to the individual treatment goals to preserve the best possible quality of life. These choices can include limited resection, a bypass, a stoma or endoscopic procedure, stenting of an obstructed colon or argon laser treatment of a bleeding tumour.

6.1.1 Curative or palliative resection

About 25–30% of colorectal cancer patients present with disseminated disease at the time of diagnosis, and about 30–40% of patients who are operated with curative intent will be diagnosed with recurrence during follow-up. The last years, the distinction between curative and palliative resection has become blurred. Most people agree that the presence of widespread carcinomatosis is an indication for palliative procedures, or even for options other than surgery. Widespread lymph node metastasis, i.e. metastasis outside the normal resection margins, widespread lung metastases and/or disseminated liver metastases indicate palliative treatment. On the other hand, resectable pulmonary or liver metastases, and even limited carcinomatosis, are now treated in a multimodal fashion that includes surgery and chemotherapy. The use of intraperitoneal chemotherapy combined with hyperthermia (HIPEC) shows a 5-year survival of 20–50%[58]. Careful evaluation of all patients by a multidisciplinary team (MDT) is now considered the standard of care. It is important that the MDT includes competence with curative and palliative treatment.

6.2 Colon cancer

The mainstay in the treatment of colon cancer with intention to cure is removal of the tumour with its accompanying draining lymph nodes. To achieve curative surgery, a sufficient margin (5–10 cm) on both sides of the tumour is removed, and an adequate length of the supplying vessels with the draining lymph nodes is removed en bloc as well. The extent of blood vessel ligation is still debated (i.e., D2 or D3 resection, Figure 4). If the tumour is invading another organ, it is crucial to remove the other organ en bloc whenever possible. These principles apply regardless of whether open or laparoscopic resection is performed. As an exception to these general rules, removal of a small possibly polypous tumour by endoscopic resection can be sufficient treatment when the tumour is either Tis or T1 with a sufficient free margin and without invasion into deeper layers of the submucosa.[59]

Following excision, bowel continuity is restored if the patient's general health is adequate. The patient's general health must be taken into consideration when deciding upon use of a stoma because of the risk of complications. Anastomotic leakage is associated with mortality of up to 39%[60], and data also suggest that in addition to the risk of postoperative mortality, there is also decreased long-term survival[61]. The risk factors that are typically reported include multivisceral resections, low anterior resections and general fitness of the patient, as well as preoperative nutrition status, blood supply, anastomotic tension and operation in an emergency setting[62].

The extent of colon resection is determined by the level of ligation of the blood supply, and, accordingly, the number of lymph nodes that are removed. The more central and radical the surgery, the greater the loss of blood supply to the remaining colon and the longer the segment of colon that has to be removed. There are diverging opinions on how radical surgery should be, and this remains an on-going debate[63,64].

If there are signs of adherence or infiltration into other organs, such as the small bowel, abdominal wall, uterus or bladder, but no other signs of advanced disease or

distant metastases, efforts should be made to remove the tumour en bloc to achieve an RO resection (i.e. macroscopically- and microscopically-free margins); still, complete removal of all cancer tissue is an unconditional prerequisite for a favourable prognosis[65].

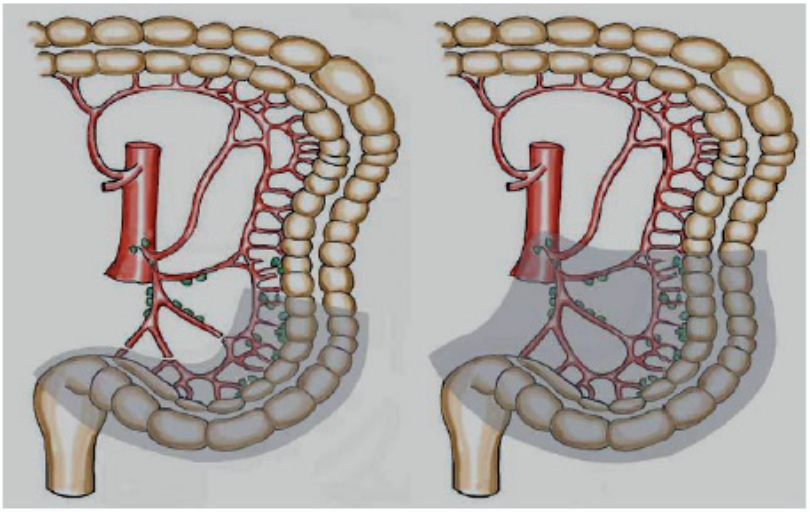


Figure 4. Colon resection: a) D1 resection with removal of only th elymph nodes near the tumour; b) D3 resection with removal of the central lymph nodes as well. Source: Norwegian Directorate of Health, Nasjonalt handlingsprogram for diagnostikk og behandling av kreft i tykk- og endetarm

What is less controversial is the importance of operating in the correct embryological planes in complete mesocolic excision or CME surgery. In the early 1980s, Heald showed that for rectal cancer, removing the mesorectum with its intact fascia resulted in a better prognosis than if the fascia was not removed.[8] Recent results suggest that the same holds true for colon cancer[66]. The type of resection depends on the location of the tumour. Figure 5 shows the most common types of resection according to tumour location.

In 2007, Hohenberger et al.[64] published a study showing a remarkable increase in survival of colon cancer patients in recent decades at his institution, with overall 5-year survival of 90% in the most recent period for patients with stage I, II and III colon cancer. He introduced the concept of CME for colon cancer based on the same principles that support TME for rectal cancer. In addition, he advocated for central dissection with removal of the lymph nodes closest to the superior mesenteric artery on the right side and removal of the inferior mesenteric artery on the left side. For cancers in the transverse colon, he also recommended removing the lymph nodes along the greater curvature of the stomach. Hohenberger et al. showed that patients who had more than 28 lymph nodes removed had a better prognosis than patients with fewer than 28 lymph nodes removed.

In a study conducted in Leeds, England, West et al.[67] looked at the quality of the removed specimens and found that intact mesentery of the colon was related to better survival compared to non-intact mesentery. He went on to compare the English specimens with specimens from Erlangen, Germany (from the institution with which Hohenberger is affiliated) and from a Japanese institution. West et al. found that almost all specimens from Erlangen had an intact mesentery, in contrast with approximately 50% of those in Leeds and 70% in the Japanese medical centre[66, 68].

Several studies show better survival for patients in whom more lymph nodes are removed and identified[69, 70]. Some claim that this is due to better staging and to additional use of chemotherapy, while others claim that a more central dissection with removal of malignant lymph nodes in itself can influence prognosis[64]. Still others claim that tumours with many enlarged lymph nodes may have different biological properties or that the patient may have a more activated immune system and therefore a better prognosis. Tumours with microsatellite instability tend to have more lymph nodes identified[28].

An American study showed that there was a trend of increased lymph node harvest over time but that this did not influence the proportion of patients with lymph node positive disease[71]. Survival increased even though the number of stage III patients did

not, calling into questioning the role of stage migration as the reason for survival gain.

One randomized trial and several additional trials compared D2 resection and D3 resection for sigmoid cancers.[72] A slight survival gain was seen with central ligation. On the other hand, studies investigating the location of the malignant lymph nodes found that in approximately 5% of sigmoid cancers, the only malignant lymph nodes with metastases were seen apically in the D3 area, i.e. so-called "skipped metastases"[73]. Finally, with regard to lymph node harvest in rectal cancer, a multivariate analysis showed that preoperative chemoradiotherapy reduces the lymph node harvest, probably by reducing the size of the nodes and thus making it harder to find and remove them[74].

There are several treatment options for obstructing left-sided colon cancer. Recently, use of a self-expanding metallic stent (SEMS) has become an option that is termed "a bridge to surgery." The reason for this term is that substantial morbidity and mortality is associated with acute surgery for left-sided bowel obstruction[75]. Therefore, by using SEMS, the tumour can be reopened with a stent; subsequently, the obstructed bowel can deflate, the patient can recover and definite surgery can be performed in an elective setting with reduced mortality. There has been some criticism regarding the possibility of perforation of the tumour, tumour spillage and reduced long-term survival[76]. No clinical trial has been performed that randomises patients between SEMS and subtotal colectomy. One study was ended early due to serious complications[77].

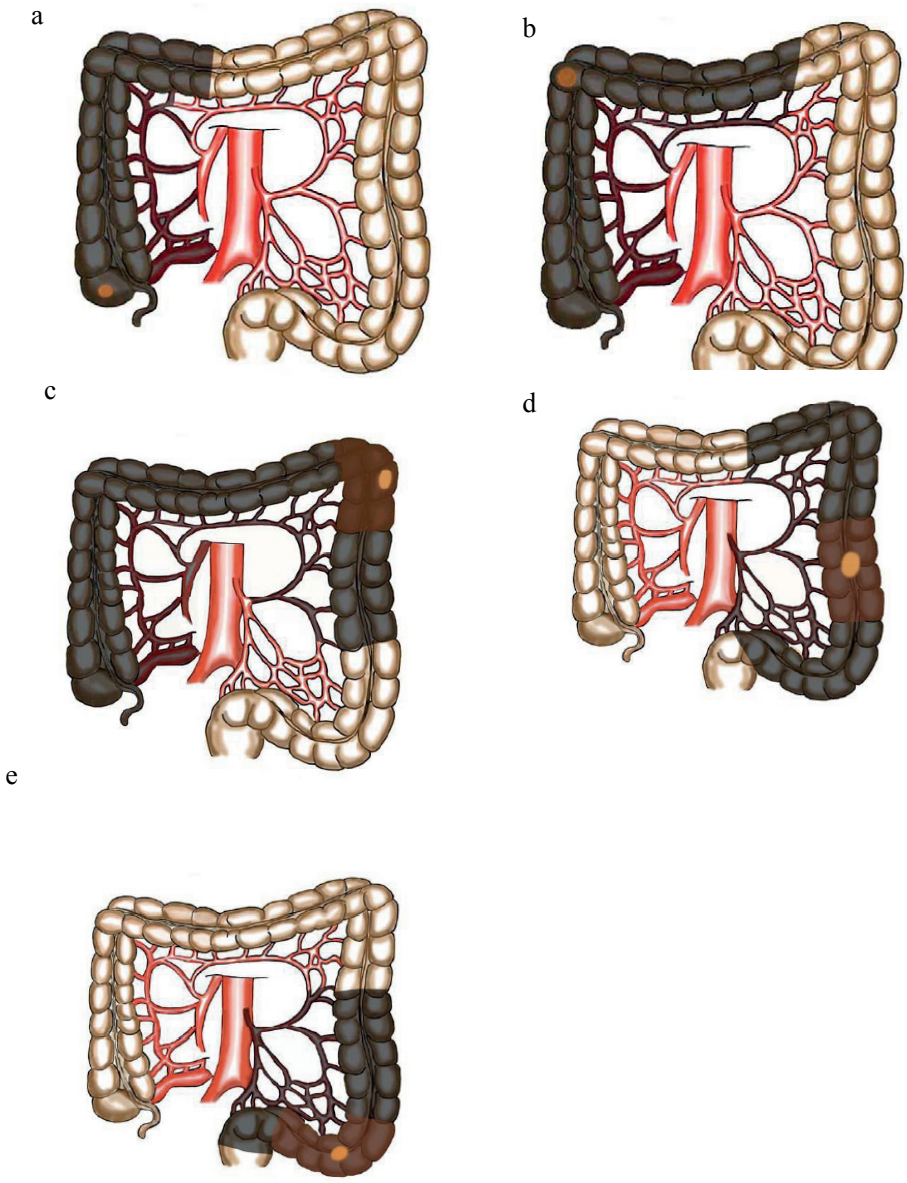


Figure 5. The most common surgical resections of the colon: a) right hemicolectomy; b) extended right hemicolectomy; c) subtotal colectomy; d) left colectomy; e) resection of the sigmoid colon. Source: Norwegian Directorate of Health, Nasjonalt handlingsprogram for diagnostikk og behandling av kreft i tykk- og endetarm

6.3 Rectal cancer

In addition to the principle of removal of the tumour with its accompanying lymph nodes, there are some key differences between rectal and colon cancer. First, the distance to the anal sphincter plays a major role for the choice of procedure. Second, the rectal tube is, at least for the lowest part, enveloped by vital structures of the pelvis and has to be dissected free using great care. Heald showed that the most important step in avoiding local recurrence is complete removal of the rectum, including the perirectal fat (which is enveloped by the mesorectal fascia) using meticulous dissection techniques. This technique, termed total mesorectal excision (TME), has become the standard of care during the past two decades. Third, there is strong evidence that some tumours of the rectum should be treated with neoadjuvant chemotherapy before surgery[78, 79]. This is indicated when preoperative evaluation (i.e. clinical examination and imaging) shows that the circumferential resection margin or CRM may be threatened. According to current Norwegian guidelines, T4 tumours or tumours with predicted CRM ≤3 mm should be irradiated preoperatively[80].

It is generally accepted that tumours in the upper part of the rectum (10–15 cm from the anal verge) should be dealt with using anterior resection, including removal of the distal part of the sigmoid colon and removal down to at least 5 cm distal of the tumour. This is termed partial mesorectal excision or PME[80]. There is still a debate as to whether the vascular supply should be divided close to the departure from the aorta (central ligation of the inferior mesenteric artery) or after the departure of the left colic artery (superior rectal artery)[63]. Usually the colon is anastomosed to the remaining rectum with a stapler.

There are some specific things to be aware of when treating tumours in the middle and lower rectum. Whenever the tumour involves the sphincter apparatus, the decision to perform an abdominoperineal excision is not controversial. When the tumour is located in the lower rectum and above the pelvic floor, a low anterior resection is often feasible. A distal margin of at least 1 cm is considered adequate if the tumour is radiated preoperatively[81]. However, an anastomosis close to the pelvic

floor may be associated with inferior functional results in terms of reduced continence, urge or emptying disorders[82]. Accordingly, these aspects must be discussed carefully with the patients before making a final decision about the surgical procedure. In cases involving a low anterior resection, a defunctioning stoma is recommended, which can be reverted after 6–12 weeks if the anastomosis appears to be healed.

Abdominoperineal excision has traditionally been performed with the patient in the lithotomy position. This position allows good access to the abdomen and pelvic cavity. However, the perineal part of the procedure may be influenced by limited access to the perineum and poorer visibility of the surgical field. Data from the Norwegian Rectal Cancer Registry showed that abdominoperineal excision was associated with 4 times as many perforations and 2–3 times more R1 resections (involved margins) than was low anterior resection[83]. Further, conventional perineal dissection has been criticised as resulting in coning of the specimen at the level of the pelvic floor, leading to insufficient CRM. Recently, a new approach termed extended abdominoperineal excision was presented by Holm and coworkers[84]. This technique includes removal of the levator muscles together with the rectum. It avoids dissection into the plane between the distal rectum and the pelvic floor by using limited dissection from above to a level that is designated by the lower coccygeal joint and the seminal vesicles in males. Perineal dissection is performed with the patient in a prone jackknife position after completion of the transabdominal part of the procedure. This technique, which is increasingly being adopted by Norwegian surgeons, seems promising, although few long-term oncologic results are available[85].

6.4 Palliative interventions

While most surgical procedures for colorectal cancer are performed for the purpose of cure, some patients are treated with the intention to restore or maintain quality of life. Palliative intervention is beyond the scope of the thesis. Briefly, colorectal resection may be warranted when bleeding, perforation or bowel obstruction is present. Internal bypass or creation of a stoma should be considered. Over the last decade, colorectal

stenting has become an excellent alternative for many patients with incurable disease[86]. Another important scenario is the presence of an asymptomatic tumour with disseminated disease. There are several randomized trails at present that are testing whether patients with an asymptomatic primary tumour with disseminated disease benefit from a resection. Some earlier studies showed better survival for patients who had the tumour removed, but these studies were not randomised and they may have had selection bias[87]. However, the success of any palliative intervention depends strongly on an individualized approach that takes into account the wishes of the patient, the patient's functional status and where the patient is in terms of the course of the disease.

7. Histopathological evaluation

Histopathological examination of the surgical specimen is of crucial importance. The pathology report is the basis for confirming complete removal of the tumour (i.e. R0 resection), determining patient prognosis (i.e. TNM stadium) and guiding further treatment, e.g. adjuvant chemotherapy for patients with lymph node metastases. Careful pathological evaluation and reporting is just as important as careful surgery.

The pathology report should contain certain information, such as tumour localisation, diameter, histologic type, histologic grade, infiltration, shortest distance from tumour to resection margin, distance from tumour to the end of the resection margin, number of lymph nodes identified, number of lymph nodes with metastases, extramural venous or perineural infiltration, TNM classification, UICC stage and any other important pathological findings. Further, the quality of the surgical specimen, e.g. preservation of intact mesorectal fascia, should be reported as well.

In Norway, efforts have been made to standardise the pathology report. For this purpose, a national report template has been developed and its use is recommended for all pathology departments[88, 89]. However, so far fewer than half of the pathology departments use the national template[88].

Additional information that should be included in the pathology report is still being discussed and might include localisation of positive lymph nodes, quality of the mesocolon, length of the removed apical vessel, area of the removed mesocolon[66] and perhaps even some genetic markers, such as MSI.[29]

8. Norwegian Colorectal Cancer Registry

Until the early 1990s, most clinicians held the traditional view that patients should be admitted to surgery after the diagnosis of cancer of the colon or rectum without further investigation; poor treatment outcomes were seen as a natural part of the disease. This was particularly true for rectal cancer, and local recurrence rates were reported as being 30% or even higher[90]. However, the British surgeon Bill Heald showed that local recurrences were mostly related to inferior surgical technique that was performed using stump manual dissection of the pelvic structures. This leads to incomplete removal of the perirectal fat (i.e. the mesorectum), leaving either metastatic lymph nodes or tumour satellites in the pelvis as the cause of recurrence. Furthermore, inferior surgical techniques were associated with either perforation of the rectum, causing spillage of tumour cells, or bleeding from the presacral venous plexus and a high frequency of pelvic nerve damage. Heald showed that local recurrences could be avoided by meticulous sharp dissection along the mesorectal fascia, thus removing the entire mesorectal fat. This is termed total mesorectal excision (TME).

In the early 1990s, the concept of TME was accepted as the national standard of surgery for rectal cancer. Late in 1993, the Norwegian Rectal Cancer Registry (NRCR) was established. At this time, it became standard for all rectal cancer patients undergoing surgery to be registered prospectively, and each institution received feedback about their own results, including local recurrence and survival. The goal was to reduce local recurrence to approximately 10% by implementing TME surgery. This was paralleled by the introduction of TME surgery via surgical workshops led by Bill Heald. As a consequence, several low volume hospitals stopped treating rectal cancer, and rectal surgery was limited to surgeons trained in the Norwegian subspecialty of gastrointestinal surgery. Several publications have emerged from analysis of data from this registry that document the effects of these measures[91-93]. Starting in 2007, the NRCR was expanded to include colon cancer and became the Norwegian Colorectal Cancer Registry (NCCR). In contrast to the main database of the CRN, this registry includes a large number of clinical-pathological

variables and thus constitutes a national quality registry. The NCCR is considered to be the first quality registry of the CRN. As such, it serves as a prototype for emerging registries for other malignant diseases, such as breast cancer, prostate cancer and others.

9. Evolution of Norwegian Treatment Guidelines

The Norwegian Colorectal Cancer Group (NGICG) consists of surgeons and oncologists who are centrally involved in colorectal cancer and other relevant specialties. The NGICG initiated and promoted the NRCR and the development of Norwegian guidelines for diagnosis and treatment of colorectal cancer. Due to overall dismal outcomes, the main focus was on local control of rectal cancer as the predominant problem. The Norwegian policy focused on surgery as the most important key to improvement, while preoperative radiotherapy was used occasionally and purely at the discretion of the individual surgeon. From 1994 to 1996, TME was recommended and then considered mandatory for all hospitals that treated rectal cancer. From 2000, the guidelines recommended preoperative radiotherapy for T4 tumours or clinically fixed tumours. In 2003, the guidelines were modified to recommend obligatory preoperative imaging with MRI, preoperative radiotherapy for patients with predicted CRM ≤3 mm and the compulsory use of a multidisciplinary team.

With regard to colon cancer, the treatment strategy was unchanged during the same time except for the recommendation of adjuvant chemotherapy for patients with pN+ disease up to 75 years of age. This recommendation was implemented in 1997–1998.

In 2010, the Norwegian guidelines for the diagnosis and treatment of cancer of the colon and rectum were reformulated by the NGICG based on the best available evidence. The reformulation was endorsed by the National Health Directorate. The guidelines are publicly accessible as a comprehensive edition and are generally re-evaluated every other year. However, the NGICG is responsible for deciding when changes must be considered due to new evidence.

The NRCR may be considered vital in terms of setting the current national standard of care for colorectal cancer, and it has been the source of numerous research projects that serve as the basis for continuous scientific evaluation, reports and other efforts to further improve treatment outcomes of colorectal cancer in Norway.

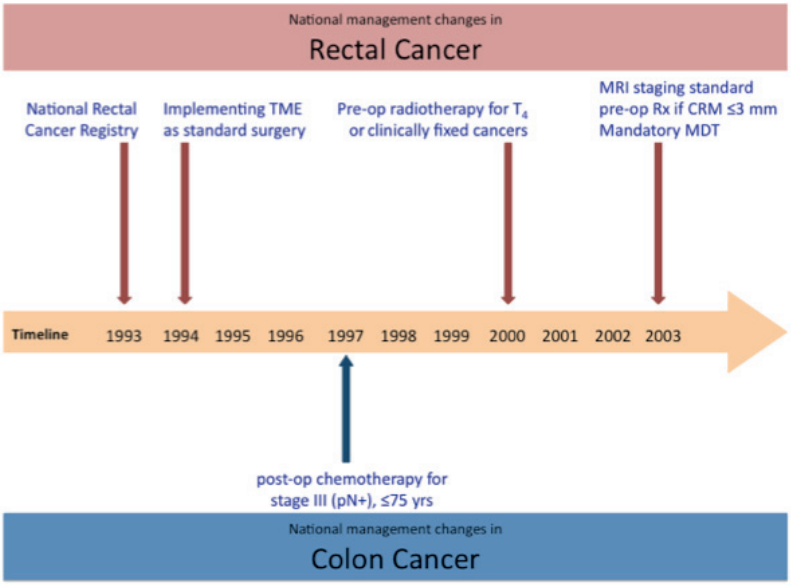


Figure 6. Evolution of colorectal treatment guidelines in Norway.

Courtesy British Journal of Surgery

10. Aim of the study

The aim of this study was to analyse the impact of the implementation of national guidelines for the treatment of patients with colon and rectal cancer on outcomes at a national level. While treatment guidelines focused strongly on rectal cancer in terms of optimal local tumour control, adjuvant chemotherapy was introduced for the subgroup of patients with regional lymph node metastases, i.e. pN+ disease, who are ≤75 years old.

The objectives of the study were as follows:

1. Paper I: To compare survival of patients curatively treated for cancer of the colon and rectum before and after implementation of national treatment guidelines
2. Paper II: To study possible differences in survival between patients treated for colon or rectal cancer by analysing excess mortality, i.e. mortality related to colon and rectal cancer, during the 5-year period after diagnosis
3. Paper III: To investigate lymph node harvest in curative resection for colon cancer in a national cohort and to identify factors related to poor lymph node harvest and their influence on diagnosing lymph node positive disease

11. Patients and methods

11.1 Databases

We used data from the Cancer Registry of Norway (CRN) to analyse data from a national perspective.

Data from 1994–2003 in the main CRN database were used to analyse the survival of patients curatively resected for cancer of the colon or rectum before and after the introduction of national guidelines (objectives 1 and 2 in the previous section). Data from the quality registry of colorectal cancer, i.e. the Norwegian Colorectal Cancer Registry, for the years 2007 and 2008 were used to study factors related to differences in lymph node harvest in curative resection for colon cancer. Reporting of all patients with a diagnosis of cancer to the CRN and NCCR is mandatory by law in Norway, which ensures high completeness and quality of data.

11.2 Patients

We identified all patients diagnosed with cancer of the colon and rectum from January 1, 1994 to December 31, 2003 in the main CRN database. We combined these data with data from the Norwegian Rectal Cancer Registry to obtain more detailed clinical information in order to differentiate between colon and rectal cancer. Tumours located up to 15 cm from the anal verge were defined as rectal cancer. All other tumours (>15 cm above the anal verge) were defined as colon cancer. Cancers of the colon or rectum were defined as histologically proven adenocarcinoma, and all other tumours were excluded from the analysis.

To analyse patients treated with curative intent, patients undergoing major resections were included while patients were excluded who were treated with minor procedures, such as local resections, polypectomies or non-resective procedures such as diverting stoma. Further, we excluded patients with more than one cancer at different sites, i.e.

synchronous cancers, or who had cancers at different times, i.e. metachronous cancers, as well as patients with distant metastases at the time of surgery.

Mortality data were provided by the Norwegian Cause of Death Registry. To study a 5-year follow-up period, dates of death were provided up to December 31, 2008. Complete follow-up was ensured by use of the unique 11-digit personal number provided to every citizen of Norway. Patients who were alive on December 31, 2008 were censored, and patients who had emigrated during the 5-year period were excluded.

Regarding objective 3, detailed clinical and pathological data for all patients with colon or rectal cancer were available starting on January 1st from the Norwegian Colorectal Cancer Registry. We identified all patients with adenocarcinoma of the colon who were diagnosed in 2007 and 2008 and who underwent major curative resection using the same criteria for inclusion as applied for objectives 1 and 2., i.e. exclusion of patients treated with minor or non-resective procedures, distant metastases, those with pathological data missing, and those with either synchronous or metachronous tumours.

11.3 Time periods and time intervals

We compared data from 1994–1996 with data from 2001–2003. The Norwegian Rectal Cancer Registry was established in late 1993; therefore reliable information that could differentiate between rectal and colon cancer was available in 1994. We wanted to compare the early period after introduction of national guidelines with a later period when the guidelines had been implemented for a while and when complete follow-up data were available for all patients with regard to 5-year survival. This study began in 2009; therefore, 2003 was the latest patient cohort we could use. The 1997-2000 period represents a time when adjuvant therapy began to be used for lymph node positive patients with colon cancer and a more systematic approach to preoperative radiotherapy was introduced.

To analyse 5-year mortality, this time span was divided into several time intervals. These time intervals were defined relative to each year post-surgery. In addition, the first year was subdivided in two intervals, 0–2 months and 3–12 months in order to have a measure of 60-day postoperative mortality. We chose to use 60 days rather than 30 days (which is more usual) for two main reasons. First, recent studies have shown an increased rate of death >30 days postoperatively compared to the general population, which may be related to improved perioperative care[94] that extends the postoperative time interval in which there are deaths that may be related to surgery. Second, our dataset includes the date of diagnosis but not the date of surgery. To ensure the anonymity of the patients, the diagnosis was approximated as the first or the fifteenth of each month, whichever was nearest the date of diagnosis.

Statistics

Continuous variables were tested for normality. Non-normally distributed continuous variables were reported as median values as a measure of central tendency and compared by the Mann-Whitney U-test. Categorical variables were analysed by contingency tables and compared by the Chi-square test. Multivariable analysis was performed when appropriate by logistic regression analysis. P-values <0.05 were regarded as significant.

Survival analysis

Survival analysis was performed to address objectives 1 and 2 of the study. Survival is one of the most important outcome measures in cancer treatment. Because death may occur from causes unrelated to cancer, these other causes contribute to mortality. To compare treatment outcomes with regard to major changes in treatment guidelines at the national level as defined by objectives 1 and 2, information about cancer-related deaths was considered essential. However, reliable information on the true cause of death was not available for all patients reported to the Norwegian Cause of Death Registry. The use of *relative survival* can compensate for this lack of information[95]. This method provides a measure of the deaths in a group of patients with a given disease by comparing the number of deaths in the patient group with a patient group matched for age and sex, the members of which are assumed not to

have the disease in question (colon or rectal cancer for our study). We calculated relative survival by matching the major demographic characteristics of the patients to subjects in the general population using the Norwegian population life tables as provided by Statistics Norway for the study period. Comparisons between groups were made using maximum likelihood estimates.[96]

Notably, we compared the two groups in two time periods, i.e. 1994 –1996 and 2001–2003. Life tables show that a 70-year-old in 2001 was expected to live 1.6 years longer than a 70-year-old in 1994. This is due to generally improved health in the population. Using relative survival corrects for this factor by comparing the patient group with members of the general population who were the same age at the same time as the patients.

Excess hazard

The mortality of patients, i.e. hazard to die, can be expressed as the hazard to die of the general population added to the hazard to die related to the disease, i.e. excess hazard.

To estimate the excess hazards of patients with colon or rectal cancer during various time intervals in their 5-year follow-up periods (objective 2 of the study), we calculated the average rate of death over a time interval multiplied by the length of the time interval and then expressed this as the number of excess deaths per 1000 patient-years.[97]

The baseline excess hazard is often estimated as a stepwise function[98] but can also be estimated as a smoothed function[99]. We used a stepwise baseline excess hazard. When we simultaneously reported excess hazard ratios for each time interval during the 5-year follow-up, we used a 1% level for the inference in each single time interval to guard against type 1 errors in multiple testing. This 1% level corresponds to the use of an overall 5% level with a Bonferroni correction for multiple testing.

Statistical analysis was performed using the software package PASW Statistics 18.0 for Mac (SPSS Inc., Chicago, IL, USA) R 2.9.2 (www.r-project.org) with the R-

package “relsurv” was used for the relative survival calculations and excess hazards calculations.[100]

12. Results

12.1 Paper I

The first study included 19,053 patients who had undergone curative resection for colon or rectal cancer. The study showed an increase in relative survival from the 1994–1996 period to the 2001–2003 period, both for colon cancer (73.8 vs. 78.0%, $p<0.001$) and rectal cancer (72.1 vs. 79.6%, $p<0.001$). However, when comparing patients with colon cancer and rectal cancer, there was significantly better relative survival for rectal cancer patients in the 2001–2003 period ($p=0.03$) while no difference in relative survival was observed in the 1994–1996 period. Improved relative survival in colon cancer patients was mainly seen in 2001–2003 in those with pN+ disease (50.7 vs. 62.1% for colon cancer and 47.6 vs. 67.2% for rectal cancer, respectively). While this was true only for colon cancer patients under 75 years i.e. those for whom adjuvant chemotherapy was recommended, relative survival increased in all age groups for rectal cancer.

12.2 Paper II

To investigate the differences in survival outcomes in patients with colon or rectal cancer, we studied the excess death at different time intervals after surgery for colon and rectal cancer patients during the time periods 1994–1996 and 2001–2003. A total of 11,437 patients who had undergone curative resection were included.
For patients treated from 1994–1996, excess mortality was similar in colon and rectal cancer patients in all time intervals. For those treated in 2001–2003, excess mortality was significantly lower in rectal cancer patients than in colon cancer patients perioperatively (in the first 60 days: excess mortality ratio=0.46, $p=0.007$) and during the first 2 postoperative years (2–12 months: excess mortality ratio=0.54, $p=0.010$; 1–2 years: excess mortality ratio=0.60, $p=0.009$). However, excess mortality in rectal cancer patients was significantly higher than in colon cancer patients during late follow-up, i.e. 4–5 years postoperatively (excess mortality ratio=2.18, $p=0.003$).

12.3 Paper III

Paper III analysed the number of LNs harvested during curative resections for colon cancer and investigated the possible factors leading to poor harvest, which was defined as ≤8 LN. A total of 2,879 patients were included in the study. The median number of LNs harvested was 14. While 69.9% of the patients had adequate LN harvest (≥12 LNs), 14.4% had poor LN harvest. The factors that were analysed to determine whether they were associated with poor LN harvest included age group, sex, tumour characteristics, specimen characteristics and the use of the national pathology report template.

Multiple logistic regression analysis showed that male sex, age >75 years, sigmoid tumours, pT category 1–2, failure to use the pathology report template and a distance of ≤5 cm from the tumour to the bowel resection margins were all independent factors for poor LN harvest. Age <65 years, pT category 3–4 and poor tumour differentiation were independent predictors of stage III, i.e. pN+, disease. An increase in the number of harvested LNs did not show a corresponding increase in stage III disease when we compared patients with ≤8, 9–11 and ≥12 harvested LNs. Moreover, use of the national report template was not associated with an increase in the proportion of patients with stage III disease.

13. Discussion

This thesis analysed the impact of implementation of national guidelines on treatment outcomes of patients with cancer of the colon and rectum. Paper I demonstrated significant improvement in relative survival for patients with colon and rectal cancer undergoing curative surgery over a 10-year period. This improved survival emerged during time periods, i.e. from the 1994–1996 time period to the 2000–2003 time period, when new strategies for the management of patients with CRC were introduced and implemented at the national level. Notably, this survival increase was more predominant in patients with rectal cancer compared to colon cancer. Thus, at the end of the study period, the long-term survival of patients with rectal cancer had changed from being worse than for colon cancer patients to being better than for colon cancer patients.

As far as we know, this is the first time this has been documented in the literature for patients undergoing curative treatment for CRC. We believe these results reflect the effects of systematic changes in disease management, with a major focus on rectal cancer. Implementation of treatment changes was mandatory and well documented by the NRCR.[101] It is reasonable to think that the Norwegian health care system, which ensures that high quality health care is provided to the entire population, was an important factor for the implementation of guidelines and thus for the major improvements in patient outcomes. In the past, studies have reported a worse prognosis for rectal cancer patients compared to patients with colon cancer.[102, 103] A recent study from Sweden showed that 5-year relative survival was similar for rectal and colon cancer.[104] The same was found in a Dutch study, i.e. worse prognosis for rectal cancer in the past and later a catch-up for rectal cancer resulting in similar survival statistics[105]. However, these studies included patients with all stages of cancer, irrespective of treatment goals (i.e. curative vs. palliative) while the current study analysed CRC patients undergoing curative surgery. Our results are in line with the hypothesis that the focus on rectal surgery has resulted in measurably improved outcomes on a national level.

There is some question about whether these changes might be related to factors other than improved treatment. For example, one possible explanation for the results could be an earlier diagnosis in the 2001–2003 period compared to the 1994–1996 period. If this was the case, it would explain better survival in both groups, but it would not explain the difference between colon cancer and rectal cancer patients. We do not believe that this is the explanation as there was no CRC screening in either period, and, more importantly, there was a stage migration towards more patients with lymph node positive disease in the later period. In fact, this observation could be interpreted as meaning that the diagnosis was made later in the 2001–2003 period, not earlier. We think this is more likely the result of better staging rather than a true change in stage. Therefore we think that the observed improvement in survival is reliable and is due to changes in treatment.

It is also important to ask whether the observed improvements in survival were the result of improved surgical technique (i.e. TME) for rectal cancer as compared to colon cancer or were due to other factors, such as better perioperative care, centralisation, chemotherapy or radiation. The effect of radiation on survival of patients with rectal cancer was reviewed in a Cochrane report that concluded that there was a 2% survival gain in the 5-year period after radiation[106]. However, this review included studies performed both before and after the TME surgery era. We think that the studies published prior to the TME era might skew the effect of radiation on survival towards falsely higher outcomes. Notably, a Dutch TME trial showed that patients randomised to preoperative radiation had a 50% lower probability of local recurrence, but survival was unchanged[107]. Moreover, only 9.7% of the rectal cancer patients in our study received radiotherapy. Accordingly, the use of radiation most likely is not the main explanation for the improved survival that we observed.

The recommendation of adjuvant chemotherapy, which was the only major change in colon cancer treatment, was limited to lymph node positive patients ≤75 years old[108]. Interestingly, we did not see any survival effect in the patients with lymph node negative disease or in those patients with lymph node positive disease >75 years old.

Thus, the only increase in survival occurred in the group that were presumably given adjuvant chemotherapy. Therefore, we think that the increased survival in the colon cancer group was due mainly to adjuvant chemotherapy. Our findings are in line with a paper from the Netherlands in which a survival gain was seen for the youngest colon cancer patients but not in patients who were older than 75 years[109]. A recently published study also showed that the survival effect of adjuvant chemotherapy for patients >75 years is significant[110].

Paper II analysed possible differences in excess mortality between colon and rectal cancer patients with regard to specific time periods, age ≤ or > 75 years of age and lymph node status. The results did not show any significant survival difference for the first 60 days for either colon or rectal cancer. This contrasts with the findings of Mitry et al.[111, 112] who claimed that the major improvement in survival for colorectal cancer is mostly due to better perioperative care. We found reduced mortality rates in the time intervals during later follow-up both for colon cancer and for rectal cancer. Interestingly, mortality rates for rectal cancer patients were significantly lower during the 3 first years of follow-up and then were significantly higher during the fifth year as compared to colon cancer patients. The excess mortalities translate into absolute numbers as follows: 2 patients out of 100 who were operated for colon cancer died the fifth year after surgery, but 4 patients out of 100 who were operated for rectal cancer died the fifth year. This is in contrast to the results of Engholm et al., who did not find any differences in mortality in the fifth year after surgery. However, that group studied the period 1999–2000 and included patients with all stages of cancers from several countries, whereas our study focused on patients who were curatively treated[113].

Our observation of increased perioperative survival and better survival during the first years of follow-up has several possible explanations, such as improved intensive care or centralisation of surgical services. An English study reporting on 30-day mortality for colorectal cancer found wide variations in mortality, from 3% to 16%, and they also found lower 30-day mortality for rectal cancer compared to colon cancer[114]. Another plausible explanation is that colon and rectal cancer patients

present differently with regard to acute admissions. Recent studies report emergency operations in 25% of colon cancer patients and in only 1–3% of rectal cancer patients.[33, 115]. Unfortunately, our data do not provide sufficient clinical data with regard to emergency vs. elective presentation. However, according to a recent single-centre analysis in Norway, fewer emergency procedures were reported during early 2000 compared with previous decades, which may point to a generally lower rate of patients with acute presentation of CRC.[116] The findings from a Danish study are also notable in that they showed medical complications to be the main cause of early death after emergency surgery[117]. This underlines the importance of 24-hour availability of intensive care units, radiology and other services, which may be more accessible in larger hospitals.

The finding of inversed mortality rates, i.e. better survival for colon cancer patients than for rectal cancer patients the fifth year after surgery, was surprising. To the best of our knowledge, this is the first report to describe this observation. The reason underlying the inversed mortality rates during the fifth year is unclear; however, we speculate that rectal cancer patients may experience more metastatic disease at the end of follow-up compared to colon cancer patients. According to the national guidelines, rectal cancer patients with pN+ disease should not receive adjuvant chemotherapy because of a lack of sufficient scientific evidence[118, 119]. This is not in line with findings of a recent Cochrane review, which reported a 17% reduced risk of death in rectal cancer patients treated with adjuvant chemotherapy[120]. A survival gain was also seen in a retrospective study in Sweden that investigated adjuvant chemotherapy for stage III rectal cancer[110]. In other words, the initial survival benefit, which is probably due to better control of the primary tumour, may be reduced or even inverted by later adverse events. Due to the use of relative mortality calculations, these finding are most likely related to either the disease or treatment. We hypothesize that increased distant spread at the end of follow-up may be the reason for this higher mortality. Our findings of lower mortality rates in patients with pN+ colon cancer aged ≤75 years, i.e. those receiving adjuvant chemotherapy, may support this theory. However, we have no data to verify this hypothesis. Further

research should focus on possible differences in late recurrences in colon and rectal cancer.

Papers I and II showed that based on better outcomes for rectal cancer patients after implementation of treatment guidelines, there should be similar efforts to determine how to improve the outcomes of patients with colon cancer. In this respect, it seems obvious to focus on the quality of surgery for colon cancer. One of the strongest predictors for outcome after curative resections for colon cancer has been, and continues to be, the presence of lymph node metastases, i.e. pN0 or pN+. The presence of lymph node metastases prompts a recommendation for adjuvant chemotherapy. Accordingly, lymph node harvest is considered to be the major quality indicator for colon cancer surgery. The internationally accepted number of lymph nodes that should be harvested is at least 12, although some dispute this number[121].

In Paper III, we studied lymph node harvest in a national cohort of patients curatively resected for colon cancer. The data from the NCCR demonstrated a high overall LN yield of a median of 14 LNs. Our observation that 69.9% of the patients had a LN harvest of ≥12 LN is notable as this is more LNs than have been reported recently reported in other national cohorts[122-127]. While most other studies focus on harvesting the highest possible number of LNs , we wanted to identify factors associated with poor LN harvest. Specifically, we wanted to identify both factors that might be amenable to change, and those that were inherent to the disease. We found that poor LN harvest (≤8 LNs) was associated with male gender, increasing age, pT stage 1–2, resection margin < 5 cm, failure to use the pathology template and sigmoid resections.

These factors are discussed extensively in Paper III. Among the modifiable factors, both the surgeon and the pathologist are central in achieving adequate LN harvest. Surgeons should be aware that left-sided tumours, and in particular sigmoid cancers, need particular care in order to achieve both adequate resection margins and removal of sufficient LNs. Pathologists need to dissect meticulously to identify the largest possible number of nodes, possibly by using special fixating solutions. The number of

lymph nodes identified depends to a considerable extent on the pathologist, who must spend sufficient time and use agents that facilitate the identification of lymph nodes[128, 129]. Reese et al.[130] showed that training an assistant to harvest lymph nodes increased the yield from a median of 13 to 19 LNs from one time period (1999–2002) to another (2003–2006). Recently, Fan et al.[131] reviewed 334 CRC specimens for lymph nodes. They initially found 33.6% (122) of the patients had lymph node positive disease, but the review showed an additional 12 patients with stage III disease. This finding altered treatment in 14.8% of the patients. Moreover, considerable variations have been reported regarding the content and quality of pathology reports from different laboratories[132]. Some studies claim that use of a report template increases the LN harvest[133, 134] and improves the reporting of other key parameters[135, 136]. This is supported by our results, which showed that use of the report template was significantly associated with higher LN retrieval. Whether this difference is related solely to better reporting, or the ability to implement the national template as a proxy for high standard of pathological work is hard to say. However, the detection of patients with pN+ disease was not affected.

In addition to technical factors, the possible importance of tumour biology in LN retrieval has gained more attention. The finding of more lymph nodes on the right side of the colon may imply that that the surgery is better or that more tissue is removed, but it may also suggest that there are differences in tumour biology at different tumour sites. Different pathways of tumourigenesis in various parts of the bowel have been addressed and identified, including chromosome instability and microsatellite instability (MSI). A greater proportion of right-sided colon cancers are associated with MSI[28]. MSI, which is present in roughly 20–25% of right-sided colon tumours, has also been associated with a higher number of loco-regional LNs, which might contribute to a greater LN yield[28, 137].

It is important to emphasize that the number of lymph nodes needed for adequate staging remains controversial[138]. Parsons et al. conducted a large study in the US that showed a gradual increase in the number of nodes removed over the course of two decades; however, there was no corresponding increase in the proportion of pN+

disease[139]. That study found a node positivity rate of close to 40%. A Swedish study found the same thing: there was a steady increase in the median lymph node harvest, from 7 lymph nodes in 1996–1999 to 18 in 2005–2009[140]. In this study, they found a node positivity rate of 41.9%, 40.9% and 41.6% in the three time periods that they looked at. This indicates that there might be a critical threshold of LNs that must be harvested. Beyond this number, further increase does not substantially increase the proportion of patients with pN+ disease. This is disputed by researchers who report a relationship between increased survival and increased lymph node harvest[126, 141-143]. These apparent differences may stem from the designs and methods of the various studies. While studies favouring extensive LN harvest are based mostly on results from institutional data[64], those indicating a threshold number for optimal LN harvest (without an increase in pN+ disease beyond that threshold) are based mostly on data from large national databases[126, 139]. Accordingly, a fixed number for LN harvest as a measure of quality should be used with caution and should take into account both factors that are amenable to change as well as factors that are.

All three studies in this thesis have a number of limitations. Every study based on data from a large registry is limited in terms of the type and quality of the registration. For the first two papers, we had the patients' date of diagnosis but not the date of surgery. It is reasonable to suppose that for most of the patients, the time interval from diagnosis to surgery was limited, perhaps on the order of 2–6 weeks. However, patients with rectal cancer who received radiation preoperatively had a longer time to surgery, i.e. about three months. This might have some influence on data in the first follow-up time interval (i.e., 60-day data; Paper II). On the other hand, this was true for only a small proportion of patients (8% and 18% in the two periods, respectively). Further, we do not know whether all patients with colon cancer and pN+ disease actually received adjuvant chemotherapy: our analyses were based on the assumption that recommendations to offer this treatment to patients ≤75 years with pN+ disease were followed. However, we have reason to believe that this was a good assumption as there is a strong tradition of adherence to national directives in the health care system in Norway.

Further, the real golden standard of the number of lymph nodes needed to correctly identify all patients with pN+ disease remains unknown. If few LNs are reported, we do not know whether this is due to the surgeon or the pathologist or even due to the patient. When large volume hospitals are compared with lower volume hospitals, we have to assume there is a selection bias regarding which patients are treated where. When comparing different time periods, we found that fewer patients were offered curative resections in the 2001–2003 time period, suggesting better preoperative workup and selection. This may lead to increased survival according to the Will Rogers phenomenon[144]: exclusion of patients with metastatic disease confers by itself a better prognosis in the group of patients who are thought not to have metastases. Studying total survival without excluding those who were not operated and those with metastases could have avoided the latter. However, since our intent was to study the influence of implementation of national guidelines on patients operated with curative intention and on the quality of surgery, this possible source of error could not be avoided.

14. Conclusions

Increased attention on the management of colorectal cancer has been worthwhile. First, the focus on rectal cancer improved survival, which is currently even better than that of colon cancer. Secondly, adjuvant chemotherapy for lymph node positive patients in colon cancer seems advantageous. However, improvement of survival for patients with pN+ colon cancer > 75 years of age is lacking.

We found that mortality rates for colon and rectal cancer differed for various time intervals during the 5-year follow-up period. Even though colon cancer patients had higher excess mortality for the first years after surgery, the mortality rate of patients with rectal cancer was twice that of colon cancer patients during the 5th year of follow-up.

LN harvest is supposed to be a quality indicator of colon cancer surgery. The analysis of LN harvest in our national cohort of patients curatively treated for colon cancer showed that there are a number of factors associated with low LN harvest. While some of those factors could be modified by appropriate measures, such as optimizing surgery, pathological evaluation of the specimen and reporting, other factors related to the patient and tumour characteristics are not amenable to change. Optimal LN retrieval and evaluation remains an important objective in surgical treatment for curing colon cancer, but these factors have to be taken into account when using LN harvest as a measure of the quality of surgery.

15. Future perspectives

Our study revealed that patients with rectal cancer had better survival than patients with colon cancer after implementation of national guidelines focusing on this disease. This finding implies that there is a strong need to direct more attention to colon cancer. According to the results of Paper I, the subgroup of patients with pN+ disease >75 years of age who were not receiving adjuvant chemotherapy was a subgroup that did not show improved survival. This may indicate that treatment recommendations for those patients are suboptimal, and more research is needed to improve treatment for patients >75 years with pN+ colon cancer.

The finding of a doubled mortality rate in curatively treated patients with rectal cancer compared to colon cancer during the 5th year of follow-up is troublesome. Further research is needed to identify the possible causes, which may be related to the treatment or to the disease, such as late local recurrences or metastatic disease. Our data did not allow any conclusions to be drawn regarding the reason(s) for this difference. We hypothesise that metastases that occur during late follow-up may be one possible cause. If this hypothesis is confirmed, there may be a reason to reconsider adjuvant treatment recommendations with regard to adjuvant chemotherapy for rectal cancer patients with pN+ disease.

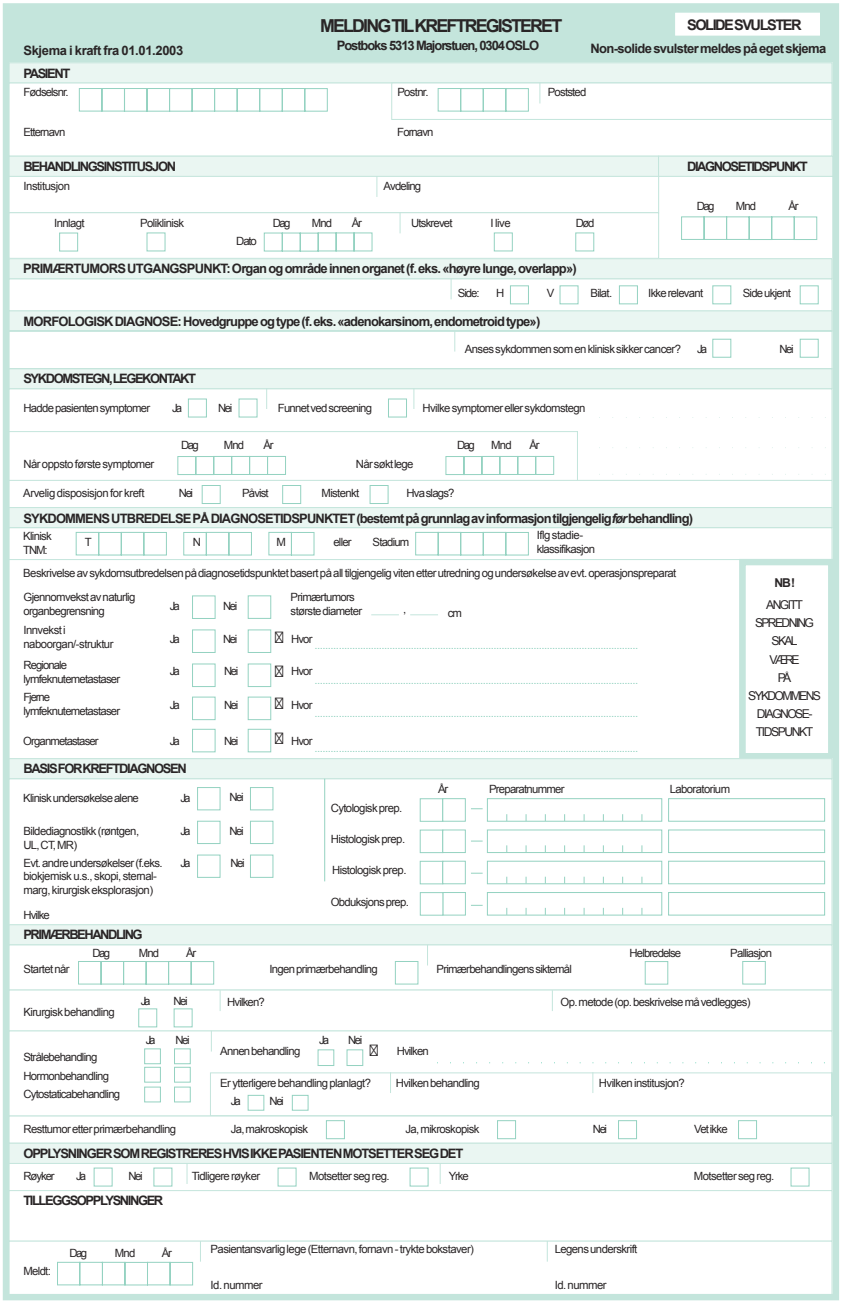
Regarding surgery for colon cancer, some new approaches to surgical treatment have been promoted recently, such as complete mesorectal excision (CME), which is analogous to the concept of TME for rectal cancer. While a number of institutional reports are promising, it is unclear whether this concept can be applied to colon cancer the way that TME applies to rectal cancer. Our study raises the question of whether there is the need to revisit the number of hospitals that offer curative surgery for colon cancer in Norway: For colon cancer, the number has remained unchanged at about 50 hospital, compared to the slightly less than 30 hospitals that treat rectal cancer. A re-evaluation of the hospitals that provide curative surgery for colon cancer

requires additional and clearer outcome measures than just LN harvest, such as surgical complications and survival.

Finally, a number of new health technologies have emerged in recent years, such as robotic-assisted surgery, single port laparoscopic surgery and the principle of natural orifice transluminal endoscopic surgery (NOTES). Careful health technology assessment that is guided by relevant outcome measures must be the unconditional prerequisite to ensure the safe introduction of new surgical approaches that will maximise the benefits of surgery for patients with cancer of the colon and rectum.

16. Appendix

Registration form for solid tumours. Cancer Registry of Norway, main database



MELDING TIL KREFTREGISTERET
Postboks 5313 Majorstuen, 0304 OSLO
SOLIDE SVULSTER
Non-solide svulster meldes på eget skjema
Skjema i kraft fra 01.01.2003

PASIENT
Fødselsnr. | Postnr. | Poststed
Etternavn | Fornavn

BEHANDLINGSINSTITUSJON | DIAGNOSETIDSPUNKT
Institusjon | Avdeling
Innlagt | Poliklinisk | Dato Dag Mnd År | Utskrevet | I live | Død
Dag Mnd År

PRIMÆRTUMORS UTGANGSPUNKT: Organ og område innen organet (f. eks. «høyre lunge, overlapp»)
Side: H V Bilat. Ikke relevant Side ukjent

MORFOLOGISK DIAGNOSE: Hovedgruppe og type (f. eks. «adenokarsinom, endometroid type»)
Anses sykdommen som en klinisk sikker cancer? Ja Nei

SYKDOMSTEGN, LEGEKONTAKT
Hadde pasienten symptomer Ja Nei | Funnet ved screening | Hvilke symptomer eller sykdomstegn
Når oppsto første symptomer Dag Mnd År | Når søkt lege Dag Mnd År
Arvelig disposisjon for kreft Nei Påvist Mistenkt Hva slags?

SYKDOMMENS UTBREDELSE PÅ DIAGNOSETIDSPUNKTET (bestemt på grunnlag av informasjon tilgjengelig *før* behandling)
Klinisk TNM: T N M eller Stadium | Iflg stadie-klassifikasjon
Beskrivelse av sykdomsutbredelsen på diagnosetidspunktet basert på all tilgjengelig viten etter utredning og undersøkelse av evt. operasjonspreparat

NB!
ANGITT SPREDNING SKAL VÆRE PÅ SYKDOMMENS DIAGNOSE-TIDSPUNKT

Gjennomvekst av naturlig organbegrensning Ja Nei | Primærtumors største diameter ___,___ cm
Innvekst i naboorgan/-struktur Ja Nei ☒ Hvor
Regionale lymfeknutemetastaser Ja Nei ☒ Hvor
Fjerne lymfeknutemetastaser Ja Nei ☒ Hvor
Organmetastaser Ja Nei ☒ Hvor

BASIS FOR KREFTDIAGNOSEN
Klinisk undersøkelse alene Ja Nei
Bildediagnostikk (røntgen, UL, CT, MR) Ja Nei
Evt. andre undersøkelser (f.eks. biokjemisk u.s., skopi, sternal-marg, kirurgisk eksplorasjon) Ja Nei
Hvilke

	År	Preparatnummer	Laboratorium
Cytologisk prep.			
Histologisk prep.			
Histologisk prep.			
Obduksjons prep.			

PRIMÆRBEHANDLING
Startet når Dag Mnd År | Ingen primærbehandling | Primærbehandlingens siktemål Helbredelse Palliasjon
Kirurgisk behandling Ja Nei | Hvilken? | Op. metode (op. beskrivelse må vedlegges)
Strålebehandling Ja Nei
Hormonbehandling Ja Nei
Cytostaticabehandling Ja Nei
Annen behandling Ja Nei ☒ Hvilken
Er ytterligere behandling planlagt? Ja Nei | Hvilken behandling | Hvilken institusjon?
Resttumor etter primærbehandling | Ja, makroskopisk | Ja, mikroskopisk | Nei | Vet ikke

OPPLYSNINGER SOM REGISTRERES HVIS IKKE PASIENTEN MOTSETTER SEG DET
Røyker Ja Nei | Tidligere røyker | Motsetter seg reg. | Yrke | Motsetter seg reg.

TILLEGGSOPPLYSNINGER

Meldt: Dag Mnd År | Pasientansvarlig lege (Etternavn, fornavn - trykte bokstaver) | Id. nummer | Legens underskrift | Id. nummer

Registration form, Norwegian Rectal Cancer Registry, 1993 – 2006

Sykehus: SUS (1107)

Kontaktperson: Dr.

Rectumcancerregisteret

REGISTRERINGSSKJEMA RECTUMCANCER

ved laparotomi for cancer lavere enn 20 cm

Pasientdata (klistrelapp)
F. nr
Navn
Postnr.

PREOPERATIVE DATA

Tumorkarakteristika

Avstand fra analåpning .....cm

Lokalisasjon fra kl ..... til kl ..... (sett nedenfra)

Mobil ☐ Fiksert ☐ Ukjent ☐

Preoperativ strålebehandling
Ja ☐ Nei ☐ Dose.....

Utredning

CT bekken utført Ja ☐ Nei ☐
MR bekken utført Ja ☐ Nei ☐
Rectal UL utført Ja ☐ Nei ☐

Påvist fjernmetastaser ved UL/CT/MR
Ja ☐ Nei ☐ Hvor.....

OPERASJONSDATA

Operasjonsdata
Dato ..../..../....

Ø. hjelp. opr. Ja ☐ Nei ☐
Kurativt siktemål Ja ☐ Nei ☐ Usikkert ☐

Lav fremre ☐ Amputasjon ☐ Hartmann ☐
Kun avlastning ☐ Annen op. .....

Mesorectal excision Ja ☐ Nei ☐

Perforasjon rectum Ja ☐ Nei ☐
Perforasjon tumor Ja ☐ Nei ☐

Skylling rectumstump Ja ☐ Nei ☐

Makrosk. resttumor Ja ☐ Nei ☐ Hvor.....

Anastomoseteknikk

Håndsydd ☐ Dobbelstapl ☐ Trippelstapl ☐

Ende-ende ☐ Side-ende ☐
J-Pouch/Reservoir ☐ Coloplastikk ☐

Avlastende stomi Ja ☐ Nei ☐

Anastomosenivå .....cm over analåpning

Peropr. påvist
Synkron cancer Ja ☐ Nei ☐ Hvor.....
Metastase Ja ☐ Nei ☐ Hvor.....
Innvekst Ja ☐ Nei ☐ Hvor.....

Peropr. reseksjon av (organer).....

POSTOPERATIVE DATA

Postoperative komplikasjoner

Anastomoselekkasje Ja ☐ Nei ☐ Dato .../..../....
Reoperasjon Ja ☐ Nei ☐ Dato .../..../....
Andre kompl Ja ☐ Nei ☐

Hvilke .....

Tilleggsbehandling etter primæroperasjon
Postoperativ strålebehandling
Ja ☐ Nei ☐ Dose.....

Cytostatika
Ja ☐ Nei ☐

Recidiv og metastaser

Lokalt recidiv Dato.../..../....
Hvor.....

Metastaser Dato.../..../....
Hvor.....

Behandling etter recidiv og/eller metastaser
Operert recidiv Dato.../..../....
Operert metastase Dato.../..../....
Radikalt reoperert Ja ☐ Nei ☐

Strålebehandling ja ☐ nei ☐ Dose.....
Cytostatika ja ☐ nei ☐

Registration form, Norwegian Colorectal Cancer Registry, from 2007 - 2012

KREFT registeret
INSTITUTT FOR POPULASJONSBASERT KREFTFORSKNING

MELDING TIL COLORECTALCANCERREGISTERET
Kreftregisteret, Postboks 5313 Majorstuen, 0304 Oslo

Svulster i colon/rectum – skjema i kraft fra 01.01.2007

1. PASIENT/BEHANDLINGSINSTITUSJON

Fødselsnr |__|__|__|__|__|__|__|__|__|__|__|

Fornavn .....

Etternavn .....

Postnr |__|__|__|__| Poststed .....

Institusjon .....

Avdeling .....

○ Innlagt ○ Poliklinisk Dato |__|__|__|__|__|__|

Utskrevet ○ I live ○ Død

2. MELDINGSTYPE (bare ett kryss)

○ Primær tumor ○ Residiv* Dato |__|__|__|__|__|__| ○ Metastase* Dato |__|__|__|__|__|__|

○ Obduksjon** Dato |__|__|__|__|__|__|

* Gå til punkt 5 * *Fyll kun ut punkt 4

3. SYKDOMSTEGN OG DIAGNOSTIKK

Hadde pasienten symptomer?	○ Ja ○ Nei	Symptomdebut (måned/år) |__|__|__|__|
Arvelig predisposisjon	○ Ja ○ Nei	
Colo/rectoskopi	○ Ja, tumor sett ○ Utført, tumor ikke sett ○ Ikke utført	
Rtg colon	○ Ja, tumor sett ○ Utført, tumor ikke sett ○ Ikke utført	
CT-abdomen	○ Ja, tumor sett ○ Utført, tumor ikke sett ○ Ikke utført	
Colografi (CT)	○ Ja, tumor sett ○ Utført, tumor ikke sett ○ Ikke utført	
Klinisk undersøkelse alene	○ Ja, sikker tumor	
Biopsi av tumor	○ Ja ○ Nei Pat. lab	Diagnosetidspunkt |__|__|__|__|__|__|

4. TUMORS LOKALISASJON

Tumors lokalisasjon (Hvis flere, kryss av for de aktuelle)

☐ Appendix ☐ Cøkum ☐ Ascendens ☐ Høyre fleksur

☐ Transversum ☐ Venstre fleksur ☐ Descendens ☐ Sigmoideum (≥ 20 cm)

☐ Rectosigmoid (16–< 20 cm) ☐ Rectum (< 16 cm fra analåpning på stivt skop) ..... cm

Målt ved MR: øvre kant av m. puborektalis til nedre kant av tumor ..... cm

5. SYKDOMSUTBREDELSE VED DIAGNOSE

			Utførte undersøkelser (basis for diagnostikk)			
Levermetastaser	○ Nei ○ Ja ○ Mistenkt →		☐ Ultralyd	☐ CT	☐ MR	☐ Ingen
Lungemetastaser	○ Nei ○ Ja ○ Mistenkt →		☐ Rtg thorax	☐ CT	☐ MR	☐ Ingen
Andre fjernmetastaser (inkl. perit. carcinomatose)	○ Nei ○ Ja ○ Mistenkt →		☐ Ultralyd	☐ CT	☐ MR	☐ Ingen
	Hvis ja, hvor:				**CEA**:	
Dybdevekst av tumor i rectum og rectosigmoid	○ I tarmvegg (T1-T2) ○ Gjennom tarmvegg (T3) ○ Innvekst naboorgan (T4)	→	☐ Ultralyd	☐ CT	☐ MR	☐ Ingen
Antatt CRM	|__|__| mm	**Antatt positive lymfeknuter** ○ Ja ○ Nei ○ Ikke utført			

6. FORBEHANDLING

☐ Ingen ☐ Strålebehandling ☐ Kjemoterapi ☐ Radiokjemoterapi ☐ Avlastende stomi ☐ Stenting

7. BEHANDLING

Operert ○ Ja Dato |__|__|__|__|__|__| ○ Nei Årsak:

Hastegrad ☐ Elektiv ☐ Akutt pga obstruksjon ☐ Akutt pga perforasjon

☐ Akutt pga annet .....

Kirurgens preop. intensjon ○ Kurativt ○ Palliativt ○ Usikker ASA-score:

GJENNOMFØRT OPERASJON **Opr. type** ○ Åpen ○ Laparoskopi ○ Laparoskopi, konvertert åpen

a) Reseksjon av tumor ○ Ja ○ Nei (gå til b) Pat. lab .....

Colon		**Rectum**	
☐ Hemicol. dxt	☐ Utvidet hemicol. dxt	☐ Fremre reseksjon	☐ Hartmann
☐ Hemicol. sin	☐ Utvidet hemicol. sin	☐ Amputatio recti	☐ Polypektomi
☐ Transv. reseksjon	☐ Transv. + fleksurreseksjon	☐ Lokal reseksjon	☐ Transanal endoskopisk mikrokirurgi
☐ Sigmoidreseksjon	☐ Subtotal kolektomi	☐ Annen	
☐ Annen			
○ Medialt/sentralt først	○ Lateralt først	**Anastomosenivå** |__|__| cm over analåpning	

Lymfeknutedisseksjon

○ D3 Kar avsatt inntil a. mes. sup./aorta
○ D2 Intermediær avsetting av kar
○ D1 Tarmnær avsetting av kar

Anastomoseteknikk:
○ ende-ende ○ side-ende ○ J-Pouch/Reservoir

Anastomose etter reseksjon ○ Ja ○ Nei **Avlastende stomi etter res./anast.** ○ Ja ○ Nei

Endestomi ○ Ja ○ Nei

b) Operasjon uten reseksjon av tumorbærende tarmsegment:

☐ Bypass ☐ Avlast. stomi ☐ Kun ekspl. lap. ☐ Stenting

INTRAOPERATIVT FUNN/DIAGNOSE:				**KONSEKVENS**:	
Levermetastaser	○ Nei	○ Ja, klinisk sikker	○ Ja, mistenkt	☐ Biopsi tatt	☐ Reseksjon utført
Peritoneal met./carcinomat.	○ Nei	○ Ja, klinisk sikker	○ Ja, mistenkt	☐ Biopsi tatt	☐ Reseksjon utført
Lymfeknutemet. utenfor res. område	○ Nei	○ Ja, klinisk sikker	○ Ja, mistenkt	☐ Biopsi tatt	☐ Reseksjon utført
Innvekst i naboorgan	○ Nei	○ Ja, klinisk sikker	○ Ja, mistenkt	☐ Biopsi tatt	☐ Reseksjon utført

Hvilke(t) organ: .....

Perforasjon under operasjonen ☐ Nei ☐ Tarm ☐ Tumor

Resttumor lokalt (kirurgens vurdering) ○ Nei ○ Ja, sikker ○ Mulig

8. KOMPLIKASJONER TIL OPERASJON

Komplikasjoner ☐ Nei ☐ Anastomoselekkasje ☐ Annen Spesifiser: .....

Reoperasjon ○ Nei ○ Ja Dato |__|__|__|__|__|__| Spesifiser: .....

9. ETTERBEHANDLING

Planlagt etterbehandling ☐ Nei ☐ Ikke avklart ☐ Ja

Hvis ja: ☐ Strålebehandling ☐ Kjemoterapi ☐ Radiokjemoterapi ☐ Kirurgi for metastaser

Institusjon: .....

Meldingsdato Meldt av (navn (blokkbokstaver) + ID-nr.) Signatur

|__|__|__|__|__|__|

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